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REVIEW

Neuroimaging in hereditary spastic paraplegias: from qualitative cues to precision biomarkers

Grainne Mulkerrin[a], Marcondes C. França Jr[b], Jasmin Lope[c], Ee Ling Tan[c] and Peter Bede [a,c]

[a]Department of Neurology, St James's Hospital, Dublin, Ireland; [b]Department of Neurology, the State University of Campinas, São Paulo, Brazil; [c]Computational Neuroimaging Group, Trinity College Dublin, Ireland

ABSTRACT

Introduction: Hereditary spastic paraplegias (HSP) include a clinically and genetically heterogeneous group of conditions. Novel imaging modalities have been increasingly applied to HSP cohorts, which helps to quantitatively evaluate the integrity of specific anatomical structures and develop monitoring markers for both clinical care and future clinical trials.

Areas covered: Advances in HSP imaging are systematically reviewed with a focus on cohort sizes, imaging modalities, study design, clinical correlates, methodological approaches, and key findings.

Expert opinion: A wide range of imaging techniques have been recently applied to HSP cohorts. Common shortcomings of existing studies include the evaluation of genetically unconfirmed or admixed cohorts, limited sample sizes, unimodal imaging approaches, lack of postmortem validation, and a limited clinical battery, often exclusively focusing on motor aspects of the condition. A number of innovative methodological approaches have also been identified, such as robust longitudinal study designs, the implementation of multimodal imaging protocols, complementary cognitive assessments, and the comparison of HSP cohorts to MND cohorts. Collaborative multicenter initiatives may overcome sample limitations, and comprehensive clinical profiling with motor, extrapyramidal, cerebellar, and neuropsychological assessments would permit systematic clinico-radiological correlations. Academic achievements in HSP imaging have the potential to be developed into viable clinical applications to expedite the diagnosis and monitor disease progression.

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1. Introduction

Hereditary spastic paraplegia (HSP) is an umbrella term for a group of genetically and phenotypically diverse inherited neurodegenerative disorders, characterized by progressive spasticity and weakness primarily affecting the lower limbs. As proposed by Harding's criteria [1], HSP can be clinically divided into 'pure' and 'complicated' forms. Pure-HSP (pHSP) presents with insidious onset progressive spasticity of the lower limbs, hyperreflexia, and upper motor neuron (UMN) sign. Weakness of the lower limbs can be mild, with a characteristic discordance between the severity of spasticity and relatively preserved power. In complicated-HSP (cHSP), spastic paraparesis is accompanied by additional neurological signs. Optic atrophy, extrapyramidal features, cerebellar signs, cognitive impairment, sensorineural deafness, and epilepsy are some of the additional neurological manifestations associated with cHSP. Initial symptoms are typically subtle; gait disturbance, stiffness and falls, and disease progression is often slow, but can lead to significant disability [2].

Over 100 loci/88 genes have been implicated in the pathogenesis of HSP to date [3]. Inheritance can be autosomal dominant (AD), autosomal recessive (AR), X-linked, mitochondrial, or sporadic [4]. The genetic classification for HSP is based on sequential numbering of genes, using a spastic paraplegia gene (SPG) prefix. The most common genotypes seen in clinical practice are SPG4 and SPG11. SPG4 is a pHSP that exhibits AD-inheritance of the spastin (*SPAST*) gene and accounts for up to 60% of all HSP cases. SPG11 is the most prevalent AR-inherited HSP accounting for approximately 8% of all HSP cases and categorized as a cHSP with additional features such as cognitive impairment, peripheral neuropathy, ataxia, and urinary symptoms. SPG3A is a clinically pure HSP phenotype and the second most common AD-inherited HSP, accounting for 5–10% of AD HSPs that are negative for *SPAST* mutation. SPG15 is inherited in an AR manner and phenotypically similar to SPG11. Finally, SPG7 that tends to manifest in the fourth decade with spastic paraparesis and cerebellar signs, is a cHSP inherited in an AR manner [5].

There is a striking paucity of postmortem studies on HSP. The 'dying-back axonopathy' phenomenon is traditionally considered as the pathological basis of the condition [6] with length-dependent degeneration of the corticospinal tracts, fasciculus gracilis, and spinocerebellar tracts [6]. Recent postmortem studies seem to support the 'dying-back' theory by describing axonal degeneration of the corticospinal tracts, with distal axons more severely affected [7].

The clinical indication for neuroimaging in HSP is to rule out alternative structural, vascular neoplastic, and

CONTACT Peter Bede bedep@tcd.ie Computational Neuroimaging Group, Trinity Biomedical Sciences Institute, Pearse Street, Trinity College, Dublin 2, Ireland

Article highlights

- Hereditary spastic Paraplegias (HSP) include a clinically and genetically heterogeneous group of conditions with diverse disability profiles.
- Radiological cues, such as the 'ear of the lynx' sign, thinning of the corpus callosum, cerebellar atrophy, high signal along the corticospinal tracts, and optic nerve hypoplasia have limited specificity to HSP genotypes.
- The practical relevance of robust, prospective computational imaging studies stems from their ability to ascertain HSP-specific imaging signatures, the prospect of expediting the diagnosis, and the development of viable monitoring markers for both clinical care and future pharmaceutical trials.
- A wide range of quantitative gray and white matter techniques have been recently applied to HSP cohorts including cortical thickness measurements, morphometric approaches, cortical and subcortical volumetry, spinal cord protocols, tractography, spectroscopy, PET, and SPECT.
- Stereotyped shortcomings of existing imaging studies include the evaluation of genetically unconfirmed or genetically admixed cohorts, limited sample sizes, unimodal imaging approaches, and a limited clinical battery often exclusively focusing on the motor aspects of the condition.
- Collaborative initiatives with harmonized protocols may overcome sample limitations; comprehensive clinical profiling with motor, extrapyramidal, cerebellar, cognitive, and behavioral assessments would permit systematic clinico-radiological correlations, and multitimepoint longitudinal study designs will allow the nuanced characterization of anatomical propagation patterns.

neuroinflammatory diagnoses, such as spinal spondylosis, spinal or cerebral AVMs, Chiari malformation, and primary progressive multiple sclerosis. Metabolic causes such as B12 vitamin deficiency or infectious causes such as HIV-myelopathy, HTLV1, or neurosyphilis are also potential differential diagnoses to consider during the initial investigations. Given the relatively low incidence of the condition, insidious onset, slow progression, the heterogeneity of initial presentations, and wide range of differential diagnoses, patients often face a protracted diagnostic journey. Diagnostic delay, misdiagnoses, and unnecessary interventions are not uncommon [8]. The cost of testing for large panels of HSP-associated genes may be prohibitive in some jurisdictions, family history may not be readily available in some cases, and clinical overlap with other neurodegenerative conditions such as primary lateral sclerosis (PLS) may also contribute to diagnostic delay [9]. Patients often seek second opinions and may attend multiple specialists before the diagnosis is confirmed. Patients may be initially referred to orthopedic services, neurosurgeons, or physiotherapists before review in a tertiary neurology service. Establishing the diagnosis in a timely manner is hugely important so that unnecessary interventions can be avoided, multidisciplinary interventions can be promptly initiated, and genetic counseling can be organized. In the absence of effective disease-modifying therapies, supportive care is the mainstay of HSP management. A multidisciplinary approach comprising pharmacological management of spasticity, fall prevention, physiotherapy for rehabilitation, and occupational therapy for disability are key strategies to maintain independence. No effective disease-modifying therapies have been confirmed to date, and clinical trials for new agents are limited by the lack of a reliable biomarker for the disease.

