

## **Hereditary Spastic Paraparesis and other Hereditary Myelopathies**

Jon Marsden<sup>1</sup> , Lisa Bunn<sup>1</sup> Amanda Denton<sup>1</sup>and Krishnan Padmakumari Sivaraman Nair<sup>2</sup>

<sup>1</sup> School of Health Professions, Faculty of Health and Human Sciences, University of Plymouth, Plymouth, UK

<sup>2</sup> Department of Neurology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

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This chapter will explore the impact of spasticity and associated symptoms in hereditary myelopathies with a particular focus on Hereditary Spastic Paraparesis (HSP). Hereditary myelopathies include syndromes with a genetic cause that involves spinal cord structures. To a variable extent they will have upper motor neuron (UMN) symptoms of spastic paraparesis. Importantly in the majority of cases structures outside the spinal cord are affected resulting in a diversity of symptom presentation. Four main clinical groups can be distinguished <sup>1</sup>.

1. Distal Axonopathies of the spinal cord eg HSP
2. Spinocerebellar Degenerations eg Spinocerebellar ataxia3 (SCA3), Late onset Freidreich's ataxia,
3. Motor Neuron Disorders eg Familial Amyotrophic lateral sclerosis
4. Inborn errors of metabolism eg Adrenomyeloneuropathy, Biotinidase deficiency, Cerbrotendinous xanthomatosis ,Glycogenosis type IV, Krabbe's disease Metachromatic leucodystrophy and Phenyl Ketoneuria,

Based on clinical presentation alone it can be often quite difficult to distinguish between conditions. People with the complex forms of HSP, for example, can have cerebellar signs and mimic the presentation seen in spinocerebellar ataxias. Similarly spinocerebellar ataxias such as SCA3 (Machado-Joseph disease) can present with significant spasticity and mimic HSP<sup>3</sup>. Adrenomyeloneuropathy can sometimes mimic HSP <sup>4-7</sup>.

An example of the clinical presentation and management from each clinical group of hereditary myelopathies will be described. The level of understanding of the underlying genetics can vary between the different hereditary myelopathies and this will be briefly described. Further, the hereditary myelopathies can have quite diverse additional symptoms and pharmacological and rehabilitation management which will be described with a particular emphasis placed on evidence for the management of spasticity and the upper motor neuron syndrome and its impact on functional ability.

### **Distal Axonopathies: Hereditary Spastic Paraparesis**

#### ***Prevalence and genetics***

Hereditary Spastic Paraparesis (Strumpell-Lorrain syndrome) has a prevalence of 4-6 per 100,000 although this can rise up to ~20 per 100,000 in isolated populations <sup>8</sup>. It is a heterogeneous genetic condition. More than 50 gene loci have been identified that can cause HSP <sup>9</sup>. All types of inheritance have been described: Autosomal Dominant (70% of cases), Autosomal Recessive, X Linked and maternal mitochondrial. The age of onset can vary from childhood to late adult life(70 yrs) <sup>9</sup>

There is also a high incidence of spontaneous mutations and asymptomatic carriers <sup>10</sup>. In SPAST(SPG4), the most common type of autosomal dominant HSP (40-45% of cases), spontaneous mutations to the spastin gene can occur in 13% of cases where symptoms are restricted to the legs<sup>11</sup>. Epidemiological studies suggest that 45-67% of autosomal dominant and 71-82% of autosomal recessive cases diagnosed with spastic paraparesis have no genetic diagnosis after systematic testing <sup>12</sup>.

### **Clinical Presentation**

Anita Harding originally described two broad classifications for HSP<sup>13</sup>. The type 1, uncomplicated presentation is characterised by the symptoms of lower limb spasticity, hyperreflexia, paresis and a positive (upgoing) Babinski response. Additional symptoms of urinary urgency and impaired vibration thresholds may also be present. Most cases of autosomal dominant HSP are the type 1, pure presentation.

In the type 2 presentation people have the same spastic paraparesis presentation as seen in type 1 but with other additional symptoms. Autosomal recessive presentations tend to have a complicated presentation and additional symptoms include:

- Cerebellar ataxia and signs
- Dementia and cognitive deficits. These are associated with thinning of the corpus callosum.
- Amyotrophy
- Peripheral neuropathy
- Cataracts or pigmentary retinopathy
- Dry, Itchy skin (ichthyosis)
- Epilepsy

The most common types of HSP for each mode of inheritance and pertinent clinical features are presented in table x.1 with more rare presentations described in detail elsewhere<sup>9,14</sup>

Gene name & locus	Protein	Cellular Function	Estimated Prevalence	Pertinent features
<b>Autosomal Dominant (AD-HSP)</b>				
SPAST (SPG4) 2p22	Spastin protein	Microtubule severing, ER morphogenesis, Endosomal trafficking, Inhibition of Bone Morphogenic Protein signalling	40-45% of AD cases	Childhood-late adult Mainly pure HSP
SPG3A 14q12-q21	Atlastin	Intracellular trafficking; ER morphogenesis and BMP signalling	10% of cases	Early onset Pure HSP
<b>Autosomal Recessive (AR-HAP)</b>				
SPG11 15q	Spatascin	Endosomal trafficking,	50% of AR –HSP	Thin corpus callosum; cognitive impairment and severe axonal neuropathy
SPG7 16q	Paraplegin	Mitochondrial m-AAA ATPase	~ 30 families	Variable onset, cerebellar signs, optic atrophy, neuropathy
<b>X-Linked</b>				
SPG1 Xq28	L1CAM	Cell adhesion and signalling, neurite outgrowth, neuronal cell migration and survival	Over 100 cases	Cognitive impairment hypoplasia of the corpus callosum, adducted thumbs and hydrocephalus
SPG2	PLP1	Major myelin protein in oligodendroglia	<100 cases	Quadriplegia; nystagmus, cognitive impairment, seizures
<b>Mitochondrial</b>				
No SPG designation	ATP synthase 6	Mitochondrial localization, ATP synthesis	1 family	Late onset disorder

*Table x.1: Genetic location; protein and broad cellular function; prevalence and key clinical features.  
Adapted from Salinas et al 2008 and Noreau et al 2014.*

## Pathology

### Cellular changes

There has been an increase in the understanding of the changes in neuronal cell function that lead to HSP in the last decade. This section will briefly review these changes and more detail can be gained from recent reviews of this area <sup>9,14</sup>.

Neurons within ascending and descending tracts that connect the brain and the lower segments of the spinal cord are over 1 m long. Protein and lipid synthesis and detoxification of harmful substances mainly occurs within the cell body and the endoplasmic reticulum(ER)-golgi apparatus system. A system of axonal transport is therefore required that actively transports newly synthesized materials from the cell body to the axon and neurotrophic factors and damaged organelles from the axon terminal to the cell body <sup>15</sup>. Axonal transport relies on a cytoskeletal network within the axon made of microtubules and actin filaments. Specialized motor proteins bind to and move substances in an anterograde or retrograde direction through this network, a process that is ATP dependent i.e. requires energy. Genes causing HSP encode proteins that are involved in, the ER-golgi system (e.g. ATL-1 (SPG3A); REEP (SPG31); RTN2 (SPG12)) or axonal transport. SPAST (SPG4), for example, plays a role in microtubule turnover whilst KIF5A (SPG10) is a member of the kinesin family of motor proteins <sup>9</sup>.

Molecules can be internalized (endocytosis) or externalized (exocytosis) into the cells or degraded by lysosomes. Endosomes are central to the movement of vesicles that contain these molecules. The endosomes are linked with the plasma membrane, golgi apparatus and lysosomes. There are several genes linked with HSP that encode proteins that are involved in endosomal trafficking (e.g. in SPG47 & SPG50-52 components of protein complexes that play a role in secretory/endocytic pathway are affected).

All cells require the mitochondria to produce ATP via oxidative phosphorylation. Longer axons with their large volume and reliance on axonal transport seem particularly susceptible to disorders of mitochondrial function and several genes have been identified that impair mitochondrial regulation and cause HSP (e.g. SPG7 encodes paraplegin and SPG13 encode Chaperonin 6)

More recently genes involved in lipid metabolism have been associated with HSP. Lipids are involved in energy storage; signaling and in the formation of the plasma and intracellular membranes; which cover a large area in longer neurons. Proteins have been described, for example, that are involved in lipid metabolism hydrolyzing phospholipids into fatty acids (DDHD2, SPG54) or in the processing of gangliosides that are signal transducers within the plasma membrane (eg B4GALNT-1, SPG26). The production of the myelin sheath by oligodendrocytes can also be affected and genes causing HSP can be expressed in oligodendroglia, but not in motor neurons (eg SPG2) <sup>9,14</sup>.

Overall the pattern suggests that abnormal cellular trafficking/ axonal transport results in degeneration of the nerves. The distal most part of the long axons are first affected as molecules need to be transported across a long distance and this requires more energy to function (ie those axons projecting to/from the spinal cord segments supplying the lower limb). The recent finding of genes being involved in lipid metabolism and in oligodendrocyte function however highlights that a common mechanism for all causes of HSP may not be present. Given the heterogeneous presentation of HSP more work is required to understand the genotype-phenotype relationship in terms of symptom presentation, longitudinal progression and prognosis with intervention.

### *Changes in descending and ascending tract function*

The pathology in HSP is one of a dying back axonal degeneration predominately affecting the corticospinal tracts. The longer tracts that supply the lower limbs are affected first with shorter tracts supplying the trunk and arms being affected later with disease progression<sup>16</sup>. In keeping with this; the lower limb motor evoked potentials (MEPs) following stimulation of the motor cortex using transcranial magnetic stimulation (TMS) are either absent or have a higher threshold. Further, when a response is present the central conduction time is prolonged. In contrast, hand muscle responses to motor cortex stimulation are usually normal<sup>17-21</sup>.

The most common MRI change is thinning of the cervical and thoracic spinal cord. Although, MRI and volume based morphometry of the brain may be normal, in SPAST (SPG4) changes are seen with Diffusion Tensor Imaging (DTI)<sup>22</sup>. The DTI reveals white matter changes in the posterior limb of the internal capsule and peritrigonal white matter. Frontal lobe white matter changes are more marked with longer disease duration<sup>22</sup>. In complicated presentations, such as SPG11, white matter changes are more marked and also involve the striatum and brainstem<sup>23-25</sup>.

Degeneration of the ascending tracts lying in the fasciculus gracilis of the dorsal columns carrying somatosensory information from the lower limbs have also been described<sup>18</sup>. Lower limb somatosensory evoked potentials can be reduced in size. A reduction in vibration threshold is seen in ~40-60% of patients although interestingly other sensory signs are not commonly seen on clinical testing<sup>26</sup>. Similarly, although people with HSP do not usually present with brainstem signs white matter loss in the brainstem and abnormal brain stem auditory evoked responses may be seen<sup>27</sup>. Degeneration of the spinocerebellar tracts and an associated with loss of volume in the posterior fossa have also been described in SPG4<sup>28</sup> and in complicated forms overt cerebellar signs can be seen. Cerebellar signs are particularly prominent in SPG7 and 15.

### *Changes in cortical activation with movement*

On fMRI comparisons have been made between activation patterns associated with movement of the relatively unaffected hand and ankle movements. Ankle movements in Autosomal Dominant (AD)-HSP and SPG4 show variable changes with reduced contralateral sensorimotor cortical activation<sup>29</sup> and increased activation of bilateral motor cortex and supplementary and premotor cortex<sup>30</sup> and the

ipsilateral cerebellum<sup>29</sup>. In two studies normal activation was seen with hand movements<sup>29,30</sup> whilst Koritnik et al 2009 found increased contralateral sensorimotor cortex and bilateral posterior parietal cortex activation with hand movements<sup>31</sup>. The finding that changes in activation may be seen when moving an unaffected body part (the hand) is suggestive of functional reorganisation. Therefore, changes in cortical activation when moving an affected body part (the ankle) may not be solely related to performance differences between people with HSP and healthy controls<sup>31</sup>. As described after stroke the different patterns of cortical activation may reflect differences in the degree of pathology affecting the sensorimotor system with more widespread, bilateral changes reflecting more severe pathology<sup>32</sup>. Patterns of functional re-organisation will also reflect additional factors such as the impact of environmental factors and task-related activity.



