L-2-Hydroxyglutaric aciduria: a report of 29 patients

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L-2-hydroxyglutaric aciduria (L2HGA) is a chronic slowly progressive neurodegenerative disease characterized mainly by psychomotor developmental delay and cerebellar dysfunction. We report the clinical, biochemical, and neuroimaging features of 29 patients from 22 families. The mean age at the time of diagnosis was 13.4 years (2.5-32 years). The mean follow-up period of patients was four years (1.5-16 years). The main clinical findings were mental retardation and cerebellar involvement with ataxic gait and intentional tremor. Additional findings were mental retardation, macrocephaly and seizures. Diagnosis was confirmed by increased urinary excretion of L-2-hydroxyglutaric acid in all patients and highly specific magnetic resonance imaging (MRI) pattern showing subcortical leukoencephalopathy with bilateral high signal intensity in dentate nuclei and putamens. During the follow-up period, all patients had a static encephalopathy course. The underlying metabolic defect and the possible role of L-2-hydroxyglutaric acid are studied in a subgroup of these families and under evaluation for publication.

Key words: L-2-hydroxyglutaric aciduria, magnetic resonance imaging, biochemical findings.

L-2-hydroxyglutaric aciduria (L2HGA) is rare chronic progressive neurodegenerative disorder in the group of organic acidurias, with predominant neurological manifestations and a suggested autosomal recessive mode of inheritance[1,2]. The disease was first described by Duran et al.[1] in 1980 and since then about 75 patients have been reported world-wide[4-14].

Clinically the disease is characterized by mild psychomotor delay in the first years of life, followed by progressive cerebellar ataxia, dysarthria, and moderate-to-severe mental deterioration[1-14]. Pyramidal and extrapyramidal signs, seizures, macrocephaly and stunting of growth may be the additional findings[1-14]. Episodes of acute metabolic decompensation do not occur and brain damage is not related to acidosis or other metabolic imbalance, as in other forms of organic acidurias[14]. The disease has a slowly progressive course extending well into adolescence and adulthood.

Magnetic resonance imaging (MRI) characteristically shows lesions in the subcortical white matter, cerebellar atrophy and abnormal signals in the dentate nuclei and putamens[7,15]. The centripetal extension of the white matter involvement establishes a distinct feature that differs from other leukodystrophies[7,15]. MR spectroscopy shows a reduction N-acetyl aspartate and an increase in the choline and myoinositol peaks[16].

Biochemically, L2HGA is characterized by increased concentration of L-2-hydroxyglutaric acid in urine, cerebrospinal fluid (CSF) and, to a lesser extent, in plasma. Diagnosis depends on detection of increased levels of L-2-hydroxyglutaric acid in urine by means of gas chromatography-mass spectrometry, with 90% of isoforms representing the L-form[17-20]. L-2-hydroxyglutaric acid is increased more than 10-fold in urine (800-1300 mmol/mol creatinine) compared to normal levels in

subjects of under 52 mmol/mol creatinine[17-19]. The plasma levels are 4- to 6-fold higher than in normal controls, and more than 10 times higher in the CSF[17-19]. Concentrations of glycolate, glycerate, pyruvate, laurate, 2, -4 hydroxybutyrate, citrate, isocirtate, palmitate, myristate, oleate and stearate have also been reported to be moderately increased (about 2-fold the values in plasma and/or in CSF)[18]. Increased levels of L-lysine and pipecolate in CSF, suggesting a defect in the alternative degradation pathway of lysine, have also been defined in some patients[5,12,21,22]. Concentrations of 2-ketoglutarate, one of the intermediates of the Krebs cycle, were found to be increased relative to controls in culture medium from cells of two patients with L2HGA[23,24]. A NAD^+ -dependent L-2-hydroxyglutaric acid dehydrogenase is present in human liver, but normal activity of this enzyme in patients excluded a pathogenic role for this protein[23,24].

The aim of this study was to define the clinical, biochemical and MRI findings of 29 Turkish patients from 22 families with L-2-hydroxy-glutaric aciduria.

The precise role of L-2-hydroxyglutaric acid in normal intermediary metabolism in human beings and the underlying enzymatic defect in L2HGA remain unknown to date. The molecular genetic studies to define the underlying metabolic defect are being performed in a subgroup of these patients and are under evaluation for publication at this moment.