Computational neuroimaging is increasingly recognized as a powerful noninvasive tool in low-incidence neurodegenerative conditions [10–13], which readily capture disease-specific patterns of pathology in vivo based on regional integrity metrics. Quantitative neuroimaging is also increasingly utilized to track disease burden patterns longitudinally and has a viable biomarker role in a multitude of neurodegenerative conditions [14]. A novel frontier of neuroimaging is quantitative spinal cord imaging, which has successfully captured segmental gray and white matter alterations in motor neuron diseases, spinal muscular atrophy, and spinal and bulbar muscular atrophy [15–19]. Given the considerable progress in MR technology, the emergence of high-field and ultra-high field scanners, the availability of robust image processing pipelines and open-source analysis suites, we sought to systematically review the imaging literature in HSP.

2. Body

2.1. Methods

A formal literature review was conducted on PubMed between October 2021 and December 2021 using the keywords 'hereditary spastic paraplegia' and 'hereditary spastic paraparesis' in combination with the individual search terms: 'imaging,' 'neuroimaging,' 'magnetic resonance imaging,' 'magnetic resonance spectroscopy,' 'positron emission tomography,' and 'diffusion tensor imaging.' Only articles published in English were included. No exclusion criteria were set based on the year of publication. Additional articles were also included based on references to relevant review articles. Review articles, opinion pieces, and editorials were excluded. Identified original papers were systematically reviewed for sample size, genetic screening, choice of controls (healthy/disease), qualitative versus quantitative imaging, primary imaging methods (structural, diffusion, spectroscopy, functional, metabolic, spinal, etc.), unimodal versus multimodal imaging, image analysis software, postmortem validation, clinical assessment (scales, scores, motor, and cognitive), clinico-radiological correlations, and main study findings.

2.2. Results

Based on the above search criteria, a total of 108 original research papers were identified. Forty-one of these described qualitative findings, primarily on MRI. Sixty-seven studies utilized quantitative imaging such as diffusion tensor imaging (DTI – 30 studies), MR spectroscopy (MRS – 16 studies), PET-CT (18 studies) and functional MRI (fMRI – 3 studies). The vast majority of studies focused on cerebral imaging. Spinal alterations were specifically appraised by 23 studies, but only 4 utilized quantitative approaches.

The majority of imaging studies on HSP suffer from grave sample size limitations. Only two imaging studies were identified with greater than 50 HSP patients [20,21]. Forty-five studies included less than 10 participants, and a further 18 studies were single patient case-reports. The vast majority of identified studies were cross-sectional in design, while longitudinal imaging follow-up was only performed in

eight studies. Some clinical assessment was performed in almost all studies, and disease severity, mainly SPRS, was reported in 23 studies. Clinico-radiological correlations were explored in 23 studies, most commonly with disease duration [20,22–29], cognition [22,30–35] and spasticity [20–27,29,34,36–38]. We identified no studies that correlated in vivo imaging patterns to postmortem pathological findings.

2.3. Typical findings on visual inspection – qualitative imaging

The diagnosis of HSP can be challenging, especially given the clinical and genetic heterogeneity of the condition. While MRI may look normal on visual inspection [39–46], stereotyped cerebral and spinal cord alterations are commonly appreciated (Figure 1).

2.3.1. Spinal cord atrophy

A large study of genetically unconfirmed pHSP and cHSP detected considerable cervicothoracic spinal cord atrophy compared to demographically matched controls [47]. The same study found no difference between the pHSP and cHSP subgroups. In another group of clinically confirmed HSP patients, a reduced cervical spine cross-sectional area was observed in patients in comparison to controls [34]. The anteroposterior (AP) diameters of the thoracic spine at T3 and T9 were significantly lower than controls in another qualitative study looking at clinically confirmed pHSP [48]. In genetically confirmed HSP, spinal cord atrophy may be observed in SPG5 [41], SPG6 [42], SPG7 [49]. Interestingly, a syrinx was observed in two SPG54 patients [50]. However, cord atrophy is not a consistent finding; in other studies, MRI of the spinal cord looked relatively normal in SPG3A [51,52], SPG4 [39], SPG7 [53,54], SPG11 [55], SPG15 [56] and SPG46 [57]. This inconsistency highlights the limitations of visual inspection, disease-associated radiological cues, and qualitative assessments. None of the above articles describing ante mortem qualitative spinal changes provided descriptions of postmortem cord changes.

2.3.2. The 'ears of the lynx' sign

The 'ears of the lynx' sign refers to T2/FLAIR hyperintensity on axial views at the tip of the frontal horn of the lateral ventricles, named after the tufts of hair at the tips of the ears of a lynx cat. This sign is typically associated with SPG11 and SPG15 mutations [58]. The ears of the lynx sign is found to be relatively sensitive (78.8–97%) and rather specific (90.9–100%) to SPG11 and SPG15 in a blinded study with four different raters [58].

2.3.3. Thin corpus callosum

Thin corpus callosum (TCC) is a common finding in HSP. Prior to the discovery of the many genetic subtypes of HSP, autosomal recessive HSP with thin corpus callosum (AR-HSP-TCC)

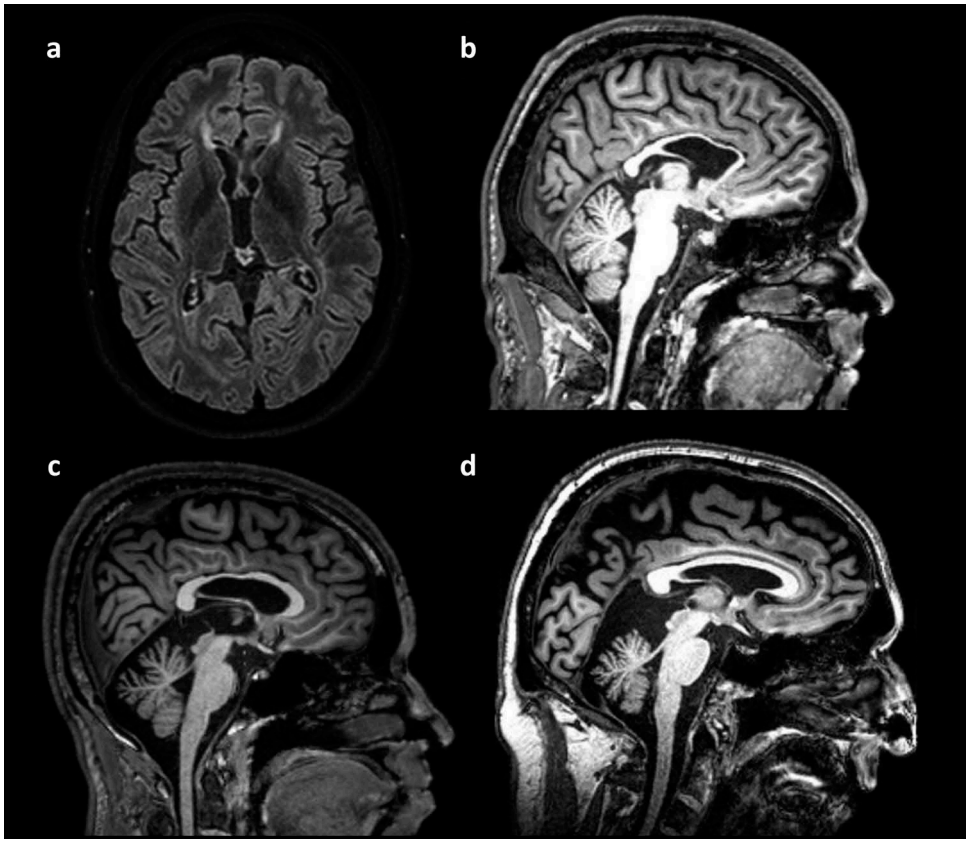

Figure 1. Illustrative examples of radiological changes commonly observed in HSP on visual inspection. a: 'Ears of the lynx' sign on axial FLAIR imaging in a 21 year-old female patient with SPG11. b: thin corpus callosum on sagittal T1-weighted imaging in a 25 year-old male patient with SPG11. c: Cerebellar atrophy on sagittal T1-weighted imaging in a 37 year-old male patient with SPG15. d: Cerebellar atrophy and arachnoid cyst on sagittal T1-weighted imaging in a 35 year-old male patient with SPG7.

