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Case Report

L-2-Hydroxyglutaric Aciduria: Report of Four Turkish Patients from the Same Family

A. Destina YALCIN[1], Pinar TEKTURK[2], Zuhal YAPICI[2]

[1]*Department of Neurology, Umraniye Education and Research Hospital, Istanbul, Turkey*
[2]*Department of Neurology, Division of Child Neurology, Istanbul Faculty of Medicine, Istanbul, Turkey*

Abstract

Background: L-2-Hydroxyglutaric aciduria is a rare slow progressive autosomal recessively inherited neurometabolic disease.
Methods: In this study we describe the clinical genetic and magnetic resonance imaging findings of four Turkish patients from the same family.
Results: All siblings were mentally retarded, had cerebellar symptoms and gait ataxia.The index patient presented with absences, generalized tonic clonic seizures and repeated nonconvulsive status epilepticus episodes before treatment. Their magnetic resonance images demonstrated subcortical white matter and basal ganglia alterations combined with cerebellar atrophy. In all patients the level of L-2-Hydroxyglutaric acid in urine and cerebrospinal fluid were found to be high which confirmed the diagnosis. One prominent feature regarding the course of the disease in our patients is that their neurological status remained more or less unchanged during the follow-up period lasting 20 years which is the longest described in the literature.
Conclusion: Considering the autosomal recessive inheritance pattern of this disorder, and the high rate of consanguineous marriage in Turkey, one should bear in mind this rare disorder while confronted with patients suffering from a combination of progressive cerebellar syndrome, mental retardation and seizures.

Keywords: L-2-Hydroxyglutaric aciduria

L-2-Hidroksiglutarik Asidüri: Aynı Aileden Dört Türk Hastanın Raporu

Özet

Giriş: L-2 Hidroksiglutarik asidüri, nadir görülen, yavaş seyirli, otozomal resesif kalıtımlı bir nörometabolik hastalıktır.
Metod: Bu çalışmada, aynı aileye mensup dört Türk hastanın klinik, genetik ve manyetik rezonans görüntüleme bulguları tanımlanmıştır.
Bulgular: Tüm kardeşlerde mental retardasyon, serebellar semptomlar ve yürüme ataksisi mevcuttu. Indeks hasta absans, jeneralize tonik klonik nöbetler ve tedavi öncesi tekrarlayıcı nonkonvülzif status epileptikus ile başvurdu. Manyetik rezonans görüntülemeleri serebellar atrofiyle birlikte subkortikal ak madde ve bazal gangliya değişiklikleri gösteriyordu. Tüm hastalarda idrar ve serebrospinal sıvıda L-2-hidroksiglutarik asit düzeyi tanıyı destekler şekilde yüksek bulundu. Hastalığın seyri gözönüne alındığında hastalarımızdaki en belirgin özellik, şimdiye kadar literatürde tanımlanmış en uzun takip süresi olan 20 yılda nörolojik durumlarının aşağı yukarı değişmemiş olmasıydı.

Sonuç: Nadir görülen bu hastalık, otozomal resesif kalıtımlı olması ve Türkiye'de akraba evliliği oranının fazla olması gözönüne alındığında, ilerleyici serebellar sendrom, mental retardasyon ve nöbet birlikteliğiyle başvuran hastalarda akla gelmelidir.

Anahtar Kelimeler: L-2-hidroksiglutarik asidüri

INTRODUCTION

L-2-hydroxyglutaric aciduria (L2HGA) is a rare slow progressive neurometabolic disease inherited as an autosomal recessive trait[10]. It was first reported in 1980 in a 5 year old boy from Morocco who was suffering from psychomotor retardation and growth deficiency[4]. Since 1980, approximately 100 additional cases were published[12]. The main clinical features of the disease are mild to moderate mental retardation, motor dysfunction with ataxia, extrapyramidal and pyramidal signs, and epilepsy[10,12].

Biochemically, L2HGA is established by increased concentration of L-2 hydroxyglutaric acid in urine, cerebrospinal fluid and, to a lesser extent, in plasma, which is necessary for confirming the diagnosis[6,1].

