Case Report

Findings on serial MRI in a childhood case of L2-hydroxyglutaric aciduria

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ABSTRACT

We report of a 15-year-old patient who initially presented to the specialist children's hospital with neurologic problems including developmental delay, behavioral difficulty and poor cognition. Upon organic acid testing, the patient received a diagnosis of L2-hydroxyglutaric aciduria (L2HGA).

Serial MRI scans were performed throughout the patients childhood, demonstrating an evolution of imaging features as the disease progressed.

A radiologist's recognition of the key findings associated with L2HGA can help prompt the diagnosis in cases of a nonspecific clinical presentation. This case report highlights the key radiological features associated with L2HGA, whilst illustrating how these changes may evolve and appear over the time course of a patient's journey.

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Case presentation

We present the case of a now 15-year-old male patient who initially presented to the regional specialist children's hospital aged 4 with symptoms of poor cognition, developmental delay, and behavioral difficulties.

On initial admission, screening tests for congenital TORCH infection and underlying haematological disorders were performed. At the same time, urine was tested test for organic acids, an investigation that offers a comprehensive snapshot of a patient's metabolic function. Initial blood results came back showing raised ESR levels (34; Normal range 0-10mm/hr)

and lymphocytes (5.13, Normal range 1.8–4.10). The patient was also found to be positive for Epstein-Barr virus, consistent with the raised inflammatory blood markers.

A short while after testing results for urinary organic acids returned showing raised levels of L2-hydroxyglutaric acid, consistent with a diagnosis of L2-hydroxyglutaric aciduria (L2HGA).

The patient had a female sibling 1 year younger than them. Due to the familial nature of the patient's newly discovered diagnosis, the sibling was also tested for urinary organic acids. She too was found to have abnormally high levels of L2-hydroxyglutaric acid also giving a diagnosis of L2HGA; however her symptoms were not yet clinically apparent.

Table 1 – L2HGA levels on biochemical testing. Riboflavin was commenced upon diagnosis in 2008, and whilst lowering L2HGA levels, there is still evidence of significant biomarker elevation. Due to the rarity of the disease and associated limitations in research, treatments have proven to be of variable efficacy.

Year	L-2 hydroxyglutaric acid level (umol/mmol)
2008	219
2009	175
2010	159
2011	171
2012	171
Early 2013	183
Late 2013	144
2015	148

Nonradiological Investigations

At the time of initial diagnosis, the patient's L2-hydroxyglutaric acid levels were 219 umol/mmol, significantly elevated above baseline. The level of L2-hydroxyglutaric acid is known to be consistent with disease activity, this correlated with the patient experiencing worsening symptoms at the time of diagnosis. At this time, the patient was commenced on treatment with riboflavin, otherwise known as vitamin B2, a component required by the human body to facilitate several enzymatic reactions; including the conversion of carbohydrates into adenosine triphosphate, which is then utilised in metabolism. Riboflavin use in L2HGA is thought to aid motor symptoms and decrease systemic levels of L2-hydroxyglutaric acid via enzymatic conversion and breakdown.

Between the ages of 5-10 years the patient had regular follow up appointments to closely monitor his progress. This required annual urine testing for L2HGA levels (Table 1).

To accompany his laboratory tests, the patient had yearly MRI scans requested to assess his intracranial appearances.

Over the next few years, the patient began having sporadic seizures, which were thought to be part of the L2HGA diagnosis. As a result, the patient was started on anti-epileptic medication to good effect, dramatically reducing seizure frequency.

Another symptom significantly limiting patient mobility was spasticity. His legs were largely fixed in an equinus position and hip adductors in spasm. Regarding this, muscle relaxant therapy (Baclofen) was given to provide moderate relief of symptoms.

In 2015, aged 11, the patient was deemed stable and for a period of 3 years no follow up was performed, with an open door policy offered to the parents should symptoms deteriorate.

In late-2018, aged 14, the parents re-presented to clinic reporting a dramatic deterioration in the patient's symptoms. The patient now had significantly greater seizure activity and reduced motor function. Gradually walking less and less, the patient had now become wheelchair bound when outside. When indoors, they were only able to walk for brief periods of time, and when attempting this they walked on their tiptoes due to worsening lower limb spasticity. In the upper limbs, the parents reported the patient had lost their dominant right hand function, making everyday tasks such as eating and writing a significant struggle.