### **Box1: People's experience of HSP: Potential benefits of activities and exercise classes**

Bob was a keen runner, he experienced symptoms of pain around the pelvis for 7-8 years before in 1999 he was diagnosed with HSP type SPG4. With hindsight his pain may have been related to strategies he adopted while running to compensate for his increasing stiffness in the legs.

Following diagnosis Bob trialled Baclofen at a low dose, he described "minor, if any" improvement in his walking, and unfortunately he experienced significant and intolerable side effects of fatigue, drowsiness and "brain fog". Bob stopped taking the baclofen and has not tried any other type of anti-spasticity medication. In part this is because he feels that his spasticity still has a low to medium impact on his walking but also because he has taken up flying on a regular basis and cannot take baclofen under civil aviation authority rules.

Bob's walking difficulties have progressed over time; he currently has difficulty walking in the house and tends to cling onto furniture and walls. Outside he uses two crutches, he finds ball point ferrules provide the most effective grip when he places his crutches at more acute angles. He drives an automatic car with hand controls.

Bob describes "my legs they refuse to do what my Brain is telling them to do. When walking my knees hyperextend, and I get this swelling, pain and tenderness at the back of my knees. I often drag my toes and then my foot turns in (inverts) and can roll over." Bob describes his legs as stiff when he walks; he does get ankle clonus but very rarely spasms. To compensate for the stiffness in his legs Bob moves his trunk a lot while walking; unsurprisingly he has gradually over the years developed low back pain and reduced standing balance. He falls occasionally and this tends to be immediately after getting up from sitting for a prolonged period (>1 hr) of time. Bob can experience significant fatigue particularly toward the end of the day, at these times he may choose to use a wheelchair or rollator. Bob is clear that his fatigue is not only related to how much he physically does but also the degree of concentration required to safely move and function plus the emotional stress and impact this can have.

For the first 10-15 years Bob found functional electrical stimulation (FES) useful. He worked with the clinicians at the National FES centre in the UK where he developed a stimulation pattern of the trunk and hip abductors that helped to minimise the excessive trunk sway he experienced while walking (described in <sup>2</sup>). Bilateral stimulation for foot drop was also useful for a time. Recently Bob decided to stop using FES as it was no longer significantly helping his walking. He feels that FES may be more beneficial in the early stages of the condition. Instead he uses rigid Ankle foot orthoses; these keep his toes up and stop the inversion of his foot.

Throughout the years of managing his symptoms Bob has remained active and incorporates daily stretches for up to 5-10 minutes targeting his plantarflexors, hamstrings and quadriceps. Once a week he attends a 30 minute exercise class that is run by a trainer who is an ex-Olympic athlete with Multiple Sclerosis. In addition Bob has recently discovered 'riding 4 the disabled', he describes this as "fantastic"; as well as being enjoyable it helps his balance and core trunk strength.

## *Symptoms associated with HSP*

### **Limb Stiffness:**

Increased limb stiffness is a defining feature of HSP. Hypertonia is due to a combination of increased passive stiffness and enhanced excitability of the stretch reflexes<sup>33</sup>. People with HSP do not seem to have continuous muscle activity whilst trying to rest i.e. “spastic dystonia”. Cramps, particularly of the ankle plantarflexors, and lower limb flexor/extensor spasms, elicited by stimulation of the plantar aspect of the foot, have been reported.

Increases in passive stiffness can be seen when the joints of relaxed participants (as confirmed using surface EMG) are slowly stretched at speeds that do not elicit a stretch reflex (e.g. at 5°/s). Faster stretches elicit a short latency stretch reflex that is higher in amplitude compared to healthy controls and results in a further increase in stiffness. The difference between the stiffness measured at fast and slow speeds is an estimate of the stretch-reflex mediated stiffness and is proportional to the evoked EMG response<sup>33</sup>. The stiffness measured in this way, however, does not take into account the impact of passive changes and stretch reflex activity on the viscous response<sup>34</sup>. We have recorded stretch reflex thresholds as low as 10°/s in people with HSP. This has implications for clinical assessments using scales such as the Tardieu scale where the slow stretch that measures the passive component should be purposefully below the stretch reflex threshold (eg a 90° movement should take >9s to perform).

The mechanisms underlying hypertonia in HSP have not been as fully explored as they have been in other conditions. Whether increased passive stiffness is associated with an increase or change in the amount/ quality of the connective tissue as seen in cerebral palsy and spinal cord injury or is associated with shortened muscle fascicles as measured using ultrasound has not been reported to date<sup>35,36</sup>.

A limited exploration of the role of altered spinal cord inhibitory circuits in the genesis of spasticity has been performed. Mazzocchio and Rossi (1989) found in people with progressive spastic paraparesis and HSP that the Renshaw mediated recurrent inhibition was less than healthy controls. Further, there was a smaller reduction in recurrent inhibition with volitional movement compared to controls<sup>37</sup>. This may in part explain why stretch reflex mediated stiffness is not significantly different from healthy controls when a muscle is preactivated to ~10% of the maximum voluntary contraction and then stretched<sup>33</sup>. A theoretical explanation based on current evidence from people with HSP and other conditions is as follows: At rest reductions in spinal cord inhibitory circuits (eg recurrent and reciprocal inhibition) in people with spasticity contribute to a heightened stretch reflex size<sup>38</sup>. In contrast, with preactivation of the muscle inhibitory activity reduces in healthy participants but does not reduce as much in people with HSP<sup>39</sup>. This could result in similar values of spinal cord inhibition when the muscle is preactivated and thus a similar response to muscle stretch. Further, the overall stiffness is in part mediated by active cross bridge formation resulting in similar stiffness values between the two groups. From a practical basis, as other groups have highlighted, this has implications for the role of spasticity in causing difficulties with functional movements<sup>40,41</sup>. The high resistance to movement

when a resting muscle is passively stretched during a clinical examination on a treatment couch may therefore not correspond to the resistance occurring when the same muscle is stretched during a functional task when it is pre-activated (see also impact on functional ability below).

Changes in other spinal cord inhibitory circuits such as reciprocal and presynaptic inhibition; the development of motoneuronal plateau potentials and changes in 1a afferent neurotransmitter release that occurs with repetitive stimulation (reduction in postactivation depression) reported in other UMN syndromes have not been assessed in people with HSP. Recent work has found that there are differences in the pattern of inhibitory spinal cord circuit alterations in adults where spasticity developed over the developmental period (people with cerebral palsy) compared to adults with acquired spasticity (people with adult onset stroke)<sup>42</sup>. In adult cerebral palsy a reduction in presynaptic inhibition is observed but there are no reductions in reciprocal inhibition in contrast to the person with adult acquired spasticity<sup>42</sup>. Given that many types of HSP have an onset in early childhood (1 yr and above<sup>43</sup>), it would be interesting to compare spinal cord inhibitory circuitry in early and late onset HSP and whether this leads to any quantifiable impact on the response to muscle stretch and function.

Cortical modulation of stretch reflexes is also abnormal in HSP. Usually in healthy control participants the soleus H reflex is facilitated by prior stimulation of the motor cortex leg area at interstimulus intervals of 10 and 20 ms and 70-90ms. This early facilitation is lost in people with HSP and a new form of facilitation at an interstimulus interval of 40 ms is seen. This was felt to reflect the longer desynchronised central conduction times in HSP<sup>44</sup>. These changes were not related to motor function. Whether soleus H reflex modulation during stance and swing phase of walking is disrupted in HSP as described in other conditions with spasticity is currently unknown. However, phase dependent modulation of cutaneous reflexes elicited in tibialis anterior and biceps femoris by stimulation of the sural nerve are smaller in HSP<sup>45</sup>

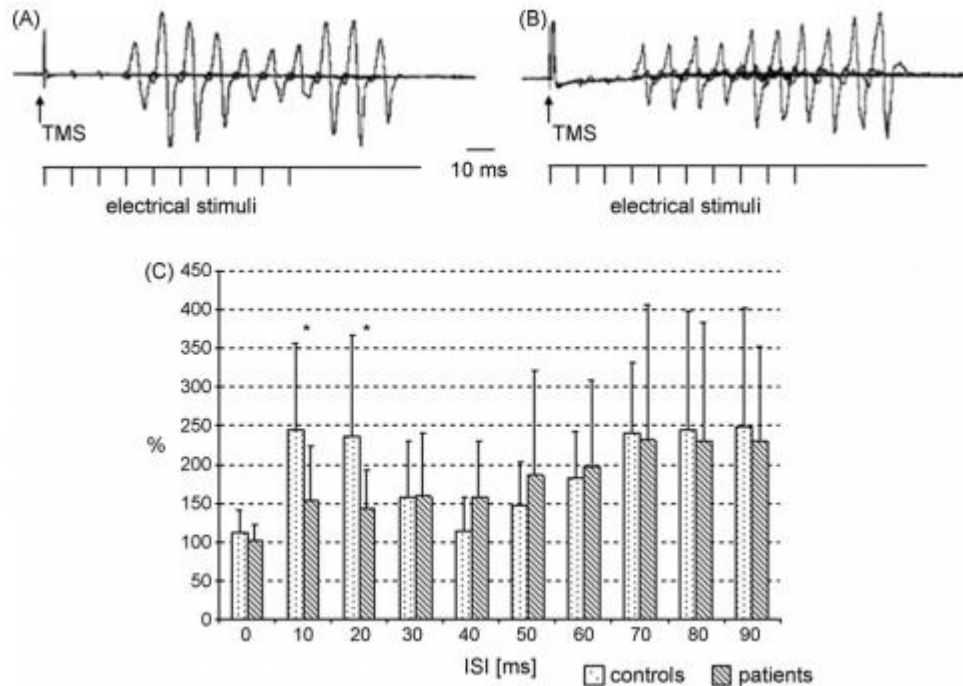


Figure x.1 Cortical modulation of the H reflex was assessed by stimulating the cortex using TMS at different inter-stimulus intervals (ISI) in the range 0-100 ms prior to stimulating the H reflex. The H reflex responses for a health participant (A) and person with HSP (B) are shown with ISI 0-90 ms superimposed. A comparison of the control (n=10) and HSP (n=10) groups show that early facilitation of the H reflex at ISI =10 and 20ms is less in HSP possibly reflecting longer desynchronised central conduction times (adapted from 44)

As with other conditions the central changes resulting in spasticity in HSP are unclear. The degree of spasticity (as measured by the Modified Ashworth test) is negatively correlated to activity in Brodman's area 4 and 1-2-3 measured using fMRI during ankle movements<sup>29</sup>. However, here spasticity may simply be a marker of disease severity and not reflect a causative relationship. The cortical silent period is an interruption of a voluntary muscle contraction following stimulation of the contralateral motor cortex using TMS. Earlier inhibition is in part spinally mediated whilst later suppression reflects the activation of GABA<sub>B</sub> (gamma-aminobutyric acid) receptor-mediated cortical inhibitory circuits<sup>46</sup>. In HSP (SPG4) the cortical silent period is shortened indicating reduced activity of motor cortical inhibitory interneurons. The reduction in the cortical silent period in turn was associated with the degree of spasticity as measured by the Ashworth scale<sup>47</sup>. This has correlates in stroke and Amyotrophic lateral sclerosis (see below), where a shortened cortical silent period is associated with the development of spasticity<sup>48-50</sup>. Using paired-pulse TMS other groups have found an increase in intracortical facilitation in AD-HSP<sup>51</sup>. The increase in intracortical facilitation may reflect a reduction in GABA-interneuronal activity (in keeping with the shortened cortical silent period) but may also reflect an increase in glutamateric transmission or a compensatory mechanism to increase corticospinal transmission. Interestingly the changes in intracortical facilitation were found in areas controlling hand

muscles. Thus, the association between changes in cortical silent period and spasticity may either be causative or reflect the co-occurrence of paresis and spasticity and compensatory mechanisms to maintain / increase corticospinal output<sup>51</sup>.

#### Paresis:

Lower limb weakness co-occurs with spasticity in HSP. Muscle strength is commonly described as being clinically less affected than that seen in other acquired UMN syndromes (Salenius, 2008). Objectively isometric maximal voluntary contraction of lower limb muscles in HSP has been measured using dynamometry<sup>52</sup>. The isometric contraction aimed to avoid reductions in applied torque by stretch reflex activation in antagonist muscle groups that may occur during isokinetic testing. Isometric muscle strength was lower in all lower muscle groups tested. When combined flexor and extensor muscle strength at the ankles, knees and hips was compared to healthy controls there was a proximal to distal gradient of weakness.