Material and Methods

This study included 29 Turkish patients from 22 families with L-2-hydroxyglutaric aciduria who admitted to Hacettepe University İhsan Doğramacı Children's Hospital, Department of Pediatric Neurology, and İstanbul University Cerrahpaşa Faculty of Medicine, Department of Neurology, between 1993 and 2003. The diagnosis of L2HGA was based on clinical, biochemical and neuroradiological findings. Laboratory tests were performed in the biochemical screening laboratory in Hacettepe University and in the laboratory for Genetic Metabolic Diseases in the University Hospital, Amsterdam. Routine screening for organic acids using gas chromatography revealed increased and isolated urinary excretion of L-2-hydroxy-glutaric acid in all patients, and absolute configuration of DR-hydroxyglutaric acid and L-2-hydroxyglutaric acid was determined by capillary gas-liquid chromatography after esterification with 2-butanol and acylation with acetic anhydride as described by Duran et al.[1] MRIs were obtained in all except five of the patients, and were performed on 0.5-T and 1.5-T Philips Gyroscan and 0.5-T GE Max systems. T1-weighted sagittal and axial and T2-weighted axial images were obtained. Additional T1- or T2-weighted coronal images were also obtained if indicated. There was consanguinity in 14 of the 22 families. All patients received L-carnitine therapy following diagnosis.

Results

Clinical findings

We detected 29 patients (16 boys and 13 girls) from 22 families from rural areas of Turkey in Central and South East Anatolia with L-2-hydroxyglutaric aciduria. The clinical features of the families and patients are summarized in Tables I and II. The mean age at the time of diagnosis was 13.4 years (2.5-32 years). The mean follow-up of the patients was four years (1.5-16 years). The main clinical findings were mental retardation and cerebellar involvement with ataxic gait and intentional tremor. IQ levels were between 50-75 in all patients, and below 10 years of age there was short attention span and hyperactivity. During childhood, patients tended to be talkative almost in an uninhibited manner; however this is replaced by a depressed mood after adolescence. Additional findings were macrocephaly (n=8), and febrile or afebrile, partial or generalized (n=21) seizures. The seizures were all well controlled with anticonvulsants. Electroencephalographic (EEG) findings included irregular background activity and slowing, focal or generalized spikes, and slow wave discharges. Visual evoked potentials (VEP) and brainstem auditory evoked potentials (BAEP) became abnormal and/or showed deterioration on serial examinations. During the follow-up period, cerebellar system involvement became more prominent around 12 years of age, and no deterioration developed after 14 years of age. All patients followed a static encephalopathy course except for two patients: one had medulloblastoma and the other developed dystonia in the course of their disease. None of our patients became whellchair bound.

Table I. Clinical Characteristicts of the Patients with L-2-Hydroxyglutaric Aciduria

Family	Consanguinity	Patient number	Sex	Affected siblings	Age at onset (yr)/age at diagnosis (yr)
F1	+	1	F	–	2/2.5
F2	–	2	M	–	1/8
F3	+	3	F	–	3/5
F4	+	4	M	–	7/10
F5	+	5	F	–	1.5/2.5
F6	+	6	M	1	2/9
		7	F	1	2.5/17
F7	+	8	F	2	2/16
		9	M	2	9/18
F8	–	10	F	1	5/7
F9	+	11	F	1	13/15
F10	+	12	M	–	4/7
F11	+	13	M	–	2/4
F12	–	14	M	–	1.5/7
F13	+	15	F	1	4/9.5
		16	M	1	5/12
F14	–	17	M	–	?/2.5
F15	–	18	M	–	17/20
F16	–	19	M	–	15/18
F17	+	20	M	4	1.5/2.5
		21	M	4	6/12
F18	+	22	M	–	18/25
F19	+	23	M	–	7/12
F20	–	24	M	1	?/22
		25	M	1	17/28
F21	+	26	F	1	9/16
		27	F	1	12/19
F22	–	28	M	1	30/32
		29	F	1	25/29