To investigate seizure activity further, the patient underwent an electroencephalogram. This showed frequent bursts of 1-2 Hz at 40-120 amplitude uV. This was consistent with a 'sharp waves and spike slow wave' pattern at both parasagittal regions (right>left) demonstrating the seizures came from multiple areas of the brain rather than a single focus.

A repeat MRI was performed in early 2019, which demonstrated a significant decline in intracranial appearances, consistent with a worsening disease activity profile.

The parents were subsequently recounseled on the chronic, debilitating consequences of L2HGA where symptomatic management is the only available current treatment for the disease. The patient continues to be under the case
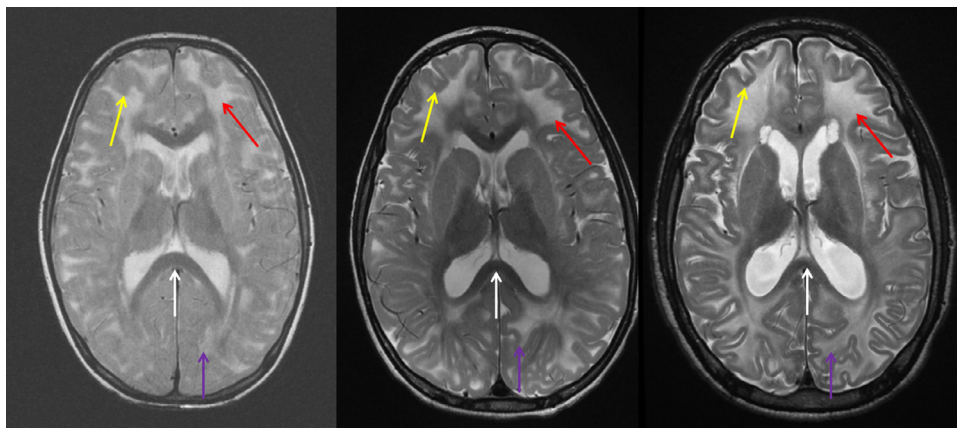

Fig. 1 – T2W MRI images of the patient aged 4 (left), 7 (middle) and 15 (right) years highlighting the increasing prominence of gyral broadening. Over the course our patient's childhood, there is clear broadening and rarefaction of cortical gyri (yellow arrows) secondary to expanding high T2 white matter oedema. The marked high T2 signal seen in the frontal subcortical white matter (red arrows) demonstrates an anterior to posterior gradient over time (purple arrows). The splenium of the corpus callosum remains spared of high T2 signal change throughout the disease process (white arrows). (Color version of figure is available online.)
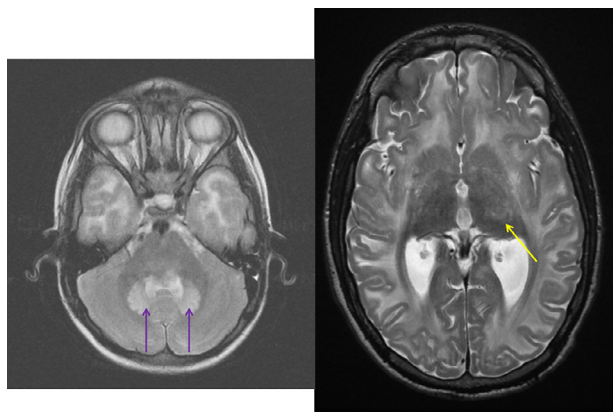
Fig. 2 – Aged 4 years (right) and 15 years (left). T2W images show involvement of the dentate nucleus (purple arrows) and thalamus (yellow arrow). Whilst the dentate nucleus is thought to be an area involved in L2HGA, there can be considerable variability in appearances and several patients have been reported with dentate nucleus sparing [12]. Thalamic involvement is not a typical finding of the disease however has been noted as a feature seen in patients with L2HGA. Due to the predominant subcortical white matter involvement in L2HGA, the disease is often grouped in the leukodystrophy category; however as we can see, deep grey nuclei involvement in the latter stages means that this is not strictly accurate. (Color version of figure is available online.)

of the specialist metabolic team with regular input from the neurology department regarding best supportive care.

Imaging findings

On MRI, findings progressed as the patient aged and became more symptomatic (Figs. 1–5).