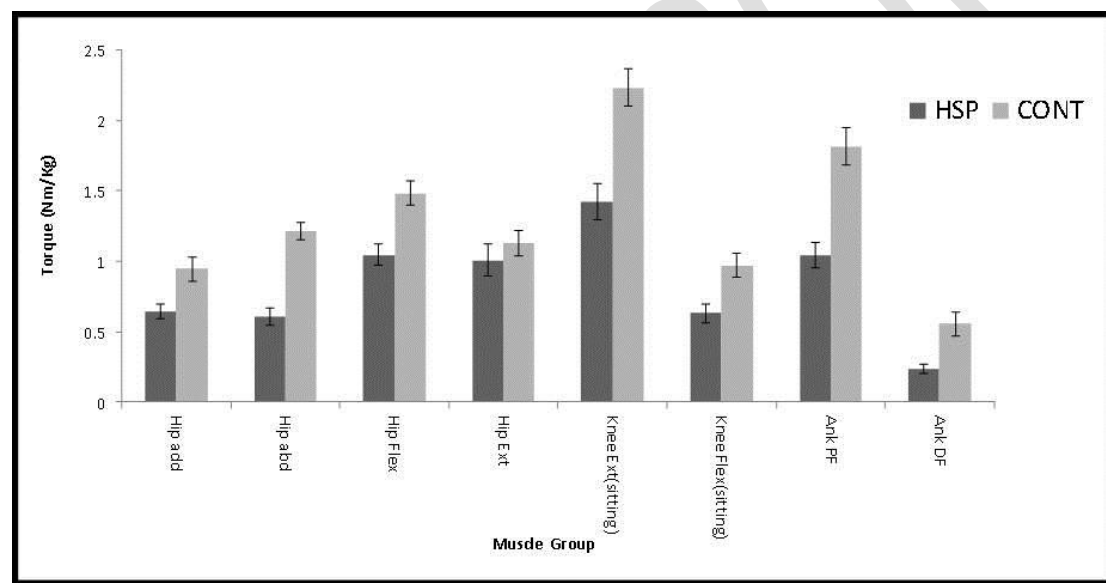


Figure x.2 Differences in isometric strength between people with HSP (n=20) and Healthy Controls (n=18)

The two muscles most affected were the ankle dorsiflexors and the hip abductors that were on average ~50% the strength of that seen in age and gender matched controls.<sup>52,53</sup>. Significant differences in the ratio between agonist-antagonist muscle strength are also seen. The ratio of hip abductor/hip adductor strength, for example is significantly lower in people with HSP. This muscle imbalance with relative sparing of some muscle groups such as the hip adductors may account for

“spastic gait patterns” such as scissoring while walking rather than being attributable to spasticity per se.

#### Sensory loss:

Vibration threshold is increased in ~40% of people with HSP and is greater distally at the hallux<sup>26</sup>. This may reflect degeneration of the fasciculus gracilis but also spinocerebellar degeneration as conscious perception of vibratory signals may be mediated by both pathways<sup>54,55</sup>.

#### Bladder:

Bladder dysfunction is seen in ~75% of people with HSP<sup>56,57</sup> but is often not reported. A retrospective review revealed symptoms of urgency (51.0-72.4%), frequency (55.1-65%), urinary incontinence (55.2-69.4%), hesitancy (51.7%) and incomplete bladder emptying (36.75%)<sup>56,57</sup>. Urodynamic analysis revealed detrusor overactivity in 82.7% of cases and detrusor sphincter dyssynergia in 65.5% of cases. Detrusor overactivity was associated with higher post-void residuals and symptoms of urinary frequency and nocturia<sup>56</sup>.

#### Bony changes

As HSP is a condition that can have an onset during development there is the potential for bony change similar to that seen in CP or Friedreich's ataxia / Charcot-Marie Tooth disease. These may contribute to motor dysfunction. In children with HSP hip joint motion in the transverse plane while walking is similar to typically developing children in contrast to children with Cerebral Palsy and spastic Diplegia (CP-SD) who demonstrate high internal rotation. Although not confirmed by X rays this suggests that in early onset HSP there is a physiological correction of femoral anteversion compared to children with CP-SD in whom symptoms are present from birth. Pes cavus is commonly seen in HSP. The high arched foot and altered heel alignment could affect the line of pull of the plantarflexors reducing the effective plantarflexor torque during the push off phase of walking. People with HSP commonly have an increased lumbar lordosis and, as highlighted below, trunk motion is often increased while walking; this is associated with a high incidence (>75%) of low back pain.

#### Fatigue

As with other long term neurological conditions fatigue is common and shows similar complexities. The degree of fatigue, for example, is not always related to the amount of physical activity performed and cognitive tasks, stress and anxiety may also impact on fatigue and walking performance.

#### Mood and Quality of Life

Reduced mobility is also associated with the presence of depression as measured by the Beck depression inventory with 28/48 (58%) of cases showing depression which in 75% of these cases was mild<sup>58</sup>. Quality of life is reduced in people with HSP and is lower in people with more severe disease (as measured by the Spastic Paraplegia Rating Scale<sup>59</sup>); reduced walking ability and the presence of a type 2, complicated presentation<sup>60,61</sup>.

### ***Impact of Spasticity and associated symptoms on Functional ability***

People with HSP in particular have difficulties with walking, balance and falls. Discussion and focus groups with people with HSP in the UK (n=30 Unpublished observations, <sup>62</sup>,) have highlighted the difficulties with functional tasks. Understanding these perceptions are important when elucidating the relative impact of symptoms such as spasticity and limb stiffness. People with HSP find that walking backwards (such as stepping back to open a door), walking on uneven terrain and on cambers/slopes particularly difficult. Falls can be precipitated by a loss of balance but also by tripping caused by foot drop as the foot either contacts external objects or catches the other foot/leg in swing phase. Walking is reported to require increased attention as people have to concentrate on their foot placement and performing concurrent tasks (ie walking and talking) can be difficult. Walking and lower limb stiffness was often (> 50% of respondents) modulated by the environmental temperature with stiffness higher and walking more difficult in cold weather compared to warm weather although very hot, humid climates were reported to cause excessive fatigue and limit walking ability.

### ***Balance***

Causes of poor balance in HSP could be due to multiple factors such as impaired central afferent and/or efferent signal processing, poor central integration of multi-sensory afferent signals, spasticity and secondary changes in muscle strength and musculo-tendinous stiffness.

People with HSP show delayed lower limb muscle responses to forward and backward postural perturbations<sup>63</sup>. This is presumably in part due to dorsal column-medial lemniscal and spinocerebellar degeneration leading to impaired processing of afferent signals that detect the onset, size and direction of the perturbation. An important role in afferent as opposed to efferent pathway pathology in causing balance dysfunction is supported by the fact that the onset of the lower limb muscle response following a perturbation is normalised when the perturbation is paired with an acoustic signal elicits a startle response<sup>64,65</sup>. This suggests that the efferent pathways mediating the startle response (presumed to be the reticulospinal tract) are intact. An improvement in muscle onset times with a startle response is also seen in healthy controls but it is more marked in people with HSP<sup>64,65</sup>.

Enhanced startle responses have been reported following pontine stroke where they are felt to arise due to a disruption of the cortical control of lower brain stem centres<sup>66</sup>. As many cortical projections to the brainstem arise from collaterals of the corticospinal tract a similar cause of enhanced responses to a startle could occur in people with HSP. The relative importance of abnormal processing of afferent information is supported by other groups that have found that higher degrees of standing postural sway are associated with increased vibratory thresholds<sup>53</sup>.

Muscle weakness also contributes to poor balance. Greater postural sway in the mediolateral plane is associated with greater weakness in the hip abductors. Greater antero-posterior sway during quiet standing and following a forward perturbation is correlated with greater weakness in the ankle plantarflexors<sup>53,67</sup>.

The role of spasticity in mediating imbalance remains unclear. de Niet et al 2012 found that greater stiffness (as measured by the modified ashworth scale) resulted in greater imbalance following a toe-

up perturbation in HSP<sup>67</sup>. This perturbation stretches the ankle plantarflexors and requires a stabilising response in the tibialis anterior. Interestingly the strength of the tibialis anterior (as measured using manual testing) did not affect the response size. In contrast Marsden and Stevenson 2012 measured ankle passive and stretch reflex mediated stiffness in people with HSP using motor-driven perturbations. They found that greater total ankle stiffness and stretch-mediated stiffness were associated with less antero-posterior sway<sup>53</sup>. They suggested that higher ankle stiffness may serve to aid stability.

### *Walking:*

Walking difficulties is a characteristic feature in HSP. A study of 194 people with HSP in Norway highlighted that 31% were classified as having mild symptoms; 32% as walkers that were unable to run; 25% as walkers dependent on walking aids and 11% as wheelchair dependent<sup>43</sup>.

People with HSP walk with a slower velocity, have a smaller step length, an increased stride and step time and a larger base of support<sup>68-70</sup>. The walking pattern in HSP has been characterised in several studies. Using cluster analysis Wolf et al (2011)<sup>70</sup> identified 5 clusters similar to that described previously for children with cerebral palsy<sup>71-73</sup> (figure x.1):



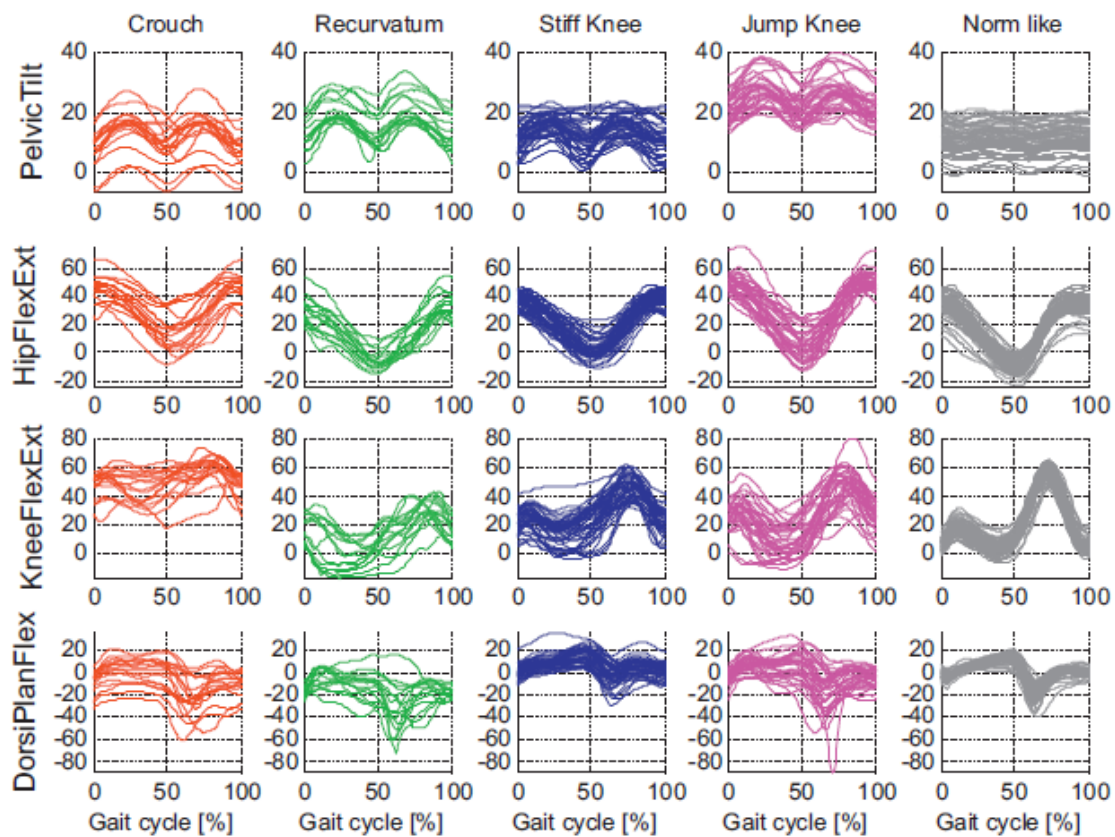


Fig. 1. Clusters of sagittal gait kinematics found across all subjects (HSP, CP, and NORM).

