

3-Methylglutaconic Aciduria Type I

A Rare Cause of Late-Onset Leukoencephalopathy

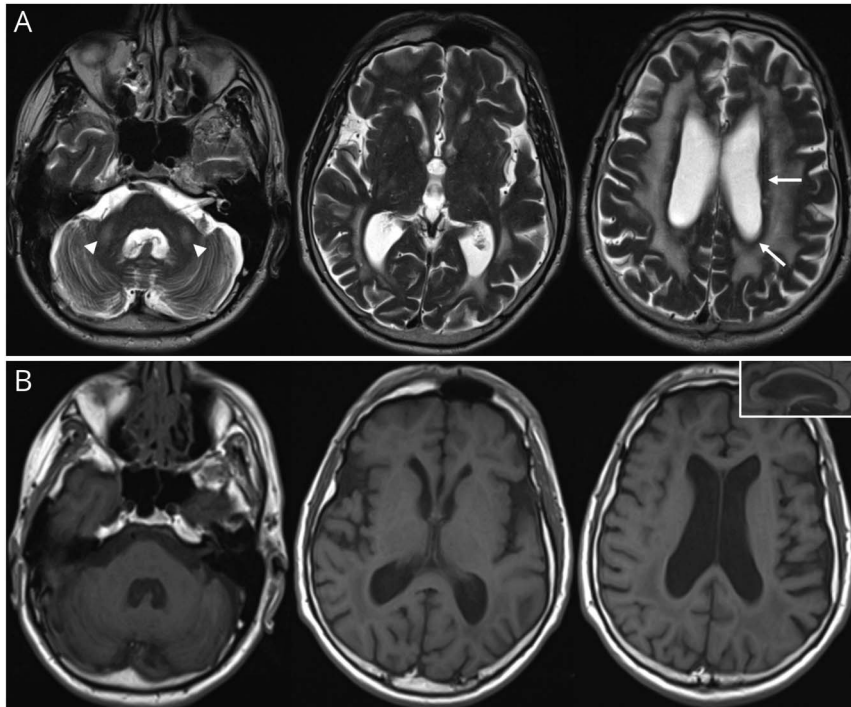
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Neurol Genet 2022;8:e200023. doi:10.1212/NXG.000000000200023

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Figure 1 Brain MRI Findings in 3-Methylglutaconic Aciduria



(A) Axial T2-weighted images showing a diffuse WM hyperintensity with the characteristic sparing of a periventricular rim (arrows) and U-fibres and involvement of middle cerebellar peduncles (arrowheads).³ (B) T1-weighted WM hypointensity, corpus callosum thinning (inset), and mild-to-moderate cerebral atrophy are also evident. WM = white matter.

A 61-year-old man presented with a 7-year-history of slightly progressive unsteadiness. At neurologic examination, autonomous ataxic-spastic gait and mild executive-attentional dysfunction were present. Brain MRI showed a diffuse leukoencephalopathy (Figure 1) while cerebral ¹⁸F-DG-PET and nerve conduction studies were unremarkable. The authors made a diagnosis of 3-methylglutaconic aciduria type 1 (MGCA1, OMIM: 250950) by using a custom leukodystrophy-targeted gene panel which led to the identification of a novel, homozygous pathogenic variant in *AUH* (c.996_1004delGCCCCCTCG, p.Arg332_Arg335delinsSer). In