Differential diagnosis

In this particular case, the patient had already been given a diagnosis of L2HGA based on gold-standard laboratory urine testing, which is highly specific and little else would be likely to give such findings.
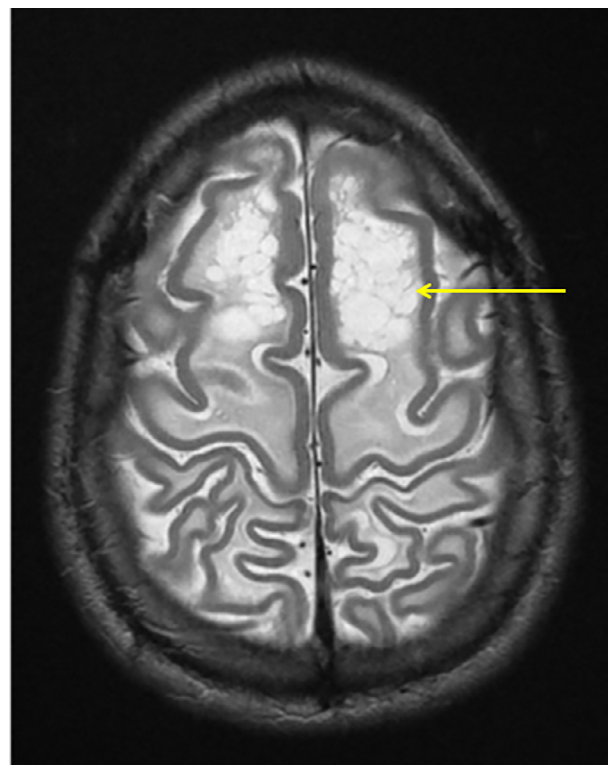

Fig. 4 – Aged 15 years, later features of L2HGA. T2W image demonstrating extensive white matter signal changes and subcortical U-fibre involvement. There is new cystic degeneration most prominent in the anterior frontal lobes (yellow arrow). This pattern of cystic change would be expected to take the same anterior to posterior course by which white matter signal change is seen.

However there are many times where a patient has an MRI scan prior to a suspected metabolic abnormality, which is when awareness of imaging features in L2HGA is highly important to suggestion to the correct diagnosis.

Abnormal high T2 signal changes start at the subcortical U-fibres in a multi-focal distribution, taking an anterior to posterior gradient and coalescing over time. This is often described as a 'centripetal pattern', to which few other diseases exhibit this feature.

One of these few is Canavan disease. A distinguishing feature in Canavan's however includes additional involvement of
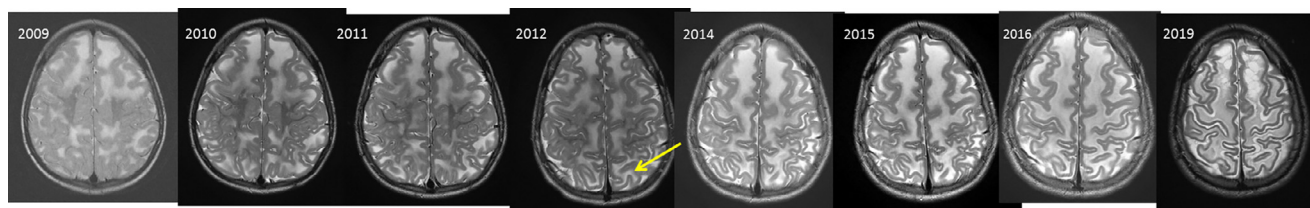