*Fig x.1 Walking patterns in people with HSP and CP highlighting different types of gait presentation.*

Crouch gait – characterised by increased hip and knee flexion during stance phase

Recurvatum – characterised by increased knee hyperextension in midstance

Stiff knee- characterised by reduced knee motion in swing phase

Jump Knee- characterised by increased knee flexion at loading response and almost normal knee function later in the gait cycle

Normative- a gait cycle similar to normative data obtained from healthy control participants.

Comparisons have been made between people with HSP and spastic diplegia due to cerebral palsy (CP-SD). In part this is driven by the desire to identify characteristics that may aid in the differential diagnosis of CP-SD. The proportion of people with prolonged knee and hip extension characteristic of a recurvatum pattern and prolonged ankle plantarflexion in stance phase was higher in people with HSP<sup>68,70</sup>. Increased amplitude and speed of trunk movement in the sagittal plane was also greater in people with HSP compared to people with CP-SD who tend to show higher shoulder motion (flexion / extension and elevation) akin to the “guarding” seen by infants in the early stages of walking<sup>69</sup>

There are several impairments that correlate with the characteristic walking patterns seen in people with HSP. For example, greater stiffness in the hip flexors, as assessed using the Ashworth scale, is associated with reduced active range of movement and slower walking speeds. Other studies have focused on specific aspects of the gait cycle such as ankle equinus and stiff knee gait as outlined below.

Early studies modelling walking have highlighted that movement of the leg in swing phase from knee flexion through to knee extension in terminal swing is in part passive in nature reflecting the motion of a multi-linked pendulum moving as a result of torques generated at the end of stance phase<sup>74</sup>. More recent modelling studies have highlighted the importance of muscle activity during swing phase in regulating the motion of the leg<sup>75,76</sup>. Eccentric lengthening of the rectus femoris muscle, for example, controls the initial rapid knee flexion at the start of swing phase whilst hamstring muscle activity acts to control the subsequent extension of the knee at the end of swing phase. Modelling studies have also highlighted the importance of the ankle plantarflexors and hip flexors in generating torques that initiate swing phase<sup>77,78</sup>.

Using dynamometry to produce motor-driven perturbations and test strength Marsden et al (2012) explored impairments that were associated with reduced knee flexion; the stiff knee gait. Of the variables prospectively assessed (knee extensor passive and stretch-mediated stiffness, ankle plantarflexion and hip flexion strength) they found that increased knee extensor passive stiffness and weakness in the ankle plantarflexors were associated with reduced ankle power and an increased knee extensor moment in preswing and in turn reduced knee flexion velocity and amplitude<sup>52</sup>. Lower knee flexion velocity at the start of swing phase was also associated with less knee extension at the end of stance phase reflecting the impact on the pendular motion of the leg (unpublished observations).

This study highlights the relative importance of passive stiffness and weakness in producing stiff knee gait. It also brings into question the relative role of knee extensor spasticity in limiting knee motion. Although knee extensor spasticity was significantly higher in people with HSP compared to controls this was not correlated with a limitation in knee flexion<sup>52</sup>. This could reflect the fact that with activation of the muscle at the end of stance phase the stretch-reflex mediated stiffness is normalised, as described above. However, the lack of correlation could also reflect the methods used. Knee extensor stiffness was measured with the participant in supine while they rested / preactivated the muscle. Although this reflects the assessment of limb stiffness in clinical practice stretch reflex activation

during walking was not assessed. In other UMN conditions it has been reported that the stretch reflex activity in the knee extensors normally modulates while walking being higher in amplitude during stance as opposed to swing phase. This is felt to reflect changes in the degree of muscle activation (and so the excitability of the motoneurone pool) but also modulation in pre- and post-synaptic inhibitory circuits within the spinal cord<sup>79</sup>. In other conditions with spasticity this degree of modulation is reduced<sup>80</sup>. Therefore stretch reflex behaviour at rest may not reflect that seen during functional movements. However, in support of the finding of a lack of relationship between knee extensor spasticity and stiff knee gait Piccini et al (2011) recorded less rectus femoris activity while walking in children with HSP in contrast to those with CP-SD where excessive activity was noted<sup>69</sup>. Other studies measuring spasticity using motor driven stretches have highlighted a potential role of spasticity in limiting joint motion while walking. Higher plantarflexor stiffness (due to a combination of passive and stretch-mediated stiffness) was associated with reduced ankle dorsiflexion during walking<sup>2</sup>. This effectively lengthens the limb during swing phase and contributes to the trips and falls seen in people with HSP.

Central motor conduction time to leg muscles as assessed using TMS does not correlate with gait parameters in HSP<sup>81</sup>. This is in keeping with studies in stroke suggesting that corticospinal tract damage (as determined via DTI, MRI and TMS) may not be key determinant in limiting walking ability<sup>82,83</sup> unlike its fundamental role in fine fractionated finger motion and hand function. This may be because walking is more dependent on subcortical circuitry<sup>84</sup> and/or because people are able to compensate for weakness by using other body segments to aid progression and by altering lower limb alignment relative to the ground reaction force to aid stability in stance.

There are several compensatory strategies that people with HSP seem to adopt to aid walking. Increased hip flexion during swing phase is associated with greater toe clearance<sup>2,69</sup>. The excessive trunk and pelvic motion seen in many people with HSP may also aid leg swing<sup>69</sup>. Higher trunk and pelvic horizontal and coronal motion is seen in people with less flexion of the knee during swing phase (unpublished observations) and may aid leg swing. Knee recurvatum brings the ground reaction force in front of the knee and could be a compensatory strategy to compensate for weakness in antigravity muscles such as the knee extensors which are more frequently MRC grade 1-2 and weaker compared to people with CP-SD<sup>68,69</sup>. Alternatively, knee hyperextension may be related to an increase in the plantarflexion/knee extension couple associated with increased plantarflexion stiffness as is often reported in CP-SD<sup>69</sup>. Determining the exact reasons for knee hyperextension in HSP is important in guiding treatments as reducing the ability to hyperextend the knee (eg with splinting) may result in instability in the presence of knee extensor weakness<sup>69</sup>.

These potential compensatory strategies may not be wholly beneficial. Increased trunk motion associated with an increased lumbar lordosis, anterior tilt of the pelvis<sup>69,70</sup> and tight hip flexors may contribute to the high incidence of low back pain. Further, knee recurvatum can be associated with stretching of the soft tissue on the posterior aspect of the knee and subsequent knee pain.

### *Outcome measurement*

There is a relative paucity of disease-specific rating scales for HSP. The Spastic Paraplegia Rating Scale (SPRS) described by Schule et al 2006 is a standardised, 13 item tool that combines measures of walking performance, stair climbing, rising from a chair, lower limb spasticity, muscle power, range of movement, pain and bladder and bowel function. An inventory of complicating signs and symptoms differentiates between pure and complex forms of HSP. The SPRS takes 15 minutes to complete and higher scores indicate worsening disease severity. The SPRS has high levels of inter-rater agreement (intraclass correlation coefficient=0.99), internal consistency (Cronbach  $\alpha$ =0.91), criterion ( $r=0.83$ ,  $p < 0.001$ ) and construct validity<sup>59</sup>.

## **Box2: People's experiences of HSP: The benefits of ITB and keeping active**

Pam describes symptoms of HSP occurring throughout all of her life, she was finally diagnosed 18 years ago, after 2 years of investigations, she was 33. Within her family, her grandmother, mother and brother all experience walking difficulties. She does not have a genetic diagnosis and does not feel that having one would make much difference.

Pam walks with one stick, she describes poor balance and the need to rest every 5 minutes as her legs become tired. She has difficulty climbing and descending stairs. Pam has lost confidence in her walking and falls about once a week. She tends to catch her toes as she lifts her feet, "I go straight down and am unable to use my arms to save myself". Pam explains that her legs can feel both stiff and weak and is particularly marked after any activity. She used to do stretches but did not find them helpful, instead she explains "I find a couple of hours out in the afternoon wandering around the shops is more beneficial than being sat in the house doing exercises".

Pam has an intrathecal baclofen pump that was implanted 1 ½ years ago. She found oral Baclofen made her very sleepy but this is no longer a problem with the ITB pump. Since having the pump Pam feels she stoops less and has a more upright posture when walking.

Before the operation she had symptoms of urgency ("wanting to go quickly"). In the last year Pam feels her bladder function has deteriorated. She now feels she wants to go but the urinary flow has stopped leading to her having an accident afterwards (symptoms akin to bladder sphincter dyssynergia). She has her pump filled locally and finds this very convenient and sees a Rehabilitation consultant once a year.

## **Interventions**

### ***Pharmacological and surgical treatment of spasticity***

The role of anti-spasticity medications in the management of spasticity and function have been explored in several studies. However, they show considerable bias with studies showing low sample sizes, a lack of control groups and blinding. A retrospective review of botulinum toxin injections into the hamstrings, hip adductors and gastrocnemius of 12 children (6.9 yrs+/- 4.9yrs) with HSP reported a decrease in stiffness (as measured by the Ashworth scale) and improvement in motor function (as measured by a 2.4 +/-3.2 change in the Gross Motor Function Measure GMFM) over an average 13.2 month (11.0) period<sup>85</sup>. The GMFM is an ordinal measure assessing movement ability in lying; sitting; standing and walking. Given the lack of a control group the results on function should be interpreted with caution. Comparing the results to children with CP of the same age and severity (as measured by the Gross Motor Classification Scale) the GMFM changes by ~5 points over a 1 year period<sup>86</sup> as the child develops new skills. Therefore, these results could simply result from changes in motor function with development. Subjectively 11/12 parents felt there was an improvement in motor function with

2/12 reporting an improvement in activities of daily living<sup>85</sup>. A series of 19 case reports in adolescents and adults with HSP described the use of Botulinum toxin injections into multiple muscle groups (hip adductors, iliopsoas, plantarflexors, rectus femoris and posterior tibial). Reductions in stiffness were widely reported and this could be associated with changes in posture (e.g. the ability to cross the legs) and function (e.g. walking) although 7/19 reported no or minimal global subjective effect. The functional effects were more marked in people with mild or moderate spasticity. Increased weakness was reported in 3/19 people which was felt to be an unmasking of underlying weakness following spasticity reduction<sup>87</sup>. Similar effects have been reported in 15 people with HSP who had injections into the hip adductors, plantarflexors or posterior tibial muscles. Reductions in adductor and plantarflexor spasticity were reported and 6/15 showed an improvement in walking velocity. The Functional Ambulation Category (FAC), and Rivermead Motor Assessment did not change<sup>88</sup>.

Oral anti-spasticity medications are frequently used in HSP including baclofen and tizanidine. To date there have been no trials of these medications in HSP. Clinical opinion suggests that they can be associated with widespread fatigue and improve spasticity in only a limited number of people<sup>87,88</sup>. Gabapentin is a GABA agonist originally used to treat epilepsy and neuropathic pain. Its effects were assessed in a cross-over trial of 10 people with HSP (SPG4)<sup>89</sup>. Blood samples confirmed a therapeutic dose (4000 mg/day) was present during the intervention periods. There were no differences between gabapentin and placebo in terms of subjective report of disability, clinical assessment of lower limb reflexes; strength or limb stiffness, walking scales or motor intracortical excitability as measured using TMS. In an open label trial of methylphenidate in people with sporadic and HSP no effect was found on walking speed or walking parameters after a 6 month period of use<sup>90</sup>.

Intrathecal baclofen has the advantage of reducing side effects associated with oral baclofen such as weakness and fatigue. Double blind administration of a bolus of baclofen into the intrathecal space is associated with a clear reduction in stiffness and deep tendon reflexes that is maintained with long term administration<sup>91</sup>. However, the impact on walking has only been assessed using case studies. Without the use of control groups or single case study designs with multiple baseline measures these studies clearly present with a risk of bias although they do highlight some potential benefits and limitations. Improvements have been seen in walking speed, walking kinematics/kinetics and angle-angle plots with either a single bolus or continuous infusion over time<sup>92-94</sup>. Other movements such as squatting also show a normalisation with a change from co-contraction to a reciprocal pattern of lower limb activation with a bolus of baclofen<sup>95</sup>. The timing of administration and the titration of the ITB dose is important. Satisfaction is higher in people in whom the implant occurs while they are still ambulant. Initially people can report weakness<sup>96</sup>. The reported therapeutic dose has varied from 60-264 micrograms per day and may vary depending on the underlying pattern of symptoms<sup>91</sup>. As well as potentially impacting on walking ability ITB may improve sleep time and efficiency and reduce periodic leg movements. These improvements reported in a study on 20 people with spasticity of whom 1 had HSP; they were not accompanied by any change in lung function tests or sleep related respiratory patterns<sup>97</sup>. Bladder function has also reported to improve with ITB<sup>98</sup>.

