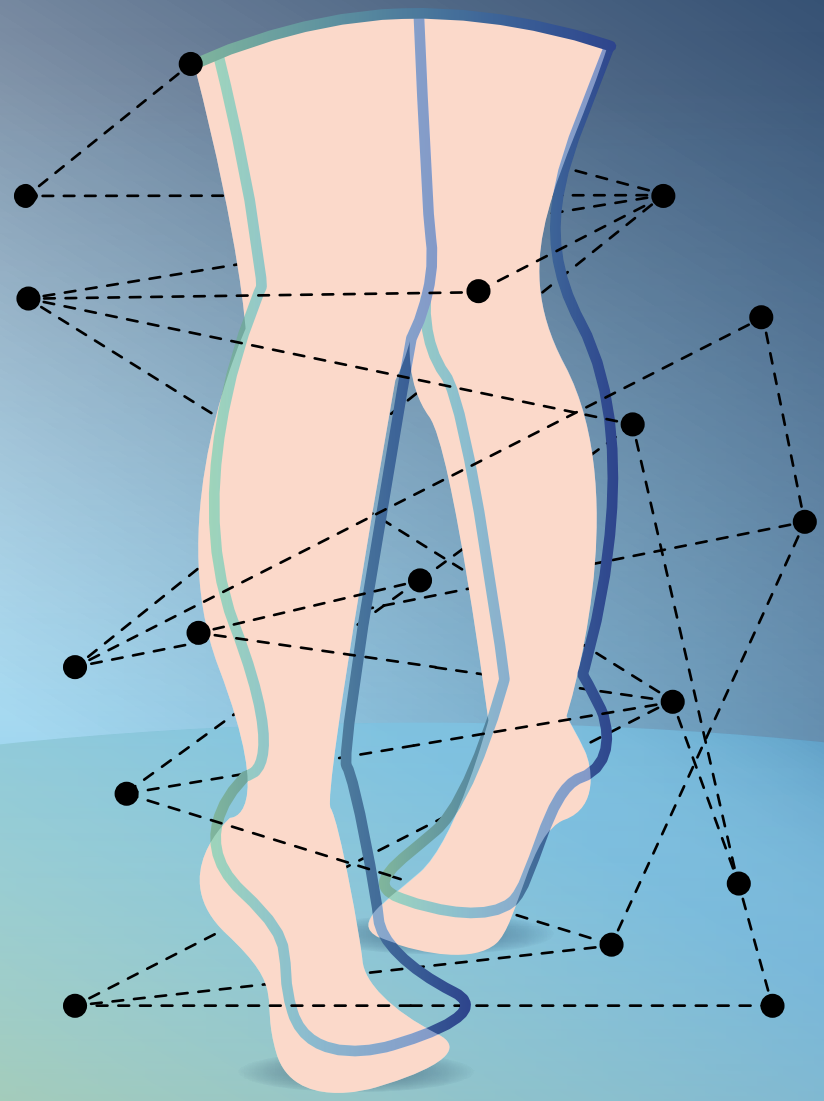
BALANCE AND GAIT PROBLEMS

IN PEOPLE WITH

HEREDITARY SPASTIC PARAPLEGIA

patient experience, underlying mechanisms and clinical management



DONDERS SERIES

Bas van Lith

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The studies presented in this thesis were carried out at the Department of Rehabilitation, Donders Institute for Brain, Cognition and Behaviour, Radboud university medical center, Nijmegen, the Netherlands.

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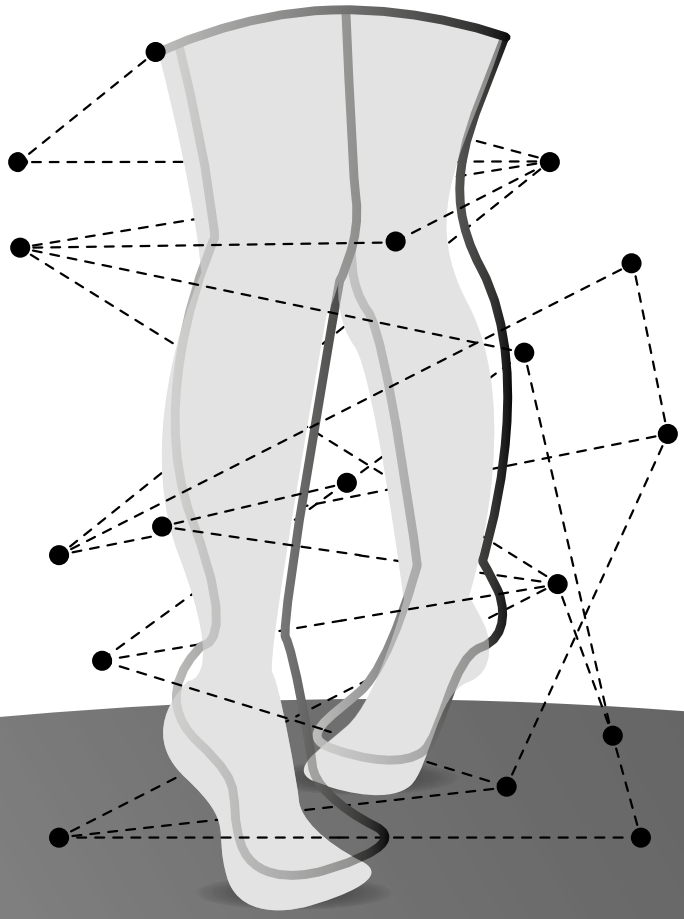


CHAPTER 1

General introduction and thesis outline

Introduction

Hereditary spastic paraplegia (HSP) refers to a heterogeneous group of inherited disorders with an estimated prevalence of 3.3-6.6/100,000 individuals [7]. Patients with HSP are clinically characterized by progressive lower extremity spasticity, and to a lesser extent, muscle weakness and sensory loss [8,9]. In addition, many patients experience urinary problems related to a spastic bladder. The common pathological feature in HSP is retrograde axonal degeneration of the corticospinal tracts, posterior spinal columns, and to a lesser extent the spinocerebellar fibers [10,11]. The axonal degeneration is presumably due to abnormal axonal membrane trafficking processes, which primarily affect the distal parts of axons but additional pathophysiological mechanisms are involved [12].

HSP is characterized by autosomal dominant, autosomal recessive, X-linked or maternal patterns of inheritance. The genetic classification for HSP is based on sequential numbering of genetic loci, according to the order of discovery, using a spastic paraplegia gene (SPG) designation [13]. To date, up to 80 SPG genes have been identified. Still, a genetic diagnosis cannot be not made in 51–71% of all suspected cases [14-18], indicating an even larger genetic heterogeneity. HSP can be divided into pure (uncomplicated) and complicated forms, depending on the presence or absence of other neurological symptoms in addition to spastic paraparesis. Complicated phenotypes may include symptoms such as dementia, ataxia, severe amyotrophy, optic atrophy, mental retardation, extrapyramidal signs, deafness, peripheral neuropathy and/or epilepsy. In pure HSP, the neurological impairments are mainly restricted to lower limb spasticity and bladder involvement. In this thesis, the focus is on patients with pure HSP.

Pure HSP may manifest at any age, but the first symptoms and signs mostly occur before the age of 40 years [19-21]. The first presenting symptoms are subtle with development of leg stiffness. As the disease progresses, gait and balance impairments develop, which may result in falls and fall-related injuries, and which increasingly affect safe and independent mobility. Several reports on pure HSP indicate the presence of gait and balance impairments and subsequent increased fall risk as the most prominent functional consequences of HSP [9,22-24]. Gait abnormalities in HSP patients are typically described as "foot drag", "crouch gait" and/or "scissoring" [11,25,26]. Yet, the role of spasticity in gait and balance impairments remains poorly understood. Unfortunately, curative treatments for HSP do not exist. As a consequence, current

treatments aim at supportive measures and symptomatic relief. One of the primary treatments to reduce focal spasticity is injection of botulinum toxin type-A (BTX-A; Box 1), but very little is known about the functional effects of this treatment on balance and gait. Hence, it is important to get insight in the functional complaints and problems of patients with pure HSP and to investigate the underlying mechanisms and possible treatments of their balance and gait problems.

BOX 1. Botulinum toxin type A

Botulinum toxin type A (BTX-A) inhibits the acetylcholine release from the presynaptic neuromuscular terminals. Local BTX-A injections are used to selectively reduce neural activation of targeted muscles [4], with the degree of reduction depending on the dosage [5]. In neurology and rehabilitation medicine, BTX-A injections are mainly used to treat overactive muscles, such as in dystonia and spasticity. BTX-A injection is therefore one of the spasmolytic treatment options.

Outline of the thesis

The overall aim of this thesis is to gain more insight into the motor control deficits of patients with pure forms of hereditary spastic paraplegia (HSP) that underlie their gait and balance problems and into the effects of treatment with BTX-A.

Part 1 of this thesis focuses on the daily life problems encountered by patients with HSP. **Chapter 2** starts with an overview of the pathophysiology, diagnostic workup and management of balance impairments in HSP. In **chapter 3**, the results of an online survey are provided that was designed to investigate the influence of muscle spasticity on experienced complaints, activity limitations and loss of motor capacities in patients with HSP.

Part 2 is focused on the underlying mechanisms of motor control in patients with pure HSP. In **chapter 4**, the role of hyperexcitable short-latency stretch reflexes in balance control is investigated by exposing patients to toes-up and toes-down perturbations. These balance perturbations are imposed by the Radboud Falls Simulator (Box 2). It is expected that exaggerated short-latency reflexes in the triceps surae lead to difficulties in sustaining toes-up perturbations.

BOX 2. Balance and gait analysis

In this thesis, the Radboud Falls Simulator (RFS; BAAT, Enschede, The Netherlands 6) is used to investigate balance control. The RFS is a motorized platform of which the support surface (upon which the subject is standing) can suddenly translate or rotate by powerful torque motors that assure standardized delivery of perturbations (figure 1). During gait assessments, participants walk across a 10 meter walkway (figure 2). During both balance and gait assessments, body segments are identified by attachment of reflective markers and tracked by a 3D motion analysis system (Vicon Motion Systems, Oxford, United Kingdom) in order to analyze kinematics. In addition, forces are obtained from force platforms (AMTI® force plate, Watertown, United States) and muscle activation patterns are recorded using surface-based electromyography (EMG) (ZeroWire, Aurion, Italy).

FIGURE 1. The Radboud Falls Simulator

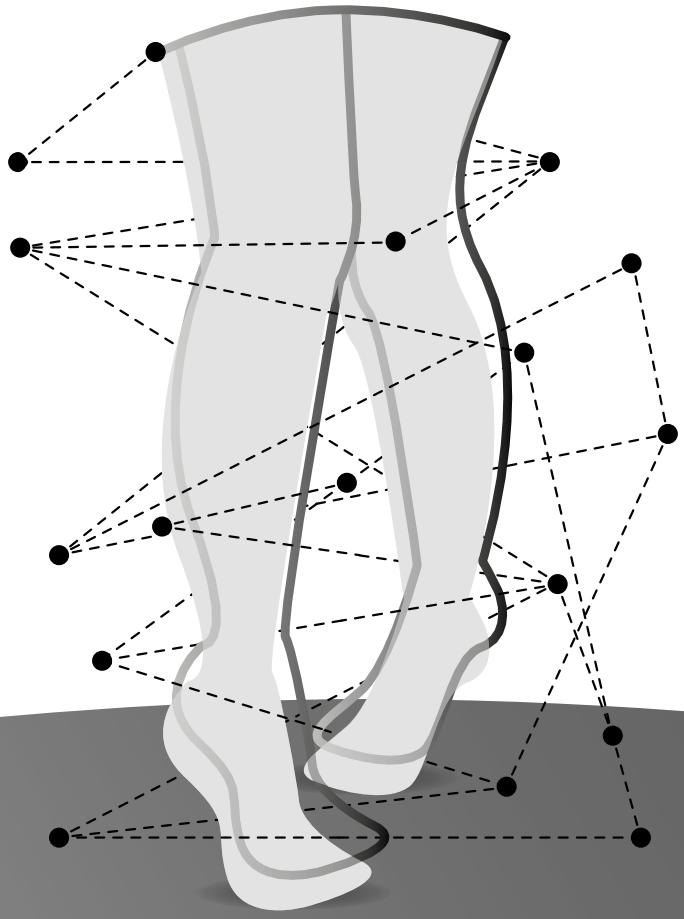
In **chapter 5**, we examine whether the reticulospinal tract can be utilized to control voluntary whole-body movements by applying the StartReact paradigm (Box 3) during gait initiation. It is expected that the reticulospinal tract is able to play a compensatory role in such voluntary control.

BOX 3. StartReact

StartReact is the phenomenon that reaction times are accelerated when a startling stimulus is presented simultaneously with an imperative stimulus for executing the requested movement. Although the exact neural structures that are involved in the StartReact effect are not uncontested, there is ample evidence that the accelerated motor responses are due to the startling stimulus directly releasing a subcortically pre-prepared movement, which is then conveyed by the reticulospinal tract 1-3.

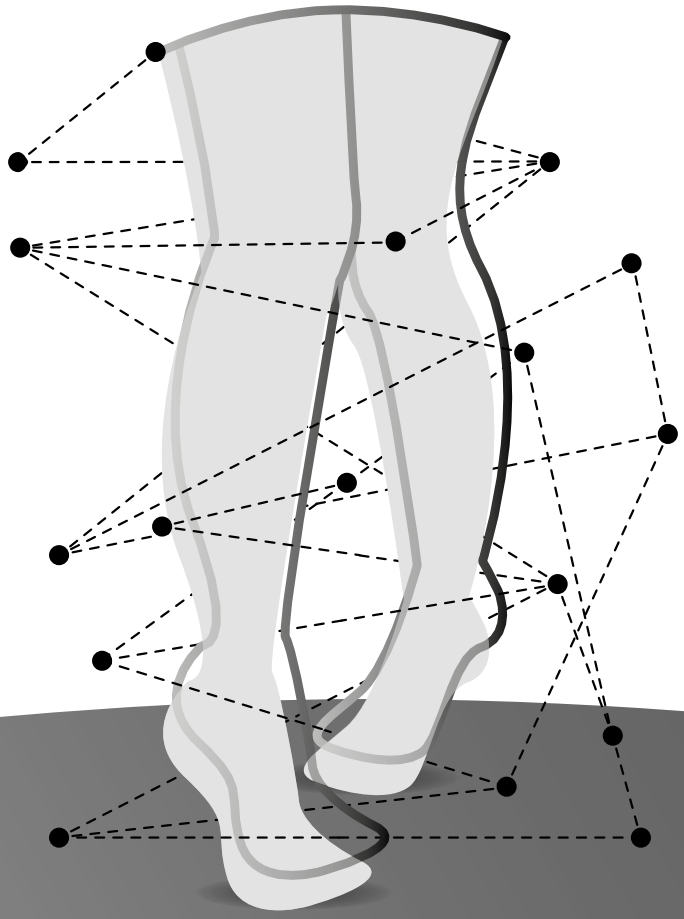
Part 3 consists of clinical studies that aim to gain insight in the effects of BTX-A on balance and gait. In **chapter 6**, we address the question how ankle kinematics and kinetics during gait are modified by BTX-A injections in the calf muscles. A previous study from our group showed a decrease in calf muscle tone and a slight decrease in calf muscle strength resulting in an increased gait velocity [9]. It is expected that a decrease in negative work (due to decreased muscle tone) outweighs a possible decrease in positive work (due to decreased muscle strength). In **chapter 7**, we explore the functional effects of BTX-A treatment and subsequent stretching of the spastic hip adductors on gait and lateral balance control. It is expected that reduced spasticity following treatment translates into an increased gait width and improved lateral stepping capacity.

A summary and general discussion in **chapter 8** finalize this thesis.



PART 1

DAILY PROBLEMS OF LIVING WITH HSP



CHAPTER 2

Pathophysiology, diagnostic work-up, and management of balance impairments and falls in patients with hereditary spastic paraplegia.

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Abstract

Balance impairments are common in patients with hereditary spastic paraplegia (HSP) and among the most debilitating symptoms, as they frequently result in falls and fall-related injuries. Several features of HSP contribute to balance impairments and multiple treatment options exist. However, an overview of these underlying mechanisms and their treatment is currently lacking. We review the pathophysiology, diagnostic workup, and management of balance impairments in HSP. Recommendations are based on scientific evidence, when available, and otherwise reflect practice-based evidence supported by clinical experience. We argue that through diligent history taking and thorough clinical examination, followed by multidisciplinary treatment tailored to the identified underlying mechanisms, balance capacities in patients with HSP can be improved and at least a proportion of falls can be prevented.

Introduction

Hereditary spastic paraplegia (HSP) is a diverse group of inherited disorders that are clinically characterized by progressive spasticity, muscle weakness and reduced proprioception in the lower extremities [27,28]. In addition, many patients experience urinary problems related to a spastic bladder. The common underlying mechanism of these symptoms is retrograde axonal degeneration of the corticospinal tracts, posterior spinal columns, and to a lesser extent the spinocerebellar fibers [10,11]. HSP can be divided into pure (uncomplicated) and complicated forms, depending on the presence of other neurological symptoms, such as ataxia, optic atrophy, mental retardation, extrapyramidal signs, dementia, deafness and epilepsy [28]. The first presenting symptoms and signs of HSP are subtle with development of leg stiffness and minor gait impairments. Although the disease may manifest at any age, the first symptoms and signs mostly occur before the age of 40 years [19-21]. As the disease progresses, balance impairments develop, which may result in falls and fall-related injuries. Unfortunately, the prevalence of balance impairments and frequency of falls in HSP has – to our knowledge – not yet been studied. Moreover, the consequences of balance impairments and falls have been mapped insufficiently, but clinical experience shows that these may seriously impact on daily life, as they result in fall-related injuries, fear of falling, reduced mobility (approximately 10% of the patients with pure HSP become wheelchair bound [29]), loss of independence, and reduced quality of life.

Most publications about HSP concern its genotypes and the genotype-phenotype coupling. Far less publications have considered the functional consequences of HSP, and most of these address the (management of) spastic gait impairments such as 'foot drag', 'crouch gait', and 'scissoring' [11,25,26]. Very few publications have been focused on balance impairments and related falls as specific consequences of HSP [22]. To fill this gap, we here elaborate on the pathophysiology, diagnostic workup, and management of balance impairments and falls in patients with HSP. This review is based on scientific evidence when available (see box 1), and otherwise reflects practice-based evidence supported by clinical experience.

BOX 1. Search strategy

We searched PubMed for relevant articles published in English from database inception to January 1, 2017. Potential papers were identified with the terms 'hereditary spastic paraplegia', 'Strumpell-Lorrain disease', 'HSP', 'balance', 'balance impairments', 'falls' and ' treatment'. Selected articles were also obtained from the reference lists of papers identified by the PubMed search and from searches of the authors' own files.

Pathophysiology: Why do patients with HSP fall?

In general, falls can be the result of intrinsic or extrinsic risk factors, or a combination of both [30]. An icy pavement, wet bathroom tiles, or loose carpets are examples of extrinsic risk factors that may cause a trip or a slip inducing a fall. However, as in other neurological conditions such as stroke and Parkinson's disease [31,32], falls in HSP are mainly due to intrinsic risk factors. These intrinsic factors hamper feet-in-place balance responses and contribute to suboptimal stepping responses when a feet-in-place response is no longer sufficient to maintain balance. In HSP, four main contributors to balance impairments can be identified.

The *first* intrinsic risk factor is spasticity, which can have a direct (negative) influence on balance responses when fast muscle stretch – induced by active or passive body perturbations – results in destabilising muscle responses. This is best documented for 'toes-up perturbations', during which rotation of the support surface induces fast ankle dorsiflexion and backward body perturbation [33]. In healthy subjects, stretch-induced calf muscle activity is suppressed during these toes-up perturbations, allowing ventral leg and trunk muscles to pull the body forward and restore balance [34,35]. However, in patients with HSP, there is insufficient suppression of stretch-induced calf muscle activity due to reduced corticospinal inhibition of stretch reflexes, as part of the so-called 'upper motor neuron syndrome' [22,24]. This may result in a destabilising plantar flexion moment at the ankles that counteracts the ventral muscles, which pulls the centre of mass (further) backwards, and threatens balance [22]. As such, toes-up perturbations may cause backward falls in HSP. However, as toes-up perturbations in daily life are relatively rare, their potential contribution to actual fall risk is probably limited. Moreover, the available evidence suggests that calf muscle spasticity does not contribute to balance impairments in HSP during backward balance perturbations induced by forward support-surface translations (when the

calf muscles are shortened instead of stretched) or by any type of forward body perturbation [22]. Hence, the direct contribution of spasticity of distal musculature to balance impairments in HSP seems limited. Still, spasticity of proximal musculature (e.g. the adductors or hamstrings) may directly contribute to balance impairments as it hampers the capacity to make sufficiently fast stepping responses in situations where feet-in-place responses do not suffice. For example, hip adductor spasticity may reduce the efficacy of balance-correcting side steps upon lateral perturbations and hamstrings spasticity may seriously limit the capacity to make a forward step of sufficient length upon forward body perturbations.

Although the direct contribution of leg muscle spasticity to impaired feet-in-pace balance may be limited, spasticity can indirectly contribute to balance impairments and falls in HSP, because it predisposes to the development of muscle contractures and joint deformities (*second* risk factor), which negatively influences the ability to perform feet-in-place balance responses as well as stepping responses. The most commonly encountered deformity in patients with HSP is pes equino(varus) due to structural shortening of the calf muscles, long toe flexors and/or tibialis posterior muscle. Structural pes equinus results in a (severely) reduced base of support, particularly when the heels do no longer have contact with the ground. This situation prevents the use of normal 'ankle strategies' for maintaining feet-in-place balance in the sagittal plane, requiring the recruitment of less efficient 'hip strategies'. In addition, patients may adopt compensatory postural adjustments at the knees (e.g. hyperextension), hips (e.g. hyperflexion) and trunk (e.g. forward lean) in order to maintain balance when standing. In some patients, there is varus deformity at the ankles, which can be aggravated by a concomitant pes cavus. As a consequence, the base of support in the frontal plane will be reduced, which will impair the use of ankle strategies during one-legged stance, for example during the single-support phase of gait. Apart from a direct influence on balance, pes equinovarus obviously predisposes to gait impairments such as 'foot drag' and 'hooking', which increases the risk of tripping over one's own feet while walking or when making a balance-correcting stepping response. Moreover, varus deformity at heel strike and during the stance phase of gait will predispose to ankle instability, ankle sprain, and falling sideways. In addition to pes equinovarus, knee flexion contractures (due to shortened hamstrings) and hip adduction contractures (due to shortened hip adductors) are common in patients with HSP. In our experience, their impact on balance is – as with spasticity of proximal musculature – stronger through impaired stepping responses than through impaired (feet-in-place) equilibrium reactions.

The *third* intrinsic risk factor for balance impairments and falls in HSP is muscle weakness. Indeed, there is evidence that reduced calf muscle strength is associated with postural instability during forward body perturbations induced by backward support-surface translations [22]. In contrast, however, the relationship between tibialis anterior strength and backward body perturbations (induced by forward support-surface translations) appears to be less clear [22]. Generally, muscle weakness does not seem to be the major impairment in patients with HSP, even though the name 'paraplegia' suggests otherwise. There is growing support for the notion that muscle weakness induced by lateral corticospinal tract dysfunction can be compensated by reticulospinal activation originating from the brainstem [36,37]. Indeed, there is strong evidence for intact reticulospinal control over voluntary and postural leg movements in patients with HSP [1,23,38]. Hence, compensatory reticulospinal activity may be quite effective to produce sufficient muscle strength, although less differentiated in comparison to the more selective corticospinal control over muscles [39]. However, as with other neurological diseases [40], patients with HSP are prone to sarcopenia and loss of muscle strength due to 'disuse' induced by lack of activity. Lack of activity can have several reasons, one of which is fear of falling. Disuse-induced muscle weakness commonly induces a vicious circle in which balance impairments become worse, resulting in falls and fear of falling, and eventually more disuse.

A *fourth*, least known or appreciated risk factor for balance impairments in HSP is reduced proprioception, resulting in delayed postural responses. We evaluated balance responses to forward and backward body perturbations in patients with pure HSP, and found that patients were less stable than healthy aged-matched control subjects, as reflected by a larger percentage of trials in which they had to take a corrective step or grasp a handrail [23]. Moreover, compared to controls, their postural responses to backward and forward perturbations were on average delayed by 38 and 34 ms, respectively [23]. This delay may appear small in absolute terms, but entails a relative increase of 25-30% compared to healthy subjects. This delay in postural responses could theoretically be the result of a slowness of signals in the afferent (posterior spinal columns) or efferent (reticulospinal) tracts, or in a combination of both. By combining balance perturbations with an auditory startling stimulus we were able to disentangle both mechanisms [1,36,41]. The results indicated that delayed postural responses in patients with HSP are primarily due to a delay of signals in the posterior spinal columns, i.e. due to impaired proprioception [23].

Overall, we believe that impaired feet-in-place responses in patients with pure HSP are mainly due to delayed postural responses and to the biomechanical influence of predominantly *distal* muscle contractures. In contrast, the contribution of distal muscle weakness and spasticity seems to be restricted to specific types of body perturbations. Nevertheless, spasticity, shortening, and weakness of the *proximal* leg muscles may hamper the capacity to make sufficiently fast and large stepping responses in situations where feet-in-place responses do not suffice. Obviously, it should be kept in mind that ataxia, extrapyramidal symptoms and/or visual impairments may contribute to balance impairments in patients with complicated forms of HSP.

Diagnostic workup: individual identification of fall mechanisms in HSP

Although balance impairments and falls in HSP are common, the presence and relative contribution of the various intrinsic and extrinsic risk factors may vary considerably between patients. Therefore, history taking and clinical examination is necessary to determine the contribution of each factor to individual balance impairments [30]. In this diagnostic process, it is important to value each risk factor as well as their possible interactions, as often multiple factors are relevant for individual patients.

History taking

In both healthy populations and in patients with a neurological disorder, the strongest risk factor for a fall is the presence of a fall-history [42,43]. It is therefore essential to ask whether the patient has fallen during the last year(s) and, if so, whether he or she has fallen recurrently, under which circumstances, and whether any injury has ever occurred. In the case of recurrent falls, it is important to establish whether there is a typical pattern or direction to the fall [30]. Even if the patient indicates not to fall, the identification and treatment of risk factors is still important for the prevention of future falls. Patients with HSP can usually indicate whether they are easily 'pulled backward' or whether they fall forward or sideways instead. It is not useful to ask for underlying mechanisms (e.g. spasticity, slowness, or contractures), as patients find it difficult to judge any of such possible relationships. Yet, fall circumstances, fall pattern, and type of injury can point towards a specific mechanism like 'backward instability'. When a patient has fallen, it is important to ask whether he or she recalls hitting the floor to exclude loss of consciousness due to head trauma. Because patients

with HSP rarely lose their consciousness when falling, other underlying mechanisms such as vasovagal syncope or cardiac arrhythmias should be suspected. As in the general population, use of medication – especially polypharmacy – can increment fall risk and, thus, an evaluation of prescribed drugs should take place. Benzodiazepines and antidepressants are notorious in this respect [44], in addition to neuroleptics, antihypertensive medication, and anti-arrhythmics [45]. In addition to intrinsic factors, it is important to screen for the presence of extrinsic factors, for example the type of footwear and the home situation. It is not uncommon to discover that patients who suffer recurrent falls live in a house with loose high carpets and without extra support points in the bathroom or toilet.

Finally, it is informative to inquire about the impact of balance impairments, particularly fear of falling and a related reduction of in- and outdoor activities. In this way, the clinician is also able to screen for disuse. In fearful patients, fall frequency is not an adequate measure of balance problems, as these patients have often adjusted their lives in such a way that falls hardly occur. The downside of this adjustment is, however, a seriously reduced quality of life for both themselves and their relatives as well as an enhanced risk of co-morbidity related to immobility, such as cardiovascular disease, osteoporosis and sarcopenia, reinforcing a vicious circle of functional incapacity and inactivity.

Clinical examination

When the patient's history is suspicious of balance impairments, a thorough clinical examination is mandatory to confirm the presence of balance impairments and to identify underlying mechanisms. Table 1 provides an overview of useful clinical tests of balance, gait and neurological functions.

A useful test to indicate the presence of balance impairments is assessing the ability to rise from a chair, to stand on two legs as well as on one leg with the foot flat on the ground and eyes opened. An inability to perform such tests without any external support strongly suggests the presence of balance impairments. A key element in the clinical assessment of postural instability is the retropulsion test, in which the assessor induces a balance perturbation by applying a (preferably unexpected) shoulder pull [46]. The absence of a balance corrective step or a suboptimal quality of the balance corrective step is indicative of postural instability. In patients with HSP, we recommend to perturb the patient not only in the backward direction, but also in the forward and lateral directions to test the quality of the stepping responses in the oth-

er directions as well. By sitting on a stool in front of the patient the clinician can easily pull the pelvis forward or apply sideways forces to the pelvis, while the patient is able to grasp the shoulders of the clinician or the clinician can stop a falling motion when needed. As a more elaborate test we advice to perform the mini-BESTest, consisting of a 14-item, 3-point rating scale evaluating four sub-items: transitions/anticipatory postural control, reactive postural control, sensory orientation, and stability in gait [47]. Another option is the Berg Balance Scale (BBS)[48], which is a standardized 14-item, 4-point rating scale to indicate the presence of postural instability while sitting, standing and making postural movements in place. Both the mini-BESTest and the BBS include several elements of the tests described above. However, no standardized balance test has yet been validated for patients with HSP.

TABLE 1. Key elements of the clinical examination in patients with HSP

Tests that help to indicate the presence of balance impairments

• Rising from sit to stance
• Two- and one-legged stance
• Retropulsion test (plus perturbations in forward and lateral directions)
• Mini-BESTest or Berg Balance Scale
• Evaluation of the gait pattern
  • Standardized gait observation
  • Observation of tandem gait

Evaluation of the four main intrinsic risk factors for balance impairments in HSP

• Evaluation of muscle tone (e.g. Modified Ashworth Scale)
• Evaluation of joint mobility (e.g. Debrunner notation)
• Evaluation of muscle strength (e.g. MRC-scale)
• Evaluation of proprioception
  • Vibration sense at lateral malleolus and first metatarsophalangeal joint
  • Romberg's test
  • Gait with and without a walker or 'finger support'

Balance capacity while walking can be assessed by testing tandem gait (i.e., the ability to take 10 consecutive steps along an imaginary line without one or more side steps). This test is very sensitive for subtle balance impairments and often no longer possible in patients with HSP. Of course, the gait pattern should be observed for the identifi-

cation of specific gait impairments that increase the risk of tripping and falling, such as foot drag, hooking of the feet, and excessive scissoring with collision of the knees.

The four main risk factors for balance impairments in HSP must always be identified by a systematic evaluation. We recommend to assess muscle tone of distal and proximal leg musculature using the Modified Ashworth Scale (MAS) [49], to evaluate joint mobility with goniometry using the Debrunner notation [50], and to assess muscle strength using the Medical Research Council (MRC) scale [51]. Although both the MAS and the MRC scales have been criticized for their lack of reliability and sensitivity [52], alternative clinical tools for measuring muscle tone (e.g. the Tardieu scale [53] and strength (e.g. hand-held dynamometry) are quite time-consuming to be applied to all joints of the lower limbs and do not necessarily provide more reliable information. Importantly, with regard to management, the clinician should try to carefully discriminate loss of muscle length (contracture) from increased muscle tone (spasticity) using goniometry for all relevant muscle groups, with the calves evaluated with both an extended (gastrocnemius) and flexed (soleus) knee, preferably in a supine position. Regarding the evaluation of proprioception, it is useful to evaluate vibration sense at the lateral malleolus and at the first metatarsophalangeal joint. An easy way to evaluate the contribution of impaired proprioception to balance impairment is Romberg's test, in which the clinician evaluates body sway and the presence of balance corrective movements of the head, trunk and arms while the patient stands erect with the feet together and the hands by the side. This test is performed with eyes opened and closed and is considered positive when body sway increases to the extent that a patients tends to fall with the eyes closed compared to when they are opened. A positive test is indicative of balance impairments due to sensory dysfunction and, thus, useful to find proof of impaired leg somatosensation in HSP. Nevertheless, a false-positive outcome may occur due to uncertainty or fear, while a false-negative outcome may be due to insensitivity to subtle sensory deficits. One study did not find increased postural sway in four patients with HSP compared to controls (18), but future studies are needed to further map postural sway in patients with HSP, both in mildly and severely affected patients.

Another functional test that is sensitive to somatosensory deficits is comparing comfortable gait speed with and without a walker. Although a walker may provide mechanical support and increases the base of support while walking, its most important influence is often the provision of sensory feedback through the upper extremities especially in patients that do not really lean on the walker. When such patients walk

much faster with a walker than without, this finding is suspicious of impaired leg somatosensation. In the same vein, providing 'a fingertip' of support to the hand of a patient while standing or walking is also a strong indicator of reduced somatosensation[54], if it leads to better postural stability and higher gait speed.

As outlined in the introduction, patients with a complicated form of HSP can have a wide variety of other symptoms in addition to their spastic paraparesis, such as ataxia, signs of parkinsonism or visual disorders. As these symptoms may significantly contribute to the balance impairments, it is important to screen and monitor them and, if present, to manage treatable symptoms accordingly (this will not be covered in the management section of this paper).

Ancillary testing

In most patients, history taking and clinical examination will be sufficient to obtain a good general overview of the presence and severity of the balance impairments and of the underlying risk factors. Yet, a more in-depth evaluation of balance impairments may be conducted with posturography.

Using 'static posturography' equipment for recording quiet standing[6], body sway can be quantified and compared to reference values obtained from healthy, age-matched individuals. In addition, the Romberg quotient can be determined, which is the ratio between the body sway assessed with eyes closed divided by the sway assessed with eyes opened [55]. Such an instrumented Romberg quotient is much more sensitive than the clinical Romberg's test, but the necessary equipment may not be available in many clinical practices.

So-called 'dynamic posturography' is a technique that employs physical perturbations of stance (often by a motorized balance platform) to systematically and quantitatively evaluate both feet-in-place balance responses and stepping responses. Although this technique has proven its value for research purposes, it has so far no clear additional value for clinical practice in comparison to the tests described above [6]. However, when balance impairments and gait impairments coincide, or when gait impairments frequently result in falls, instrumented assessment of the kinematics (joint motion), kinetics (joint moment of force and power) and muscle activations (electromyography) during walking (instrumented 'gait analysis') can be useful to analyse specific gait impairments to indicate the need for well targeted interventions (e.g. focal spasmolysis, ankle-foot orthosis) [56,57].

Management: how to prevent patients with HSP from falling?

Adequate management of balance impairments and falls in patients with HSP will greatly depend on the identification of risk factors as described above. In this paragraph, we will discuss the treatment options based on each of these factors. The evidence for these treatment options is sparse, because very few studies have been performed and the available studies are non-randomised. In addition, the evidence of these interventions on balance performance in other patient groups with an upper motor neuron syndrome is also sparse, as most studies evaluated the effect on gait and not on balance control or the prevention of falls [57-59]. Hence, most treatment options are based on expert opinion.

Spasticity

If a patient's history and clinical examination is indicative of calf muscle spasticity contributing to a tendency to fall backwards, focal spasmolysis of the calf muscles must be considered. The main treatment option is neuromuscular blockade by the administration of bilateral botulinum toxin type A (BTX-A) injections in the gastrocnemius and soleus muscles to reduce the amplitude of the balance destabilizing responses. The efficacy of these injections has, however, not yet been proven. We found 10% improvement of comfortable gait speed after such injections in patients with HSP, but no improvement on the BBS, dynamic posturography, or the Activities-specific Balance Confidence scale (ABC)[9]. Despite the absence of a significant effect at group level on all balance-related outcomes, it is our clinical experience that well-selected individual patients with destabilizing calf muscle spasticity and a relative mild pes equinus contracture may profit from focal spasmolysis and subsequent stretching exercises of the calf muscles with regard to their backward postural stability. This notion is supported by a recent retrospective study reporting that focal spasmolysis with BTX-A combined with physiotherapy aimed at optimizing joint mobility of the treated segments helps to acquire an adequate postural alignment in patients with HSP [60]. In addition to intramuscular injections with BTX-A, chemical or thermal neurolysis of the tibial nerve and selective surgical neurotomy of specific branches of the tibial nerve are techniques to reduce disabling calf muscle spasticity [61,62]. However, chemical or thermal neurolysis carries the risk of inducing sensory deficits and/or neuropathic complaints, while selective neurotomy is complex and performed only by very few expert teams worldwide.

As mentioned above, spasticity of the proximal muscles may hamper stepping responses in both the sagittal and frontal planes. As such, it would intuitively be right to apply focal spasmolysis by intramuscular BTX-A injections (followed by stretching exercises) for instance in the hamstrings to improve forward stepping and in the hip adductors to improve lateral stepping in individual patients with HSP. Currently, we are conducting an uncontrolled pre-post trial to study the efficacy of bilateral BTX-A injections in the hip adductors to improve spontaneous gait width as well as side stepping responses upon lateral body perturbations in patients with HSP and hip adductor spasticity (Toetsingonline.nl: NL5353904.091.15).

The use of oral spasmolytic drugs is usually not effective to obtain focal results in specific muscles [63] and carries the risk of systemic side effects, such as nausea, drowsiness, loss of (leg) muscle strength, and dizziness. Yet, oral spasmolytic drugs (e.g. baclofen, tizanidine or tolperison) should be considered when there is severe 'lower body' spasticity affecting several distal and proximal leg muscles, hampering effective stepping responses. When effective, such patients will probably also profit from this medication with regard to their gait capacity. If oral spasmolytic drugs are insufficient (and multilevel intramuscular BTX-A injections not feasible or impractical), intrathecal baclofen therapy (ITB) should be considered for this relatively severe subgroup of patients. ITB has shown to reduce spasticity-related complaints and improve walking capacity in these patients [64], but its effect on balance capacity has not yet been shown.

Contracture and deformity

As stated above, pes equino(varus) is the main and often first deformity seen in patients with HSP due to shortening of the dorsal leg muscles. In addition to muscle contracture, spasticity may contribute to this deformity when spastic muscles are no longer able to fully relax. From this perspective, focal spasmolysis of the calf muscles, tibialis posterior and/or long toe flexors may also be indicated to reduce ankle deformity, but such treatment should always be accompanied by intensive stretching exercises to improve muscle length and inhibit muscle tone. Especially selective BTX-A injections in the tibialis posterior muscle may be effective to reduce varus deformity, unless fixed varus contracture has developed. In the case of a fixed contracture, ankle deformity can be compensated by providing orthopaedic footwear but the effectiveness of such footwear to improve balance capacity in patients with HSP has not yet been studied. The main goal of orthopaedic footwear is to restore a full base of support in both the antero-posterior and medio-lateral directions

and to provide ankle stability in the case of structural varus deformity. When there is concomitant pes cavus, a well adjusted insole can accommodate for this latter deformity. Orthopaedic footwear should always be as light-weighted as possible and allow sufficient mobility at the talocrural (superior) ankle joint for optimal use of ankle strategies and for an optimal roll-off motion during gait. In addition, the external sole should not aggravate any tendency towards foot drag.

Another option for restoring a normal base of support is to surgically lengthen the shortened dorsal muscles of the lower leg, particularly for more severe contractures and for those patients that do not want to rely on adjusted footwear. Usually, percutaneous Achilles tendon (AT) lengthening is sufficient to correct pes equinus. Interestingly, it is our experience that AT lengthening will often reduce the degree of post-operative calf muscle spasticity as well. Tenotomy of the tibialis posterior muscle may be effective to correct pes varus, but an (complementary) arthrodesis of the talonavicular joint may be a more viable treatment option. In addition, tenotomy of the long toe flexors may be necessary for the AT lengthening to be truly effective. Osteotomy of the first metatarsal bone can be performed to correct a concomitant severe and structural pes cavus.

Any treatment that is able to reduce equinovarus deformity at the ankle joints will eventually be beneficial for static and dynamic balance by allowing better use of ankle strategies in both planes and by a reduced risk of tripping, hooking, ankle instability or ankle sprain. Redression of equinovarus deformity will also improve standing posture by requiring less postural adjustments at the knees, hips, and trunk.

Knee flexion and hip adduction contractures must preferably be treated by an intensive stretching regime, supported by BTX-A injections in the hamstrings and hip adductor muscles, respectively. As for the hip adductors, the adductor magnus, adductor longus, and gracilis are the most relevant target muscles given their anatomical lever with respect to the hip joint [65]. In our experience, the medial hamstrings are a better target than the lateral hamstrings if there is a tendency towards internal rotation at the hips. Besides passive stretching exercises, active stepping and agility training is recommended to incorporate improved joint range of motion into the motor programs used for standing and walking.

Muscle weakness

As indicated above, muscle weakness does not seem to be the major determinant of balance impairments in HSP. This is probably related to reticulospinal compensation originating from the brainstem [1]. Exercise training to improve muscle strength is therefore not very likely to improve balance capacity in most patients with HSP. However, patients with HSP are prone to 'disuse' phenomena due to lack of activity and fear of falling. So if a patient's history and/or clinical examination indicates disuse, a comprehensive physical training program, guided by a physical therapist is recommended. As prolonged walking frequently leads to increased leg muscle tone, this may not be the optimal training activity for patients with HSP. We therefore advice to regularly perform cycling exercises, preferably under natural circumstances using a (adapted) bicycle, or otherwise a home trainer. Most patients experience a beneficial effect of cycling exercises not only on their muscular and cardiopulmonary endurance, but also on their leg muscle spasticity and stiffness during walking. Usually, this kind of aerobic training can be done at home or in a community-based fitness practice and needs merely remote guidance from a physical therapist. The effectiveness of regular (cycling) exercises to prevent disuse phenomena, to improve muscular and cardiopulmonary endurance, and to reduce leg muscle spasticity in HSP is an important topic for future research.

