INTRODUCTION

L-2-Hydroxyglutaric aciduria (L-2-HGA) is an autosomal recessive neurometabolic disease, belonging to the group of organic acidurias with a slowly progressive course. It is characterized by increased levels of L-2-hydroxyglutaric acid in urine, cerebrospinal fluid and plasma. In this condition clinical features mainly consist of mental deterioration, ataxia and motor deficits.

Case Outline

The patient is a 16-year-old girl, the first and only child of healthy, non-consanguineous parents of Serbian origin. At the age of 4 years her walk became unsteady and ataxic. Other signs of cerebellar involvement were soon observed. Head circumference was above two standard deviations (55 cm). Mild mental retardation was revealed by formal intelligence testing (IQ 60). MR examination of the brain showed confluent subcortical white matter lesions spread centripetally, and atrophy of the cerebellar vermis with involvement of dentate nuclei, without deep white matter abnormalities. Laboratory investigation revealed increased amounts and a very large peak of HGA in urine and plasma. Enantiomeric analysis confirmed the L-configuration (>90%) establishing the diagnosis of L-2-HGA. The first epileptic seizure, partial with secondary generalization, occurred at age of 8 years. Favorable seizure control was achieved. A slow progression of neurological impairment was noted. Therapeutic trials with oral coenzyme Q10 and with oral riboflavin showed no biochemical and clinical effects. Recently, the diagnosis was proven by the presence of a mutation in the L-2-HGA gene.

Conclusion

To our knowledge, this is the first report of L-2-HGA in Serbia. L-2-HGA must be considered in the differential diagnosis based on specific findings in cranial MRI.

Keywords: hydroxyglutaric aciduria; epilepsy; white matter lesions; ataxia
parents of Caucasian, Serbian origin. Family history was uninformative. Pregnancy was uneventful. Caesarean section was performed, as an elective procedure, because of the fetal malpresentation. Birth weight was 2800 g, birth length 50 cm and head circumference 36 cm. The neonatal period was normal. A psychomotor delay was evident in the second year of life. She was able to stand up and walk without support at about 26th months of life. Development of her speech was delayed.

At the age of 4 years her gait became worse, she was unsteady, with ataxic walk and other signs of cerebellar involvement as dysmetria, truncal ataxia, intention tremor and dysarthria. Her head circumference was above two standard deviations (55 cm). Psychomotor development, measured with the Brunet-Lezine scale, showed the development quotient of 60. Ocular fundus examination was normal, but high degree myopia had been diagnosed. Electroencephalogram (EEG) showed diffuse non-specific abnormalities. Molecular genetic tests for Friedreich’s ataxia were negative. Electroneurographic examination was normal.

Magnetic resonance imaging of the brain performed at age of 4 years, showed diffuse, bilaterally symmetric T2 white matter hyperintensity, with atrophy of the cerebellum suspected to be one of leukoencephalopathies accompanied by macrocephaly as Canavan leukodystrophy (Figure 1). Follow-up MR imaging and MR spectroscopy (done at age 8 years) showed confluent subcortical white matter lesions predominantly of the frontal-parietal lobes, atrophy of the cerebellar vermis with involvement of the dentate nuclei, without deep white matter abnormalities (normal appearance of corpus callosum, internal capsule, periventricular white matter) and the diagnosis of L-2-HGA was suggested (Figures 2 and 3). Arcuate U fibers affection and centripetal involvement were seen. The subsequent screening for inborn errors of metabolism included the analysis of amino acids, organic acids, oligosaccharides, mucopolysaccharides, very long-chain fatty acids and lysosomal enzymes. Urine and blood samples were analyzed at the Erasmus University Metabolic Center in Rotterdam. Repeated urinary organic acid analyses performed by gas chromatography and mass spectrometry (GC-MS) revealed highly increased amounts and a very large peak of 2-hydroxyglutaric acid. L-2-HGA in urine was 1740 mmol/mol of creatinine (controls <18.6) while in plasma it was 32 μmol/L (controls 0.3-1). Further enantiomeric analysis confirmed the L-configuration (>90% L-2-HG) establishing the diagnosis of L-2-HGA.