In four adults with pure (type 1) hereditary spastic paraparesis (genetic diagnosis not given) the effects of selective dorsal root rhizotomy from L2-S2 nerve roots have been described. Following the procedure reductions in tone and spasm frequency accompanied a subjective improvement in standing posture, stability and walking with a decrease in scissoring of gait <sup>99</sup>

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### **Box3: People's experiences of HSP: HSP across the lifespan**

Bill is 54 years old, he has experienced symptoms since birth. Up to the age of 27 his diagnosis was described as a "best estimate" of cerebral palsy. There was no known family history in previous generations. When his elder brother became affected in his early 30s this acted as a trigger for Bill to get 're-diagnosed'. At the time there was no specific gene testing but they were both given the diagnosis of HSP. Gene testing followed later with a positive diagnosis of SG4. Since that time Bill's Mother (aged 80) has tested positive for SPG4. She had experienced difficulty with mobility since her mid-60s but not to the same extent as her son's, she has recently had a fairly severe stroke and now is unable to weight bear. Another brother has also recently tested positive for SPG4 but so far is not showing any symptoms.

Bill walked without aids for several years, people would often comment 'we don't know how he walks, but he does'. Bill describes "typically I used to aim at where I needed to be, and grabbed hold of walls / furniture / shoulders to get there". He started to use a wheelchair at the age of 38. It had been suggested a number of years previously, but he had resisted. It turned out to be of great benefit, enabling outdoor mobility that he had previously lost. Bill now uses a wheelchair for most of his community mobility, at home he uses elbow crutches, but is limited to very short distances and describes his walking as "both uncomfortable and very slow". He tends to swing on his crutches, rather than take steps. Bill can just manage the stairs so long as there are hand rails on both sides, but it too is very effortful and slow.

A significant problem continues to be spasticity and painful spasms, these are problematic in the day, but also at night causing sleep disturbance. This exacerbates his fatigue which is an ongoing symptom requiring management. He also experiences a constant 'ache' and the feeling that "my muscles never properly relax." Bill did experience bladder frequency & urgency, this is now managed with self-catheterisation.

Bill had an Intrathecal Baclofen Pump implanted in 2011. He describes this as very beneficial, he has noticed a big improvement in his spasticity, with the drug now delivered over 24 hours without any of the unwelcome side effects of the oral medications. He had tried most of the anti-spasticity medications and had found them problematic mostly for two main reasons. "The dose required to positively affect my legs caused too much weakness in my upper body – which was a key part in enabling me to get around. So overall the drugs tended to make me less mobile and secondly they caused fatigue and I needed to sleep most afternoons'.

Bill has tried various other treatments over the years. Plaster casts to stretch his calf muscles were a regular feature in his younger years. He remembers "hating those casts". He would wear casts for 6-8 weeks a year, with them being changed weekly to increase the stretch. At other times in his childhood he had removable plaster casts for regular but intermittent use.

Bill has tried Functional Electrical Stimulation but did not find any benefit from it unlike other HSP support group members. He has found physiotherapy, exercises and stretching to be "very beneficial", but finds physiotherapy difficult to get to. He regularly stretches and feels it is important for stretching at home to become 'routine'. Bill has invested in a 'Theratrainer Cycle' and an 'EasyStand' hydraulic chair, he aims to use each of them for 30 mins once a week.



### *Physical Interventions*

Physical therapy is commonly prescribed for people with HSP. Techniques include progressive resisted exercises, stretches, task related training of walking and interventions targeting cardiovascular fitness<sup>100,101</sup>. Although focus groups highlight that people feel they benefit from physical therapy there have been no studies exploring their benefits. Given the paucity of evidence following systematic reviews for techniques such as stretching on spasticity and passive stiffness in other upper motor neuron syndromes it is important that this is evaluated<sup>102</sup>.

Orthoses have been prescribed to aid foot drop caused by combined anterior tibial weakness. If plantarflexor spasticity/stiffness is marked the orthosis often needs to be quite rigid; hinging the ankle joint in these cases can aid stair descent which requires a degree of ankle dorsiflexion. The aim of an orthosis has to be clearly defined. Some people with HSP may hyperextend their knee to compensate for knee extensor weakness in these cases reducing ankle plantarflexion may actually enhance instability by bringing the ground reaction force behind the knee joint requiring knee extensor activation<sup>69</sup>.

Marsden et al (2013) investigated the immediate effects of functional electrical stimulation (FES) of the common peroneal nerves bilaterally to aid foot drop during swing phase<sup>2</sup>. Participants were long term (>1yr) users of FES with either sporadic or hereditary spastic paraparesis. Walking speed increased with FES by 10% compared to no stimulation; there was no effect on walking efficiency as measured using the physiological cost index. Some participants had novel patterns of stimulation including stimulating the contralateral hip abductors and ipsilateral trunk extensors at the start of swing phase that also aided the clearance of the toe during swing phase<sup>2</sup>. Chronic electrical stimulation to improve muscle strength has also been reported in one case with familial spastic paraparesis. Here the quadriceps and tibialis anterior muscles were stimulated bilaterally 2-3x/week over 3 months. A 27% improvement in walking speed was observed with an improvement in the degree of crouch in stance phase<sup>103</sup>. Further work is required to ascertain whether there are long term carry over effects of FES and whether isolated electrical stimulation produces objective changes in muscle strength and function.

Hydrotherapy offers people with HSP the opportunity to use the buoyancy and drag of water to perform range of motion, strengthening and endurance exercises and to take advantage of the effects of warming (see below). A 10 week hydrotherapy (5 weeks group, 5 weeks individual with sessions x2/week) program was assessed in 10 people with HSP. Following the program the participants showed reduced total range of movement at the ankle, knee and hip in the transverse plane, enhanced hip internal rotation and an increase in hip extension moment in initial stance phase while walking. This was interpreted as being due to an increased use of compensatory strategies (see above) to aid foot clearance rather than a change in underlying impairment<sup>104</sup>.

The effects of localised changes in temperature of neuromuscular function, foot tap speed and walking ability have been explored in HSP by Denton et al 2015 (in submission). On separate days the temperature of one shank was raised ( $\sim 10^{\circ}\text{C}$ ) or lowered ( $\sim 13^{\circ}\text{C}$ ) using a temperature controlled water bath. Increases in lower limb peripheral nerve conduction velocity, the rate and amplitude of ankle muscle force output and a reduction in plantarflexor stretch-reflex mediated stiffness was observed with warming with opposite effects being seen with cooling. Further, despite one leg only being targeted there was an increase in maximal walking speed with warming ( $\sim 10\%$ ) and a similar sized decrease with cooling. Many of the effects on temperature were similar in magnitude in people with HSP compared to matched controls. However, the decrease in walking speed with cooling was more marked in people with HSP. This was interpreted as resulting from the fact that due to bilateral lower limb involvement a slight reduction in neuromuscular function in one leg has a marked effect on functional ability. In contrast healthy participants were able to compensate for this by using other body parts (eg trunk and opposite leg). These findings support the subjective view of people with HSP that their symptoms are worse in cold weather and suggests that strategies such as the use of insulating garments in colder weather, external warming (eg with heat packs, hydrotherapy) or exercise to increase internal temperature may aid stiffness and mobility.

### **Service Delivery**

Due to the rarity of HSP knowledge of the condition and service delivery for this condition can be variable. Poor local knowledge about the condition and its management by health care professionals, difficulty in accessing specialist services (in terms of availability and time), poor service co-ordination (eg between neurologists, genetic counsellors and allied health professionals) and access to evidence based treatments were issues raised in focus groups of people with HSP in a rural setting within the UK. Further, focus groups with carers highlighted the often large and continual burden placed upon them and the need to establish supportive networks<sup>62</sup>. One particular source of network support are the national support groups present in many countries that provide educational and emotional support throughout the disease process

## **Spinocerebellar Degenerations:**

### **Autosomal Dominant**

Anita Harding originally described three classifications of Autosomal Dominant Cerebellar Ataxias (ADCAs)<sup>13</sup>. Type 1 is characterised by a cerebellar syndrome with ophthalmoplegia, pyramidal or extra pyramidal signs, cognitive impairment or peripheral neuropathy. This presentation is caused by variable degenerations of the cerebellum, basal ganglia, cerebral cortex, optic nerve, pontomedullary systems, spinal tracts, or peripheral nerves. Pigmentary retinopathy accompanies a variable presentation of cerebellar and extra-cerebellar signs in ADCA II, otherwise similar to ADCA I. A third group, ADCA type III includes relatively pure cerebellar ataxias where the degenerative process is

limited to the cerebellum. Clinically characterised ADCAs are now increasingly also referred to as the spinocerebellar ataxias (SCA) denoting the genetic classification system. There are numerous SCAs identified and some labels reserved, as outlined in table x.2. The SCAs are clinically heterogeneous but they often present with progressive cerebellar ataxia. This usually starts with symptoms of ataxia while walking and poor balance followed by symptoms of limb ataxia, dysarthria and visual problems. Visual problems, although often not the first signs/symptoms detected by the patient have been proposed as an early sign, since the advent of pre-symptomatic genetic testing<sup>105</sup>. Visual problems can be caused by either oculomotor abnormalities secondary to cerebellar degeneration (eg saccadic dysmetria, impaired smooth pursuit and nystagmus) or non-cerebellar causes (eg maculopathy, gaze palsies, slowed saccades). Maculopathy can precede the appearance of the cerebellar ataxia in SCA7 by up to 20 years<sup>106,107</sup>. Cerebellar degeneration often is accompanied by involvement of the brainstem and spinal cord although relatively isolated cerebellar degeneration can occur (eg in SCA6)<sup>108</sup>. A description of the pathology, clinical presentation and intervention of SCA3 the most common SCA presenting with additional UMN signs will be described.

Table x.2: Adapted from Giunti and Wood, 2007<sup>109</sup>

Gene name (chromosome location and locus)	Protein & mutation	Pertinent features
<b>ADCA I</b>		<b><i>Cerebellar syndrome plus ophthalmoplegia, pyramidal or extra pyramidal signs, cognitive impairment or peripheral neuropathy</i></b>
<b>SCA1</b> (6p22.3 ATXN1)	Ataxin 1 CAG repeat	Ataxia, pyramidal signs, neuropathy, ophthalmoplegia
<b>SCA2</b> (12q24.13 ATXN2)	Ataxin 2 CAG repeat	Ataxia, slow saccades, neuropathy
<b>SCA3</b> (14q32.12 ATXN3)	Ataxin 3 CAG repeat	Ataxia, pyramidal signs, ophthalmoplegia, neuropathy, dystonia
<b>SCA4</b> (16q24-qter SCA4)	Unknown	Ataxia, sensory neuropathy
<b>SCA8</b> (13q21 KLHL1AS)	Kelch-like 1 CTG repeat	Ataxia, sensory neuropathy
<b>SCA9</b> Reserved	Unknown	
<b>SCA10</b> 22q13.31 ATXN10	Ataxin 10 ATTCT repeat	Ataxia and epilepsy
<b>SCA12</b> 5q32 PPP2R2B	PPP2R2B CAG repeat	Ataxia, tremor
<b>SCA13</b> 19q13.33 KCNC3	KCNC3 MM	Ataxia, mental retardation
<b>SCA14</b> 19q13.42 PRKCG	PRKCG MM	Ataxia, myoclonus dystonia
<b>SCA17</b> 6q27 TBP	TBP CAG repeat	Ataxia, chorea, psychiatric manifestations, dementia, epilepsy
<b>SCA18</b> 7q31-q32	Unknown	Ataxia, sensory neuropathy
<b>SCA19*</b> 1p21-q21	Unknown	Ataxia, myoclonus, cognitive impairment
<b>SCA20</b> 11	Unknown	Ataxia, disphonia
<b>SCA21</b> 7p21.3-p15.1	Unknown	Ataxia, parkinsonism
<b>SCA22*</b> 1p21-q23	Unknown	Ataxia
<b>SCA23</b> 20p13-p12.2	Unknown	Ataxia, sensory neuropathy
<b>SCA25</b> 2p21-p15	Unknown	Ataxia, sensory neuropathy
<b>SCA27</b> 13q33.1 FGF14	FGF14 MM	Ataxia tremor mental retardation
<b>SCA28</b> 18p11.22-q11.2	Unknown	Ataxia, ophthalmoplegia
<b>DRPLA</b> 12p13.31 ATN1	Atrophin 1 CAG repeat	Ataxia, myoclonus, seizures, psychiatric manifestation, dementia

