Clinical features and management of hereditary spastic paraplegia

Aspectos clínicos e manejo das paraplegias espásticas hereditárias

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ABSTRACT

Hereditary spastic paraplegia (HSP) is a group of genetically-determined disorders characterized by progressive spasticity and weakness of lower limbs. An apparently sporadic case of adult-onset spastic paraplegia is a frequent clinical problem and a significant proportion of cases are likely to be of genetic origin. HSP is clinically divided into pure and complicated forms. The later present with a wide range of additional neurological and systemic features. To date, there are up to 60 genetic subtypes described. All modes of monogenic inheritance have been described: autosomal dominant, autosomal recessive, X-linked and mitochondrial traits. Recent advances point to abnormal axonal transport as a key mechanism leading to the degeneration of the long motor neuron axons in the central nervous system in HSP. In this review we aim to address recent advances in the field, placing emphasis on key diagnostic features that will help practicing neurologists to identify and manage these conditions.

Keywords: hereditary spastic paraplegia, spastic paraplegia, muscle spasticity, genetics, mutation.

RESUMO

Paraplegias espásticas hereditárias (PEH) constituem um grupo de desordens geneticamente determinadas caracterizadas por espasticidade e paraparesia de progressão insidiosa. Paraplegia espástica aparentemente esporádica de início no adulto constitui problema frequente na prática neurológica. Evidências recentes sugerem que uma proporção significativa destes casos é geneticamente determinada. O grupo das PEH é dividido clinicamente em formas puras e complicadas de acordo com a concomitância de outras manifestações clínicas e neurológicas. Até o momento 60 tipos genéticos foram identificados. Todos os modos de herança monogênica já foram descritos: autossômica dominante, autossômica recessiva, ligada ao X e mitocondrial. Avanços recentes indicam que alterações do transporte axonal estão implicadas na degeneração dos longos axônios motores no sistema nervoso central na PEH. Nesta revisão abordamos recentes avanços na área com ênfase nos aspectos clínicos chave que ajudam o neurologista geral no diagnóstico e manejo correto deste grupo de doenças.

Palavras-chave: paraplegia espástica hereditária, paraplegia espástica, espasticidade muscular, genética, mutação.

Hereditary spastic paraplegia (HSP) is a diverse group of single-gene disorders characterized by retrograde degeneration of the long axonal fibers of the corticospinal tracts and posterior columns of the spinal cord. The key clinical feature is slowly progressive pyramidal pattern of weakness[1].

There are few epidemiological studies in HSP, but prevalence is estimated to range between 1.3 to 9.6 cases per 100,000 people[2]. In addition to clearly familial cases, a significant proportion of patients with sporadic spastic paraplegia also have a genetic etiology. HSP represents a large proportion of subjects attending specialized Movement Disorders, Neuromuscular and Neurogenetics outpatient clinics. Although traditionally regarded as a rare disorder, HSP is almost as common as other disorders well known by the general neurologist, such as: hereditary cerebellar ataxias (prevalence rate of up to 8.9 people out of 100,000)[3], motor neuron disease (6.3 per 100,000)[4,5] and multiple system atrophy (4-5 per 100,000 people)[6].

In recent years, several genes and loci associated to HSP have been mapped[1,7]. On clinical grounds, these findings helped neurologists to perform more accurate and earlier diagnoses, as well as a sounder genetic counseling.

Furthermore, key molecular pathways leading to neurodegeneration were unraveled, which might have short term implications for novel therapies and result in a better understanding of closely related disorders, such as motor neuron diseases and spinocerebellar ataxias.

In the present article, we review the core clinical features of HSP, as well as the available therapeutic strategies. Our ultimate objective is to help practicing neurologists to recognize and to properly manage patients with HSP.

