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The Wide Phenotypic Spectrum of L-2 Hydroxyglutaric Aciduria in Adults

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We read with great interest the case report from Shah and colleagues who described a previously undiagnosed 28-year-old woman with developmental delay, cognitive impairment, seizures, and a progressive spinocerebellar syndrome since early childhood due to L-2 hydroxyglutaric aciduria (L2HGA).[1] Indeed, the clinical presentation of this rare neurometabolic disorder is highly variable. Progressive spinocerebellar signs and a range of movement disorders, such as dystonia and myoclonus are often documented. We here wish to further highlight the phenotypic variability of adults with L2HGA and contribute unpublished cases of two brothers, who presented with a combination of neurological and neuropsychiatric symptoms and signs, and where distinct neuroimaging findings enabled correct diagnosis.

Both siblings, born of consanguineous parents, have a history of developmental delay with mild intellectual disability, and unremarkable family history. The older 32-year-old brother (case 1), presented with chronic headaches since the age of 19, as well as forgetfulness and hypersomnia (sleeping approx. 16 hrs/day). He reported being disturbed by intermittent tremulousness of the upper extremities and required help for certain tasks such as shaving. Increased impulsivity was noted. On examination, we documented difficulties to initiate volitional saccades, mild dysdiadochokinesia and intention tremor of the upper extremities (Video S1). The younger brother is a 29-year-old male who complained of continuous back pain. He also reported suffering from impulsivity and poor anger control. On neurological examination, impaired initiation of volitional saccades, dystonic arm posturing and mild truncal dystonia, spasticity of the lower limbs, dysdiadochokinesia, and impaired tandem stand (Video S2) were noted. Brain MRI in both cases revealed severe leukoencephalopathy (Fig. 1), and urinary organic acid and chiral analyses confirmed the diagnosis of L2HGA. Subsequent genetic analyses revealed a pathogenic homozygous mutation in *L2HGDH* (c.528G>T). Both brothers receive carnitine and riboflavin supplementation.[2]

The cases we present here demonstrate that beyond a positive history of developmental delay and intellectual disability, which are almost universally present,[3] the clinical presentation of adults with L2HGA could be highly variable and mild features could often go undetected. Importantly, the clinical presentation in adulthood can be quite different from the classical phenotype in childhood. We also noted the presence of saccadic initiation difficulties in both cases and suggest that this might serve as a useful diagnostic clue, specifically in adults with spinocerebellar signs and neuropsychiatric features. Brain MRI, as described by Shah et al., and also documented in our cases, is typically characteristic. MR spectroscopy reveals reduced N-acetylaspartate and choline peaks.[4] Importantly, as L2HGA predisposes to the growth of cerebral neoplasms, regular imaging studies of the brain are advised.[5]

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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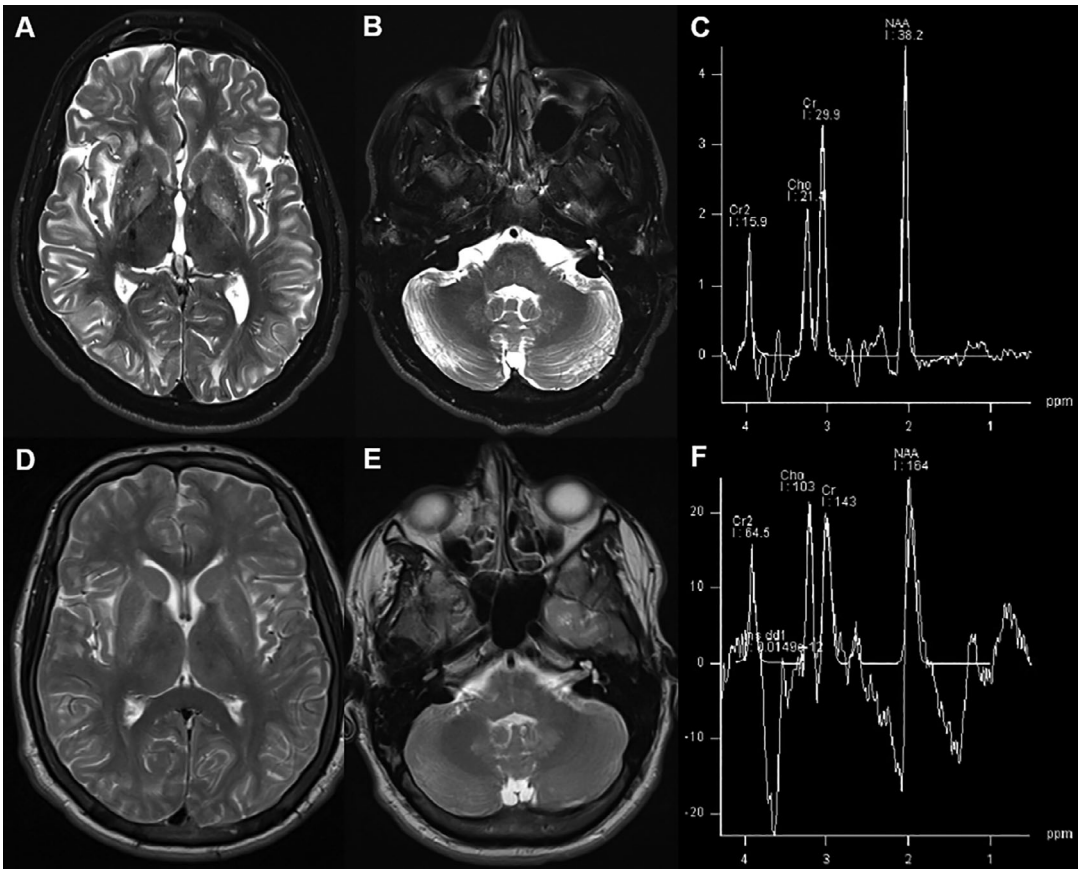

FIG 1. Axial cerebral magnetic resonance imaging (T2 weighted sequences) shows marked symmetrical leukoencephalopathy with basal ganglia involvement and hyperintensities of the dentate nucleus (**A**, **B**: case 1; **D**, **E**: case 2). Magnetic resonance spectroscopy indicates a reduction of N-acetylaspartate and choline peaks in case 1 (**C**) and a slight reduction of the choline peak in case 2 (**F**).

Disclosures

Ethical Compliance Statement: This work was conducted in accordance with the Declaration of Helsinki. The authors confirm that the approval of an institutional review board was not required for this work. The patients and their legal guardians gave informed consent including being videotaped for publication online. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Video S1. On oculomotor examination, the 32-year-old male showed normal smooth pursuit and reflexive saccades, whilst he had marked difficulties to initiate volitional saccades. There was no bradykinesia. Mild dysdiadochokinesia was noted. Luria's fist-edge-palm test was impaired. There was intention tremor on both sides. Tandem gait was not impaired.

Video S2. The 29-year-old younger brother showed broken smooth pursuit and marked difficulties to initiate and maintain volitional saccades on oculomotor examination. Dystonic posture of the hands and trunk were noted. Dysdiadochokinesia of the upper extremities was seen. There was spasticity of the lower extremities. Tandem stand was impaired.