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# Hereditary Spastic Paraplegia With Hypoplastic Corpus Callosum in a Turkish Family

Kivilcim Gucuyener, MD, Tugba Hirfanoglu, MD, Ikbal Ok, MD, Ali Cansu, MD, and Ayse Serdaroglu, MD

Hereditary spastic paraplegia is composed of a heterogeneous group of neurodegenerative disorders and is classified as pure or complicated due to its clinical variability. Autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum is a rare form of complicated hereditary spastic paraplegia. In complicated hereditary spastic paraplegia, autosomal dominant, autosomal recessive, and X-linked modes of inheritance have been noted. The diagnostic criteria of autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum are inheritance consistent with autosomal recessive trait, slowly progressive spastic paraparesis and mental detoriation, hypoplasia of corpus callosum revealed by brain computerized tomography or magnetic resonance imaging, and exclusion of other disorders by magnetic resonance imaging of the spine and brain as well as other laboratory tests. In this report, the authors present the case of 3 affected siblings in a family from Turkey, whereas 1 child and the consanguineous parents were healthy. To the authors' knowledge, it is the first reported case of autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum from Turkey.

**Keywords**: hereditary spastic paraplegia; hypoplastic corpus callosum; mental deterioration

Hereditary spastic paraplegia is a heterogeneous group of neurodegenerative disorders and is classified as pure or complicated forms due to its clinical variability.[1] In pure form, patients present with family history, progressive gait disturbances, hyperreflexia, spasticity of lower limbs, and extensor plantar responses. In complicated hereditary spastic paraplegia, the symptoms are much more complex; in addition to spastic paraplegia, cognitive decline, epilepsy, optic atrophy, extrapyramidal signs, and muscle atrophy may also be seen.[2,3] Autosomal dominant, autosomal recessive, and X-linked modes of inheritance have been noted.[1]

Autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum is a rare form of complicated hereditary spastic paraplegia mainly described in Japanese patients.[4,5] It was first thought to occur only in this population and was taken as a Japanese subtype. However, this understanding was challenged when patients were reported from North America, Brazil, Spain, Italy, Germany, Portugal, and China, indicating a worldwide distribution.[6-11] To further assess the clinical features and geographic distribution of patients with autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum, we report 3 siblings in a family from Turkey.

From the Department of Pediatric Neurology (KG, TH, AC, AS) and the Department of Pediatrics (IO), Gazi University, Faculty of Medicine, Besevler, Ankara, Turkey.

Address correspondence to: Tugba Hirfanoglu, MD, Gazi University, Faculty of Medicine, Department of Pediatric Neurology, 10th Floor, 06500 Beşevler/Ankara, Turkey; e-mail: tluleci13@yahoo.com.

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## Cases

In this family, 3 siblings were affected, whereas 1 child and the consanguineous parents were healthy. There is no other similar case in the family.

### Case 1

The first proband is a boy, who is now 24 years old. He had normal motor and intellectual development until the age of 10 years, when bilateral progressive horizontal nystagmus, hand tremor, and gait disturbance first appeared. Three years later, speech impairment had started, and at the age of 16 years, neurologic examination showed hyperreflexia in his lower limbs, extensor plantar reflexes, increased muscle tone with normal strength, and mild cognitive impairment. At the age of 20 years, his walking had worsened, and spasticity and dysarthria had increased. His present examination



**Figure 1.** A T1-weighted image reveals hypoplastic corpus callosum and nonspecific white matter abnormalities (case 1).