Impaired proprioception

Unfortunately, it is not possible to restore impaired proprioception in patients with HSP. Management should therefore focus on the use of optimal compensation strategies. Compensation involves an increased reliance on other sensory resources than proprioceptive information from the feet and lower legs (such as visual input or somatosensory information from the upper legs or provided by a walking aid). To train this type of compensation, we recommend patients with HSP to perform daily balance exercises at home, e.g. by alternately standing on one leg, in front of a high table or low cupboard, while gradually reducing the amount of hand/finger contact with the object. In our clinical practice, all patients are taught how to perform these exercises by an expert physical therapist during one treatment session.

When balance impairments are so severe that falls occur regularly, the use of walking aids cannot be avoided. Preferably, patients should use such aids not to lean on, but to obtain extra somatosensory information through the upper extremities. Thus, Nordic Walking sticks are preferred above conventional canes or crutches. Some patients prefer to use a walker, as these devices often provide additional comfort such

as a seat and basket. Even when patients start to rely on walking aids, they must be challenged to maintain their balance capacity by continuing the daily performance of balance exercises to avoid the detrimental consequences of disuse. Eventually, some patients may need to rely on a wheelchair, even to cross short distances, depending on the age of onset and the progressiveness of the disease. We recommend consultation of an occupational therapist for offering advice on suitable wheelchairs.

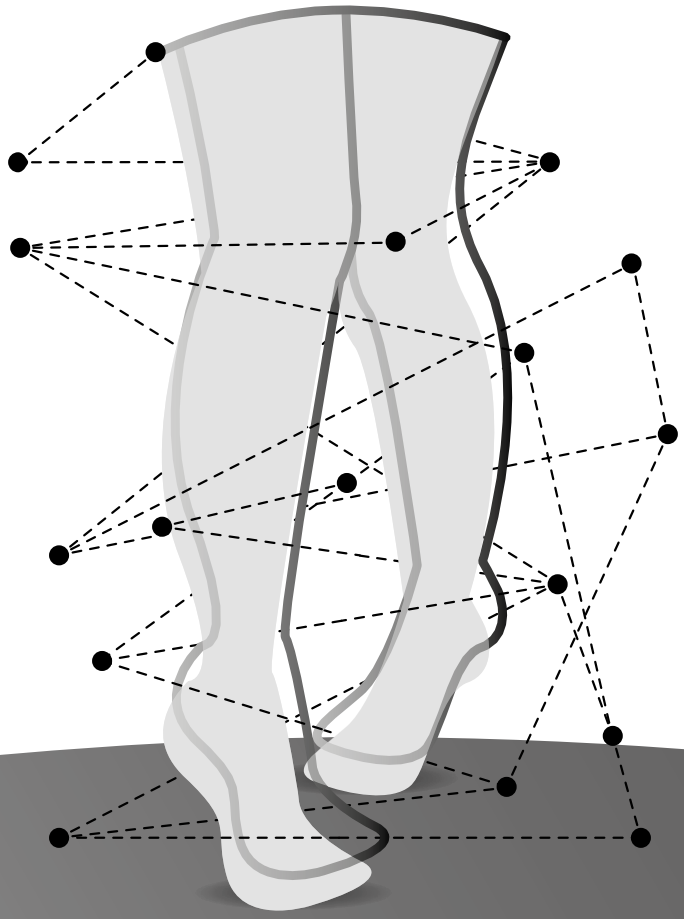
Conclusion and future perspectives

Balance impairments are an important and 'independent' functional consequence of HSP. Inadequate feet-in-place responses are predominantly due to progressively delayed balance responses and contractures of distal musculature. In addition, spasticity, contractures and, to a lesser extent, weakness of proximal leg muscles result in suboptimal stepping responses. Falls are a threatening consequence of balance impairments and many clinicians perceive falls in HSP as untreatable. However, it is our experience that diligent history taking and thorough clinical examination, followed by a multidisciplinary treatment tailored to the identified underlying mechanisms, is able to ameliorate balance capacities in patients with HSP and to prevent at least a proportion of these falls. Many treatment options that we have discussed need to be validated by further research. We conclude this review with some examples of topics for future studies. We have already highlighted the need for studying the effect of focal spasmolysis by intramuscular BTX-A injections followed by stretching exercises in proximal musculature to improve stepping responses. With respect to contractures, future studies need to investigate the timing of soft-tissue surgery. We hypothesize that timely surgical treatment, for example of a pes equino(varus) deformity, will improve balance capacities and prevent falls in comparison to prolonged treatment with orthopaedic shoes.

With respect to functional balance training, the use of new technological tools should be investigated. One example is C-mill training, during which a diversity of visual targets is projected on a treadmill that need to be hit (or avoided) with various degrees of complexity, while safety is ensured by two parallel bars that patients can grasp in case of balance loss. The type and complexity of the visual targets can be individually adjusted, which makes it possible that every patient can train at his own level and can experience both benefit and reward. In our centre, we regularly provide

10 sessions of C-mill training (2 sessions per week, during 5 weeks) to patients with HSP for improving their dynamic balance. Such a training has been shown to be effective for patients with stroke [66] and for patients with hereditary forms of (spino) cerebellar ataxia[67], but studies in patients with HSP have yet to be performed. Another potentially useful type of functional exercise is robotic training using the Lokomat, a robotic gait orthosis combined with a harness-supported body weight system. In an uncontrolled study of 13 patients with pure HSP [68], a six-week robot-aided gait training significantly improved balance performance assessed with the BBS. Future work is needed to investigate whether these promising results can be replicated by controlled studies.

With respect to the organization of multidisciplinary treatment for balance impairments in HSP, we expect that in the near future, patients will be supported by specifically designed e-health systems, monitoring their individual condition and connecting them to their primary healthcare providers. The feasibility and clinical value of such e-health systems needs to be evaluated by future studies as well.



CHAPTER 3

Experienced complaints, activity limitations and loss of motor capacities in patients with pure hereditary spastic paraplegia: a web-based survey in the Netherlands.

PUBLISHED AS

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Abstract

Background

Hereditary spastic paraplegia (HSP) is a group of inherited disorders characterized by progressive spastic paresis of the lower limbs. Treatment is often focused on reducing spasticity and its physical consequences. To better address individual patients' needs, we investigated a broad range of experienced complaints, activity limitations, and loss of motor capacities in pure HSP. In addition, we aimed to identify patient characteristics that are associated with increased fall risk and/or reduced walking capacity.

Methods

We developed and distributed an HSP-specific online questionnaire in the Netherlands. A total of 109 out of 166 questionnaires returned by participants with pure HSP were analyzed.

Results

Participants experienced the greatest burden from muscle stiffness and limited standing and walking activities, while 72% reported leg and/or back pain. Thirty-five and 46% reported to use walking aids (e.g. crutches) indoors and outdoors, respectively; 57% reported a fall incidence of at least twice a year ('fallers'); in 51% a fall had led to an injury at least once; and 73% reported fear of falling. Duration of spasticity and incapacity to rise from the floor were positively associated with being a 'faller', whereas non-neurological comorbidity and wheelchair use were negatively associated. Higher age, experienced gait problems, not being able to stand for 10 minutes, and incapacity to open a heavy door showed a negative association with being a 'walker without aids' (>500m).

Conclusions

Our results emphasize the large impact of spastic paraparesis on the lives of people with pure HSP and contribute to a better understanding of possible targets for rehabilitation.

Background

Hereditary spastic paraplegia (HSP) is a group of inherited disorders, characterized by progressive bilateral lower limb spasticity and, to a lesser extent, muscle weakness [27]. HSP can be classified as 'pure' ('uncomplicated') or 'complicated', depending on the presence of other neurologic abnormalities such as ataxia, seizures, cognitive impairment, and/or involvement of the upper extremities and speech [10,19,28,69]. In patients with pure HSP, the main neurological feature is a progressive spastic paraparesis (SP). As HSP cannot be cured, treatment is often focused on reducing or stabilizing spasticity and its physical consequences. However, rehabilitation strategies should focus on a broad range of experienced complaints and limitations to address the needs of patients. Thus, gaining more knowledge of SP-related complaints, activity limitations, and loss of motor capacities as experienced by patients is important for better disease management and tailoring interventions to individual patients' needs. In various patient groups with lower limb spasticity (e.g. stroke, spinal cord injury and multiple sclerosis), spasticity appears to be a significant contributor to experienced complaints, activity limitations, and loss of motor capacities [70-72]. Recently, an international survey in patients living with spasticity was conducted that emphasized the large impact of spasticity on daily life and the need for better collaboration, communication and sharing of information between patients and their healthcare providers to fulfill individual needs [73]. Yet, patients with pure HSP may differ from the population with spastic paraparesis at large, as their condition is inherited and slowly progressive. Existing reports on pure HSP typically indicate the presence of gait and balance impairments and an increased risk of falling as the most prominent functional consequences [9,22,23,69,74,75]. In addition, some studies mentioned the occurrence of pain, fatigue, urinary symptoms, sleeping problems, unpredictable day-to-day fluctuations, activity limitations and participation restrictions. However, these studies included either small patients samples [76,77] or lumped patients with pure and complex HSP [78-80].

Against this background, we developed a disease-specific online questionnaire to investigate the experienced complaints, activity limitations, and loss of motor capacities as well as the experienced healthcare needs in a large, representative group of patients with pure HSP in the Netherlands. In the current study, we specifically focus on SP-related complaints, activity limitations and loss of motor capacities to better understand the impact of the disease. Besides motor problems, we included autonomic (micturation, defecation, and sexual) dysfunctions, as we expected

that the latter might be related to spasticity as well. In addition, as balance and gait impairments are considered key problems in HSP, we aimed to identify specific demographic, clinical and functional characteristics that are associated with increased fall risk and/or reduced walking capacity. Data on the experienced needs will be reported in a separate publication.

Methods

Recruitment and inclusion of participants

Participants were recruited through the national patient organization for neuromuscular disorders in the Netherlands ("Spierziekten Nederland"; www.spierziekten.nl). On our request, they sent all the members of the HSP working group an e-mail with information about the web-based survey. In addition, all patients with pure HSP known at the national expertise center for inherited movement disorders of the Radboud university medical center in Nijmegen were sent a letter with information about the survey. People could participate if they had genetically confirmed HSP, or were very likely to have HSP based on their clinical symptoms and family history. In addition, participants had to be 18 years or older. Persons with HSP and their relatives were requested to contact the primary researcher (BvL) by e-mail if they were willing to participate. After receiving an e-mail, the primary researcher sent a unique link to the web-based questionnaire to each patient who had indicated willingness to participate. This study was approved by the regional medical ethics committee "Commissie Mensgebonden Onderzoek Arnhem-Nijmegen" (number 2016-2922) and conducted according to the declaration of Helsinki.

Web-based questionnaire

The structure and content of the web-based survey were designed by a team of expert physicians, researchers, physical therapists, and persons with HSP. Part of the questionnaire was based on a previous international survey of patients living with spasticity [73], while other questions were based on a qualitative study in patients with pure HSP who were interviewed about the daily life consequences of spastic paraparesis and their related healthcare needs (note: data on healthcare needs are reported elsewhere) [77]. The structure and formulation of the questions and predefined answering options were improved during an iterative process, until all authors agreed on the final questionnaire.

Completion of the questionnaire by participants was estimated to take about 20 minutes, but there was no set time limit. Participants were able to pause the questionnaire and continue later. To some extent, the amount of questions was variable for each participant, depending on his/her answer to a preceding question. Answering options were based on multiple choice, but some questions included a text entry as one of the options. Overall, the questions in this study were grouped into three response categories: A. 'participant characteristics', B. 'complaints and activity limitations', and C. 'loss of motor capacities' (see Appendix). Whereas the questions in category B were focused on the problems participants experienced when performing certain daily life activities, the questions in category C were focused on the self-rated capacity to execute specific activities. To obtain a homogeneous sample of persons with pure HSP, specific questions were included to identify patients with neurological comorbidity and/or a complicated form of HSP.

Data analysis

Patients were excluded from further analysis if they indicated that they had a complicated form of HSP (or a genetic defect invariably associated with a complicated form of HSP); experienced upper limb paresis, speech problems, or cognitive problems; or reported any neurological comorbidity that could influence spasticity, motor control, physical fitness, or activity. As we were interested in SP-related complaints, activity limitations, and loss of motor capacities, participants who reported that they did not experience spasticity (or had spasticity for less than 1 year) were also excluded from further analysis.

Statistical analysis

Descriptive statistics were used to analyze the primary data obtained from the questionnaires. In addition, univariate logistic regression analyses were performed on two dependent variables: being a 'walker without aids' (i.e., self-report of walking distance without crutch or walker > 500m), and being a 'faller' (i.e., self-report of at least two falls a year). The threshold of at least two falls a year was chosen to make sure that subjects were not classified as a 'faller' based on a single (perhaps coincidental) fall. To prevent overfitting of the model in case of many correlations between possible determinants and dependent variables, we continued with multivariate logistic *forward* regression analyses. Thus, possible determinants from each of the three response categories that were associated with a specific dependent variable in the univariate analyses ($p<0.10$) were entered in a multivariate logistic forward regression

analysis ($p<0.05$) to identify clinically relevant, independent determinants for this dependent variable.

Results

A. Participant characteristics

A total of 194 respondents requested to participate, of which 166 persons returned a fully completed questionnaire. Subsequently, 57 respondents not meeting the criteria outlined above were excluded (n=16 established complicated form of HSP; n=12 upper limb paresis; n=21 speech problems; n=19 cognitive problems; n=15 neurological comorbidities; n=4 spasticity < 1 year). Finally, 109 respondents were included for further analysis. The participants showed an equal sex distribution (49.5% male and 50.5% female) and had a mean age of 52.8 years (age range 19-84 years). Most participants (83%) indicated a positive family history for pure HSP and 53% reported that HSP was also genetically confirmed. Participants without a positive family history or genetic diagnosis (n=7) were e-mailed by the primary investigator to confirm that the clinical diagnosis of pure HSP was made by a neurologist. All participant characteristics are summarized in table 1.

B. Complaints and activity limitations

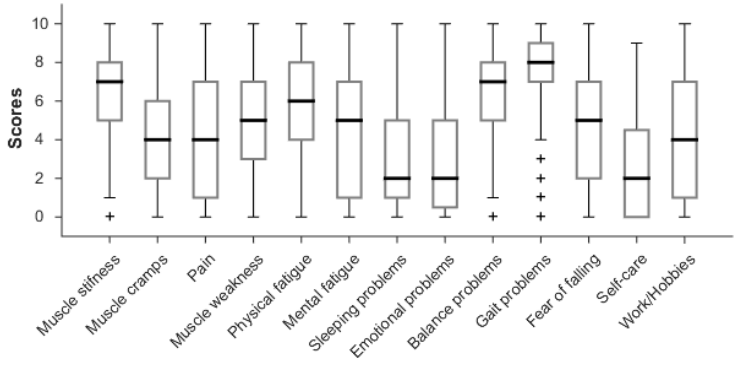
Experienced complaints and activity limitations were scored on a numeric scale (range 0-10; 0: no burden/hindrance, 10: extreme burden/hindrance). Overall, the participants experienced the greatest burden or hindrance from their muscle stiffness and from problematic standing and walking activities (figure 1). They also reported to experience a substantial burden from both physical and mental fatigue. Sleeping problems, self-care problems, and emotional problems were relatively mild.

TABLE 1. Demographic and clinical characteristics

	N=109	
Patient characteristics	n	mean (SD)
Sex (male/female)	54/55	
Age (years)		52.8 (14.2)
Duration of spasticy symptoms (years)		
1-5 years	21	
6-10 years	21	
11-15 years	16	
> 15 years	51	
Genetic defect	57	
SPG-3a	4	
SPG-4	36	
SPG-5a	2	
SPG-7	3	
SPG-8	3	
SPG-10	2	
SPG-17	1	
SPG-31	5	
SPG-72	1	
Positive family history		
First degree relatives	83	
Other family members	47	
First degree relatives and/or other family members	90	
Unknown	8	
No	11	
Non-neurological comorbidities		
Asthma/COPD	6	
Diabetes	1	
Hypertension	9	
Joint disorders	13	
Cardiac problems	4	
Other non-neurological comorbidities	7	

**Rheumatism and osteoarthritis were given as examples to participants. Patients were instructed that this category did not include non-specific back complaints.*

FIGURE 1. Median, interquartile range, and total range of the level of burden/hindrance that participants experienced in various categories (Questions B1-B13) (0: no burden/hindrance, 10: extreme burden/hindrance). +: outlier.



Seventy-two percent of the participants reported pain. Fifty-five participants (50%) reported back pain, predominantly in the lower back, and 59 participants (54%) reported leg pain. The majority described leg pain as nerve pain (i.e., burning or tingling pain; n=25), cramps (n=32), or restless legs (i.e., strong urge to keep the legs moving; n=33).

Autonomic dysfunctions

Forty-nine (50%) and 21 (19%) of the participants reported micturation and defecation problems, respectively. These problems were related to extreme urge (n=22 and n=11, respectively), impaired sphincter control (n=45 and n=14, respectively), or slowness of gait (n=30 and n=11, respectively). Forty-three of the participants (39%) reported sexual problems, whereas 46 (42%) experienced no sexual problems and 20 (18%) did not know. The most frequently reported reasons for sexual problems were related to spasticity (n=26) and pain (n=14). Some men reported ejaculation problems (n=4) or erectile dysfunction (n=8), whereas some women experienced vaginal dryness (n=5). Eleven participants reported other sexual problems, among which difficulties with having an orgasm (n=6).

C. Loss of motor capacities

Table 2 provides an overview of the devices applied for supporting functional mobility. The devices were categorized into orthoses (including orthopedic footwear),

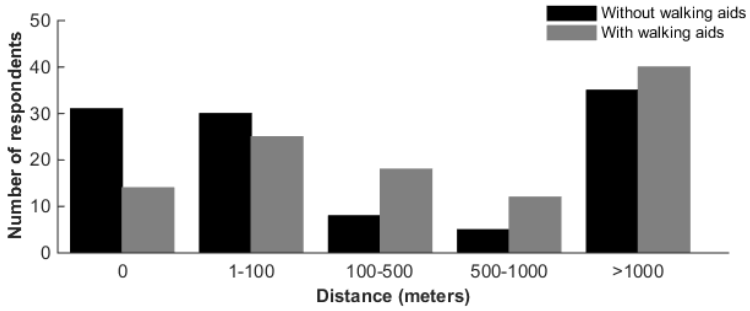
walking aids, and wheelchairs. The most often used devices were walking aids, such as canes or crutches: 35% reported to use walking aids indoors, whereas 46% used walking aids outdoors. Outdoors, an (electric) wheelchair was often applied as an alternative for walking.

TABLE 2. Use of mobility-supporting devices (N=109)

	n (%)	
Type of device	Indoors	Outdoors
Orthoses	32 (29%)	44 (40%)
Ankle-foot orthosis	13 (12%)	19 (17%)
Orthopedic footwear	28 (26%)	34 (31%)
Walking aids	38 (35%)	50 (46%)
Walker	26 (24%)	30 (28%)
Cane/Crutch	28 (26%)	41 (38%)
Wheelchairs	23 (21%)	50 (46%)
Wheelchair	22 (20%)	43 (39%)
Electric wheelchair	7 (6%)	29 (27%)
Other	11 (10%)	10 (9%)
None	44 (40%)	23 (21%)

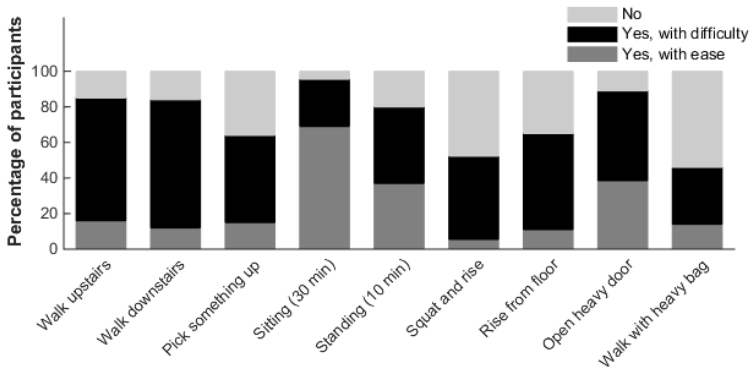
Without a walking aid, the majority of the participants was either unable to walk (28%) or walk up to 100 meters (28%), or was able to walk more than 1000 meters (32%). Only 12% reported to be able to walk between 100 and 1000 meters without a walking aid. With the use of walking aids, there was a more equal distribution of walking capacity due to a general shift from very short to longer distances (figure 2). Indeed, a total of 45 participants (41%) was able to walk further with than without the use of a walking aid. Many participants described their gait pattern as characterized by drop foot (75%), scissoring (30%), and/or crouch gait (13%).

FIGURE 2. Walking distance with and without aids.



As shown in figure 3, relatively few participants were not able to sit for 30 minutes or to open a (heavy) door. In contrast, stair walking, picking something up from the floor, squatting and rising, rising from the floor, and walking with a heavy bag was difficult or even impossible for the majority of the participants.

FIGURE 3. Percentage of participants that responded to be able to execute specific motor capacities with ease, with difficulty, or not at all.

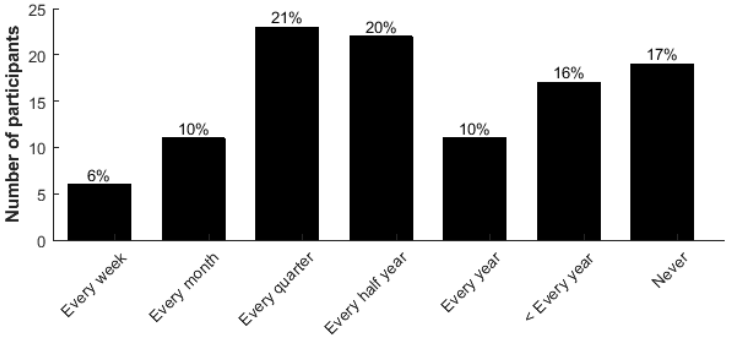


Falls

Since the onset of spasticity symptoms, 93 of the participants (85%) had fallen at least once, which had occurred within 5 years of symptom onset in 63 of 93 subjects (68%). Most participants (67%) reported a fall incidence of at least once a year; 57% reported to fall at least twice a year ('faller') (figure 4). In 56 participants (51%) a fall had led to an injury at least once, such as a skin injury (n=34), bruise (n=33), and/or

bone fracture (n=13). Only 29 of the participants (27%) reported not to be afraid of falling, whereas 66 (60%) were moderately afraid and 14 (13%) were very afraid to fall.

FIGURE 4. Self-reported fall frequency of participants.



Regression analyses

Univariate logistic regression analyses (n=109) revealed nine determinants that were associated with being a 'faller'. These determinants were entered into a multivariate forward regression analysis (table 3, upper part). In the final model, duration of spasticity symptoms and the incapacity to rise from the floor were positively associated with being a faller, whereas non-neurological comorbidities and the use of a wheelchair were negatively associated. The overall explained variance was 45%.

The 27 participants who were not able to stand for 10 minutes or who were not able to open a heavy door, were never able to walk more than 500 meters without walking aids. These participants could not be included in the (multivariate) logistic regression, because of the 1:1 associations. Univariate logistic regression analyses of the remaining participants (n=82) yielded 29 determinants that were associated with being a 'walker without aids'. These determinants were entered into a multivariate forward logistic regression analysis (table 3, lower part). In the final model, difficulties with standing for 10 minutes and with opening a heavy door showed a strong negative association with being a 'walker without aids', whereas age and experienced gait problems showed a small to moderate negative association, respectively. The overall explained variance was 58%.

TABLE 3. Multivariate forward logistic regression analyses

Dependent variable: 'faller' (self-report of at least two falls a year) (n=109)

Cofactor	Level of cofactor	n	OR (95 % CI)	p-value
Duration of spasticity symptoms	*Reference:* 1-5 years	21		
	5-10 years	21	39.070 (5.405-282.410)	<0.001
	10-15 years	16	7.789 (1.419-42.757)	0.018
	>15 years	51	18.025 (3.813-85.220)	<0.001
Comorbidity	*Reference:* No	101		
	Yes	8	0.162 (0.052-0.509)	0.002
Walking aids indoors	*Reference:* No wheelchair	87		
	Wheelchair	22	0.130 (0.029-0.577)	0.007
Rise from floor	*Reference:* Yes, with ease	12		
	Yes, with difficulty	59	17.897 (2.759-116.108)	0.002
	No	38	17.934 (2.333 -137.878)	0.006
Overall explained variance R^2 = 0.450				

Dependent variable: 'walker without aids'
(self-report of walking distance without crutch or walker > 500 m) (n=82)

Cofactor	Level of cofactor	n	OR (95 % CI)	p-value
Age	19-84	82	0.944 (0.899-0.994)	0.030
Gait problems	0-10	82	0.604 (0.400-0.911)	0.016
Standing (10 min)	*Reference:* Yes, with ease	40		
	Yes, with difficulty	42	0.286 (0.085-0.970)	0.045
Open heavy door	*Reference:* Yes, with ease	41		
	Yes, with difficulty	41	0.165 (0.049-0.564)	0.004
Overall explained variance R^2 = 0.583				

Discussion

Given the estimated prevalence of 800 persons with pure HSP in the Netherlands [81], this web-based survey probably included a fairly representative sample of 109 persons who showed an equal sex distribution, a wide age range, a large variation in duration of spasticity symptoms, and an expected (skewed) distribution of underlying genetic defects. This study sample reported many subjective complaints and activity limitations, of which muscle stiffness and problems with performing standing and walking activities were most severe (medians $\geq$ 7 on a numeric rating scale 0-10).

Balance, gait and falls

Several studies have reported problems with performing standing and walking activities and an increased fall risk in patients with HSP [9,19,22,23,75], but the published data on severity or prevalence of these problems are still very limited. Only one survey reported that 47% of the participants with HSP had fallen at least once over the past three months [79], yet this estimate also included patients with complicated forms of HSP. In the current survey, both the reported severity of the balance and gait problems, fear of falling, and the high prevalence of falls and fall-related injuries indicate that safe and efficient postural and ambulatory control is a major problem in people with pure HSP. The observed proportion of 67% of people who reported at least one fall per year seems to be comparable to other patients with spastic paraparesis caused by, for instance, multiple sclerosis, tropical spastic paraparesis or spinal cord injury of whom 50-75% report at least one fall per year [82-91].

Unfortunately, the present data do not allow us to make inferences on the effect of walking aids on falls, but many participants reported the use of different types of walking aids to increase their walking distance. Without a walking aid, 63% indicated that they could not walk at least 500 meters, while 28% were not able to walk at all. Besides walking aids, several participants used some type of ankle-foot orthosis or orthopedic footwear to improve their walking capacity, probably to prevent foot drag during the swing phase and/or optimize ankle stability during the stance phase. Based on the results of this study, it is not possible to conclude which walking aid and/or orthosis is generally most effective. Our experience has learned that a thorough individual clinical assessment, sometimes supported by an instrumented gait analysis, is the best way to provide an individually tailored advice for the use of medical devices. This advice should take into account both the gait pattern (e.g., foot

drag, crouch, scissoring) and the execution of other daily life activities than upright standing and walking, such as stair climbing, squatting, cycling, driving a car etc. [75]. Several interventional studies have provided indications of improved gait capacity by robotic training [68], botulinum toxin injections in spastic calf muscles or hip adductors [65,92-94], and intrathecal baclofen [64]. However, these studies mainly focused on gait speed and/or gait pattern as outcomes, and not on walking distance, performance of daily life activities, or falls. Studies on surgical interventions in HSP have not been conducted yet. Overall, it is fair to conclude that there is an urgent need for future studies in people with HSP that investigate the underlying mechanisms of their balance and gait problems and increased fall risk in order to develop novel and convenient intervention strategies to preserve life-long ambulatory capacity and gait-related activities, and prevent falls. Remarkably, even sitting for 30 minutes appeared to be a problem for 30% of the participants, perhaps due to back pain or severe stiffness. Further research on sitting problems is necessary, particularly regarding wheelchair mobility.

Muscular and non-motor symptoms

Unsurprisingly, muscle stiffness, muscle cramps and weakness appeared to be significant problems in our participants. Usually stiffness and cramps are treated with muscle relaxant medication, but apparently these symptoms are still very troublesome for many patients. Our results further showed that pain, fatigue, and autonomic problems are major (non-motor) symptoms in patients with pure HSP. Only few previous studies have mentioned pain as an important problem in this population [76,77,79,95], even though pain in the legs and/or back was reported by 72% of our participants. This number was similar to the reported frequency in previous studies [76,79]. The nature of leg pain was most often described as nerve pain, cramping pain or restless legs. Back pain was most prevalent in the *lower* back. In our clinical experience, low back pain often has a continuous character, possibly related to postural deviation (i.e., anterior pelvic tilt with lumbar hyperlordosis). On average, the severity of pain yielded a median score of 4 on a numeric rating scale (0-10), but from a recent qualitative study, using semi-structured interviews in 14 patients with pure HSP, we learned that, in individual patients, pain may be severe enough to seriously affect their quality of life [77]. Besides pain, many participants experienced fatigue, both physically and mentally, with median severity scores of 6 and 5, respectively. From our recent qualitative study it became clear that spasticity and muscle stiffness impact on physical fitness, while the high levels of attention needed to cope with balance and gait problems

seem to cause mental fatigue [77]. Generally, fatigue and pain are serious problems in many types of chronic neurological disorders such as spinal cord injury, stroke, Parkinson's disease, multiple sclerosis, and neuromuscular disease, which require specific clinical attention and treatment [91,96-100]. Our results indicate that people with HSP form no exception to this rule, and probably remain undertreated in these respects. The present results confirm previously described micturation and defecation problems in people with pure HSP [101,102]. As underlying causes for these problems our data indicate, on the one hand, extreme urge and problematic sphincter control [80] and, on the other hand, problems to reach the toilet in time. The latter problems may well be primarily related to the gait disorder due to the spastic paraparesis. Whereas urological consultation is needed in the case of bladder and sphincter abnormalities, adequate treatment of spasticity and gait problems may be additionally helpful to reduce micturation and defecation problems. Sexual problems were also frequently mentioned by our participants. This result confirms a previous study reporting sexual complaints in 7 out of 11 patients with pure HSP, indicating pain and spasticity as most important underlying causes [102]. Hence, also for sexual problems, a combination of urological / gynecological consultation and adequate spasticity management seems to be crucial.

Predicting unsupported walking capacity and falling

The duration of spasticity symptoms appeared to be a strong predictor of being a faller. However, unexpectedly, people with an intermediate duration of spasticity symptoms (6-10 years) showed the highest risk, much higher than those with a shorter duration (1-5 years), and also higher than those with a duration of more than 15 years. A possible explanation for this finding may be that in this stage of the disease (6-10 years) people are becoming increasingly affected by spastic paraparesis, while they are still trying to remain as active as possible in terms of standing and walking activities. This discrepancy might bring about an increased fall risk. In the next phase (11-15 years symptom duration), there seems to be a marked drop in fall risk, which might be related to a gradual adjustment of the activity pattern, increased carefulness, and perhaps the use of walking aids. Symptom duration longer than 15 years seems to increase fall risk again, perhaps due to the severity of the balance problems, affecting basic activities such as rising to stance, sitting down, and making transfers. Unfortunately, our data do not allow more detailed interpretation of the observed risk pattern, which warrants further investigation. Difficulty or inability to rise from the floor was another important risk factor of being a faller, which is an intuitive finding,

as rising from the floor requires both sufficient lower extremity strength and basic balance capacity. Testing the individual capacity to independently rise from the floor may, therefore, be an interesting clinical test to assess increased fall risk. The use of a wheelchair and the presence of non-neurological comorbidities appeared to be strong 'protectors' against being a faller. The remarkable result of non-neurological comorbidities being negatively associated with falling may be related to a lower level of standing and walking activities in these people, which may lead to a reduced fall risk. However, further research should shed more light on these findings.

With regard to walking, higher age was associated with a lower chance of being able to walk without aids for at least 500 meters, which probably results from a combination of normal ageing and disease progression. The observed odds ratio of 0.944 implies that, with every year, the chance of being a walker without walking aids decreases by a factor 0.944. Over 30 years, the chance of being a walker without aids would thus decrease to a mere 17.8% (0.944^{30}). Experienced problems with gait-related activities also appeared to be a strong predictor of the inability to walk without aids. Lastly, the inability (or difficulty) to stand for 10 minutes and/or open a heavy door were also very strong predictors. This points towards the notion that standing balance capacity is an important prerequisite for independent walking. Asking patients in clinical practice whether they can easily stand for 10 minutes and/or open a heavy door may, thus, provide a good indication of their independent walking capacity. Again, further research should provide more insight in these relationships.

Strengths and limitations

A limitation inherent in using questionnaires is the subjective nature of the results and the lack of physical examination data, which is why we emphasized that our data reflect the *experienced* complaints, activity limitations, and loss of motor capacities in people with HSP. Still, experiences may reveal problems that remain unnoticed when focusing on objective assessments. In addition, the design process of the questionnaire was not unbiased, as it was based on professionals' preconception of what important aspects of HSP might be. Yet, although participants often had the option to provide additional information next to the predefined multiple choice options, they used this option only sparsely.

Another limitation is that only the subjects without a positive family history or genetic diagnosis were checked for a formal diagnosis of pure HSP made by a neurologist. By including and excluding subjects based on specific questions, we tried to obtain

a homogeneous sample with pure HSP, but it is possible that some people were incorrectly enrolled or excluded. Our study sample was limited in absolute numbers, which precluded subgroup analyses based on for instance genetic defect, or duration of spasticity symptoms. Nevertheless, our study is the largest survey in people with pure HSP until now. In addition, our participants showed an equal sex distribution, wide age range, and a large variation in SP-related symptoms, which supports their representativeness of the Dutch population with pure HSP, of which we probably included about 15% [81]. Since we excluded patients with complicated forms of HSP, our results cannot be generalized to the entire population with HSP.

Conclusion

The results of this web-based survey indicate that people with pure HSP experience many physical complaints, activity limitations, and loss of motor capacities. Of these, muscle stiffness, limited standing and walking activities, and increased fall risk are most prominent, but also pain, fatigue, autonomic dysfunctions, fear of falling, and problems with performing working and hobby activities are relevant symptoms and/or areas of disability with an inherent loss of quality of life. Future research, using objective next to subjective measures, is needed to better understand the full functional impact of HSP on the daily lives of patients, to study underlying mechanisms of disabling symptoms, and to find new roads to interventions that are able to preserve balance and ambulatory capacity as well as limit the burden of the non-motor symptoms.

Appendix

APPENDIX 1. Overview of variables and answers

	Variable	Description	N	Answer (n) / mean ± SD / median [IQR]
A	**Participant characteristics**			
1	Age	Age of participants	109	52.81 ± 14.22
2	Sex	Sex of participants	109	Male (54)
				Female (55)
3	Spierziekten Nederland	Membership of Spierziekten Nederland	109	No (37)
				Yes (72)
4	Genetic defect	Genetic defect causing HSP is known	109	No (49)
				Yes (60)
5	Duration of LLS symptoms	Time since onset LLS symptoms in years	109	1-5 (21)
				6-10 (21)
				11-15 (16)
				>15 (51)
6	Employment	Type of employment	109	Full-time (27)
				Part-time (14)
				Self-employed (8)
				Student (3)
				Retired (20)
				Not able to work / disabled (27)
				Currently unemployed (10)
7	Comorbidity*	Non-neurological comorbidities	105	Asthma/COPD (6)
				Diabetes (1)
				Hypertension (9)
				Joint disease (13)
				Heart disease (4)
				Other (7)
				None (71)
8	Gene	Genetic defect causing HSP	109	SPG2 (1)

				SPG3A (4)
				SPG4 (36)
				SPG5A (2)
				SPG7 (3)
				SPG8 (3)
				SPG10 (2)
				SPG17 (1)
				SPG31 (5)
				SPG72 (1)
				Unknown (51)
9	HSP in family*	Relatives with known or presumed HSP	109	First degree (83)
				Other than first degree (47)
				Unknown (10)
				None (14)
B	**Complaints and activity limitations**			
1	Muscle stifness	Score on hindrance/burden of muscle stiffness (0-10)	109	7 [3]
2	Muscle cramps	Score on hindrance/burden of muscle cramps (0-10)	109	4 [4]
3	Pain	Score on hindrance/burden of pain (0-10)	109	4 [6]
4	Muscle weakness	Score on hindrance/burden of muscle weakness (0-10)	109	5 [4]
5	Physical fatigue	Score on hindrance/burden of physical fatigue (0-10)	109	6 [4]
6	Mental fatigue	Score on hindrance/burden of mental fatigue (0-10)	109	5 [6]
7	Sleeping problems	Score on hindrance/burden of sleeping problems (0-10)	109	2 [4]
8	Emotional problems	Score on hindrance/burden of emotional problems (0-10)	109	2 [4.5]
9	Balance problems	Score on hindrance/burden of balance problems (0-10)	109	7 [3]
10	Gait problems	Score on hindrance/burden of gait problems (0-10)	109	8 [2]
11	Fear of falling	Score on hindrance/burden of fear of falling (0-10)	109	5 [5]
12	Self-care	Score on hindrance/burden of self-care (0-10)	109	2 [4.5]
13	Work/Hobbies	Score on hindrance/burden of work/hobbies (0-10)	109	4 [6]

14	Sleeping problems	Experience of sleeping problems	109	No (56)
				Only falling asleep (6)
				Only sleeping through (32)
				Both (15)
15	Pain*	Experience of pain	109	No (30)
				Back pain (55)
				Leg pain (including restless legs) (59)
				Other (18)
16	Location back pain*	Location of back pain	55	Lower back (55)
				Middle back (10)
				Higher back and neck (16)
17	Lower back pain	Pain score in the lower back (0-10)	55	6 [2]
18	Middle back pain	Pain score in the middle back (0-10)	10	5 [4]
19	Higher back pain	Pain score in the higher back/neck (0-10)	16	6 [4]
20	Leg pain*	Type of leg pain	59	Nerve pain (25)
				Cramps (32)
				Restless legs (33)
				Other (9)
21	Nerve pain	Score of experienced nerve pain (0-10)	25	6 [4]
22	Cramps	Score of experienced cramping pain (0-10)	32	5.5 [3]
23	Restless legs	Score of experienced restless legs (0-10)	33	6 [4]
24	Sport	Capacity to perform sports	109	No (47)
				Yes (62)
25	Sport adaptations	Need of adaptations to be able to play sports	62	No (37)
				Yes (25)
26	Reason of sport disability	Reason why not being able to play sports	47	HSP (46)
				Other (1)
	Autonomic dysfunctions			
27	Micturation problems	Difficulties to reach the toilet for micturation	109	No (54)
				Yes (55)

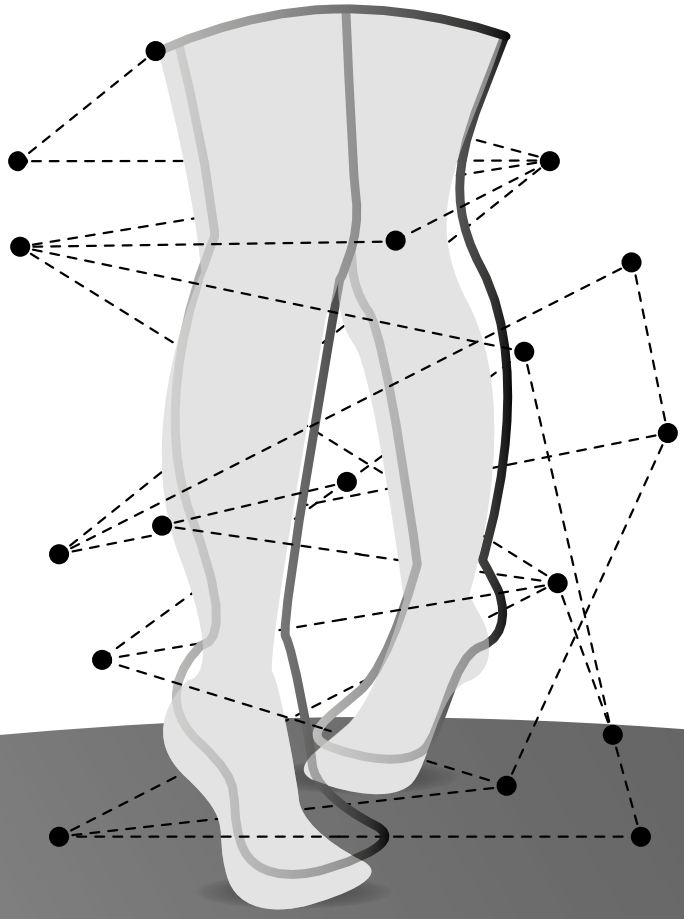
28	Reason of micturation problems*	Reason of difficulty to reach the toilet for micturation	55	Extreme urge (22)
				Sphincter control (45)
				Gait problems (30)
				Other (2)
29	Defecation problems	Difficulties to reach the toilet for defecation	109	No (88)
				Yes (21)
30	Reason of defecation problems *	Reason of difficulty to reach the toilet for defecation	21	Extreme urge (11)
				Sphincter control (14)
				Gait problems (11)
				Other (3)
31	Sexual problems	Difficulties with sexual intercourse	109	No (46)
				Yes (43)
				Unknown (20)
32	Reason of sexual problems*	Reason of difficulty with sexual intercourse	43	Pain (14)
				Spasticity (26)
				Ejaculation problems (4)
				Erectile dysfunction (8)
				Orgasm problems (6)
				Vaginal dryness (5)
				Other (11)
C	**Loss of motor capacities**			
1	Mobility supportive devices indoors*#	Type of device indoors	109	Cane/Crutches (28)
				Ankle-foot orthoses (13)
				Walker (26)
				Wheelchair (22)
				Electric wheelchair (7)
				Orthopedic footwear (28)
				Other (11)
				None (44)
2	Mobility supportive devices outdoors*#	Type of device outdoors	109	Cane/Crutches (41)
				Ankle-foot orthoses (19)

				Walker (30)
				Wheelchair (43)
				Electric wheelchair (29)
				Orthopedic footwear (34)
				Other (10)
				None (23)
3	Distance without aids	Walking distance without aids (meters)	109	0 (31)
				1-100 (30)
				100-500 (8)
				500-1000 (5)
				>1000 (35)
4	Distance with aids	Walking distance with aids (meters)	109	0 (14)
				1-100 (25)
				100-500 (18)
				500-1000 (12)
				>1000 (40)
5	Walk upstairs	Capacity to walk up a normal staircase	109	No (16)
				Only when holding rail(s) (75)
				Without holding rail(s) (18)
6	Walk downstairs	Capacity to walk down a normal staircase	109	No (17)
				Only when holding rail(s) (79)
				Without holding rail(s) (13)
7	Gait pattern*	Experienced characteristics of the gait pattern	109	Drop foot (82)
				Scissoring gait (33)
				Crouch gait (14)
				Other (20)
				Inability to walk (8)
8	Pick something up	Capacity to pick up something from the floor	109	No (39)
				With difficulty (54)

				With ease (16)
9	Sitting (30 min)	Capacity to sit down for 30 minutes	109	No (5)
				With difficulty (29)
				With ease (75)
10	Standing (10 min)	Capacity to stand for 10 minutes	109	No (22)
				With difficulty (47)
				With ease (40)
11	Squat and rise	Capacity to squat and rise again	109	No (52)
				With difficulty (51)
				With ease (6)
12	Rise from floor	Capacity to stand up from the floor	109	No (38)
				With difficulty (59)
				With ease (12)
13	Open heavy door	Capacity to open a heavy door	109	No (12)
				With difficulty (55)
				With ease (42)
14	Walk with heavy bag	Capacity to walk with a heavy bag for 100 meters	109	No (59)
				With difficulty (35)
				With ease (15)
15	Falls	Fall incident since onset symptoms	109	No (16)
				Yes (93)
16	Time until first fall	Time in years of first fall since onset symptoms	93	< 1 year (20)
				1-5 years (43)
				5-10 years (15)
				>10 years (15)
17	Fall frequency	Estimate of fall frequency	109	Weekly (6)
				Monthly (11)
				Every 3 months (23)
				Every 6 months (22)
				Yearly (11)
				Less than once a year (17)

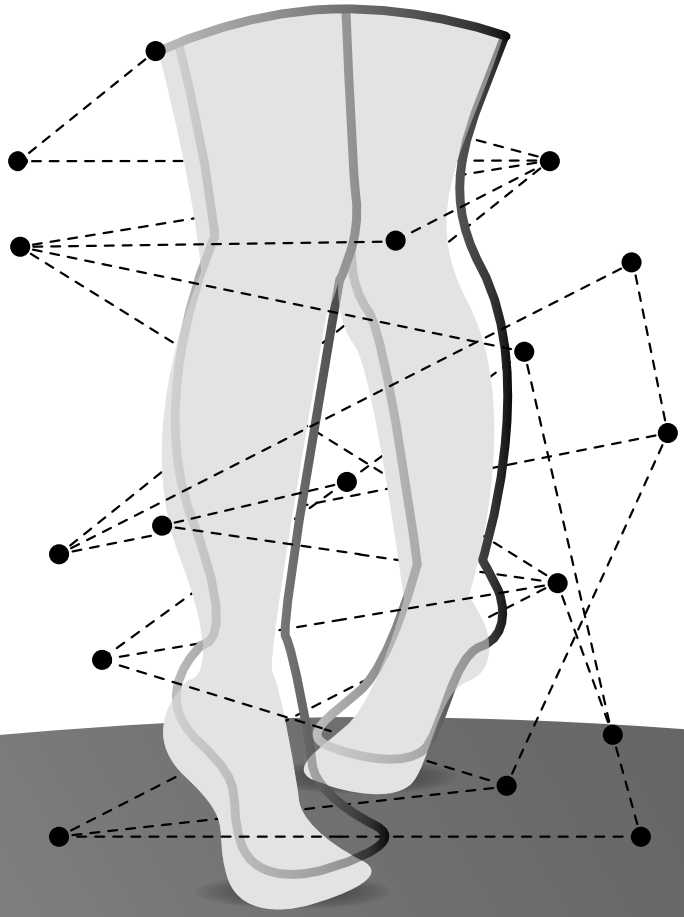
				Never (19)
18	Fall location	Location at which participants fall most	93	Indoors (27)
				Outdoors (35)
				Both just as often (31)
19	Fall injury	Injury after a fall	93	No (37)
				Once (27)
				More than once (29)
20	Type of injury*	Type of injury after a fall	56	Bruise (33)
				Bone fracture (13)
				Skin injury (34)
				Other injury (4)
21	Fear of falling	Afraid to fall (again)	109	No (29)
				A little (66)
				Very much (14)

**Multiple answers allowed #no frequence of use was stated. Participants were asked which mobility supportive devices they used indoors and outdoors*



PART 2

MOTOR CONTROL MECHANISMS IN PATIENTS WITH HSP



CHAPTER 4

Excessive short-latency stretch reflexes in the calf muscles do not cause postural instability in patients with hereditary spastic paraplegia.

