L-2-Hydroxyglutaric Aciduria

Clinical, Neuroimaging, and Neuropathological Findings

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Background: L-2-Hydroxyglutaric aciduria is a rare, infantile-onset, autosomal recessive organic aciduria affecting exclusively the central nervous system. To our knowledge, only 1 complete report of the neuropathological findings in an adult has been published.

Objective: To present the clinical, neuroimaging, and neuropathological findings of L-2-hydroxyglutaric aciduria.

Design: Case report.

Setting: Complexo Hospitalario de Pontevedra, Pontevedra, Spain.

Patient: A 15-year-old boy who had early infantile-onset progressive psychomotor regression, mild choreo-dystonia affecting the distal part of the upper limbs, pyramidal signs, and epilepsy.

Results: The diagnosis of L-2-hydroxyglutaric aciduria was confirmed by the finding of highly elevated levels of L-2-hydroxyglutaric acid in the serum, urine, and cerebrospinal fluid. The neuroimaging findings showed striking confluent subcortical white matter lesions and minimal basal ganglia (pallidum, thalamic, and putaminal) abnormalities. The patient died of a spontaneous mesenteric thrombosis. The postmortem neuropathological findings showed spongiosis and cystic cavitations in subcortical white matter, with minimal abnormalities of the basal ganglia. The dentate nucleus, a structure usually affected in neuroimaging studies, showed minimal neuronal loss but was surrounded by important spongiosis and microvacuolation with astrocytic proliferation.

Conclusions: This case reaffirms that L-2-hydroxyglutaric aciduria is a spongiform type of leukencephalopathy with cystic cavitations predominating in the subcortical areas. Although the neuroimaging findings are highly characteristic of the disease, in this patient cerebellar abnormalities were minimal and dentate signal abnormalities were not present.

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REPORT OF A CASE

A 15-year-old boy was examined because of a well-controlled epileptic syndrome. The family history was noncontributory and his parents were not consanguineous. Pregnancy and labor had been uneventful. A slight psychomotor delay had been evident in the first few months of life, although the patient had been able to stand up and walk with aid. Although he did not develop complete language ability, he did...
develop effective communicating ability. He had experienced a generalized seizure at the age of 18 months. At 18 to 24 months, his gait had worsened, with limb clumsiness, language regression, and progressive intellectual deterioration. The epileptic seizures recurred with variable frequency, and he was treated with phenobarbital; seizures did not recur after the age of 7 to 8 years.

At the age of 15 years, when first examined in our Neurology Service, the patient was wheelchair bound and completely dependent, even for feeding. He had severe mental retardation, dysphasia, pseudobulbar signs, bilateral optic atrophy, strabismus, hypacusis, spastic tetraparesis, and choreodystonia in the upper limbs. Right plantar reflex was flexor and the left, extensor. The cranial perimeter measured 55.5 cm.

Routine biochemical serum measures were normal, as were results of other specific biochemical analyses including creatine kinase, calcium, ammonium, lactate, ceruloplasmin, prothrombin time, international normalized ratio, partially activated thromboplastin time, hexosaminidase A and B activity, β-mannosidase activity, and phytic acid. Blood smear did not show acanthocytes. The cerebrospinal fluid was acellular with normal protein and glucose levels. An electrocardiogram, echocardiogram, plain chest radiograph, muscle biopsy specimen, electromyogram, and results of nerve conduction studies were all normal. Auditory and somatosensory evoked potentials were highly abnormal.

Organic acid studies showed increased concentrations of 2-HG in serum (23 µmol/L; control value, undetectable), urine (942 mmol/mol of creatinine; control value, <2.5 mmol/mol), and cerebrospinal fluid (30 µmol/L; control value, undetectable), which was proved to be 1-2-HG by C. Jakobs, PhD (Metabolic Unit, Department of Clinical Chemistry, Free University, Amsterdam, the Netherlands).