was a commonly used terminology to describe what is now a probably genetically diverse subgroup. HSP-TCC is most commonly reported in association with SPG11 [55,59–66] and SPG15 [56,59,63,67–69]. However, TCC may also be a feature in SPG3A [51,52], SPG21 [70], SPG 28 [71], SPG30 [62,72], SPG35 [63,73], SPG45 [74], SPG46 [57,75], SPG47 [76], SPG48 [63], SPG52 [62], SPG54 [50,62,77–80] and SPG78 [81]. TCC is not a consistent finding in many of these subtypes, for example, in a study of SPG3A it was only noted in 1 of the 18 patients imaged [51]. In a small study (n = 2) which imaged patients with SPG11 longitudinally, TCC progressed over a 5-year interval [55]. In contrast, however, another case report of AR-HSP-TCC detected no progressive thinning of the corpus callosum over a 4 years interval [82]. It is noteworthy that thin corpus callosum (CC) is by no means specific to HSP and is commonly observed in ALS, PLS, CBS, and other neurodegenerative conditions [83–87].

2.3.4. Cerebellar atrophy

Cerebellar atrophy has been described in SPG7 [54,59,88–90], SPG21 [70], SPG30 [62,91], SPG31 [62], SPG35 [62,63,92], SPG39 [59], SPG 46 [57,75], SPG50 [93], SPG78 [81,94], and SPG54 [80]. Cerebellar atrophy is thought to be progressive on longitudinal imaging in a small (n = 2) SPG30 study [72], and in a single patient with SPG78 who was followed longitudinally [94]. In contrast, other case reports of SPG 30 [91] and SPG47 [76] observed relatively stable cerebellar volumes over time. Other posterior fossa abnormalities, such as retro-cerebellar fluid collection and cerebellar hypoplasia in SPG4 [95] and uncomplicated arachnoid cysts of the cerebellopontine angle in SPG4 [96] were also reported. In some cases, cerebellar atrophy is accompanied by brainstem hypoplasia/atrophy, e.g. SPG35 may present with pontocerebellar hypoplasia [92]. Similar to the above qualitative cues, cerebellar atrophy is far from unique to HSP, and is commonly observed in motor neuron disorders and other neurodegenerative conditions [97–100].

2.3.5. Cerebral atrophy

Cerebral atrophy on routine brain MRI has been commonly observed in HSP. In a group of genetically heterogeneous HSP patients, cortical atrophy was reported in 25/58 patients imaged [21]. Likewise, in clinically (but not genetically) confirmed HSP, mild brain atrophy was observed in 4 of 9 patients [101]. In studies that looked at those with a causative gene for HSP, cerebral or cortical atrophy was noted in SPG4 [32], SPG7 [49], SPG11 [60,61], SPG 21 [70], SP30 [62], SPG56 [62], and SPG78 [81]. In a subset of SPG4 patients with cognitive impairment, frontotemporal atrophy was correlated with the degree of cognitive impairment [102]. As with the above signs, cerebral volume loss is notoriously nonspecific and has a limited role in swaying a diagnostic dilemma.

2.3.6. White matter hyperintensities

White matter hyperintensities (WMH) are nonspecific findings associated with numerous pathological processes. WMH has been reported in SPG2 [103], SPG4 [62], SPG5 [104], SPG11 [61–63,105], SPG15 [63,67,68], SPG21 [70], SPG31 [62], SPG35 [62,63,73,92,106], SPG45 [74], SPG47 [107], SPG48 [63], SPG52 [62] and SPG54 [50,62,77]. In a case series of two related SPG2 patients, the index patient was initially misdiagnosed with primary progressive multiple sclerosis based on presentation and imaging findings [103]. In one patient with SPG2 who was imaged longitudinally, the WMH was stable on repeat imaging [108].

2.3.7. Subcortical alterations

While deep brain structure abnormalities have been observed on routine brain MRI in certain HSP subtypes, these findings are inconsistent in the literature. In SPG35, mild hypointensity of the globus pallidus was noted in 77% of cases on the retrospective review of MR images [92]. Hypothalamic atrophy was observed in SPG11 cases compared with controls in another study [24]. Atrophy of the caudate nucleus was noted in an imaging study of three related patients with genetically confirmed SPG78 exhibiting prominent extrapyramidal signs [81]. Hyperintensity of the dentate nucleus was observed both in SPG7 [89] and KIF1A [109,110]. Subcortical iron deposition has been observed in SPG28 [71]. Iron deposition has also been described in SPG35 cases [106], but not confirmed by a larger series (n = 19) on the same gene [92].

2.3.8. Optic nerve atrophy

Optic nerve atrophy or hypoplasia has been described in several HSPs, including SPG30/KIF1A [109,110], SPG7 [111] and SPG54 [62]. The spectrum of ophthalmological abnormalities observed in HSP [112] comprises other changes such as yellow retinal 'flecks' in SPG11 and SPG15, progressive external ophthalmoplegia in SPG7 [113], and supranuclear gaze palsy in SPG7 [49], but the discussion of these manifestations and macular optical coherence tomography (OCT) findings is beyond the scope of this review.

2.4. Computational neuroimaging – quantitative imaging

2.4.1. Spinal cord imaging

There is a striking scarcity of quantitative spinal imaging studies on HSP. Existing studies have either performed morphometric [38] or diffusivity analyses [114]. Spinal cord cross-sectional area reductions were captured in SPG11 patients in comparison to controls [26] which correlated inversely with both disease duration and severity. Spinal cord atrophy, involving both gray and white matter components, has been observed in SPG11 and SPG4, but not in SPG3A or SPG7 [28]. The gray matter area of the spinal cord was inversely correlated with the disease duration in the SPG4 group, but no significant correlation was seen in the other genetic subtypes [28]. One study ascertained CST FA reductions at the cervical level [37], which correlated with disease duration, but not symptom severity as assessed by the SPRS. A recent SPG4 study detected FA reductions and increased radial diffusivity (RD) at cervical and thoracic levels in both the lateral and dorsal columns. Key study characteristics of imaging studies evaluating cord alterations are summarized in Table 1.

2.4.2. Structural, morphometric, and volumetric studies

Cerebral, cerebellar, and corpus callosum volume reductions are commonly detected by quantitative HSP studies [115].

Table 1. Imaging studies commenting on spinal alterations.

