CASE REPORT

L-2 Hydroxyglutaric aciduria presenting with anxiety symptoms

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Dr Sedat Işıkay, dr.sedatisikay@mynet.com**SUMMARY**

L-2 Hydroxyglutaric aciduria is a rare autosomal recessively inherited metabolic disorder of organic acid metabolism. Cerebellar and pyramidal signs with progressive neurological syndromes, mental deterioration, tremors, seizures, epilepsy and rarely macrocephaly are clinical findings of the disease. The diagnosis depends on increased levels of L-2 hydroxyglutaric acid in urine, plasma and cerebrospinal fluid. Brain MRI shows peripheral white matter abnormalities in cerebral hemispheres, bilateral symmetrically abnormal signal intensity in basal ganglia and dentate nuclei. In this case report, we present a 13-year-old patient who presented with tremors and anxiety symptoms and was diagnosed as L-2 hydroxyglutaric aciduria after consultation with the child neurology department. We present a patient suffering from psychiatric symptoms with a metabolic disorder.

BACKGROUND

L-2-Hydroxyglutaric aciduria is a rare organic acid metabolism dysfunction, which was defined for the first time in Turkey by Duran *et al*¹ in the year 1980 on a 5-year-old boy with psychomotor retardation and leukodystrophy. It is characterised by multiple acyl coenzyme A dehydrogenase enzyme deficiency and autosomal recessive inheritance. Symptoms seen include psychomotor growth retardation, which starts clinically in the first year of life, then advances slowly to progressive cerebellar ataxia, dysarthria and tremors.^{2–4} Epileptic seizures and pyramidal symptoms in late stages of the disease may further be included therein.^{5–6} While cases may present symptoms in the neonatal stage, it may remain asymptomatic until late adulthood stage. Unlike other organic acidurias, acute metabolic crisis is not traced. Despite deep white matter being preserved in the brain MRI, subcortical white matter, basal ganglion (putamen, caudate nucleus and globus pallidus) and dentate nucleus involvement are quite instructive in diagnosis.⁷ Diagnosis is performed by showing increased amounts of blood, urine and CSF (cerebrospinal fluid) gas chromatography, and L-2 hydroxyglutaric acid. While there is no specific treatment of the disease, supportive cares are recommended.^{2–4}

We hereby present a rare case, which applied to child psychiatry polyclinic with anxiety disorder, and was diagnosed with L-2-hydroxyglutaric aciduria after examinations were conducted. This case is important for raising awareness about feasibility of the initial application to child psychiatry polyclinic for metabolic diseases being seen during childhood stage.

CASE PRESENTATION

A 13-year-old male patient presented with being overanxious, learning disorder and with tremors in the head. In the history given by his family, his case had tremors in his hands and head, and that such tremors might happen anytime, particularly when he was anxious. His success at school was at medium level and his writing was illegible because of his tremors. He was an introverted child and also his weakness in fine motor skills caused his friends to make fun of him. Besides, the child was suffering intense stress while entering into social environments because of the fear of feeling ashamed. He had difficulty in expressing himself when he displayed any performance. It was learned that his family had appealed to psychologists in the last 2 years but they had had no result. WISC-R test was applied on him, his IQ was found to be 81. There were no features either in his own or in his family's background. During the interview, the child's speech was found to be dysarthric. Consultation was required from child neurology polyclinic for tremors and dysarthric speaking.

In the physical examination, his height, weight and head circumference were within normal limits. His axillary body temperature was found to be 37°C, pulse was 98/min, respiratory rate was 18/min and blood pressure was 90/70 mm Hg. Intentional tremors, truncal ataxia, titubation, dysmetria, dysdiadokinesia and dysarthria were found in his hands as a result of cerebellar tests. No peculiarity was found among the other examination findings. Ophthalmoscopy was normal.