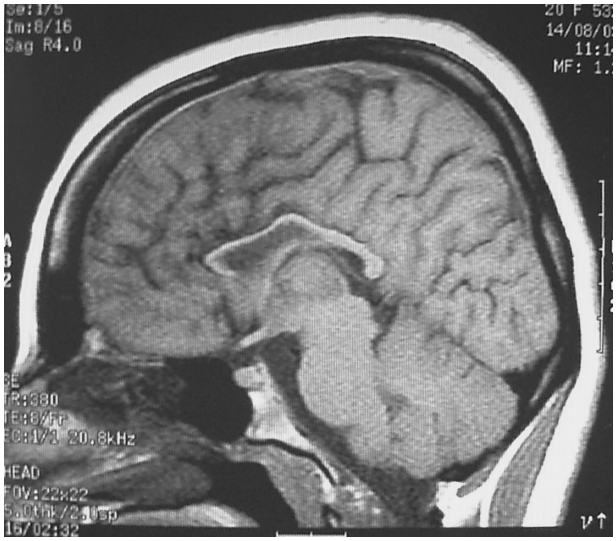


**Figure 2.** A T1-weighted image reveals hypoplastic corpus callosum (case 2).

showed bilateral horizontal nystagmus and hand tremor, severe spasticity, gait impairment, brisk tendon reflexes, bilateral sign with ankle clonus, and muscle atrophy. He also had dysarthria, mild cerebellar signs, and cognitive impairment. His IQ score as measured by the Weschler Adult Intelligence Scale (WAIS) was 68. His electroencephalography (EEG) and electromyography (EMG) results were normal; cranial magnetic resonance imaging (MRI) showed hypoplastic corpus callosum and nonspecific white matter abnormalities (Figure 1).

### Case 2

The first patient's 20-year-old sister had quite similar disease progression. She was considered to be normal until the age of 10 years, and by then, a 10-year history of progressive hand tremor, bilateral horizontal nystagmus, dysarthia, and gait impairment with cognitive deterioration was seen. Her present examination showed bilateral pes cavus and Achilles contracture, severe spasticity with hyperreflexia in her lower limbs, bilateral Babinski and Hoffmann sign, and ankle clonus. Brisk tendon reflexes were also noted in the upper limbs, she was severely dysarthric, she had mild cerebellar signs, and she required assistance while walking. She had mild mental deterioration, with an IQ of 70. Her EEG and EMG results were normal, and her cranial MRI showed hypoplastic corpus callosum (Figure 2).

### Case 3

The third sibling is a young boy (aged 15 years) who had normal motor and intellectual development until 10 years of age. At this age, his main symptoms were bilateral rotatory nystagmus and mild stiffness while walking. Four years later, his walking had worsened and bilateral hand tremor while writing had developed, which gradually progressed into gait disturbance and hand clumsiness. His present neurologic examination showed bilateral rotatory nystagmus and moderate spasticity more evident in his lower limbs with brisk tendon reflexes and Babinski sign. His cerebellar tests were moderately impaired; he also had dysarthria and ataxic gait. His cognitive impairment was mild, with an IQ of 72. His EEG and EMG results were normal, and cranial MRI revealed thin and hypoplastic corpus callosum (Figure 3).

## Results

### Laboratory Results

All 3 siblings underwent biochemical screening tests based on the list of differential diagnosis of hereditary spastic paraplegia. These tests were complete blood count, glucose, electrolytes, thyroid function tests, serum vitamin $B_{12}$, folic acid, vitamin E levels, plasma and cerebrospinal fluid lactate and pyruvate levels, urine-blood organic acids and amino acid levels, tandem mass spectroscopy results of very-long-chain fatty acids, and lysosomal enzymes in leucocytes; all were within normal levels. All siblings had normal EEG and EMG results but abnormal cranial MRI findings with hypoplastic corpus callosum.

According to a personal communication with Dr A. Crosby, genetic analysis of all the patients was not consistent with both the linkages to chromosome 16 and 15 (with the SPG 11 locus both overlapping and not related to Andermann syndrome). The genes were also screened for mutation analysis of the SPG 11 gene maspardin, which also showed no mutation.




**Figure 3.** A T2-weighted image reveals hypoplastic corpus callosum (case 3).

Because there was consanguinity, the transmission is considered to be autosomal recessive. The age at onset for motor symptoms was between 10 and 15 years. All 3 siblings had bilateral pyramidal tract involvement, which was more prominent in the lower limbs, but over the years, 1 sibling also had upper limb involvement to some extent. The 2 older siblings required some assistance with walking. Dysarthria and hand tremor with mild cerebellar signs were present in all. Interestingly, all siblings showed nystagmus and mild to moderate cognitive impairment (IQ between 68 and 72), with attention problems and learning difficulties detected at the primary school age starting at the same time as motor signs.