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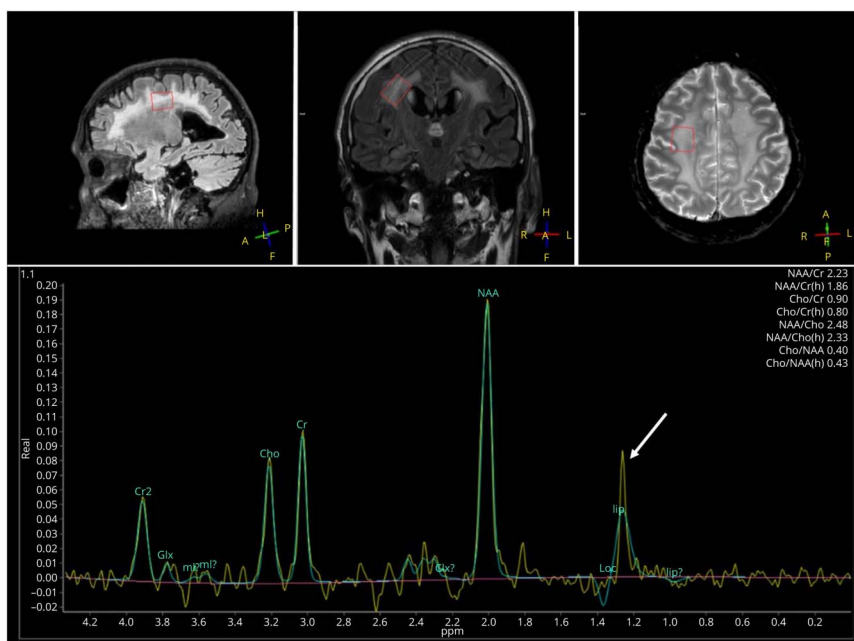
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Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/NG](https://www.neurology.org/NG).

The Article Processing Charge was funded by the authors.

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Figure 2 Brain Proton Magnetic Resonance Spectroscopy (^1H -MRS)



^1H -MRS showing an abnormal metabolite peak among 1.2 and 1.3 ppm likely corresponding to 3-hydroxyisovaleric acid accumulation (white arrow)¹ and normal levels of choline, creatine, and N-acetyl-aspartate.

agreement with the genetic result, the authors subsequently demonstrated a markedly increased urinary excretion of 3-methylglutaconic acid. In fact, the authors had not previously hypothesized the disease for its rarity, and there were neither clinical manifestations (e.g., macrocephaly, psychomotor delay, or learning disabilities) nor neuroimaging findings (e.g., predominantly subcortical white matter abnormalities, widening of the Sylvian fissures, and basal ganglia abnormalities), which could suggest another, more frequent cerebral organic aciduria (e.g., L-2-hydroglutaric aciduria and glutaric acidemia type 1)² and justify urinary organic acid screening. The authors also documented the spectroscopy findings characteristic of the disease (Figure 2).¹ Although very rare,^{3,4} MGCA should be considered in the differential diagnosis of late-onset leukoencephalopathy with ataxia and cognitive impairment.

Study Funding

This study was partially funded by the Italian Ministry of Health (grant RF-2016-02361285 to D. Di Bella) and by the Fondazione Regionale per la Ricerca Biomedica (FRRB grant Care4NeuroRare CP_20/2018 to F. Taroni).

Disclosure

All the authors report no disclosure relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/NG](https://www.neurology.org/NG).

Publication History

Received by *Neurology: Genetics* March 24, 2022. Accepted in final form July 7, 2022. Submitted and externally peer reviewed. The handling editor was Margherita Milone, MD, PhD.

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Appendix *(continued)*

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References

1. Engelke UFH, Kremer B, Kluijtmans LAJ, et al. NMR spectroscopic studies on the late onset form of 3-methylglutaconic aciduria type I and other defects in leucine metabolism. *NMR Biomed.* 2006;19(2):271-278.
2. Wajner M. Neurological manifestations of organic acidurias. *Nat Rev Neurol.* 2019; 15(5):253-271.
3. Eriguchi M, Mizuta H, Kurohara K, et al. 3-Methylglutaconic aciduria type I causes leukoencephalopathy of adult onset. *Neurology.* 2006;67(10):1895-1896.
4. Wortmann SB, Kremer BH, Graham A, et al. 3-Methylglutaconic aciduria type I redefined: a syndrome with late-onset leukoencephalopathy. *Neurology.* 2010;75(12): 1079-1083.

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DOI 10.1212/NXG.0000000000200023

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