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**These author contributed equally to this work*

Abstract

Objective

To identify the role of hyperexcitable short-latency stretch reflexes (SLRs) on balance control in people with hereditary spastic paraplegia (PwHSP).

Methods

Sixteen PwHSP with triceps surae spasticity and 9 healthy control subjects were subjected to toes-up support-surface perturbations. EMG data were recorded from gastrocnemius, soleus and tibialis anterior. Furthermore, center-of-mass trajectories were recorded.

Results

PwHSP were less able to withstand the perturbations. Triceps surae SLRs (40-80ms post perturbation) in PwHSP were increased compared to healthy subjects. Furthermore, a sustained triceps surae EMG activity at 220-320ms post perturbation was observed in PwHSP, whereas control subjects demonstrated suppression of triceps surae activity. Center of mass trajectories started to diverge between PwHSP and controls only after ~500ms, with greater excursions being observed in the PwHSP.

Conclusions

The present results confirm that balance control is impaired in PwHSP. However, the late instant of center of mass divergence argues against a direct, causative role of hyperexcitable SLRs in the triceps surae.

Significance

We postulate that enhanced short-latency stretch reflexes of the triceps surae do not underlie poor balance control in PwHSP. Instead, we suggest the lack of suppression of later triceps surae activity to be the main cause.

Introduction

Hereditary spastic paraplegia (HSP) describes a heterogeneous group of neurodegenerative disorders characterized by slowly progressive leg muscle spasticity and muscle weakness [11,28,103] The main neuropathological feature is axonal degeneration of the longest descending and ascending nerve fibres (i.e. crossed and uncrossed corticospinal tracts to the legs, fasciculus gracilis fibers and, to a lesser extent, spinocerebellar fibers [11]). HSP can be phenotypically classified into pure and complicated forms. Complicated phenotypes include symptoms such as dementia, ataxia and peripheral neuropathy, in addition to leg muscle spasticity. In contrast, people with pure HSP (PwHSP) mainly experience lower limb spasticity with relatively preserved muscle strength, motor selectivity and proprioception [11,56,104]. The spasticity in the lower extremities causes the typical gait abnormalities observed in PwHSP, which include forefoot landing, foot drag during swing, and increased hip adduction ('scissoring' gait). Furthermore, it becomes increasingly evident that PwHSP also suffer from impaired balance control (e.g. de Niet et al. (2013) [22], de Niet et al. (2015) [9], Nonnekes et al. (2013) [23] and Nardone et al. (2001) [24]). However, the mechanism underlying these balance impairments – and in particular the role of leg muscle spasticity - is yet poorly understood.

Spasticity is commonly defined as the velocity-dependent hyperexcitability of spinal stretch reflexes [105]. Nardone et al. (2001) [24] have shown that patients suffering from calf muscle spasticity indeed exhibit exaggerated short latency stretch reflexes (SLR) in the triceps surae following a sudden rotation in toes-up direction, imposed by a moveable platform (inducing ankle dorsiflexion movements). Toes-up rotations induce backward falls. To overcome this perturbation, the tibialis anterior muscle has to generate a corrective ankle dorsiflexion torque to pull the center of mass in the forward direction. Muscle activity of the antagonist muscles - i.e. the triceps surae – may thus be detrimental for balance recovery following toes-up perturbations. An earlier study of our group [22] suggested a detrimental effect of triceps surae spasticity on postural stability. The maximal magnitude of rotational toes-up perturbations that PwHSP could sustain without stepping (i.e. stepping threshold) was associated with clinical scores of triceps surae spasticity; patients with more severe spasticity had lower stepping thresholds. The latter result may seem to concur with a destabilizing effect of hyperexcitable stretch reflexes of the triceps surae.

However, it is questionable whether the SLR can generate sufficiently large torques at the ankle joint to induce a loss of balance [106]. Some previous studies suggested that increased SLRs as a result of spasticity contributed to functional impairments in both balance and gait [22,107-110], whereas other studies suggested there was no evident functional consequence of an increased SLR [24,111,112]. Hence, is it important to further investigate the effects of excessive SLRs on balance control. Furthermore, it cannot be excluded that later phases of the postural response may also be defective in PwHSP.

The purpose of the current study was to gain further insight into the mechanisms underlying impaired balance control in PwHSP. To address this aim, toes-up support-surface balance perturbations at several intensities, imposed by a rotational platform, were applied in PwHSP and healthy control subjects. Previous research from our lab showed that after such toes-up perturbations, PwHSP overall had lower success rates, compared to healthy controls [9]. However, to provide insight in the underlying mechanisms, success rates for different intensities, electromyographic (EMG) responses from the triceps surae, and the time course of center-of-mass (CoM) excursions and velocities following perturbations were investigated in the current study. The instant where CoM trajectories start to diverge between PwHSP and controls provides crucial information on the causal role of hyperexcitable stretch reflexes in the impaired ability of PwHSP to withstand these toes-up perturbations. We hypothesized that exaggerated SLRs in the triceps surae of PwHSP would lead to difficulties in sustaining toes-up perturbations. This would be reflected by an early divergence (<200ms post perturbation) of their CoM trajectories in PwHSP compared to those of control subjects.

Methods

Study design

For addressing the present research question, we used the baseline data as obtained in the FEBOCH-I study [9]. The FEBOCH-I study aimed to assess the effects of botulinum toxin injections in the triceps surae, with success rates of balance recovery to multidirectional translational and rotational perturbations as secondary outcomes. These were assessed at baseline and at 4 and 18 weeks post intervention. The baseline assessment also included EMG measurements, which allowed us to conduct this addi-

tional mechanistic study on the role of excessive stretch reflexes in recovering balance following rotational 'toes-up' perturbations.

Participants

Participants were recruited from all symptomatic PwHSP who visited the Rehabilitation and/or Neurology outpatient clinics of our university hospital during a period of one year. In addition, active recruitment took place through advertisements and oral presentations for the national patient council (Spierziekten Nederland). PwHSP could be included if they were (1) having autosomal dominant pure HSP (either genetically proven or based on family history), (2) having clinical symptoms of spasticity (e.g. clonus, stiffness, muscle cramps pain), and (3) being a community ambulator (Functional Ambulation Categories (FAC) score 5 [113]). Exclusion criteria were (1) Modified Ashworth Scale (MAS) score of the calf muscle with the knee flexed or extended greater than 2 [49], (2) passive ankle range of motion with an extended knee less than 10° dorsiflexion, (3) leg muscle strength (both calf and tibialis anterior muscles) lower than 4 on the Medical Research Council (MRC) scale [114], and (4) motor selectivity lower than stage 5 of the Brunnström stages, all on either side of the body [115]. After screening 32 PwHSP, 16 PwHSP met the inclusion criteria and were included in this study. Demographics and clinical characteristics of the included PwHSP are listed in Table 1. In addition, 9 healthy controls of similar age were recruited. The study was approved by the regional medical ethics committee and was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent before the experimental procedures.

Balance assessment

Subjects stood barefoot on a moveable platform with their knees extended and their feet at shoulder width. They wore a safety harness, which was attached to the ceiling, and prevented them from falling. The platform imposed rotational (toes-up and toes-down) and translational (forward and backward) perturbations. Perturbations were applied at four intensity levels (3, 5, 7 and 9 degrees rotation; translations at 0.25, 0.50, 0.75 and 1.00 $m \cdot s^{-2}$). For detailed specifications of the perturbations and the platform, see de Niet et al. (2013) [22].

The protocol consisted of four familiarization trials of each of the four perturbations at the lowest intensity (i.e. 3 degrees rotation or translation at 0.25 $m \cdot s^{-2}$) to familiarize the participants with the experimental setup. Thereafter, a total number of 64 perturba-

tions were imposed in random order with four perturbations at each intensity level for each type of perturbation (e.g. 4 types x 4 intensities x 4 repetitions). Participants were instructed to respond to the perturbations without stepping or grabbing for support. For each trial it was determined whether the participant was successful in recovering balance with the requested feet-in-place response. This resulted in a success rate (proportions of successfully performed trials) for each type of perturbation. In this paper, only the results for the toes-up rotations are reported, as those perturbations applied a rapid stretch to the triceps surae and were thus related to stretch-related activity.

Kinematics and EMG

Three-dimensional kinematic data of the lower limbs and the trunk were collected using a motion capture system (Vicon Motion Systems®, Oxford, UK) at a sample frequency of 100 Hz. Twenty-one reflective markers were placed on the trunk and lower limbs according to the full-body PlugInGait configuration (Vicon Motion Systems®, Oxford, UK). Furthermore, bilateral muscle activity was recorded by surface electromyography at a sample frequency of 1000 Hz from the medial head of the gastrocnemius (GM), soleus (SOL) and tibialis anterior (TA) muscles with electrodes (Ag-AgCl, ARBO ECG electrodes, Tyco Healthcare, Neustadt, Germany) placed according to SENIAM guidelines.

Data processing and analysis

The marker data were processed using the PlugInGait model in Vicon Nexus (Vicon Motion Systems®, Oxford, UK; [116]). Based on the hip markers and anthropologic data, the Vicon system determined a virtual CoM according to the PlugInGait model. Subsequently, CoM position data were low-pass filtered at 10 Hz (2nd order zero-lag Butterworth filter) and CoM velocity data were derived from CoM position data. EMG signals were band-pass filtered (10-499 Hz, 2nd order zero-lag Butterworth filter), rectified and low-pass filtered with 100 Hz. Thereafter, the EMG signal was normalized (i.e. expressed as a percentage of the background EMG activity averaged over 100ms prior to onset perturbation). For each subject and perturbation intensity, kinematic and EMG data were ensemble averaged across trials and across the left and right leg. We determined the mean (normalized) EMG amplitude over four time windows following the start of the perturbation; 40-80ms (short-latency response, SLR), 80-120ms (medium latency response, MLR), 120-220ms (long latency responses, LLR) and 220-320ms (post-LLR, [109,117]).

Statistical analysis

The success rates of balance recovery without stepping were compared between the PwHSP and controls using a factorial ANOVA with *group* as between-subjects factor

and *perturbation intensity* as within-subjects factor. Post-hoc analysis involved bonferroni-corrected independent t-tests.

The (normalized) EMG amplitudes were compared between the PwHSP and controls for each time window of interest (i.e. SLR, MLR, LLR and post-LLR) by means of a repeated-measures ANOVA with *group* as between-subjects factor and *perturbation intensity* as within-subjects factor. An independent students t-test was used to compare background activity between PwHSP and controls. Finally, to determine the instant that CoM trajectories started to diverge between PwHSP and controls, we compared the CoM excursions and velocities for each intensity of perturbation using consecutive one-sided independent t-tests at time intervals of 10ms following the onset of the perturbation. The α-level was set at 0.05 for all analyses.

Results

TABLE 1. Demographic and clinical characteristics of patients with autosomal dominant hereditary spastic paraplegia and control subjects

	HSP	**Healthy controls**
N	*16*	*9*
Age (mean $\pm$ SD)	*48.8 $\pm$ 12.8*	*47.3 $\pm$ 11.8*
Gender (male/female)	*12/4*	*6/3*
Genetic diagnosis		
SPG-4	*9*	
SPG-3A	*1*	
SPG-8	*1*	
Unknown genotype	*5*	
MAS calf muscle[‡]		
SOL	*1 (n=6); 2 (n=10)*	
GM	*1 (n=8); 2 (n=8)*	
MRC calf muscle[‡]	*5 (n=10); 4 (n=6)*	
MRC dorsiflexion[‡]	*5 (n=16)*	
Vibration sense (mean $\pm$ SD)*	*4.0 $\pm$ 2.0*	

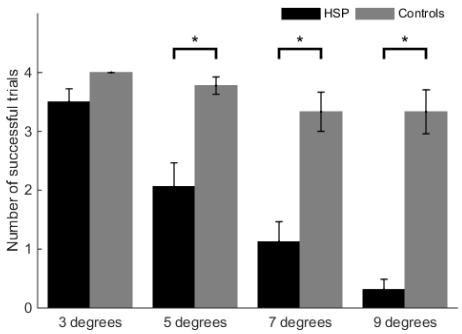
*HSP, Hereditary Spastic Paraplegia; MAS, Modified Ashworth Scale; MRC, Medical Research Council; [‡] Left and right leg scored equally, *Assessed with Rydel-Seiffer tuning fork*

For the most severely affected PwHSP (n=4) it was too demanding - both in terms of fatigue and safety - to undergo the total number of perturbations (64 trials). Therefore, the perturbations at the highest intensity of each type were omitted, leaving 48 perturbations for these participants. In the remainder of the paper, the EMG results for the three levels of perturbation intensities that could be collected in all PwHSP will be reported. Yet, subgroup analysis for the 12 PwHSP who underwent the full number of perturbations yielded a similar pattern of results (appendix).

Success rates following toes-up perturbations

PwHSP were less capable of withstanding toes-up perturbations without stepping or grabbing for support (main effect of *group*, $t(23)=5.439$, $p<0.001$). PwHSP exhibited a large decrement in performance at higher perturbation intensities, whereas the controls barely failed to recover balance at all (*group*intensity,* $F(3,69)=10.141$, $p<0.001$, figure 1). Post-hoc tests yielded significant differences between the groups at perturbations of 5° ($t(23)=4.000$, $p=0.001$), 7° ($t(23)=4.251$), $p<0.001$), and 9° ($t(23)=8.326$, $p<0.001$), whereas success rates at perturbations of 3° did not differ ($t(23)=1.661$, $p<0.001$).

FIGURE 1. Mean success rates (SD) of PwHSP (black) and control subjects (grey) at the three intensities of rotational toes-up perturbations. Asterisks mark significant differences between the groups.



EMG responses – between-group differences

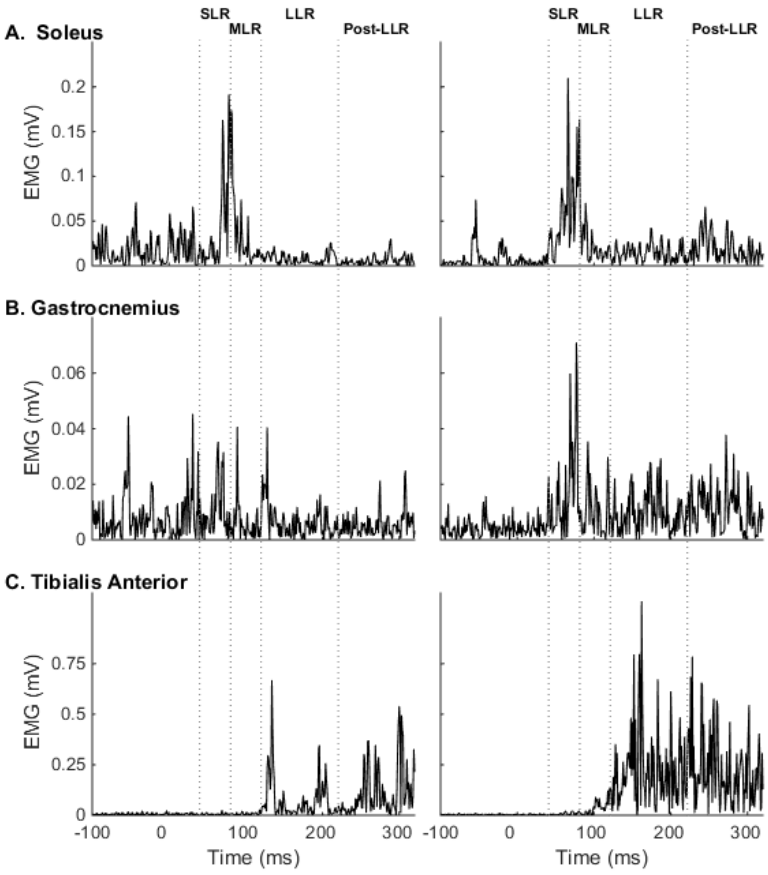
Mean SOL, GM and TA EMG traces of a representative control subject and participant with HSP during toes-up perturbations are shown in figure 2. All EMG results of each muscle per time interval are presented in table 2. The average background activity prior to perturbation was not significantly different between PwHSP and controls in GM ($t(9.6)=2.2124$, $p=0.052$), SOL ($t(23)=0.440$, $p=0.664$), or TA ($t(22.2)=-1.509$, $p=0.145$).

TABLE 2. EMG outcome measures per time window for PwHSP and healthy controls

			Mean percentage EMG from background ± SD				
Muscle	**Time window**	**Group**	**3 degrees**	**5 degrees**	**7 degrees**	**Intensity effect**	**Group effect**
SOL	SLR	HSP	227 ± 110	245 ± 153	220 ± 61	F(2,46)= 0.463, p=0.632	**F(1,23)= 4.516, p=0.045**
		Control	136 ± 31	139 ± 29	176 ± 59		
	MLR	HSP	204 ± 61	233 ± 91	233 ± 76	F(2,46)= 1.470, p=0.241	F(1,23)= 0.014, p=0.907
		Control	218 ± 146	197 ± 92	243 ± 139		
	LLR	HSP	121 ± 61	167 ± 87	162 ± 73	F(2,46)= 2.072, p=0.138	F(1,23)= 0.080, p=0.780
		Control	147 ± 104	152 ± 104	176 ± 107		
	Post-LLR	HSP	104 ± 52	107 ± 56	98 ± 44	F(2,46)= 0.284, p=0.754	**F(1,23)= 4.394, p=0.047**
		Control	68 ± 47	58 ± 31	67 ± 34		
GM	SLR	HSP	191 ± 47	204 ± 69	254 ± 178	F(1.427, 32.818)= 3.191, p=0.069*	**F(1,23)= 4.847, p=0.038**
		Control	127 ± 51	138 ± 43	178 ± 92		
	MLR	HSP	181 ± 47	215 ± 114	279 ± 241	F(1.353, 31.123)= 3.311, p=0.067*	F(1,23)= 0.014, p=0.906
		Control	206 ± 92	219 ± 122	268 ± 172		
	LLR	HSP	188 ± 115	277 ± 206	306 ± 244	F(1.299, 29.875)= 2.986, p=0.085*	F(1,23)= 0.583, p=0.453
		Control	179 ± 85	174 ± 104	277 ± 294		
	Post-LLR	HSP	114 ± 45	127 ± 53	146 ± 66	**F(2,46)= 6.190, p=0.004**	**F(1,23)= 7.429, p=0.012**
		Control	71 ± 48	65 ± 36	87 ± 54		
TA	SLR	HSP	116 ± 23	117 ± 35	121 ± 41	F(1.553, 35.710)= 0.362, p=0.645*	F(1,23)= 3.458, p=0.076
		Control	111 ± 20	97 ± 13	100 ± 17		
	MLR	HSP	265 ± 261	359 ± 468	482 ± 756	F(1.541, 35.448)= 0.747, p=0.448*	F(1,23)= 0.449, p=0.510
		Control	228 ± 111	333 ± 481	232 ± 130		
	LLR	HSP	1196 ± 1175	1237 ± 1356	1455 ± 1666	F(1.407, 32.369)= 1.298, p=0.277*	F(1,23)= 0.094, p=0.762
		Control	1402 ± 750	1223 ± 762	1669 ± 658		
	Post-LLR	HSP	1632 ± 1025	1899 ± 1112	2207 ± 1385	**F(1.551, 35.675)= 8.778, p=0.002***	F(1,23)= 0.193, p=0.665
		Control	1731 ± 937	1859 ± 1171	2714 ± 1214		

** Sphericity not assumed, Greenhouse-Geisser test used. SOL, Soleus; GM, Gastrocnemius; TA, Tibialis anterior; SLR, short-latency reflex; MLR, medium-latency reflex; LLR, long-latency reflex*

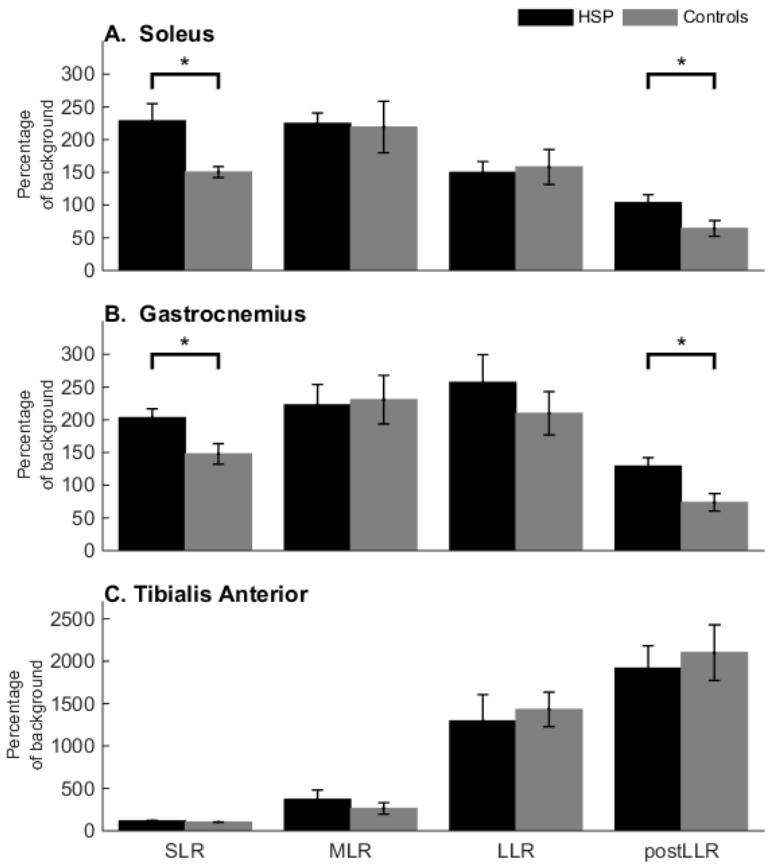
FIGURE 2. Representative rectified raw EMG traces of a control subject (left column) and an participant with HSP (right column) after a 7 degrees toes-up perturbation. Time zero is the time of the perturbation onset. SLR and post-LLR responses in SOL and GM compared to the control subject. SOL, Soleus; GM, Gastrocnemius.



In figure 3, the SOL, GM and TA responses (normalized to background activity) following perturbations are shown for PwHSP and controls. SLR amplitudes were larger in PwHSP than in controls in both the SOL (figure 3a, $F(1,23)=4.516$, $p=0.045$) and GM muscle (figure 3b, $F(1,23)=4.847$, $p=0.038$). In contrast, the response amplitudes in both the MLR and LLR time windows did not differ between the groups in either calf muscle. In the post-LLR time window, however, the PwHSP demonstrated greater muscle activity again compared to controls in GM ($F(1,23)=7.429$, $p=0.012$) and

SOL ($F(1,23)=4.394$, $p=0.047$). The response amplitudes in the TA muscle were not different between the groups in any of the time windows (figure 3c).

FIGURE 3. Overall EMG activity (averaged over 3 intensities) for each post-perturbation time window in (A) SOL, (B) GM and (C) TA. Black bars represent data of PwHSP, grey bars of the control group. Asterisks mark significant differences between the groups. SOL, Soleus; GM, Gastrocnemius; TA, Tibialis anterior.



EMG responses – effects of perturbation intensity

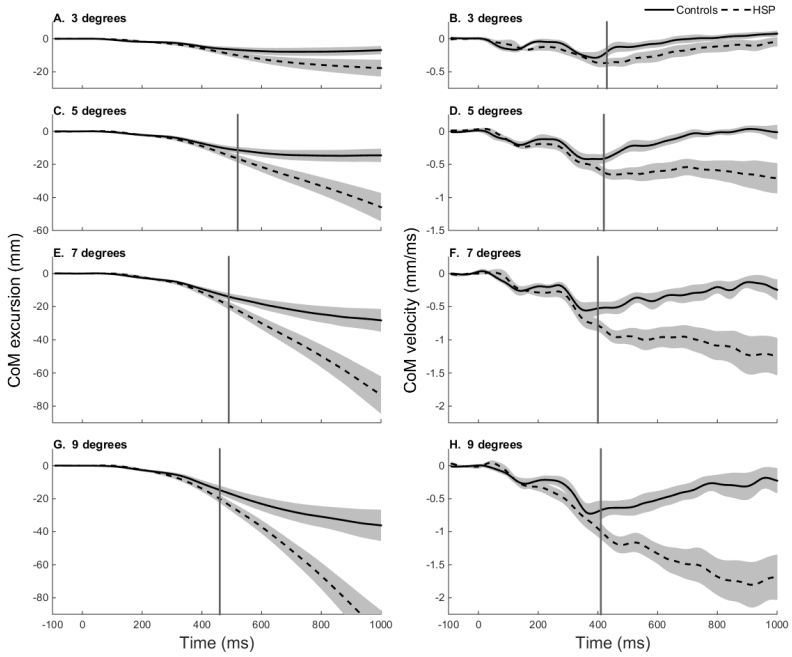
In the SOL, no effects of perturbation intensity were shown in any of the response amplitudes. For the GM, greater post-LLR amplitudes were observed at higher perturbation intensities ($F(2,46)=6.190$, $p=0.004$), whereas there was no perturbation

intensity effect in SLR, MLR and LLR response amplitudes. For TA, post-LLR response amplitudes increased with increasing perturbation intensities ($F(1.552,35.675)=8.778$, $p=0.002$), which effect was not present in the other TA response windows. None of the *intensity * group* interaction effects reached significance.

Center-of-mass displacement

The averaged CoM displacements and velocities of the groups are depicted at each intensity of perturbation (figure 4).

FIGURE 4. Average CoM excursion (left) and CoM velocity (right) patterns of PwHSP (dashed line) and controls (solid line) for (A,B) 3 degrees perturbations, (C,D) 5 degrees, (D,E) 7 degrees and (F,G) 9 degrees. The onset of perturbation is at 0 ms. Points of divergence based on significance of independent t-test are marked with grey solid vertical line. CoM, Center of Mass.



The CoM trajectories were very similar between individual participants and between the groups in the first ~300ms post perturbation. From ~500ms onwards, the variability in trajectories between subjects increased considerably, which was particularly evident in the HSP group. As shown in figure 4a, no point of divergence of CoM excursions could be identified up to 1000ms for perturbations of 3°. The statistical

points of divergence between the CoM excursions of both groups were at 520ms ($t(23)=1.777$, $p=0.044$), 490ms ($t(23)=1.785$, $p=0.043$) and 460 ms ($t(19)=1.767$, $p=0.047$) for perturbations of 5°,7° and 9°, as shown in figure 4c, 4e and 4g respectively. The statistical points of divergence between the CoM velocities of both groups were detected at 430 ms ($t(23)=1.793$, $p=0.043$) , 420 ms ($t(23)=2.012$, $p=0.028$), 400 ms ($t(23)=1.857$, $p=0.038$) and 410 ms ($t(19)=1.780$, $p=0.046$) for the 3°, 5°, 7° and 9° perturbations, as shown in figure 4b, 4d, 4f and 4h, respectively.

Discussion

The main aim of this study was to identify whether hyperexcitability of triceps surae short-latency stretch reflexes (SLRs) is a key determinant of the poor balance control in PwHSP in response to toes-up support-surface rotations. In line with their pronounced leg muscle spasticity, we indeed observed increased SLRs in the triceps surae of the PwHSP compared to healthy controls. The great difficulty that the PwHSP experienced in sustaining the perturbations was evident from their lower success rates and greater CoM excursions and velocities in comparison to the controls. The PwHSP also demonstrated enhanced triceps surae activity in the post long-latency reflex (LLR) time window (220-320ms) compared to the controls, whereas the MLR and LLR response amplitudes did not differ. For TA activity, no differences between the groups were found in any of the time windows.

The present results confirm previous findings of impaired balance control and increased short-latency stretch reflexes in spastic triceps surae upon sudden toes-up support-surface rotations [22,24]. Yet, studies on the significance of leg muscle spasticity for defective balance control are yet sparse and the results disparate. This lack of knowledge might be due to the fact that spasticity in patients with upper motor neuron syndromes often coexists with other impairments (e.g. paresis, sensory loss, contractures, involvement of other structures relevant for balance control). HSP, however, is mainly characterized by spasticity, whereas muscle strength, somatosensation and range of joint motion are relatively well preserved. HSP thus provides a 'naturalistic model' for studying how spasticity contributes to impaired balance control. Our study adds to the existing knowledge on the impact of leg muscle spasticity in balance control as, contrary to our hypothesis, the results demonstrate that

there does not seem to be a direct, causative relationship between hyperexcitable SLRs in triceps surae and poor balance performance. Furthermore, we here report a yet unidentified abnormality in the spastic triceps surae (i.e. sustained activity in the post-LLR window), which potential significance will be further eluded on.

The PwHSP had more difficulties to recover from the perturbations without stepping than the control subjects. Indeed, the PwHSP demonstrated greater CoM excursions and velocities compared to controls, which became apparent in the statistical analyses of CoM velocities at 400-430ms post perturbation. People recover from "toes-up" rotational balance perturbations by generating corrective ankle dorsiflexion torques, through MLR and LLR responses at onset latencies of ~100-115ms (Allum et al. , 2002, Campbell et al. , 2009). In a previous study on toes-up rotational balance perturbations in people with leg muscle weakness, it was demonstrated that distal weakness (i.e. a reduced capacity to generate large corrective torques) resulted in evident divergence of COM velocity from that of healthy subjects at ~225 ms post perturbation (Horlings et al. , 2009). These results point at a time lag of ~110-125 ms between (differences in) EMG activity and (differences in) COM velocity. Therefore, it seems unlikely that increased SLRs in the (spastic) triceps surae have a direct, causal relation with the larger CoM excursions in PwHSP. Conversely, the relatively late instants of divergence between CoM trajectories of PwHSP and healthy controls more likely correspond with the enhanced triceps surae activity that was observed in our PwHSP at 220-320ms post perturbations. In this (post-LLR) time window, the PwHSP generally demonstrated sustained triceps surae activity, whereas control subjects showed strong inhibition of these muscles (i.e. below background activity levels). As TA activity has to overcome the triceps surae activity to recover balance following toes-up perturbations, the sustained triceps surae (i.e. antagonist) activity must be considered detrimental for balance control.

The observation of sustained triceps surae activity in the post-LLR time window in the PwHSP was an unexpected finding, and the mechanisms underlying this lack of inhibition can only be speculated upon. One suggestion may be related to the degeneration of the long descending tracts as a key neuropathological feature of the disease [11,28,103]. Dendrites of motoneurons have voltage dependent channels that provide the capacity to generate persistent inward currents. It has been demonstrated that, due to a lack of descending input, large persistent inward currents make the spinal cord hyperexcitable, which may lead to a self-sustained firing of motoneurons after muscle activation [118-120]. The evoked activity post perturbation in the spastic triceps surae of PwHSP may cause a self-sustained firing of motoneurons, causing further prolongation of muscle respons-

es. An alternative (and not mutually exclusive) suggestion for the prolonged triceps surae activity could be a lack of reciprocal inhibition in the lower leg muscles, which has previously been demonstrated in PwHSP [121]. Following toes-up perturbations, activity of TA muscles is required for maintaining balance. This mechanism normally leads to inhibition of the triceps surae (which we indeed observed in the healthy controls), but may have been defective in the PwHSP. A different notion is a possible neurophysiological relationship between excessive SLRs and muscle activity during the post-LLR window, but the fact that we found no group differences in the MLR and LLR time windows seems to argue against this possibility. It must be mentioned, though, that all these suggested explanations for the (newly identified) sustained triceps surae activity remain speculative, as our study was not designed to elucidate the neural processes involved.

In addition to the results on triceps surae activity, the lack of between-group differences in tibialis anterior activity may be considered as another HSP-related abnormality. Given the enhanced triceps surae activity in the PwHSP compared to controls, greater activity of TA – as the agonist muscle for recovering balance - would be expected to compensate for that. However, the absence of differences in TA activity suggests that the PwHSP had difficulties recruiting such compensatory activity (and thus corrective torques), which may also have contributed to their lower recovery success rates. In the present group of PwHSP, however, muscle strength of ankle dorsiflexors was normal (MRC = 5; see table 1), which suggests that the rate of TA recruitment may be more of a problem than its absolute strength.

Our results suggest that sustained muscle activity in the post-LLR window may help explain the observed difficulties that the PwHSP experienced in recovering from toes-up perturbations. Although rotational perturbations do not occur often in daily life, sustained muscle activity may also compromise other postural tasks for which quick inhibition is important. This could be the case for larger balance perturbations that necessitate stepping to recover. Any perturbation to balance evokes an automated postural response, which leads to bilateral activation of leg muscles for counteracting the perturbation-induced CoM excursions. When the CoM excursions exceed the boundaries of the base of support and a compensatory step is needed to recover, making this step requires rapid inhibition of postural muscle activity in the stepping leg. Future research should identify which neural mechanism underlies the sustained triceps surae activity in PwHSP, and whether this sustained activity may indeed contribute to poor balance control.

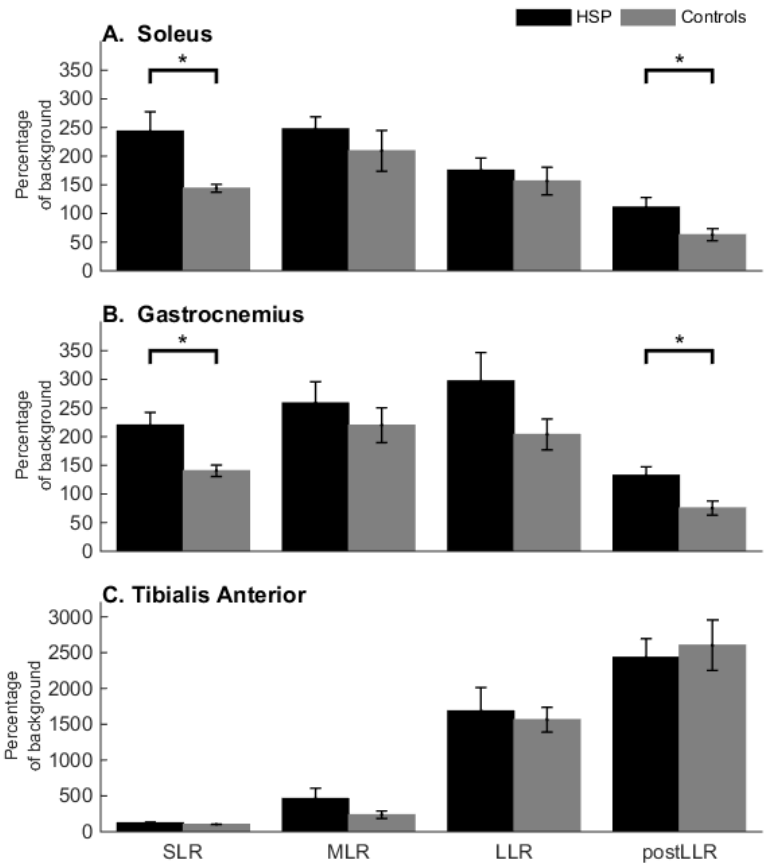
A limitation of this exploratory study is that the group of PwHSP was relatively small (inherent to the rarity of the disease) and heterogeneous (despite our restriction to 'pure' HSP phenotypes). We, therefore, chose not to adjust the statistical criterion for multiple testing, as this would introduce a substantial risk of type II (false-negative) errors. Although multiple testing at uncorrected alpha levels bears a risk of type I (false-positive) errors, we would like to emphasize that we observed a consistent pattern of significant between-group differences in the SLR and post-LLR time-windows for both the soleus and gastrocnemius muscles. In addition, the direction of this effect in the SLR window was coherent with the underlying pathophysiological mechanism and with results from a previous study in HSP [24]. Hence, it is deemed unlikely that the present results represent false-positive outcomes. Another limitation is that we did not measure corrective ankle torques. Such data would have allowed us to appreciate the mechanical effects of the HSP-related differences in triceps surae activity more directly. Furthermore, it remains difficult to provide conclusive evidence for cause-and-effect relationships from discrete perturbations due to the complex interplay of the various systems involved in balance control. Interestingly, a powerful new computational method (closed-loop system identification technique) has recently been proposed to identify such causal relationships from imposed continuous mechanical perturbations and recorded responses at the level of EMG, joint torques and body sway [122]. The application of this method may provide further insight into the mechanisms underlying defective balance control in PwHSP.