Table II. Clinical Findings of the Patients with L-2-Hydroxyglutaric Aciduria

Patient number	Delay in speech/dysarthria	Delay in walking/ataxia	Learning disability/mental retardation	Febrile/afebrile seizures	Tremor	Macrocephaly	Abnormal cerebellar Tests
1	–/+	+/+	–/–	+/–	–	+	+
2	+/–	+/–	+/+	+/+	–	+	+
3	+/+	+/+	+/+	+/–	+	–	+
4	–/–	–/+	+/+		–	–	–
5	–/–	+/+	–/–	+/+	–	–	–
6	+/–	+/–	+/+	+/–	–	+	–
7	+/–	+/–	+/+		–	+	+
8	+/+	–/+	+/+	+/–	+	+	+
9	–/+	–/–	+/+		+	–	+
10	+/+	–/+	–/–		–	+	+
11	–/–	–/–	–/–		–	–	–
12	+/–	+/–	+/+	+/–	–	–	+
13	–/+	–/+	+/+	+/–	+	–	+
14	–/–	+/+	+/+		–	+	+
15	–/–	–/–	+/+		+	–	–
16	–/–	–/–	+/+		+	–	–
17	+/+	+/–	–/–		–	+	–
18	–/–	–/–	+/+		–	–	–
19	–/–	–/–	+/+	+/+	–	–	–
20	–/–	–/+	–/–		–	–	+
21	–/–	–/–	+/+		–	–	–
22	–/+	–/+	+/+		+	–	+
23	+/+	+/+	+/+		–	+	+
24	+/+	+/+	+/+	+/+	+	+	+
25	–/+	–/+	+/+	+/+	+	+	+
26	+/+	+/+	+/+	+/+	+	+	+
27	–/+	–/+	+/+		+	+	+
28	–/–	–/–	+/+		+	+	+
29	–/+	+/+	+/+		+	+	+

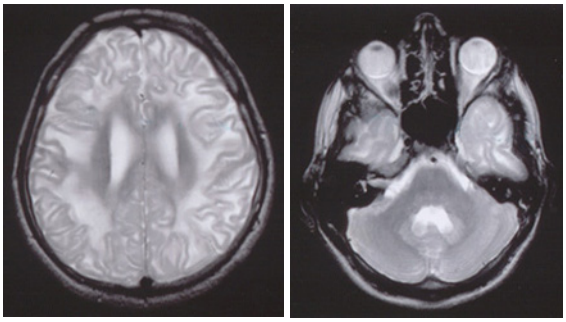
There is no specific treatment of the disease and the approach is supportive, by means of controlling seizures, L-carnitine (50-100 mg/kg/day) supplementation, physical therapy and rehabilitation and special training. Severe cerebellar symptoms, movement disordes and dystonia were responsive to treatment with benserazide hydrochloride and levodopa combination (Madopar®).

Biochemical Findings

Urinary excretion of L-2-hydroxyglutaric acid was increased in all patients ranging from 1000 to 5520 mmol/mol creatinine (N: 1.3-19 mmol/creatinine).

Neuroradiological Findings

Magnetic resonance imaging examination was performed in all patients except five. MRI findings are summarized in Table III. Highly characteristic neuroimaging findings that may suggest the diagnosis are myelin breakdown, which is predominantly subcortical rather than periventricular, centripetal extension of white matter involvement, and symmetric bilateral dentate nuclei lesions with variable basal ganglia involvement (Fig. 1 a and b). Vermian (n=5) and hemispheric atrophy (n=8) in the cerebellum were also observed.



(1a) (1b)

Fig. 1a and b: T-2 weighted MRI images showing subcortical and periventricular white matter involvement with bilateral symmetric dentate nuclei lesions.

Discussion

L-2-hydroxyglutaric aciduria is an autosomal recessive metabolic encephalopathy. The disease is characterized by psychomotor delay and