First author, year of publication	Study design Imaging modality	Study groups	Main conclusions
Hsu, 2021 [51]	Cross-sectional, 2 centers, retrospective descriptive, qualitative MRI brain and spinal cord	SPG3A (n = 18) No controls	MRI brain: thin corpus callosum in one patient, otherwise normal Normal cervicothoracic spine
List, 2019 [37]	Cross-sectional, single-center, quantitative imaging, clinico-radiological correlation Brain and spinal cord DTI, TBSS, and ROI analyses	SPG4, SPG5, SPG31 Disease (n = 20) Control (n = 17)	TBSS revealed corticospinal tract degeneration in pHSP. Reduced FA and increased AD in CC, CST, optic radiation, frontal lobe, parieto-occipital regions, temporal lobe, and brainstem. No cerebellar FA changes. Significant negative correlation between disease duration and C Spine FA. No correlation found between imaging findings and SPRS.
Nielsen, 1998 [39]	Single-center, cross-sectional, qualitative MRI brain and spinal cord	SPG4 (n = 16) imaged, age- and sex-matched healthy controls	No obvious brain or spinal cord MRI abnormalities compared with controls
Lan, 2014 [41]	Single-center, cross-sectional, qualitative, no clinico-radiological correlations, MRI brain and spine	SPG5 (n = 5) HSP (n = 25) No controls	Normal MRI brain in SPG5. Thoracolumbar atrophy (not quantified) was present in 3/5 patients with SPG5.
Agosta, 2015 [34]	Single-center, cross-sectional, quantitative, clinico-radiological correlations, MRI brain and cervical cord, DTI, VBM, TBSS	pHSP (n = 20) cHSP (n = 24) Healthy controls (n = 7)	VBM: no difference between HSP and controls. TBSS: pHSP and cHSP FA reduction in CST, CC, external capsule, and most association WM tracts compared to controls. Reduced cervical spinal cord cross-sectional area in HSP compared to controls. WM alterations correlate with spasticity and cognitive impairment.
Sperfeld, 2005 [47]	Single-center, Cross-sectional, qualitative, no clinico-radiological correlations, MRI cervical and thoracic cord	HSP (n = 30) Not genetically confirmed Controls (n = 96)	Significant cervical and thoracic spinal cord atrophy in HSP compared to controls. No difference between pHSP and cHSP.
Krabbe, 1997 [48]	Single-center, cross-sectional, qualitative, no clinico-radiological correlations, MRI brain and whole spine	HSP (n = 16) Not genetically confirmed Controls (n = 15)	The patients had thinner corpus callosum than controls. The anteroposterior diameters of the spinal cord at T3 and T9 were significantly reduced in patients compared to controls
Faber, 2018 [26]	Single-center, cross-sectional, quantitative clinico-radiological correlations, DTI, cortical thickness, deep gray matter volumes, spinal cord morphometry	SPG11 (n = 25) Genetically confirmed age- and sex-matched controls (n = 25)	Reduced SC area was in SPG11 compared with controls. Cortical thickness reductions in bilateral motor cortices, limbic structures, cingulate gyri, left parahippocampal gyrus, bilateral superior temporal sulcus, left precuneus, and superiorparietal cortices. SPRS negatively correlated with cortical thickness in precentral and paracentral cortices bilaterally. Reduced deep gray matter structure volumes. Widespread and diffuse WM alterations. SPRS and disease duration correlated inversely with spinal cord area.
Servelhere, 2021 [28]	Single-center, cross-sectional, quantitative clinico-radiological correlations, MRI cervical spine: T2*weighted 3D imaging	SPG3A (n = 7), SPG4 (n = 12), SPG7 (n = 10), SPG11 (n = 8), healthy controls (n = 21)	No spinal cord atrophy identified in SPG3A and SPG7. In SPG4 & SPG11: spinal cord atrophy compared to controls, in both GM and WM. Inverse correlation between GM area and disease duration in In SPG4.
Warnecke, 2007 [49]	Cross-sectional, single-center, descriptive, no clinico-radiological correlations, MRI brain & cervicothoracic spine, DTI Brain (FA)	SPG7 (n = 6) Controls (n = 50)	Qualitative descriptions: normal cervicothoracic MRI, cerebellar atrophy and mild frontal cerebral atrophy. DTI: reduced WM integrity in CST, the frontal lobes, and the midbrain
Guo Liu, 2008 [42]	Single-center, cross-sectional, qualitative, no clinico-radiological correlations, MRI brain & cervicothoracic cord	SPG6 (n = 6) Healthy controls (does not quantify)	Spinal cord atrophy observed in all affected patients. Reduced anteroposterior diameters, transverse diameters and cross-sectional areas at the C2, C3, C7, T1, T2, T3, and T4 levels. MRI brain: normal
Winner, 2004 [55]	Single-center, longitudinal (imaging 5 years apart), qualitative and quantitative, no clinico-radiological correlations, MRI brain & spine, PET CT brain	SPG11 (n = 2) No controls	MRI brain: progressive CC thinning, symmetrical white matter lesions, not progressive. MR spine: normal. PET-CT: hypometabolism in frontotemporal and temporal cortices. Progressive in 1 of 2 patients.
Orlacchio, 2011 [52]	Single-center, cross-sectional, qualitative no clinico-radiological correlations, MRI brain and spinal cord	SPG3A (n = 1)	MRI brain: thin corpus callosum, MRI spine: normal
Hourani, 2009 [101]	Single-center, cross-sectional, qualitative no clinico-radiological correlations, MRI brain and whole spine	HSP (n = 9) Clinically confirmed (Harding's criteria) No controls	White matter hyperintensities in 6/9 patients, mild brain atrophy in in 4/9 patients, thin corpus callosum in 4/9, mild spinal cord atrophy in 3/9
Cao, 2013 [124]	Single-center, cross-sectional, qualitative and quantitative, no clinico-radiological correlations, MRI brain & spinal cord DTI	SPG11 (n = 2) controls (n = 11)	MRI brain: thin CC, MRI spinal cord: normal, DTI: increased MD and decreased FA in CC, frontal WM, temporal lobe WM compared to healthy controls
Rezende, 2015 [38]	Single-center, cross-sectional, clinico-radiological correlations, volumetric analyses, TBSS, and tractography	SPG4 (n = 11) Healthy controls (n = 23)	Spinal cord volumetric analysis: atrophy in HSP group. Brain volumetric analyses: no abnormality. TBSS: reduced FA in CST, cingulate gyri and splenium of the CC. FA of the CC and CST correlated with disease severity (SPRS). No correlation between tractography and SPRS.
Navas-Sánchez [114]	Cross-sectional, clinico-radiological correlations, volumetric analyses, FA and RD, assessments	SPG4 (n = 12) Controls (n = 14)	Reduced cervical cord cross-sectional area with anteroposterior flattening. Reduced FA and increased RD at cervical and thoracic levels in both the lateral and dorsal columns. FA changes correlate with disease severity.

However, in some studies, volumetric analyses have not captured brain atrophy in SPG4-associated HSP [38,44]. In genetically confirmed HSP, reduced cortical thickness has been observed in SPG4 [22], SPG11 [20,26], and SPG8 [20]. Conversely, the lack of cortical thickness reduction was highlighted by some SPG4 and SPG3A studies [20]. Voxel-based morphometry often captures gray matter alterations in the prefrontal cortex [25] and the thalami [23,25,26,29]. Brain parenchymal fractions also reveal significant brain atrophy in HSP patients compared with controls [31,116]. Basal ganglia atrophy is a common finding in HSP patients and has been reported both in SPG4 [20,22,23] and SPG11 [20,117]. In line with subjective and qualitative observations, cerebellar atrophy has also been detected in SPG11 [20], SPG7 [20] and SPG4 [23].

2.4.3. Diffusion tensor imaging (DTI)

Tract-based spatial statistics (TBSS) typically reveals corticospinal tract degeneration in HSP [23,25,34,37,38,118]. In genetically confirmed HSP, corticospinal white matter alterations were specifically observed in SPG4 [22,23,38,44], SPG7 [40,49] and SPG11 [64,119]. White matter changes are also commonly observed in other brain regions, often with limited change over time on longitudinal follow-up [25]. Specific anatomical locations that exhibit reduced white matter integrity in HSP include the corpus callosum [25,34,37,38,116,118,120], the brainstem [37], the optic radiation [37], the frontal lobes [37], fronto-occipital regions [25], parieto-occipital regions [37], the external capsule [34], the temporal lobes [37], the longitudinal fasciculi [25,118], the cingulate gyri [25,38] and the thalamic radiations [118]. Anatomically widespread, 'generalized,' white matter degeneration was observed in SPG11 with reference to controls [26,121]. The corpus callosum is affected in SPG4 [22,23], SPG7 [20,122] and SPG11 [20,64,119,121–124]. Extra-motor fractional anisotropy (FA) reductions are commonly observed in SPG11 including the thalamus [123], the frontal and peritrigonal white matter [122], periventricular white matter [125] and the cerebellum [123]. In SPG7, the corticospinal tract [40,49], frontal lobes [40,49], and midbrain [49] exhibit reduced white matter integrity. Multiple SPG4 studies describe particularly widespread white matter degeneration, in particular in the corticospinal tracts [23,44], thalamus [23], brainstem [23] and cerebellum [23]. The distinguishing WM signature of HSP in comparison to PLS and ALS is poorly characterized [126–128]. The main study characteristics of structural and diffusivity studies are summarized in Table 2.

