We describe 2 brothers with L-2-hydroxyglutaric aciduria who developed severe spastic tetraparesis in their 30s. They also had an underlying condition of high-grade cervical spinal canal stenosis diagnosed by magnetic resonance imaging. They were operated on to decompress the spine, and the preexisting gait disturbances slowly diminished after the decompression. Since most people with L-2-hydroxyglutaric aciduria show spastic signs in their legs and arms, we conclude that cervical spinal canal stenosis may be the underlying reason and may be linked to this rare metabolic disorder.

L-2-hydroxyglutaric aciduria was first described by Duran et al in 1980 in a 5-year-old boy with psychomotor retardation and dystrophy. Since 1992, this rare disorder of organic acid metabolism has been recognized with increased frequency around the world. Approximately 46 cases have been reported to date.1-15

Clinical signs in this probably recessively inherited condition consist of seizures, macrocephaly, mental retardation, ataxia, and various disturbances of the motor system. Only rarely are very young children2,3 affected, and generally symptoms develop during early childhood.

Diagnosis is established by increased levels of L-2-hydroxyglutaric acid in urine, serum, and cerebrospinal fluid with a concomitant increase in serum and cerebrospinal fluid lysine levels.

Typical results of imaging examinations, especially magnetic resonance imaging (MRI), have been described as subcortical and paraventricular hyperintensities sparing the central periventricular white matter.4,6,10-14 Cerebellar signal abnormalities and atrophy seem to vary.

We had the opportunity to perform MRI not only of the head but also of the spinal canal in 2 affected brothers. A rapidly progressive spastic tetraparesis in both brothers prompted the MRI.

REPORT OF CASES

PATIENT 1

Patient 1 was 34 years old at the time of the first admission to our hospital and was the youngest brother of 3 siblings. One brother and the parents were healthy. The oldest brother showed symptoms similar to those of the patient, who had had febrile seizures during his childhood. After a rubella infection, the patient's preexisting abnormal motor development deteriorated.

He was admitted to our hospital because of sudden pain in his legs and a rapidly progressive tetraparesis. An outpatient computed tomographic examination of the lumbar spine was normal. On clinical examination he had dysarthria, head titubation, dysmetria, and ataxia. Sensation in the left arm and left leg was markedly reduced. Deep tendon reflexes were brisk in his arms and legs and muscle tone was increased. He could walk with 2 walking aids, and his gait was spastic-ataxic.

A cervical spinal MRI (Figure 1) revealed a severe cervical spinal stenosis. Myelopathy was diagnosed by a medullary signal increase at C5-6, and neurosurgical decompression was performed, after which his gait disturbances diminished slowly and he regained the ability to walk without help.

Because of moderate mental retardation, a head MRI was performed that revealed an abnormal signal increase in the...
subcortical and paraventricular white matter. We suspected that he had a metabolic disorder, and intensive screening examinations revealed an increase in urine excretion of L-2-hydroxyglutaric acid. After 7 years of follow-up, his mental state had not deteriorated significantly, but he had to quit his job in a factory because of residual tetraparesis.

PATIENT 2

A 39-year-old at the time of first admission to our hospital and the oldest brother of patient 1, this patient came to our attention because his parents reported disturbances in gait similar to those in their youngest son. Like his younger brother, this patient also had experienced febrile seizures during childhood. He could not graduate from school because he was mentally retarded and was working as an assistant in the grocery store run by his parents.

Neurological examination revealed dementia, dysarthria, ataxia, dysmetria, head titubation, brisk deep tendon reflexes, and spasticity of all extremities. He was able to walk unassisted. Head MRI showed areas of hyperintensities on T2-weighted images similar to those in his brother, and biochemical examinations confirmed the diagnosis of L-2-hydroxyglutaric aciduria. Spinal MRI was not performed at the time of his first admission. Three years later his gait suddenly deteriorated and newly developing disturbances in sensory evoked potentials raised the suspicion of cervical myelopathy. Magnetic resonance imaging of the cervical spine (Figure 2) revealed severe spinal stenosis; neurosurgical decompression was performed. Afterward the gait disturbances diminished slowly.

COMMENT

Since the first description by Duran et al. in 1980, approximately 46 patients from all over the world with L-2-hydroxyglutaric aciduria have been described in the literature.1-15

Typical clinical findings are mental retardation, seizures (in some cases only febrile seizures), ataxia, dysmetria, dystonia, macrocephaly, and, particularly, motor deficits with pyramidal signs.

Diagnosis can be established by the presence of abnormal excretion of L-2-hydroxyglutaric acid in urine and elevated levels of this organic acid in serum and cerebrospinal fluid. Imaging findings on MRI are very specific and consist of subcortical and paraventricular T2 hyperintensities with characteristic sparing of the periventricular white matter.4,6,10-14 In a few cases, pathohistological examinations reveal spongiform changes and
gliosis in the affected white matter with preservation of the cortex.  

Most patients who develop this disorder have an uneventful early childhood; neurological deficits develop later, and young children with symptoms of this disease have been described very rarely (only 1 affected newborn has ever been described).

Only the imaging findings in the brains of individuals with L-2-hydroxyglutaric aciduria have been described in the literature thus far. Neurological disorders such as the motor disturbances that occur in most older patients have previously been ascribed to pathological changes of the cerebral white matter and brainstem. However, we propose that the spastic-ataxic problems, especially those in walking that are reported in nearly all older patients, may also have a myelopathic basis.

Of 46 patients described in the literature, 25 showed signs of disturbed pyramidal tracts, such as spasticity or increased tendon reflexes. There was no mention of pyramidal signs in 7 reports, and in 2 of these some type of gait disorder was reported. Only 13 patients were described with no pyramidal disturbances, and, of these, only 5 patients were older than 10 years. Thus, only 5 patients (13%) older than 10 years out of 38 evaluable patients had no pyramidal signs. The oldest evaluable patient without pyramidal tract deficits was 19 years old.

We had the opportunity to perform spinal examinations on 2 affected brothers who were 34 and 42 years old. The indication for these spinal MRI studies was a random coincidence of such a rare metabolic disorder. A rapid progression of tetraparesis and the development of sensory disturbances in the extremities accompanied by pain. We suspected an underlying myelopathy as the cause, which was confirmed by MRI. Neurosurgical decompression of the cervical spine in both patients resulted in continuous improvement of spasticity, and both regained the ability to walk.

In view of the reported motor deficits in most of older patients with L-2-hydroxyglutaric aciduria, it seems justifiable to assume that a constitutional spinal canal stenosis and subsequent early myelopathy may be linked to this metabolic disorder.

A random coincidence of such a rare metabolic disorder and a cervical myelopathy as a result of a constitutional spinal canal stenosis in 2 out of about 40 patients seems unlikely. Since our patients’ walking capacity improved after a successful neurosurgical procedure despite myelopathic signal increase on T2-weighted MRI of the cervical cord, we encourage ruling out spinal stenosis in all patients with L-2-hydroxyglutaric aciduria and tetraparesis. Unlike progressive cerebellar signs and dementia, loss of motor function could be prevented or at least delayed.

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REFERENCES