The first epileptic seizure, partial with secondary generalization, occurred at age of 8 years. After repeated unprovoked seizures and EEG examination (bilateral paroxysmal activity with focal discharges over the left parietal-temporal region) antiepileptic therapy with valproate (VPA) was started. With VPA 1g/daily (92 μg/ml) a partial control of seizure was achieved. Comedication with lamotrigine was introduced, resulting in improved seizure control (1 complex partial seizure monthly). EEG records improved in time with nonspecific right-sided abnormalities. Since April 2010 levetiracetame (2 g/daily) was added to lamo-

trigine (300 mg/daily), while VPA was withdrawn. Favorable seizure control was achieved.

Additional neurological signs and symptoms occurred over time, such as increased tremor, distal dystonia, orofacial dyskinesia and pyramidal signs (bilateral clonus, hypreflexia and spastic hypertonia). At the age of 6 years, a mild mental retardation was revealed by formal intelli-
gence testing (IQ 60) without later deterioration. Her head circumference stopped increasing, but remained significantly above the 97th percentile (60 cm).

Because of spastic pes equinovarus, her walk was possible with assistance only. She developed lumbosacral scoliosis. A retention orthosis was recommended at age of 12. Last year applied therapy with botulinus toxin was beneficial and resulted in decreased spasticity. In 2011 the diagnosis was proven by the presence of a mutation in the L-2-HGA gene (missense mutation c.185C>A located in the exon 2). Therapeutic trials with oral coenzyme Q10 beneficial and resulted in decreased spasticity. In 2011 the diagnosis was proven by the presence of a mutation in the L-2-HGA gene (missense mutation c.185C>A located in the exon 2). Therapeutic trials with oral coenzyme Q10 resulted in decreased spasticity. In 2011 the diagnosis was proven by the presence of a mutation in the L-2-HGA gene (missense mutation c.185C>A located in the exon 2).

The EXON 2 feature [19]. A 5-year-old boy with eyelid myoclonia with seizures occurred in more than 50% of patients with L-2-HGA. The onset of L-2-HGA showed a burst suppression pattern on EEG, making this disorder another entity, which should be considered in the differential diagnosis of neonatal seizures [18]. The patient, a 9-month-old female infant, homozygous for the p.Lys81Glu (c.241A>G) missense mutation in the L-2-HGA gene, was reported with acute hemi-convulsion-hemiplegia-epilepsy syndrome as a presenting feature [19]. A 5-year-old boy with eyelid myoclonia with absences, bilaterally synchronous EEG polyspike/spike and wave discharges and L-2-OHG was described. The patient became seizure-free with a combination therapy of clonazepam, levetiracetam, and lamotrigine [20]. Our patient presented with complex partial seizures with secondary generalization. Favorable seizure control was achieved with valproate, lamotrigine and levetiracetam in combinations.

Marked intra- and inter-familial variability in clinical phenotype has been reported [16, 21]. In the majority of cases, as in our patient, the severity of associated neurologic and cognitive impairments appears to progress slowly, with many of them surviving adulthood. However, a sudden deterioration may occur in occasional cases and some patients have a downhill neurologic course at a later age, sometimes as late as at 6-17 years of age [8]. There is one report of a neonate with L-2-HGA and a rapidly fatal outcome [18]. An 11-month-old girl, born to consanguineous parents of Tamil origin suddenly died at 11 months of age, during an intercurrent illness [22]. There was no correlation between the severity of clinical symptoms and the amount of L-2-OHG acid in urine or CSF [12]. Delay of L-2-HGA diagnosis until adulthood has been described [5, 14], because of mild clinical symptoms and lack of typical MRI abnormalities [4].

Neuroimaging findings of L-2-HGA are very specific. Cranial MRI reveals characteristic scattered or diffuse subcortical white-matter abnormalities fading centripetally [14]. A retrospective review of MR images in patients with L-2-HGA disclosed that initially, abnormalities of subcortical white matter were at least partially multifocal, later became more confluent and spread centripetally, but the periventricular rim remained relatively spared. Bilateral involvement of the globus pallidus, caudate nucleus, putamen and dentate nucleus was seen at all stages. The cerebellar white matter was never affected [9]. Confluent subcortical white matter lesions, atrophy of the cerebellar vermis with involvement of the dentate nuclei, without deep white matter abnormalities, were shown on MRI scans in our patients, supporting the diagnosis of L-2-HGA.