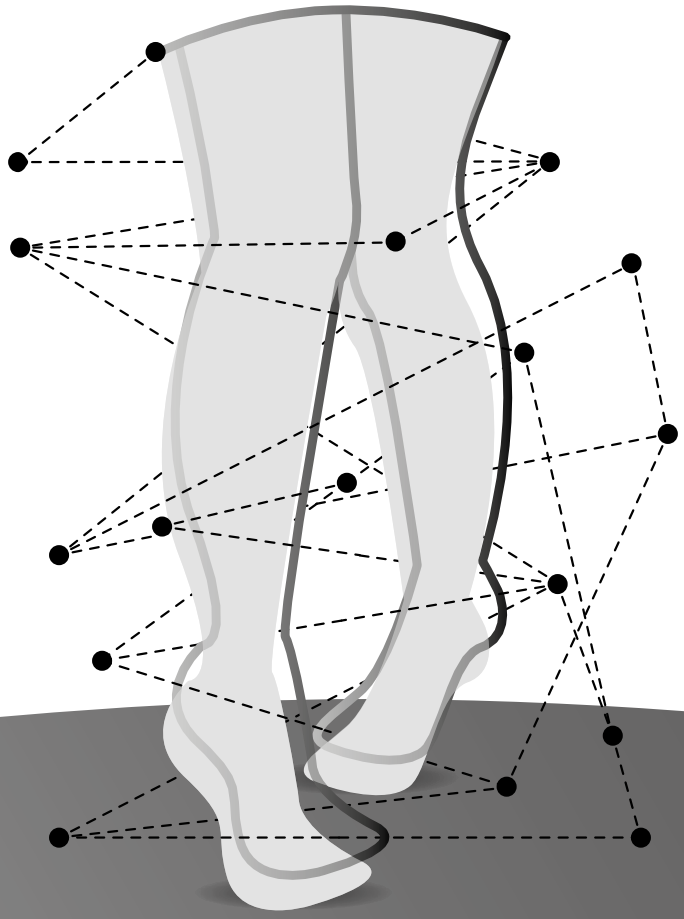
Conclusion

The present results confirm that balance control is impaired in PwHSP. These balance impairments, however, do not seem to be directly related to hyperexcitable short-latency stretch reflexes of spastic triceps surae muscles. Rather, they seem to be due to lack of triceps surae activity suppression in the post long-latency reflex time window. Further research into the neural underpinnings of defective balance control in HSP should particularly focus on the possible role of impaired reciprocal inhibition and/or enhanced (self-sustained) firing of the motoneurons that innervate the triceps surae.

Appendix

FIGURE APPENDIX 1. Overall EMG activity (averaged over 4 intensities) of the participants that underwent all perturbation intensities for each post-perturbation time window in (A) SOL, (B) GM and (C) TA. Black bars represent data of HSP patients, grey bars of the of the control group. Asterisks mark significant differences between the groups. SOL, Soleus; GM, Gastrocnemius; TA, Tibialis anterior.





CHAPTER 5

StartReact during gait initiation reveals differential control of muscle activation and inhibition in patients with corticospinal degeneration.

PUBLISHED AS

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Abstract

Corticospinal lesions cause impairments in voluntary motor control. Recent findings suggest that some degree of voluntary control may be taken over by a compensatory pathway involving the reticulospinal tract. In humans, evidence for this notion mainly comes from StartReact studies. StartReact is the acceleration of reaction times by a startling acoustic stimulus (SAS) simultaneously presented with the imperative stimulus. As previous StartReact-studies mainly focused on isolated single-joint movements, the question remains whether the reticulospinal tract can also be utilized for controlling whole-body movements.

To investigate reticulospinal control, we applied the StartReact paradigm during gait initiation in 12 healthy controls and 12 patients with 'pure' hereditary spastic paraplegia (HSP; i.e. retrograde axonal degeneration of corticospinal tract). Participants performed three consecutive steps in response to an imperative visual stimulus. In 25% of 16 trials a SAS was applied. We determined reaction times of muscle (de)activation, anticipatory postural adjustments (APA) and steps.

Without SAS, we observed an overall delay in HSP patients compared to controls. Administration of the SAS accelerated tibialis anterior and rectus femoris onsets in both groups, but more so in HSP patients, resulting in (near-)normal latencies. Soleus offsets were accelerated in controls, but not in HSP patients. The SAS also accelerated APA and step reaction times in both groups, yet these did not normalize in the HSP patients.

The reticulospinal tract is able to play a compensatory role in voluntary control of whole-body movements, but seems to lack the capacity to inhibit task-inappropriate muscle activity in patients with corticospinal lesions.

Introduction

Patients with an upper motor neuron syndrome (UMNS; e.g. stroke, spinal cord injury, cerebral palsy, hereditary spastic paraplegia) have impaired voluntary motor control due to absent or reduced corticospinal output to the alpha motoneurons in the spinal cord. As a result, volitional movements like gait initiation or reaching while standing are impaired in these patients [123-125]. Such movements are typically preceded by anticipatory postural adjustments (APAs) to optimize postural control during movement [126,127]. Corticospinal pathways are strongly involved in the control of these APAs [128]. As a consequence, UMNS patients show smaller APA magnitudes and delayed APA latencies compared to healthy controls [123-125,129,130].

Interestingly, recent findings in animals and humans suggest that some degree of voluntary motor control may be taken over by the reticulospinal tract as a compensatory neural pathway [1,37,39,131-134]. In humans, evidence for the potential utility of this compensatory pathway for voluntary movements comes from studies that evaluated the StartReact effect. StartReact refers to the phenomenon that reaction times are greatly accelerated when a startling stimulus is presented simultaneously with an imperative stimulus for executing the requested movement. The exact mechanisms underlying StartReact are, however, still under debate, as the extent of the reaction time acceleration seems to depend on various factors. For instance, the StartReact effect is more likely to occur when there is a high level of motor preparedness and a strong familiarity with the task [36,135-137]. Furthermore, the mechanism underlying StartReact appears to depend on the type of action. For example, SAS-induced dexterous hand movements likely engage transcortical pathways, whereas subcortical pathways are more involved in mediating SAS-induced locomotor actions and postural adjustments [135-137]. Although the exact neural structures that are involved in the StartReact effect are not uncontested, there is ample evidence that StartReact during standing and walking is conveyed by the reticulospinal tract [2,36,138,139].

A previous StartReact study from our group in patients with hereditary spastic paraplegia (HSP) has substantially contributed to the notion of compensation by the reticulospinal tract [1]. In its pure form, HSP is clinically characterized by bilateral muscle spasticity and weakness in the legs, whereas the arms commonly remain unaffected [10,27,28]. The main underlying pathological feature in HSP is axonal degeneration of the corticospinal tract [11], particularly affecting the distal parts of the longest descend-

ing axons [12]. This degeneration is reflected in lengthened central motor conduction times to the leg muscles upon transcranial magnetic stimulation, e.g. amounting to 150% of reference values from healthy subjects [1]. Indeed, reaction times of voluntary ankle dorsiflexion movements were substantially delayed compared to those of healthy individuals, yet the presentation of a startling acoustic stimulus (SAS) accelerated reaction times to equivalent values in HSP patients and healthy controls [1]. This finding points at an intact reticulospinal system in HSP, and this system may be instrumental for allowing these patients volitional motor control of the lower extremities in the presence of a dysfunctional corticospinal tract.

Previous studies that demonstrated intact StartReact effects on voluntary movements in various groups of patients with UMNS invariably included simple reaction tasks of isolated ankle, hand, wrist or elbow movements performed in a seated position [1,38,134,140,141]. In contrast, the one study that investigated the StartReact effect in a standing reach task failed to demonstrate a significant SAS-induced acceleration of the requested movement in stroke patients [123]. These discrepant results cast some doubt on the potency of compensatory reticulospinal control for executing complex, multisegmental movements. To shed more light on the potential utility of the reticulospinal system for controlling such movements, we studied the StartReact effect during gait initiation in patients with pure HSP. The APA prior to gait initiation involves concerted tibialis anterior (TA) muscle activation and soleus (SO) inhibition of the stepping leg to move the centre of pressure of the ground reaction forces backwards and towards the stepping leg in order to accelerate the centre of mass forwards and towards the stance leg [127,142].

In a gait initiation task in healthy young individuals, it was previously demonstrated that muscle onsets and offsets as well as APA and step onsets were substantially accelerated when a SAS was presented simultaneously with the imperative signal [143]. Based on the majority of StartReact studies in UMNS patients, we hypothesized that HSP patients, compared to healthy controls, would demonstrate delays in all gait initiation parameters when responding to the imperative stimulus alone, but that the presentation of a SAS would result in greater acceleration of muscle onsets and offsets, thus yielding roughly equivalent SAS-induced reaction times in HSP patients and controls.

Materials and Methods

Ethical approval

The study was approved by the regional medical ethics committee (Commissie Mensgebonden Onderzoek Arnhem-Nijmegen) and was conducted in accordance with the Declaration of Helsinki. All subjects gave written informed consent before the experimental procedures.

Participants

Twelve patients with autosomal dominant forms of HSP (9 men, 3 women; mean age 51 years, range 27-71 years) and 12 aged-matched healthy controls (9 men, 3 women; mean age 53 years, range 27-71) participated. The patients were recruited from the rehabilitation outpatient clinic of our expert centre for genetic movement disorders. All patients fulfilled the diagnostic clinical criteria for "pure" HSP [28].

Clinical assessment

Clinical assessments were performed prior to the experiment. Muscle tone of the triceps surae (TS) (ankle dorsiflexion with knee both flexed and extended), TA (ankle plantarflexion), rectus femoris (RF) (knee flexion with hip extended) and biceps femoris (BF) (knee extension with hip flexed) was assessed bilaterally using the Modified Ashworth Scale (0-5), with higher scores indicating more hypertonia [144]. Muscle strength was assessed bilaterally using the Medical Research Council (MRC) scale (0-5) for the TS, TA, RF and BF muscles, with lower scores indicating more muscle weakness [51]. Vibration sense was tested bilaterally at the medial malleolus and at the first metatarsophalangeal joint using the semiquantitative tuning fork (0-8; Rydel Seiffer, Neurologicals, Poulsbo, Washington), with lower scores indicating more sensory loss [145]. We took the mean of the left and right leg for each measure (Table 1).

TABLE 1. Clinical characteristics of HSP patients

			Median	(range)
Rectus femoris	MAS		1	(1-2)
	MRC		4	(3-5)
Biceps femoris	MAS		1	(0-2)
	MRC		4.25	(3-5)
Tibialis anterior	MAS		0	(0-1)
	MRC		4	(3-5)
Triceps surae	MAS:	knee extended	1	(0-3)
		knee flexed	1	(0-3)
	MRC		4	(3-5)
forefoot	vibration sense		3	(0-6)
ankle	vibration sense		4	(1-6)

All values are means of values for the left and right body side. Vibration sense was tested using a semiquantitative tuning fork (scale range 0 – 8; Rydel Seiffer, Neurologicals, Poulsbo, Washington). MAS: Modified Ashworth scale (scale range 0-5). MRC: Medical Research Council scale (scale range 0-5).

Experimental design

Familiarization

The subjects received three SAS while standing to familiarize them with the stimuli. The SAS were given through binaural earphones and consisted of 50 ms white noise (1500 Hz) with an intensity of 120 dB (measured by Investigator 2260 and Artificial Ear B&K 6cc type 4152, Bruel and Kjaer, Nærum, Denmark). The SAS was generated by a custom-made noise generator.

Gait initiation

The participants stood in front of a box consisting of two blocks with light-emitting diodes (LED). Illumination of the first LED represented a warning signal and illumination of the second LED represented the imperative stimulus. Warning periods (1-3.5 s) and inter-trial periods (6-10 s) were variable and random. The participants were instructed to stand on the two force plates with their weight equally distributed between the legs. Equal loading of both legs was visually checked online by the primary investigator from the force plate signals. In the case of clear deviation from a symmetrical loading pattern, the subjects were instructed to adjust the loading based on

verbal feedback from the primary investigator. As soon as the imperative stimulus was presented, the participants had to start walking as fast as possible and perform at least three steps (one trial), starting with their preferred leg. The preferred leg was defined as the leg with which the participant would kick a football. The participants performed a total of 16 trials; in 25% of these trials a SAS was presented simultaneously with the imperative stimulus using a synchronous analog pulse to the LED box and the startle generator. Prior to the task, the participants performed four practice trials.

Data collection

Electromyographic (EMG) (ZeroWire, Aurion, Italy) data were collected from both sternocleidomastoid (SCM) muscles and TA, RF and SO muscles of the preferred leg of the participant. The EMG electrodes were placed according to Seniam guidelines [144]. EMG signals (sampled at 2000 Hz) were consecutively band-pass filtered at 20-450 Hz (zero-lag, second order Butterworth filter), rectified and low-pass filtered at 30 Hz (zero-lag, second order Butterworth filter).

Ground reaction forces under both feet were recorded at a sample rate of 2000 Hz by two force plates (60x180 cm each; AMTI Custom 6-axis composite force platform, USA), which were embedded in the surface.

Reflective markers were placed at anatomical landmarks on the heel, ankle and toe of both feet. Marker positions were recorded by an 8-camera 3D motion analysis system (Vicon Motion Systems, United Kingdom) at a sample rate of 100 Hz.

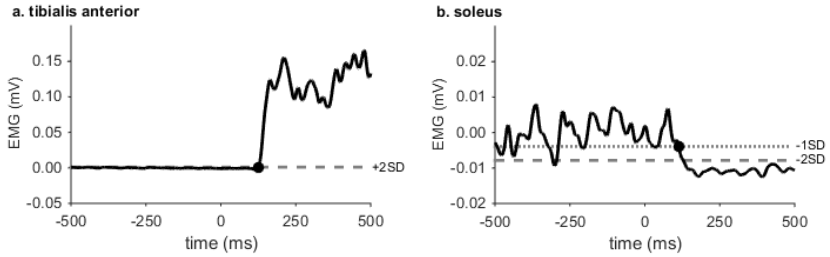
Data analysis

Data analyses were all conducted by the primary investigator. For all signals baseline activities and the respective standard deviations (SD) were calculated over 500 ms prior to the imperative stimulus. The baseline activity was subtracted from all signals. The ensemble average EMG traces of the TA, RF and SO EMG were calculated separately for trials with and without a SAS. We determined muscle onset latencies for TA and RF. We defined the onset as the first instant that a signal exceeded the threshold of 2 SD above baseline activity (figure 1a), which was determined by a semi-automatic computer algorithm.

For determining SO offsets, we chose to apply a somewhat more liberal criterion (figure 1b). This was done because, compared to the baseline activity of TA and RF, the tonic SO activity at baseline demonstrated greater fluctuations, resulting in large

standard deviations. A threshold of -2 SD would therefore have resulted in SO offsets being identified relatively late. We first identified when SO activity went below a threshold of -2 SD, and then worked backwards to find the instant where the EMG signal exceeded the mean baseline activity –1 SD. This instant was taken as the SO offset. All onset and offset latencies were visually approved or corrected [1,23,41].

FIGURE 1. Representative TA and SO EMG signals of the stepping leg in a healthy control participant during gait initiation. TA onset and SO offset are indicated by a dot. Note that the SO baseline is fluctuating much more than the TA baseline. Therefore, TA muscle onset was determined as the instant where the signal exceeded 2 SD above baseline activity, whereas SO muscle offset was determined as the last instant where the EMG signal went below -1 SD before going below -2 SD for at least 50ms.



For each trial, it was determined whether an anticipatory postural adjustment (APA) occurred prior to the step. To define a weight shift as an APA the force under the stepping leg had to exceed 5% of the total body weight. In addition, the difference between the vertical loading underneath the stepping and stance leg was calculated. The difference had to rise above the threshold of 2 SD above the mean difference 500ms prior to the imperative stimulus. This moment was defined as the APA onset. In addition, for each APA, the maximum increase in vertical force under the stepping leg was determined and normalized for body weight (BW) [146].

For step onsets, 3D vectors (*x,y* and *z* direction) of the heel and toe markers of the stepping leg were calculated for each trial. The step onset was defined as the first instant when one of the two vectors rose above the threshold of 2 SD above baseline (calculated over 500ms prior to the imperative stimulus). Step length was determined for each trial separately using the horizontal displacement of heel and toe markers [146].

For each trial with a SAS, we determined whether a startle reflex occurred in SCM. A

startle reflex was defined as short latency response in any of the SCM muscles starting within 130 ms following the SAS.

Statistical analysis

All outcome measures were tested using repeated-measures ANOVA. Group (*HSP patients - healthy controls*) was used as the between-subjects factor and SAS (*SAS - no SAS*) was used as the within-subjects factor. For parameters with interaction effects, post-hoc analysis was done to determine the 95% confidence interval (CI) of the mean difference between patients and controls for SAS and no SAS trials separately. Furthermore, we tested for differences in APA occurrences between the two groups using a chi-squared test. We used the chi-squared test also to test for differences in occurrence of startle reflexes between HSP patients and controls in SAS trials.

As a secondary analysis, we tested for differences in onset latencies between SAS trials with a startle reflex (SCM^+) and SAS trials without a startle reflex (SCM^-), for those participants who presented both. A repeated measures ANOVA was used with startle reflex (*SCM^-- SCM^+)* as within-subjects factor and group (*HSP patients - healthy controls*) as between-subjects factor. This secondary analysis was performed because there is an ongoing debate on whether the StartReact effect critically depends on the occurrence of a startle reflex. As such, this analysis was used to determine the potential impact of our decision of analyzing *all* SAS trials (as opposed to only including SCM+ trials) on our primary results and conclusions. Note that for all our other analyses, *all* SAS trials were included.

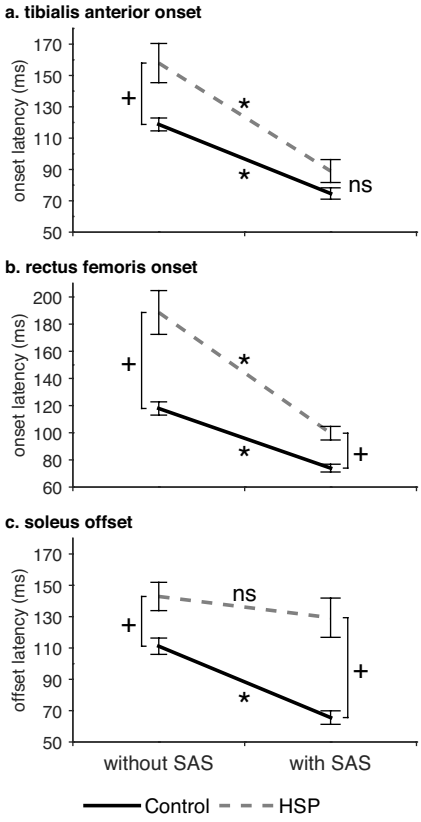
Statistical analyses were performed using IBM SPSS Statistics Version 20 for Windows. For all analyses, the α level was set at 0.05.

Results

EMG onset and offset latencies

The EMG pattern of the stepping leg during gait initiation was characterized by near-simultaneous TA activation, RF activation and SO inhibition in healthy controls, whereas activation of RF followed shortly after near-simultaneous TA activation and SO inhibition in HSP patients (see figure 2).

FIGURE 2. Mean EMG onset/offset latencies (SE) during gait initiation. * Indicates post-hoc significant difference between trials with and without a SAS. + Indicates post-hoc significant differences between groups with and without a SAS. n.s. = not significant.



Without SAS, TA onsets during gait initiation occurred earlier in controls (119 ± 14 ms) than in HSP patients (158 ± 43 ms). Administration of the SAS accelerated these onsets in both groups (*SAS*, $F_{(1,22)} = 92.216$, $p < 0.001$), as shown in figure 2A. Yet, with the addition of the SAS we observed a larger acceleration in TA onsets in the HSP group (89 ± 25 ms) compared to controls (75 ± 13 ms; *SAS x group,* $F_{(1,22)} = 4.454$, $p = 0.046$; *group,* $F_{(1,22)} = 8.384$, $p = 0.008$). The mean delay in HSP patients was significant without a SAS (95% CI: 12-66 ms, $p = 0.010$), but with a SAS the onsets were no longer different from controls (95% CI: -3-31 ms, $p = 0.093$).

With regard to RF onset latencies, the HSP patients showed an overall delay compared to controls (*group,* $F_{(1,22)}$ = 29.254, p <0.001; figure 2B). The SAS accelerated RF onsets in both the control group (118 ± 17 ms to 74 ± 10 ms) and HSP group (189 ± 56 ms to 100 ± 17 ms; *SAS,* $F_{(1,22)}$ = 55.663, p < 0.001). Although the SAS-induced acceleration was significantly greater in HSP patients than in the controls (*SAS x group,* $F_{(1,22)}$ = 6.388, p = 0.019), the delay in RF onsets in the HSP patients compared to healthy controls remained significant with a SAS (mean 26 ms, 95% CI: 14-38 ms, p < 0.001).

The SO offset without SAS was also delayed in HSP patients (143 ± 31 ms) compared to controls (111 ± 18 ms; *SAS*, $F_{(1,22)}$ = 19.388, p < 0.001; figure 2C). The SAS accelerated the SO offsets, but in contrast to the results for TA onsets, the SAS-induced acceleration was greater in healthy controls than in HSP patients. Therefore, with addition of the SAS, the SO offsets in healthy controls (66 ± 15 ms) occurred earlier than in HSP patients (129 ± 43 ms; *SAS x group,* $F_{(1,22)}$ = 5.687, p = 0.026; *group,* $F_{(1,22)}$ = 23.469, p < 0.001). Without a SAS, the mean delay in HSP patients was 32 ms (95% CI: 10-53 ms, p = 0.006), which delay increased to 64 ms in the SAS trials (95% CI: 35-92 ms, p < 0.001).

Anticipatory postural adjustments

APAs were detected in 87% of the trials in HSP patients, whereas APAs were detected in all the trials of the healthy controls ($F_{(1,393)}$ = 20.855, p < 0.001). The HSP patients had delayed APA onsets both without SAS (231 ± 23 ms) and with SAS (152 ± 31 ms) compared to the control group (without SAS: 189 ± 26 ms; with SAS: 129 ± 26 ms; *group*, $F_{(1,22)}$ = 11,62, p = 0.003; figure 3A). The SAS significantly accelerated APA onsets (*SAS,* $F_{(1,22)}$ = 154.299, p < 0.001), yet without differential effects between the two groups (*SAS x group,* $F_{(1,22)}$ = 2.693, p = 0.115).

APA amplitudes were smaller in HSP patients compared to healthy controls, both without SAS (control: 26 ± 5, HSP: 19 ± 8% BW) and with SAS (control: 27 ± 4, HSP: 18 ± 7% BW; *group*: $F_{(1,22)}$ = 12.355, p = 0.002; figure 3B). There was no effect of the SAS on APA amplitudes in either group (*SAS,* $F_{(1,22)}$ = 0.016, p = 0.901; *SAS x group,* $F_{(1,22)}$ = 2.247, p = 0.148).

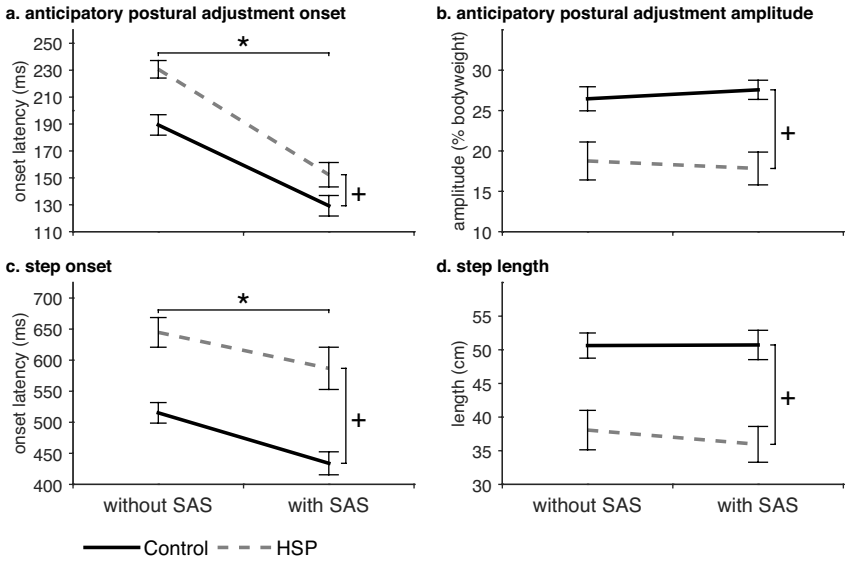
Step onset and step length

Step onsets in HSP patients were delayed compared to healthy controls (*group,* $F_{(1,22)}$ = 19.898, p < 0.001), as shown in figure 3C. The SAS accelerated step onsets in both

in healthy controls (515 ± 57 to 434 ± 64 ms) and in HSP patients (645 ± 83 to 587 ± 118 ms; *SAS,* $F_{(1,22)}$ = 28.507, p < 0.001). There was no differential effect of the SAS between HSP patients and healthy controls (*SAS x group,* $F_{(1,22)}$ = 0.801, p = 0.381).

No effects of the SAS were found on step length (*SAS,* $F_{(1,22)}$ = 1.168, p = 0.291; *SAS x group,* $F_{(1,22)}$ = 1.375, p = 0.254; figure 3D). In both without SAS and with SAS conditions, HSP patients made shorter steps (38 ± 10 and 36 ± 9 cm) than healthy controls (51 ± 6 and 51 ± 8 cm; *group*, $F_{(1,22)}$ = 16.877, p < 0.001).

FIGURE 3. Mean onset latencies (SE) during gait initiation (left graphs) and mean anticipatory postural adjustment amplitudes and step lengths (right graphs). * Indicates significant difference between trials with and without a SAS. + Indicates significant differences between groups with and without a SAS. n.s. = not significant.



Startle reflex

The occurrence of the startle reflex in SCM during SAS trials was 64% HSP patients and 65% in healthy controls ($c^2_{(1,93)}$ = 0.000, p = 0.989). There were no differences in TA onset between the SCM^- trials and SCM^+ trials in either HSP patients (117 ± 14 and 110 ± 13 ms) or healthy controls (85 ± 4 and 85 ± 4 ms; *SCM*, $F_{(1,14)}$ = 0.715, p = 0.412, *SCM* x *group*, $F_{(1,14)}$ = 0.950, p = 0.346).

Discussion

The aim of the present study was to gain more insight in the potency of the reticulospinal tract to act as a compensatory pathway for executing voluntary complex, multisegmental movements. Therefore, we investigated the effects of StartReact on gait initiation in HSP patients. Compared to healthy controls, the HSP group responded to the imperative visual stimulus alone with delayed TA and RF onsets, SO offsets, as well as APA and step onsets. Pairing the imperative stimulus with a SAS resulted in earlier onsets in TA, RF, APA and step onsets both in healthy controls and HSP patients. The SAS-induced acceleration in APA and step onsets was similar between groups, whereas a significantly greater StartReact effect was observed in TA and RF onset latencies in the HSP patients than in the controls, resulting in (near)-normal TA and RF onsets in the HSP group. In response to the visual stimulus alone, we observed TA onsets and SO offsets at approximately the same time. In the healthy controls, the SAS similarly accelerated TA onsets and SO offsets, such that the relative timing between these events was not affected. Yet, remarkably, no SAS-induced acceleration in SO offsets was observed in the HSP patients.

Our study adds to the existing body of knowledge on StartReact effects in patients with upper motor neuron lesions [1,123,140,141,147] by demonstrating that patients with HSP showed greatly accelerated reaction times in a gait initiation task, as an example of a common voluntary whole-body movement. Without a SAS, there was a difference in TA onset between HSP patients and healthy controls, probably due to a delayed corticospinal conduction time. With the SAS, the normalization of TA onsets in HSP patients suggests that these patients now used the same neural pathway as healthy controls (i.e. the reticulospinal tract) to generate the SAS-induced movements, irrespective of whether acceleration of reaction times may have been limited by physiological floor effects. It is important to mention that the observed SAS-induced reaction times in this study (75-89ms) are in the same order of magnitude as those previously reported during both voluntary ankle dorsiflexion and gait initiation in various populations [1,143,146]. In addition, our SAS-induced TA onsets are in line with previously reported startle reflex onsets in TA [1,148], which further supports the notion that the SAS-induced response is conveyed by the reticulospinal tract.

This finding complements previous work on single-joint movements. In our previous study in HSP patients, delayed onset latencies of TA activity and ankle dorsiflexion

movements were observed in a single-joint reaction task, yet with a SAS the patients' reaction times were comparable to those of healthy individuals [1]. Similarly, in stroke survivors, onset latencies of isolated elbow flexion and hand extension movements were delayed without a SAS, whereas these reaction times were also normalized with the SAS [140,141]. To our knowledge, only one previous study has investigated the StartReact effect in a voluntary whole-body movement in a group of UMNS patients. During forward standing reaches with the paretic arm, people with stroke demonstrated delayed onsets of both the anticipatory postural adjustment (APA) and the focal reaching movement compared to healthy control subjects. Administration of a SAS led to a significant reduction in reaction times in the controls. In contrast, in the people with stroke the SAS did not speed up APA onsets, whereas it even caused a further delay in reaching onsets [123]. The discrepancy between these and our present findings may be related to damage of cortical areas responsible for motor preparation (e.g. pre-motor cortex, supplementary motor cortex) after stroke, whereas HSP (in its pure form) does not affect neurons originating from these secondary motor areas. As the StartReact phenomenon typically depends on the requested movement being readily prepared when the SAS is administered, (partial) sparing of these cortical motor preparation areas seems imperative, with the degree of sparing likely becoming more critical as the task becomes more complex.

In this study, we found no difference in SAS-induced onset latencies between SCM+ and SCM- trials, which is consistent with previous StartReact studies that included lower-extremity movements [1,23,36,135]. In contrast, small but significant differences have been demonstrated in several studies that focused on upper extremity movements [140,149,150]. Based on these results it was previously suggested that a true StartReact effect could only occur when a startle reflex in SCM was also elicited. Yet, at present, startle reflexes and acceleration of motor responses by a startling stimulus are considered to be dissociated phenomena [36]. The small difference between SCM+ and SCM- trials that has been reported by some authors is likely explained by the presence of a startle reflex in SCM being a marker of preparedness, with a higher level of preparedness in SCM+ trials leading to shorter reaction times [36,135,137]. Although it remains elusive why this effect is not observed in lower extremity movements, our results confirm that the presence of a startle reflex is not conditional for the occurrence of the StartReact effect.

An unexpected finding of the present study was the lack of acceleration of soleus inhibition in the HSP patients upon administration of the SAS. In contrast, the SAS did

accelerate SO offsets in the healthy controls, which result is in agreement with the observations from a previous study that investigated the StartReact phenomenon in a gait initiation task in healthy young participants [143]. In that study, SO offsets and TA onsets during gait initiation were both accelerated to latencies of ~50-70 ms by a SAS [143,151], which is consistent with the latencies observed in our healthy control group. StartReact effects on muscle inhibition have also been demonstrated in healthy young participants in a reaction time paradigm where they had to actively inhibit a baseline elbow flexion force with and without a SAS [151]. Hence, it appears that our HSP patients differ from healthy participants in their lack of SAS-induced inhibitory motor control. As both SO inhibition and TA activation are known to contribute to the generation of the APA [127], the observed disparity in excitatory and inhibitory StartReact effects in the HSP patients may also explain why their APA onsets were not accelerated to healthy control levels with the SAS.

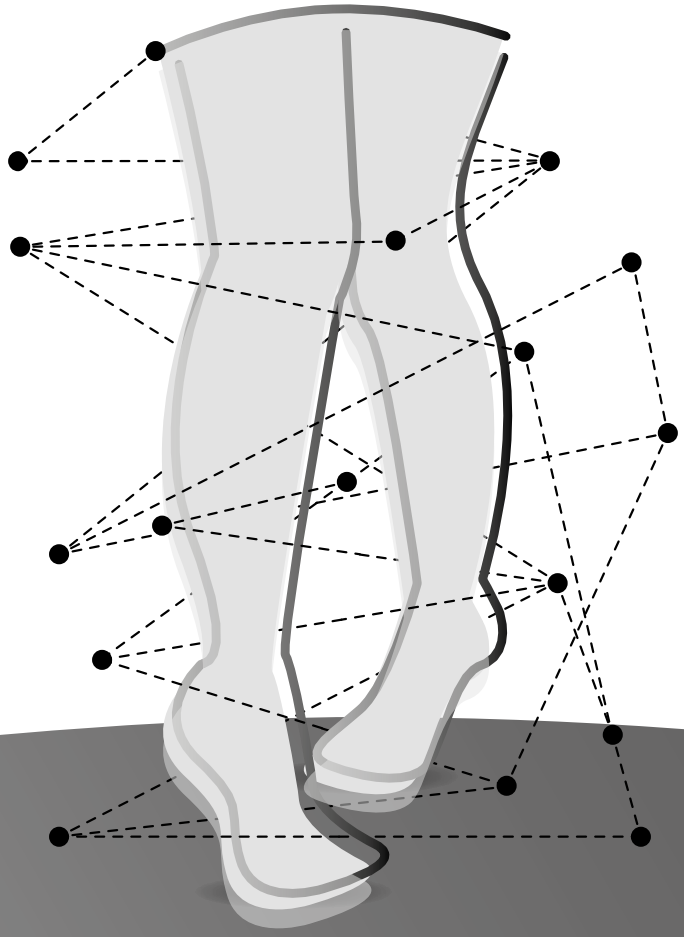
The results of the current study raise the question which mechanism(s) may underlie the absent StartReact effect on muscle inhibition in the HSP patients. Here we can only speculate, as our study was not designed to address this unexpected finding. One suggestion may be that inhibitory control of the reticulospinal tract on spinal motoneurons is less potent than its excitatory effects. This relative difference between inhibitory and excitatory strength would be in line with previous observations in cats, where it has been shown that the reticulospinal tract has fast-conducting excitatory (activating) fibers that project directly onto motoneurons, while inhibitory reticulospinal projections merely appeared to be indirect (i.e. via interneurons) [152]. Yet, under this assumption, one would expect SAS-induced differences in relative timing of TA onsets and SO offsets in the healthy controls as well, which we did not observe.

Another possibility is that HSP differentially affects the dorsal and medial fascicles of the reticulospinal tract. Animal studies have suggested that inhibitory commands are predominantly conducted by the dorsal reticulospinal tract (which runs closely to the corticospinal tract [153]) , whereas the medial reticulospinal tract mainly conducts excitatory commands from the reticular formation [154,155]. Hence, the lack of SAS-induced acceleration in SO offsets may be due to affliction of the dorsal reticulospinal tract, while the medial reticulospinal may remain unaffected in the presently studied genotypes of HSP. Yet, we are unaware of any (post-mortem) studies in patients with HSP in support of this hypothesis.

A third and perhaps most plausible mechanism is that the inhibitory SAS-induced

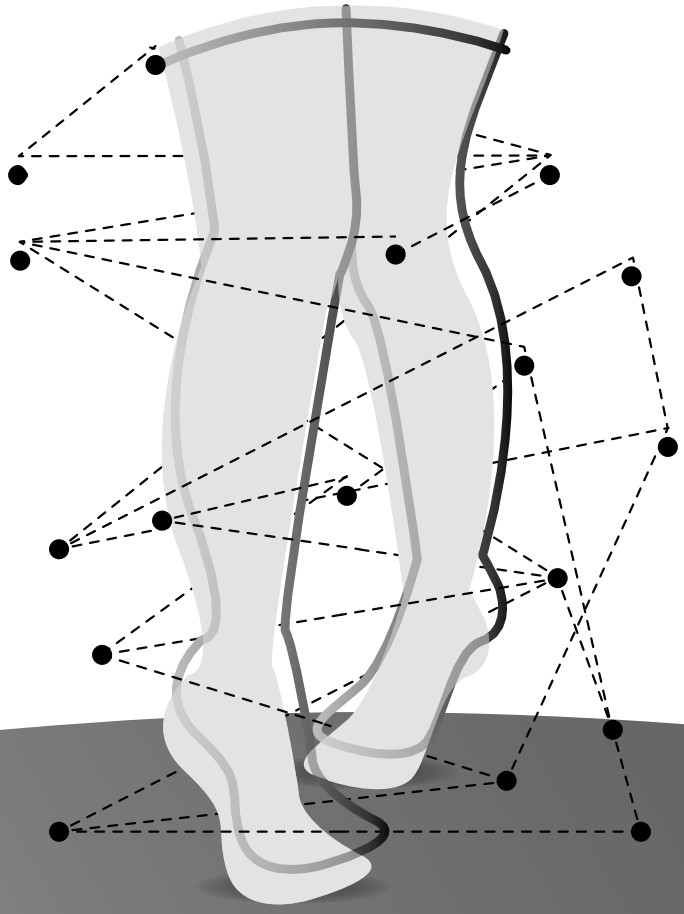
command may lack strength to overcome the tonic calf muscle activity that is present when standing upright. Indeed, calf muscle tone is typically higher in UMNS patients compared to healthy controls. Due to the lack of descending inputs in UMNS, muscle activity can cause motoneurons to activate voltage-dependent persistent inward currents. These persistent inward currents can lead to self-sustained firing of motoneurons, resulting in a long-lasting involuntary enhancement of muscle activity [118] that may override the effect of the inhibitory SAS-induced reticulospinal command. However, there is no direct evidence in support of this suggestion and further research is warranted to elucidate the mechanisms underlying defective StartReact effects on muscle inhibition in HSP.

The present findings may shed new light on the functional utility of the reticulospinal tract for bypassing defective corticospinal control. Animal studies have provided strong evidence for the potential of a compensatory role of the reticulospinal tract in recovery of upper-extremity motor function (for review: see Baker [39]) and lately also of lower-extremity function. For instance recovery of function after complete corticospinal lesions was shown to coincide with an increased output from the reticulospinal system as measured with intracellular recordings [37,132,133,156]. Also in humans after stroke, the notion of reticulospinal contributions to functional recovery is gaining support, particularly concerning those with severe damage to the primary motor cortex and/or the corticospinal tract [39,157-160]. However, reticulospinal motor control has limitations compared to corticospinal control due to the greater dispersion of reticulospinal projections on spinal motor neurons [161], limiting the degree of refined fractionated movements. The results of the present study suggest that reticulospinal motor control may also be inferior because this system lacks the capacity to inhibit task-inappropriate muscle activity. Yet, the exact mechanisms remain elusive and can only be speculated upon. Together, these considerations may explain why in HSP patients spasticity and lack of refined motor control are often more prominent impairments than muscle weakness [75]. During our task of gait initiation, the functional disadvantages of defective soleus inhibition on, for instance, step onset appeared to be rather minimal, however poor inhibitory control may be more detrimental to performance in other postural tasks, such as postural perturbations. Further research is needed to fully understand the potential and limitations of compensatory reticulospinal motor control in upper motor neuron syndrome.



PART 3

CLINICAL MANAGEMENT: FUNCTIONAL EFFECTS OF BTX-A IN PATIENTS WITH PURE HSP



CHAPTER 6

Which changes in ankle kine(ma)tics following BTX-A treatment and subsequent stretching of the calves contribute to increased comfortable speed in patients with pure hereditary spastic paraplegia?

SUBMITTED AS

van Lith BJH, van Bon GEA, Geurts ACH, Weerdesteyn V. Which changes in ankle kine(ma)tics following BTX-A treatment and subsequent stretching of the calves contribute to increased comfortable speed in patients with pure hereditary spastic paraplegia?

Abstract

Background

Botulinum toxin type A (BTX-A) is a common treatment for focal spasticity. Patients with pure Hereditary Spastic Paraplegia (HSP) constitute a good clinical model to investigate the functional effects of BTX-A treatment, because their lower limb spasticity is often more prominent than muscle weakness or sensory loss. In a group of patients with pure HSP, we previously showed increased comfortable gait speed after BTX-A treatment and subsequent stretching of the calves, but the underlying mechanisms remained unclear.

Research question

How do changes in ankle kinematics and kinetics following BTX-A treatment and subsequent stretching of the calves lead to increased comfortable gait speed in patients with pure HSP?

Methods

Sixteen patients with troublesome calf spasticity, confirmed by surface electromyography during gait, were treated with bilateral BTX-A injections in the triceps surae and performed daily self-administered stretching exercises for 18 weeks. In 13 participants, spatiotemporal variables and ankle kinematics and kinetics could be determined by instrumented gait analyses before intervention (baseline) and 4 (T1) and 18 (T2) weeks thereafter.

Results

Stride length and comfortable gait speed were larger at T1 and T2 compared to baseline ($p<0.05$), whereas cadence did not change significantly. Peak ankle power and positive work during late stance improved at T1 and T2 ($p<0.05$), while negative work during early-midstance did not significantly change, nor did ankle angles (maximal ankle dorsiflexion and plantarflexion; maximal ankle range of motion), peak ankle torque, or the ground reaction force angle in the plane of progression at peak ankle power.