Table III. Magnetic Resonance Imaging Findings of the Patients

Patient number	SWM (F/P/T/O)	SWM (scattered/ confluent)	Periventricular involvement	Basal ganglia (CN/Pt/GP)	Corpus callosum	Internal /External capsule	Cerebellum (WM/Atrophy)	Nucleus dentatus
1	+ (O)	+/–	+	NC/Pt/GP	–	+/–	–	+
2	+	+/–	+	GP	–	–/–	+/+	–
3	+	–/+	–	NC/Pt/GP	–	+/+	–	+
4	+	+/–	+	–	–	–/–	–	–
5	+	+/–	+	–	–	–/–	–	–
6	+ (F/P)	+/–	–	Pt	–	–/–	–	+
7	NA							
8	NA							
9	+ (F/P/T)	–/+	+	–	–	–/–	–	–
10	NA							
11	NA							
12	+ (F/T)	+/–	–	Pt/GP	–	–/–	+/–	+
13	+	–/+	–	NC/Pt/GP	–	+/+	+/–	+
14	+ (F/T)	+/–	–	–	–	–/–	+/–	+
15	+ (F/P/T/O)	+/–	–	–		–/–	–/+	+
16	+	+/–	–	Pt/GP	–	–/–	–	+
17	+ (P/T)	–/+	+	GP	–	+/–	+/–	+
18	NA							
19	+ (F/P/T/O)	+/–	+	C/Pt	+	+/–	–	+
20	NA							
21	+	+/–	–	NC/Pt/GP	–	–/–	–	+
22	+	–/+	–	NC/Pt/GP	–	+/+	–	+
23	+	–/+	–	GP	–	+/+	–/+	+
24	+	–/+	–	NC/GP	+	+/+	–/+	+
25	+	–/+	–	NC/GP	–	+/+	–	+
26	+	–/+	–	Pt/GP	+	+/+	–/+	+
27	+	–/+	+	NC/Pt/GP	+	+/+	–/+	+
28	+	–/+	+	NC/Pt	+	–/+	–/+	+
29	+	–/+	+	–	+	+/+	–/+	+

SWM: subcortical white matter, F: frontal region, P: parietal region, T: temporal region, O: occipital region, CN: caudate nucleus, Pt: putamen, GP: globus pallidus, WM: white matter.

cerebellar and extrapyramidal signs in infancy, often associated with seizures and macrocephaly[1,2]. There is usually a very slowly progressive course without peculiar clinical signs. Neuroradiological features of a subcortical leukoencephalopathy with dentate nuclei and basal ganglia involvement are rather specific and should lead to further biochemical investigations[7-15]. Definitive diagnosis depends on detection of L-2-hydroxyglutaric acid in urine, blood and CSF by means of gas chromatography-mass spectrometry (GC-MS), with more than 90% of the isoforms found in L-configuration[17-20].

The clinical, biochemical and neuroradiological features in this series of 29 patients from 22 families showed that the disease is characterized by a slowly progressive chronic neurodegenerative course with progressive ataxia and developmental delay. Definitive diagnosis was made by the presence of increased urinary excretion of L-hydroxyglutaric acid in all patients. Additional clinical findings were macrocephaly and seizures. All patients showed mild-to-moderate mental retardation; below 10 years of age there was short attention span and hyperactivity. In the pre-adolescence period, patients tended to be talkative in an uninhibited manner; however, this was replaced by a depressive mood after 15 years of age. The patients were usually diagnosed during childhood and adolescence. The parents recognized developmental problems at the time the children started to walk when they appeared to have gait disturbances. Two patients were diagnosed at the ages of 29 and 32 respectively. Head circumference was above 97th percentile for age in 15 of the 29 patients, although in the remaining ones it was above the 50th percentile. Macrocephaly is a finding that must alert the clinicians to the possibility of a cerebral organic aciduria, although it is shared by several other metabolic diseases such as glutaric aciduria type I and Canavan's disease. In glutaric aciduria type I, the most common clinical presentation is dystonia and choreoathetosis with neuroimaging findings showing enlarged sylvian fissures, frontotemporal atrophy, and white matter and basal ganglia changes[25-27]. Canavan's disease is a form of spongioform leukodystrophy characterized clinically by motor and mental deterioration, spasticity, seizures and optic atrophy in a child with macrocephaly[28,29]. Brain stem involvement and centripetal extension of white matter abnormalities differentiate Canavan's disease from L2HGA.