Computed tomography of the brain showed generalized atrophy with diffuse hypodense lesions in subcortical white matter (Figure 1). Brain magnetic resonance imaging (Figure 2) showed generalized atrophy, atrophy of the corpus callosum, and extensive white matter hyperintense signals on T2-weighted and proton-density images, without cerebellar or thalamic lesions.

Folic acid supplementation at a dosage of 10 mg/d was started 6 months after the diagnosis. Ten months after the initial evaluation, while at school, the patient experienced spontaneous abdominal pain and lower gastrointestinal tract bleeding. An emergency laparotomy confirmed a massive mesenteric thrombosis. He died a few days later of multiorgan failure. Permission for postmortem examination was obtained, and the examination was performed a few hours after death.

On pathological examination, lesions were observed in various organs. Transmural necrosis affected the total length of the small intestine, with massive thrombus in mesenteric vessels. Foci of hepatic infarcts were present. Slight atherosclerotic changes were seen in the abdominal aorta. Bilateral bronchopneumonia was present.

Neuropathological examination showed an unfixed brain weighing 1250 g. Gross examination showed thin gyri with a pseudomicrogyral pattern, clear leptomeninges, and discrete venous congestion. The cerebellum presented an increased consistency with widening of the cerebellar sulci.
This patient’s condition was diagnosed on the basis of highly elevated levels of L-2-HGA in urine, serum, and cerebrospinal fluid. The clinical presentation of L-2-HGA, in this case, was similar to those previously described with early infantile-onset progressive psychomotor regression, mild choreodystonia affecting the distal part of the upper limbs, pyramidal signs, and epilepsy. However, optic atrophy, an unusual manifestation not previously noted in this disease, was present.

The neuroimaging findings of L-2-HGA are considered highly suggestive of the diagnosis. The structures mainly affected are the white matter, cerebellum, and basal ganglia. The subcortical white matter abnormalities are extensive, multifocal or confluent, with involvement of the extreme and external capsules; they characteristically fade in a centripetal distribution. The corpus callosum and brainstem are usually spared. Typically, the cerebellum is atrophic and the dentate nuclei show abnormally high T2-weighted signals on magnetic resonance images. The findings in this case showed striking confluent subcortical white matter lesions and minimal basal ganglia (pallidum, thalamic, and putaminal) abnormalities. The caudate nucleus was not affected. Cerebellar abnormalities were minimal, without dentate signal abnormalities or cerebellar atrophy.

Neuropathological reports of this disease are scarce. The only complete report describing an adult was that of a patient with a family history of L-2-HGA. He died.

Figure 2. Magnetic resonance images of the brain. A, Axial T1-weighted image showing hypointense signals in subcortical white matter sparing the cortical rim. The thalamus shows a normal signal intensity. B, Coronal T2-weighted image showing hyperintense T2-weighted signal in bihemispheric white matter, prominent in the subcortical, peripheral white matter and with relative sparing of the internal capsule. No abnormal signal is observed in the caudate, putamen, pallidum, and thalami. Brain atrophy is evident, with bilateral ventricular dilation. C, Axial fluid-attenuated inversion recovery image. Posterior fossa shows normal signal intensity of the dentate nuclei. Cerebellar atrophy is not apparent, although slight dilation of the fourth ventricle is evident. D, Sagittal T1-weighted image showing hypointense signals in peripheral subcortical white matter.
suddenly, with fever, but the cause of death was not mentioned. The pathological study was limited to the brain and showed diffuse demyelination, spongiosis, and cystic cavitations in the subcortical regions. Severe cell loss and spongiosis were present in the dentate nucleus and pallidum, with less severe involvement of the striatum.