Significance

BTX-A treatment and subsequent stretching of the calves in patients with pure HSP and proven troublesome calf spasticity during gait may enhance comfortable gait

speed by allowing more efficient use of calf muscle strength during push-off, leading to increased stride length.

Introduction

Intramuscular injections with botulinum toxin type A (BTX-A) are a common treatment for focal spasticity, but evidence for the efficacy of treatment on walking capacity is rather limited. This may be due to the confounding effects of co-existing impairments, such as loss of muscle strength and somatosensation, which are highly prevalent in the patient groups studied (e.g. stroke and cerebral palsy (CP)) [162,163]. Patients with pure Hereditary Spastic Paraplegia (HSP) constitute a good clinical model to investigate the functional effects of BTX-A treatment, because of their progressive bilateral lower limb muscle spasticity, while leg muscle strength and somatosensation are often preserved [27]. Therefore, functional effects of BTX-A injections can be investigated relatively unconfounded by paresis or somatosensory impairment. A previous study from our group investigated the effects of BTX-A treatment and subsequent stretching of the calves in a group of patients with pure HSP. It was shown that – after the combined treatment – there was a substantial reduction of calf muscle tone, which coincided with a slight decrease in calf muscle strength during clinical examination (Medical Research Council (MRC) scale), although quantitative assessment of muscle strength showed no significant change. These effects at the level of the calf muscle resulted in a 10% gain in comfortable gait speed as well as in subjective gait benefits for most patients, without affecting antero-posterior balance capacity [9]. Although an overall beneficial functional effect was found, the question remained how the observed increase in comfortable gait speed after BTX-A treatment and subsequent stretching of the calves came about. Therefore, the focus of the current paper is on the ankle kinematics and kinetics before and after this combined treatment to better understand the observed beneficial effects in gait speed.

Generally, the presence of calf muscle spasticity in patients with upper motor neuron syndrome leads to a gait pattern referred to as 'toe walking', which is characterized by initial midfoot or forefoot contact, early heel rise, lack of push-off power, toe dragging and limited step length [164]. A midfoot or forefoot landing may be caused by premature calf muscle activity during the swing phase, often accompanied by lack of activity of the ankle dorsiflexors, leading to an abnormal (often reversed) roll-off motion of the

ankle and foot [112,165]. BTX-A treatment of the calves may enhance ankle dorsiflexion angles at initial contact and improve the first rocker, as was shown in people with stroke and children with CP [166,167]. In the case of an initial heel strike, premature calf muscle activity early after loading may counteract normal ankle dorsiflexion movement during roll-off [165,168], leading to increased negative work (i.e., energy absorption) at the ankle joint [169]. A reduction in mid stance calf muscle activity following BTX-A injections, which has previously been reported in people with stroke [170,171], may thus improve the second rocker and reduce energy absorption. Indeed, in patients with stroke and CP, larger ankle dorsiflexion angles [166,167,172-174] and a lower peak in energy absorption at the ankle [173] were observed following BTX-A treatment of the calf muscles. Lastly, during late stance, calf muscle spasticity coincides with reduced ankle power and slower ankle plantarflexion movement [165], which hampers forward propulsion. In such cases, BTX-A treatment might – on the one hand – facilitate active push-off if muscle tone is reduced, while – on the other hand – it may reduce voluntary muscle strength, which would limit push-off power during the third rocker. Yet, previously reported effects of BTX-A treatment of the calves on peak ankle power are inconsistent [166,173,175-177], which calls for further study.

The purpose of the current study was to identify how changes in ankle kinematics and kinetics after BTX-A treatment and subsequent stretching of the calf muscles led to an increase in comfortable gait speed in patients with pure HSP as observed in our previous study [9]. We expected that the combined treatment would lead to a decrease in negative work during the loading and/or midstance phase of gait as a consequence of improved ankle dorsiflexion movement. In addition, we expected a slight decrease in positive work during late stance as a consequence of a possible decrement in calf muscle strength. However, we hypothesized that the decrease in negative work would outweigh the decrease in positive work, which would explain the observed increase in comfortable gait speed. For correct interpretation of the results, we also compared ankle kinematics and kinetics during gait of our patients with HSP with those of healthy age- and sex-matched controls walking at a similar speed.

Methods

Participants

In short, the inclusion criteria for patients were: (1) a pure form of autosomal dom-

inant HSP; (2) aged between 18 and 75 years; (3) calf muscle spasticity (Modified Ashworth Scale (MAS) score 1-2); (4) bilateral premature calf muscle activity during the loading and/or midstance phase of gait as determined by surface EMG; (5) balance- and/or gait-related activity limitations in daily life; (6) Functional Ambulation Categories (FAC) score 5 [113]; (7) passive ankle range of motion (ROM) more than 10° dorsiflexion with an extended knee, and (8) normal or near-normal calf and tibialis anterior muscle strength (MRC score 4-5) [114]. In addition, 10 healthy controls with the same age and sex distribution were included to provide reference data [9]. All subjects gave their written informed consent prior to participation. The study was approved by the regional medical-ethical committee and conducted in accordance with the Declaration of Helsinki.

Intervention

Each patient was treated with one cycle of bilateral BTX-A injections (Dysport®) in the calf muscles of each leg, either 500 U (when MAS 1) or 750 U (when MAS 2), distributed evenly over the three heads of the triceps surae: soleus (5 sites) and medial (2 sites) and lateral (2 sites) heads of gastrocnemius. Furthermore, participants were instructed to perform stretching exercises of the calf muscles for approximately 10 minutes, twice daily, during the 18-week study period. During this period, every 2 weeks, patients were asked by the primary investigator whether they did their daily exercises to check adherence to the protocol. For a more detailed description of the intervention, we refer to our previous paper [9].

Design

The gait assessments of the patients with HSP were performed one week before treatment (baseline; T0), 4 weeks after treatment (T1), and 18 weeks after treatment (T2). T1 was set at 4 weeks after treatment, because at this time interval the physiological effects of BTX-A on spasticity were expected to have reached a maximum [178]. The effects of BTX-A were expected to diminish progressively until about 18 weeks after the injections. The healthy control subjects performed the gait assessment just once and were compared to the baseline data of the patients.

Gait assessment

We used the instrumented gait analysis data as obtained in the previous study [9]. Gait was evaluated barefoot and without the use of walking aids on a 10 meter walkway. All patients wore a safety harness attached to an overhead railing that prevented

them from falling. The subjects with HSP walked at an individually preferred ('comfortable') speed. Healthy control subjects were instructed to walk at low velocity in order to match their gait speed to the average speed of the patients.

During the gait assessments, kinematic data were recorded by a 6-camera 3D motion analysis system (Vicon MX, Oxford Metrics, Oxford, UK) at a sample rate of 100 Hz. Reflective markers were placed at anatomical landmarks according to the full-body PlugInGait configuration [179]. Simultaneously, ground reaction forces (GRFs) were recorded from two force plates (40 x 105 cm AMTI® force plate, Watertown, MA, USA), embedded in the middle part of the 10 meter walkway, at a sampling rate of 1000 Hz. Subjects walked back and forth repeatedly in order to obtain at least 5 valid measurements for each leg (i.e. a complete support phase on one force plate without the opposite foot touching the same plate).

Data analysis

For each trial, existing of one gait cycle for the left and one for the right leg, we determined the following variables:

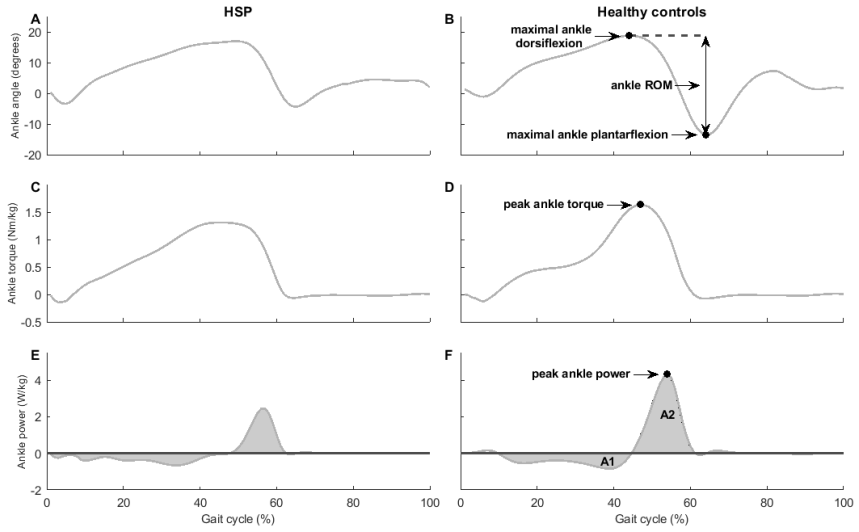
Spatiotemporal characteristics: gait speed, stride length and cadence (based on kinematic data).

Kinematics: the maximal ankle dorsiflexion and plantarflexion angles and the total ankle ROM across the gait cycle (figure 1B); we also determined the angle of the foot with the horizontal (in the plane of progression) at initial contact, with positive angles representing a heel landing and negative angles representing a midfoot/forefoot landing.

Kinetics: peak ankle torque (figure 1D), peak ankle power (figure 1F), and negative work (A1; energy absorption; figure 1F) during the early and midstance phase, and positive work (A2; energy generation; figure 1F) during the late stance phase; we further calculated the GRF angle at maximal ankle power, defined as the angle of the force with the ground (in the plane of progression), with 90° representing a vertical force and smaller angles indicating a force directed more horizontally.

For each subject, the ensemble averages for ankle angles, ankle torques and ankle powers in the sagittal plane of all trials were calculated for each leg separately. Subsequently, values for ankle kine(ma)tic outcomes were identified from these ensemble averages, resulting in one value for the left and one value for the right leg. Thereafter, these values were averaged resulting in a single value per variable per subject.

FIGURE 1. Representative ensemble averages of the ankle angle (a and b), ankle torque (c and d), and ankle power (e and f) trajectories in the sagittal plane of a representative patient (left column) and control subject (right column), with the kine(ma)tic variables of interest. Ankle kinetics were normalized for body weight. Area under the curve: A1 = negative work; A2 = positive work.



Statistical analysis

The effects of the combined treatment were assessed using a repeated measures ANOVA with *time* (*T0-T1-T2*) as within-subjects factor. In the case of a significant *time* effect, post-hoc paired t-tests were used. In addition, we performed independent t-tests to compare the gait variables between groups. Statistical analyses were performed using IBM SPSS Statistics Version 20 for Windows. For all analyses, the α level was set at 0.05.

Results

Of the 16 patients included in our previous paper [9], three patients were unable to deliver the full series of gait assessments due to technical problems (n=2) or because the gait assessments were too burdensome (n=1). Hence, the three consecutive gait assessments of 13 patients were used in this study, together with the single assessments of 10 healthy controls.

TABLE 1. Demographic characteristics of the patients with HSP and the healthy control subjects.

	HSP	Control
N	13	10
Age (mean ± SD)	48.46 ± 12.80	46.10 ± 11.82
Sex (male/female)	10/3	6/4

Time effects in HSP

The data of the patients are summarized in table 2. Gait speed differed between the assessments ($F(2,24)=5.626$, $p=0.010$), with higher speeds at T1 ($t(12)=-2.960$, $p=0.012$) and T2 ($t(12)=-2.835$, $p=0.015$) compared to baseline (figure 2A). Stride length was also different between the assessments ($F(2,24)=5.914$, $p=0.008$), as strides were longer at T1 ($t(12)=-2.687$, $p=0.020$) and T2 ($t(12)=-3.123$, $p=0.009$) (figure 2B) than at baseline. There were no *time* effects for cadence ($F(2,24)=2.635$, $p=0.124$).

The ankle angles showed no differences between the assessments (maximal dorsiflexion: $F(1.16,13.87)=0.734$, $p=0.426$; maximal plantarflexion: $F(2,24)=0.414$, $p=0.666$; ankle ROM: $F(2,24)=0.862$, $p=0.435$), nor did the foot angle at initial contact ($F(2,24)=2.599$, $p=0.095$).

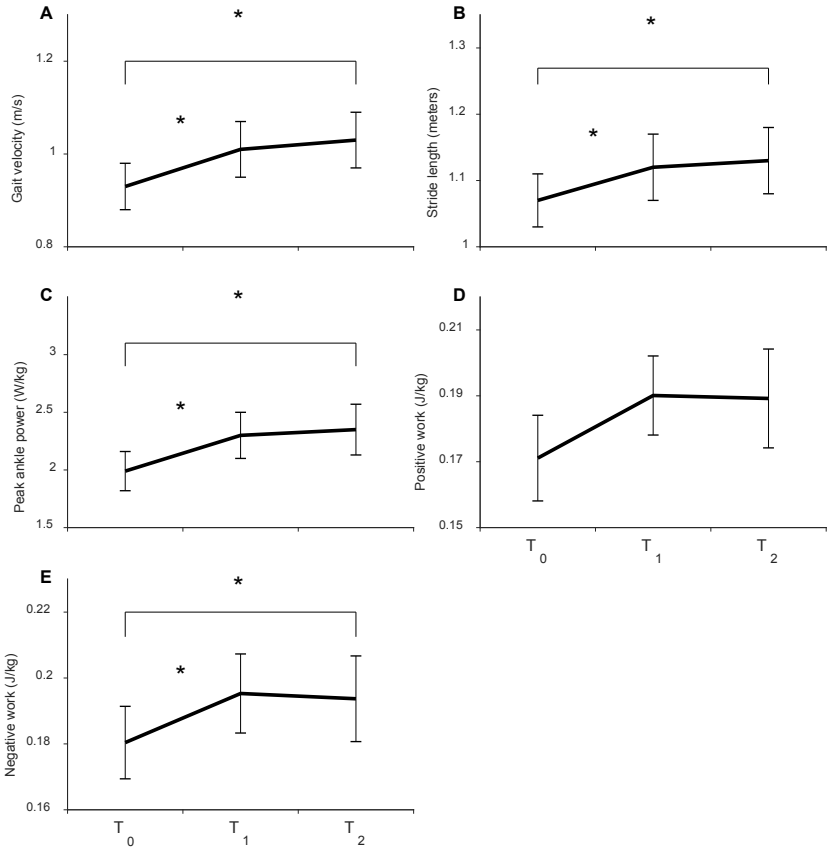
TABLE 2. Outcomes for within-subjects comparisons

	T0	T1	T2	Repeated-measures ANOVA
	(mean ± SD)			
Gait speed (m/s)	0.93 ± 0.19	1.01 ± 0.22	1.03 ± 0.22	**F(2,24) = 5.626, p = 0.010**
Stride Length (m)	1.07 ± 0.15	1.12 ± 0.19	1.13 ± 0.18	**F(2,24) = 5.914, p = 0.008**
Cadence (strides/s)	0.87 ± 0.10	0.90 ± 0.07	0.90 ± 0.09	F(2,24) = 2.635, p = 0.124
Maximal ankle dorsiflexion (°)	17.19 ± 4.96	17.87 ± 4.72	16.92 ± 5.13	F(1.16,13.87) = 0.734, p = 0.426*
Maximal ankle plantarflexion (°)	4.70 ± 6.65	3.61 ± 5.43	3.71 ± 4.83	F(2,24) = 0.414, p = 0.666
Ankle ROM (°)	21.89 ± 5.01	21.48 ± 3.94	20.63 ± 3.02	F(2,24) = 0.826, p = 0.435
Foot angle at initial contact (°)	11.91 ± 3.37	12.30 ± 3.63	11.07 ± 3.62	F(2,24) = 2.599, p = 0.095
Peak ankle torque (Nm/kg)	1.24 ± 0.20	1.28 ± 0.18	1.25 ± 0.18	F(2,24) = 1.288, p = 0.294
Peak ankle power (W/kg)	1.99 ± 0.60	2.30 ± 0.74	2.35 ± 0.79	**F(2,24) = 7.958, p = 0.002**
Negative work (J/kg)	0.17 ± 0.05	0.19 ± 0.04	0.19 ± 0.05	F(2,24) = 2.834, p = 0.079
Positive work (J/kg)	0.18 ± 0.04	0.20 ± 0.04	0.19 ± 0.05	**F(2,24) = 4.104, p = 0.029**
GRF angle (°)	79.54 ± 4.00	78.84 ± 4.46	79.06 ± 3.81	F(2,24) = 0.886, p = 0.426

*Bold values indicate statistical significance. *Sphericity not assumed, Greenhouse-Geisser test used. GRF angle: angle of the ground reaction forces with respect to the horizontal in the plane of progression at peak ankle power.*

Although peak ankle torque did not differ between the assessments (F(2,24)=1.288, p=0.294), there was a significant difference for peak ankle power (F(2,24)=7.958, p=0.002), with increased peak powers at 4 weeks (t(12)=-3.215, p=0.007) and at 18 weeks (t(12)=-3.648, p=0.003) after BTX-A treatment (figure 2C). No differences between the assessments were found for negative work (F(2,24)=2.834, p=0.079; figure 2D). In contrast, positive work did differ between the assessments (F(2,24)=4.104, p=0.029), with higher positive work at T1 (t(12)=-2.784, p=0.017) and T2 (t(12)=-2.241, p=0.045) compared to baseline (figure 2E). There were no *time* effects for GRF angle at maximal ankle power (F(2,24)=0.886, p=0.426).

FIGURE 2. Gait velocity (A), stride length (B), peak ankle power (C), negative work (D) and positive work (E) of the patients at T0, T1 and T2. *Indicates post-hoc significant effect of time.



Group differences between HSP and control

Table 3 summarizes the group results for all variables. The preferred gait speed of patients at baseline was similar to the slow gait speed of healthy controls (t(21)=1.035, p=0.312). Patients walked with shorter stride lengths (t(21)=2.990, p=0.007) than healthy controls, while cadence was higher in patients compared to controls, but the latter difference did not reach significance (t(21)=-1.559, p=0.134).

No group difference was found for maximal ankle dorsiflexion angle (t(14.586)=-1.357, p=0.195), but patients had lower maximal ankle plantarflexion angles than healthy controls (t(21)=-2.979, p=0.007). As a result, the total ankle ROM was lower in patients compared to controls (t(19.299)=2.947, p=0.008). Furthermore, foot angles at initial contact were smaller in patients than in healthy controls (t(21)=5.843, p<0.001).

TABLE 3. Outcomes for between-subjects comparisons

	HSP-T0	**Controls**	**Independent samples t-test**
	(mean ± SD)		
Gait speed (m/s)	0.93 ± 0.19	1.00 ± 0.11	t(21)=10.035, p=0.312
Stride Length (m)	1.07 ± 0.15	1.24 ± 0.10	**t(21) = 2.990, p = 0.007**
Cadence (strides/s)	0.87 ± 0.10	0.81 ± 0.06	t(21) = -1.559, p = 0.134
Maximal ankle dorsiflexion (°)	17.19 ± 4.96	15.22 ± 1.45	t(14.586) = -1.357, p = 0.195*
Maximal ankle plantarflexion (°)	4.70 ± 6.65	11.50 ± 3.12	**t(21) = -2.979, p = 0.007**
Ankle ROM (°)	21.89 ± 5.01	26.73 ± 2.75	**t(19.299) = 2.947, p = 0.008***
Foot angle at initial contact (°)	11.91 ± 3.37	19.40 ± 2.26	**t(21) = 5.843, p < 0.001**
Peak ankle torque (Nm/kg)	1.24 ± 0.20	1.48 ± 0.09	**t(17.270) = 3.844, p = 0.001***
Peak ankle power (W/kg)	1.99 ± 0.60	2.80 ± 0.40	**t(21) = 3.630, p = 0.002**
Negative work (J/kg)	0.17 ± 0.05	0.19 ± 0.04	t(21) = -1.116, p = 0.277
Positive work (J/kg)	0.18 ± 0.04	0.25 ± 0.03	**t(21) = 4.850, p < 0.001**
GRF angle **(°)**	79.54 ± 4.00	75.39 ± 1.87	**t(21) = -3.026, p = 0.006**

*Bold values indicate statistical significance. *Equal variances not assumed. GRF angle: angle of the ground reaction forces with respect to the horizontal in the plane of progression at peak ankle power*

Both peak ankle torque and peak ankle power were lower in patients compared to healthy controls ($t(17.270)=3.844$, $p=0.001$ and $t(21)=3.630$, $p=0.002$, respectively). No group difference was observed for negative work ($t(21)=-1.116$, $p=0.277$), but patients generated less positive work than controls ($t(21)=4.850$, $p<0.001$). Lastly, the GRF angles at maximal ankle power of patients were more vertically oriented than those of controls ($t(21)=-3.026$, $p=0.006$).

Discussion

The results of this study do not corroborate our hypothesis that the increase in comfortable gait speed observed after BTX-A treatment and subsequent stretching of spastic calf muscles in patients with HSP was associated with reduced negative work during the loading and/or midstance phase of gait due to improved ankle dorsiflexion movement. Only one previous study has addressed changes in midstance kinetics after BTX-A injections in the calves and reported a decrease in peak negative work in children with spastic CP [173]. This treatment was, however, combined with a 1.5 ± 0.5 months rehabilitation program for at least three days a week, which makes it difficult to compare the results with the current findings. The lack of changes in ankle dorsiflexion angles that we observed is also not in line with several studies in patients with stroke and CP that did report improved ankle dorsiflexion movements after BTX-A treatment (for review, see [180,181]). However, in the majority of studies that investigated both ankle dorsiflexion angles and gait speed [167,171-177,182-184], improvements in dorsiflexion angles were not accompanied by an increase in gait speed [167,172-174,176,183,184], whereas another study reported higher gait speeds in the absence of improvements in ankle dorsiflexion angles [171]. Hence, it seems unlikely that improved ankle dorsiflexion movement during the stance phase of gait and/or reduced energy absorption at the ankle importantly underlie improvements in gait speed following BTX-A treatment.

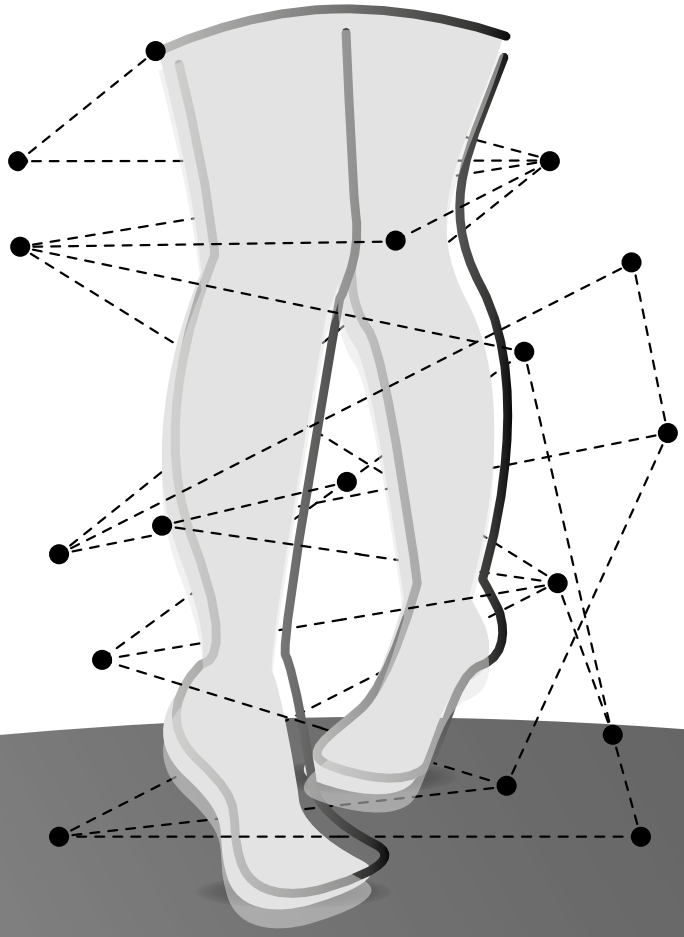
Surprisingly, we did not find a decrease but an *increase* in positive work (+11% at T1) during the late stance phase of gait after BTX-A treatment in our patients, which coincided with improved peak ankle power (+16% at T1), increased stride length (+5% at T1), and increased comfortable gait speed (+9% at T1), while cadence remained constant. A previous study on BTX-A treatment of the calf muscles in patients after stroke showed similar results, with an increase in both peak power and gait speed [177]. Indeed, in healthy people greater late-stance ankle power generation is strongly

associated with higher gait speed [185], which suggests that a similar mechanism may have been at work in our present study. Yet, it may not be the only mechanism underlying improvements in gait speed, as another study on BTX-A treatment of the calves in children with CP reported a higher gait speed in the absence of greater peak ankle power [175].

When the patients with pure HSP in our study were compared to healthy controls, several kinematic and kinetic variables were deviant, such as ankle plantarflexion angle, peak ankle torque, peak ankle power, positive work and the GRF angle at maximal ankle power, which underlines the potential for improvement of the ankle dynamics in our patients. The observed improvement of ankle dynamics after BTX-A treatment in the present study may – nonetheless – be considered as counterintuitive, given the fact that BTX-A causes a presynaptic block of the neuromuscular junctions. This might coincide with some loss of maximal muscle strength besides a reduction of muscle tone. Indeed, in our previous study [9], we observed a slight temporary decrease in calf muscle strength on clinical examination (MRC scale), but this result was not confirmed by quantitative muscle strength assessment. Hence, the loss of calf muscle strength after BTX-A treatment (if any) may be negligible. In contrast, the current study shows that peak ankle power and positive work during late stance actually *increased* after BTX-A treatment. Since peak ankle torque remained constant, the observed increase in peak ankle power (torque · angular velocity) suggests enhanced ankle plantarflexion *velocity* underlying the improved ankle dynamics. Possibly, muscle tone reduction due to BTX-A injections provides a better basis for efficient muscle recruitment, leading to faster concentric calf muscle contraction during push-off [165]. This notion would imply that the common fear of clinicians that BTX-A treatment of calf muscles may induce clinically troublesome loss of knee stability or reduced push-off power during gait might not be justified, but more well-focused research is needed to further underscore this notion.

Interestingly, the observed improvements of positive work, peak ankle power, stride length and gait speed were not restricted to the first assessment 4 weeks after BTX-A treatment, but were all retained at the second assessment 18 weeks after treatment. This pattern of results implies that improvements in ankle dynamics after BTX-A treatment for calf muscle spasticity may reach beyond the typical 'period of BTX-A effectiveness' of three to four months. Possibly, the intensive stretching regime that was performed by the patients during the entire 18-week follow-up is responsible for this long-lasting result of BTX-A treatment, as repetitive muscle stretch may have a modulating (inhibiting) effect on muscle tone as well [186].

A limitation of this study is that we focused on the kinematics and kinetics of the *ankle joint*, where concurrent dynamic changes at the hips may have occurred that might have contributed to (or perhaps hampered) comfortable gait speed after BTX-A treatment of the calves. Indeed, it has been shown that generation of e.g. ankle and hip power are interrelated in healthy subjects [187]. Another limitation is that the current study only investigated changes in ankle dynamics after *one cycle* of BTX-A treatment. The observed improvements may therefore not be generalized to the effects of multiple treatment cycles over several months or years, such as is common in clinical practice. The present results may not be generalized to other patient groups either. They do, however, warrant more extensive mechanistic and clinical research into the (long-term) functional effects of BTX-A treatment in order to obtain a better understanding of why and how this treatment may be functionally beneficial to patients with spastic gait disorders.



CHAPTER 7

Functional effects of botulinum toxin type A in the hip adductors and subsequent stretching in patients with hereditary spastic paraplegia.

PUBLISHED AS

van Lith BJH, den Boer J, van de Warrenburg BPC, Weerdesteyn V, Geurts AC. Functional effects of botulinum toxin type A in the hip adductors and subsequent stretching in patients with hereditary spastic paraplegia. Journal of Rehabilitation Medicine (2019) 51:434-441.

Abstract

Objective

To investigate the functional effects of bilateral botulinum toxin A (BTX-A) treatment and subsequent stretching of spastic hip adductors on gait and reactive lateral stepping responses in patients with pure hereditary spastic paraplegia (HSP).

Design

Explorative pre-post intervention study

Patients

Twenty-five patients with pure HSP

Methods

Patients were treated with bilateral BTX-A injections in the hip adductors and performed daily self-administered stretching exercises for 16 weeks. Before the intervention (T0), and 6 (T1) and 16 (T2) weeks thereafter, we assessed gait width, gait speed, and leg angles at first stepping-foot contact after lateral balance perturbations, as well as the corresponding success rates of reactive lateral steps.

Results

Compared to baseline, gait width increased by 12.6% and 9.7% and comfortable gait speed by 8.3% and 11.5% at T1 and T2, respectively. In known perturbation directions, leg angles increased by 5.9% at T1 and 8.0% at T2, while success rates increased from 70% at baseline to 90% at T1 and T2. No effects were found for maximal gait speed or lateral stepping responses in unknown perturbation directions.

Conclusions

BTX-A treatment and subsequent stretching of the hip adductors may improve gait and reactive lateral stepping in patients with pure HSP.

Introduction

Patients with pure hereditary spastic paraplegia (HSP) show a slow, retrograde axonal degeneration of the corticospinal tract, which leads to bilateral progressive lower extremity spasticity. Although muscle strength and somatosensation are often affected as well, the degree of paresis and sensory loss is usually milder than in other conditions with spastic paraparesis (e.g. spinal cord injury or multiple sclerosis) [8,9]. Hip adductor spasticity is often prominently present in patients with pure HSP. Besides loss of gait propulsion and balance deterioration in the plane of progression,[8,188] patients are usually troubled by frontal-plane imbalance as well, to which hip adductor spasticity is suggested to be an important contributing factor [75]. This may be explained by spasticity of the hip adductors leading to forced, spontaneous narrowing of the base of support while standing and walking ('scissoring'). In addition, HSP patients may experience difficulties stepping sideways to recover from a lateral balance perturbation, as the hip abductors have to overcome the involuntary activity of the spastic hip adductors. The small base of support in combination with the presumed side-stepping difficulties likely increase the risk of falling in HSP patients.

Botulinum toxin type-A (BTX-A) injections are commonly used for reducing spasticity in HSP patients[9,65,76,93,189], although BTX-A is still on off-label prescription in HSP for all commercially available toxins. BTX-A treatment of the hip adductors, calf muscles and hamstrings has been suggested to lead to functional improvements in balance and gait capacities [75,189]. However, despite the high prevalence of hip adductor spasticity in HSP patients, there are no studies that have systematically investigated the effects of BTX-A injections in these muscles, neither on clinical indicators of spasticity, nor with respect to balance and gait capacity. In a few previous studies with limited numbers of HSP patients, the hip adductors were injected in some of the participants (n=5 to 12), yet often in combination with other muscle groups (i.e. calves, tibialis posterior, iliopsoas and rectus femoris) [65,93,94]. Furthermore, these studies did not include stretching exercises following BTX-A treatment, as recommended by international consensus [5]. Hence, the specific effects of BTX-A injections in the hip adductors with subsequent stretching exercises remain to be established.

In this exploratory study, we focused on the effects of BTX-A injections in spastic hip adductors and subsequent stretching exercises in patients with pure HSP, using two primary outcomes: (1) gait width and (2) the quality of sideways reactive step-

ping responses following lateral balance perturbations. In addition, comfortable and fast gait speed, success rates of the lateral stepping responses, and various clinical (physical and functional) tests served as secondary outcome measures. The physiological effect of BTX-A usually reaches its maximum 6 weeks after the injections [178] and diminishes progressively until about 16 weeks after the injections. Therefore, we hypothesized that reduced hip adductor tone would translate in improvements in both gait width and lateral stepping at 6 weeks post treatment, whereas a reduction of these effects was expected at 16 weeks after treatment.

Methods

Participants

Participants were recruited from all patients with HSP and hip adductor spasticity known at the expert centre for genetic movement disorders of our university hospital. In addition, active recruitment took place through the national patient organisation "Spierziekten Nederland". Inclusion criteria were: (*1*) a 'pure' form of autosomal dominant HSP (either genetically proven, or based on family history); (*2*) 18 years or older; (*3*) bilateral hip adductor spasticity (Modified Ashworth Scale (MAS) score 1-4); (*4*) balance- and/or gait-related activity limitations in daily life; (5) able to walk > 50 m independently with (adapted) shoes and/or orthoses (but without walking aids such as crutches or a walker); and (*6*) comfortable gait velocity > 0.4 m/s. Participants were excluded if they suffered from cognitive impairments or from any comorbidity affecting their gait capacity. In addition, the last BTX-A treatment of the hip adductors should have been administered longer than 6 months before the first measurement. Regular BTX-A treatments of other muscle groups should have been performed either within 3 to 4 weeks or longer than 4 months before the first measurement in order to have either an optimal or otherwise an absent effect of these prior injections during the study period.

For participants recruited at the outpatient departments, all inclusion criteria were checked by the attending physician. Participants who responded to the recruitment letters via the patient organisation were interviewed by telephone by the primary investigator to check inclusion criteria *1, 2,* and *4*, whereas inclusion criteria *3, 5* and *6* were checked by a physiotherapist at the first visit for the study. Out of 75 patients,

25 patients fulfilled the inclusion criteria and were included. Their demographic and clinical characteristics are listed in Table 1.

TABLE 1. Patient characteristics at T0

			Number of patients
Sex; male/female			12/13
Gene	*SPG-4*		12
	SPG-10		2
	SPG-17		1
	SPG-31		2
	AD, genotype not confirmed		8
			Median (range)
Tibialis anterior	MAS		0 (0-1)
	MRC		5 (2-5)
Triceps surae	MAS	knee extended	2.5 (1-4)
		knee flexed	2.5 (0-4)
	MRC		5 (2-5)
Hip adductors	MAS		3 (1-4)
	MRC		5 (2-5)
Hip abductors	MRC		5 (2-5)
BBS			49.5 (27-56)
			Mean (range)
Age			53.5 (26-72)
Hip abduction	ROM		38.8 (20.0-52.5)
6MWT			367.5 (196-515)
TUG			11.1 (6.3-23.0)
ABC			49.83 (17-95.3)

AD: autosomal dominant inheritance; MAS: Modified Ashworth Scale; MRC: Medical Research Council scale; BBS: Berg Balance Scale; ROM: range of motion; 6MWT: 6-min Walk Test; TUG: Timed Up and Go test; ABC: Activities-specific Balance Confidence scale

Ethics statement

All subjects gave their written informed consent prior to participation. The study was approved by the regional medical-ethical committee and conducted in accordance with the Declaration of Helsinki. Due to lack of prior research on gait width and quality of reactive sidesteps in patients with HSP, no formal power calculation could be performed. Given the exploratory nature of our study, a required number of 25 patients seemed optimal, feasible and justified, and was agreed upon by the medical ethical committee.

Intervention

Each participant was treated with bilateral BTX-A injections in the hip adductors by one of three rehabilitation physicians of our university hospital. A solution of 100 U Xeomin® per 5 ml saline 0.9% was used. A dose of 150 or 200 U per leg was injected, depending on the degree of hypertonia (Modified Ashworth Scale (MAS) 1: 150 U; MAS ≥2: 200 U). The BTX-A was distributed over the gracilis, adductor magnus and adductor longus muscles according to table 2. Muscle selection was based on muscle volume and its moment arm with respect to the hip joint. Thigh length was measured from the pubic bone to the medial femoral condyle and thigh length percentages were calculated from the pubic bone (see Figure 1). All BTX-A injections were placed under ultrasound guidance.

FIGURE 1. Schematic view of injection locations in percentages thigh length from the pubic bone to the medial femoral condyle. At the indicated thigh lengths, BTX was injected into adductor longus (L), adductor magnus (M) and gracilis (G).

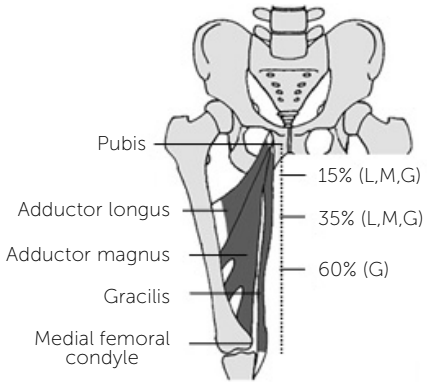


TABLE 2. Distribution of botulinum toxin per leg

	Percentage	Units/ml	
	thigh length*	MAS 1	MAS ≥2
Gracilis	15%	15/0.75	20/1.00
	35%	15/0.75	20/1.00
	60%	15/0.75	20/1.00
Adductor Magnus	15%	30/1.50	40/2.00
	35%	30/0.75	40/2.00
Adductor Longus	15%	30/1.50	40/2.00
	35%	15/0.75	20/1.00

** Upper leg length was calculated from pubis bone to medial femoral condyle.*
Thigh-length percentages were expressed from pubis.

During the 16-week study period, participants were instructed to perform stretching exercises of the hip adductors (with the hips both flexed and extended) for approximately 10 minutes, three times per day, and to log their exercises in a diary. The exercises were individually demonstrated and instructed by a physiotherapist at the day of the BTX-A injections until each participant was able to correctly perform the exercises independently.

Outcome measures

Instrumented gait assessments

For instrumented gait assessment, the GAITRite system was used (CIR Systems, Inc., Sparta, NJ), which is a 4.88 meters long carpeted walkway that contains pressure sensors that detect the position of each footfall [190]. Participants started at one end of the GAITRite and were instructed to walk three times across the walkway with (adapted) shoes and/or orthoses at their preferred speed. Subsequently, they walked three times across the walkway at their maximal speed without risking a fall. For each step, gait width was determined by the GAITRite system (which is stored as 'stride width') and exported to Microsoft Excel. For each participant, the median gait width of all steps was calculated to avoid a disproportional influence of a single outlying step. Gait width was determined for both the preferred (primary outcome) and maximal gait speed. In addition, the mean preferred and mean maximal gait speed of the three trials was calculated.

Instrumented dynamic balance assessments

For instrumented dynamic balance assessments, the Radboud Falls Simulator was used (RFS). The RFS is a moveable platform (240 x 174 cm; BAAT, Enschede, The Netherlands [6]) that can translate in multiple directions. In this way, perturbations can be imposed that mimic natural situations. In this study, only sideways perturbations were used, where a leftward platform translation resulted in a rightward balance perturbation and vice versa. In the remainder of this text, we consistently refer to the direction of the balance perturbations.

At the start of each measurement, participants were instructed to sustain all perturbations by making a single lateral step without grabbing the handrails, while the perturbation direction was known to the participants. All participants wore a safety harness attached to the ceiling that prevented them from falling. In addition, a railing system was present at both sides that participants could grab in the case of a fall. At the first measurement (T0), participants were exposed to increasing perturbation intensities that started at 0.125 m/s^2 and were increased by at least 0.125 m/s^2 between trials. The maximum perturbation intensity that each participant could successfully sustain with a *single* step at least once out of three trials (without falling or grabbing the railing system) defined the individual limit of stability. To familiarize them with the test situation, during the subsequent measurements (T1 and T2), participants were again exposed to at least 15 incremental perturbation intensities until their individual limits of stability were reached.

During all measurements each participant was twice (randomly) exposed to five leftward and five rightward perturbations at their individual limits of stability. During the first 10 perturbations, the perturbation direction was known to the participant, whereas during the last 10 trials the perturbation direction was unknown. These 20 trials were used for statistical analysis.

During all balance assessments, kinematic data were recorded by an 8-camera 3D motion analysis system (Vicon Motion Systems, UK) at a sample rate of 100 Hz. Reflective markers were placed at anatomical landmarks according to the full-body PlugInGait configuration [179]. For all trials in which the participant succeeded to make a sidestep following the perturbation, the leg angle (primary outcome) was calculated at the instant of stepping-foot contact, as the body configuration at step contact appears to critically determine the successfulness of balance recovery responses [191]. The leg angle was defined as the angle between the absolute vertical and a line

connecting the mid-pelvis and the ankle marker of the stepping foot. The medians of the five right and five left leg angles were calculated to avoid a disproportional influence of a single outlying value. These medians were averaged for each person into a single leg angle score for the perturbations with known and unknown directions separately. Furthermore, the success rates of the lateral stepping responses were calculated for the perturbations with known and unknown directions separately. A trial was scored as successful if the participant maintained balance with a single sidestep.

Physical tests

Muscle strength of the hip adductors and hip abductors was assessed with the Medical Research Council (MRC) scale (0-5) with lower scores indicating more muscle weakness [51]. Muscle tone of the hip adductors was assessed using the MAS (0-5) with higher scores indicating more hypertonia [49]. Furthermore, passive range of motion (ROM) on hip abduction was measured using a goniometer. All outcomes were averaged for both sides into a single score.

Functional tests

Functional balance was assessed barefooted with the Berg Balance Scale (BBS, range 0-56) [192]. The Timed Up and Go (TUG) test) [193] was performed with (adapted) shoes and/or orthoses, but without other walking aids. Endurance was assessed with the 6-min Walk Test (6MWT),[194] during which all walking aids were allowed. Lastly, the Activities-specific Balance Confidence (ABC) scale [195] was obtained as a subjective measure of mobility and balance.

Procedure

All outcome measurements were performed on the day of treatment prior to the injections (baseline; T0), 6 ($\pm$1) weeks after treatment (T1), and 16 ($\pm$1) weeks after treatment (T2). T1 was set at 6 weeks after treatment, because at this point in time the physiological effects of BTX-A on spasticity were expected to have reached a maximum [178]. The effects of BTX-A were expected to diminish progressively until about 16 weeks after the injections. Hence, T2 was set at 16 weeks post treatment to test the possible presence of a long-term effect of the combined treatment. The instrumented assessments were taken by the primary investigator. All other tests were assessed by an independent physiotherapist.