In all Turkish patients MRI showed subcortical leukoencephalopathy with bilateral high signal intensity in the dentate nuclei and putamens [15]. Atypical imaging anomalies, such as basal ganglia atrophy were described in an adult patient with L-2-OHG [5]. Moroni et al. [12] observed a good correlation between the severity of the disease and the extent of lesions on MRI. As cranial MRI findings raise suspicion of L-2-HGA, one must consider other diseases that have similar MRI findings for a differential diagnosis. These diseases include Van der Knaap disease, Canavan disease and Alexander disease. We encountered the same initial diagnostic difficulties.

Increased incidence of brain tumors has been noted among patients with L-2-HGA [12]. Meta-analysis of published data identified 14 patients with L-2-HGA associated with cerebral neoplasms, suggesting an approximately 5% prevalence rate of CNS neoplasms in these patients [13]. A male infant with L-2-HGA and Wilms tumor, the most common renal malignancy of childhood, was reported as example of an extracranial tumor associated with L-2-HGA [11].
Neither cerebral nor extracranial neoplasm was found in our patient.

A possible therapeutic role of FAD, cofactor of the enzyme, and of its precursor riboflavin was investigated. Nevertheless, it appears that this approach is only effective in “mild” missense mutations of L2HGDH (supplementation with FAD 30 mg/day) and levocarnitine chloride (900 mg/day), whereas truncated enzymes (presumed null mutations) are not responsive [1]. Therapeutic trials with oral coenzyme Q10 (400 mg/day) during 6 months and with oral riboflavin (200 mg/day) during 2 months showed no biochemical and clinical effects [22]. We could confirm this observation in our patient. No significant clinical benefit of oral coenzyme Q10 (400 mg/day) during 6 months and with oral riboflavin (200 mg/day) during 4 months was noted.

REFERENCES


doi: 10.2298/SARH1406337J
**L-2-хиドロキシグルタリル酸アセチルアミダ**: приказ болесника

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КРАТАК САДРЖАЈ

Увод

L-2-хидроксиглутаричка ацидурија (L-2-ХГА) је аутоимин алфа-неника са споро прогресивним током, која се одликује повишеним нивоима хидрокси-

глутаричке киселине (L-2-ХГ) у мокраћи, цереброспинало- 

tечности и плазми. Клиничка слика најчешће укључује менталну нарушеност, атаксију и моторне испаде.

Приказ болесника

Шестнаестогодишња болесница рођена је као прво и једино дете здравих родитеља српског поре-

кла и без крвног сродства. У узрасту од четири године њено ходње је постало нестабилно и атаксично. Други знаки за-

хађања се лицева (55 cm). Благо ума заосталост показана је формалном проценом интели-

генције (IQ) је био 60. Магнетна резонанција мозга показала је конфулатива, супертракциона оштећења беле масе са цен-

тралитетним шirenjem и атрофијом маломожданог вермиса

уз захваћеност дентатних једара, без оштећења дубоке беле масе. Лабораторијска испитивања показала су веома високе вредности L-2-ХГ у мокраћи и плазми. Етанометричка ана-

лиза потврдila је L-конфигурацију (>90% L-2-ХГ), чиме је постављена дијагноза L-2-ХГА. Први епилептички напад, жа-

ришни са секундарном генерализацијом, јавио се у осмој го-

дини. Постигнута је повољна контрола напада. Запажено је споро напредовање невроопште нарушенностери. Терапијска 

орална пријема коензима Q10 и рибофлавина није довела до бихемијских и клиничких ефеката. Ускоро је дијагноза 

побуђена налазом мутације L-2-ХГА гена.

Закључак

Колико нам је познато, ово је први приказ боле-

сната са L-2-ХГА у Србији. У складу с клиничком сликом и 

магнеторезонанским снимком мозга, L-2-ХГА треба да се 

уврсти у диференцијалну дијагностику неврометаболичких 

болести.

Кључне речи: хидроксиглутаричка ацидурија; епилепсija; 

оштећења беле масе; атаксија

Примљен • Received: 23/05/2013

Прихваћен • Accepted: 02/08/2013