INVESTIGATIONS

In the laboratory tests, out of the complete blood count, haemoglobin was found to be 11 g/l, white blood cells was 5400/mm³ and thrombocyte count was 276 000/mm³ and out of the peripheral blood smear, 65% neutrophils, 30% lymphocyte and 5% monocyte were found. In the blood biochemistry, glucose was 105 mg/dl, sodium was 137 mEq/l, chloride was 110 mEq/l, urea was 24 mg/dl, creatinine was 0.4 mg/dl, aspartate aminotransferase was 25 U/l and alanine aminotransferase was 27 U/l. Out of the blood gas examinations, pH was 7.45 mmol/l, pO₂ was 118 mm Hg, PaCO₂ was 36 mm Hg and HCO₃ was 14 mEq/l. C reactive protein was 0.3 mg/dl and out of full-urine examination, pH was 5 and density was 1015. Lactate was 14.2 mg/dl (4.5–19.8 mg/dl) and ammonia was 45 µg/dl (31–123 µg/dl). Tandem mass screen test was found to be normal. Out of brain MRI, signal increases with blurred contours were found, in

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patches, in bilateral dentate nucleuses, in basal ganglions, in sub-cortical white matter (figure 1) and in T₂ and fluid-attenuated inversion recovery-A sequences (figure 2). Out of the urine organic acid analysis, 2-hydroxyglutric acid 643 mg/g creatine (normal value <10) and 3-hydroxyglutricaciduria 27.1 mg/g creatine were found.

DIFFERENTIAL DIAGNOSIS

Canavan's disease, other metabolic diseases and leukodystrophies should be considered in differential diagnosis of macrocephaly, neurological deterioration and deep white matter lesions. Macrocephaly is a finding that must alert clinicians to the possibility of cerebral organic aciduria, although it is shared by several other metabolic diseases such as glutaric aciduria type I and Canavan's disease. Brain stem involvement and centripetal extension of white matter abnormalities differentiate Canavan's disease from L-2-hydroxyglutric aciduria.

TREATMENT

Riboflavine (200 mg/day) and carnitine (100 mg/day) therapies were initiated with the patient, having been diagnosed with L-2-hydroxyglutric aciduria out of the clinical, laboratory and

imaging findings, and he was kept under follow-up by the child neurology division.

OUTCOME AND FOLLOW-UP

It was planned to follow-up the results of the therapy and start psychotropic drugs for anxiety symptoms if necessary. Under follow-up, reduction in the symptoms of dysarthric speaking and tremors and also timidity and anxiety, improvement in his relationship with other children owing to increase in self-confidence were observed so that he was on follow-up at the child psychiatry department with monthly interviews. He has been followed-up for nearly 1 year, his anxiety symptoms have significantly reduced, his handwriting has improved, the tremors in his hands and head completely recovered in the fifth month of the treatment. However, he still has problems about lessons.

DISCUSSION

L-2-Hydroxyglutric aciduria is a rare slowly progressive neuro-degenerative metabolism disorder. Age range varies widely from neonatal period up to mid-50s. Average diagnostic age is 13. Main clinical findings are mental retardation, cerebellar involvement-dependent ataxic walking and intentional tremors. It shows indications in early ages with retardation in motor development steps, seizure and macrocephaly. In later ages, walking disorder because of ataxia and mental retardation may draw attention. Minor dystonia, seen mostly in hands, as well as pyramidal symptoms and seizures are additional clinical findings.²⁻⁵ Besides cases accompanying status epilepticus serious autistic symptoms were further reported.⁶⁻⁸

Not finding acute metabolic decompensation attacks in L-2-hydroxyglutric aciduria, unlike other organic acidemias, may mislead specialists. L-2-Hydroxyglutric aciduria has been, until recently, considered among diseases underlying metabolic defect which cannot be identified.² It has been learned that acute metabolic attack table could not have been developed, despite the rise of respective complaints long before diagnoses.

Macrocephaly is found among most patients, and may sometimes be the initial symptom. On the other hand, macrocephaly

Figure 1 Coronal (A), axial (B) T2-weighted sequences subcortical white matter and bilateral dentate nuclei hyperintense appearance (white arrows).

Figure 2 Axial T2-fluid-attenuated inversion recovery images of our patient, hyperintensity of subcortical white matter involving frontal region.

may be the initial symptom in other serious metabolic diseases, such as Canavan's disease and type-1 glutaric aciduria.⁹ While macrocephaly was not found in our case, these diseases were excluded from clinical and radiological findings, and from results from acid analysis.

