L-2-Hydroxyglutaric Aciduria: An Ever-Expanding Phenotypic Spectrum

Sir,

L-2-Hydroxyglutaric aciduria (L-2-HGA) is a rare inborn metabolism error characterized by hydroxyglutaric acid accumulation. The accumulating metabolite could be the levo (L-2-HGA) isomer, less commonly the dextro (D-2-HGA) isomer, and very rarely both types (L-2-HGA and D-2-HGA), each having distinctive features. We report a unique presentation of L-2-HGA.

An eighteen-year-old boy, born to consanguineous parentage, had seizures and intellectual disability from early childhood. Initially, he had generalized tonic–clonic seizures with a recent change in the semiology to left focal seizures, occurring twice weekly. He had three cousins having seizures of varied types of semiology and the death of a paternal uncle due to a central nervous system (CNS) neoplasm. On examination, he had dysmorphic features—low-set ears and macrocephaly, and subnormal mentation. The cranial nerve examination was unremarkable. Motor system examination revealed minimal spasticity and brisk tendon reflexes. Examination of muscle power, sensory system, and cerebellar system was normal. Complete blood counts, liver and renal function tests, serum ammonia, and lactate were normal. Electroencephalography and multimodal evoked potentials were normal. Magnetic resonance imaging of the brain revealed diffuse symmetric T2 hyperintensities in the supratentorial compartment's

subcortical and lobar white matter with a relative sparing of the periventricular white matter, especially in the parieto-occipital regions and the posterior body and splenium of the corpus callosum [Figure 1a-c]. There was an inversion of the signal changes in fluid-attenuated inversion recovery (FLAIR) images in some subcortical regions [Figure 1d]. This was coupled with an ill-defined lesion in the right frontal lobe and insula, demonstrating differential T2 hyperintensity and extension to the right basal ganglia. A mass effect was noted on the ipsilateral lateral ventricle. Diffusion-weighted imaging (DWI) revealed patchy areas of diffusion restriction within the lesion [Figure 1e]. T2-weighted perfusion imaging revealed high relative cerebral blood volume (rCBV) values within the lesion [Figure 1h]. These features along imaging findings on post contrast, SWI and spectrometry [Figure 1f-i] prompted an imaging differential of a metabolic etiology with leukodystrophy and a predisposition to high-grade brain neoplasms, with L-2-HGA being an important consideration. Screening for inborn errors of metabolism by tandem mass spectrometry in the blood and by gas chromatography revealed elevated levels of L-2-HGA in the urine.

A stereotactic biopsy of the lesion was performed, and the histopathology revealed a highly cellular glial neoplasm, composed of small, undifferentiated glial cells, diffusely infiltrating the neuroparenchyma along with a high nuclear: cytoplasmic ratio and brisk mitotic activity. The tumor cells were variably positive for glial fibrillary acidic protein (GFAP) and negative for epithelial membrane antigen (EMA) and synaptophysin. MIB-1 (anti-KI67) labeling was about 20% [Figure 2a-d]. The tumor was negative for IDH1R132H and p53 and showed retained *a-Thalassemia, mental retardation, X-linked syndrome (ATRX)* and *Integrase interactor 1 (INI1)* expression. The histological features were consistent with pediatric-type high-grade glioma (anaplastic astrocytoma, World Health Organization (WHO) grade III).

Genetic analysis with clinical exome sequencing demonstrated a novel homozygous splice acceptor variant c. 257-2A >G in intron 2 of the L2HGDH gene. To our knowledge, the splice acceptor variant NM_024884.3(L2HGDH):c. 257-2A >G has not been reported previously as a pathogenic or benign variant. The c. 257-2A>G variant is novel in databases such as gnomAD,