2.4.4. PET-CT

PET-CT, SPECT, and DAT studies on HSP suffer from considerable sample size limitations. Nonetheless, these studies provided important academic insights with regard to metabolic signatures in specific HSP subtypes and the likely substrate of the motor and extra-motor deficits observed clinically. Thalamic hypometabolism is routinely observed in SPG11 on FDG-PET-CT [60,65,66]. This may be progressive in some patients over a 10-year follow-up [60]. In another study of genetically unconfirmed HSP-TCC, progressive thalamic hypoperfusion was observed on SPECT over 4 years [82]. Reduced striatal density has also been observed in clinically confirmed HSP [129], SPG11 [27], SPG78 [94], SPG7 [54]. This correlated with SPRS and disease duration in the SPG11 group [27]. Cortical hypometabolism may also be a feature of HSP. This has been reported in the frontal cortex of SPG3A [130], and in the frontotemporal cortical regions in SPG11 [55]. On SPECT, hypoperfusion of the frontotemporal cortices in SPG4 was linked to cognitive impairment [32]. Other studies noted reduced regional cerebral blood flow in the left frontotemporal cortex in SPG4, without direct correlations with cognitive profiles [35]. Cerebellar hypometabolism is also commonly observed in HSP; it has been described both in SPG11 [131] and SPG5 [104]. On SPECT, cerebellar hypoperfusion has also been observed in SPG4 [132].

Similar to initiatives in other MNDs such as ALS [133,134], functional reorganization in response to structural degeneration is increasingly investigated. Cortical activation patterns in SPG4-linked HSP were evaluated by rCBF PET-CT during affected and unaffected lower limb tasks [135]. During ankle movement, patients exhibited increased rCBF in the primary motor cortices (PMC), the supplementary motor areas (SMAs), and the premotor cortex compared to controls; which may be indicative of motor cortical reorganization or adaptation to degenerative change. Conversely, there are also reports of normal PET-CT imaging HSP, specifically in SPG2 [108] and SPG7 [54].

2.4.5. MR spectroscopy (MRS)

Sixteen studies utilized magnetic resonance spectroscopy to evaluate the underlying biochemical and metabolic processes determining the clinical phenotypes of HSP. Metabolic abnormalities may be a consistent feature of HSP, however the inconsistency between studies with regard to region-of-interest (ROI) makes the systematic integration of study findings challenging. Investigated ROIs include the centrum semiovale [60,108,136,137], basal ganglia [50,77,78,138], corpus callosum [105,119], the frontal white matter [30,136], occipito-parietal regions [46,60], occipito-frontal region [108], mid-occipital region [108], parietal region [136], the cerebellum [119], supraventricular white matter [65], periventricular white matter [105], precentral white matter [21], the internal capsule [60], the corona radiata [105] and the brainstem [136]. The most common MRS finding in HSP is N-acetyl-aspartate (NAA) level reduction in various brain regions, but a large study (n = 70) identified normal precentral metabolite levels [21]. In SPG11, NAA reductions were reported in the frontal white matter [60], corona radiata [105], periventricular white matter [65,105], the centrum semiovale [136], and corpus callosum [119]. In genetically diverse HSP, reduced NAA/Cr levels were observed in the right prefrontal region [25]. However, the findings are inconsistent; NAA was reduced in the occipito-frontal white matter in only one of the two patients with SPG2 in another study [108], and increased NAA levels were also reported in the centrum semiovale [137]. NAA/Cr reductions in the corona radiata in SPG11 inversely correlated with disability scores [105]. Myoinositol (MI) changes are the second most common MRS alterations reported in HSP. Increased mI/Cr ratio has been described in occipito-parietal regions in SPG5A [46], occipito-frontal areas

Table 2. Structural and diffusion studies.

First author, year of publication	Study design Imaging modality	Study groups	Main conclusions
Servelhere, 2021 Servelhere, Rezende [20]	Single-center, cross-sectional, clinico-radiological correlations, DTI, cortical thickness, BG volumetry, cerebellar GM analyses, WM integrity analyses	SPG3A (n = 9), SPG4 (n = 27), SPG7 (n = 10), SPG8 (n = 9), SPG11 (n = 29), healthy controls (n = 84)	SPG3A: No brain abnormality, SPG4: Posterior WM changes, caudate and thalamic atrophy, SPG7: CC alterations, cerebellar atrophy, SPG8: cortical thinning at pre- and post-central gyri, pallidum atrophy, SPG11: Cerebral cortical thinning, cerebellar, BG atrophy, WM changes in CC, CR, and subcortical pathways. Clinico-radiological correlations only in SPG11 cases.
Lindig, 2015 [23]	Single-center, cross-sectional, retrospective, quantitative, clinico-radiological correlations, TBSS, VBM	SPG4 (n = 15), controls (n = 15)	Widespread WM change in the CC, medio-dorsal thalamus, parieto-occipital regions, upper brainstem, cerebellum, and corticospinal tract. Imaging findings correlated with disease duration and severity (SPRS)
Kassubek, 2006 Kassubek, Sperfeld [31]	Single-center, cross-sectional, clinico-radiological correlations with cognitive domains, brain parenchymal fractions	p-HSP (n = 21), c-HSP (n = 12) not genetically confirmed, healthy controls (n = 30)	"Global" brain atrophy in HSP, with cHSP more severely affected than pHSP. No significant correlation between MMSE and degree of atrophy.
Aghakhanyan, 2014 Aghakhanyan, Martinuzzi [118]	Single-center, cross-sectional, no clinico-radiological correlations, DTI-TBSS	pHSP (n = 12), SPG10 (n = 1), SPG3a (n = 1), SPG4 (n = 7), SPG7 + SPG4 (n = 1), SPG5 (n = 2), healthy controls (n = 12)	Widespread FA reductions, increased mean RD, MD, and AD compared to controls. Decreased FA in the bilateral anterior thalamic radiations, corticospinal tracts, corpus callosum with forceps major and minor, inferior and superior longitudinal fasciculi.
Martinuzzi, 2016 Martinuzzi, Montanaro [21]	Multicenter, cross-sectional, clinico-radiological correlations, DTI, MRS	SPG3a (n = 7), SPG4 (n = 32), SPG5 (n = 7), SPG7 (n = 4), SPG10 (n = 3), SPG11 (n = 11), SPG15 (n = 3), SPG31 (n = 1), SPG35 (n = 2), healthy controls (n = 22)	Standard MRI brain: WM alterations in 19/58, "ears of the lynx" sign in 9/58 (and 8/10 of SPG11), cortical atrophy in 25/58, CC abnormality in 15/58. SPRS – FA correlations. MRS: inconclusive.
Uttner, 2007 Uttner, Baumgartner [33]	Single-center, cross-sectional, clinico-radiological correlations, neuropsychological assessments, brain parenchymal fractions	pHSP (n = 20), cHSP (n = 9), not genetically confirmed	BPF – neuropsychological performance correlations. pHSP cohort: BPF correlated only with MMSE. cHSP cohort: BPF correlated only with CPM
Kassubek, 2007 Kassubek, Juengling [116]	Single-center, cross-sectional, no clinico-radiological correlations, DTI, VBM	pHSP (n = 21), cHSP (n = 12), age- and sex-matched controls (n = 30)	GM: moderate regional abnormalities in pHSP & significant pericentral GM changes in cHSP. WM: small regional reductions in WM seen in pHSP group & considerable volume reduction in cHSP, particularly in the CC
Montanaro, 2020 Montanaro, Vavla [25]	Single-center, longitudinal, clinico-radiological correlations, DTI – TBSS, VBM, MRS	HSP (n = 31) – follow-up (n = 23) genetically confirmed, controls (n = 36)	VBM: gray matter reductions in the thalami and right prefrontal cortex. TBSS: widespread WM alterations at baseline with no significant progression on longitudinal assessment. No relevant clinico-radiological correlations identified. MRS: reduced prefrontal NAA/Cr, increased Rt. pre-central Cho/Cr, and increased Lt. pre-central ml/Cr. No significant changes on follow-up.
Muller, 2012 Muller, Unrath [126]	Single-center, cross-sectional, no clinico-radiological correlations, DTI -tractography	pHSP (n = 20), cHSP (n = 12), ALS (n = 20), PLS (n = 20)	Reduced FA in the CST and CC of both pHSP and cHSP patients compared to controls; also seen in the ALS and PLS cohort.
Unrath, 2010 Unrath, Muller [127]	Single-center, cross-sectional, no clinico-radiological correlations, DTI tractography	HSP (n = 24), not genetically confirmed, PLS (n = 25), X-SBMA (n = 20), healthy controls (n = 24)	Reduced FA in the CST, CC, capsula extrema, brain stem and limbic system in HSP with reference to controls. Also seen in PLS patients and to a lesser extent in X-SBMA.
Navas-Sanchez, 2021 Navas-Sánchez, Fernández-Pena [29]	Single-center, cross sectional, clinico-radiological correlations, subcortical segmentation & volumetry, vertex analyses	SPG4 (n = 12), controls (n = 22)	Reduced thalamic volume bilaterally. No hippocampal, putamen, globus pallidus, or caudate volume reductions. Negative correlation between SPRS and thalamic volume. Negative correlation was found between the disease duration and the Rt thalamic volume.
Lin, 2020 Lin, Zheng [22]	Single-center, cross-sectional, clinico-radiological correlations, DTI TBSS, cortical thickness, subcortical segmentation	SPG4 (n = 7), healthy controls (n = 7)	CC volume reductions in SPG4. Reduced cortical thickness in the bilateral superior frontal gyri, inferior precentral cortices, central cortices, and inferior parietal cortices; Lt. inf. frontal triangular cortex, postcentral gyrus, and sup. temporal gyrus; and the Rt. middle cingulate cortex and sup occipital cortex. Cortical thickness of Rt inferior frontal cortex negatively correlated with SPRS. Subcortical gray matter atrophy which correlated with disease duration. Reduced FA & AD, increased MD & RD in CC splenium and CST.
Garaci, 2014 Garaci, Toschi [122]	Single-center, cross-sectional, no clinico-radiological correlations, DTI TBSS	SPG11 (n = 4), SPG4 (n = 3), healthy controls (n = 16)	*SPG11*: increased MD and decreased FA in centrum semiovale, frontal WM, PLIC, and CC. *SPG4*: increased MD and decreased FA in centrum semiovale, PLIC, genu of CC.