CLASSIFICATION

HSPs are a group of heterogeneous monogenic diseases. They may segregate as an autosomal dominant, an autosomal recessive, X-linked or mitochondrial trait[1]. To date, there are up to 60 genetic types described[7]. Clinically, they are classified as pure or complicated forms. The later are associated with a variety of other neurological and systemic abnormalities, whereas the former essentially present with lower limb weakness and spasticity. Most cases of pure HSP are autosomal dominant, while complicated forms are inherited mostly as autosomal recessive conditions. X-linked forms may present either as pure or complicated HSP. This distinction is clinically useful, but is not always found in genotype-phenotype correlation studies[1].

AUTOSOMAL DOMINANT- HEREDITARY SPASTIC PARAPLEGIA (AD-HSP)

AD-HSP represents 70% to 80% of HSPs. Almost half of those are caused by mutations in the *SPG4* gene that encodes for the protein spastin[8]. *SPG4* is also responsible for approximately 10% of sporadic cases. In Brazil, we have recently found that *SPG4*-related HSP accounts for 35% of AD cases[9]. It shows a wide inter and intra-familial variability in age of onset and disease severity suggesting the existence of modifying factors[10]. It classically presents as a pure spastic paraplegia. Recent studies though highlighted a frequent association with cognitive decline, hand tremor and other complicating features[11,12].

Table 1. Current genetic classification of autosomal dominant hereditary spastic paraplegia.

Disease	Gene symbol locus	Protein	Key clinical features
SPG3A	*SPG3A* 14q22.1	Atlastin	Pure early onset.
SPG4	*SPAST* 2p24-p21	Spastin	pure HSP, highly variable onset. Late onset cognitive impairment.
SPG6	*NIPA1* 15q11.2	NIPA1 (Not imprinted in Prader-Willi/Angelman 1)	Pure, slowly progressive adult-onset.
SPG8	*KIAA0196* 8q24.13	Strumpellin	Pure adult-onset.
SPG9	Gene unknown 10q23.3-q24.1	Unknown	Complicated: Cataracts, motor neuropathy, gastroesophageal reflux.
SPG10	*KIF5A* 12q13.13	Kinesin Family member 5A	Pure or Complicated. Early-onset, distal amyotrophy.
SPG12	*RTN2* 19q13	Reticulon 2	Pure, early-onset.
SPG13	*HSPD1* 2q33.1	Heat shok 60KDa protein 1 (chaperonin) (M)	Pure, adult-onset.
SPG17	*BSCL2* 11q12-q13.5	Seipin	Complicated: amyothrophy of hand muscles (Silver-syndrome).
SPG19	Gene unknown 9q33-q34	Unknown	Pure.
SPG29	1p31-p21	Unknown	Complicated: deafness, persistent vomiting from hiatal hernia.
SPG31	*REEP1* 2p11.2	Receptor expression enhancing protein 1 (REEP1)	Pure. May be complicated by Silver-syndrome.
SPG33	*ZFYVE27* 10q24.2	Protrudin	Pure.
SPG36	Gene unknown 12q23-q24	Unknown	Early adulthood associated with polyneuropathy.
SPG37	Gene unknown 8p21.1-q13.3	Unknown	Pure.
SPG38	Gene unknown 4p16-p15	Unknown	Complicated: Silver-syndrome.
SPG41	Gene Unknown 11p14.1-p11.2	Unknown	Pure or mild Silver-syndrome.
SPG42	*SCL33A1* 3q25.3	SCL33A1 (acetyl-CoA transporter)	Pure, variable-onset incomplete penetrance.

Mutations in the *SPG3a* gene, encoding for the protein atlastin-1, are the second most common cause of AD-HSP and the most common cause of early-onset disease[13]. Most patients present with pure spastic paraplegia initiating before the age of ten. *SPG 31*, related to mutations in the *REEP 1* gene, accounts for approximately 5% of AD-HSP. It typically presents as early-onset spastic paraplegia plus lower motor neuron disease, known as Silver-syndrome[14].

Mutations in the SPG 6[15] and SPG 8[16] are pure HSPs that have already been identified in the Brazilian population. SPG 6 presents as a slowly progressive, mostly pure spastic paraplegia in early-adulthood[15] (Table 1).