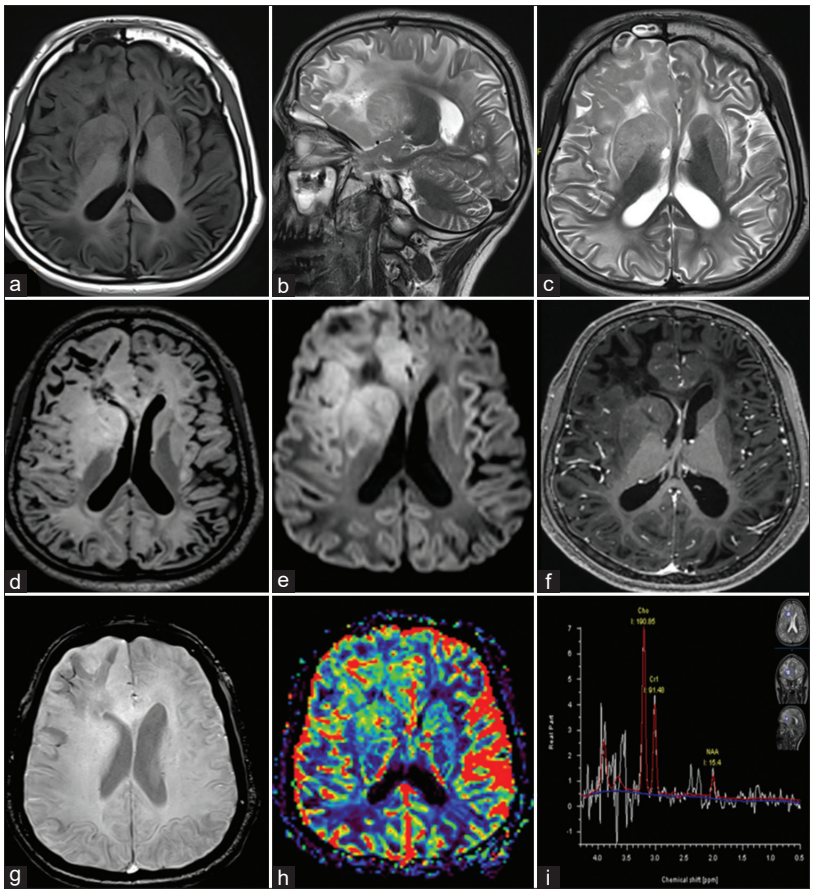

Figure 1: MRI brain axial (a) T1-weighted image (T1WI) sections showing symmetric T1 hypointensity in the subcortical and deep white matter of bilateral cerebral hemispheres with corresponding areas of hyperintensities on sagittal (b) and axial (c) T2-weighted image (T2WI) sections. A diffusely infiltrative T2 hyperintense lesion showing differential signal intensity in the frontal region, extending into the genu of the corpus callosum (star). Axial FLAIR (d) images show patches of inversion in the subcortical white matter. Patchy areas of diffusion restriction on the axial DWI sequence (e) are seen within the lesion. No enhancement was noted (f). Foci of blooming on SWI images (g) along the subcortical white matter are seen. Axial Dynamic susceptibility contrast MRI (DSC) map (h) of rCBV demonstrates elevated perfusion in the areas corresponding to the right frontal mass, suggesting neoplasm. Single voxel spectrometry (i) shows the elevation of choline peak with the reduction in N-acetyl aspartate (NAA)

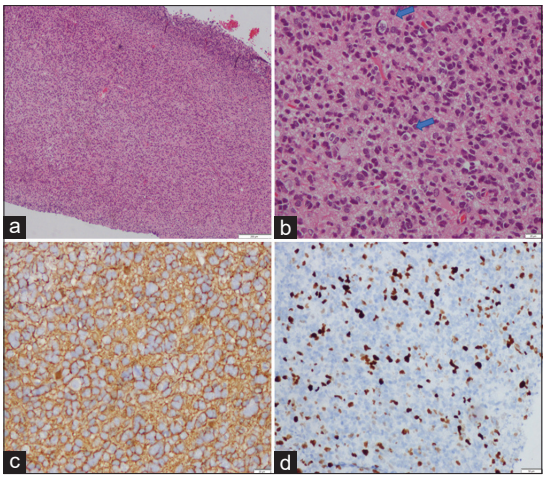

Figure 2: Stereotactic biopsy shows a linear fragment of neuroparenchyma, diffusely infiltrated by a highly cellular glial neoplasm (a). The tumor cells are small and undifferentiated, with a high N: C ratio. Few overrun neurons are seen (arrows) (b). The thin rim of the tumor cell cytoplasm and the glial stroma is GFAP-positive (c). MIB-1 labeling is high (d). Magnification is indicated by the scale bar

