HEREDITARY SPASTIC PARAPLEGIA ASSOCIATED WITH THIN CORPUS CALLOSUM

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ABSTRACT - Autosomal recessive hereditary spastic paraplegia (AR-HSP) associated with thin corpus callosum was recently described in Japan, and most families were linked to chromosome 15q13-15. We report two patients from two different Brazilian families with progressive gait disturbance starting at the second decade of life, spastic paraparesis, and mental deterioration. One patient presented cerebellar ataxia. Magnetic resonance imaging (MRI) of the head of both patients showed a thin corpus callosum. AR-HSP with a thin corpus callosum is a rare disorder, mainly described in Japanese patients. We found only 4 Caucasian families with AR-HSP with thin corpus callosum described in the literature. Further studies including additional Caucasian families of AR-HSP with thin corpus callosum are required to delineate the genetic profile of this syndrome in occidental countries.

KEY WORDS: hereditary spastic paraplegia, corpus callosum, MRI.

Paraplegia espástica hereditária associada a hipoplasia de corpo caloso


PALAVRAS-CHAVE: paraplegia espástica hereditária, corpo caloso, ressonância magnética.

Hereditary spastic paraplegia (HSP) is a heterogeneous group of genetic neurodegenerative disorders characterized by progressive spasticity of the lower limbs. In 1981, Harding¹ suggested clinical criteria for classifying HSP into pure and complicated forms. Pure HSP patients present with family history, progressive gait disturbance, spasticity of lower limbs, hiperreflexia, and extensor plantar responses. In complicated HSP the spastic paraparesis is only one feature of a much more complex phenotype. Complicated HSP has been associated with many conditions including mental retardation or deterioration, optic atrophy, retinopathy, extrapyramidal disease, amytrophy, ataxia and cerebellar signs, deafness, ichthyosis, and peripheral neuropathy². HSP is also genetically heterogeneous and autosomal dominant, autosomal recessive, and X-linked mode of inheritance have been described². Recently, a new form of complicated autosomal recessive HSP (AR-HSP) associated with thin corpus callosum was described in Japan³,⁴. Because few cases were reported in Caucasian population, herein we present two patients from two different families with HSP and thin corpus callosum.

CASES

Patient 1. A 18-year-old Caucasian girl presented a 4-year history of frequent falls, gait disturbance, progressive muscular weakness, and pain in the lower limbs. She had normal achievement of motor milestones. There was

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no family history and her parents were unrelated. General physical examination was normal. On neurological examination, she presented mild dysarthria, muscular strength in the lower limbs grade IV/V (Medical Research Council), spasticity in the lower limbs, patellar and ankle deep tendon reflexes grade ++/IV, left extensor cutaneous plantar response, and spastic gait. Sensation and coordination was normal. Ophthalmological examination was normal. Complete blood count, glucose, electrolytes, thyroid function tests, serum vitamin B12, and cerebrospinal fluid analysis were normal. Serum HTLV-1 antibody assay was negative. Needle electromyography showed active denervation in anterior tibial, and first dorsal interosseous of the right foot. Nerve conduction studies were normal. MRI of the head showed a dysgenesis of corpus callosum (thin corpus callosum) (Fig 1). Electroencephalogram showed diffuse slowing of background rhythm.

**Patient 2.** A 16-year-old Caucasian boy started having progressive gait disturbance, and frequent falls at 12 years of age. He had normal achievement of motor milestones. There was history of consanguineous marriage of his parents, and there were two cousins with similar disease. Aside from bilateral pes cavus, general physical examination was otherwise normal. On neurological, he presented mild mental retardation, dysarthria, and bilateral rectus lateral paresis. He presented normal muscle bulk, spasticity in the lower limbs, muscular strength grade IV/V (Medical Research Council); brisk deep tendon reflexes in the lower limbs (grade ++/IV), bilateral extensor cutaneous plantar responses, mild coordination impairment in the upper limbs, resting and postural tremor in the upper limbs, and spastic gait. Sensation was normal. Ophthalmological examination was normal. Complete blood count, glucose, electrolytes, thyroid function tests, serum vitamin B12, and cerebrospinal fluid analysis were normal. Serum HTLV-1 antibody assay was negative. Needle electromyography and nerve conduction studies were normal. MRI of the head showed dysgenesis of the corpus callosum, mainly in the anterior limb (Fig 2).