(*Continued*)

Table 2. (Continued).

First author, year of publication	Study design Imaging modality	Study groups	Main conclusions
Chen, 2008 [123]	Single-center, cross-sectional, no clinico-radiological correlations, DTI	SPG11 (n = 2), healthy controls (n = 20)	Increased MD and decreased FA in CC, cerebellum, and thalamus in SPG11 patients compared with healthy controls
Pan, 2013 Pan, Huang [121]	Single-center, cross-sectional, no clinico-radiological correlations, DTI-tractography	SPG11 (n = 5), controls (n = 10)	Widespread FA reductions. Tractography: reduced integrity in commissural and association fibers in particular prefrontal and motor portions of the CC.
Schneider-Gold, 2017 Schneider-Gold, Dekomien [119]	Single-center, cross-sectional, no clinico-radiological correlation, GM volumetry, brain parenchymal fractions, DWI, MRS	SPG11 (n = 2), healthy controls (n = 5)	CC atrophy, BPF: brain atrophy, FA reduction & increased MD in CC. MRS: reduced NAA/Cr and NAA/mI in the CC in one of the two patients
Duning, 2010 Duning, Warnecke [44]	Single-center, cross-sectional, no clinico-radiological correlations, GM volumetry, DTI	SPG4 (n = 6), controls (n = 32)	Normal brain volumetry. Widespread FA reductions particularly in CST and temporal lobes
Oguz, 2013 [120]	Single-center, cross-sectional, no clinico-radiological correlations, DTI-TBSS	HSP-TCC n = 4 – not genetically confirmed, healthy controls (n = 15)	MRI brain: TCC in all patients. Mild to moderate cerebral atrophy. T2 hyperintensities in the periventricular white matter. DTI: Significantly lower FA in the corpus callosum, thalami, internal and external capsules, anterior thalamic radiations, bilateral cingulum, fornices, superior longitudinal fasciculi, uncinate fascicu- li, sagittal stratum, brain stem, and the cerebellum in patients compared with controls.
Franca, 2012 França, Yasuda [117]	Single-center, cross-sectional, no clinico-radiological correlations, DTI – TBSS, VBM	SPG11 (n = 5), controls (n = 15)	VBM: significant gray matter atrophy in thalamus, lentiform and caudate nucleus in SPG11 compared with controls TBSS: Reduced FA involving symmetrically subcortical white matter of the temporal and frontal lobes, the cingulate gyrus, cuneus, striatum, corpus callosum and brainstem

in SPG2 [108], in the supraventricular white matter in SPG11 [65] and in pre-central regions in genetically diverse HSP [25]. The basal ganglia were specifically evaluated in four MRS studies. Abnormal basal ganglia lipid profiles were described in SPG54 [50,78,138], while levels of other metabolites in the basal ganglia may be normal [138]. In contrast, another study found normal lipid levels in the basal ganglia in SPG54 [77].

2.4.6. Functional MRI (fMRI)

Despite its advantages to characterize functional alterations and network integrity alterations noninvasively [10], very few studies utilized fMRI in HSP. One resting state study revealed widespread cerebral connectivity alterations [139]. Other fMRI studies implemented a motor task to assess disease-associated cerebral activation profiles [36,140]. One study identified increased cerebral activation [140], and the other found decreased activation [36]. Specific study characteristics of metabolic and functional studies are summarized in Table 3.

3. Conclusions

Our review illustrates that a wide variety of neuroimaging techniques have been used in HSP, often with strikingly inconsistent findings. The literature is dominated by case studies, case series, and studies of very small sample sizes. Unifying conclusions are difficult to draw from the available PET, MRS, and fMRI studies due to the considerable differences in study designs. In contrast, DTI studies show relatively consistent results, highlighting CST and CC degeneration as a relatively consistent feature of HSP. Despite sample limitations and methodological differences, spinal cord atrophy and spinal corticospinal degeneration are also a relatively consistent observation in HSP. Cerebellar involvement, thalamic abnormalities, and preferential corpus callosum atrophy are other commonly detected radiological features.

Clinical parameters of disease severity and disability scales (such as the widely used SPRS) may be of relatively limited value for the precision tracking of accruing disease burden. Functional scales are merely indirect proxies of pathological change in the central nervous system (CNS) and may be less likely to change during the typical duration of a clinical trial than a quantitative biomarker. This is in contrast to neuroimaging, which provides objective, observer-independent, anatomically coded quantitative integrity markers. An additional benefit of neuroimaging is that the vast majority of advanced imaging modalities are noninvasive and require no contrast administration. MR scanners are widely available at most institutions, and the vast majority of suspected HSP patients undergo cerebral and spinal imaging anyway as part of their diagnostic work-up. The inclusion of high-resolution structural and diffusion pulse sequences adds little additional time and data processing can be run on a number of open-source and user-friendly cloud-based applications.