Characteristic brain magnetic resonance imaging (MRI) findings include subcortical white matter abnormalities together with bilateral involvement of putamen, globus pallidus, caudate nucleus and dentate nucleus on T2-weighted and FLAIR images, and with the disease progression, cerebral and cerebellar atrophy[9].

Genetically, the disease is caused by a mutation in a gene present on chromosome 14q22.1 and encoding L-2-hydroxyglutarate dehydrogenase. The FAD-linked mitochondrial enzyme catalyses the irreversible conversion of L-2-hydroxyglutarate to alpha-ketoglutarate[14].

In this report we describe the clinical, genetic and MRI findings of four Turkish patients from the same family.

CASE PRESENTATION

Index Patient: This 30 year old woman was the third child of a consanguineous marriage. She was admitted to our epilepsy outpatient clinic after a prolonged generalized tonic clonic seizure at the age of 10 years. She was suffering from random generalized seizures since 6 years of age. During neurological examination several episodes characterized by staring and blinking of eyes, accompanied by unresponsibility-unresponsiveness, lasting 10-20 seconds were witnessed, and interpreted as absences. Her parents were describing absences for one year but they did not apply to any doctor since they did not recognize these conditions as seizures. Her neurological examination revealed mild mental retardation, dysarthria, mild gait ataxia and intentional tremor. She attended primary school for 3 years but could not learn reading and writing. Repeated EEG findings included slowing of background activity and generalized spike-wave discharges of 2,5 Hz frequency sometimes accompanied by absences. Her brain MRI showed increased signal intensities in dentate nuclei, globuspallidi and subcortical white matter in the frontal and temporal lobes on T2 sequences (Figure 1a,b). Her parents complained about episodes lasting many hours, sometimes even the whole day, where the patient seemed drowsy, confused, and repeated the same movement over and over again. An EEG recorded during one of these episodes showed prominent slowing of the background activity intermixed with frequent generalized spike-wave discharges, confirming the diagnosis of nonconvulsive status epilepticus. Her seizures were controlled with a combination therapy of valproic acid and levetiracetam, and the nonconvulsive

episodes did not repeat. During the follow-up period lasting 20 years her neurological status remained more or less stable.She is independent in her daily activities keeping her talkative manner. Her EEG's show even today generalized spike-wave discharges of 2,5 Hz frequency on a slow background activity mainly provoked during hyperventilation.

We learned that three of her siblings (two boys and one girl) were also suffering from mental retardation and gait disturbance. None of them had seizures of any kind. The parents mentioned that the first sign of the disease in all their affected children was gait ataxia noticed at the age of two or three years as they began to walk. They all were able to walk without assistance but fell frequently, particularly when they ran. On neurological examination, all of them had mild mental retardation, gait ataxia, intentional tremor, and one of them had titubation in addition. All attended school but could not learn reading and writing. In terms of their behavior in daily life, they all tend to be talkative almost in an uninhibited manner and spent their time by playing with children in preschool age in the street.

Their cranial MRI showed the features similar to those observed in the index patient with bilateral, symmetrical hyperintensities in dentate nuclei, globus pallidus, putamen, and diffuse subcortical white matter involvement particularly in the frontal and temporal lobes on T2 and FLAIR sequences(Figures 1, 2). In all patients the level of L-2-Hydroxyglutaric acid in urine and CSF were found to be high which confirmed the diagnosis of L-2-HCGA (Table 1). During the 20-year follow-up in our clinic, their symptoms were stable. They are independent in all their daily activities even today.

