L-2-Hydroxyglutaric Aciduria: Pattern of MRI Abnormalities in 53 patients

M. E. Steenweg[1], N. M. Verhoeven[2], C. Jakobs[2], G. S. Salomons[2], and M. S. van der Knaap[1]

[1]Department of Child Neurology, VU University Medical Center, Amsterdam, Netherlands, [2]Metabolic Unit of the Department of Clinical Chemistry, VU University Medical Center, Amsterdam, Netherlands

Introduction. L-2-hydroxyglutaric aciduria (L2HGA) is a rare neurometabolic disorder with an autosomal recessive mode of inheritance. Clinically, affected individuals have only neurological manifestations consisting of mild to moderate psychomotor retardation, cerebellar ataxia, macrocephaly, and epilepsy. Biochemically, affected individuals have elevated levels of L-2-hydroxyglutarate in their urine. MRI demonstrates a rather consistent pattern of signal abnormality of subcortical white matter, cerebellar atrophy, and signal abnormalities in the basal ganglia. However, the details of this pattern have not been confirmed using a standard protocol for reviewing MR images. Furthermore, the course of the MRI abnormalities over time has not been explored.

Material and methods. We retrospectively reviewed the MRIs of 53 patients with genetically confirmed L-2-hydroxyglutaric aciduria. The MRIs were sent to us by many different centers and, consequently, different pulse sequences had been used. However, at least a complete series of transverse T2-weighted images was available for every patient. The images were reviewed according to a previously established scoring list. The scoring of the MRI abnormalities was related to the disease duration. Statistical analyses (independent samples t-test/one-way ANOVA) were performed to assess the MRI course of L2HGA. A P-value of less than 0.05 was considered to be evidence of a significant relationship.

Results. MRI showed that most severe white matter abnormalities were present in the directly subcortical white matter (figure 1). Central white matter structures were better preserved. The white matter changes were confluent and had a symmetrical distribution. The subcortical white matter often had a mildly swollen aspect, with broadening of gyri. In patients with longer disease duration, white matter atrophy could be present with dilatation of the lateral ventricles and subarachnoid spaces (table 1). Bilateral involvement of the globus pallidus and the caudate nucleus was invariably seen (figure 1). The thalamus was rarely involved. The cerebellar white matter was never affected, but bilateral involvement of the dentate nucleus was present in all patients (figure 1). Cerebellar atrophy was seen in some patients.

Table 2 Pattern of MRI abnormalities in L2HGA

MR imaging abnormalities	
White matter	Frontal, subcortical preference
	External/extreme capsule abn.
Aspect of white matter	Multifocal or confluent lesions
	Symmetrical lesions
Gray matter	Caudate nucleus abn.
	Putamen abn.
	Globus pallidus abn.
	Dentate nucleus abn.
Time course	Whiet matter atrophy

Discussion and Conclusions. The MRI abnormalities in L2HGA start with isolated subcortical white matter lesions in the frontal lobe. As the disease progresses the abnormalities spread to the parietal, temporal, and finally occipital lobe (antero-posterior progression). Part of the central white matter also becomes involved (centripetal progression). The corpus callosum, internal capsule and brainstem are spared in all stages. Furthermore, the initially isolated lesions merge to yield a more confluent aspect. Over time white matter atrophy occurs. Table 2 summarizes the pattern of MRI abnormalities. The most specific abnormality is the bilateral involvement of the dentate nuclei. In combination with subcortical white matter changes the differential diagnosis mainly consists of Canavan Disease.

.

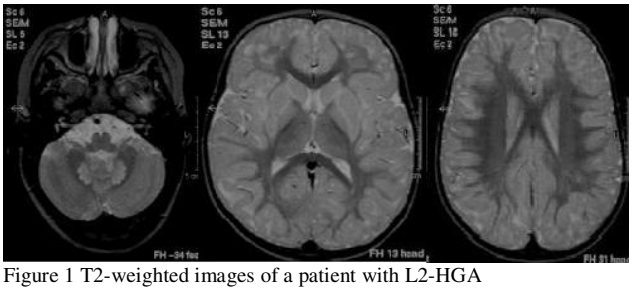

Figure 1 T2-weighted images of a patient with L2-HGA

Table 1 MRI abnormalities in L2-HGA over time

MRI abnormality		Number of Patients	Mean duration (years)	σ
Preference WM	Subcortical	29	6.7	0.003
	Subc+Central	14	13.8	
Preference Lobe	Frontal	23	6.3	0.016
	Fron+Temp/Par	7	9.3	
	Global	13	13.7	
Isolated WM lesions	Absent	18	12.1	0.02
	Present	25	6.7	
Confluence lesions	Frontal	9	7.2	0.059
	Fron+Temp/Par	15	6.2	
	Global	19	12.1	
WM atrophy	Absent	30	6.9	0.005
	Present	13	13.7	