The systematic review of imaging in HSP helps not only to identify stereotyped shortcomings but also to outline desirable study designs for future studies. As with other low incidence MNDs, collaborative efforts, national repositories, and multi-site studies may help to boost cohort sizes and conduct larger imaging studies. Ideally, several genotypes should be included in one study in an attempt to delineate genotype-specific imaging traits. Harmonized protocols have been extensively used in other neurodegenerative conditions such as AD, ALS, FTD, HD [143,144]. In other conditions, presymptomatic imaging has revealed considerable structural, metabolic, and functional changes long before symptom manifestations [18,145,146] this also is of considerable interest in HSP [147]. The evaluation of presymptomatic changes may help to clarify emerging biological concepts such as 'motor reserve,' factors leading up to phenoconversion, and the chronology of motor and extra-motor changes. From a practical standpoint, the characterization of presymptomatic changes may help to establish the optimal window for pharmacological intervention in future trials and the development of predictive models with regard to projected symptom onset. Longitudinal radiological changes are poorly characterized in HSP despite their relevance to anatomical propagation patterns, flooring- and ceiling-effects of MR metrics, etc. Longitudinal studies are not merely of academic importance, they are also crucial for the development of monitoring markers for clinical practice and markers to appraise response to therapy in future trials. Multi-timepoint and multi-modal studies with uniform follow-up intervals are ideally suited to characterize progressive changes. While machine-learning (ML) applications based on imaging variables have been extensively tested in other neurological disorders, these have not been implemented in HSP to date [148–153]. Given the long diagnostic journey most patients with HSP face, imaging-based patient categorization into specific subgroups may help to expedite the diagnosis. Cluster analyses based on imaging have also contributed important insights in motor neuron disorders but are yet to be applied to HSP data [154,155]. Another important trend in neuroimaging is the characterization of disease burden in single patients instead of describing group-level signatures, which helps the precision tracking of accruing pathology in individual patients [156,157]. Stereotyped limitations of identified HSP studies include the exclusive focus on cerebral imaging, small sample sizes, the assessment of genetically admixed groups, inclusion of genetically not confirmed patients, lack of correlations with clinical variables, lack of extra-motor assessments (cognition, behavior, apathy, language, extra-pyramidal features, etc.), lack of longitudinal follow-up, and the absence of postmortem validation. Desirable future study features would include multi-site/multicenter projects, harmonized imaging protocols, the genetic screening of each participant, in-depth clinical profiling, characterization of extra-motor features, spinal imaging, and the inclusion of asymptomatic mutation carriers. Clinical assessments accompanying imaging should ideally include a bladder questionnaire, as well as tests for executive function, language, memory, and social cognition. Delineation of radiological changes observed in primary lateral sclerosis (PLS) needs to be clarified as there is a considerable overlap in both clinical and radiological features. Imaging studies of PLS also invariably describe PMC, CST, CC, and BG changes similar to those observed in genetically confirmed HSP [158,159]. PLS studies should, therefore, meticulously screen their participants for known HSP mutations [160].

It is noteworthy that more recent white matter techniques such as neurite orientation dispersion and density imaging

Table 3. Metabolic and functional studies on HSP.

First author, year of publication	Study design Imaging modality	Study groups	Main conclusions
Doi 2014 [78]	Single-center, cross-sectional, no clinico-radiological correlations, MRI brain, MRS: lipids in thalamus and BG	SPG54 (n = 2) Genetically confirmed No controls	MRI brain: thin corpus callosum, MRS: Increased lipid in basal ganglia
Erichsen 2009 [30]	Single-center, cross-sectional, clinico-radiological correlations, MRS	SPG4 (n = 8), controls (n = 8)	MRS: Decreased total Cho & decreased Cho/Cr in PMC. Cho/Cr reduction correlated with verbal learning memory performance
Hehr 2007 [60]	Single-center, longitudinal, no clinico-radiological correlations, MRI brain, FDG-PET-CT, MRS: frontal, parieto-occipital, centrum semiovale, IC	SPG11 (n = 20), MRS (n = 1), FDG-PET-CT (n = 3)	MRI brain: thin CC, WM hyperintensities. PET-CT: progressive cortical and thalamic hypometabolism. MRS: mild frontal NAA reduction
Liguori 2014 [141]	Single-center, cross-sectional, no clinico-radiological correlations, MRS: CSF and cortex	SPG28 (n = 2), no controls	MRS: no cortical change. Lactate accumulation in ventricular CSF in one patient, not in the other
Lossos 2015 [137]	Single-center, longitudinal (4-year follow-up), no clinico-radiological correlation, MRI brain, MRS: frontal, parieto-occipital centrum semiovale, IC	SPG75 (n = 3), no controls	MRI brain: WM hyperintensities, progressive CC and cerebellar atrophy. MRS: decreased NAA in the frontal WM
Orlen 2009 [65]	Single-center, cross-sectional, no clinico-radiological correlations, MRI brain, PET-CT, MRS: supraventricular white matter	SPG11 (n = 4), healthy controls (n = 5)	MRI: TCC. MRS (n = 1): reduced NAA/Cr and elevated mI/Cr in supraventricular WM. PET-CT (n = 2): bilateral thalamic and sensorimotor cortex hypometabolism
Roos 2014 [46]	Single-center, Cross-sectional, no clinico-radiological correlations, MRI brain, MRS: occipito-parietal lobe	SPG5A (n = 4), no controls	MRI brain: WM hyperintensities in 1 of 4 patients. MRS (n = 2): Increased mI/Cr in occipito-parietal region
Schuurs-Hoeijmakers, 2012 [50]	Single-center, cross-sectional, no clinico-radiological correlations, MRI brain, MRI C spine, MRS: basal ganglia and thalamus	SPG54 (n = 11), no controls	MRI brain: thin CC & periventricular WM hyperintensities. MRS (n = 5): abnormal lipid peak in the BG and thalamus. MRI spine (n = 2): syrinx in 2/2
Stromillo 2011 [105]	Single-center, cross-sectional, no clinico-radiological correlations, MRI brain, MRS: CC, sup. corona radiata, periventricular WM	SPG11 (n = 10), controls (n = 10)	MRI brain: WM hyperintensities & volume loss. MRS: Decreased NAA/Cr in CR and periventricular WM. Cerebral volume and CR NAA/Cr correlates with disability
Svenstrup 2010 [108]	Single-center, longitudinal, no clinico-radiological correlations, MRI brain, PET, MRS: occipito-frontal WM, occipital GM, centrum semiovale	SPG2 (n = 2)	MRI brain: periventricular WM hyperintensities – no progression longitudinally. MRS: Reduced WM NAA, increased WM Cho and MI in white matter (n = 2) PET CT normal
Estrada-Cuzcano, 2017 Estrada-Cuzcano, Martin [94]	Single-center, cross-sectional, no clinico-radiological correlations, MRI brain, DAT	SPG78 (n = 5), no controls	MRI: cerebellar atrophy, predominantly vermian. DAT scan: decreased putaminal dopamine transporter density
Terada, 2013 Terada, Kono [130]	Single-center, cross-sectional, no clinico-radiological correlations, PET-CT	SPG3a (n = 2), one control (n = 1)	Reduced frontal glucose metabolism
Samaranch, 2008 Samaranch, Riverol [66]	Single-center, cross-sectional, no clinico-radiological correlations, MRI, PET-CT	SPG11 (n = 4), one control (n = 1)	MRI: TCC and WM hyperintensities. FDG-PET: reduced paracentral and thalamic metabolism
Anheim, 2009 Anheim, Lagier-Tourenne [142]	Single-center, cross-sectional, clinico-radiological correlations, ^{123}I-ioflupane SPECT	SPG11 (n = 2), one control (n = 1)	Reduced striatal ligand uptake
Seon Kim, 2013 Kim, Kim [129]	Single-center, cross-sectional, no clinico-radiological correlations, DAT-SPECT	HSP (n = 9), not genetically confirmed	Normal DAT scan in 5 patients, reduced striatal ligand uptake in 4/9 patients
Criscuolo, 2009 Criscuolo, Filla [104]	Single-center, cross-sectional, no clinico-radiological correlations, MRI brain, PET CT	SPG5 (n = 6), no controls	MRI brain: WM hyperintensities, PET CT: cerebellar hypometabolism in one patient
Orlacchio, 2005 Orlacchio, Kawarai [32]	Single-center, cross-sectional, clinico-radiological correlations, MRI brain, SPECT	SPG4 (n = 11)	Frontotemporal hypoperfusion correlated with cognitive impairment.
Scheuer, 2006 Scheuer, Nielsen [135]	Single-center, cross-sectional, clinico-radiological correlations, rCBF PET CT	SPG4 (n = 13), controls (n = 13)	Increased PMC & SMA rCBF during motor task.
Scheuer, 2005 [35]	Single-center, cross-sectional, clinico-radiological correlations, PET-CT	SPG4 (n = 18), controls (n = 18)	Decreased left frontotemporal rCBF. No correlations with cognitive impairment.