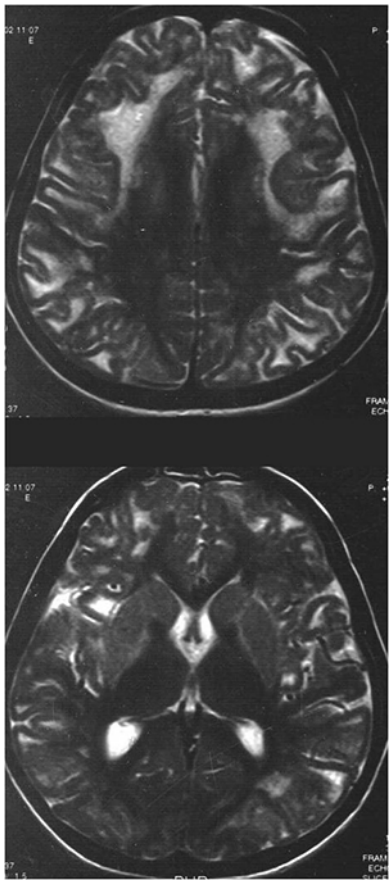

Figure 1a,b: *(T2 axial images of index patient): Increased signal intensities in the subcortical white matter particularly in the frontal and temporal lobes, and bilateral putamen.*

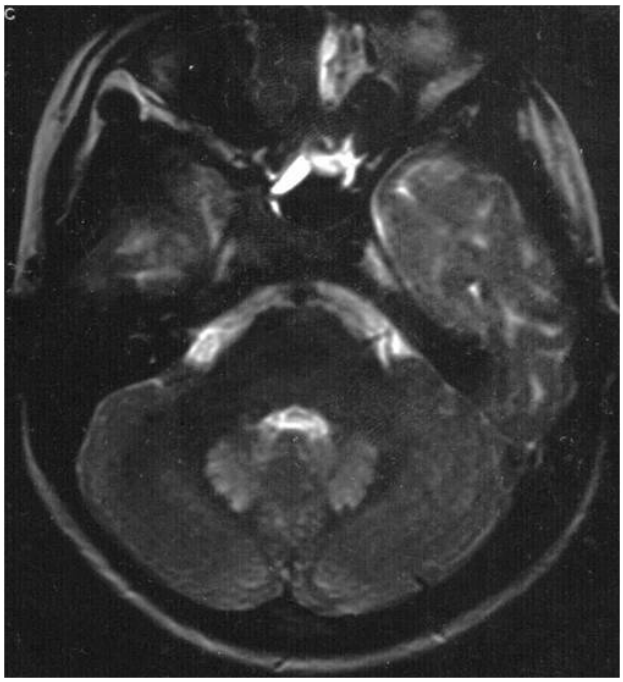

Figure 2: *(T2 axial image of index patient): Bilateral, symmetrical hyperintensities in dentate nuclei.*

Table 1: Laboratory investigations of the patients

The patients	Urine (1.3-18.9 mmol/mol creatinine)	CSF (0.25-2.34 µmol/l)	Mutation
FA (female)	*1261* Creatinine 18.5 mmol/l	31 µmol/l	c.905 C > T ; p.Pro 302 Leu Homozygous mut (+)
SA (female, index patient)	1144 Creatinine 4.7 mmol/l	41 µmol/l	c.905 C > T ; p.Pro 302 Leu Homozygous mut (+)
NA (male)	1084 Creatinine 8.1 mmol/l	27.7 µmol/l	c.905 C > T ; p.Pro 302 Leu Heterozygous mut (+)
OA (male)	1750 Creatinine 3.4 mmol/l	34.5 µmol/l	c.905 C > T ; p.Pro 302 Leu Homozygous mut (+)

DISCUSSION

According to the age of onset various clinical patterns have been described[5]. A severe early form, beginning shortly after birth, has a rapid progressive course characterized by hypotonia, apnea, and therapy resistant convulsions of different types[2]. The childhood form generally has a very slow progressive course with gait ataxia and mental retardation[5]. Therefore the right diagnosis can delay in many cases until adulthood. The third form, more recently identified, affects the adults[5]. In all our patients, the first symptoms were gait ataxia and the course was very slow as described in many patients with childhood form of L2HGA. However, in some cases,after a long stable period a sudden and unexpected worsening of the symptomscan occur resulting in a rapid progressive clinical decline. Different clinical courses even in patients within the same family were reported[6,2]. During the 20 year follow-up which is the longest in the literature, the neurological status of our patients remained more or less stable and they are independent in their daily activities even today.

