



Abstract

L-2 Hydroxyglutaric Aciduria and Anaplastic Oligodendroglioma: A Rare Association

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L-2 hydroxyglutaric aciduria (L2HGA) is an inherited neurometabolic disease characterized by elevated levels of L-2 hydroxyglutaric acid in urine, plasma, and cerebrospinal fluid. The disease has a progressive clinical course presenting with ataxia, seizure, and psychomotor retardation. Magnetic resonance imaging (MRI) is helpful to make the diagnosis by providing specific findings, such as subcortical white matter, symmetrical globi pallidi, and dentate nuclei hyperintensities, on T2-weighted images. Another important role of MRI is to detect associated intracranial malignancies in patients with L2HGA. The association between L2HGA and cerebral neoplasms has not been clearly elucidated to date; however, a few cases reports in the literature support this association. We report a patient with L2HGA associated with anaplastic oligodendroglioma and review the relevant literature.

Keywords: Metabolic disorders, L-2 Hydroxyglutaric aciduria, malignant brain tumor, oligodendroglioma, magnetic resonance imaging, magnetic resonance spectroscopy

Introduction

L-2 hydroxyglutaric aciduria (L2HGA) is a very rare autosomal recessive, inherited disease, which presents with ataxia, epilepsy, developmental retardation, and macrocephaly (1, 2). L2HGA levels in cerebrospinal fluid (CSF) and plasma are increased. However, the elevation in urine is essential to make a precise diagnosis (3). Magnetic resonance imaging (MRI) findings of the bilateral symmetrical globi pallidi, dentate nuclei, subcortical white matter involvement with preserved cerebellar white matter, and thalami are peculiar to L2HGA (3, 4). Intracranial neoplasms can be observed in a small number of patients (5-7). Diagnosis of an intracranial neoplasm in a patient with L2HGA may be challenging because of common neurological symptoms and signs that both L2HGA and neoplasms can cause. Herein, we present a patient with L2HGA associated with anaplastic oligodendroglioma and review the current literature.

Case Report

An 11-year-old boy presented with afebrile convulsion. His physical examination revealed psychomotor delay, ataxia, and macrocephaly. His family history was unremarkable. Complete blood count, routine blood biochemical parameters, and urinalysis were within normal limits. Contrast-enhanced cranial MRI was performed to display a possible intracranial epileptogenic lesion. MRI demonstrated extensive white matter hyperintensity predominantly involving the subcortical white matter (U-fibers) and symmetrical globi pallidi and dentate nuclei hyperintensities on T2-weighted and fluid attenuation inversion recovery images. Periventricular and cerebellar white matter, bilateral thalami, and putamina were spared. Additionally, there was a small non-enhancing lesion lateral to the left basal ganglia, which could be visualized only in a single-section axial T2-weighted image (Figure 1). These findings were highly suggestive of a neurometabolic disease, particularly L2HGA. Therefore, organic acid analysis of his urine was performed, which yielded elevated L2HGA levels (920 mmol/mol creatinine). The diagnosis of L2HGA was made on the basis of radiological findings and elevated urine L2HGA levels. Oral antiepileptic therapy was initiated, and a control MRI was arranged on the third month for the follow-up of the small focal lesion. However, the patient did not visit for the scheduled follow-up MRI examination. Six months later, the patient was admitted with anisocoria, right hemiplegia, and right central facial paralysis after the recurrence of epileptic seizures. A contrast-enhanced MRI revealed a significant increase in the size of the previously noted focal lesion in the left cerebral hemisphere, showing slight enhancement on post-contrast T1-weighted images and marked mass effect. On diffusion-weighted MRI, the lesion did not show significant restriction. Marked perilesional vasogenic brain edema and the effacement of the sulci midline, shifting to the right (subfalcine herniation) were

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observed (Figure 2). The vasogenic edema was indistinguishable from the affected white matter due to L2HGA. Single-voxel magnetic resonance (MR) spectroscopy was performed, which revealed a prominent increase in choline levels, a marked decrease in N-acetyl aspartate peak, and a high choline/N-acetyl aspartate ratio compatible with a high-grade glioma (Figure 3). A biopsy was performed, which yielded anaplastic oligodendroglioma.

Patient's family was informed, and their verbal consent was obtained to report the case.