AUTOSOMAL RECESSIVE- HEREDITARY SPASTIC PARAPLEGIA (AR-HSP)

AR-HSP frequently present with pleomorphic associated neurological and clinical abnormalities. While this adds considerable challenges in the diagnostic workup, certain specific complicating features may guide the differential diagnosis between the different HSPs. As seen in other recessive conditions, AR-HSP are more frequent in consanguineous populations.

Mutations in the gene *SPG11,* encoding spastacsin, are the most frequent cause of AR-HSP, corresponding to up to 20%[17]. This proportion increases to 60-80% when considering patients with thinning of the corpus callosum and mental impairment[18]. Patients typically present around the first or second decades with gait disturbances followed by cognitive deterioration, peripheral neuropathy and movement disorders, including dopa-responsive parkinsonism[19]. Thinning of the corpus callosum is a hallmark of this condition. In our center, SPG 11-HSP accounts for 45% of patients with HSP and thinning of the corpus callosum[20]. Atrophy of the corpus callosum is also a hallmark of *SPG15*, associated with pigmental retinopathy and polyneuropathy[21]. Mutations in the *SPG7* gene, which encodes paraplegin, is the second most common cause of AR-HSP. Its characteristic features include cerebellar ataxia, peripheral neuropathy and optic atrophy[22]. SPOAN syndrome, first described in Brazil is characterized by early and rapidly progressive spastic paraplegia, optic atrophy and peripheral neuropathy, but its gene is yet to be identified[23] (Table 2).

X-LINKED

SPG1 gene encodes the protein NCAM[24]. Affected males typically present with spastic paraplegia and hydrocephalus, together with mental retardation, aphasia, shuffling gait and adducted thumbs (MASA-syndrome).

SPG2 gene is also called proteolipoprotein or *PLP1* gene[25]. The typical phenotype is composed of spastic paraplegia associated with peripheral neuropathy and white matter abnormalities. Interestingly, duplications of this gene give rise to the congenital hipomyelinating Pelizaeus-Merzbacher disease[25]. SPG34 disease is a pure X-linked form of HSP whose locus was first identified in Brazil, but its gene is yet to be identified[26,27] (Table 3).

MITOCHONDRIAL

A single family with five affected members has been recently described with a mtDNA mutation in the *ATP6* gene clinically expressed as late onset spastic paraplegia[28].

DIAGNOSIS

Diagnosis of HSP is based upon individual and family-history as well as clinical and neurological findings such as spastic weakness, hyperreflexia and extensor plantar responses. These will guide further investigation to rule out acquired causes of spastic paraplegia and orient specific molecular diagnosis. The absence of family history should not eliminate the diagnosis of HSP. At times, mildly affected members or false paternity are not recognized, so a detailed history and examination of apparently healthy family members is desirable. HSP is characterized by normal motor development followed by slowly progressive spasticity and weakness of the lower limbs. The clinical spectrum and the age of onset vary widely. Disproportionate spasticity in contrast with mild weakness is a hallmark of this disorder. Mild reduction of vibration sense, or other sensory abnormalities together with urinary symptoms are frequent even in pure forms[1]. Complicated HSP comprise a large number of abnormalities such as ataxia, peripheral neuropathy, amyotrophy, seizures, movement disorders, cognitive impairment, retinopathy, optic atrophy, deafness and others[29,30].

An apparently sporadic case of slowly progressive spasticity and weakness of the lower limbs is a fairly frequent clinical problem in neurological practice. HSP is a diagnosis of exclusion, especially in the absence of family history. Spinal cord compression, infectious, inflammatory, metabolic and ischemic myelopathies must be ruled out. We suggest a basic workup composed of: serology for human T cell leukemia virus, HIV and syphilis, as well as measurement of serum copper, ceruloplasmin, ferritin, vitamin B12 and vitamin E levels. In selected cases, quantification of serum very long chain fatty acids may be desirable to screen for adrenomyeloneuropathy. Magnetic resonance of the cervical spine is necessary to exclude spinal cord compression, inflammatory or ischemic myelopathies. Brain MRI is desirable since it

Table 2. Current genetic classification of autosomal recessive hereditary spastic paraplegia.