Final diagnosis is established on display of increased level of L-2-hydroxyglutamic acid in body fluids (blood, cerebrospinal fluid (CSF) and urine). Amounts being found in CSF are in general higher than those being found in plasma.⁹ Level of L-2-hydroxyglutamic acid had increased in urine 10 times more than normal (800–1300 mmol/mol creatine). Increase in lysine level may also be found in blood amino acid chromatography. Normally, being two isoforms of 2-hydroxyglutamic acid, L and D configurations are found in urine in equal amounts. Two different clinical conditions have been identified with regard to increase in L-D configurations. While D-2-hydroxyglutamic aciduria is a grave neurological syndrome, arising in the neonatal stage, L-2-hydroxyglutamic aciduria is a neurological encephalopathy form, progressing more slowly.^{2–4} In our case, despite lack of an L-D isoform separation, the patient was diagnosed with L-2-hydroxyglutamic aciduria in the light of clinical and imaging findings.

Despite significant developments regarding the clinical features, and diagnosis of L-2-hydroxyglutamic aciduria, neither the metabolic defect and pathogenetic mechanisms, causing leukoencephalopathy, have been brought to light, nor a specific treatment has yet been developed. Mutations in the L2HGDH (C14orf160/duranin) gene located on 14q22.1 have been identified as causative for this disease.¹⁰ Treatment approaches, physical treatment and rehabilitation are composed of L-carnitine (50–100 mg/kg/day) and riboflavin (200 mg/day) supports, and such supportive treatments as control of epileptic seizures with drugs. The relation between riboflavin treatment and urinary hydroxyglutamic acid excretion has not yet been sorted out.^{3, 9, 11} We, therefore, prescribed L-carnitine and riboflavin treatments for the case in oral form, as has been stated in the literature. During follow-up, we observed clinical recovery in cerebellar findings and in probably related psychiatric symptoms. Owing to the fact that there were anxiety disorder symptoms in this case and the tremors were attributed to anxiety of the child, the family perceived the origin of these behaviours as being psychological and made doctors seek remedy mostly in this direction. During L-2-hydroxyglutamic aciduria, there are no acute metabolic symptoms, the clinical symptoms are minor and show slow progress and the disease can be seen in quite a wide age range, so that the diagnosis can be difficult. The main diagnosis for the child was not done and the required treatment was not applied on time. Mental retardation can be seen among children in similar conditions and they have low success in their lesson. Owing to this situation, treatments are sought in the psychiatry area. The child with L-2-hydroxyglutamic aciduria recovered from not only the neurological symptoms but also anxiety symptoms during treatment. Hence, our opinion was supported with the information received from the interview with his family that the child's self-confidence and his participation in social activities increased after treatment.

Anamnesis should be taken properly from patients who come to the child psychiatry clinic with neurological findings and uncertain cases should be referred to the child neurology

department. Therefore, knowledge of the specialists servicing the field of child psychiatry about neurological diseases seen rarely accompanying psychiatric symptoms should be improved and cooperation with child neurology is essential in earlier diagnoses and treatment of these diseases. The importance of our study is to be the first L-2-hydroxyglutamic aciduria case in the literature who primarily referred to the child psychiatry clinic with psychiatric symptoms and was diagnosed with further examinations and child neurology consultations.

Learning points

- ▶ Anamnesis should be taken properly from patients who come to the child psychiatry clinic with neurological findings and uncertain cases should be referred to the child neurology department.
- ▶ L-2-Hydroxyglutamic aciduria should be considered in children with clear delay and learning disability which in association with cerebellar symptoms will help in thinking of the diagnosis.
- ▶ Neuroradiologic features of a subcortical leukoencephalopathy with dentate nuclei and basal ganglia involvement are rather specific and should lead to further biochemical investigations. Definitive diagnosis depends on detection of L-2-hydroxyglutamic acid in urine, blood, and cerebro-spinal fluid by means of gas chromatography-mass spectrometry.

Competing interests None.

Patient consent Obtained.

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