Discussion

L2HGA is a rare neurometabolic disorder with a gene defect of L-2 hydroxyglutarate dehydrogenase (L2HGDH) located on the 14q22.1 chromosome (8, 9). The defect of the L2HGDH gene results in the accumulation of L2HGA in body fluids and tissues. The accumulation of L2HGA in brain tissues has been proposed to have two important effects. The first effect is encephalopathy, which occurs in a slow chronic process and is typically observed in all L2HGA patients. The second effect is an oncogenic effect, which is still in the hypothesis stage and appears as an intracranial neoplasm in a small number of patients (9, 10).

An association between intracranial neoplasms and L2HGA was suggested on the basis of some case reports. In total, 15 cases with L2HGA associated with intracranial tumor have been reported to date (Table I) (3, 5-7, 11-15). One of the previously reported cases of L2HGA related to intracranial tumor did not have a histopathological assessment (6). Only one patient with oligodendroglioma was reported as was the case of our patient (7). The mass was located in the supratentorial region in 12 cases, located in the infratentorial region in two cases, and the localization of the mass was not known in one report (7). Additionally, a calvarial osteoma and a Wilms tumor accompanying L2HGA have been reported in the literature; however, they are considered to be coincidental coexistence (16, 17). There are a few comments regarding the occurrence of oncogenesis in L2HGA patients. Firstly, IDH1 and IDH2 gene defects were suspected, which were proven to have a role in the development of astrocytoma by inhibiting histone demethylation and promoting the proliferation of astrocytes. Nevertheless, the accumulated organic acid in this case is D-2 hydroxyglutaric acid, the enantiomer of that accumulated in L2HGA (10, 18). Secondly, epidermal growth factor receptor amplification has been identified in a patient with L2HGA who developed anaplastic astrocytoma, which was thought to be related to demyelination and the oncogenic effect of accumulated L2HGA (10). This finding has been described in one report, and more data are needed to illuminate the effect of epidermal growth factor receptor on oncogenesis.

Selective peripheral involvement of the cerebral white matter (U-fibers) in early stages of the disease is a typical MRI finding of L2HGA that helps to differentiate it from other neurometabolic diseases. The presence of a combination of peripheral white matter involvement with a bilateral involvement of globi pallidi and dentate nuclei is highly suggestive the diagnosis being made (7, 19). In contrast, to diagnose an intracranial mass in this patient group may be challenging because of the marked parenchymal changes, such as diffuse white matter hyperintensity, caused by L2HGA (5). Moreover, clinical find-

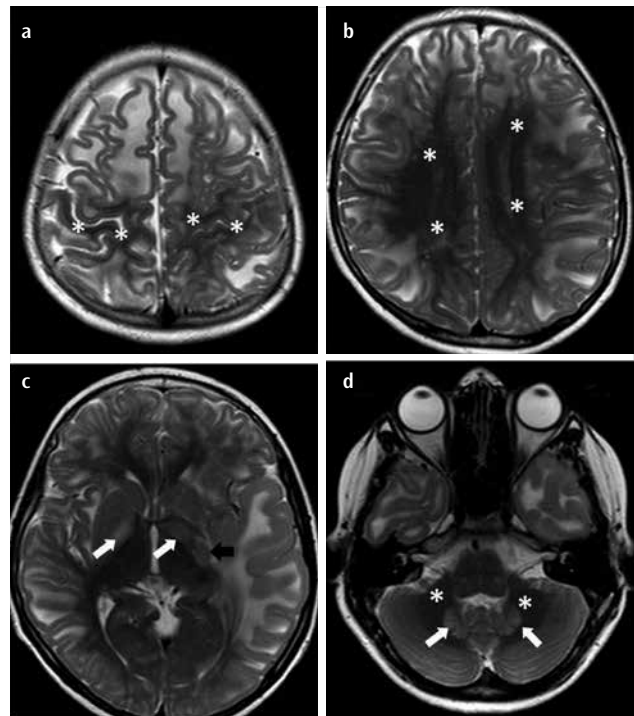


Figure 1. a-d. Subcortical white matter hyperintensity with centripetal involvement is seen on T2-weighted axial images. Note that periventricular and periolandic subcortical white matter is relatively spared (asterisks) (a, b). Bilateral globi pallidi and dentate nuclei hyperintensities are seen (white arrows) (c, d). A small focal lesion lateral to the left basal ganglia is seen (black arrow) (c). The cerebellar white matter is spared (asterisks) (d)

