Child Neurology: Hereditary spastic paraplegia in children

Because the medical literature on hereditary spastic paraplegia (HSP) is dominated by descriptions of adult case series, there is less emphasis on the genetic evaluation in suspected pediatric cases of HSP. The differential diagnosis of progressive spastic paraplegia strongly depends on the age at onset, as well as the accompanying clinical features, possible abnormalities on MRI, and family history. In order to develop a rational diagnostic strategy for pediatric HSP cases, we performed a literature search focusing on presenting signs and symptoms, age at onset, and genotype. We present a case of a young boy with a REEP1 (SPG31) mutation.

CASE REPORT A 4-year-old boy presented with progressive walking difficulties from the time he started walking at the age of 12 to 13 months. His family history was significant for minimal gait abnormalities with onset after age 35, occurring in the patient’s mother, maternal grandfather, and maternal aunt; none of them had ever sought medical attention. Neurologic examination revealed a mildly spastic gait and marked lower limb hypertreflexia with bilateral Babinski signs present. Vibration perception was reduced at the ankles. Neurologic examination of the patient’s mother and maternal aunt revealed subtle gait abnormalities with bilateral Babinski signs present.

MRI of the brain and spinal cord and general metabolic screening revealed no abnormalities. Diagnostic genetic testing in both the patient and his mother revealed a pathogenic mutation (c.417 + 1 G>T) in REEP1 (SPG31) which causes a pure HSP. Mutations in ATL1 (SPG3A) and SPAST (SPG4) had previously been excluded.

DISCUSSION HSP is a genetically and clinically heterogeneous group of disorders in which the main clinical feature is progressive lower limb spasticity secondary to pyramidal tract dysfunction. HSP is classified as pure if neurologic signs are limited to the lower limbs (although urinary urgency and mild impairment of vibration perception in the distal lower extremities may occur). In contrast, complicated forms of HSP display additional neurologic and MRI abnormalities such as ataxia, more significant peripheral neuropathy, mental retardation, or a thin corpus callosum. HSP may be inherited as an autosomal dominant, autosomal recessive, or X-linked disease. Over 40 loci and nearly 20 genes have already been identified.1 Autosomal dominant transmission is observed in 70% to 80% of all cases and typically results in pure HSP.2

Spastic paraplegia is a common problem in the daily practice of pediatric neurologists, generally caused by acquired brain disorders such as perinatal asphyxia or infections early in life resulting in cerebral palsy. In addition, there is a long list of more rare disorders to consider when confronted with spastic paraplegia including structural, infectious, demyelinating, and metabolic disorders (table).3 Only in a small minority of cases does HSP underlie the spastic syndrome. Many patients with childhood-onset HSP are mistakenly diagnosed with cerebral palsy.4,5 In children with spastic paraplegia in whom no acquired cause can be identified, HSP should be considered. A positive family history aids with the diagnosis. Our case illustrates the importance of neurologic examination of family members who may be mildly affected.

Since the medical literature on HSP is dominated by adult case series, it is difficult to decide how the genetic evaluation should be structured when a child is suspected to have HSP. In order to develop a rational diagnostic strategy for HSP in children, we per-
formed a literature search focusing on presenting signs and symptoms, age at symptom onset, and genotype. We also share some of our personal experiences from a clinic-genetic database, as our institution has served as a tertiary referral center for Dutch HSP patients for over 2 decades.

Characteristics. In the medical literature, symptom onset before age 18 has been documented in many HSP cases, particularly in the complicated forms, which show a clear overlap with many metabolic disorders and leukodystrophies. In a series of 23
children with HSP, 15 of 23 (65%) were reported to have a complicated (mostly recessively inherited) HSP, compared to 8 of 23 (35%) with a pure HSP. In our HSP database, an early age at symptom onset (prior to age 18) was found in 72 of 175 (41%) patients, with a heterogeneous genetic background: 47 of 72 (65%) autosomal dominant cases, 12 of 72 (17%) autosomal recessive cases, and 13 of 72 (18%) sporadic cases. Gaits difficulties were the presenting symptom in 81%, with a mean age of 8 years. A complicated phenotype was present in 25%. Of these 72 early-onset HSP patients, at least 20 (28%) had presented in childhood. Prior reviews have provided in-depth descriptions and overviews of all known HSP forms.1,2 In this article, we focus on the most prevalent (≥5 families described) forms of HSP with a possible childhood onset.

