L-2-HYDROXYGLUTARIC ACIDURIA: A REPORT OF SIX CASES AND REVIEW OF THE LITERATURE

Yousef Shafeghati MD, Ghazal Vakili MD, Ali Entezari MD

L-2-hydroxyglutaric aciduria is a rare and novel autosomal recessive inherited neurometabolic disorder. Since its first description by Duran in 1980, less than 100 cases have so far been reported. Occurring mostly in childhood, it is characterized by slowly progressive neurological dysfunction with cerebellar ataxia, pyramidal signs, intellectual decline, seizure, and extrapyramidal symptoms. MRI scanning is highly characteristic and screening for organic acid (L-2-hydroxyglutaric acid) in urine, serum, and cerebrospinal fluid is diagnostic.

We investigated six Iranian children, aged 4, 14, 16, and 16 years, (the last one had two affected brothers and both of them died of similar illness at the ages of 20 and 22), by urinary organic acids assay and MRI scanning with suspicion of this rare disorder. Symptoms were suspicious for one of the leukoencephalopathies accompanied by macrocephaly.

Affected cases were evaluated because of mild to moderate psychomotor retardation and regression. Head circumferences were above 2 standard deviations. Urine levels of L-2-hydroxyglutaric acid were strongly increased. MRI scanning of the brain showed hyperintense signal on T2W images of the subcortical white matter and basal ganglia in all of them.

Because of its inheritance pattern (autosomal recessive) and the high rate of consanguineous marriages in Iran, the prevalence of this disorder might be high among the mentally-handicapped patients, especially those with macrocephaly. Therefore, this entity should be considered in the differential diagnosis of mentally-retarded patients with macrocephaly.

Keywords: Duranin gene • L-2 hydroxyglutaric aciduria • macrocephaly • OH-glutarate dehydrogenase • urine organic acid screening

Introduction

Organic acidurias represent a group of inherited metabolic disorders characterized by increased urinary excretion of organic acids. Some of these disorders are accompanied by episodes of severe neurologic disease. L-2-hydroxyglutaric aciduria, a syndrome for which no primary biochemical defect has so far been found, belongs to the latter category.

Gas chromatography of urinary organic acids, especially in combination with mass spectrometry, has become a powerful tool in elucidation of an increasing number of metabolic causes of mental retardation and neurological handicaps. A solitary large and persistent increase of L-2-hydroxyglutaric acid in the urine was reported for the first time in 1980 in a 5-year-old boy from Morocco (Berber), who was investigated for nonspecific mental and motor delay and growth deficiency. Additional patients were reported later. The total number of published cases are now less than 100. Based on the pedigree analysis, L-2-hydroxyglutaric aciduria must be considered as an autosomal recessive disorder. A more or less characteristic clinical picture has emerged. Most of the patients have mental and motor retardation, often with gait ataxia. In general, these symptoms appear to be nonprogressive or slightly progressive. A fair number of patients survive into adulthood. However, quite sudden mental deterioration may be observed. Recently, a neonatal presentation with rapidly fatal outcome has been reported. Macrocephaly presents in nearly 50% of the
patients. All the investigated patients showed characteristic subcortical white matter abnormalities on magnetic resonance imaging (MRI) investigation.\textsuperscript{1,2,3,6} More than half of the patients have seizures. The patient with neonatal onset had also a burst suppression pattern on electroencephalogram, making this disorder another entity, which should be considered in the differential diagnosis of neonatal convulsions.\textsuperscript{5} Although, in the majority of the so-called organic acidemias, a simple enzyme defect could be identified, some disorders are still in the “descriptive stage.” In these cases the abnormal metabolites could be identified, but there is no clue to the underlying enzymatic defect. Following description of the first case by Duran et al in 1980,\textsuperscript{3} since 1992, this rare disorder of organic acid metabolism has been recognized with increased frequency around the world. Including our three cases, the total reported cases so far would be about 100.