Undefined** 16q22.1	PLEKHG4 Puratrophin 1 5' SNS	Ataxia, sensory neuropathy
<b>ADCA II</b>  SCA7 3p14.1 ATXN7	  Ataxin 7 CAG repeat	<b>Variable similar presentation to ADCA plus the presence of pigmentary retinopathy</b>  Cerebellar ataxia, pyramidal signs, pigmentary maculopathy
<b>ADCA III</b>  <b>SCA6</b> 19p13.13 CACNA1A  <b>SCA5</b> 11q13.2 SPTBN2 <b>SCA11</b> 15q14-q21.3 SCA11 <b>SCA15</b> 3p24.2-pter ITRP1  <b>SCA16</b> 8q23-q24.1  <b>SCA24</b> 1p36  <b>SCA26</b> 19p13.3	  CACNA1A CAG repeat  Beta-III spectrin D, MM  Unknown  ITRP1 D  Unknown  Unknown  Unknown	<b>Relatively pure cerebellar ataxias where the degenerative process is limited to the cerebellum</b> Almost pure cerebellar ataxia (occasional dystonia or Parkinsonianism described)  Almost pure cerebellar ataxia  Almost pure cerebellar ataxia  Almost pure cerebellar ataxia  Almost pure cerebellar ataxia  Almost pure cerebellar ataxia  Almost pure cerebellar ataxia

### SCA3 or Machado-Joseph disease (MJD)

Depending on ethnicity SCA3 accounts for between 21-56% of SCA cases<sup>110</sup>. Prevalence varies according to founder effects. It is a polyglutamate (polyQ) disease caused by a CAG repeated expansion of the ATXN3 gene on chromosome 14q. The protein encoded by ATXN3, Ataxin-3, is a deubiquitinating enzyme that cleaves ubiquitin off substrates. It is felt that this enzyme's function and thus biochemical pathways dependent on ubiquitin are affected in SCA3<sup>111</sup>. The age of onset varies from childhood to late adult life and there is an inverse correlation between the number of CAG repeats and the age of onset and disease severity<sup>112</sup>.

The pathology includes atrophy of the middle cerebellar peduncles, dentate nucleus of the cerebellum and pontine nuclei i.e. cerebello-thalamo-cortical motor loops. The pathology also affects the substantia nigra, subthalamic nuclei (basal ganglia thalamocortical loops), red nuclei, anterior horn cells, motor cranial nerves. Additional pathology has been described in the somatosensory, auditory and oculomotor systems. Brainstem involvement affecting dopaminergic and cholinergic system is also present. The corticospinal tract however is not severely affected and central motor conduction times have been found to be normal.<sup>110,113-115</sup>

Symptoms include progressive ataxic gait and balance and dysarthria. Associated with this are symptoms of spasticity, hyperreflexia and nystagmus. In some cases cerebellar-cognitive changes are also observed, namely deficits in memory, executive dysfunction, naming and attention; visuo-spatial processing and calculation, however, appear spared<sup>116</sup>. In later stages there is ophthalmoplegia and slowing of saccades; amyotrophy and dystonic posturing. There can also be peripheral nerve involvement leading to a loss of distal sensation and areflexia that is more prominent in older people. Difficulty falling asleep, increased nocturnal waking is more common in older people with brainstem involvement and can be associated with central apnoea and restless legs syndrome<sup>110</sup>.

The presenting symptoms vary with the age of onset and different types of presentation have been described (table x.3), type 2 being the most common seen in ~57-75% of cases. Earlier onset cases and those with large CAG repeat expansions tend to have signs of spasticity<sup>113</sup>. The presence of early UMN signs with minimal cerebellar signs can make SCA3 difficult to distinguish from HSP and this has been described as the type 5 presentation<sup>3,113,117</sup>

SCA3 Type	Mean age of onset (Range)	Symptoms
1	25yrs	Spasticity, rigidity, bradykinesia with minimal ataxia
2	38 yrs (20-50)	Progressive ataxia and upper motor neuron signs (spasticity , paresis)
3	48 yrs (40-75)	Ataxia and peripheral nerve involvement with amyotrophy and generalised areflexia
4	Variable age of onset	Parkinsonian phenotype
5	25yrs (12-48) <sup>117</sup>	"Pure" progressive spastic paraplegia

*Table x.3 Clinical and Subtype Clinical Characteristics*

#### Box 4: Symptom Presentation and Balance dysfunction in SCA3 and SCA6

Despite balance being an early and well-described symptom, the mechanistic underpinnings of balance impairment remain poorly understood. Tables 1-4 compare the differences between a relatively pure group of 16 people with cerebellar ataxia (SCA6) to four individual subjects with SCA3. These presentations outline the variability of SCA3 presentations and the multi-factorial potential for signs and symptoms to contribute to balance impairment, in contrast to SCA6 where the balance impairment involved is likely to solely be due to cerebellar disease. Table 1 highlights differences in clinical scores

SCA type:	Age:	Sex :	Age at onset	SARA (/40, most severe ataxia)	Highest scoring elements of SARA:	Berg score (/56, best balance function)	Falls in last 6 months	Loss of functional independence, (FIM score /126, best independence) :	Mobility aid use:	Abnormal MMSE (score):
SCA3 a	40	m	28	17	Gait	31	Y (n=3, lost balance)	Y (117)	Y (rollator)	N (24)
SCA3 b	53	f	45	2	Gait	56	N	N (126)	N	N (30)
SCA3 c	49	M	35	14	Gait	20	Y (n=3, legs gave way/lost balance)	Y (120)	Y (sticks)	N (24)
SCA3 d	54	f	40	27.5	Gait	5	Y (n=7, lost balance)	Y (117)	Y (WCH)	Y (12)
SCA6: Mean (SD)	62.3 (10.2)	7m: 9f	52.2 (16.4)	12 (6.1)	Gait	35.0 (17.4)	1.9 (2.1)	Y 122.3 (4.7)	None (n=8) Stick (n=5) Crutch (n=3) Rollator (n=2) WCH (n=2, outdoor only)	Abnormal MMSE (score):

Table 1 Functional overview of individual SCA3 cases contrasted to typical SCA6 group

#### Box 4 Continued

#### Symptom Presentation and Balance dysfunction in SCA3 and SCA6

As can be seen by table 2 people with SCA3 more frequently have abnormalities in upper motor neuron signs , sensory loss and spasticity / spasms.

SCA type:	Proprioceptive loss (hallux longus position in space test):	Abnormal Babinski:	Abnormal monofilament (<9/10):	Muscle weakness (triceps surae), (/5, best muscle strength):	Increase in tone (Ashworth scale, ankle PF):	ROM restrictions:	Spams (Penn spasm scale)
SCA3a	N	N	N (av 10)	N (5/5 bilateral)	N (1/5 bilateral)	N	N
SCA3b	N	Y (absent)	Y (av 8.5)	N (5/5 bilateral)	N (1/5 bilateral)	Y (-5 DF bilateral)	N
SCA3c	Y (bilateral)	N	Y (av 1)	Y (4/5 bilateral)	Y (3/4 bilateral)	Y (-5 DF bilateral)	Y (4)
SCA3d	Y (bilateral)	Y (absent)	Y (av 4)	N (5/5 bilateral)	N (1/5 bilateral)	N	Y (2)
SCA6: Mean (SD)	No	No	No (Mean: 9.9 SD: 0.3)	Mean:4.6 SD: 0.6	No	No	None

Table 2 Individual SCA3 sensorimotor assessment contrasted to typical SCA6 group

SCA type:	Gait	Stance	Sitting balance	Speech	Finger chase (dysmetria)	Nose to finger (tremor)	Hand movements (dysdiadochokinesia)	Heel shin (co-ordination)	Total	BalSARA
SCA3a	5	2	2	0	3	1	2	2	17	9
SCA3b	1	0	0	0	0.5	0	0	0.5	2	1
SCA3c	3	3	0	2	1	1	1	3	14	6
SCA3d	6	5	2	3	3	3	2.5	3	27.5	13
SCA6: Mean (SD)	3 (1.7)	1.5 (1.0)	0.3 (0.7)	2.1 (1.1)	1.3 (1.0)	0.5 (0.5)	1.6 (1.0)	1.7 (1.2)	12.0 (6.1)	4.8 (3.1)

Table 3 Individual SCA3 SARA scores contrasted to typical SCA6 group

### **Symptomatic Management**

SCAs are progressively degenerative in nature and ultimately lead to death over a typical period of 15 to 30 years. SCA6 is, however, an exception due to the late onset and slower progressive nature of the disease and is often not life limiting. No therapeutic strategies are as yet available to target primary disease pathways in those with SCA and therefore current management approaches involve designing treatments to alleviate symptoms.

Recommendations for the symptomatic treatments of spasticity, parkinsonism, dystonia and cramps have been outlined and include benzodiazepines, baclofen and carbamazepine<sup>118,119</sup>. A case study has described the use of botulinum toxin injections for lower limb spasticity and cramps that produced no side effects although the clinical benefits were not described<sup>120</sup>. In contrast botulinum toxin injections for associated cervical dystonia have been associated with dysphagia<sup>121</sup>. A double blind randomised controlled trial<sup>122</sup> of the antibiotics sulfamethoxazole and trimethoprim (co-trimoxazole) have not supported the improvements in spasticity and rigidity described by earlier smaller trials.<sup>123,124</sup> . Some people with SCA3 can show levodopa-responsive dystonia and therefore patients should undergo a levodopa trial if dystonia is present. SCAs involving parkinsonian features, such as SCA2 and 3 (MJD) often respond to dopaminergic therapy, such as levodopa<sup>125-128</sup> and dopaminergic drugs can also be helpful in ameliorating restless legs to aid uninterrupted sleep<sup>128,129</sup><sup>130</sup>. Amantadine is sometimes used to treat dystonia and bradykinesia<sup>128,131</sup>. Those experiencing muscle cramps, most commonly encountered in SCA3, can trial magnesium, chinine, quinine or mexiletine drug therapies<sup>132</sup>. As with other SCAs and cerebellar disorders the pharmacological management of ataxia is limited<sup>118,133</sup>. Tandospirone may improve symptoms of ataxia, depression and insomnia<sup>119</sup>.

Rehabilitation is recommended including physical therapy to address strength, balance and gait and offer advice on falls management as well as speech therapy and dietetics to address issues of dysphagia and dysarthria, to prevent aspiration pneumonia, weight loss and dehydration<sup>134</sup>. Maintenance of mobility and fatigue management with appropriate use of walking aids and wheelchairs is also required as the disease progresses and it is recommended that these should be prescribed before falls cause fractures and long lasting immobilisation<sup>128</sup>. Splints and orthoses may prevent trauma from over-supination or pain from over-extension of the knee<sup>128</sup>. No evidence exists however for the efficacy of these interventions leading to uncertainty and variability in approaches. Management recommendations for SCA3 are currently mainly based on the evidence base for treating people with Parkinson's disease<sup>111,135</sup>.

### **Autosomal Recessive**

Most autosomal recessive ataxias have symptoms of limb ataxia and impaired balance and walking. Additional signs include vertigo, dysphagia and diplopia<sup>136</sup>. Unlike the autosomal dominant ataxia that present with associated extrapyramidal and pyramidal signs the autosomal recessive ataxias often have additional signs of sensorimotor neuropathy resulting in loss of proprioception and vibration sense<sup>136</sup>.