Disease	Gene symbol locus	Protein	Key clinical features
SPG5	*CYP7B1* 8p12-q13	Cytochrome P450, family 7, subfamily B, polypeptide 1	Pure or complicated: generalized muscle atrophy and white matter lesions.
SPG7	*SPG7* 16q24.3	Paraplegin	Pure and complicate: amyotrophy, dysarthria, dysphasia, cerebellar and optic atrophy.
SPG11	*SPG11* 15q14	Spatacsin	Pure and complicated/early onset, cognitive impairment, neuropathy, movement disorders, TCC.
SPG14	Gene Unknown 3q27-q28	Unknown	Complicated: polineuropathy, mental retardation.
SPG15 (Kjellin)	*ZFYVE26* 14q24.1	Spastizin	Complicated: spastic paraplegia with macular dystrophy, mental retardation and amyotrophia (Kjellin syndrome).
SPG18	*ERLIN2* p11.23	Erlin-2	Complicated: mental retardation, TCC.
SPG20 (Troyer)	*SPG20* 13q12.3	Spartin	Complicated: dysarthria and distal amyotrophy.
SPG21 (Mast)	*SPG21* 15q21-q22	Maspardin	Complicated: cognitive decline, movement disorders, TCC, white matter abnormalities.
SPG23 (Lison)	Gene unknown 1q24-q32	Unknown	Complicated/skin and hair pigmentary lesions, skeletal abnormalities.
SPG24	Gene unknown 13q14	Unknown	Pure/spastic dysarthria and pseudobulbar signs
SPG25	Gene unknown 6q23.3-q24.1	Unknown	Complicated: multiple disc herniation, cataract, congenital glaucoma.
SPG26	Gene unknown 12p11-q14	Unknown	Child onset, complicated:distal amyotrophy cognitive impairment, dysarthria.
SPG27	Gene unknown 10q22-q24	Unknown	Pure or complicated: cognitive impairment, ataxia, dysarthria, polyneuropathy, short stature, dismorphic face.
SPG28	*DDHD1* 14q22.1	DDHD1	Pure early-onset.
SPG29	Gene unknown 1p31.1-p21.1	Unknown	Pure, childhood onset.
SPG30	*KIF1A* 2q37.3	Kinesin family member 1A	Complicated: ataxia, sensory neuropathy.
SPG32	Gene unknown 14q12-q21	Unknown	Complicated: mental retardation, ataxia, brainstem dysraphia and cerebellar atrophy.
SPG35	*FA2H* 16q21-q23.1	Fatty acid 2-hydroxilase	Childhood onset, complicated: cognitive decline, movement disorders, epilepsy. Brain white matter lesions and iron accumulation.
SPG39	*PNPLA6* 19p13.2	Neuropathy Target Esterase (NTE)	Complicated: childhood onset, marked distal wasting in all four limbs.
SPG43	Gene unknown 19p13.11-q12	Unknown	Complicated: Silver-syndrome and dysarthria.
SPG44	*CJC2* 1q42.13	Connexin 47	Adulthood onset complicated: cognitive decline, spasticity of four limbs.
SPG45	Gene unknown 10q24.3-q25.1	Unknown	Childhood onset complicated: mental retardation, optic athrophy.
SPG46	Gene unknown 9p21.2-q21.12	Unknown	Dementia, congenital cataract, ataxia, TCC.
SPG47	*AP4B1* 1p13.2	AP-4 complex subunit beta-1	Complicated: neonatal hypotonia, progressive hypertonia, severe mental retardation, ataxia, seizures, TCC.
SPG48	*KIAA0415* 7p22.1	KIAA0415	Pure.
SPG49	*TECPR2* 14q32.31	Unknown	Delayed psychomotor development, early spasticity, dismorphic features, TCC, central apnea.
SPG50	*AP4M1* 7q22.1	Adaptor-related protein complex 4, mu 1 subunit	Complicated/neonatal hypotonia that progresses to hypertonia. Severe mental retardation.
SPG51	AP4E1 15q21.2	Adaptor-related protein complex 5, zeta 1 subunit	Complicated: neonatal hypotonia that progresses to hypertonia. Severe mental retardation. Same phenotype as SPG50.
SPG52	*AP4S1* 14q12	AP4S1	Complicated: neonatal hypotonia that progresses to hypertonia. Dysmorphic features.
SPG53	Gene unknown 8p22	VSP37A	Complicated: psychomotor delay, spasticity of four limbs.
SPG54	*DDHD2* 8p11	Unknown	Psychomotor delay, cognitive impairment, dismorphic features. TCC and white matter lesions.
SPG55	*C12orf65* 12q24.31	C12orf65	Early onset. Complicated: polyneuropathy and optic atrophy.
SPG56	*CYP2U1* 4q.25	CYP2U1	Early onset, spasticity of four limbs, polyneuropathy.
SPOAN	Gene unknown 11q13	Gene unknown	Early onset, spastic paraplegia, optic atrophy and axonal neuropathy.

