MACHADO-JOSEPH DISEASE VERSUS HEREDITARY SPASTIC PARAPLEGIA

Case report

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ABSTRACT - Machado-Joseph disease (MJD) is the most common autosomal dominant spinocerebellar ataxia and presents great phenotypic variability. MJD presenting with spastic paraparesis was recently described in Japanese patients. We report the case of a 41-year-old woman with the phenotype of complicated hereditary spastic paraplegia. Her father died at the age of 56 years due to an undiagnosed progressive neurological disease that presented parkinsonism. She had an expanded allele with 66 CAG repeats and a normal allele with 22 repeats in the gene of MJD. MJD should be considered in the differential diagnosis of autosomal dominant complicated HSP. A patient with the phenotype of complicated HSP and relatives with other clinical features of a neurodegenerative disease should raise the suspicion of MJD.

KEY WORDS: spinocerebellar ataxia, Machado-Joseph disease, hereditary spastic paraplegia.

Machado-Joseph disease (MJD) is the most common autosomal dominant spinocerebellar ataxia. MJD has a wide phenotypic variation and five clinical subtypes have been described. Type I patients show pronounced pyramidal signs and extrapyramidal signs such as dystonia. Type II patients have cerebellar and pyramidal signs. Type III patients present with cerebellar signs, and peripheral neuropathy. Type IV patients develop predominantly parkinsonism, and distal amyotrophy. Type V was recently described in Japanese patients and courses with spastic paraparesis. The differentiation between MJD with spastic paraparesis and the several types of hereditary spastic paraplegia (HSP) can be difficult on clinical grounds. We report a patient with the phenotype of “complicated” HSP and genetic test compatible with MJD.

CASE

A 41-year-old woman presented a 3-year history of progressive weakness in the lower limbs, and impairment of gait. One-year before admission she started with tremor in the lower limbs. Her father died at the age of 56 years due to an undiagnosed progressive neurological disease that suggested parkinsonism. General physical examination was normal. On neurological examination, she presented normal cranial nerves, normal muscle bulk, spasticity in the lower limbs, and muscular strength grade IV in the lower limbs (Medical Research Council). She had a resting and

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Table 1. Genetic classification of hereditary spastic paraplegia (HSP).

<table>
<thead>
<tr>
<th>Genome database designation</th>
<th>Chromosome</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Genetic defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPG1</td>
<td>Xq28</td>
<td>X-linked</td>
<td>Complicated</td>
<td>L1CAM</td>
</tr>
<tr>
<td>SPG2</td>
<td>Xq22</td>
<td>X-linked</td>
<td>Both</td>
<td>PLP</td>
</tr>
<tr>
<td>SPG3*</td>
<td>14q11.2-24.3</td>
<td>AD</td>
<td>Pure</td>
<td>Unknown</td>
</tr>
<tr>
<td>SPG4</td>
<td>2p22-21</td>
<td>AD</td>
<td>Both</td>
<td>Spastin</td>
</tr>
<tr>
<td>SPG5</td>
<td>8p12-q13</td>
<td>AR</td>
<td>Pure</td>
<td>Unknown</td>
</tr>
<tr>
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<td>15q11.1</td>
<td>AD</td>
<td>Pure</td>
<td>Unknown</td>
</tr>
<tr>
<td>SPG7</td>
<td>16q24.3</td>
<td>AR</td>
<td>Both</td>
<td>Paraplegin</td>
</tr>
<tr>
<td>SPG8</td>
<td>8q24</td>
<td>AD</td>
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</tr>
<tr>
<td>SPG9*</td>
<td>10q23.3-24.2</td>
<td>AD</td>
<td>Complicated</td>
<td>Unknown</td>
</tr>
<tr>
<td>SPG10</td>
<td>12q13</td>
<td>AD</td>
<td>Pure</td>
<td>Unknown</td>
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<tr>
<td>SPG11</td>
<td>15q13-15</td>
<td>AR</td>
<td>Both</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Types of HSP with overlapping clinical features with Machado-Joseph disease.

Postural tremor of all four limbs, increased deep tendon reflexes in the lower limbs, and bilateral extensor plantar responses. There was mild ataxia of the limbs, sensation was normal, and the gait was spastic. There were no bulging eyes, fasciculation, myokymia, or dystonia. HTLV-1 and 2 serology was negative. Computed tomography of head was normal. Genetic diagnosis for MJD was performed through polymerase chain reaction according to previously described methods. She had an expanded allele with 66 CAG repeats and a normal allele with 22 repeats in the gene of MJD. In normal individuals the MJD gene contains 12 to 34 CAG repeats, while in affected patients the repeat number ranges from 61 and 84 repeats.

**DISCUSSION**

Sakai and Kawakami first described two patients with MJD and spastic paraplegia and proposed a new clinical subtype for this condition. After that, Kaneko et al. described a new patient with MJD presenting as spastic paraplegia. As in our case there was a great intra-familial phenotypic variability in both two previously reported families. Our father’s patient was not examined by us, but due to the occurrence of parkinsonism he would probably be classified as a different MJD subtype. This phenotypic difference among individuals of a same family is well documented in MJD.

The mechanism responsible for the phenotype differences in MJD is unknown. Several possibilities have been considered, including the number of trinucleotide repeats, features of the normal allele, imprinting, somatic mosaicism, modifying genes, polymorphism in the affected allele, environmental factors, and homozygosity.

HSP is a heterogeneous group of inherited disorders in which the main clinical feature is progressive lower limbs spasticity. Families with autosomal dominant, autosomal recessive, and X-linked inheritance have been described. In 1981, Harding 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 optic atrophy, retinopathy, extrapyramidal disease, amyotrophy, dementia, ataxia and cerebellar signs, mental retardation, deafness, ichthyosis, and peripheral neuropathy.

The clinical overlap between MJD and complicated HSP is extensive since both entities can present spastic paraparesis, extrapyramidal dysfunction,
amyotrophy, dementia, ataxia and cerebellar signs, and peripheral neuropathy\(^9,10\).

MJD should be considered in the differential diagnosis of autosomal dominant complicated HSP (Table 1). A patient with the phenotype of complicated HSP and relatives with other clinical features of a neurodegenerative disease should raise the suspicion of MJD.

REFERENCES