### Friedreich's ataxia and Late onset Friedreich's ataxia

Friedreich's ataxia (FRDA) is the most common autosomal recessive ataxia affecting 2 per 100,000. In ~98% of cases it is caused by a GAA repeat expansion on the Frataxin gene on chromosome 9q13. The age of onset is inversely related to the size of the repeat. Frataxin is localised to the mitochondrial matrix, it associated with iron metabolism and homeostasis. It is deficient in FRDA and increased mitochondrial iron accumulation, increased oxidative stress, impaired ATP production and cell death are seen <sup>136,137</sup>.

Degeneration of the dorsal columns, spinocerebellar tracts and dentate nucleus occurs in FRDA. It is characterised by progressive ataxia (affecting balance, walking limbs and speech) and sensory signs. Axonal sensory neuropathy results in areflexia and a loss of proprioception and vibration sense. Corticospinal tract involvement leads to paresis and extensor plantar responses <sup>138</sup>. Non – neurological involvement includes cardiomyopathy in ~50% and diabetes mellitus in ~10%. With disease progression symptoms of kyphoscoliosis and pes cavus/equinovarus become prominent and these can affect respiratory function and walking <sup>139</sup>.

Variations of the typical Friedreich's ataxia presentation exist in ~10% of cases having a positive molecular test for Friedreich's ataxia. People can show Friedreich's ataxia with retained reflexes (FARR) and also late onset Friedreich's ataxia (LOFA) or very late onset Friedreich's ataxia (VLOFA) where symptom onset occurs after 25 and 40 yrs respectively <sup>140</sup>. Unlike typical Friedreich's ataxia people with LOFA show signs of spasticity (40% of cases) and have retained reflexes (46% of cases) <sup>141,142</sup>. Non neurological symptoms such as cardiomyopathy, sphincter disturbances, scoliosis and pes cavus are less frequent in atypical FRDA <sup>142</sup>. In VLOFA a spastic tetraparesis without marked ataxia or neuropathy has been described <sup>143</sup>. Oculomotor abnormalities may be absent in atypical FA. People with LOFA have a slower progression and smaller GAA expansions. Another atypical FRDA is found in Acadian families from New Brunswick, Canada. These individuals can have the same onset and symptoms as FRDA but without the involvement of cardiomyopathy and diabetes and may also show retained reflexes and spasticity.

### Management of FRDA

There is currently no specific information on the management of LOFA and VLOFA. Therefore a brief overview of the management of FRDA will be provided.

Co enzyme Q10 and Idebenone:

Co-enzyme Q10 is a mitochondrial molecule that is part of the electron transfer chain. It is a potent antioxidant and can maintain other antioxidants such as vitamin E. Idebenone is a structural analog of co-enzyme Q10 but it is more water soluble and has a lower molecular weight and may thus show greater bioavailability <sup>137</sup>. There is some evidence from randomised controlled trials in the USA and Europe to suggest improved cardiac function and maintenance / improvements in fine motor skills following idebenone <sup>137</sup>. However, as reviewed by Parkinson et al this seems to be dependent on the prescribed dose and baseline disease severity (improvements may be more marked in ambulant, less

severe children). The impact on neurological signs and in particular functional ability and quality of life is unclear<sup>137</sup>.

### Symptomatic management

Rehabilitation for FRDA involves a multi-disciplinary team including speech therapists and dieticians (to address communication issues, dysphagia, diabetes-management), occupational therapy, orthotists and physiotherapy<sup>144</sup>. A retrospective review of in-patient rehabilitation in people with FRDA found improvements in function (as measured by the functional independent measure) that continued to improve on discharge<sup>145</sup>. Physiotherapy commonly consists of progressive resisted exercises and stretching<sup>146</sup>. In addition mobility can be aided by aids (eg walking aids/ wheelchairs) and orthoses / shoes for pes cavus<sup>147</sup>. Orthopaedic management of scoliosis may also be required and early management of the pes cavus foot has been suggested<sup>148</sup>.

Uptake of home rehabilitation programmes by people with FRDA can be sparse (~10%)<sup>146</sup>. This could be related to perceptions of a lack of expertise by prescribing therapists about the condition as well as a lack of access to appropriate therapists. Issues around a lack of time and energy and the association of treatment with the presence of disability are further barriers highlighted<sup>146</sup>. The compliance with therapy may be increased by the use of interactive whole-body controlled video game technology. Intensive training over an 8 week period of balance and co-ordination skills resulted in improvements in ataxic symptoms, balance and walking<sup>149,150</sup>. Endurance training is feasible in people with FRDA and can lead to improvements in markers of cardiovascular fitness. A static exercise bike was used for training, which has the advantage of reducing balance requirements, and cardiac function was monitored during training<sup>151</sup>.

Intrathecal baclofen has been used to reduce painful spasms in a case with FRDA<sup>152</sup> whilst oral baclofen and botulinum toxin have been recommended for spasticity management<sup>144</sup>. There are no clinical trials or reports on the management of spasticity in late onset FRDA.

### Motor Neuron Disorders and Familial Amyotrophic lateral sclerosis

Motor Neuron Disease: Amyotrophic lateral sclerosis (ALS) accounts for 70-90% of cases of Motor Neuron Disease and is characterised by predominant lower motor neuron (LMN) signs of weakness in combination with mild UMN signs of spasticity and brisk reflexes. A minority of people with ALS, termed UMN-Dominant, have pyramidal signs and severe spino-bulbar spasticity with slight LMN signs. In 2-5% of people with Motor Neuron Disease there is exclusive involvement of UMNs termed primary lateral sclerosis. In contrast, people without any clinical or electrophysiological UMN signs and only LMN signs are labelled as progressive muscular atrophy. The remaining subtypes of MND are characterised by LMN signs affecting the bulbar muscles (Progressive bulbar palsy) or UMN involvement affecting the bulbar muscles (Pseudobulbar palsy)<sup>153</sup>.

## Amyotrophic lateral sclerosis

### Prevalence and Genetics

ALS has a prevalence of 3.4-5.4 per 100,000. The age of onset is usually in late adult hood (65yrs), and survival time is 2-3 yr for bulbar onset and 3-5 yrs for limb presentation onset. People with an UMN-Dominant presentation have a longer survival time <sup>153</sup>.

Familial ALS (FALS) is diagnosed where there is a first or second degree relative of the index case. FALS accounts for 4.6% of cases of ALS <sup>154</sup>. Familial ALS is usually inherited in an autosomal dominant manner but autosomal and recessive patterns of inheritance have been described.

Mutations in the SOD1 gene, the first gene on chromosome 21 found to cause FALS, accounts for 20% of Familial ALS cases. The gene C9ORF72 is linked to chromosome 9p21 and makes up ~43% of FALS and 7% of sporadic cases. This form of FALS is associated with Frontotemporal dementia. The genes TARDBP, FUS, VCP, UBQLN2 and OPTN comprise the majority of the remaining genes causing FALS <sup>155,156</sup>.

### Pathology

ALS is associated with degeneration of the corticospinal tract and alpha and gamma motor neurons and interneurons in the spinal cord and Betz cells within the primary motor cortex. There is additional degeneration in the deep frontal and temporal white matter, corpus callosum, brainstem (including serotonergic neurons) and motor nuclei of the basal ganglia <sup>157</sup>. People with ALS and an expansion in the gene C9ORF72 have additional pathology in the frontal cortex and hippocampus (CA4 area) in keeping with the association of frontotemporal dementia <sup>156</sup>.

Hyperexcitability in the motor cortex is seen early on in the disease course; there is a reduction in GABA<sub>A</sub>-mediated short interval intracortical inhibition (SICI); a reduced motor threshold and an increase in the cortical silent period, which is mediated in part by GABA<sub>B</sub> interneurons. Cortical hyperexcitability is felt to reflect degeneration of inhibitory interneurons in the motor cortex and may contribute to the presence of positive symptoms such as cramps, fasciculations, fibrillations, sharp waves and spasticity. With disease progression there is a reduction in cortical excitability reflecting degeneration of corticomotorneuronal pathways <sup>158</sup>.

Signs of hyperexcitability in the motor system such as the UMN positive signs are poor prognostic indicators. In SOD1 carriers cortical hyperexcitability can be seen prior to symptom onset and is associated with early weakness <sup>159,160</sup>. The reduction in SICI correlates with disease duration and motor deficit. It is hypothesised that cortical hyperexcitability can alter glutamate metabolism and lead to a dying forward of connected anterior motor neurons. An alternate hypothesis is that the hyperexcitability reflects a compensatory process that aims to increase central drive to the degenerating LMNs <sup>158</sup>.

### **Clinical Presentation**

In ALS the onset of symptoms is usually focal weakness in the proximal or distal upper or lower limbs. Weakness develops in the other segments and limbs and this may be accompanied by bulbar and respiratory weakness. On examination muscle fasciculations are visible. Upper limb symptoms are associated with bulbar signs (dysphagia and dysarthria)<sup>161</sup>. The degree of lower limb weakness predicts the level of walking ability (eg independent in the community, home ambulation, unable)<sup>162-164</sup>. Loss of ambulation occurs when the lower limb strength was on average 13.7% ( $\pm 7.4$ ) of the predicted normal level<sup>162</sup>. In one cohort loss of ambulation occurs on average after 46.7 months, about 11-15 months after provision of gastrostomy and Non Invasive Ventilation<sup>165</sup>. In people with genetic linkage to chromosomes 9p21 and an expansion in the gene C9ORF72 there are associated signs of frontotemporal dementia in 35% of cases including personality change, irritability, obsessions, poor insight, and deficits in frontal executive tests<sup>156,166</sup>. In many people painful cramps and flexor spasms can occur in the latter stages. Bulbar symptoms may be UMN and LMN in nature. Tongue movements may be slow due to spasticity and fasciculations and wasting of the tongue may be present. The jaw jerk may be brisk especially with bulbar onset disease. Respiratory muscle weakness can lead to dyspnoea on exertion, orthopnoea, disturbed sleep, morning headaches, daytime somnolence, weak cough and paradoxical abdomen movements<sup>153</sup>. Death is usually due to respiratory failure and pulmonary complications.

Spasticity is present in ALS as determined using clinical and electrophysiological measures (ie the H reflex)<sup>167 168</sup>. However, upper motor neuron signs can be difficult to elicit in ALS with only 50% of cases showing an extensor plantar response<sup>157</sup>. Spasticity is often hard to detect in weak muscles in ALS<sup>157</sup>. This may reflect the co-occurrence of lower motor neuron signs that mask patterns of cortico-spinal tract induced paresis and enhanced tendon reflexes. LMN signs are not seen in progressive lateral sclerosis and here spasticity is more marked<sup>157</sup>. In addition interneuronal degeneration within the spinal cord in ALS could also limit the emergence of hyperexcitable tendon reflexes<sup>157</sup>. Direct pathology affecting the Renshaw cells within the spinal cord, for example, may explain why the Renshaw-mediated recurrent inhibition is reduced to a greater extent than seen after spinal cord injury<sup>168</sup>.

Rigidity, felt as an increased resistance of a limb to movement in both directions, can also be present in ALS. Extrapyramidal signs as indicated by rigidity and a shortening reaction were assessed in a selected cohort of people with ALS (n=39) who had stiffness (> 2 Ashworth in both legs) but minimal weakness (at least 4/5 MRC manual testing). People who met this inclusion criterion made up 17% of the total sample assessed. In this subsample extrapyramidal signs in combination with spasticity were seen in 69% with the remainder presenting with spasticity alone<sup>169</sup>. People with mixed rigid-spasticity presentation had worse balance, more retropulsion and more severe neck stiffness<sup>169</sup>. The presence of extrapyramidal signs is reflected in the reduced dopaminergic activity assessed using PET and reduced D2-receptor binding as assessed using SPECT<sup>170-172</sup>. As there are large corticostriatal connections, striatal involvement may be caused by glutamate excitotoxicity.

In ALS degeneration of serotonergic (5-HT) neurons that project to the spinal cord is observed post mortem and in the SOD1 animal model<sup>173</sup>. In spinal cord injury loss of serotonergic projections from the brainstem dorsal raphe nuclei leads to secondary up-regulation of 5HT receptors on lower motor neurons that results in hyperexcitability, plateau potential generation and spasticity<sup>174,175</sup>. Therefore, the loss of serotonergic neurons in ALS may underlie the development of spasticity.