Statistical analysis

All instrumented (parametric) outcome measures were tested using repeated-measures ANOVA. The primary outcomes gait width and sidestep leg angle were tested using *time* (*T0 – T1- T2*) as within-subjects factor. For gait width and gait speed, also *gait condition* (*preferred – maximal*) was introduced as a within-subjects factor. We applied Bonferroni corrected post-hoc tests in the case of a significant main effect of *time*. All other (non-parametric) outcome measures (physical and functional tests) were analyzed with a Friedman's test using *time* (*T0 – T1 – T2*) as a within-subject factor. Wilcoxon's tests were used for post-hoc comparisons in the case of a significant *time* effect. All statistical analyses were performed using IMB SPSS Statistics Version 22 for Windows. The α-level was set at 0.05 for all analyses, with no adjustment for multiple outcomes.

Results

Participants

From the total of 25 patients included in the study, three patients were lost between the first (T0) and the second measurement (T1): one patient suffered from increasing shoulder complaints that were already present before the first visit. One patient was lost due to spontaneous severe back pain, which had also repeatedly occurred in the past. A third patient left the study due to personal circumstances. No other adverse events occurred during the study.

Instrumented gait assessments

Table 3 summarizes the group results for all measurements. There was a significant *time* effect on gait width ($F(2,42)=6.143$, $p=0.005$). Gait width increased by 12.6% from baseline to T1 ($p=0.021$), and this improvement persisted at T2 (9.7%; $p=0.022$) (see figure 2a). There was no effect of *gait condition* on gait width ($F(1,21)=1.229$, $p=0.280$), nor was there a significant *time x gait condition* interaction ($F(2,42)=1.081$, $p=0.349$).

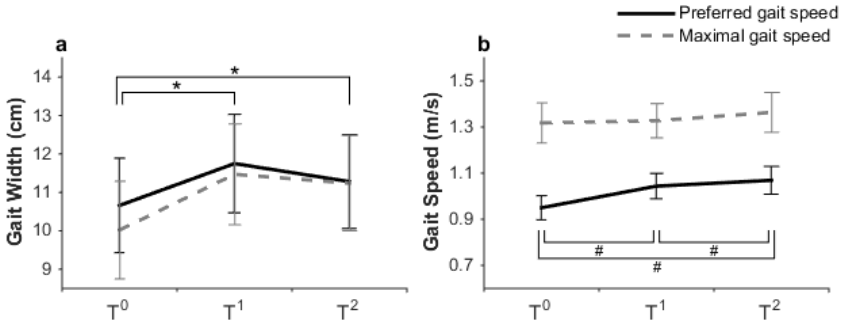
TABLE 3. Outcomes measures

Test	T0	T1	T2	Friedman's test or repeated-measures ANOVA	p-value
	Mean (SD)[95% CI] or median [IQR]				
GaitRite					
Gait width - preferred speed (cm)	10.7 (5.8)[8.1-13.2]	11.8 (6.0)[9.1-14.4]	11.3 (5.7)[8.7-13.8]	F(2,42)=6.143	p=0.005[a]
Gait width - maximal speed (cm)	10.0 (6.0)[7.4-12.7]	11.5 (6.1)[8.8-14.2]	11.2 (5.8)[8.7-13.8]		
Comfortable gait speed (m/s)	0.96 (0.25)[0.85-1.07)	1.04 (0.26)[0.93-1.16]	1.07 (0.28)[0.94-1.20]	F(2,42)=15.265	p<0.001[b]
Maximal gait speed (m/s)	1.31 (0.41)[1.14-1.50]	1.33 (0.35)[1.17-1.48]	1.36 (0.41)[1.18-1.54]	F(2,42)=1.140	p=0.330
Radboud Falls Simulator					
Leg angle - known dir	18.7 (4.1)[16.7-20.7]	19.8 (3.8)[17.9-21.6]	20.2 (4.1)[18.2-22,1]	F(2,32)=8.568	p=0.001[a]
Leg angle - unknown dir	19.1 (4.7)[16.3-22.0]	19.3 (4.7)[16.5-22.2]	19.4 (5.2)[16.3-22.6]	F(2,24)=0.107	p=0.899
Success rates - known dir (%)	70.0 [45.0]	90.0 [30.0]	90.0 [45.0]	χ^2(2, n=21)=12.559	p=0.002[c]
Success rates - unknown dir (%)	25.0 [55.0]	35.0 [72.5]	45.0 [70.0]	χ^2(2, n=22)=4.388	p=0.111
Clinical assessments					
MAS - Hip adductors	2.5 [1.3]	1.0 [1.5]	1.8 [1.0]	χ^2(2, n=22)=33.890	p<0.001[d]
MRC - Hip adductors	5.0 [0.0]	4.0 [1.0]	5.0 [0.3]	χ^2(2, n=22)=15.800	p<0.001[e]
MRC - Hip abductors	5.0 [0.1]	5.0 [1.0]	5.0 [0.0]	χ^2(2, n=22)=4.957	p=0.084
ROM - Hip abduction	38.8 (9.4)[34.6-42.9]	50.7 (12.5)[45.2-56.2]	45.0 (10.8)[40.2-49.8]	F(2,42)=31.613	p<0.001[f]
Other functional tests					
BBS	49.5 [10.0]	51.5 [9.0]	51.0 [7.8]	χ^2(2, n=22)=4.031	p=0.133
TUG (s)	10.6 (3.8)[8.6-12.6]	10.7 (4.2)[8.6-12.9]	10.5 (4.3)[8.3-12.7]	F(2,42)=0.198	p=0.821
6MWT (s)	367.5 (87.9)[322.3-412.7]	376.0 (95.8)[327.0-425.2]	382.1 (95.2)[333.2-431.0]	F(2,32)=2.498	p=0.098
ABC scale (%)	55.0 (21.85)[43.8-66.2]	54.7 (22.8)[43.0-66.4]	51.5 (23.7)[39.3-63.6]	F(2,42)=2.048	p=0.142

a = T0<T1/T2, T1=T2; b = T0<T1<T2; c = T0 < T1, T0 = T2, T1 = T2; d = T0 > T2 > T1; e = T0/2 > T1, T0 = T2; f = T0<T2<T1. MAS: Modified Ashworth Scale; MRC: Medical Research Council scale; ROM: range of motion; BBS: Berg Balance Scale; TUG: Timed Up and Go test; 6MWT: 6-min Walk Test; ABC: Activities-specific Balance Confidence scale; dir = direction

There was also a significant *time* effect on gait speed (F(2,42)=5.458, p=0.008) as well as a significant *time x gait condition* interaction (F(2,42)=5.399, p=0.008). Compared to baseline, the preferred gait speed had increased by 8.3% at T1 (p=0.001) and by 11.5% at T2 (p<0.001). In contrast, no significant changes from baseline were observed in the maximal gait speed (figure 2b).

FIGURE 2. Gait width (a) and gait speed (b) at three measurements (T0, T1, T2) for preferred and maximal gait speed (gait condition). *indicates significant post-hoc effects of time for gait width. #indicates significant post-hoc effects of time on preferred gait speed.

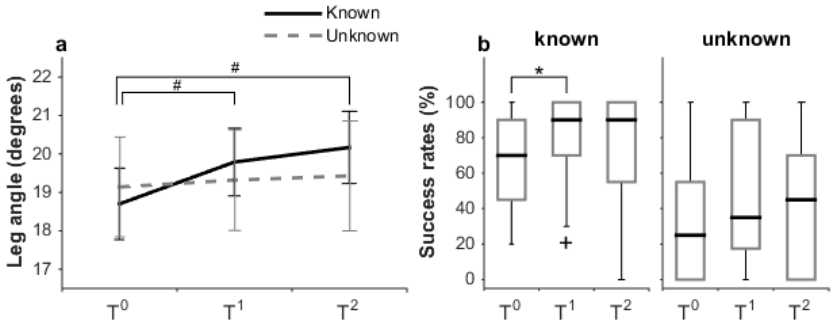


Instrumented balance assessments

Changes in leg angles across time could only be statistically tested if side steps were made at all measurements (T0-T2). As some participants failed to make any side steps (i.e. only made cross steps) or grabbed the railing system before stepping, a total of 19 participants could be included in the analysis of trials with known perturbation direction and 13 in the analysis of trials with unknown directions. The mean limit of stability was 2.135 m/s^2 (range 0.375 m/s^2 - 4.375 m/s^2).

For the known direction perturbations, the leg angle showed a main effect of *time* (F(2,36)=12.053, p<0.001). There was an increase of 5.9% in leg angle from baseline to T1 (p=0.003), which persisted at T2 (8.0%; p=0.001). In contrast, leg angle for the unknown direction perturbations did not show a significant effect of *time* (F(2,24)=0.107, p=0.899) (see figure 3a).

FIGURE 3. Leg angle (a) and success rate (b) at three measurements (T0, T1, T2) for known and unknown perturbation directions. #indicates significant post-hoc effects of time in known perturbation directions. *indicates significant effect of time.



For the known direction perturbations, there was a significant effect of *time* on success rate ($\chi^2(2)=12.559$, $p=0.002$). Compared to the 70% success rate at baseline, participants were more successful at T1 (90%; $p=0.007$), which result tended to persist at T2 (90%; $p=0.075$). For the unknown direction perturbations, no significant effects of *time* were found ($\chi^2(2)=4.388$, $p=0.111$) (see figure 3b).

Physical tests

Hip adductor muscle tone showed a significant *time* effect (χ^2 (2)=33.890, $p<0.001$). The MAS scores decreased from baseline to T1 ($p<0.001$), and subsequently increased from T1 to T2 ($p=0.001$), although they did not reach the baseline values (T0 vs T2, $p=0.001$). Hip adductor muscle strength also showed a significant effect of *time* (χ^2)=15.800, $p<0.001$), as the MRC scores decreased from baseline to T1 ($p=0.005$), and increased from T1 to T2 ($p=0.003$) to baseline values (T0 vs T2, $p=0.480$). Hip abductor muscle strength did not significantly differ between the three measurements ($\chi^2(2)=4.957$, $p=0.084$). Furthermore, there was a significant *time* effect on hip abduction ROM ($F(2,42)=31.613$, $p<0.001$), which increased from baseline to T1 ($p<0.001$) and decreased from T1 to T2 ($p=0.001$), although it was still above baseline values at T2 (T0 vs T2, $p<0.001$).

Functional tests

Because the 6MWT was too demanding for five participants, the analysis was performed on the remaining 17 participants. This analysis showed no significant effect of *time* on the 6MWT ($F(2,32)=2.498$, $p=0.098$). Likewise, the BBS ($\chi^2(2)=4.031$,

p=0.133), TUG (F(2,42)=0.198, p=0.821, and ABC scale (F(2,42)=2.048, p=0.142) did not show significant *time* effects either.

Discussion

The aim of this study was to evaluate the effects of BTX-A treatment and subsequent stretching of the hip adductors on gait and balance capacities in patients with pure HSP. The results support our hypothesis that bilateral BTX-A injections in and subsequent stretching of the hip adductors improve both gait width and lateral stepping responses in known perturbation directions coinciding with reduced hip adductor tone 6 weeks after treatment compared to baseline. These functional effects were retained, although some recurrence of hip adductor muscle tone was found 10 weeks later. In addition, comfortable gait speed increased 6 weeks post injections, which effect was even a bit stronger after 16 weeks. In contrast, maximal gait speed and lateral stepping responses in unknown perturbation directions did not respond to the treatment nor did other functional tests (BBS, TUG, 6MWT, ABC scale).

Besides a prolonged reduction in hip adductor muscle tone lasting up to 16 weeks after treatment, we observed a similar and substantial improvement in hip abduction ROM (on average 13.3°) and a temporary reduction of hip muscle strength (on average 1 point on the MRC scale, 6 weeks after treatment). These findings are in line with several previous studies [9,65,93,94,178,188,189]. The mean improvement of muscle tone at 6 weeks post injections was 1.5 point on the MAS, which can be considered substantial and clinically relevant [196]. Interestingly, the observed temporary loss of muscle strength did not seem to have a detrimental effect on balance and gait capacities, since functional tasks improved (or remained stable) 6 weeks after treatment. This result is in agreement with a previous study from our group[9] and suggests that loss of muscle strength after BTX-A injections in spastic muscles is probably of relatively short duration and without noticeable functional disadvantage.

The observed improvement of gait width was on average 1.1 and 1.5 cm for comfortable and maximal walking speed, respectively, and was probably the direct result of reduced hip adductor tone and improved hip abduction ROM. Remarkably, this effect was found even though comfortable gait speed improved in parallel. It is conceivable that a higher gait speed might coincide with faster leg swing and, thus,

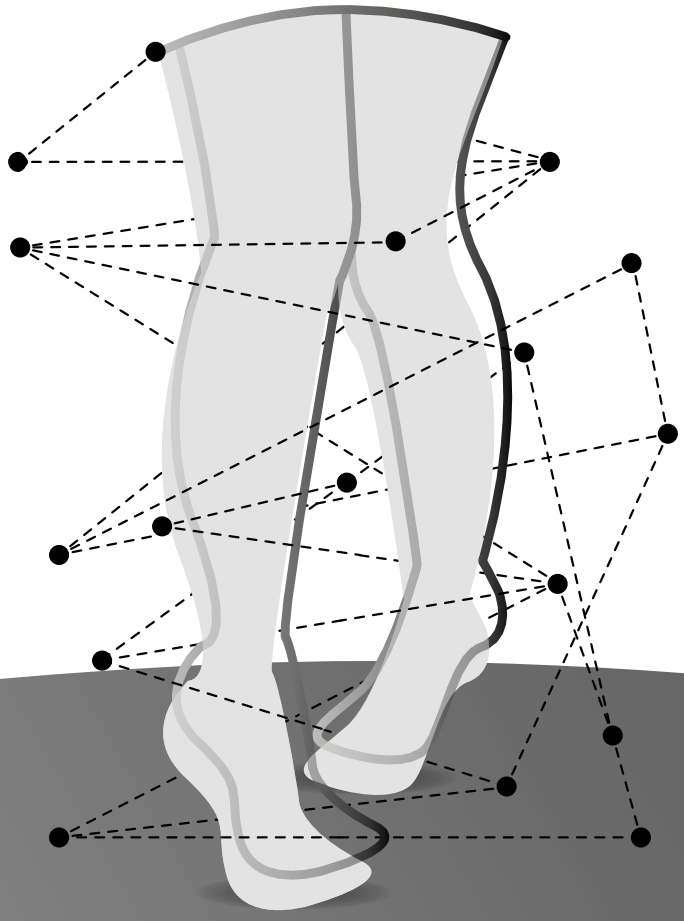
aggravate velocity-dependent hip adductor spasticity, but this effect apparently did not occur. Instead, the reason why comfortable gait speed improved may be that reduced hip adductor tone allowed patients to make larger and/or faster steps. In a prior study of patients with spastic paraparesis of various origins, BTX-A injections in the hip adductors also led to increased gait velocity [197]. In addition, previous studies of patients with HSP in which hip adductors were injected with BTX-A in combination with other muscle groups showed increased gait speed as well [65,93,94]. These findings have important clinical implications as reduced spontaneous gait speed is one of the most frequent problems reported by patients with HSP [56]. Notably, maximal gait speed did not improve after treatment, which is in agreement with the notion that the hip adductors are not the key muscles for gait propulsion [198]. Nevertheless, gait width during walking at maximal gait speed improved even stronger than during comfortable walking, indicating the robustness of the treatment effects on widening the base of support while walking. The observed effect size for gait width in this study may seem small, but it constitutes a 10-15% increase compared to baseline. Hence, the observed increase in gait width of 1.1-1.5 cm may well be clinically relevant in terms of improved frontal-plane balance, but this conclusion needs to be supported by future studies.

To our knowledge, the effects of bilateral BTX-A injections on reactive lateral stepping responses have not been investigated before. In the present study, we only observed beneficial effects on stepping responses to perturbations in known directions. Interestingly, no improvements of stepping leg angle or success rate were observed upon perturbations in unknown directions. As hip adductor spasticity decreases, less muscle activity of the hip abductors is supposedly needed to make a lateral step. One explanation for the observed discrepancy between known and unknown perturbation direction may be that the individual maximal perturbation intensity at baseline was based on tests with a known perturbation direction. As a consequence, the perturbation intensities might have been too high for the participants following perturbations in unknown directions. This may also (partly) explain the much lower number of participants able to sustain perturbations with unknown compared to known directions. Another reason might be that reactive steps following unexpected perturbations are relatively strongly influenced by delayed postural responses that occur in patients with HSP,[23,75] because patients cannot compensate by an anticipatory 'central set' if the direction is unknown. Nevertheless, the improved balance capacity following perturbations in known directions suggests that hip adductor spasticity indeed impairs the quality of lateral stepping responses and, thus, is a relevant treatment target from a frontal-plane balance perspective.

The fact that the beneficial effects on muscle tone, gait width, comfortable gait velocity, lateral balance persisted until 16 weeks after treatment seems to challenge the common opinion that the biological effects of BTX-A have worn off after this time interval. It may, therefore, be that the stretching component of the treatment protocol was responsible for the observed long-term effects.

Study limitations and future perspectives

A limitation of the present exploratory study in patients with HSP is the relatively small sample size and the lack of a control condition, while the rather stringent inclusion and exclusion criteria limit the generalisability of our findings. Nevertheless, this study provides indications for the beneficial effects of bilateral BTX-A injections in the adductor longus, adductor magnus and gracilis muscles and subsequent stretching of these muscles on gait width, comfortable gait speed, and reactive lateral stepping in known perturbation directions, whereas maximal gait speed, gait endurance, and clinical balance scores appear to be less responsive in these patients. Future research should preferably be multi-centered to increase the number of participants and use a randomized controlled design. Gait width and gait speed would be valuable and responsive outcome measures in such trials. The instrumented balance assessments used in the present study are, however, less suitable for multi-center studies as they require further development of clinically affordable systems. Clinically applicable assessments to validly test the quality of (lateral) reactive stepping responses are therefore urgently needed. As HSP is a chronic and progressive condition, it would also be relevant to conduct longitudinal, comparative cohort studies to investigate whether repetitive cycles of BTX-A treatment of spastic hip adductors improve the life-time functional ambulation prognosis in these patients.



CHAPTER 8

Summary and general discussion

Summary

The overall aim of this thesis was to gain more insight into the experienced (motor) problems and objectifiable motor control deficits in patients with pure forms of hereditary spastic paraplegia (HSP), and to evaluate the functional effects of spasticity treatment with botulinum toxin type A (BTX-A) in these patients. In the first part, we provided an overview of the pathophysiology, functional diagnosis, and clinical management of balance impairments and falls in patients with HSP, based on the literature and clinical experience within the Expert Centre for Rare and Genetic Movement Disorders of the Radboud University Medical Center (part of the European Reference Network for Rare Neurological Diseases (ERN-RND)). Next, we zoomed in on the experienced complaints, activity limitations and loss of motor capacities by means of a web-based survey amongst patients with HSP in the Netherlands. In the second part, we investigated some of the underlying motor control deficits in patients with pure HSP related to balance control and gait initiation. In the third part, we examined the functional effects of BTX-A treatment and subsequent stretching of specific spastic muscle groups on balance and gait capacities in patients with pure HSP. Here, the main findings of this thesis are summarized. In the section 'general discussion' of this chapter, the results are placed in a broader perspective and directions for future research are provided.

Part 1: Daily problems of living with HSP

Pathophysiology, functional diagnosis and clinical management

Although balance impairments and falls are both common and devastating in patients with HSP, the underlying mechanisms and possible clinical strategies have received very little attention in the literature. In **chapter 2**, we provided a narrative review that elaborates on the pathophysiology, functional diagnosis, and clinical management of balance impairments and falls in patients with HSP. Four important intrinsic risk factors for balance impairments and falls were identified: spasticity, contractures, muscle weakness, and loss of proprioception. Of these, loss of proprioception and delayed postural responses were considered to be key in causing balance problems, in addition to muscle contractures causing abnormal biomechanical constraints (e.g. pes equinus). The influence of spasticity itself on balance control is probably less

strong, but spasticity was considered to be an important risk factor for the development of muscle contractures. The influence of muscle weakness on balance problems seems to be limited but, together with the slowness of postural responses, it was thought to contribute to impaired feet-in-place as well as to impaired stepping reactions in response to postural perturbations. Based on the four identified risk factors and their interactions, diagnostic and treatment options were discussed.

Experienced complaints, activity limitations and loss of motor capacities

In **chapter 3**, we investigated the experienced complaints, activity limitations, and loss of motor capacities in patients with pure HSP. Treatment in these patients is often focused on reducing spasticity and its physical consequences but, in order to optimally address individual patients' needs, we need to better understand their experienced complaints, activity limitations, and loss of motor capacities. To this end, we developed and distributed an HSP-specific web-based questionnaire amongst Dutch patients with HSP. Of 166 respondents, 109 participants with presumably pure HSP experienced the greatest burden from muscle stiffness and limited standing and walking activities, while 72% reported leg and/or back pain. Thirty-five and 46% reported to use walking aids (e.g. crutches) indoors and outdoors, respectively. Fifty-seven percent reported a fall incidence of at least twice a year ('fallers'), and in 51% a fall had led to an injury at least once. Seventy-three percent reported fear of falling. Duration of spasticity and incapacity to rise from the floor were positively associated with being a 'faller', whereas non-neurological comorbidity and wheelchair use were negatively associated. Higher age, experienced gait problems, not being able to stand for 10 minutes, and incapacity to open a heavy door showed a negative association with being a 'walker without aids' (>500m). The results emphasize the large functional impact of spasticity on the lives of people with pure HSP and contribute to a better understanding of possible targets for rehabilitation.

Part 2: Motor control mechanisms in patients with pure HSP

Influence of hyperexcitable stretch reflexes of the calves on balance control

In **chapter 4**, we studied the role of hyperexcitable short-latency stretch reflexes (SLRs) of the triceps surae muscles on balance control. We exposed 16 patients with pure HSP and 9 healthy controls to 'toes-up' support-surface perturbations at several

intensities, imposed by a rotational platform. Surface electromyography (EMG) data were recorded from the gastrocnemius, soleus and tibialis anterior muscles, and center-of-mass trajectories (CoM) were recorded based on 3-D motion analysis. We hypothesized that exaggerated SLRs in the triceps surae would lead to difficulties in sustaining 'toes-up' perturbations, which would be reflected by an *early* divergence of the CoM trajectories in patients with HSP compared to those of control subjects. We found that the HSP group performed worse in recovering from the perturbations and, as expected, showed hyperexcitable SLRs (40-80ms post perturbation) compared to the control group. In later phases of the postural responses (220-320 ms post perturbation), we observed sustained triceps surae activity in patients with HSP where, in contrast, control subjects showed a suppression of this activity. Only this latter difference in late triceps surae activity corresponded with the instant of divergence of CoM trajectories between patients and controls. Therefore, our hypothesis was not confirmed. Instead, the results corroborated the notion that lack of *late* triceps surae *suppression* may be more important than hyperexcitable *early* SLRs in causing defective balance control after 'toes-up' perturbation in patients with pure HSP.

Differential control of muscle activation and inhibition during gait initiation

Corticospinal lesions cause impairments in voluntary motor control. Previous findings suggested that some degree of voluntary control may be taken over by a compensatory pathway involving the reticulospinal tract. In humans, evidence for this notion mainly comes from StartReact studies. StartReact is the acceleration of reaction times by a startling acoustic stimulus (SAS) simultaneously presented with the imperative stimulus. Previous studies on StartReact mainly focused on isolated single-joint movements. **In chapter 5**, we therefore investigated whether the reticulospinal tract can also be utilized for controlling whole-body movements. Twelve healthy participants and 12 patients with pure HSP performed three consecutive steps in response to an imperative visual stimulus. In 25% of the trials, a SAS was applied. We determined reaction times of muscle (de)activation, anticipatory postural adjustments (APAs) and steps. Without a SAS, we observed an overall delay in patients with HSP compared to controls. Administration of the SAS accelerated muscle onsets in both groups, but more so in the HSP group, resulting in (near-)normal latencies. In contrast, muscle offsets were accelerated in the control group, but not in the HSP group. APAs and step reaction times were accelerated in both groups, but did not normalize in the HSP group. Our results suggest that the reticulospinal tract

seems to be able to play a compensatory role in complex whole-body movements, such as during gait initiation. However, this compensation appears to be suboptimal, as it lacks the capacity to inhibit task-inappropriate muscle activity.

Part 3: Functional effects of BTX-A in patients with pure HSP

Functional effects of BTX-A treatment and subsequent stretching of the calf muscles

A previous study from our group showed an increased comfortable gait speed after BTX-A treatment and subsequent stretching of the triceps surae muscles in 15 patients with pure HSP and with EMG-confirmed troublesome calf muscle spasticity during gait analysis. However, the kinematic and kinetic mechanisms underlying this improvement remained unclear. In **chapter 6** we investigated *how* changes in ankle kinematics and kinetics after the BTX-A treatment led to an increase in comfortable gait speed in this group. Gait analysis data of 13 patients before treatment and 4 and 18 weeks thereafter were used to investigate the changes in ankle kine(ma)tics. For correct interpretation of the results, data were compared with those of 10 healthy age- and sex-matched controls walking at similar speeds. It was found that, parallel to improved gait speed and stride length, peak ankle power and positive work during the late stance phase improved following treatment, whereas no effects were observed on ankle kinematics or negative work during the early-midstance phase of gait. These results suggest that BTX-A treatment and subsequent stretching of the calves in patients with pure HSP may enhance comfortable gait speed by allowing more efficient use of residual calf muscle strength during push-off, leading to increased stride length.

Functional effects of BTX-A treatment and subsequent stretching of the hip adductors

In **chapter 7**, we investigated the effects of BTX-A treatment and subsequent stretching exercises of the hip adductors on balance and gait. Patients with pure HSP often suffer from hip adductor spasticity, causing reduced gait width and a narrow base of support. In addition, they experience difficulties stepping sideways when recovering from lateral balance perturbations. A small base of support and the presumed side-stepping difficulties likely increase the risk of falling in HSP. Botulinum toxin type-A (BTX-A) injections are commonly used to reduce spasticity in patients with

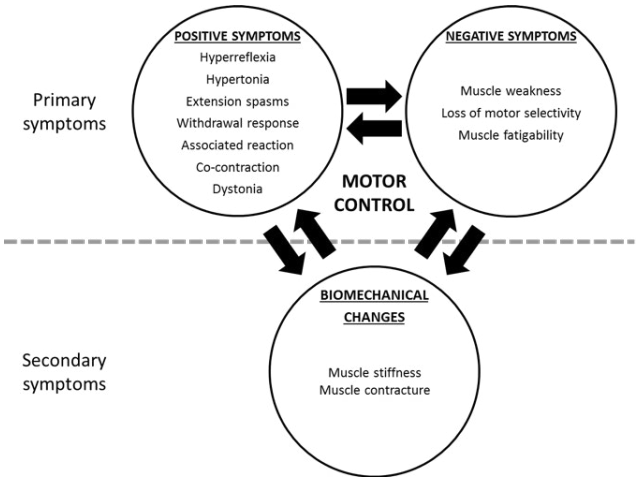
HSP, but no studies have systematically investigated the effects of BTX-A treatment and subsequent stretching of the hip adductors on gait and balance. In this study, 25 patients with pure HSP and clinically established hip adductor spasticity were treated with bilateral BTX-A injections in the hip adductors and performed daily self-administered stretching exercises for 16 weeks. The results indicated that, after BTX-A administration, there was a sustained increase (both 6 and 16 weeks post treatment) in comfortable gait speed and gait width. Furthermore, patients showed sustained improvement of reactive lateral stepping responses (both success rate and quality of stepping), but only when the perturbation direction was known. This study provided the first evidence of beneficial effects of BTX-A treatment and subsequent stretching of spastic hip adductors to improve functional balance and gait in patients with pure HSP.

General discussion

In this thesis, we have used pure HSP as a clinical model to investigate the effects of spasticity on balance and gait and to understand the functional effects of botulinum toxin type A (BTX-A) treatment on these motor capacities. Indeed, as argued in **chapter 2**, spasticity is the cardinal feature of pure HSP, whereas muscle strength is often relatively preserved. The latter observation can be explained by the fact that the reticulospinal tract is able to compensate for loss of voluntary muscle activation by the corticospinal tract; a notion supported by the results of **chapter 5**. However, these results also indicate that the *quality* of this compensatory voluntary motor control is suboptimal due to impaired inhibitory capacity of the reticulospinal tract. Together with the well-known impaired selectivity of spinal motor neuron activation through the reticulospinal tract [161], the feature of abnormally prolonged muscle activation probably underlies some of the characteristic '*positive symptoms*' related to spasticity, such as abnormal muscle co-contractions, associated reactions, or even dystonia. In addition to these and other positive symptoms (such as hyperexcitable muscle stretch reflexes, increased muscle tone upon stretch, and spontaneous muscle spasms), the so-called '*negative symptoms*' (e.g. muscle weakness, slowness of movement) and '*secondary symptoms*' (e.g. intrinsic muscle stiffness, muscle contractures) complete the clinical picture of the spastic paresis (figure 1). This picture is never simple and may actually be very diverse amongst different groups of patients

with spastic paresis and even within the same group of patients, such as those with pure HSP.

FIGURE 5. Schematic overview of primary (positive and negative) and secondary (biomechanical changes) symptoms of spastic paresis. Note that – with regard to motor control – the different types of symptoms interact with each other.



Where both paresis and spasticity are usually severe (and bilateral) in people with (near-)complete spinal cord injury and may also be severe (and unilateral) in people with a cerebral hemisphere lesion (e.g. stroke), people with HSP often show predominant spasticity with relatively mild paresis due to the intactness of the cortico-reticulospinal pathway and other neuronal pathways tracts descending from or via the brainstem [1,36,37]. Yet, secondary symptoms such as increased intrinsic muscle stiffness and muscle shortening are frequently severe and, together with the slowness of voluntary muscle activation and of postural responses, greatly determine the clinical picture of balance and gait problems in people with pure HSP. As spasticity, muscle stiffness, muscle contractures, and slowness of movement often differ in their severity and spatial distribution, they result in a complex clinical picture that is highly variable among individual patients, even if these patients all show phenotypes of so-called 'pure HSP'. This group also shows a large heterogeneity in the underlying genetic deficits [199]. Hence, it is not surprising that people with pure HSP may still show different gait patterns as well as different patterns of postural imbalance, which makes it a challenging condition for clinicians in terms of functional diagnosis and clinical management (see **chapter 2**).

The results of our survey (**chapter 3**) illustrate the variety in experienced complaints, activity limitations and loss of motor capacities in patients with pure HSP. Coherent with the above, muscle stiffness, balance and gait problems, and falls were indicated as most prominent issues by the majority of the participants. Yet, several other symptoms and impairments were reported as well, with impact on functional independence and quality of life, such as a high burden from (leg and/or back) pain, (mental and/or physical) fatigue, fear of falling, and autonomic dysfunction. Likely, chronic pain and fatigue will negatively affect balance and gait capacities and increase fall risk, which provides an argument for targeted treatment of these symptoms. Also, fear of falling should be a specific target from a therapeutic perspective, as it is well known that it is strongly associated with fall risk and often results in physical inactivity, deconditioning, morbidity and, ultimately, mortality [200]. Even autonomic dysfunction might be associated with balance and gait problems and falls, for instance, because urinary urge may cause people to urgently seek a bathroom and take risks.

It is evident that all problems mentioned above interact in a complex way in the life of an individual with HSP, but the remainder of this general discussion will be focused on the motor deficits, balance and gait problems, and their respective treatments. We will do so from the perspective of four topics of debate that are relevant for all people with spastic paresis, but with an emphasis on those with HSP. First, the functional impact of positive versus negative and secondary symptoms of spastic paresis will be discussed. Second, we will address the interplay between corticospinal versus cortico-reticulospinal systems in the voluntary motor control of people with HSP. Third, we will focus on standing balance and compare feet-in-place responses with reactive stepping in response to postural perturbations in people with HSP. Lastly, we will address the functional (net) effects of neuromuscular blockade through intramuscular BTX-A injections regarding, on the one hand, muscle tone and, on the other hand, muscle strength in people with HSP.

Functional impact: positive versus negative and secondary symptoms of spastic paresis

Spasticity was originally defined by Lance (1980) as a velocity-dependent increase in muscle resistance against passive stretch, resulting from hyperexcitable phasic and tonic stretch reflexes [201]. Yet, spastic muscles are also characterized by intermittent or sustained involuntary activation without an apparent stretch upon the muscles, as was recognized in the definition by Pandyan et al in 2005 [202]. Hence, although the term 'spasticity' is commonly used in clinical practice, it remains hard to define

and understand what spasticity exactly is and, also, what its functional impact is in the context of the complete set of symptoms of spastic paresis. Indeed, both definitions of 'spasticity' neglect the concurrent and almost inevitable negative and secondary symptoms. This is remarkable, because the positive, negative and secondary symptoms of spastic paresis strongly interact regarding their functional impact (see Figure 1). For example, positive symptoms, such as muscle overactivity during movement or at rest, may lead to reduced stretch and mobilization of the affected muscles, resulting (in the long term) in secondary symptoms such as non-neurogenic stiffness, adaptive shortening, and eventually muscle contracture. Reversely, there is ample evidence that structurally shortened muscles become more sensitive to stretch, as they reach their threshold for a specific degree of muscle stretch earlier, which may aggravate the already increased stretch reflexes. This interaction leads to what has been referred to in the literature as the 'vicious circle of the stretch-dependent spastic paresis' [203]. Also the positive and negative symptoms interact with each other. For example, loss of motor selectivity (or increased muscular 'synergism') is regarded as a typical negative (deficit) symptom of spastic paresis. Yet, reduced motor selectivity probably contributes to specific positive (excess) symptoms such as abnormal and prolonged co-contractions and associated reactions. Conversely, when an antagonist muscle exhibits a co-contraction due to loss of motor selectivity, the effective strength of the agonist muscle will be reduced, which aggravates the negative symptoms. As a result, the functional impact of positive, negative and secondary symptoms is strongly intertwined, rendering it almost impossible to clearly distinguish their individual effects clinically. Overall, it is believed that the functional impact of the negative and secondary symptoms may even be larger than that of the typical positive symptoms. Nonetheless, spasticity is considered to be an important risk factor for the development of secondary symptoms, as it predisposes to a shortened position of the affected muscles. It is also possible that increased muscle tone negatively affects the contractile properties of the affected muscles, which would imply that it might directly influence the negative symptoms. In fact, evidence for the latter notion was found in **chapter 6**, where we reported that the use of BTX-A in the calf muscles actually improved peak ankle power and positive work during the late stance phase of gait.

The complex interaction between the different symptoms of spastic paraparesis makes it hard to quantify spasticity. Spasticity is often assessed with clinical (ordinal) scales that are based on sensing the resistance against (fast) passive stretch imposed upon muscles, e.g. the (modified) Ashworth Scale (MAS) [49] and the Tardieu test [204].

However, muscle resistance is not only a consequence of neurogenic mechanisms such as activated tonic stretch reflexes, but may also be due to non-neurogenic mechanisms such as increased muscle stiffness. Because neurogenic and non-neurogenic mechanisms cannot easily be discerned in clinical practice [205], many clinicians and researchers prefer the more neutral term 'hypertonia' above the word 'spasticity' when expressing the outcome of clinical scales such as the MAS. In the same vein, the perceived resistance to passive motion (PRPM) test has been proposed as an adaptation to the MAS [206]. The underlying pathophysiologic mechanisms of non-neurogenic muscle stiffness are not yet well understood. On the one hand, changes in the contractile elements of the muscles have been proposed, such as a reduction in the number of sarcomeres and subsequent lengthening of the sarcomeres [207-209]. On the other hand, there is growing evidence that non-contractile muscle elements may play a critical role, i.e. stiffening of extracellular matrix and increase in collagen [210]. With regard to the neurogenic mechanisms underlying muscle stiffness, it becomes increasingly clear that these are strongly influenced by body position, activity, and even context. Indeed, posture may influence the vestibulospinal drive and, thus, modulate the activity of spinal reflexes and motoneuron activation. Physical activity, such as gait, may overrule abnormal resting tone or require compensatory recruitment of cortico-reticulospinal pathways causing non-selective and prolonged muscle co-activations. The (psychological) context may be either safe and familiar or challenging and unfamiliar, which may have a huge impact on the supraspinal modulation of spinal activity through stress-related mechanisms. These insights have gradually shifted the emphasis of assessing spasticity with clinical scales to the quantification of muscle activity using electromyography (EMG) during functional tasks, such as gait. However, EMG itself does not differentiate between normal and abnormal muscle activity, unless the electrical signals are clearly abnormal (e.g. short, 'spiky', bursts of activity). In the same vein, 'abnormal' (e.g. premature) timing of muscle activity may be a normal adaptation to an abnormal gait pattern. For instance, spastic gait is often characterized by forefoot landing, which may coincide with early activation of the calf muscles at the end of the swing phase. But such premature activity is also required if forefoot landing is used as a strategy to deal with impaired ankle dorsiflexion. The same holds for abnormally prolonged muscle activity. For instance, spastic gait may coincide with prolonged activation of the tibialis anterior muscle during midstance, yet this is rarely 'spastic' but rather a functional compensation to facilitate foot roll-off in the case of stiff calf muscles. The bottom line is that 'spasticity' is such a complex phenomenon that it can only be understood

in individual patients when taking into account all positive, negative and secondary symptoms, as well as body posture, physical activity, and (psychological) context, and when integrating this information with data from instrumented movement analysis and from profound knowledge of human motor control.

Voluntary motor control: corticospinal versus cortico-reticulospinal control in HSP

The corticospinal tract originates largely (but not solely) from the primary motor cortex and is the dominant descending pathway for voluntary motor control in humans. It is the primary tract for voluntary muscle activation and force production. Furthermore, it has a function in the presynaptic inhibition and modulation of spinal reflexes and for reciprocal inhibition of antagonist muscles, leading to the capacity to make precise and selective voluntary movements (i.e., fine motor control) [37,211,212]. The degree to which muscles are dependent on corticospinal innervation depends on their location in the human body. Distal muscles of the hand and ankle-foot are much more dependent on direct innervation by the neurons from the *lateral* corticospinal tract than proximal muscles of the shoulder and pelvic girdles, which is why they are more vulnerable to unilateral brain injury and least responsive to functional training. Axial muscles of the trunk and neck are almost exclusively innervated by neurons from the *medial* corticospinal tracts [211,212]. Because these medial tracts are intimately and bilaterally intertwined at different levels of the brainstem and spinal cord, the axial muscles are least vulnerable to one-sided brain injury and most responsive to functional training. Because HSP involves bilateral degeneration of the corticospinal tracts and because the longest neurons are most susceptible to this degeneration, it is not surprising that the clinical picture of pure HSP is characterized by loss of selective motor control and slowness in the lower extremities, complicated by enhanced and poorly modulated spinal stretch reflexes and abnormal muscular co-contractions. These problems are usually strongest in the distal muscles controlling the ankles and feet, but – in more advanced cases – may ascend up to the thigh, pelvic, and even the lower trunk muscles.

In the case of a selective deficit of the corticospinal tract, such as in pure HSP, it is known that the cortico-reticulospinal tract may play a role as a compensatory neural pathway [39,132,134] . Spinal motor neurons to the extremities may be activated particularly by the *lateral* reticulospinal tract originating from the reticular formation in the brainstem. Normally, this tract is considered to support the control of gross and (more or less) 'automatic' movements such as locomotion and balance maintenance as well as to modulate muscle tone at rest and during movement. In HSP,

the lateral reticulospinal tract may become more dominant to also control voluntary single- and multi-joint movements and to assist in generating sufficient force. The compensatory role of the cortico-reticulospinal system for defective corticospinal control has previously been investigated in animals. When the corticospinal tract was lesioned in primates, motor function recovered after a while and the primates were even capable again of climbing in their cages. Intracellular recordings showed that the cortico-reticulospinal systems was involved in the functional recovery after administering corticospinal lesions [37].

In humans, evidence for the compensatory role of the reticulospinal tract after corticospinal injury mainly comes from StartReact studies. The StartReact effect involves the early 'release' of a prepared motor response from the brainstem, evoked by a startling stimulus (usually a loud sound) and conveyed through the reticulospinal tract,. Compared to other upper motor neuron disorders, HSP is a suitable model to investigate this compensatory role of the cortico-reticulospinal tract, given the selective deficit of the corticospinal tract in HSP . Indeed, our group has previously reported that during single-joint movements (voluntary ankle dorsiflexion) as well as during reactive balance responses to a moving platform, people with HSP and healthy subjects showed similar reaction times of the (lower) leg muscles if the primary stimulus was combined with a startling acoustic stimulus (SAS), whereas people with HSP were clearly slower (20-40ms) without a SAS [1,23]. These results strongly support the potential of an intact cortico-reticulospinal tract compensating for a defective corticospinal tract, as the SAS presumably triggered the release of the requested prepared response at the brainstem level. In **chapter 5** of this thesis, we have been able to show that a SAS is also able to facilitate voluntary whole-body movements, such as during gait initiation, in a similar manner and to a similar extent (i.e. normalization). Remarkably, however, the SAS was not able to normalize the offset latencies of the soleus muscle, which implies that the reticulospinal tract lacks the capacity to inhibit task-inappropriate muscle activity.