may show specific findings such as thinning of the corpus callosum, white matter abnormalities and hydrocephalus, which will help guide further molecular testing. Spinal fluid analysis is warranted when history and previous tests did not exclude inflammatory and infectious myelopathies.

In the clinical setting of AD-HSP, screening for mutations in *SPG4* is the first step, followed by *SPG3a* in negative cases[13,31]. If spastic paraplegia initiated before the age of ten, *SPG3a* gene should be analyzed first. *SPG31* is the next gene to be sequenced in negative cases[32]. Screening for these three genes will likely identify mutations in more than 50% of the patients.

Molecular investigation for AR-HSP should be guided by the complicating features. *SPG11* is the most prevalent form of AR-HSP, its likelihood increases to up to 80% in the presence of cognitive decline and thinning of the corpus callosum[18]. Currently in Brazil, patients must be referred to research centers for HSP gene sequencing.

Due to its phenotypic variability, the differentiation between various forms of HSP can be difficult on clinical grounds. In selected cases, it is reasonable to consider other neurodegenerative diseases on the differential diagnosis. Motor neuron disease, spinocerebellar ataxias, and neurodegeneration with brain-iron accumulation are conditions that may show clinical overlap with HSP[33]. Spinocerebellar ataxia type 3, also named Machado-Joseph disease, is the most common autosomal dominant spinocerebellar ataxia, and has been previously highlighted as a differential diagnosis for complicated HSP in Brazil[34].

PATHOPHYSIOLOGY

HSPs are characterized by retrograde degeneration of the longest neurons of the spinal cord, the corticospinal tract and the posterior columns[35]. Due to their length and high metabolic needs, these neurons are highly susceptible to impaired transport of macromolecules and organelles. Despite its genetic heterogeneity, disruptive processes involving membrane trafficking and organelle morphogenesis and distribution seem to play a central role in the pathophysiology of most HSPs[29,30,36].

HSP-related proteins cluster into overlapping functional classes: membrane trafficking, organelle shaping, mitochondrial regulation, lipid metabolism and axon path finding. The three most common AD-HSPs (SPG4, SPG3A, SPG31) are due to altered function of proteins involved in shaping the endoplasmic reticulum, a function highly dependent on microtubules[37,38]. Microtubule-targeting drugs have shown positive results in animal models of SPG4[39].

NEUROIMAGING STUDIES

In cases of proven HSP the most common neuroimaging finding is thinning of the spinal cord[40]. Although less frequent, brain abnormalities are often found in HSPs and this may be valuable to guide genotyping strategy. SPG11, the most common cause of AR-HSP, must be suspected when thinning of the corpus callosum is present, especially when accompanied by the ears of the linx sign (Figures 1A and B) and widespread white matter abnormalities[41,42,43]. A recent study from our group showed that these patients also have significant grey matter volume reduction in specific cortical areas and the deep nuclei. These are the areas with higher expression of spastacsin in the brain and this pattern helps us to understand why movement disorders are so frequent in SPG 11[42]. Despite this, one must consider that thinning of the corpus callosum is not SPG11-specific, because it is also found in other HSPs such as: SPG 4, 7, 15, 18, 21, 46, 47, 49 and 54[3,11,21,44,45,46]. Progressive hydrocephalus due to aqueductal stenosis is highly suggestive of X-linked SPG1. White matter abnormalities may be found in some AR-HSP, such as SPG 5, SPG 21, SPG 35 or autosomal recessive spastic ataxia with leukoencephalopathy (ARSAL)[47]. In SPG2, white matter abnormalities are also typical; they resemble (but to a lesser extent) the diffuse hypomyelination found in the allelic Pelizaeus-Merzbacher disease[25,48] (Figure 2).