1000 Genomes, and our in-house database. This variant mutates a consensus splice acceptor sequence for an exon upstream from the last coding exon. It is predicted to disrupt the reading frame, resulting in nonsense-mediated decay of the clinically relevant transcript. The c. 257-2A >G variant is a loss-of-function variant in the gene L2HGDH, which is intolerant of loss-of-function variants, as indicated by the presence of existing pathogenic loss-of-function variant NP_079160.1:p.M1Lfs*32 and ten others. In addition, the proband's clinical phenotype matches the disorder caused by pathogenic variants in the L2HGDH gene. For these reasons, this variant was classified as pathogenic, confirming the diagnosis of L-2-HGA.

The biopsy and genetic reports were discussed with the patient's family, and given the tumor burden, an option of whole-brain radiotherapy was given. The family opted for a conservative approach.

No further seizures were reported after optimizing antiseizure medications (ASMs). Twelve months later, the patient developed progressive left hemiparesis and slurred speech and gradually became bedbound. Seventeen months after the initial diagnosis, the patient expired, possibly due to aspiration. No postmortem autopsy was performed.

L-2-HGA was first described in 1980 in a five-year-old boy with mental and motor retardation.[1] Click or tap here to enter text. In the subsequent reports, varied ages of onset and several features including cerebellar ataxia, seizures, pyramidal system, or extrapyramidal system involvement were identified.[2-5] Macrocephaly in the presence of leukodystrophy on imaging was commonly reported. The majority of patients developed new neurological deficits for illness, including left hemiplegia, spastic quadriparesis, raised intracranial pressure syndrome, and modifications in seizure semiology or frequency.[3,4]

Unlike the precipitous course of other organic acidurias, a slowly progressive course was observed. Beginning with Wilcke *et al*.'s report of a child with L-2-HGA developing a Primitive neuroectodermal tumor (PNET), the peculiar association between cerebral neoplasm and abrupt neurological deterioration was noted consistently.[3,4,6,7] This led to the hypothesis that perhaps L-2-HGA predisposes CNS malignancies.[8] Around 24 patients with CNS malignancies have been reported in the last three decades.[3,4,7-15]Click or tap here to enter text. The coexistence of white matter abnormalities on magnetic resonance imaging (MRI) with cerebral neoplasms is a unique feature of L-2-HGA and can be an important clue to the diagnosis. CNS neoplasms associated with L-2-HGA include astrocytoma, medulloblastoma, undifferentiated gliomas, and PNET.[3,4,7-15] A supervening, new, often rapidly deteriorating neurological syndrome in the background of a preexisting baseline deficit led to the identification of the tumor. Patients with L-2-HGA-related CNS tumors experienced a range of outcomes. Eleven patients expired within 1–2 years of tumor diagnosis. Patients' chances of survival are influenced by tumor pathology, location, and severity of neurologic deficits.[7-15]

Six patients underwent genetic analysis.[9,12-15] Unlike in our case, all the previous patients had exonic mutations, which are missense mutations.

Usually, L2HGDH metabolizes 2-hydroxyglutarate to alpha-ketoglutarate in the cell, thus preventing the toxic buildup of the former. In the absence of L2HGDH, the buildup of 2-hydroxyglutarate causes both myelotoxic and carcinogenic effects.[16] A similar buildup of 2-hydroxyglutarate had been previously observed in patients with high-grade gliomas with IDH1 mutations.[17] Whether an acquired IDH1 mutation was responsible for the tumorigenesis was studied in our patient, and another report was found in the tissue biopsy.[13]Click or tap here to enter text. However, the tumor tested negative for Isocitrate dehydrogenases (IDH) mutations in both. Thus, presumably, there are other mechanisms for tumorigenesis.

To summarize, in a child with macrocephaly and progressive psychomotor retardation, it is apt to consider L-2-HGA as a differential diagnosis. Also, if the patient develops a new-onset, rapidly progressive neurological deficit, an MRI brain can help identify malignancies. The presence of white matter abnormalities along with cerebral neoplasms should raise suspicion of L-2-HGA in appropriate clinical settings.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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