Thus, the cortico-reticulospinal system may play an important compensatory role in the voluntary motor control of people with HSP, but this compensation comes with several functional limitations. First, dependence on this bypass route leads to delayed voluntary and automatic responses in normal daily life situations, when there is no well-timed SAS available. Together with delayed afferent proprioceptive signals characteristic of pure HSP, this explains why normal, fast and accurate, balance control (both feet-in-place and stepping responses) appears to be slowed down and less

accurate in these people, causing progressive postural imbalance during many daily life activities such as rising from a chair, standing, walking, turning, squatting, stair climbing et cetera. Second, the reticulospinal tract has different projections onto the spinal motoneuron pools compared to the corticospinal tract [161]. Indeed, reticulospinal neurons typically favor the innervation of extensor muscles of the lower limbs (and flexor muscles of the upper limbs). As a result, people with HSP often have relatively preserved muscle strength in the leg extensor muscles, whereas the flexor muscles (tibialis anterior, hamstrings) are weaker. This inborn innervation preference probably explains why people with HSP typically show signs of hyperreflexia and hypertonia in the muscles that typically subserve the so-called 'extension pattern' of the lower limbs: dorsal lower leg muscles (calves, tibialis posterior, toe flexors) and medioventral thigh muscles (quadriceps, adductors). In addition, since the axons of the reticulospinal tract branch way more extensively to motoneuron pools at various levels of the spinal cord than the direct corticospinal neurons [152,213], more muscles are activated simultaneously, leading to a loss of motor selectivity and, thus, loss of fine motor control. Third, as the reticulospinal tract is probably not able to adequately compensate for the loss of reciprocal inhibition by the corticospinal tract, abnormal muscular co-activation of agonists and antagonist is often observed during functional tasks in people with HSP, a phenomenon that probably interacts with the incapacity of the reticulospinal tract to inhibit task-inappropriate muscle activity.

Overall, despite the fact that the cortico-reticulospinal system is able to compensate for the loss of direct corticospinal control in terms of voluntary muscle activation and force production, this compensation comes with a cost: apparent slowness of (alternating) movements, loss of motor selectivity, and abnormal muscular co-contractions that all impair the *quality* of motor control. Although a well-timed SAS is able to resolve the initiation slowness of single- and multi-joint, automatic and voluntary activities, this knowledge is not easily applicable in a clinical tool that can be used in daily life. To what extent intramuscular administration of BTX-A might be able to modulate abnormal muscular co-contractions will be discussed later.

Standing balance: feet-in-place responses versus reactive stepping in HSP

Strategies for standing balance are typically categorized into 'feet-in-place' strategies and 'stepping' strategies. When - after a postural perturbation - balance cannot be maintained within the existing base of support (BOS) (i.e., with a feet-in-place strategy), a stepping strategy is necessary in order to change the BOS in such a way that the accelerated center of body mass (COM) can be displaced over a larger trajec-

tory to keep it within the boundaries of the altered BOS [214]. Stepping strategies may be either voluntary and, thereby, anticipatory (e.g. when making self-initiated movements), or they may be involuntary and reactive (e.g. in response to unexpected external postural perturbations). In this paragraph, we will compare the characteristics of feet-in-place responses with reactive stepping upon external perturbations. For both types of postural responses, a correct timing and amplitude of muscle activation and subsequent muscle deactivation is necessary. When the human body is perturbed in the sagittal plane, e.g. by a sudden movement of the support surface, the first line of defense is a reflexive symmetrical muscle activation, called the automatic postural response (APR), which is presumably conveyed by the reticulospinal tract [215]. When this initial response is unable to keep the COM within the BOS, the next strategy is to make a step in the direction of the perturbation, which requires that many of the activated muscles within the APR in the stepping leg are deactivated to allow this leg to move forward or backward. This stepping strategy may be more dependent on the corticospinal tract [106]. For example, after losing balance in the forward direction, which dorsiflexes the ankles, typically the calves and hamstrings are eccentrically activated to generate a plantar-flexing ankle torque in order to decelerate the falling body and keep the feet in place (the so-called 'ankle strategy'). If, however, balance cannot be maintained with a feet-in-place strategy, the calves and hamstrings must be quickly deactivated and the antagonists (i.e., tibialis anterior and rectus femoris) concentrically activated to ensure a successful step forward as part of the stepping strategy (and vice versa for balance perturbations in the backward direction). For lateral body perturbations, it is equally complex but in a different way. Upon a sideways perturbation, the initial strategy will be to eccentrically recruit the hip abductors on the ipsilateral side to decelerate the imposed weight shift as part of a so-called 'weight-shifting strategy'. If, however, balance cannot be maintained with such a feet-in-place strategy, the ipsilateral leg must be quickly unloaded which requires a prolonged and strong activation of the hip abductors. Subsequently, strong concentric activation of the hip abductors is needed to make successful side step. In all these instances, any delay in the timing and amplitude of the protective muscle activations or in the timing and extent of muscle deactivations will result in an impaired capacity to maintain static and dynamic balance [216]. An important question is to what extent impaired balance control in patients with HSP can be attributed to spasticity. This seems to be different for feet-in-place responses compared to reactive stepping.

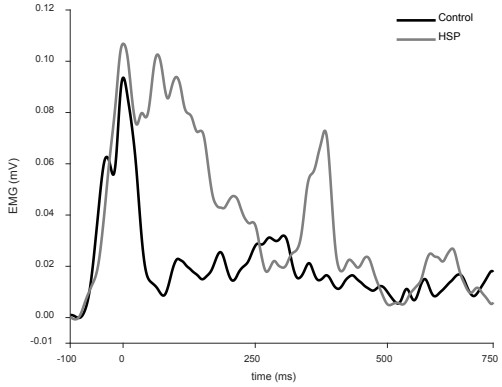
A previous study on the influence of spasticity on balance in people with HSP

showed that calf muscle tone (assessed with the MAS) was associated with an impaired capacity to execute feet-in-place strategies, but only after rotational 'toes-up' platform perturbations. These types of perturbation stretch the calf muscles, but a reactive stretch response must be strongly suppressed to avoid the calves pulling the body further backwards. Remarkably, the resistance to other types of platform perturbation (rotational 'toes down' or translational forward or backward) was not associated with lower leg muscle tone [22]. In **chapter 3** of this thesis, we provided evidence that the typical short latency stretch reflexes (SLRs) after 'toes-up' perturbations, although increased in amplitude, could not be held responsible for the divergence of the COM trajectory in the backward direction compared to healthy controls. Instead, the timing of divergence of COM trajectories suggest insufficient suppression of *late* calf muscle activity (from ~500ms post perturbation onset) to play a key role. In the case of translational body perturbations in the sagittal plane, some degree of involuntary muscle activation following stretch might even have a theoretical benefit for recovering balance with a feet-in-place strategy. For example, losing balance in the forward direction may lead to stretch-induced activation of the calves and hamstrings, which assists in decelerating the forward COM movement. Since most balance perturbations in daily life are translational (rather than rotational), the stretched and (subsequently) involuntarily activated muscles might be protective against balance loss, provided they are deactivated in time, although the magnitude of this effect is probably very small. Taken together, sensorimotor deficits other than hyperreflexia or enhanced muscle tone upon stretch are likely to play the most important role in the causation of balance problems in people with HSP. As addressed in **chapter 2**, muscle contracture, muscle stiffness, muscle weakness, loss of proprioception, and delayed postural responses are all probably more influential with regard to feet-in-place balance control than hyperreflexia or hypertonia, although the latter do have functional impact as risk factors for muscle stiffness and contracture. Indeed, when for instance the calf muscles become stiffer or lose length, they tend to pull the body backward while standing with the heels on the ground, causing a form of 'retropulsion'. In addition, an impaired capacity to deactivate muscles timely and appropriately may have a detrimental effect on the capacity to execute feet-in-place strategies (see **chapter 3**).

Compared to feet-in-place postural responses, reactive stepping seems to be relatively severely impaired in people with HSP. This can be explained in several ways. First, reactive stepping responses have to be made fast in order to be successful, and the required activation of agonist muscles may easily elicit a counteracting stretch

response of spastic antagonist muscles (e.g. the hamstrings during forward stepping, and the hip adductors during lateral stepping). As a result, the prime movers have to overcome the involuntary muscle activation due to spasticity. Second, impaired muscle deactivation is likely to aggravate the consequences of hyperexcitable stretch reflexes during reactive stepping, because the antagonist spastic muscle activity is prolonged due to inappropriate suppression. Figure 2 shows the average gastrocnemius muscle activity of the stepping leg in 12 trials of an individual with HSP versus a healthy control subject during reactive stepping after a forward perturbation. The grey line clearly indicates the prolonged, inappropriate muscle activity.

FIGURE 2. Preliminary ensemble average gastrocnemius muscle activity of the stepping leg in a person with pure HSP and a healthy control subject during a reactive forward stepping task. Time zero is the peak muscle activity. Note that the person with HSP shows prolonged muscle activity compared to the control subject.

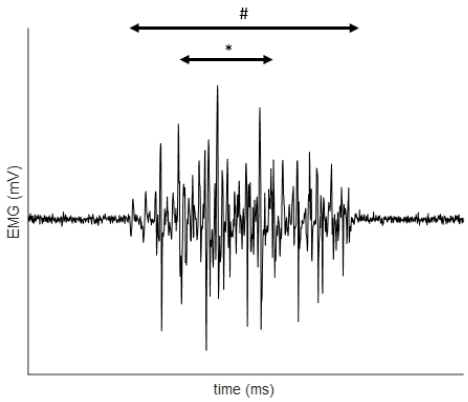


Third, effective reactive stepping probably depends on the corticospinal tract, which is the defective neural system in people with pure HSP. Instead, the reticulospinal tract - primarily responsible for feet-in-place postural responses - is spared. Overall, in people with pure HSP, reactive stepping responses are likely to be more impaired than feet-in-place responses, in terms of both amplitude and timing of the postural responses. Hence, clinically, a specific focus on improving reactive stepping strategies in people with HSP is of utmost importance. To what extent intramuscular administration of BTX-A might be able to improve reactive stepping will be discussed in the next paragraph.

Spasmolysis: influence of BTX-A on muscle tone versus muscle strength in HSP

BTX-A inhibits the acetylcholine release from the presynaptic neuromuscular terminals. It acts on the extrafusal muscle fibers, producing the muscle contraction, as well as on the intrafusal muscle fibers within muscle spindles, regulating the afferent responses to muscle stretch. Hence, focal intramuscular BTX-A injections may reduce the effects of efferent neural signals towards the targeted muscles, but also the afferent responses from these muscles upon stretch (i.e., the phasic and tonic stretch reflexes) [4]. In patients with spastic paresis, efferent signals to the muscles may be either voluntary or involuntary (e.g. in the case of associated reactions, co-contractions, or spastic dystonia) as argued in the beginning of this discussion. BTX-A injections are specifically meant to reduce the positive symptoms of spastic paresis but, inherent in their working mechanism, they cannot discriminate between intended / appropriate (volitional) versus unintended / inappropriate (involuntary) muscle activation. As a consequence, spasticity can be treated with BTX-A, but this treatment may – at least theoretically – also lead to loss of peak muscle strength. In addition, BTX-A injections cannot selectively reduce a specific part of the muscle activation pattern. On a theoretical basis, in the case of hyperexcitable tonic stretch reflexes, BTX-A injections may be intended mainly to decrease the peak of neuromuscular activation but, through its generic working mechanisms on efferent nerve fibers, BTX-A treatment will likely reduce the amplitude of the entire muscle activation pattern (see Figure 3).

FIGURE 3. Schematic representation to describe the part of the EMG signal BTX-A is aimed at and the part of the EMG signal that is effected by BTX-A injections. *Part of the signal BTX-A is aimed at. #Part of the signal that is influenced by BTX-A.



Hence, BTX-A may slightly shorten the duration of muscle activation by bringing the small activation amplitude at the start and the end of the muscle contraction below a critical value. In this way, BTX-A injections might also have a small influence on the timing of muscle activations.

Hence, the question is justified whether the unselective effect of BTX-A on neuromuscular activation may lead to a clinically relevant loss of muscle strength in patients with pure HSP. In **chapters 6 and 7**, we observed an increase in comfortable gait speed after BTX-A injections in the calf and hip adductor muscles, respectively, despite a small (temporary) loss of maximal muscle strength on clinical examination. With regard to balance control, a previous study from our group showed no beneficial or detrimental effects of BTX-A treatment of the calves on feet-in-place postural responses [9], whereas **chapter 7** of this thesis showed improved lateral reactive stepping after BTX-A injections in the hip adductor muscles when the direction of perturbation was known. Hence, from an overall perspective, the impact of BTX-A treatment on effective muscle strength seems limited or even negligible. A possible explanation for this finding is that maximal muscle strength of agonist muscles is hardly needed during regular functional tasks, such as standing and walking. In addition, loss of (maximal) muscle strength of a spastic antagonist muscle will improve the effective strength of a non-spastic agonist muscle. Indeed, if timely deactivation of antagonist muscles is critical for specific functional tasks, a lower activation amplitude after BTX-A treatment may support task execution. Remarkably, in **chapter 6**, we found evidence for the notion that BTX-A treatment may actually have a beneficial effect on the mechanical efficiency and contraction velocity of the calf muscles during the late stance phase of gait [165], as indicated by improved peak ankle power and positive work, perhaps by lowering the muscle tone just before 'push-off'. This needs to be corroborated by further research.

To sum up, in people with pure HSP, the (net) functional effect of a reduction of muscle tone versus a reduction of (maximal) muscle strength through BTX-A treatment seems to be beneficial for comfortable gait speed and reactive stepping, while it seems to be neutral for feet-in-place postural control and maximal gait speed. However, it is important to acknowledge that these conclusions are based on the studies reported in **chapters 6 and 7**, in which we included patients with relatively preserved muscle strength. It is still possible that patients with more severe muscle weakness and/or muscle fatigue might experience a net detrimental effect of BTX-A injections on the performance of functional tasks, such as standing and walking. Hence, the

severity of the negative symptoms of spastic paresis should be taken into account in individual patients, which supports the adage to 'start low and go slow' when initiating BTX-A treatment in people with spastic paresis. If the goal of BTX-A treatment is to improve motor control, a thorough clinical examination of all symptoms of spastic paresis is key. Preferably, this should be extended with a neurophysiological and biomechanical assessment of functional activities (e.g. by instrumented gait analysis) to identify the right muscular targets for BTX-A treatment and support individual goal setting.

It is important to mention here that BTX-A treatment in patients with HSP can also be installed to reduce spasticity-related focal pain and/or stiffness complaints without the aim to improve function. In addition, BTX-A injections can be indicated to facilitate the performance of muscular stretching exercises to prevent or reduce muscle contractures and maintain function in the long term. For these indications, the possibility of a slight temporary loss of (maximal) muscle strength after BTX-A treatment is usually accepted by the patient and the clinician without further consideration.

Directions for future research

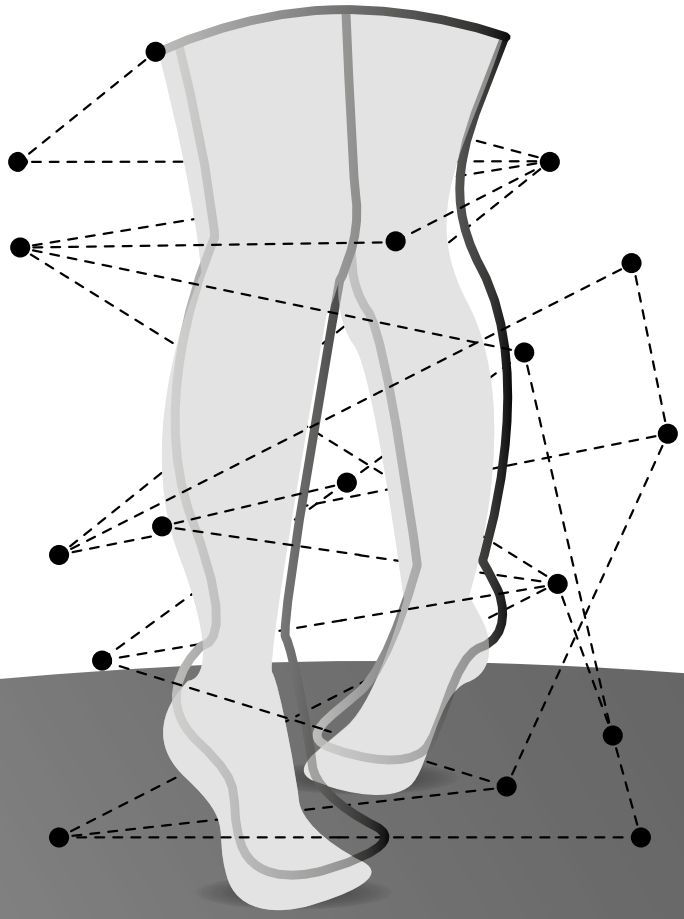
This results of this thesis emphasize the need for future studies that investigate the underlying mechanisms and treatment of balance and gait problems in people with pure HSP. In order to improve motor control, these studies should focus on all (positive, negative, and secondary) symptoms of spastic paresis and take into account the influence of body posture, physical activity, and context as well. From a clinical point of view, it seems to be most critical to improve dynamic balance capacity and reduce muscular stiffness and slowness of the lower extremities during voluntary activities such as gait. Merely focusing on a neurophysiological reduction of muscle tone will have limited functional impact. Maintaining muscle compliance and adequate muscle length through physical exercises and muscle stretching seems to be key to preserve balance capacity and mobility as long as possible.

With regard to spasticity, impaired muscle deactivation seems to play a critical role in causing some of the balance and gait deficits in people with HSP, particularly during functional tasks that require fast alternating movements, such as playful leisure and sports activities. Therefore, further research is needed to better understand the functional implications of impaired muscle deactivation and how muscle deactivation might be improved during functional tasks, including the effect of BTX-A treatment. In addition, future research should further explore the potential and limitations of

compensatory cortico-reticulospinal motor control and how cortico-reticulospinal control could be optimized to improve balance and gait capacities.

As for balance control, especially fast reactive stepping responses are impaired in people with pure HSP, most prominently if the direction of perturbation is unknown (see **chapter 7**). These situations require fast muscle activations of agonists and de-activation of antagonist, without being able to use anticipatory strategies. Future studies should, therefore, focus on how reactive stepping strategies may be improved, for instance by dynamic balance training on a moving platform. In addition, pro-active stepping strategies should be improved, for instance by gait adaptability training on an instrumented treadmill. The recently initiated Move-HSP study [217] is an example of the latter type of training. If such training would prove to be successful, it could have a significant impact on fall risk and social participation.

Lastly, the working profile of BTX-A treatment in people with spastic paresis should be studied in more depth to better understand how extrafusal and intrafusal neuromuscular blockade affects muscle activation and deactivation during functional activities. Apart from single cycle experiments, longitudinal studies with repetitive BTX-A cycles should be conducted to compare the added functional effects of this treatment compared to regular exercises, including muscle stretching. These longitudinal studies should preferably make use of easily applicable tools for patients to monitor their complaints and functioning on a daily basis over a prolonged time period. In this perspective, our group has started a feasibility study aimed at investigating the surplus value of an online monitoring tool for patients with spastic paresis that can be read out by clinicians as well to determine the (long-term) efficacy of BTX-A treatment, including possible side effects. Such a monitoring tool may also facilitate shared decision making with regard to the indication, timing, and targets of BTX-A treatment in people with spastic paresis.



CHAPTER 9

Samenvatting in het Nederlands

Dit hoofdstuk geeft een beknopte Nederlandse samenvatting en is vooral gericht op lezers zonder achtergrondkennis. De resultaten worden gedetailleerd samengevat en bediscussieerd in het hoofdstuk 'Summary and general discussion'.

Hereditaire spastische paraplegie (HSP) is een groep van progressieve erfelijke aandoeningen die wordt gekenmerkt doordat de motorische zenuwbanen vanuit de hersenen naar de benen (corticospinale zenuwbanen) zijn aangedaan. Hierdoor hebben mensen met HSP tijdens hun leven vaak toenemend last van stijfheid (spasticiteit) en zwakte van de beenspieren, waardoor loop- en balansproblemen ontstaan die geleidelijk verergeren. Er worden twee groepen HSP onderscheiden: pure HSP en complexe HSP. Pure HSP wordt vooral gekenmerkt door spasticiteit en zwakte van de beenspieren. Mensen met complexe HSP hebben vaak ook nog andere symptomen zoals cognitieve problemen, spraakproblemen of motorische problemen van de armen. In dit proefschrift werd onderzoek gedaan naar mensen met pure HSP.

Het doel van dit proefschrift was om meer inzicht te krijgen in de ervaren (motorische) problemen en motorische stoornissen van mensen met pure HSP en om de effecten van behandeling van spasticiteit met botulinetoxine op de balans- en loopvaardigheid bij deze mensen te testen. In het eerste deel geven we een overzicht van de pathofysiologie, functionele diagnostiek en het klinisch handelen gericht op balansproblemen en valproblematiek bij mensen met HSP, gebaseerd op de literatuur en op de klinische ervaring binnen het Radboudumc Expertisecentrum voor Erfelijke Bewegingsstoornissen. Tevens hebben we onderzoek gedaan naar de ervaren klachten en motorische beperkingen door middel van een digitale vragenlijst, afgenomen bij mensen met pure HSP in heel Nederland. In het tweede deel hebben we onderzoek gedaan naar een aantal onderliggende mechanismen van de balansproblematiek en het (starten met) lopen bij mensen met pure HSP. In het derde deel hebben we de effecten getest van behandeling met botulinetoxine, gevolgd door rekoefeningen, van specifieke spastische spiergroepen op de balans- en loopvaardigheid bij mensen met pure HSP.

Deel 1: Dagelijkse problemen van het leven met HSP

Pathofysiologie, functionele diagnostiek en klinisch handelen

Ook al zijn balansproblemen en vallen veelvoorkomend en een groot probleem bij

mensen met HSP, de onderliggende mechanismen en mogelijke behandelstrategieën zijn beperkt onderzocht. In **hoofdstuk 2** hebben we op basis van bestaande literatuur en eigen klinische expertise een overzicht gemaakt van de pathofysiologie, functionele diagnostiek en het klinisch handelen gericht op balans- en valproblematiek bij mensen met HSP. Vier belangrijke intrinsieke factoren voor balansproblemen en vallen werden geïdentificeerd: spasticiteit, contracturen, spierzwakte, en verlies van proprioceptie. Van deze factoren worden verlies van proprioceptie en daarmee samenhangende vertraging van evenwichtsreacties beschouwd als belangrijkste oorzaak voor de balansproblemen, samen met de ontwikkeling van spierverkortingen en gewrichtsdeformaties zoals spitsvoeten. De invloed van spasticiteit op de balansproblematiek wordt als minder groot beschouwd, maar spasticiteit wordt wel benoemd als belangrijke risicofactor voor de ontwikkeling van spierverkortingen. De unieke invloed van spierzwakte op de balansproblemen lijkt relatief gering maar, samen met de traagheid van evenwichtsreacties, kan deze wel bijdragen aan een verzwakking van de statische en dynamische balanshandhaving. Gebaseerd op de vier geïdentificeerde risicofactoren en hun interacties werden diverse diagnostische- en behandelingsopties bediscussieerd.

Ervaren klachten en motorische beperkingen

In **hoofdstuk 3** hebben we de ervaren klachten en motorische beperkingen van mensen met pure HSP onderzocht. Behandeling van deze mensen is vaak gericht op het verminderen van spasticiteit en de fysieke gevolgen hiervan, maar om aan individuele behoeften te voldoen is het belangrijk om beter te begrijpen wat patiënten zelf ervaren. We hebben daarom een digitale HSP-specifieke vragenlijst ontwikkeld en verstuurd naar patiënten met HSP in heel Nederland. Het bleek dat de meeste mensen de grootste hinder ervoeren van spierstijfheid en van beperkingen in het uitvoeren van staande en lopende activiteiten. Daarnaast gaf bijna driekwart van de deelnemers aan last te hebben van been- en/of rugpijn. Respectievelijk 35% en 46% van de mensen gebruikte binnenshuis en buitenshuis loophulpmiddelen (zoals een stok). 57% gaf aan minimaal 2 keer per jaar te vallen en werd geïdentificeerd als 'valler'. Bij 51% had een val minimaal 1 keer tot een blessure of verwonding geleid en 73% was bang om te vallen. De duur van de ervaren spasticiteit (in jaren) en het onvermogen om op te staan van de grond waren positief geassocieerd met het de identificatie als 'valler', terwijl niet-neurologische co-morbiditeit en het gebruik van een rolstoel hiermee negatief geassocieerd waren. Een hogere leeftijd, ervaren loopproblemen, het niet kunnen staan gedurende 10 minuten, en onvermogen om

een zware deur te openen waren negatief geassocieerd met (> 500m) kunnen lopen zonder loophulpmiddel. Deze resultaten benadrukken de grote impact van HSP op het dagelijks leven en dragen bij aan het beter stellen van behandeldoelen bij de revalidatie van deze mensen.

Deel 2: Onderliggende motorische stoornissen bij mensen met pure HSP

De invloed van verhoogde rekreflexen van de kuiten op balanshandhaving

Spastische spieren hebben als eigenschap dat zij een versterkte motorische respons tonen als reactie op spierrek (rekreflex). In **hoofdstuk 4** hebben we de rol van (verhoogde) rekreflexen van de kuitspieren op de balanshandhaving onderzocht bij mensen met pure HSP en bij gezonde vrijwilligers. Mensen moesten een roterende balansverstoring ondergaan , waarbij met verschillende snelheden de tenen naar boven werden gekanteld en de kuiten werden gerekt. Mensen met HSP waren hierbij minder goed in staat om hun balans te handhaven en lieten – zoals verwacht –

hogere rekreflexen zien dan gezonde vrijwilligers. Maar ook in een latere fase van de evenwichtsreactie werd verhoogde spieractiviteit van de kuiten geobserveerd bij de mensen met HSP, terwijl deze late activiteit bij gezonde vrijwilligers tijdig en effectief werd onderdrukt. Dit late verschil in spieractiviteit tussen mensen met HSP en gezonden kwam overeen met het moment dat er ook een verschil werd gevonden in het bewegingstraject van het lichaamszwaartepunt tussen de twee groepen. Deze bevindingen suggereren dat een verstoorde de-activering van late kuitspieractiviteit belangrijker is dan een versterking van de vroege rekreflexen voor het veroorzaken van balansproblemen bij mensen met pure HSP.

Spieractivering versus spierde-activering tijdens starten met lopen

Schade aan de zenuwbanen vanuit de hersenen naar het ruggenmerg c.q. de corticospinale banen leidt tot verstoringen in de aansturing van willekeurige bewegingen. Bevindingen uit eerder onderzoek suggereren dat een bepaalde mate van willekeurige aansturing overgenomen zou kunnen worden door zenuwcircuits die via de hersenstam verlopen c.q. het cortico-reticulospinale baansysteem. Bij mensen is dit vooral getest door middel van het StartReact effect. Het StartReact effect is de versnelling van de reactietijd van een willekeurige beweging die optreedt als – tegelij-

kertijd met de primaire stimulus – een schrikreactie wordt ontlokt, veelal door middel van een hard geluid. Er wordt verondersteld dat de willekeurige beweging dan primair wordt aangestuurd via de hersenstam. Eerder onderzoek werd vooral uitgevoerd op basis van enkelvoudige bewegingen van één gewricht. In **hoofdstuk 5** hebben we getest of het hersenstamcircuit ook kan worden gebruikt om complexe bewegingen te initiëren, waarbij coördinatie van meerdere lichaamssegmenten nodig is. Deelnemers moesten na het verschijnen van een visuele stimulus zo snel mogelijk starten met lopen. Zonder een schrikgeluid waren de reactietijden van mensen met HSP vertraagd vergeleken met gezonde vrijwilligers. Indien tegelijkertijd met de visuele stimulus een schrikgeluid werd aangebonden, bleek de spieractivering van beide groepen versneld, maar verhoudingsgewijs méér bij de mensen met HSP, waardoor de reactietijden even snel werden in beide groepen. Spierde-activering werd eveneens versneld door gelijktijdige aanbieding van een schrikgeluid, maar alleen bij de gezonde vrijwilligers. Deze resultaten suggereren dat het hersenstamcircuit potentieel ook kan compenseren bij de initiatie van complexe multisegmentale bewegingen, zoals tijdens starten met lopen. Echter, deze compensatie is niet optimaal, aangezien dit circuit niet in staat lijkt te zijn tot adequate de-activering van spieren.

Deel 3: Functionele effecten van botulinetoxine bij mensen met pure HSP

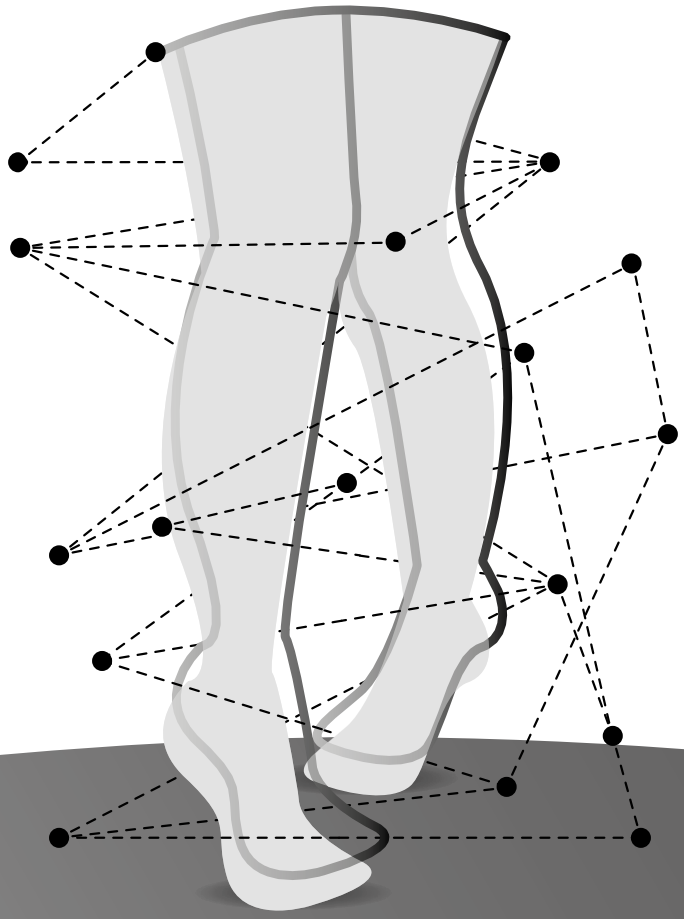
Functionele effecten van behandeling met botulinetoxine en rekoefeningen van de kuiten

Botulinetoxine wordt vaak gebruikt om spasticiteit te verminderen. Naast een vermindering van spasticiteit kan er ook milde spierverzwakking optreden. In een eerdere publicatie van onze groep werd beschreven dat de comfortabele loopsnelheid toenam in een groep mensen met pure HSP na behandeling met botulinetoxine en aanvullende rekoefeningen van de kuitspieren. Echter, de onderliggende mechanismen die ten grondslag lagen aan de gevonden verbetering van loopsnelheid werden niet gerapporteerd. In **hoofdstuk 6** hebben we onderzocht hoe in dezelfde groep patiënten eventuele veranderingen in bewegingsuitslagen, krachtenspel en energieontwikkeling rond de enkels tot een hogere loopsnelheid na de behandeling hebben geleid. Gangbeeldanalyse liet zien dat er – naast een verbetering van loopsnelheid en een grotere schredelengte – sprake was van een grotere afzetkracht en meer energieontwikkeling rond de enkels tijdens de late standfase, terwijl er geen veranderin-

gen optraden in bewegingsuitslagen of in de krachten of energieabsorptie tijdens de vroege en middenstandfase van het lopen. Deze resultaten suggereren dat behandeling met botulinetoxine, aangevuld met rekoefeningen van de kuiten bij mensen met pure HSP de loopsnelheid kan verhogen door een efficiënter gebruik van de beschikbare kuitspierkracht tijdens de afzetfase, leidend tot een grotere schredelengte.

Functionele effecten van behandeling met botulinetoxine en rekoefeningen van de heupadductoren

In **hoofdstuk 7** hebben de we op soortgelijke wijze de functionele effecten van behandeling met botulinetoxine en aanvullende rekoefeningen van de heupadductoren op de balans- en loopvaardigheid onderzocht bij mensen met pure HSP. De heupadductoren bevinden zich aan de binnenzijde van het bovenbeen. Mensen met HSP hebben vaak last van spasticiteit van de heupadductoren, waardoor de benen tijdens het lopen naar binnen neigen met een (te) smal gangspoor tot gevolg. Dit veroorzaakt balansproblemen. Mensen met HSP ervaren daarnaast vaak moeilijkheden bij het zijwaarts stappen om hun balans te handhaven tijdens dynamische omstandigheden. Een smal gangspoor en de veronderstelde problemen bij het zijwaarts stappen leiden waarschijnlijk tot een verhoogd valrisico. Intramusculaire injecties met botulinetoxine worden vaak gebruikt om spasticiteit te verminderen, maar er is nog geen onderzoek dat systematisch heeft onderzocht wat de functionele effecten zijn van behandeling van de heupadductoren bij mensen met pure HSP. De resultaten lieten zien dat er na behandeling een verhoogde comfortabele loopsnelheid en gangspoorbreedte was. Daarnaast lieten patiënten zien dat het zijwaarts stappen verbeterde zowel wat betreft het effect als wat betreft de kwaliteit van de stap. Dit laatste werd vastgesteld aan de hand van de beenhoek t.o.v. de verticaal, maar bleek alleen het geval tijdens de condities waarin de patiënten vooraf de richting van de balansverstoring kenden. Deze studie geeft de eerste aanwijzingen dat behandeling met botulinetoxine en aanvullend rekken van spastische heupadductoren de balans- en loopvaardigheid kan verbeteren bij mensen met pure HSP.



APPENDICES

Reference list

Dankwoord

Curriculum vitae

List of publications

Portfolio

Research data management

Donders Graduate School
for Cognitive Neuroscience

Reference list

1. Nonnekes J, Oude Nijhuis LB, de Niet M, et al. StartReact restores reaction time in HSP: evidence for subcortical release of a motor program. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2014;34(1):275-281.
2. Rothwell JC. The startle reflex, voluntary movement, and the reticulospinal tract. *Supplements to Clinical neurophysiology.* 2006;58:223-231.
3. Valls-Sole J, Kumru H, Kofler M. Interaction between startle and voluntary reactions in humans. *Experimental brain research.* 2008;187(4):497-507.
4. Abbruzzese G, Berardelli A. Neurophysiological effects of botulinum toxin type A. *Neurotox Res.* 2006;9(2-3):109-114.
5. Wissel J, Ward AB, Erztgaard P, et al. European consensus table on the use of botulinum toxin type A in adult spasticity. *Journal of rehabilitation medicine.* 2009;41(1):13-25.
6. Nonnekes J, de Kam D, Geurts AC, Weerdesteyn V, Bloem BR. Unraveling the mechanisms underlying postural instability in Parkinson's disease using dynamic posturography. *Expert review of neurotherapeutics.* 2013;13(12):1303-1308.
7. Ruano L, Melo C, Silva MC, Coutinho P. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. *Neuroepidemiology.* 2014;42(3):174-183.
8. Hesse S, Werner C, Bardeleben A, Brandl-Hesse B. Management of upper and lower limb spasticity in neuro-rehabilitation. *Acta Neurochir Suppl.* 2002;79:117-122.
9. de Niet M, de Bot ST, van de Warrenburg BP, Weerdesteyn V, Geurts AC. Functional effects of botulinum toxin type-A treatment and subsequent stretching of spastic calf muscles: a study in patients with hereditary spastic paraplegia. *Journal of rehabilitation medicine.* 2015;47(2):147-153.
10. Harding AE. Classification of the hereditary ataxias and paraplegias. *Lancet.* 1983;1(8334):1151-1155.
11. McDermott C, White K, Bushby K, Shaw P. Hereditary spastic paraparesis: a review of new developments. *Journal of neurology, neurosurgery, and psychiatry.* 2000;69(2):150-160.
12. Blackstone C, O'Kane CJ, Reid E. Hereditary spastic paraplegias: membrane traffic and the motor pathway. *Nature reviews Neuroscience.* 2011;12(1):31-42.
13. Bellofatto M, De Michele G, Iovino A, Filla A, Santorelli FM. Management of Hereditary Spastic Paraplegia: A Systematic Review of the Literature. *Frontiers in neurology.* 2019;10:3.
14. Schule R, Wiethoff S, Martus P, et al. Hereditary spastic paraplegia: Clinicogenetic lessons from 608 patients. *Annals of neurology.* 2016;79(4):646-658.
15. Chrestian N, Dupre N, Gan-Or Z, et al. Clinical and genetic study of hereditary spastic paraplegia in Canada. *Neurol Genet.* 2017;3(1):e122.
16. Kara E, Tucci A, Manzoni C, et al. Genetic and phenotypic characterization of complex hereditary spastic paraplegia. *Brain : a journal of neurology.* 2016;139(Pt 7):1904-1918.
17. Loureiro JL, Brandao E, Ruano L, et al. Autosomal dominant spastic paraplegias: a review of 89 families resulting from a portuguese survey. *JAMA Neurol.* 2013;70(4):481-487.
18. Shribman S, Reid E, Crosby AH, Houlden H, Warner TT. Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches. *The Lancet Neurology.* 2019.
19. Fink JK. Hereditary Spastic Paraplegia Overview. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. *GeneReviews(R).* Seattle (WA)1993.
20. de Souza PV, de Rezende Pinto WB, de Rezende Batistella GN, Bortholin T, Oliveira AS. Hereditary Spastic Paraplegia: Clinical and Genetic Hallmarks. *Cerebellum.* 2016.
21. Bot STd. *Hereditary Spastic Paraplegias in the Netherlands*. Nijmegen: Department of Neurology, Radboud University Medical Centre; 2013.

22. de Niet M, Weerdesteyn V, de Bot ST, van de Warrenburg BP, Geurts AC. Does calf muscle spasticity contribute to postural imbalance? A study in persons with pure hereditary spastic paraparesis. *Gait & posture.* 2013;38(2):304-309.

23. Nonnekes J, de Niet M, Oude Nijhuis LB, et al. Mechanisms of postural instability in hereditary spastic paraplegia. *Journal of neurology.* 2013;260(9):2387-2395.

24. Nardone A, Galante M, Lucas B, Schieppati M. Stance control is not affected by paresis and reflex hyperexcitability: the case of spastic patients. *Journal of neurology, neurosurgery, and psychiatry.* 2001;70(5):635-643.

25. Cimolin V, Piccinini L, D'Angelo MG, et al. Are patients with hereditary spastic paraplegia different from patients with spastic diplegia during walking? Gait evaluation using 3D gait analysis. *Functional neurology.* 2007;22(1):23-28.

26. Wolf SI, Braatz F, Metaxiotis D, et al. Gait analysis may help to distinguish hereditary spastic paraplegia from cerebral palsy. *Gait & posture.* 2011;33(4):556-561.

27. Harding AE. Hereditary spastic paraplegias. *Seminars in neurology.* 1993;13(4):333-336.

28. Salinas S, Proukakis C, Crosby A, Warner TT. Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms. *The Lancet Neurology.* 2008;7(12):1127-1138.

29. Erichsen AK, Koht J, Stray-Pedersen A, Abdelnoor M, Tallaksen CM. Prevalence of hereditary ataxia and spastic paraplegia in southeast Norway: a population-based study. *Brain : a journal of neurology.* 2009;132(Pt 6):1577-1588.

30. Voermans NC, Snijders AH, Schoon Y, Bloem BR. Why old people fall (and how to stop them). *Practical neurology.* 2007;7(3):158-171.

31. Weerdesteyn V, de Niet M, van Duijnhoven HJ, Geurts AC. Falls in individuals with stroke. *Journal of rehabilitation research and development.* 2008;45(8):1195-1213.

32. van der Marck MA, Klok MP, Okun MS, et al. Consensus-based clinical practice recommendations for the examination and management of falls in patients with Parkinson's disease. *Parkinsonism & related disorders.* 2014;20(4):360-369.

33. Gollhofer A, Horstmann GA, Berger W, Dietz V. Compensation of translational and rotational perturbations in human posture: stabilization of the centre of gravity. *Neuroscience letters.* 1989;105(1-2):73-78.

34. Nashner LM. Adapting reflexes controlling the human posture. *Exp Brain Res.* 1976;26(1):59-72.

35. Diener HC, Dichgans J, Bootz F, Bacher M. Early stabilization of human posture after a sudden disturbance: influence of rate and amplitude of displacement. *Experimental brain research.* 1984;56(1):126-134.

36. Nonnekes J, Carpenter MG, Inglis JT, Duysens J, Weerdesteyn V. What startles tell us about control of posture and gait. *Neurosci Biobehav Rev.* 2015;53:131-138.

37. Zaaimi B, Edgley SA, Soteropoulos DS, Baker SN. Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey. *Brain : a journal of neurology.* 2012;135(Pt 7):2277-2289.

38. Fisher KM, Chinnery PF, Baker SN, Baker MR. Enhanced reticulospinal output in patients with (REEP1) hereditary spastic paraplegia type 31. *Journal of neurology.* 2013;260(12):3182-3184.

39. Baker SN. The primate reticulospinal tract, hand function and functional recovery. *The Journal of physiology.* 2011;589(Pt 23):5603-5612.

40. Scherbakov N, von Haehling S, Anker SD, Dirnagl U, Doehner W. Stroke induced Sarcopenia: muscle wasting and disability after stroke. *International journal of cardiology.* 2013;170(2):89-94.