Diagnosis is established by detection of increased levels of L-2-hydroxyglutaric acid in urine, serum, and cerebrospinal fluid. Typical results of imaging examinations, especially MRI, have been described as subventricular white matter abnormality. Cerebellar signal abnormalities and atrophy seem to vary.\textsuperscript{7} In view of the reported motor deficits in most of older patients with L-2-hydroxyglutaric aciduria, it seems reasonable to assume that a constitutional spinal canal stenosis and subsequent early myelopathy may be linked to this metabolic disorder.\textsuperscript{8} L-2-hydroxyglutaric aciduria, although a very rare metabolic disorder, has been recently diagnosed in six cases of three Iranian families. It should be considered in the differential diagnosis of patients with psychomotor retardation accompanied by macrocephaly.

During the past decade more than 56 families, including 91 affected cases, were referred to our center who were suspected of having one of neurometabolic disorders. Of these, in three families with six cases, the final diagnosis was L-2-hydroxyglutaric acidemia.

**Case Reports**

**Family 1**

T.J. was a 4 ½-year-old boy from North-East of Iran. He had a birth weight of 3,350 g, height of 50 cm, and a head circumference of 35.5 cm. Parents are healthy and first cousins. The growth and development of the patient was normal during the first four months of his life. Thereafter, his parents noticed that the neurodevelopmental milestones in the patient were slightly delayed, and that the child’s head grew faster so that in the 4th month, his head circumference was 41.5 cm. These were found to be 46, 53, 54, and 55 cm, after six months, one year, three years, and 4 ½ years, respectively. All the measurements were above 95th percentile for the ages.

After the age of 10 months, he had several seizure attacks. He was able to stand, walk, and talk a few words, when he was one year old. His condition began to deteriorate gradually thereafter so that he had difficulty in standing and walking.

![Figure 1. MRI scanning of the case 1; you can easily see the subcortical hyperintense white matter signal in T2W image (left).](image-url)
His gait was ataxic and he frequently fell down. At the present, he can move with the aid of orthopedic facilities and braces. Besides, he has had several episodes of respiratory and gastrointestinal infections. Figure 1 shows the MRI of the patients.

Family 2 (cases 2 and 3)

Two brothers aged 16 and 14 years, both of whom being the products of an uneventful pregnancy and normal vaginal delivery. The parents are first cousins and completely healthy. Their birth weights were 3,300 and 3,500 g, respectively. Their growth and development were only slightly delayed until the age of 6 years. The only significant symptom was seizure attacks that occurred after 11 months of age in the older brother; the attacks started from the age of three years in the younger one and recurred several times. After the age of 10 years, they also had severe convulsions. Figure 2 shows the pedigree.

Currently, they are suffering from moderate to severe psychomotor retardation; the IQ test done in both of them was found to be around 30 to 35. They also suffer from gait disturbance and seizure. The head circumference of the older brother is 58 cm and that of the younger one is 60 cm. Brain MRI scanning showed intense white matter signals in T2W images, especially in the subcortical areas (Figure 3). We followed and investigated the problem for white matter abnormalities such as leukodystrophies, Canavan’s disease, Alexander’s disease, and glutaric aciduria types I and II. The urine, blood, and skin biopsy samples were sent to the Erasmus University Metabolic Center in Rotterdam and Academic Medical Center in Amsterdam. In these two brothers, the urine analysis for organic acids by gas chromatography and mass spectrometry (GC-MS) revealed strongly increased amounts of L-2-hydroxyglutaric acid.

Family 3

Proband was a 16-year-old girl, the fifth child of the family. She was the product of an uneventful pregnancy and delivery. Her growth and development during neonatal, infantile, and early
childhood were within normal limits. Symptoms of her illness began from about the age of 7, and progressed gradually. The cardinal clinical findings: ataxia, gait disturbance, speech difficulty, dysarthria, open mouth, sialorea, seizure attacks, and mental retardation.