(*Continued*)

Table 3. (Continued).

First author, year of publication	Study design Imaging modality	Study groups	Main conclusions
Faber, 2018, Faber, Martinez [27]	Single-center, cross-sectional, clinico-radiological correlations, DAT SPECT – TcTRODAT	SPG11 (n = 22), healthy controls (n = 19)	Decreased striatal density, inverse correlation with disease duration. Reduced caudal and putaminal tracer uptake. SPRS score DAT correlations
Liao, 2018 Liao, Huang [139]	Single-center, cross-sectional, clinico-radiological correlations, rsfMRI	SPG4 (n = 12), healthy controls (n = 10)	Decreased low-frequency fluctuation amplitudes in left insular cortex and higher in right precentral and superior frontal gyrus. Increased right PMC values correlated negatively with SPRS scores. Increased functional connectivity between left middle frontal gyrus to the left middle orbitofrontal gyrus.
Koritnik, 2009 Koritnik, Azam [140]	Cross-sectional, single center, no clinico-radiological correlations, task fMRI	HSP (n = 12), not genetically confirmed, healthy controls (n = 12)	Increased PMC and posterior parietal cortex activation during finger tapping
Tomberg, 2012 Tomberg, Braschinsky [36]	Cross-sectional, single center, clinico-radiological correlations, task fMRI	SPG4 (n = 7), ADHSP not genetically confirmed (n = 2), controls (n = 14)	Activation clusters in HSP were smaller than in controls in the sensorimotor area during motor task, and more pronounced in the cerebellum. The degree of sensorimotor cortex was associated with spasticity.

(NODDI), diffusion kurtosis imaging (DKI), and high angular resolution diffusion imaging (HARDI) have not been applied to larger patient cohorts yet, despite their superior potential to characterize white matter integrity especially with regard to crossing fibers. Furthermore, novel multi-voxel whole-brain spectroscopy sequences that have been extensively used to other MNDs are yet to be applied to HSP [161,162]. Other imaging modalities, which have been extensively utilized in MNDs, such as connectomic approaches, quantitative susceptibility mapping (QSM), motor imagery-based fMRI, and texture analysis, are yet to be implemented in HSP [163–165]. Another stereotyped shortcoming of existing HSP imaging studies is the lack of relevant disease controls such as ALS or PLS, which would help to appraise the specificity of purported radiological signatures to HSP. Anatomically expanded activation patterns observed on task-based fMRI studies need to be interpreted with caution. There is a notion that slowly progressive neurodegenerative conditions and neurological syndromes with initial insult in childhood, such as post-poliomyelitis syndrome, may be associated with compensatory processes and structural adaptation, which may be detected by advanced imaging methods [166]. The existence of such adaptive or compensatory processes needs to be clarified in HSP. Contrary to other MNDs, these mechanisms have not been studied in HSP to date.

4. Expert Opinion

Irrespective of the underlying genotype, hereditary spastic paraplegias are associated with significant diagnostic challenges, motor disability, and quality-of-life implications. HSP also exhibit considerable clinical heterogeneity with respect to extra-motor manifestations, progression rates, and age of onset. A unifying feature of HSPs is the lack of disease modifying therapies, scarcity of drug development initiatives, and lack of non-clinical quantitative monitoring markers. Key barriers to the effective management of this low-incidence condition include the lengthy diagnostic journey, limited understanding of the pathophysiology of the genetic subtypes, and a lack of disease modifying therapies.

MRI brain and whole spine are routinely performed in all patients presenting with spastic paraparesis to rule out the relevant disease mimics. While reviewing clinical scans for HSP-associated radiological cues such as thin corpus callosum, 'ears-of-the-lynx sign,' and cord atrophy may be helpful, the limited specificity of these qualitative findings to HSP is very important to recognize. Proposed associations between radiological cues and genotypes, such as thin corpus callosum in SPG11 and SPG4 and the 'ears-of-the-lynx sign' in SPG11 and SPG15 should be treated with caution and MR findings alone should not guide genetic screening. Postmortem studies in HSP are notoriously scarce [6,7] despite their importance in deciphering underlying processes and the preferential involvement of specific anatomical regions.

From all the quantitative imaging modalities explored in the academic setting, diffusion tensor-based white matter imaging yielded the most unifying imaging signature, consistently revealing bilateral corticospinal tract degeneration and corpus callosum changes. There are other important lessons to consider from the advances in neuroimaging in MNDs [167]. Presymptomatic changes are not only important to characterize for academic reasons but also so that pharmacological intervention could be informedly timed. An additional caveat of existing HSP imaging studies is the limited scope of modalities; studies are either primarily structural, diffusion, metabolic, or functional. Ideally, multimodal studies should be conducted, so the comparative detection sensitivity of the various imaging methods can be juxtaposed. The design of the few longitudinal studies identified may also be improved. Ideally, enrollment into longitudinal studies should be relatively uniform with regard to symptom duration, and only multi-timepoint longitudinal studies are suitable for characterizing linear versus non-linear changes in integrity metrics and exploring possible ceiling and flooring effects. Only high-quality, multimodal, and multi-timepoint studies can adequately characterize natural disease trajectories, anatomical propagation patterns, and progression rates. Ultimately, only robust longitudinal studies can lead to the development of sensitive monitoring markers with practical utility in future clinical trials. In future studies, patients should be carefully stratified by the underlying genotype as admixed HSP cohorts are unsuitable for the development of imaging-based biomarkers. Existing imaging studies on HSP overwhelmingly perform group-level descriptive analyses to describe cohort-associated radiological traits. While this is of interest in the academic setting, future studies should capitalize on recent advances in machine-learning and focus on the categorization of individual patient scans into clinically relevant subgroups.

HSP imaging is an exciting and relatively underexplored frontier of MND research. There are ample methodological lessons to consider from imaging initiative in other neurodegenerative conditions. The implementations of novel imaging sequences (QSM, spinal cord, DKI, NODDI, etc.), pooled data from multiple sites, and meticulous stratification by genotype is likely to advance our understanding of pathophysiology in HSP. Ultimately, advanced neuroimaging techniques have the potential to be developed into viable clinical applications, curtailing the diagnostic delay and serving as noninvasive monitoring markers in future clinical trials.

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ORCID

Peter Bede http://orcid.org/0000-0003-0492-4772

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