Fig. 3 – Aged 7 years, pattern of subcortical U-fibre involvement through time. One of the most striking features of L2HGA is progressive involvement of subcortical U-fibres. Whilst nonspecific, it can be seen from early stages of the disease (yellow arrow), and continues to progress as the patient ages. (Color version of figure is available online.)
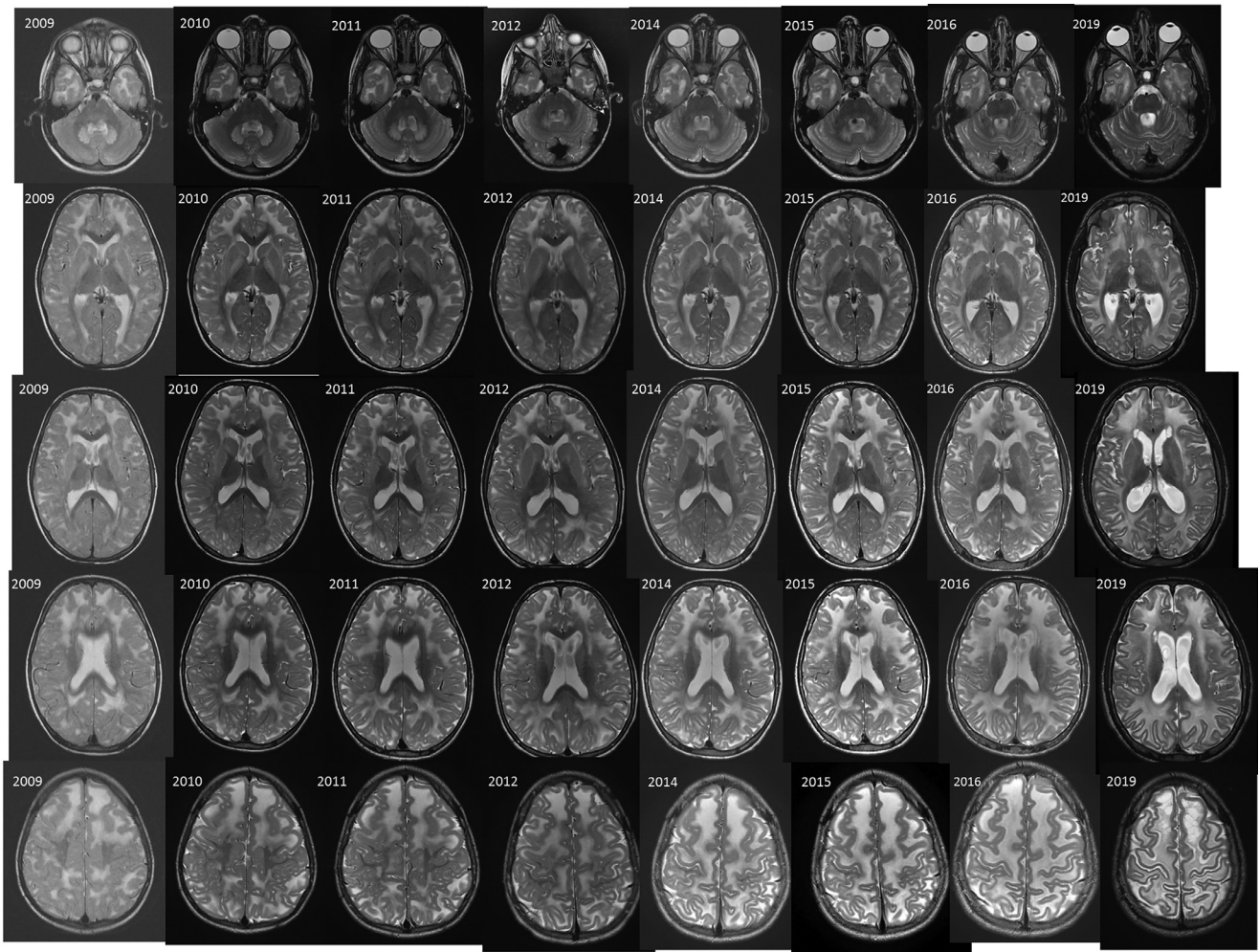
Fig. 5 – An overview of radiological findings in our patient aged 4 to 15 years demonstrating the diffuse, and progressive, nature of brain involvement in L2GHA.

the brainstem, with relative sparing of the basal ganglia and dentate nuclei [1].

The other differential to consider is Kearns-Sayre syndrome, however here there is additional involvement of the brainstem and thalami, with mineralised appearances of the globus pallidus and caudate nuclei on CT.

Discussion

First reported in 1980, and with little over 100 documented cases worldwide, L2HGA is a rare inherited metabolic condition associated with progressive brain damage and elevated levels of L-2-hydroxylate [2]. Only in 2004 was it discovered that L2HGA arises from a mutation in the L2HDGH gene, which is inherited in an autosomal recessive fashion [3,4]. Although a rare disease, L2HGA has been shown to be more common in cases of consanguineous parents [5].

Whilst l-2-hydroxyglutarate has no function, it is thought that it may represent a toxic degraded by-product that has been formed from the action of the l-2-dehydroxyglutarate dehydrogenase enzyme [6,7].