41. Nonnekes J, Scotti A, Oude Nijhuis LB, et al. Are postural responses to backward and forward perturbations processed by different neural circuits? *Neuroscience.* 2013;245:109-120.

42. Pickering RM, Grimbergen YA, Rigney U, et al. A meta-analysis of six prospective studies of falling in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society.* 2007;22(13):1892-1900.

43. Tromp AM, Pluijm SM, Smit JH, Deeg DJ, Bouter LM, Lips P. Fall-risk screening test: a prospective study on predictors for falls in community-dwelling elderly. *Journal of clinical epidemiology.* 2001;54(8):837-844.
44. Ensrud KE, Blackwell TL, Mangione CM, et al. Central nervous system-active medications and risk for falls in older women. *Journal of the American Geriatrics Society.* 2002;50(10):1629-1637.
45. Ziere G, Dieleman JP, Hofman A, Pols HAP, van der Cammen TJM, Stricker BHC. Polypharmacy and falls in the middle age and elderly population. *Brit J Clin Pharmaco.* 2006;61(2):218-223.
46. Nonnekes J, Goselink R, Weerdesteyn V, Bloem BR. The retropulsion test: a good evaluation of postural instability in Parkinson's disease? *Journal of Parkinson's disease.* 2015;5(1):43-47.
47. Potter K, Brandfass K. The Mini-Balance Evaluation Systems Test (Mini-BESTest). *Journal of physiotherapy.* 2015;61(4):225.
48. Berg KO, Maki BE, Williams JI, Holliday PJ, Wood-Dauphinee SL. Clinical and laboratory measures of postural balance in an elderly population. *Archives of physical medicine and rehabilitation.* 1992;73(11):1073-1080.
49. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Physical therapy.* 1987;67(2):206-207.
50. Ryf C, Weymann A. The neutral zero method - a principle of measuring joint function. *Injury.* 1995;26:11.
51. Council MR. *Aids to the examination of the peripheral nervous system, London: Her Majesty's Stationary Office* 1981.
52. Fleuren JFM, Voerman GE, Erren-Wolters CV, et al. Stop using the Ashworth Scale for the assessment of spasticity. *J Neurol Neurosur Ps.* 2010;81(1):46-52.
53. Patrick E, Ada L. The Tardieu Scale differentiates contracture from spasticity whereas the Ashworth Scale is confounded by it. *Clin Rehabil.* 2006;20(2):173-182.
54. Dickstein R, Shupert CL, Horak FB. Fingertip touch improves postural stability in patients with peripheral neuropathy. *Gait & posture.* 2001;14(3):238-247.
55. Tjernstrom F, Bjorklund M, Malmstrom EM. Romberg ratio in quiet stance posturography--Test to retest reliability. *Gait & posture.* 2015;42(1):27-31.
56. Klebe S, Stolze H, Kopper F, et al. Gait analysis of sporadic and hereditary spastic paraplegia. *Journal of neurology.* 2004;251(5):571-578.
57. Patrick JH, Keenan MA. Gait analysis to assist walking after stroke. *Lancet.* 2007;369(9558):256-257.
58. Renzenbrink GJ, Buurke JH, Nene AV, Geurts AC, Kwakkel G, Rietman JS. Improving walking capacity by surgical correction of equinovarus foot deformity in adult patients with stroke or traumatic brain injury: a systematic review. *Journal of rehabilitation medicine.* 2012;44(8):614-623.
59. Eckhardt MM, Mulder MC, Horemans HL, van der Woude LH, Ribbers GM. The effects of high custom made shoes on gait characteristics and patient satisfaction in hemiplegic gait. *Gait & posture.* 2011;34(4):543-547.
60. Riccardo M, Angela L, Angela D, et al. Combined Treatment Fkt-Botulinum Toxin Type A (Btx-A) in Patients with Strumpell-Lorrain Disease. *Curr Pharm Design.* 2016;22(6):758-763.
61. Moore TJ, Anderson RB. The use of open phenol blocks to the motor branches of the tibial nerve in adult acquired spasticity. *Foot & ankle.* 1991;11(4):219-221.
62. Le Bocq C, Rousseaux M, Buisset N, Daveluy W, Blond S, Allart E. Effects of tibial nerve neurotomy on posture and gait in stroke patients: A focus on patient-perceived benefits in daily life. *Journal of the neurological sciences.* 2016;366:158-163.
63. Halpern R, Gillard P, Graham GD, Varon SF, Zorowitz RD. Adherence associated with oral medications in the treatment of spasticity. *PM & R : the journal of injury, function, and rehabilitation.* 2013;5(9):747-756.
64. Margetis K, Korfias S, Boutos N, et al. Intrathecal baclofen therapy for the symptomatic treatment of hereditary spastic paraplegia. *Clin Neurol Neurosurg.* 2014;123:142-145.
65. Rousseaux M, Launay MJ, Kozlowski O, Daveluy W. Botulinum toxin injection in patients with hereditary spastic paraparesis. *Eur J Neurol.* 2007;14(2):206-212.

66. van Ooijen MW, Heeren A, Smulders K, et al. Improved gait adjustments after gait adaptability training are associated with reduced attentional demands in persons with stroke. *Experimental brain research.* 2015;233(3):1007-1018.

67. Fonteyn EM, Heeren A, Engels JJ, Boer JJ, van de Warrenburg BP, Weerdesteyn V. Gait adaptability training improves obstacle avoidance and dynamic stability in patients with cerebellar degeneration. *Gait & posture.* 2014;40(1):247-251.

68. Bertolucci F, Di Martino S, Orsucci D, et al. Robotic gait training improves motor skills and quality of life in hereditary spastic paraplegia. *NeuroRehabilitation.* 2015;36(1):93-99.

69. Fink JK. The hereditary spastic paraplegias: nine genes and counting. *Arch Neurol.* 2003;60(8):1045-1049.

70. Martin A, Abogunrin S, Kurth H, Dinet J. Epidemiological, humanistic, and economic burden of illness of lower limb spasticity in adults: a systematic review. *Neuropsychiatr Dis Treat.* 2014;10:111-122.

71. Welmer AK, von Arbin M, Widen Holmqvist L, Sommerfeld DK. Spasticity and its association with functioning and health-related quality of life 18 months after stroke. *Cerebrovasc Dis.* 2006;21(4):247-253.

72. Jorgensen S, Iwarsson S, Lexell J. Secondary Health Conditions, Activity Limitations, and Life Satisfaction in Older Adults With Long-Term Spinal Cord Injury. *PM & R : the journal of injury, function, and rehabilitation.* 2017;9(4):356-366.

73. Barnes M, Kocer S, Murie Fernandez M, Balcaitiene J, Fheodoroff K. An international survey of patients living with spasticity. *Disabil Rehabil.* 2017;39(14):1428-1434.

74. Fink JK. Advances in the hereditary spastic paraplegias. *Exp Neurol.* 2003;184 Suppl 1:S106-110.

75. Nonnekes J, van Lith B, van de Warrenburg BP, Weerdesteyn V, Geurts ACH. Pathophysiology, diagnostic work-up and management of balance impairments and falls in patients with hereditary spastic paraplegia. *Journal of rehabilitation medicine.* 2017;49(5):369-377.

76. Servelhere KR, Faber I, Saute JA, et al. Non-motor symptoms in patients with hereditary spastic paraplegia caused by SPG4 mutations. *Eur J Neurol.* 2016;23(2):408-411.

77. Kerstens H, Satink T, Nijkrake MJ, et al. Stumbling, struggling, and shame due to spasticity: a qualitative study of adult persons with hereditary spastic paraplegia. *Disabil Rehabil.* 2019:1-8.

78. Braschinsky M, Rannikmae K, Krikmann U, et al. Health-related quality of life in patients with hereditary spastic paraplegia in Estonia. *Spinal Cord.* 2011;49(2):175-181.

79. Fjermestad KW, Kanavin OJ, Naess EE, Hoxmark LB, Hummelvoll G. Health survey of adults with hereditary spastic paraparesis compared to population study controls. *Orphanet J Rare Dis.* 2016;11(1):98.

80. Schneider SA, Beckinger VE, Moller B, Knupfer S, Hamann M, Deuschl G. Urinary symptoms, quality of life, and patient satisfaction in genetic and sporadic hereditary spastic paraplegia. *Journal of neurology.* 2019;266(1):207-211.

81. Fink JK. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. *Acta Neuropathol.* 2013;126(3):307-328.

82. Shovlin E, Kunkel D. A survey to explore what information, advice and support community-dwelling people with stroke currently receive to manage instability and falls. *Disabil Rehabil.* 2017:1-7.

83. Mackintosh SF, Hill K, Dodd KJ, Goldie P, Culham E. Falls and injury prevention should be part of every stroke rehabilitation plan. *Clin Rehabil.* 2005;19(4):441-451.

84. Ashburn A, Hyndman D, Pickering R, Yardley L, Harris S. Predicting people with stroke at risk of falls. *Age Ageing.* 2008;37(3):270-276.

85. Hyndman D, Ashburn A, Stack E. Fall events among people with stroke living in the community: circumstances of falls and characteristics of fallers. *Arch Phys Med Rehabil.* 2002;83(2):165-170.

86. Gunn HJ, Newell P, Haas B, Marsden JF, Freeman JA. Identification of risk factors for falls in multiple sclerosis: a systematic review and meta-analysis. *Physical therapy.* 2013;93(4):504-513.

87. Gianni C, Prosperini L, Jonsdottir J, Cattaneo D. A systematic review of factors associated with accidental falls in people with multiple sclerosis: a meta-analytic approach. *Clin Rehabil.* 2014;28(7):704-716.

88. Morgan P, McGinley J. Performance of adults with cerebral palsy related to falls, balance and function: a preliminary report. *Dev Neurorehabil.* 2013;16(2):113-120.

89. Facchinetti LD, Araujo AQ, Chequer GL, de Azevedo MF, de Oliveira RV, Lima MA. Falls in patients with HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). *Spinal Cord.* 2013;51(3):222-225.

90. Brotherton SS, Krause JS, Nietert PJ. Falls in individuals with incomplete spinal cord injury. *Spinal Cord.* 2007;45(1):37-40.

91. Finnerup NB. Neuropathic pain and spasticity: intricate consequences of spinal cord injury. *Spinal Cord.* 2017;55(12):1046-1050.

92. van Lith BJH, den Boer JD, van de Warrenburg BPC, Weerdesteyn V, Geurts AC. Functional effects of botulinum toxin type A in the hip adductors and subsequent stretching in patients with hereditary spastic paraplegia. *Journal of rehabilitation medicine.* 2019.

93. Hecht MJ, Stolze H, Auf dem Brinke M, et al. Botulinum neurotoxin type A injections reduce spasticity in mild to moderate hereditary spastic paraplegia--report of 19 cases. *Mov Disord.* 2008;23(2):228-233.

94. Dunne JW, Heye N, Dunne SL. Treatment of chronic limb spasticity with botulinum toxin A. *Journal of neurology, neurosurgery, and psychiatry.* 1995;58(2):232-235.

95. Richardson D, Thompson AJ. Management of spasticity in hereditary spastic paraplegia. *Physiother Res Int.* 1999;4(1):68-76.

96. Chen K, Marsh EB. Chronic post-stroke fatigue: It may no longer be about the stroke itself. *Clin Neurol Neurosurg.* 2018;174:192-197.

97. Hadjimichael O, Kerns RD, Rizzo MA, Cutter G, Vollmer T. Persistent pain and uncomfortable sensations in persons with multiple sclerosis. *Pain.* 2007;127(1-2):35-41.

98. Herlofson K, Kluger BM. Fatigue in Parkinson's disease. *Journal of the neurological sciences.* 2017;374:38-41.

99. Harrison RA, Field TS. Post stroke pain: identification, assessment, and therapy. *Cerebrovasc Dis.* 2015;39(3-4):190-201.

100. Anton HA, Miller WC, Townson AF, Imam B, Silverberg N, Forwell S. The course of fatigue after acute spinal cord injury. *Spinal Cord.* 2017;55(1):94-97.

101. Jensen LN, Gerstenberg T, Kallestrup EB, Koefoed P, Nordling J, Nielsen JE. Urodynamic evaluation of patients with autosomal dominant pure spastic paraplegia linked to chromosome 2p21-p24. *Journal of neurology, neurosurgery, and psychiatry.* 1998;65(5):693-696.

102. Kanavin OJ, Fjermestad KW. Gastrointestinal and urinary complaints in adults with hereditary spastic paraparesis. *Orphanet J Rare Dis.* 2018;13(1):58.

103. Schule R, Schols L. Genetics of hereditary spastic paraplegias. *Seminars in neurology.* 2011;31(5):484-493.

104. Nielsen JE, Krabbe K, Jennum P, et al. Autosomal dominant pure spastic paraplegia: a clinical, paraclinical, and genetic study. *Journal of neurology, neurosurgery, and psychiatry.* 1998;64(1):61-66.

105. Lance JW. What is spasticity? *Lancet.* 1990;335(8689):606.

106. Jacobs JV, Horak FB. Cortical control of postural responses. *Journal of neural transmission.* 2007;114(10):1339-1348.

107. Crenna P. Spasticity and 'spastic' gait in children with cerebral palsy. *Neurosci Biobehav Rev.* 1998;22(4):571-578.

108. Nielsen JF, Andersen JB, Barbeau H, Sinkjaer T. Input-output properties of the soleus stretch reflex in spastic stroke patients and healthy subjects during walking. *NeuroRehabilitation.* 1998;10(2):151-166.

109. Sinkjaer T, Andersen JB, Nielsen JF, Hansen HJ. Soleus long-latency stretch reflexes during walking in healthy and spastic humans. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 1999;110(5):951-959.

110. Lamontagne A, Malouin F, Richards CL. Locomotor-specific measure of spasticity of plantarflexor muscles after stroke. *Arch Phys Med Rehabil.* 2001;82(12):1696-1704.

111. de Niet M, Latour H, Hendricks H, Geurts AC, Weerdesteyn V. Short-latency stretch reflexes do not contribute to premature calf muscle activity during the stance phase of gait in spastic patients. *Arch Phys Med Rehabil.* 2011;92(11):1833-1839.

112. van der Krogt MM, Doorenbosch CA, Becher JG, Harlaar J. Dynamic spasticity of plantar flexor muscles in cerebral palsy gait. *Journal of rehabilitation medicine.* 2010;42(7):656-663.

113. Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and meaningfulness. *Physical therapy.* 1984;64(1):35-40.

114. Medical Research C. *Aids to the examination of the peripheral nervous system. Memorandum no. 45.* London: Her Majesty's Stationery Office; 1981.

115. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med.* 1975;7(1):13-31.

116. Delp SL, Anderson FC, Arnold AS, et al. OpenSim: open-source software to create and analyze dynamic simulations of movement. *IEEE Trans Biomed Eng.* 2007;54(11):1940-1950.

117. Gottlieb GL, Agarwal GC. Response to sudden torques about ankle in man: myotatic reflex. *Journal of neurophysiology.* 1979;42(1 Pt 1):91-106.

118. Heckmann CJ, Gorassini MA, Bennett DJ. Persistent inward currents in motoneuron dendrites: implications for motor output. *Muscle & nerve.* 2005;31(2):135-156.

119. Nielsen JB, Crone C, Hultborn H. The spinal pathophysiology of spasticity--from a basic science point of view. *Acta Physiol (Oxf).* 2007;189(2):171-180.

120. Li S, Francisco GE. New insights into the pathophysiology of post-stroke spasticity. *Front Hum Neurosci.* 2015;9:192.

121. Crone C, Petersen NT, Nielsen JE, Hansen NL, Nielsen JB. Reciprocal inhibition and corticospinal transmission in the arm and leg in patients with autosomal dominant pure spastic paraparesis (ADPSP). *Brain : a journal of neurology.* 2004;127(Pt 12):2693-2702.

122. Pasma JH, Engelhart D, Schouten AC, van der Kooij H, Maier AB, Meskers CG. Impaired standing balance: the clinical need for closing the loop. *Neuroscience.* 2014;267:157-165.

123. McCombe Waller S, Yang CL, Magder L, Yungher D, Gray V, Rogers MW. Impaired motor preparation and execution during standing reach in people with chronic stroke. *Neuroscience letters.* 2016;630:38-44.

124. Sousa AS, Silva A, Santos R. Ankle anticipatory postural adjustments during gait initiation in healthy and post-stroke subjects. *Clin Biomech (Bristol, Avon).* 2015;30(9):960-965.

125. Rajachandrakumar R, Fraser JE, Schinkel-Ivy A, et al. Atypical anticipatory postural adjustments during gait initiation among individuals with sub-acute stroke. *Gait & posture.* 2017;52:325-331.

126. Massion J. Movement, posture and equilibrium: interaction and coordination. *Progress in neurobiology.* 1992;38(1):35-56.

127. Crenna P, Frigo C. A motor programme for the initiation of forward-oriented movements in humans. *The Journal of physiology.* 1991;437:635-653.

128. MacKinnon CD, Bissig D, Chiusano J, et al. Preparation of anticipatory postural adjustments prior to stepping. *Journal of neurophysiology.* 2007;97(6):4368-4379.

129. Girolami GL, Shiratori T, Aruin AS. Anticipatory postural adjustments in children with hemiplegia and diplegia. *Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology.* 2011;21(6):988-997.

130. Krishnan V, Kanekar N, Aruin AS. Anticipatory postural adjustments in individuals with multiple sclerosis. *Neuroscience letters.* 2012;506(2):256-260.

131. Honeycutt CF, Kharouta M, Perreault EJ. Evidence for reticulospinal contributions to coordinated finger movements in humans. *Journal of neurophysiology.* 2013;110(7):1476-1483.

132. Baker SN, Zaaimi B, Fisher KM, Edgley SA, Soteropoulos DS. Pathways mediating functional recovery. *Progress in brain research.* 2015;218:389-412.

133. Herbert WJ, Powell K, Buford JA. Evidence for a role of the reticulospinal system in recovery of skilled reaching after cortical stroke: initial results from a model of ischemic cortical injury. *Experimental brain research.* 2015;233(11):3231-3251.

134. Baker SN, Perez MA. Reticulospinal Contributions to Gross Hand Function after Human Spinal Cord Injury. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2017;37(40):9778-9784.

135. Marinovic W, Tresilian JR. Triggering prepared actions by sudden sounds: reassessing the evidence for a single mechanism. *Acta Physiol (Oxf).* 2016;217(1):13-32.

136. Kirkpatrick NJ, Ravichandran VJ, Perreault EJ, Schaefer SY, Honeycutt CF. Evidence for startle as a measurable behavioral indicator of motor learning. *PloS one.* 2018;13(5):e0195689.

137. Marinovic W, de Rugy A, Lipp OV, Tresilian JR. Reply to Maslovat et al. *Journal of neurophysiology.* 2015;113(9):3455-3456.

138. Valls-Sole J, Rothwell JC, Goulart F, Cossu G, Munoz E. Patterned ballistic movements triggered by a startle in healthy humans. *The Journal of physiology.* 1999;516 (Pt 3):931-938.

139. Carlsen A, Chua R, Inglis JT, Sanderson DJ, Franks IM. Prepared movements are elicited early by startle. *Journal of motor behavior.* 2004;36(3):253-264.

140. Honeycutt CF, Tresch UA, Perreault EJ. Startling acoustic stimuli can evoke fast hand extension movements in stroke survivors. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* 2015;126(1):160-164.

141. Honeycutt CF, Perreault EJ. Planning of ballistic movement following stroke: insights from the startle reflex. *PloS one.* 2012;7(8):e43097.

142. Lu C, Amundsen Huffmaster SL, Harvey JC, MacKinnon CD. Anticipatory postural adjustment patterns during gait initiation across the adult lifespan. *Gait & posture.* 2017;57:182-187.

143. Queralt A, Valls-Sole J, Castellote JM. Speeding up gait initiation and gait-pattern with a startling stimulus. *Gait & posture.* 2010;31(2):185-190.

144. Hermens HJ, Freriks B, Merletti R, et al. European recommendations for surface electromyography. *Roessingh Research Development.* 1999;8:13-54.

145. Pestronk A, Florence J, Levine T, et al. Sensory exam with a quantitative tuning fork: rapid, sensitive and predictive of SNAP amplitude. *Neurology.* 2004;62(3):461-464.

146. Nonnekes J, Geurts AC, Nijhuis LB, et al. Reduced StartReact effect and freezing of gait in Parkinson's disease: two of a kind? *Journal of neurology.* 2014;261(5):943-950.

147. Marinovic W, Brauer SG, Hayward KS, Carroll TJ, Riek S. Electric and acoustic stimulation during movement preparation can facilitate movement execution in healthy participants and stroke survivors. *Neuroscience letters.* 2016;618:134-138.

148. Brown P, Day BL, Rothwell JC, Thompson PD, Marsden CD. The effect of posture on the normal and pathological auditory startle reflex. *Journal of neurology, neurosurgery, and psychiatry.* 1991;54(10):892-897.

149. Carlsen AN, Dakin CJ, Chua R, Franks IM. Startle produces early response latencies that are distinct from stimulus intensity effects. *Experimental brain research.* 2007;176(2):199-205.

150. Maslovat D, Franks IM, Leguerrier A, Carlsen AN. Responses to startling acoustic stimuli indicate that movement-related activation is constant prior to action: a replication with an alternate interpretation. *Physiol Rep.* 2015;3(2):e12300.

151. Carlsen AN, Almeida QJ, Franks IM. Startle decreases reaction time to active inhibition. *Experimental brain research.* 2012;217(1):7-14.

152. Peterson BW, Pitts NG, Fukushima K. Reticulospinal connections with limb and axial motoneurons. *Experimental brain research.* 1979;36(1):1-20.

153. Engberg I, Lundberg A, Ryall RW. Reticulospinal inhibition of interneurones. *The Journal of physiology.* 1968;194(1):225-236.

154. Trompetto C, Marinelli L, Mori L, et al. Pathophysiology of spasticity: implications for neurorehabilitation. *Biomed Res Int.* 2014;2014:354906.

155. Magoun HW, Rhines R. An inhibitory mechanism in the bulbar reticular formation. *Journal of neurophysiology.* 1946;9:165-171.

156. Jankowska E, Cabaj A, Pettersson LG. How to enhance ipsilateral actions of pyramidal tract neurons. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2005;25(32):7401-7405.

157. Jang SH, Chang CH, Lee J, Kim CS, Seo JP, Yeo SS. Functional role of the corticoreticular pathway in chronic stroke patients. *Stroke.* 2013;44(4):1099-1104.

158. Lang CE, Schieber MH. Differential impairment of individuated finger movements in humans after damage to the motor cortex or the corticospinal tract. *Journal of neurophysiology.* 2003;90(2):1160-1170.

159. Lang CE, Schieber MH. Reduced muscle selectivity during individuated finger movements in humans after damage to the motor cortex or corticospinal tract. *Journal of neurophysiology.* 2004;91(4):1722-1733.

160. Owen M, Ingo C, Dewald JPA. Upper Extremity Motor Impairments and Microstructural Changes in Bulbospinal Pathways in Chronic Hemiparetic Stroke. *Frontiers in neurology.* 2017;8:257.

161. Peterson BW, Maunz RA, Pitts NG, Mackel RG. Patterns of projection and braching of reticulospinal neurons. *Experimental brain research.* 1975;23(4):333-351.

162. Gupta AD, Chu WH, Howell S, et al. A systematic review: efficacy of botulinum toxin in walking and quality of life in post-stroke lower limb spasticity. *Syst Rev.* 2018;7(1):1.

163. Blumetti FC, Belloti JC, Tamaoki MJ, Pinto JA. Botulinum toxin type A in the treatment of lower limb spasticity in children with cerebral palsy. *Cochrane Database Syst Rev.* 2019;10:CD001408.

164. Perry J. *Gait analysis : normal and pathological function.* Thorofare, NJ: SLACK; 1992.

165. van der Krogt MM, Doorenbosch CA, Becher JG, Harlaar J. Walking speed modifies spasticity effects in gastrocnemius and soleus in cerebral palsy gait. *Clin Biomech (Bristol, Avon).* 2009;24(5):422-428.

166. Choi JY, Jung S, Rha DW, Park ES. Botulinum Toxin Type A Injection for Spastic Equinovarus Foot in Children with Spastic Cerebral Palsy: Effects on Gait and Foot Pressure Distribution. *Yonsei Med J.* 2016;57(2):496-504.

167. Bollens B, Gustin T, Stoquart G, Detrembleur C, Lejeune T, Deltombe T. A randomized controlled trial of selective neurotomy versus botulinum toxin for spastic equinovarus foot after stroke. *Neurorehabil Neural Repair.* 2013;27(8):695-703.

168. Knutsson E, Richards C. Different types of disturbed motor control in gait of hemiparetic patients. *Brain : a journal of neurology.* 1979;102(2):405-430.

169. Barber L, Carty C, Modenese L, Walsh J, Boyd R, Lichtwark G. Medial gastrocnemius and soleus muscle-tendon unit, fascicle, and tendon interaction during walking in children with cerebral palsy. *Dev Med Child Neurol.* 2017;59(8):843-851.

170. Fujita K, Miaki H, Hori H, Kobayashi Y, Nakagawa T. How effective is physical therapy for gait muscle activity in hemiparetic patients who receive botulinum toxin injections? *Eur J Phys Rehabil Med.* 2019;55(1):8-18.

171. Hesse S, Krajnik J, Luecke D, Jahnke MT, Gregoric M, Mauritz KH. Ankle muscle activity before and after botulinum toxin therapy for lower limb extensor spasticity in chronic hemiparetic patients. *Stroke.* 1996;27(3):455-460.

172. Balaban B, Tok F, Tan AK, Matthews DJ. Botulinum toxin a treatment in children with cerebral palsy: its effects on walking and energy expenditure. *Am J Phys Med Rehabil.* 2012;91(1):53-64.

173. Galli M, Cimolin V, Valente EM, Crivellini M, Ialongo T, Albertini G. Computerized gait analysis of botulinum toxin treatment in children with cerebral palsy. *Disabil Rehabil.* 2007;29(8):659-664.

174. Sutherland DH, Kaufman KR, Wyatt MP, Chambers HG, Mubarak SJ. Double-blind study of botulinum A toxin injections into the gastrocnemius muscle in patients with cerebral palsy. *Gait & posture.* 1999;10(1):1-9.

175. Lee JH, Sung IY, Yoo JY, Park EH, Park SR. Effects of different dilutions of botulinum toxin type A treatment for children with cerebral palsy with spastic ankle plantarflexor: a randomized controlled trial. *Journal of rehabilitation medicine.* 2009;41(9):740-745.

176. Zwick EB, Svehlik M, Steinwender G, Linhart WE. Short-term Effects of Botulinum Toxin A and Serial Casting on Triceps Surae Muscle Length and Equinus Gait in Children with Cerebral Palsy. *Cesk Slov Neurol N.* 2009;72(6):553-558.

177. Pradon D, Hutin E, Khadir S, Taiar R, Genet F, Roche N. A pilot study to investigate the combined use of Botulinum toxin type-a and ankle foot orthosis for the treatment of spastic foot in chronic hemiplegic patients. *Clin Biomech (Bristol, Avon).* 2011;26(8):867-872.

178. Kaji R, Osako Y, Suyama K, et al. Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial. *Journal of neurology.* 2010;257(8):1330-1337.

179. Davis RB, Ounpuu S, Tyburski D, Gage JR. A Gait Analysis Data-Collection and Reduction Technique. *Hum Movement Sci.* 1991;10(5):575-587.

180. Cofre Lizama LE, Khan F, Galea MP. Beyond speed: Gait changes after botulinum toxin injections in chronic stroke survivors (a systematic review). *Gait & posture.* 2019;70:389-396.

181. Nieuwenhuys A, Papageorgiou E, Pataky T, De Laet T, Molenaers G, Desloovere K. Literature Review and Comparison of Two Statistical Methods to Evaluate the Effect of Botulinum Toxin Treatment on Gait in Children with Cerebral Palsy. *PloS one.* 2016;11(3):e0152697.

182. Metaxiotis D, Siebel A, Doederlein L. Repeated botulinum toxin A injections in the treatment of spastic equinus foot. *Clin Orthop Relat Res.* 2002(394):177-185.

183. Sutherland DH, Kaufman KR, Wyatt MP, Chambers HG. Injection of botulinum A toxin into the gastrocnemius muscle of patients with cerebral palsy: a 3-dimensional motion analysis study. *Gait & posture.* 1996;4(4):269-279.

184. Ackman JD, Russman BS, Thomas SS, et al. Comparing botulinum toxin A with casting for treatment of dynamic equinus in children with cerebral palsy. *Developmental Medicine and Child Neurology.* 2005;47(9):620-627.

185. Lelas JL, Merriman GJ, Riley PO, Kerrigan DC. Predicting peak kinematic and kinetic parameters from gait speed. *Gait & posture.* 2003;17(2):106-112.

186. Bovend'Eerdt TJ, Newman M, Barker K, Dawes H, Minelli C, Wade DT. The effects of stretching in spasticity: a systematic review. *Arch Phys Med Rehabil.* 2008;89(7):1395-1406.

187. Lewis CL, Ferris DP. Walking with increased ankle pushoff decreases hip muscle moments. *J Biomech.* 2008;41(10):2082-2089.

188. Gracies JM, Singer BJ, Dunne JW. The role of botulinum toxin injections in the management of muscle overactivity of the lower limb. *Disabil Rehabil.* 2007;29(23):1789-1805.

189. Riccardo M, Angela L, Angela D, et al. Combined Treatment Fkt-Botulinum Toxin Type A (Btx-A) in Patients with Strumpell-Lorrain Disease. *Curr Pharm Des.* 2016;22(6):758-763.

190. Cutlip RG, Mancinelli C, Huber F, DiPasquale J. Evaluation of an instrumented walkway for measurement of the kinematic parameters of gait. *Gait & posture.* 2000;12(2):134-138.

191. Weerdesteyn V, Laing AC, Robinovitch SN. The body configuration at step contact critically determines the successfulness of balance recovery in response to large backward perturbations. *Gait & posture.* 2012;35(3):462-466.

192. Berg KO, Wood-Dauphinee SL, Williams JI, Maki B. Measuring balance in the elderly: validation of an instrument. *Can J Public Health.* 1992;83 Suppl 2:S7-11.

193. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc.* 1991;39(2):142-148.

194. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. *Br Med J (Clin Res Ed).* 1982;284(6329):1607-1608.

195. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol A Biol Sci Med Sci.* 1995;50A(1):M28-34.

196. Esquenazi A, Albanese A, Chancellor MB, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of adult spasticity in the upper motor neuron syndrome. *Toxicon.* 2013;67:115-128.

197. Takenaga S, Kawahigashi Y, Sonoda Y, et al. [Treatment of spastic paraparesis with botulinum toxin with reference to beneficial effects, disease severity and long-term treatment]. *Rinsho Shinkeigaku.* 1995;35(3):251-255.

198. Ellis RG, Sumner BJ, Kram R. Muscle contributions to propulsion and braking during walking and running: insight from external force perturbations. *Gait & posture.* 2014;40(4):594-599.

199. de Souza PVS, de Rezende Pinto WBV, de Rezende Batistella GN, Bortholin T, Oliveira ASB. Hereditary Spastic Paraplegia: Clinical and Genetic Hallmarks. *Cerebellum.* 2017;16(2):525-551.

200. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. *Maturitas.* 2013;75(1):51-61.

201. Lance J. symposium synopsis, in felman RG, Young RR, Koella WP (eds): spasticity: Disordered Motor Control Chicago. *Year Book Medical Publishers.* 1980;494.

202. Pandyan AD, Gregoric M, Barnes MP, et al. Spasticity: clinical perceptions, neurological realities and meaningful measurement. *Disabil Rehabil.* 2005;27(1-2):2-6.

203. Gracies JM. Pathophysiology of spastic paresis. I: Paresis and soft tissue changes. *Muscle & nerve.* 2005;31(5):535-551.

204. Haugh AB, Pandyan AD, Johnson GR. A systematic review of the Tardieu Scale for the measurement of spasticity. *Disabil Rehabil.* 2006;28(15):899-907.

205. Fleuren JF, Voerman GE, Erren-Wolters CV, et al. Stop using the Ashworth Scale for the assessment of spasticity. *Journal of neurology, neurosurgery, and psychiatry.* 2010;81(1):46-52.

206. Federatie Medisch Specialisten. Cerebrale en/of spinale spasticiteit. https://richtlijnendatabase.nl/richtlijn/cerebrale_en_of_spinale_spasticiteit/evaluatie_van_spasticiteit.html. Published 2016. Accessed.

207. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. *The Lancet Neurology.* 2007;6(8):725-733.

208. Lieber RL, Steinman S, Barash IA, Chambers H. Structural and functional changes in spastic skeletal muscle. *Muscle & nerve.* 2004;29(5):615-627.

209. Friden J, Lieber RL. Spastic muscle cells are shorter and stiffer than normal cells. *Muscle & nerve.* 2003;27(2):157-164.

210. Smith LR, Lee KS, Ward SR, Chambers HG, Lieber RL. Hamstring contractures in children with spastic cerebral palsy result from a stiffer extracellular matrix and increased in vivo sarcomere length. *The Journal of physiology.* 2011;589(Pt 10):2625-2639.

211. Lawrence DG, Kuypers HG. The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. *Brain : a journal of neurology.* 1968;91(1):1-14.

212. Lawrence DG, Kuypers HG. The functional organization of the motor system in the monkey. II. The effects of lesions of the descending brain-stem pathways. *Brain : a journal of neurology.* 1968;91(1):15-36.

213. Dewald JP, Pope PS, Given JD, Buchanan TS, Rymer WZ. Abnormal muscle coactivation patterns during isometric torque generation at the elbow and shoulder in hemiparetic subjects. *Brain : a journal of neurology.* 1995;118 (Pt 2):495-510.

214. Maki BE, McIlroy WE. The role of limb movements in maintaining upright stance: the "change-in-support" strategy. *Physical therapy.* 1997;77(5):488-507.

215. Maki BE, McIlroy WE. Cognitive demands and cortical control of human balance-recovery reactions. *Journal of neural transmission.* 2007;114(10):1279-1296.

216. Thelen DG, Muriuki M, James J, Schultz AB, Ashton-Miller JA, Alexander NB. Muscle activities used by young and old adults when stepping to regain balance during a forward fall. *Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology.* 2000;10(2):93-101.

217. van de Venis L, van de Warrenburg BP, Weerdesteyn V, van Lith BJH, Geurts ACH. Improving gait adaptability in patients with hereditary spastic paraplegia (Move-HSP): study protocol for a randomized controlled trial. *Manuscript submitted for publication.* 2020.

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Curriculum vitae

Bas van Lith was born in Oss on December 16th, 1990. After graduating from secondary school (Maaslandcollege, Oss) in 2010, he started the bachelor Movement Sciences at the University of Groningen. In 2013 he started the master Biomedical Sciences, with the specialization Clinical Human Movement Sciences, at the Radboud University in Nijmegen. This is when Bas became highly interested in motor control. He started his first research internship at the Sensorimotor Lab, which is part of the Donders Institute for Brain, Cognition and Behaviour. Under supervision of dr. Luc Selen, he investigated how adaptation of movements in a certain direction generalize to other directions over time. Thereafter, Bas started his major research internship at the Department of Rehabilitation of the Radboud university medical center to focus on impaired motor control during balance and gait. Under supervision of Dr. Vivian Weerdesteyn he investigated the compensatory role of the reticulospinal tract, using the StartReact effect, in people with hereditary spastic paraplegia (HSP). In 2016, Bas received his master's degree. He started as a PhD candidate in 2015 to investigate balance and gait problems in people with HSP. Currently, he is working as a freelance project manager with focus on keeping the primary health care accessible, despite the increasing demand for care and the shortage on the labor market, using intelligent application of technology. Bas lives together in Uden with his fiancée Renée van den Brand.

List of publications

Nonnekes J, **van Lith B**, van de Warrenburg BP, Weerdesteyn V, Geurts ACH. Pathophysiology, diagnostic work-up, and management of balance impairments and falls in patients with hereditary spastic paraplegia. Journal of Rehabilitation Medicine (2017) 49:369-377.

van Lith BJH, Coppens MJM, Nonnekes J, van de Warrenburg BPC, Geurts AC, Weerdesteyn V. StartReact during gait initiation reveals differential control of muscle activation and inhibition in patients with corticospinal degeneration. Journal of Neurology (2018) 265:2531-2539.

van Lith BJH*, de Niet M*, van de Warrenburg BPC, Geurts AC, Weerdesteyn V. Excessive short-latency stretch reflexes in the calf muscles do not cause postural instability in patients with hereditary spastic paraplegia. Clinical Neurophysiology (2019) 130:1188-1195.

**These authors contributed equally to this work.*

Kerstens HCJW, Satink T, Nijkrake MJ, De Swart BJM, **Van Lith BJH,** Geurts ACH, Nijhuis-van der Sanden MWG. Stumbling, struggling, and shame due to spasticity: a qualitative study of adult persons with hereditary spastic paraplegia. Disability and Rehabilitation (2019) Online ahead of print.

van Lith BJH, den Boer J, van de Warrenburg BPC, Weerdesteyn V, Geurts AC. Functional effects of botulinum toxin type A in the hip adductors and subsequent stretching in patients with hereditary spastic paraplegia. Journal of Rehabilitation Medicine (2019) 51:434-441.

van Lith BJH, Kerstens HCJW, van den Bemd LAC, der Sanden MWGN, Weerdesteyn V, Smeets RJEM, Fheodoroff K, van de Warrenburg BPC, Geurts ACH. Experienced complaints, activity limitations and loss of motor capacities in patients with pure hereditary spastic paraplegia: a web-based survey in the Netherlands. Orphanet Journal of Rare Diseases (2020) 15:64.

van Lith BJH, van Bon GEA, Geurts ACH, Weerdesteyn V. Which changes in ankle kine(ma)tics following BTX-A treatment and subsequent stretching of the calves contribute to increased comfortable speed in patients with pure hereditary spastic paraplegia? Submitted.

van de Venis L, van de Warrenburg BPC, Weerdesteyn V; **van Lith BJH**; Geurts ACH; Nonnekes J. Improving gait adaptability in patients with hereditary spastic paraplegia (Move-HSP): study protocol for a randomized controlled trial. Submitted

Portfolio

Courses and workshops	Organizer	Year	ECTS
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	Radboud university medical center	2015	1.5
Management voor Promovendi	Radboud university	2016	2
Cambridge Advanced English	Radboud in'to languages	2016, 2017	3.4
Writing week	Department of Rehabilitation, Radboud university medical center	2016, 2017, 2018, 2019	8
The Art of Presenting Science	Radboud university	2017	1.5
Scientific Integrity Course	Radboud university medical center	2017	0.6
Advanced Conversation	Radboud university	2017	1.5
Reanimatiecursus	Radboud university medical center	2017	0.15
ESP69 Causal Mediation Analysis	Erasmus MC	2017	0.5
Personal development week	Department of Rehabilitation, Radboud university medical center	2018	1.3
Innovation and Entrepreneurship	Radboud university	2018	3
BROK herregistratie	Radboud university medical center	2019	0.15

Lectures and conferences	Location	Year	ECTS
Congress on NeuroRehabilitation and Neural Repair of the Dutch Society for NeuroRehabilitation and Belgian Society for NeuroRehabilitation	Maastricht	2015, 2017	1.5
Radboud research round: disorders of movement.	Nijmegen	2015, 2017	0.25
Society for Movement Analysis Laboratories in the Low Lands (SMALLL) congress	Nijmegen, Maastricht, Enschede, Leuven, (Belgium), Groningen	2015, 2016, 2017, 2018, 2019	1.5
Research meeting at the Department of Rehabilitation	Nijmegen	2015, 2016, 2017, 2018, 2019	2.5
Donders Discussions at the Donders Institute for Brain, Cognition and Behaviour	Nijmegen	2016	0.25
World Congress of the International Society of Posture and Gait Research (ISPGR)	Fort Lauderdale (US)	2017	1.5

Research data management

Research data management according to FAIR principles

General information about the data collection

Research projects within this thesis involve human subject data. Written informed consent for collecting these data was obtained from the participants. Pre-existing data and new data were collected and stored at the Radboud university medical center, Nijmegen, the Netherlands.

FAIR principles

Findable

Data were stored on the server of the department of Rehabilitation at the Radboud university medical center. Most data of the survey (chapter 3) were also stored in the online database management system Castor EDC. Paper CRF files were stored in the department's archives. Documentation to describe the data sets is provided on the department's server. Data sets stored at the department's server can be found at *Q:\Research\044 HSP Startle* and *Q:\Research\056 FEBOCH II*.

Accessible

All data will be available on request by contacting the staff secretary of the department of Rehabilitation at the Radboud university medical center (secretariaatstaf.reval@radboudumc.nl).

Interoperable

Documentation was added to the data sets to make the data interpretable (Q:\Research\044 HSP Startle\FAIR). The documentation contains links to publications, references to the location of the data sets and description of the data sets. The data were stored in the following file formats: .xlsx (Microsoft Office Excel) and .mat (Matlab, Mathworks, USA). No existing data standards were used such as vocabularies, ontologies or thesauri.

Reusable

The data will be stored for at least 10 years and can therefore also be reused in this time period. There is no embargo on the accessibility of the data.

Donders Graduate School for Cognitive Neuroscience

For a successful research Institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009. The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

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For more information on the DGCN as well as past and upcoming defenses please visit: http://www.ru.nl/donders/graduate-school/phd/.

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