She had had 2 older affected brothers exactly with the similar disease, and they died at the ages of 20 and 22, with the same course and severity. Her second brother’s MRI showed diffuse subcortical leukoencephalopathy. The parents are healthy; they are first cousins (Figure 5). We suspected, at the beginning, the following metabolic disorders: Canavan’s disease; Alexander’s disease; metachromatic leukodystrophy; GM1-gangliosidosis; and exceptionally, L-2-hydroxyglutaric aciduria because of our experience with the previous cases.

Enzymatic assay for the above-mentioned disorders were all within normal limits, but urine and blood screening for organic acids by GC-MS method showed that 2-OH-glutaric acid was strongly increased and more than 90% of that was L-isomer. So, in this family too, L-2-hydroxyglutaric aciduria was the final diagnosis.

According to the history and clinical data of neurodevelopmental delay and regression, macrocephaly, white matter abnormality in the brain MRI, and seizure, the following differential diagnoses were suspected in these six cases: Alexander’s disease; Canavan’s disease; GM1-gangliosidosis; glutaric aciduria types I and II; and metachromatic leukodystrophy.

At the beginning, with these diagnoses in mind, relevant enzyme assays were requested and carried out. The results were normal for all the above-mentioned disorders. The only abnormal finding was the relatively high amounts of hydroxyglutaric acid in the urine of our patients. By further follow-up and reevaluation of urine organic acids by GC-MS, more than 90% of the increased hydroxyglutaric acid was found to be due to the L-2 type isomer. So, the final diagnosis made in these six cases was L-2-hydroxyglutaric acidemia. We were not able to perform the same test on blood and CFS samples of our patients. Figure 4 shows the MRI of the case 4.

Discussion

L-2-hydroxyglutaric aciduria is a rare autosomal recessive inherited neurometabolic disorder. It is mostly diagnosed in infancy and childhood. However, one patient was diagnosed and reported in the neonatal period. There are some reports that this disease could also occur in much older adult patients. The disorder has a remarkably consistent biochemical and clinical pattern. Virtually all patients showed mild to moderate (and sometimes severe) MR. Most of the patients, as ours, have been normal in infancy, and the parents became aware of the developmental problems when the children started to walk, and appeared to have an unsteady gait. Other patients had a downhill neurologic course at a later age, sometimes as late as 6 – 17 years.

This disorder characterized by: slowly progressive neurological dysfunction; MR; Gait disturbance and ataxia; seizure; macrocephaly; and MRI abnormalities.

No specific biochemical function or catabolic pathway involving L-2-hydroxyglutaric aciduria is known in mammals, including the human. Macrocephaly, cerebellar signs, and abnormalities suggesting leukodystrophies on brain imaging are diagnostic clues. All of these clues indicate the need for urinary analysis of organic acids. Our first three cases had prominently large heads and abnormal signal on MRI scanning, but the forth one’s head size was normal.

Macrocephaly is not specific and is a symptom shared by several other neurometabolic disorders and organic acidurias. One should bear in mind the so-called “cerebral organic acidurias” in infants and children with an enlarged head circumference. Considering the autosomal recessive inheritance pattern of this disorder, and because the rate of consanguineous marriage is high in Iran, we should bear in mind this rare neurometabolic disorder while examining the patients with neurodevelopmental delay and regression, macrocephaly, seizure, and gait disturbance. Screening...
tests for detection of organic acids should become a part of our investigations of such patients.

Recently, the gene responsible for this disorder has been mapped to chromosome 14q and cloned and named Duranin gene (C14 or f160). The gene encodes enzyme OH-glutarate-dehydrogenase. Many different mutations have been detected in different populations. The metabolic role of this enzyme should be elucidated.

Acknowledgment

The authors wish to thank Prof. Huijmans, Prof. Jakobs, and Prof. Duran, for their kind cooperation in performing metabolic assays (GC-MS) and detection of abnormality in the urine samples of our patients. Special thanks go to Prof. Kariminejad and his laboratory personnel for their assistance in transferring the samples to the Netherlands.

References