**Autosomal dominant pure HSP.** *ATL1* (SPG3A). This is a pure form of HSP, comparable to SPG4, and almost never starts after age 20 years. It is the most frequent cause of HSP (twice as frequent as *SPAST*), with onset before age 10 years. Therefore, *ATL1*, which encodes atlastin (a dynamin-like GTPase), is the first candidate gene that should be tested in patients with a suspected pure autosomal dominant or sporadic HSP with symptom onset before age 10. *SPAST* (SPG4). SPG4 is the most prevalent, mostly pure form of HSP with a variable age at onset, varying from infancy through over 70 years of age. *SPAST* encodes spastin with microtubule-severing activity, necessary for axonal transport. In a large study of 172 *SPAST* patients, approximately 30% had an age at onset before 20 years.8 In our *SPAST* cohort, comparable figures were found, with walking difficulties presenting at a mean age of 7.5 years (range 1–18 years) in this young-onset group. Onset in infancy is unusual. After the description of 5 patients from 1 family,5 we identified an additional 5 patients from 4 families with symptom onset in infancy. Until that point, such a young onset had been described only in association with co-dominant mutations (genetic modifiers) in the *SPAST* gene. Therefore, *SPAST* is the second candidate gene that should be tested in patients with a pure HSP with symptom onset before age 10, after *ATL1*. With an onset of symptoms between 10 and 20 years, both genes should be tested.

*NIPA1* (SPG6), *KIF5A* (SPG10), and *SPG12*. SPG6 causes a pure HSP, occasionally with a childhood onset, but more commonly with onset of symptoms in the late teenage to early adult years.9 SPG10 and SPG12 both lead to an early-onset pure HSP. All 3 are described in fewer than 10 families.1

*REEP1* (SPG31). SPG31, a pure form of HSP, shows a variable age at onset, with an onset before 20 years in 71% of cases.10 *REEP1* encodes the mitochondrial protein receptor expression-enhancing protein 1. *REEP1* mutations were found in 8.2% of pure autosomal dominant HSP patients (of all ages), in whom *ATL1* or *SPAST* mutations had been excluded.1

We encountered 5 SPG31 patients who presented before age 18 years, with gait abnormalities and foot deformities at a mean age of 4 years. *REEP1* mutations can cause a pure HSP in children, but should only be tested after *SPAST* and *ATL1* mutations have been ruled out.

**Complicated forms of HSP.** *L1CAM* (SPG1) and *PLP1* (SPG2). These are both X-linked and complicated forms of HSP, which may be tested in boys with mental retardation and other clinical features.1,2

*SPG7*. SPG7, an autosomal recessive HSP, causes a spastic paraplegia in combination with cerebellar ataxia, cerebellar atrophy, optic atrophy, and peripheral neuropathy. Age at onset varies from 10 to 42 years in the literature, but mostly adult cases have been reported.

*SPG11 and ZFYVE26* (SPG15). SPG11 is the most frequent form of autosomal recessive HSP with onset typically in childhood (age range 1.5–21 years). It is characterized by a thin corpus callosum, mild leukencephalopathy, mild mental retardation, and peripheral neuropathy. A comparable autosomal recessive syndrome is SPG15 (Kjellin syndrome), with additional cerebellar signs, maculopathy, and onset between 5 and 19 years.

*BSCL2* (SPG17). SPG17 (Silver syndrome) has a variable age at onset. Distal amyotrophy affecting upper extremities more than lower extremities accompanies the spastic paraplegia. Inheritance is autosomal dominant.

Four SPG17 patients in our cohort, with onset between 10 and 16 years, presented with weakness of the upper extremities greater than in the lower extremities, and 3 of the 4 had foot or hand deformities.

**Genetic testing in children.** A formal diagnosis provides a prognosis, prevents additional burdensome and potentially costly diagnostic evaluation, may facilitate the prevention of complications, and allows for potential inclusion in clinical trials. In addition, a genetic diagnosis allows for genetic counseling with regard to the recurrence risk within the family. Ethical, social, and financial considerations, as well as written or verbal informed consent from the parents, according to established guidelines, are necessary before genetic testing in children.
Diagnostic approach. When confronted with a child with a pure spastic paraplegia, a thorough family history (of at least 3 generations) is essential. After neurologic examination of the child and the parents, structural lesions and white matter disorders need to be excluded by performing MRI of the brain, with transverse T1, T2,
and sagittal T1 images, and of the entire spinal cord. A positive family history or examination facilitates direct diagnostic genetic testing (figure).

In a pure, autosomal dominant HSP, \( \text{ATL1} \) (SPG3A) and \( \text{SPAST} \) (SPG4) mutation analysis would be the first tests of choice. If negative, \( \text{REEP1} \) (SPG31) could be tested subsequently. In case of a negative family history or examination, ophthalmologic examination, CSF analysis, and metabolic screening should be considered, primarily to look for conditions with disease-modifying therapies available. Finally, a trial of levodopa may be considered, since a dystonic gait and striatal toes as part of a dopa-responsive dystonia syndrome could be mistaken for spastic paraplegia.\(^3\) If these investigations are negative, \( \text{ATL1} \) and \( \text{SPAST} \) mutation analysis should be considered because sporadic cases (due to de novo mutations and incomplete penetrance) have been described in these HSP forms.\(^4,5\)

When confronted with a child with a complicated spastic paraplegia, the accompanying signs and symptoms will lead to a differential diagnosis and the required specific diagnostic evaluation (table).\(^1,2\)

**DISCLOSURE**

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**REFERENCES**

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