Signs and symptoms may begin in early childhood and, as in our case, may be associated with developmental delay, seizures and co-ordination difficulties [8,9]. Further manifestations can include cerebellar ataxia and a variable degree of macrocephaly [8,10].

The mainstay of neuroimaging in L2HGA is the predominant involvement of anterior subcortical white matter. Early patterns of white matter disease can be nonspecific, therefore annual surveillance MRI is performed to monitor disease progression and assess response to treatment, whilst helping to confirm the pattern of disease spread [11]. Imaging changes may occur before the onset of symptoms, therefore significant changes on serial imaging may be used to predict an expected deterioration in symptoms.

The basal ganglia and white matter are commonly affected in early infancy [12], with potential for further abnormality in the lentiform, caudate and invariably, dentate nuclei (Fig. 3B) [13,14].

The pattern of disease seen in our patient correlates consistently with findings observed by Steenweg et al. [13], who in a cohort of 56 patients found that the subcortical white matter and deep grey matter structures were most likely to be

Table 2 – A summary of key MRI signal characteristics seen in L2HGA.	
MRI feature	Signal characteristic
T1	Low
T2/FLAIR	High
T1 + Gadolinium contrast	No enhancement
Diffusion restriction imaging (DWI)	Low (No diffusion restriction)
Susceptibility weighted imaging (SWI)	No signal
MR Spectroscopy (MRS)	Reduced NAA and Cho peaks increased myo-inositol peak

Key learning points

- L2HGA is an inherited autosomal recessive disease seen more frequently in consanguineous parents.
- The gold standard of diagnosis in L2HGA is laboratory urine testing; however, there will be instances where patients present with imaging prior to a formal investigation of organic acids.
- Key imaging features on MRI are T2 hyperintensities predominantly in the anterior subcortical white matter and basal ganglia, classically involving the subcortical U-fibres.
- There is further potential for involvement of the caudate, lentiform and dentate nuclei.
- L2HGA characteristically spares the brainstem and corpus callosum, which can be used to differentiate from other conditions such as Canavan disease and Kearn-Sayre syndrome.
- Patients with L2HGA may exhibit stable clinical symptoms and imaging appearances for a number of years. However, this can then be followed by a sporadic and marked increase in disease severity, which is correlated by the change in intracranial appearances seen on MRI.

affected in L2HGA. In older patients, cerebral and to a lesser extent, cerebellar atrophy was also seen demonstrating the longer term implications of the disease. However, this study did not follow any of the patient's through time, therefore the exact evolution of the disease process, and associated radiological findings, were not assessed.

Characteristic areas of sparing include the brainstem, corpus callosum, and cerebellar white matter, which can be used to differentiate from other causes such as Canavan disease.

Subcortical cystic degeneration has in a few cases been described as a late manifestation of L2HGA [15], our patient included (Fig. 4 and Table 2).

L2HGA is occasionally referred to as a leukoencephalopathy, however, involvement of the deep grey basal ganglia means this is not strictly true (Fig. 4).

There is limited data regarding MR spectroscopy (MRS) findings, however there it has been shown that there are peaks of myoinositol, along with glutamate, glutamine and L2-hydroxyglutaric acid in between 1.9 to 2.5 ppm. This is coupled with decreased peaks of NAA and choline [16].

Whilst no long-term sequelae have been shown to arise directly from L2HGA, there has been suggestion that patients could be at increased risk of developing CNS tumors [17]. However, further research is required to support this as a true association.

It should be reiterated that this case demonstrates a timeline of findings seen in a single patient through time and, as in any disease process, there can be considerable interpatient variability in both the clinical and radiological presentation. Therefore, whilst we are able to highlight key findings seen in our patient's timeline, this pattern of evolution may not necessarily be replicated in every patient with a diagnosis of L2HGA.

To conclude, L2HGA can be a highly debilitating metabolic disease with a known genetic element. Due to limited availability research into L2HGA, there are few effective treatments available and of those, they are largely based upon symptomatic management. The disease demonstrates continuous progression, and can be monitored both biochemically and radiologically.

With this in mind it is important for the paediatric neuroradiologist to be aware of the radiological features involved in L2HGA, as there may not always be a preceding biochemical test. It is in these situations that the radiologist can prove crucial in suggesting the initial diagnosis.