The involvement of tracts other than corticospinal tract in the genesis of spasticity in ALS is underlined by the fact that corticospinal tract degeneration can be seen in 50% of people with a clinical diagnosis of progressive muscle atrophy who had no UMN signs when alive<sup>176</sup>. Therefore, findings such as a correlation between precentral gyrus degeneration, as measured by DTI, and spasticity<sup>177</sup> may simply reflect the co-occurrence of motor cortex pathology and spasticity in more severe cases of ALS and not reflect a causative link.

## Interventions

### *Disease modifying therapy*

Riluzole prolongs median survival by 2-3 months if taken for 18 months (100mg) in people with clinically definite ALS and symptoms of less than 5 years who are under 75yrs and have a forced vital capacity >60%<sup>178</sup>. Riluzole partly resolves the reduction in SICl and may act by inhibiting glutamate release and reducing cortical hyperexcitability<sup>179</sup>. In addition effects on peripheral nerve function (a reduction in superexcitability and refractoriness) have been reported<sup>179</sup>.

### *Symptomatic Management*

Respiratory management: Monitoring of respiratory function using force vital capacity(FVC), sniff nasal inspiratory pressures and nocturnal oximetry is important as respiratory insufficiency is the major cause of death. Criteria for starting non-invasive ventilation (NIV) are outlined in table x.2. NIV increases survival and quality of life. NIV is usually initially used for nocturnal hypoventilation with support during the day provided with increasing symptoms<sup>153</sup>.

Symptoms related to respiratory muscle weakness. At least one of:
• Dyspnoea
• Orthopnoea
• Disturbed sleep (not caused by pain)
• Morning headache
• Poor concentration
• Anorexia
• Excessive daytime sleepiness (Epworth_Sleep_Score > 9)
AND Evidence of respiratory muscle weakness (FVC $\leq$ 80% or SNP $\leq$ 40 cmH <sub>2</sub> O)
AND Evidence of EITHER:
significant nocturnal desaturation on overnight oximetry
OR
morning ear lobe blood gas pCO <sub>2</sub> $\geq$ 6.5 kPa

*Table x.4: Suggested criteria for non-invasive ventilation (NIV): Provisional European consensus criteria for NIV (European ALS/MND Consortium and European Neuromuscular Centre workshop on non-invasive ventilation in MND, May 2002) [with permission from Leigh et al. 2003]*

Nutritional management: Dysphagia and upper limb weakness can lead to aspiration, malnutrition, weight loss and dehydration<sup>153</sup>. Early management of dysphagia includes dietary advice, alteration of food consistency and teaching swallowing techniques. Due to an ~10% increase in the metabolic rate people with ALS require higher calorie intake<sup>180</sup>. Supplementary enteral feeding is recommended if the body weight falls below 10% of a person's pre-diagnostic weight. A PEG (percutaneous endoscopic gastrostomy) is the usual option for enteric feeding. However, insertion does require sedation and so may compromise respiratory function and should be performed before the FVC is <50%. Insertion of PEG under NIV assistance or percutaneous radiologic gastrostomy / radiologically inserted gastrostomy under these conditions may be required<sup>153</sup>.

Spasticity and Rigidity in ALS: Oral medications such as baclofen and gabapentin are not always effective in relieving spasticity and pain associated with spasms<sup>181,182</sup>. Side effects such as weakness, sleepiness and fatigue have also been described with higher doses of oral baclofen<sup>183</sup>. In these cases the effects of Intrathecal baclofen has been explored. In a retrospective assessment of 6 cases who had ALS for a mean of 47.4 months, ITB reduced pain in 75% of people with the degree of pain relief being predicted by the response to a preoperative bolus test dose<sup>184</sup>. In two other cases ITB was also associated with reduction in painful spasms<sup>183,185</sup>.

Exercise in ALS: Exercise trials in early-stage ALS have been systematically reviewed by Lui et al 2009<sup>186</sup>. Exercise regimes consisted of treadmill training and moderate progressive resisted exercises and stretches. Although small to moderate effect sizes were found favouring the intervention (eg for FVC, fatigue, strength and function) the variability of the effect was very large and

overall the results are inconclusive to date. Reductions in spasticity have been described following exercise but only after the first 3 months with no effect being seen after 6 months between the no exercise control group and the intervention group <sup>187</sup>.

More recently the feasibility of supported treadmill training has been investigated in ALS (n= 9). People undertook an 8 week program consisting of x3/week training for 30 minutes where 5 minutes of exercise were interspersed with 5 minutes of rest. There was a 33% drop out but improvements were seen in walking over 6 minutes and fatigue rating with no deterioration in perceived function, FVC or muscle strength which showed non-significant improvements <sup>188</sup>.

Cortical stimulation: Cortical hyperexcitability is felt to cause a dying forward of connected anterior motor neurons in ALS and is thus a potential target for therapy <sup>158</sup>. Repetitive cortical stimulation using TMS has been used to reduce cortical hyperexcitability. Other groups have used high frequency transcranial excitatory stimulation as there is evidence from animal studies that this may have a neuroprotective effect by increasing brain derived neurotrophic factor (BDNF) expression. Synapse-specific activity has been shown to regulate BDNF transcription, transport and secretion and trafficking of its receptor. BDNF in turn is felt to regulate synaptic efficacy and growth of dendrites and axons; processes that underpin synaptic plasticity <sup>189</sup>. There is evidence that a single nucleotide polymorphism in the BDNF gene can affect the response to r TMS in healthy participants and post stroke <sup>190,191</sup>. These differences in people's responsiveness to stimulation may underlie the variability in the results seen; a Cochrane review of randomised controlled trials of cortical stimulation studies in ALS till 2010 found no evidence of effect in the trials performed to date <sup>192</sup>.

### Leukodystrophies

The leukodystrophies are inherited myelin disorders affecting myelin development and maintenance in the central nervous system. A classification of the leukodystrophies is given below with examples of the more common types <sup>193</sup>. Up to half of people with leukodystrophies do not get a specific diagnosis. The age of onset varies with the type. The involvement of white matter tracts commonly leads to spasticity and UMN signs although reduced limb stiffness (hypotonia) can be seen e.g. in childhood onset. Extrapyramidal signs and ataxia may also be present. Impaired swallowing, respiration and cognition, and epilepsy may also be seen <sup>193,194</sup>.

#### *Demyelinating and Dysmyelinating Disorders*

- X Linked Adrenoleukodystrophy
- Krabbe Disease

#### *Hypomyelinating Disorders*

- Pelizaeus-Merzbacher Disease
- Alexander Disease

#### *Spongiform Disorders*



- Canavan Disease

### *Cystic Disorders*

- Vanishing white matter disease

### **Adrenoleukodystrophy**

#### **Prevalence and Genetics**

Adrenoleukodystrophy (ADL) is an X linked recessive disorder characterised by adrenal insufficiency and demyelination in the central and peripheral nervous system. They are caused by a defect in a peroximal membrane transporting protein leading to the accumulation of very long chain fatty acids in tissues and plasma. De novo mutations occur in 19% of cases (Horn <sup>195</sup> et al 2013). Clinical severity is not related to the length of the very long chain fatty acids. It occurs in 0.5-3.3 per 100000 males and there are several forms.

#### **Clinical Presentation**

The cerebral inflammatory presentation can start during childhood (3-10yrs), adolescence(11-21 yrs) or adult life (>21 yrs) onset. It accounts for ~50% of cases and is characterised by perivascular lymphocyte infiltration in parieto-occipital region (85% of cases) or frontal lobe region (15% of cases)<sup>196</sup>. Child ADL has symptoms of ataxia, spasticity, dysphagia, deafness, visual deficits, personality changes and in ~30% seizures<sup>197</sup>. Neurological deterioration occurs over 2-3 years until there is complete disability, a vegetative state and death.

Adrenomyeloneuropathy (AMN) is seen in ~45% of cases<sup>196</sup>. Here onset is 28 (+/- 9) yrs. It is characterised by non-inflammatory distal axonal loss and secondary demyelination affecting the dorsal columns and corticospinal tracts and a peripheral neuropathy<sup>198</sup>. It is characterised primarily by lower extremity spasticity, paresis and loss of vibration sensibility that affects walking and balance<sup>198</sup>. Bladder and bowel function can also be affected. Sensory loss can appear in isolation or with symptoms of paresis and spasticity<sup>198</sup>. In ~20% of cases there is additional cerebral pathology. Somatosensory and brainstem EPs and MEPs, transcortical, long latency stretch reflexes from the hand are prolonged and/or reduced in amplitude in keeping with the pathology affecting the dorsal columns and corticospinal.<sup>199-202</sup>

In AMN postural sway is increased in amplitude and correlates with the degree of lower limb weakness and sensory loss<sup>198,203</sup>. Walking is slower than normal but the pattern is relatively unimpaired in patients with isolated sensory loss. Strength loss and spasticity result in a crouch and stiff knee gait with reduced ankle motion. A cross sectional study of 142 people with AMN found that lower limb strength is the main predictor of functional ability. Vibration thresholds also predicted functional ability whilst ankle spasticity was correlated with walking velocity and timed up and go test<sup>203,204</sup>.

AMN symptoms can mimic Hereditary / familial SP<sup>4,5,205,206</sup> and symptoms of ataxia mimicking a spinocerebellar degeneration have also been described<sup>6,7</sup> Differential diagnosis is important in cases



of sporadic SP and where male to male transmission is absent as the more severe cerebral childhood form arises from the same gene mutation as AMN<sup>4</sup>

Primary adrenal insufficiency (“Addison only presentation”) comprise the remaining 20% of cases. Here people do not have neurological symptoms. Symptom free males with the gene deficit have been described.

Females are carriers and can exhibit symptoms of adrenal failure. In 55-63% of cases neurological symptoms akin to AMN are seen with/without peripheral neuropathy (~57%) and a high incidence of fecal incontinence (28%)<sup>207</sup>. The age of symptom onset in females is a decade later than males (~38yrs), the symptoms milder and the progression slower. Cerebral involvement can be seen in female carriers.

### **Interventions**

Management of AMN consists of the following<sup>196,208</sup>:

- 1) Adrenal hormone replacement therapy for those with adrenal insufficiency
- 2) Dietary therapy: Lorezo’s oil (a 4:1 mixture of glyceryl trioleate and glyceryl trierucate). and moderate reduction of fat intake can lower VLCFA in the plasma<sup>196</sup>. The therapy does not slow progression rate of those who are already symptomatic especially if they have the cerebral inflammatory presentation. Open label trials suggest that Lorezo’s oil can slow the progression of pure AMN and can be preventative in asymptomatic boys.
- 3) Hematopoietic stem cell transplantation has been reported to be effective in presymptomatic or early symptomatic childhood cerebral ADL

Treatments of symptoms such as spasticity have only been reported in case reports for example for the use of dantrolene effect in AMN<sup>209</sup> and ITB in cerebral child ADL<sup>197</sup>.

### **Summary**

The hereditary myelopathies represent a relatively rare and diverse group of conditions. As such research into the pathophysiology of a condition is often sparse and requires multi-centre and multi-national approaches. An understanding of the underlying genetics of each condition over time could lead to disease modifying therapies and improvements in the information provided during genetic counselling.

In many cases spasticity and paresis are seen in combination with a variety of other signs such as ataxia, extrapyramidal signs (rigidity, bradykinesia, tremor) and sensory loss. Symptom onset can occur at various times throughout life and this may result in differences in the presence and relative impact of secondary complications such as contracture, increased passive stiffness and bony deformity. Spasticity is therefore just one of a multitude of impairments that may impact on functional

ability. Although spasticity and hypertonia can limit mobility it may have a positive impact on stability and therefore should not be considered an obligate target for treatment. Future work will help to elucidate the relative importance of different impairments in limiting function and quality of life and the effectiveness of symptomatic interventions.

As the myelopathies are hereditary there will be symptom progression over time. Differences in the rate of disease progression and the severity and extent of CNS damage will presumably affect the ability of the neuromusculoskeletal system to adapt to environmental demands (eg training and rehabilitation) and therefore the effectiveness of interventions that aim to restore functional ability. In cases where the adaptability and plasticity of the system is limited compensatory techniques that aim to maintain / improve functional ability through the use of altered strategies and aids and adaptations may be more appropriate. Which approach is adopted and the overall goals of treatment may vary over the disease trajectory in an individual and with the aims of the patient; their family and carers. A greater understanding of these issues will lead to improved symptomatic management.

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