Table 3. Current genetic classification of X-linked hereditary spastic paraplegia.

| Disease	Gene locus	Protein	Key clinical features
SPG1 (MASA)	*L1CAM* Xq28	L1 cell adhesion molecule	Complicated: mental retardation, aphasia, shuffling gait, adducted thumbs. Aqueductal stenosis wih hydrocephalus (MASA syndrome).
SPG2	*PLP1* Xq22	Proteolipid protein 1	Pure or complicated: optic atrophy, ataxia, mental retardation, white matter lesions.
SPG16	Gene unknown Xq11.2	unknown	Pure or complicated: aphasia, mental retardation, impaired vision.
SPG22	Xq13.2	Monocarboxylate transport 8 (MCT8)	Complicated (Allan-Herndon-Dudley syndrome): congenital neck hypotonia, psychomotor delay, early-spastcity, ataxia, dismorphic features.
SPG34	Gen unknown Xq24-q25	unknown	Pure. All families described in Brazil.
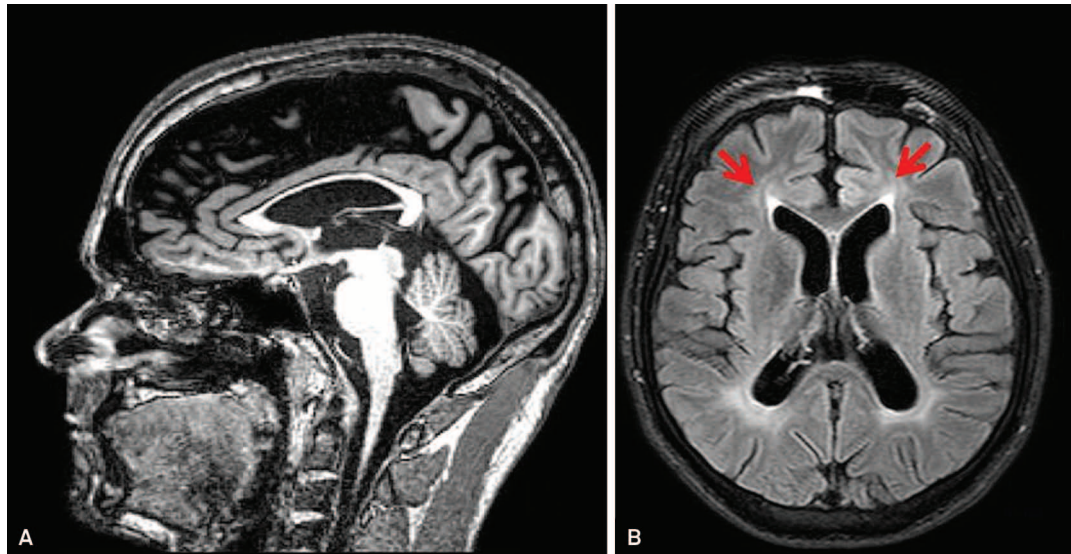
Figure 1. Magnetic resonance imaging of the brain of a patient with mutation in the *SPG11* gene (SPG11 phenotype): Sagittal T1 weighted imaging showing thinning of the Corpus Callosum (A). Axial FLAIR imaging showing the "ears of the lynx" sign (red arrows) (B).