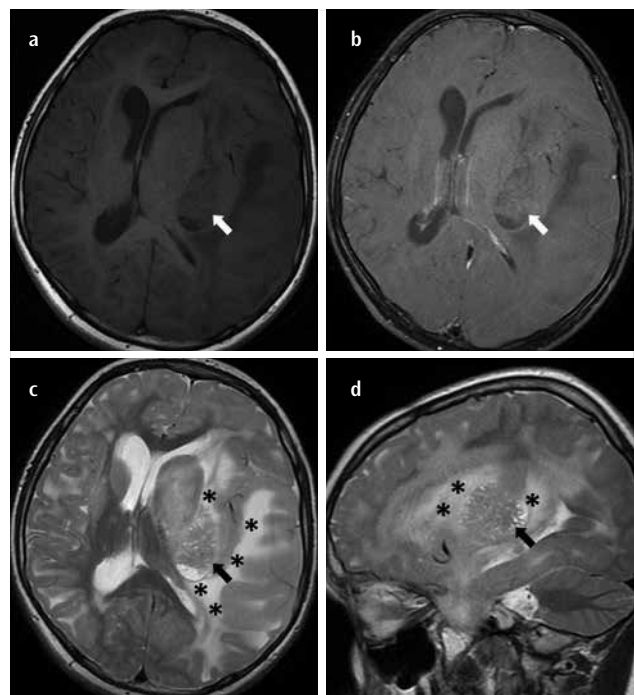


Figure 2. a-d. Control MRI examination performed 6 months after the first MRI examination demonstrated the progression of the left cerebral mass (white arrows), which shows minimal contrast enhancement on T1-weighted images (a, b). Axial and sagittal T2-weighted images demonstrate a heterogeneous mass lesion (black arrows) with small cystic component and perilesional vasogenic edema (asterisks) (c, d). The left basal ganglia and lateral ventricles are compressed. Midline shift to the right due to subfalcine herniation is seen (c)

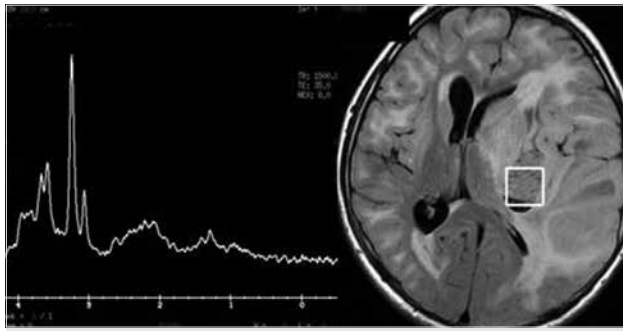


Figure 3. Single-voxel MR spectroscopy with short TE (TE=35 ms) reveals an elevated choline peak at 3.2 ppm and marked decrease of N-acetyl aspartate peak at 2.0 ppm
TE: time of echo; MS: milliseconds; PPM: parts per million

Table 1. Review of histopathological diagnoses in previously reported l2hga cases associated with intracranial neoplasia

Case number	Author, year	Age (years)	Histopathologic diagnosis
1	Wilcken et al. (15), 1993	15	PNET
2	Barbot et al. (11), 1997	10	Astrocytoma
3	Wanders et al. (14), 1997	10	Low-grade astrocytoma
4	Ozisik et al. (13), 2002	3	Medulloblastoma
5	Moroni et al. (6), 2004	13.5	PNET
6	Moroni et al. (6), 2004	26	Glioblastoma
7	Moroni et al. (6), 2004	18	-
8	Moroni et al. (6), 2004	12	Low-grade astrocytoma
9	Topcu et al. (3), 2005	-	Medulloblastoma
10	Haliloglu et al. (12), 2008	11	Glioblastoma
11	Haliloglu et al. (12), 2008	3	Medulloblastoma
12	Aghili et al. (5), 2009	17	Anaplastic ependymoma
13	Patay et al. (7), 2012	23	Anaplastic astrocytoma
14	Patay et al. (7), 2012	36	Low-grade glioma
15	Patay et al. (7), 2012	19	Oligodendroglioma

L2HGA: L-2 hydroxyglutaric aciduria; PNET: primitive neuroectodermal tumor
Data from references: 3, 5-7, 11-15.

ings of the primary disease can mask the neurologic deficits resulting from the mass (5). MR spectroscopy can be helpful in differentiating neoplastic lesions from their mimics in patients with L2HGA. In our case, MR spectroscopy revealed that the lesion was consistent with a high-grade glioma on the basis of high choline and low N-acetyl aspartate levels, which were subsequently confirmed on histopathological examination.

Conclusion

L2HGA may create oncogenic effects in brain parenchyma and performing magnetic resonance spectroscopy in addition to contrast-enhanced MRI is the key to make the diagnosis.

Informed Consent: Verbal informed consent was obtained from parents of the patient who participated in this study.

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