The main clinical findings of the disease are mild to moderate mental retardation and cerebellar involvement with gait ataxia and intentional tremor. Additional features can be pyramidal tract signs(spastic paraparesis) and extrapyramidal signs, (dystonia, choreic movements), macrocephaly and seizures[10,12,6,1,8,3]. The repeated neurological examination of our patients during the long follow-up period did not reveal pyramidal tract, extrapyramidal sign or macrocephaly. Macrocephaly is not specific for the disease and is a symptom shared by several other neurometabolic disorders and organic acidurias[8,3].

In L2HGA,different type of seizures are reported,There are also many cases presented with seizures even with status epilepticus as the first symptom[6,15].Generalized tonic-clonic seizures are the most frequently described among the seizures associated with L2HGA. Our index patient developed absences and generalized tonic-clonic seizures and repeated nonconvulsive status episodes before treatment. To our knowledge, typical absences and nonconvulsive status epilepticus were not reported previously in L2HGA. Recently, however a case suffering from eye lid myoclonia with absences as the initial symptom of L2HGA was described[7]. In the infantile form the seizures generally are therapy resistant but they are well controlled with various antiepileptic drugs in childhood form as it was the case in our patient[12,6,8].

One of the most prominent feature of our patients were their talkative manner in an uninhibited degree which made them being loved among their friends usually younger than them. During the follow-up period, their behavioral pattern remained unchanged, and was not replaced by a depressed mood after adolescence as it was the case in the series of Topçu et al.[11].

Typical MRI findings raising the suspicion of L2HGA are increased signal intensities in white matter, basal ganglia and nucleus dentatuson T2-weighted images[9]. There are however some other diseases sharing similar MRI findings and must be excluded[12,6,9,13]. These are Van der Knaap disease (megalencephalic cystic leukoencephalopathy-MCL), Canavan disease and Alexander disease[12,6,9].Van der Knaap disease affects in addition to bilateral involvement of dentate nuclei dorsal pons and mesencephalon together with bilateral temporofrontal subcortical intraparenchymal cysts which are spared in L2HGA[9,13]. Alexander disease is characterized by a typical pattern of contrast enhancement andwhite matter involvement is prominently in frontal lobes[6,9]. In Canavan disease,white matter lesions are much more widespread than in

L2HGA, thalamus and globuspallidi are frequently involved, whereas putamen and caudate nucleus are spared and dentate nucleus involvement is exceptional[9]. L2HGA has a distinct highly characteristic pattern of MRI abnormalities of predominantly subcortical cerebral white matter involvement in combination with the dentate nucleus, globus pallidus, putamen, and caudate nucleus. The appearance of the MRI in patients with a longer duration of disease is characterized by more global and confluent abnormalities of the cerebral white matter, caudate nucleus, and putamen, and by atrophy of the cerebral white matter and the cerebellar hemisphere[9].

The diagnosis of L2HGA can be established by detection of high levels of L-2-hydroxyglutaric acid in urine, cerebrospinal fluid and plasma[4,6]. In all of our patients the L-2-hydroxyglutaric acid levels in urine and cerebrospinal fluid were found to be increased (see table 1).L2HGDH gene consists of 10 exons and is mapped at 14q22.1[4]. In members of this family, c.905 C >T; p.Pro 302 Leu mutation was detected in DNA in Department of Clinical Chemistry, Metabolic Unit, VU University, Amsterdam. The open reading frame and adjacent splice sites have been analyzed by DNA sequence analysis, and there wasthe above-described homozygote mutation. The mutation consists of a C>T transition in exon 7, which results in the substitution of proline by leucine at position 302. The gene product, L2HGDH, catalyzes the conversion of L2HG acid to 2-ketoglutarate and is located in mitochondria[10]. So far, the function of L2HG is unknown.

Treatment of the disease includes a protein restricted diet and riboflavin and carnitine supplements as well as symptomatic management. There are only few cases treated successfully with riboflavin and carnitine[14].

Considering the autosomal recessive inheritance pattern of this disorder, and the high rate of consanguineous marriage in Turkey, one should bear in mind this rare disorder while confronted with patients suffering from a combination of progressive cerebellar syndrome, mental retardation and seizures.

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Correspondence to:
Pinar Tekturk
E-mail: pinartopaloglu2000@yahoo.com

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