FINAL REMARKS

Despite the lack of disease modifying therapies, adequate prognostic counseling is of great importance for patients, family members and healthcare professionals. Outcome of patients with HSP is highly variable and specific molecular
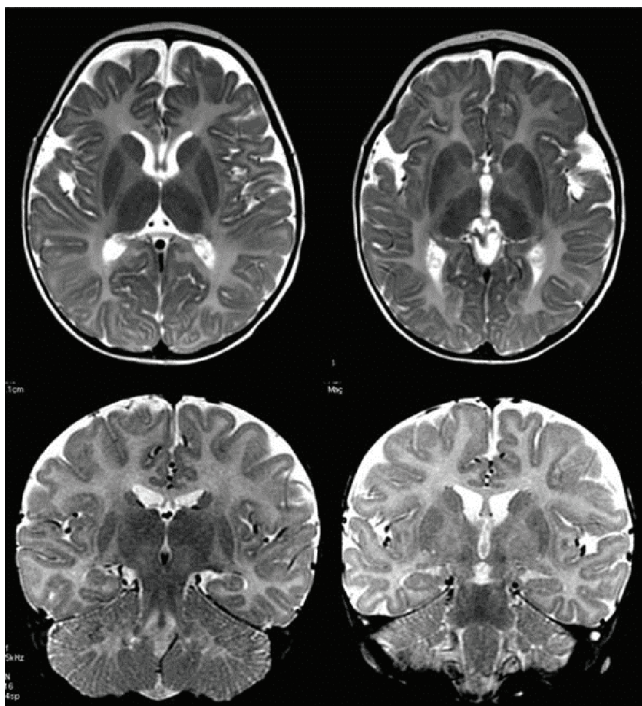

Figure 2. Magnetic resonance imaging of the brain of a patient with mutation in the *PLP1* gene (SPG2 phenotype). Axial T2 weighted images show widespread hyperintensity along cerebral white matter. (Images from Professsor Maria Augusta Montenegro, Departamento de Neurologia, Universidade Estadual de Campinas).

diagnosis provides more accurate information. Diagnosis is also warranted to prevent patients from been submitted to unnecessary diagnostic tests. Patients with pure HSP mostly have a normal life-spam. Wheelchair users, especially when this milestone is reached early in life, are more susceptible to secondary cardiovascular, pulmonary and infectious complications. In complex cases, prognosis is strongly determined by additional manifestations. The course of the spastic paraplegia itself is usually slowly progressive; in some patients with extremely early onset, the disease may even resemble a static condition such as diplegic cerebral palsy. Overall, disability in patients with pure HSP tends to progress slower than in patients with spinocerebellar ataxias[49].

Spasticity is the most disabling feature in the majority of cases. Treatment options include oral anti-spastic agents, such as baclofen and tizanidine. If these drugs are ineffective, chemodenervation with botulinum toxins may be attempted[50,51]. In our experience, the use of low doses of botulinum toxin associated with proper physical therapy (focused on stretching and strengthening) benefits the patientás ambulatory capacity, provides pain relief and prevents contractures and deformities. Signs and symptoms of parkinsonism should be actively investigated since it can be alleviated with dopaminergic drugs. Neuropathic pain is managed with antidepressants (amytriptiline, nortryptiline, duloxetin) or anticonvulsants (pregabalin, gapapentin). Urinary urgency can be alleviated with anticholinergic drugs[52].

As the disease progresses patients should be evaluated for the appropriate assistive walking devices such as walkers and wheelchairs. In case of prominent distal weakness affecting foot dorsiflexion it is reasonable to use ankle-foot orthoses. Secondary deformities such as scoliosis, tendon contractures and foot deformities may require surgical management.

CONCLUSIONS

HSP is a group of disorders in which the long motor neuron axons are predominantly affected, leading to slowly progressive pyramidal weakness of the lower limbs with relative preservation of other body parts. Phenotypic and genotypic heterogeneity contributes to under recognition of the disease. Increasing awareness about this disorder is especially important for patients and researchers nowadays, since there is rapid progression on the field. Detection of new causative genes, HSP-related proteins and its mechanisms may bring treatment perspectives in the near future as well as provide clues about other similar neurodegenerative diseases of the motor system[53].

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