## Discussion

Although the frequency of patients with autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum outside Japan seems to be underrated mainly because of misdiagnosis, both Japanese and non-Japanese patients reported in the literature more or less show the same typical clinical picture.[2-10] The onset of the disease is in the second decade of life, with progressive spastic paraplegia and mental impairment. Consanguineous marriages are frequently observed, and it is compatible with the pattern of autosomal recessive inheritance. In some patients, upper limb involvement and cerebellar ataxia are also found. The motor dysfunction, upper limb spasticity, cerebellar ataxia, and independent walking worsen progressively, and walking becomes nearly impossible after age 20 years on average. This indicates that disease duration influences clinical features and that additional symptoms appear with age.[10] Other clinical features include muscle atrophy, pes cavus, impaired vibration sense, dysarthria, nystagmus, and congenital cataract.[12-14] None of the non-Japanese patients with hypoplastic corpus callosum–thin corpus callosum defined to date showed congenital cataracts, indicating that this might to be a unique feature of Japanese patients.[12-14] The clinical features of our 3 siblings were very similar to those of the reported cases, and the model of inheritance was autosomal recessive. The onset of the disease was in the early teens, and all developed progressively spastic paraparesis and cognitive impairment, muscle atrophy, and ataxia. One sibling also had moderate extrapyramidal symptoms involving the upper extremities. All had normal EMG results, indicating the nonexistence of a peripheral neuropathy at least for the time of their investigations.

The hypoplasia of the corpus callosum seems to be a neuroradiologically distinctive feature of this syndrome but is not specific to it. Recently, Orlaccio et al,[15] in their study of 15 patients with autosomal dominant hereditary spastic paraplegia with hypoplastic corpus callosum, also found hypoplastic corpus callosum and atrophy of the cerebellum in 2 patients. The debate is whether hypoplastic corpus callosum is a result of congenital hypoplasia or a progressive degenerative process. Ueda et al[5] showed that the thickness of corpus callosum did not correlate with duration of the disease, as described by Sperfeld et al,[16] who also followed 2 cases for 4 years and found that the hypoplasia of corpus callosum seen on MRI remained unchanged between longitudinal investigations. Both observations suggest that the corpus callosum hypoplasia occurs early in the disease course, favoring an insult early in life. In our patients, the hypoplastic corpus callosum was present in all siblings, detected by the first MRI between the ages of 10 and 12 years, before the other symptoms became overt.

Recently, the genetics of autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum were found to be heterogeneous, and 2 loci have been identified. In 1999, Coutinho et al[7] found the disease linked to chromosome 15q13-15 in 2 white families and to chromosome 16 in another family. After this report, Shibasaki al[17] found the disease in 10 of 13 Japanese families with complicated hereditary spastic paraplegia with hypoplastic corpus callosum with mental impairment and thin corpus callosum, Winner et al[10] found the disease in 2 sisters with autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum, and Casali et al[9] found the disease in 5 of 12 Italian families with autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum. All demonstrated linkage to 15q13-15. The absence of linkage in 7 families in the study by Casali et al[9] also favors genetic heterogeneity. Our patients did not show any linkage either to chromosome 15q13-15 nor chromosome 16,

further stressing the genetic heterogeneity of the disorder. Interestingly, an autosomal recessive form of amyothropic lateral sclerosis has also been mapped within the autosomal recessive hereditary spastic paraplegia with the hypoplastic corpus callosum region,[18] indicating that the 2 diseases may represent alleic disorders of the same gene, although this has not yet been proven. Furthermore, the mutation analysis of the SPG 21 gene encoding maspardin, which has revealed a wild-type sequence in 2 patients with hypoplastic corpus callosum, thin corpus callosum with progressive gait disturbance, ataxia, and cognitive impairment, has also showed negative results (personal communication, Dr Andrew H. Crosby, St George Hospital Medical School, London, UK, October 2003).[19]

In conclusion, the main clinical and diagnostic features of autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum are autosomal recessive inheritance, slowly progressive spastic paraparesis with mental impairment at a young age, and hypoplasia of corpus callosum. Because the disorder is genetically heterogeneous, some other loci of autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum remain to be discovered in patients with undefined genetic loci, as in our cases. To our knowledge, our cases are the first reported from Turkey. The most recently reported cases in Europe—mostly from Italy, Spain, Germany, and Portugal, along with our patients from Turkey—suggest autosomal recessive hereditary spastic paraplegia with hypoplastic corpus callosum to be underrated in Europe and that it is more widespread than previously believed. The alertness of pediatricians and pediatric neurologists of this condition will readily lead to more and earlier diagnoses in the future.

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