REFERENCES

[1] Topçu M, Erdem G, Saatçi I, Aktan G, Simşek A, Renda Y, et al. Clinical and magnetic resonance imaging features of L-2-hydroxyglutaric acidemia: report of three cases in comparison with Canavan disease. J Child Neurol 1996;11373-:377.

[2] Fourati H, Ellouze E, Ahmad M, Chaari D, Kamoun F, Hsairi I, et al. MRI features in 17 patients with L2 hydroxyglutaric aciduria. Eur J Radiol Open 2016;3:245–50.

[3] Topçu M, Jobard F, Halliez S, Coskun T, Yalçinkayal C, Gerceker FO, et al. l-2-Hydroxyglutaric aciduria: identification of a mutant gene C14orf160, localized on chromosome 14q22.1. Hum Mol Genet 2004;13:2803–11.

[4] Rzem R, Van Schaftingen E, Veiga-da-Cunha M. The gene mutated in l-2-hydroxyglutaric aciduria encodes l-2-hydroxyglutarate dehydrogenase. Biochimie 2006;88:113–16.

[5] Kranendijk M, Struys EA, Salomons GS, Van der Knaap MS, Jakobs C. Progress in understanding 2-hydroxyglutaric acidurias. J. Inherit. Metab. Dis. 2012;35(4):571–87.

[6] Rzem R, Vincent MF, Van Schaftingen E, Veiga-da-Cunha M. l-2-Hydroxyglutaric aciduria, a defect of metabolite repair. J Inherit Metab Dis 2007;30:681–9.

[7] Struys EA, Gibson KM, Jakobs C. Novel insights into l-2-hydroxyglutaric aciduria: mass isotopomer studies reveal 2-oxoglutaric acid as the metabolic precursor of l-2-hydroxyglutaric acid. J Inherit Metab Dis 2007;30:690–3.

[8] Barth PG, Hoffmann GF, Jaeken J, Wanders RJA, Duran M, Jansen GA, et al. l-2-Hydroxyglutaric acidaemia: clinical and biochemical findings in 12 patients and preliminary report on l-2-hydroxyacid dehydrogenase. J Inherit Metab Dis 1993;16:753–61.

[9] Moroni I, D'Incerti L, Farina L, Rimoldi M, Uziel G. Clinical, biochemical and neuroradiological findings in l-2-hydroxyglutaric aciduria. Neurol Sci 2000;21:103–8.

[10] Topçu M, Aydin OF, Yalçinkaya C, Haliloğlu G, Aysun S, Anlar B, et al. l-2-Hydroxyglutaric aciduria: a report of 29 patients. Turk J Pediatr 2005;47:1–7.

[11] Van der Knaap MS, Breiter SN, Naidu S, Hart AA, Valk J. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. Radiology. 1999;213(1):121–33.

[12] Seijo-Martinez M, Navarro C, Castro del Rio M, Vila O, Puig M, Ribes A, et al. L-2-hydroxyglutaric aciduria: clinical, neuroimaging, and neuropathological findings. Arch. Neurol. 2005;62(4):666–70. doi:10.1001/archneur.62.4.666.

[13] Steenweg ME, Salomons GS, Yapici Z, Uziel G, Scalais E, Zafeiriou DI, et al. L-2-Hydroxyglutaric aciduria: pattern of MR imaging abnormalities in 56 patients. Radiology. 2009;251(3):856–65.

[14] D'Incerti L, Farina L, Moroni I, Uziel G, Savoiardo M. l-2-Hydroxyglutaric aciduria: MRI in seven cases. Neuroradiology 1998;40:727–33.

[15] Larnaout A, Hentati F, Belal S, Ben Hamida C, Kaabachi N, Ben Hamida M. Clinical and pathological study of three Tunisian siblings with L-2-hydroxyglutaric aciduria. Acta Neuropathol. 1994;88(4):367–70.

[16] Goffette SM, Duprez TP, Nassogne MC, Vincent MF, Jakobs C, Sindic CJ. L-2-Hydroxyglutaric aciduria: clinical, genetic, and brain MRI characteristics in two adult sisters. Eur J Neurol. 2006;13(5):499–504.

[17] Patay Z, Mills JC, Löbel U, Lambert A, Sablauer A, Ellison DW. Cerebral neoplasms in L-2 hydroxyglutaric aciduria: 3 new cases and meta-analysis of literature data. AJNR Am J Neuroradiol. 2012;33(5):940–3.