Myelin was normal in the corpus callosum, genu of the internal capsule, optic tract, and optic radiations. A second neuropathological report described a neonate with cardiorespiratory problems at birth who died at the age of 28 days. The neuropathological findings of the brain showed pontocerebellar atrophy, olivopontocerebellar

Figure 3. Sections of brain tissue. A, Frontal coronal section showing massive demyelination, with a bland aspect of the white matter and cystic formation in peripheral subcortical areas. The scale is in centimeters. B, Detail of the demyelinated areas in a parietal section. Note the slightly atrophic, otherwise relatively preserved, aspect of the corpus callosum.

Figure 4. Microscopic views of brain tissue. A, Cortex and white matter, showing severe spongiosis of the latter with mild involvement of the cortex (hematoxylin-eosin, original magnification ×10). B, Cystic areas surrounded by numerous hyperplastic astrocytes (hematoxylin-eosin, original magnification ×10). C, Immunodetection with glial fibrillary acidic protein. An elevated number of positive hyperplastic astrocytes surround the microcysts in the white matter (glial fibrillary acidic protein, original magnification ×20). D, Low-power image of the dentate nucleus. There is minimal neuronal loss, but spongiosis and vacuolation are present in the periphery of the nucleus (hematoxylin-eosin, original magnification ×5).
neuronal loss, and gliosis in the brainstem white matter tracts. No significant changes were reported in the subcortical central white matter.

Our findings reaffirm the basic pathological substrate in L-2-HGA, namely, spongiosis and cystic cavitations in subcortical white matter. However, we found relatively few abnormalities in the basal ganglia and dentate nuclei. The minimal pathological involvement of the dentate nuclei is of interest, since magnetic resonance imaging signal abnormalities are usually present. Nonetheless, demyelination and spongiosis surrounded this structure. These neuropathological findings, along with the radiological manifestations, should be differentiated from other conditions with spongy degeneration, namely, Canavan disease, Kearns-Sayre syndrome, merosin-negative congenital muscular dystrophy, and other organic acidurias. The major contribution in the differential diagnosis is Canavan disease, which usually presents earlier in life and has a more rapid course. Although some organic acidurias manifest early encephalopathic syndromes leading to early diagnosis, others cause nonspecific symptoms such as psychomotor delay and epilepsy, which may be well controlled, as occurred with our patient.

The origin of L-2-HG is still unknown. A number of loading and fasting studies have been conducted, without conclusive results. It is speculated that L-2-HG can be produced by reduction of 2-ketoglutarate, but so far no definite clues to the metabolic block involved have been found. The pathogenesis of L-2-HGA is also obscure, but it is probable that the accumulation of L-2-HG is toxic to the white matter, causing myelin vacuolization. Recent experimental evidence indicates that L-2-HG may directly provoke oxidative stress damage to lipids and proteins, besides reducing the brain’s capacity to effectively modulate the enhanced production of free radicals. Accumulation of L-2-HG may also interfere with neuronal energy homeostasis by inhibiting creatine kinase activity; this effect may underlie the cerebellar degeneration associated with L-2-HGA. The gene localization is still unknown, and there are no animal models.

Specific treatment is, unfortunately, not yet available for L-2-HGA. Because its structure is similar to that of glutamate, L-2-HG may competitively interfere with the addition of the glutamate “tail” to folic acid (pteroylmonoglutamate) (Hugo Moser, MD, e-mail, October 5, 2003). If the formation of folate-2-hydroxyglutarate occurs, it should not be active and may be excreted in the urine with secondary folic acid deficiency. For this reason, we treated the patient with folic acid supplementation during the 2 months until his death. An interesting aspect in this case is the cause of death, mesenteric thrombosis, which is very rare in the pediatric age group and was unexpected in this well-cared-for patient. The causes of death in previously described patients with L-2-HGA are not mentioned, and perhaps a prothrombotic state exists in some patients with this disease.

In summary, in contrast to previous reports, cerebellar imaging abnormalities were not observed in this case. The pathological findings evidenced massive demyelination of subcortical white matter and cystic cavitations in a centrifugal distribution, cortical gliosis, and spongiosis, but with minimal involvement of the dentate nuclei.

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