During the follow-up period in our series, abnormal cerebellar tests became more prominent around 12 years of age, and the patients followed a static encephalopathy course after 14 years of age except for two patients, one who had medulloblastoma and one who developed dystonia during the course of their illness. The association of L2HGA with brain malignancies has been previously reported[30,31]. As in our patient, there may be a sudden and unexpected worsening of symptoms. The presence of severe underlying white matter abnormalities may be misinterpreted as a brain mass. The relationship between the disease and brain malignancy is difficult to explain, although a demyelination-remyelination process leading to overproduction of growth factors mitogenic to neural precursor cells may stimulate key events in brain tumorigenesis. However, this is not a finding in other white matter remodeling diseases[31]. Dystonia may develop during the course of the disease, usually more prominent in hands and upper extremities. Treatment approach includes L-carnitine supplementation, treatment of seizures and physical therapy and rehabilitation. Our patients with severe cerebellar symptoms, seizures, dystonia and movement disorders responded well to treatment with Madopar®, which may be considered in severe cases.

Neuroimaging findings are highly characteristic but not specific and show subcortical white matter loss, cerebellar atrophy, bilateral signal changes in dentate nuclei and putamens and subcortical leukoencephalopathy[7,15]. Subcortical regions had low signal on T1-weighted images and high signal on T2-weighted images. The pattern is suggestive of a spongioform encephalopathy like Canavan's disease. Both diseases are characterized by predominant subcortical white matter involvement compared to periventricular involvement and dentate nuclei lesions with variable basal ganglia involvement. Canavan's disease differs from L2HGA by the presence of typical brainstem involvement[7,15]. Both vermian and hemispheric cerebellar atrophy, corpus callosum involvement and sparing of thalamus and mesencephalon may be additional neuroradiological features.

The underlying metabolic defect causing L2HGA and relevance of L-2-hydroxyglutaric acid in normal intermediary metabolism remain unknown to date. 2-hydroxyglutarate is an intermediary metabolite in C5-branched dibasic acid metabolism between glyoxylate and propionyl-CoA, in butanoate metabolism between 2-oxoglutarate and 2-hydroxyglutaryl-CoA, and in lysine degradation. A defect of 2-ketoglutarate production, and more globally in lysine metabolism in the mitochondria, has been established because of increased lysine and a decreased glutamine, indicating a block in the first step in lysine catabolism[22-24]. Beta-oxidation in the mitochondria and L-2-hydroxyglutarate dehydrogenase activity are normal[22].

This series of patients with L2HGA not only helped to define detailed clinical biochemical and radiologic characteristics of the disease but also eased the process of determining the underlying molecular pathology since most of the cases shared a common ancestry and were the product of a consanguineous marriage. In a subgroup of these patients, the molecular genetic results are presently under evaluation for publication.

Our patients' clinical and biochemical features indicate that they are very similar to previously reported cases, and this suggests that the disease has a characteristic clinical picture and typical neuroradiological findings. Briefly, mild psychomotor delay in the first years of life is followed by progressive cerebellar ataxia, dysarthria and moderate-to-severe mental deterioration. Pyramidal and extrapyramidal signs, febrile or afebrile seizures, macrocephaly, and dystonia may be additional features. Mental deterioration, language deficits, and behavior disturbances such as hyperactivity can be observed in the course of the disease. The patients usually follow a static encephalopathy course without fluctuations and/or acute deterioration. MRI is highly specific showing subcortical white matter loss, cerebellar atrophy and signal changes in dentate nuclei and putamens.

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Addendum

During the preparation period of this manuscript the underlying metabolic defect in L-2-hydroxyglutaric aciduria has been defined in a subgroup of these families. C14orf160 (*duranin*), localized on chromosome 14q22.1, encodes a putative mitochondrial protein with homology to FAD-dependent oxidoreductases. [Topçu M, Jobard F, Halliez S, Coşkun T, Yalçınkaya C, Gerçeker FO, Wanders RJ, Prud'homme JF, Lathrop M, Özgüç M, Fischer J. L-2-hydroxyglutaric aciduria: identification of a mutant gene C14orf160, localized on chromosome 14q22.1. (Hum Molec Genet 2004; 15: 2803-2811)]. It is concluded in a recent article that L-2-hydroxyglutaric aciduria is caused by mutations in the gene most likely encoding L-2-hydroxyglutarate dehydrogenase and pathological findings observed must therefore be due to a toxic effect of L-2-hydroxyglutarate on the central nervous system. (Rzem R, Veiga-da-Cunha M, Noel G, et al. Proc Natl Acad Sci USA. 2004; 30: 16849-16854).

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