**DISCUSSION**

The typical clinical picture of AR-HSP with thin corpus callosum starts at the second decade of life with gait disturbance, then spastic paraparesis and mental deterioration progresses slowly2,4. Consanguineous marriage is frequent and was present in 8 of 13 families studied by Shibasaki et al.5 Cerebellar ataxia and sensory loss in the distal parts of four extremities also occur in some patients. Other clinical features include spasticity and hiperreflexia in the upper limbs, muscle atrophy, pes cavus, impaired vibration sense, urinary disturbance, dysarthria, nystagmus, congenital cataracts, and cerebellar atrophy3,6. Disease duration influences the clinical features, since associated signs and symptoms appears as disease progresses. Because this, our patients will probably present additional neurological signs in subsequent evaluations.

In AR-HSP with thin corpus callosum, MRI of the head typically demonstrates a thin corpus callosum, which is not specific of this syndrome. Additional described findings in MRI included bilateral medial frontal atrophy, widening of the interhemispheric fissure, mild enlargement of lateral and third ventri-

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**Fig 1.** Sagittal MRI of head, T2-weighted image, showing a dysgenesis of corpus callosum (thin corpus callosum) (Patient 1).

**Fig 2.** Axial MRI of head, T2-weighted image, showing a dysgenesis of corpus callosum, mainly in the anterior limb (Patient 2).
icles, reduced size of thalamus. Whether the thin corpus callosum represents a congenital hypoplasia or a progressive atrophy remains unknown. Since the thickness of the corpus callosum did not correlate with duration from disease onset in one study, it was considered more probably a hypoplasia.

The diagnostic criteria of autosomal recessive HSP with thin corpus callosum include the following: (1) inheritance consistent with autosomal recessive trait, (2) slowly progressive spastic paraparesis and mental impairment, (3) thinning of the corpus callosum as revealed by brain CT or MRI, and (4) exclusion of other disorders by MRI of the spine and brain as well as other laboratory tests.

Among the autosomal recessive HSP, three loci were identified. The first described locus for AR-HSP showed pure HSP phenotype and was linked to chromosome 8p12-q13 in 4 Tunisian families. The second locus was identified on chromosome 16q24.3 in a large consanguineous Italian family. The gene at this 16q24 locus was called paraplegin, a nuclear-encoded mitochondrial metalloprotease. Mutations in the gene of paraplegin were shown to be responsible for both pure and complicated forms of HSP. The third locus for AR-HSP was identified as mapping to chromosome 15q13-15 in 7 families from North America and Europe whose members showed both pure and complicated forms of the disease. Recently, Shibasaki et al. showed that 10 of 13 Japanese families with AR-HSP with thin corpus callosum was linked to chromosome 15q13-15. It suggests that most AR-HSP with thin corpus callosum in Japan is linked to chromosome 15q13-15, but genetically heterogeneous. Because this, other loci of AR-HSP with thin corpus callosum remains to be discovered. Clinically and genetically, AR-HSP with thin corpus callosum was poorly studied in Caucasian population. Two Caucasian families were linked to chromosome 15q13-15, and one kindred was linked to chromosome 16.

The mapping of AR-HSP with thin corpus callosum to the 15q13-15 locus adds this condition to a group of two disorders previously mapped to this region: agenesis of the corpus callosum with peripheral neuropathy or Andermann syndrome, and amyotrophic lateral sclerosis. The overlapping genetic localization of the responsible genes suggests that these disorders may be allelic and could be caused by the same defective gene.

To our knowledge, there was only 4 Caucasian families of AR-HSP with thin corpus callosum described, including one North American, one Italian, one Spanish, and one Portuguese family. In contrast, more than 20 families of AR-HSP have been described in Japan. Herein, we described two Brazilian families of European ancestry with the typical clinical and radiological features of AR-HSP with thin corpus callosum. Further studies including additional Caucasian families of AR-HSP with thin corpus callosum is required to delineate the clinical and genetic profile of this syndrome in occidental countries.

REFERENCES