




# Cerebellar Bottom of Fissure Hyperintensities in *MT-ATP6*-Associated Ataxia

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*MT-ATP6*-associated disease is caused by mutations in the mitochondrial gene *MT-ATP6*, encoding a subunit of the ATP synthase complex.<sup>1</sup> Clinically, *MT-ATP6* mutations were first associated with a syndrome combining neuropathy, ataxia, and retinitis pigmentosa (NARP syndrome) as well as with Leigh syndrome in more than 50% of patients.<sup>2</sup> However, it has recently been shown that the phenotypic spectrum of *MT-ATP6*-associated disease is much broader, ranging from asymptomatic subjects via rather mild adult-onset CMT-like phenotypes<sup>3</sup> to early-onset multisystemic neurodegeneration.<sup>2</sup>

An 18-year-old female presented with a progressive complex ataxic gait disorder since early childhood. She had learned to walk only at age 3 years with frequent falls persisting and increasing inward rotation of the feet. She lost the ability to walk freely at age 6 years, with full wheelchair-dependency from age 10 years.

Neurological examination showed severe distal muscular atrophies, mild tetraparesis, bidirectional gaze-evoked and upbeat nystagmus in primary position. Distal loss of vibration sensation and absent deep tendon reflexes were noted. Ataxia was apparent by ataxic-paretic

gait, dysmetric heel-shin slide and truncal ataxia, with a Scale for the Assessment and Rating of Ataxia (SARA) score of 17 points at initial examination, worsening to 18.5 points at 1-year-follow-up. Nerve conduction studies showed axonal sensorimotor polyneuropathy. Motor-evoked potentials indicated pyramidal tract lesions. Targeted NGS revealed a known pathogenic homoplasmic *MT-ATP6* mutation (m.8993T > C; p.L156P)<sup>2</sup> that has been associated with a Leigh syndrome clinically and on MRI.

Sequential neuroimaging at age 15 revealed development of T2-hyperintensities (Fig A,B) and corresponding T1-hypointense signal (Fig C,D) at the bottom of cerebellar fissures compared to initial MRI 10 years earlier at age 5 years (Fig E,F).

Ethical approval was granted by the local ethics committee (#598/2011BO1) and written informed consent from the patient and her legal guardian were obtained prior to study inclusion.

MRI signal alterations are frequent findings in mitochondrial disorders, e.g. necrotic, T2-hyperintense lesions of the basal ganglia in Leigh syndrome. In *MT-ATP6*-

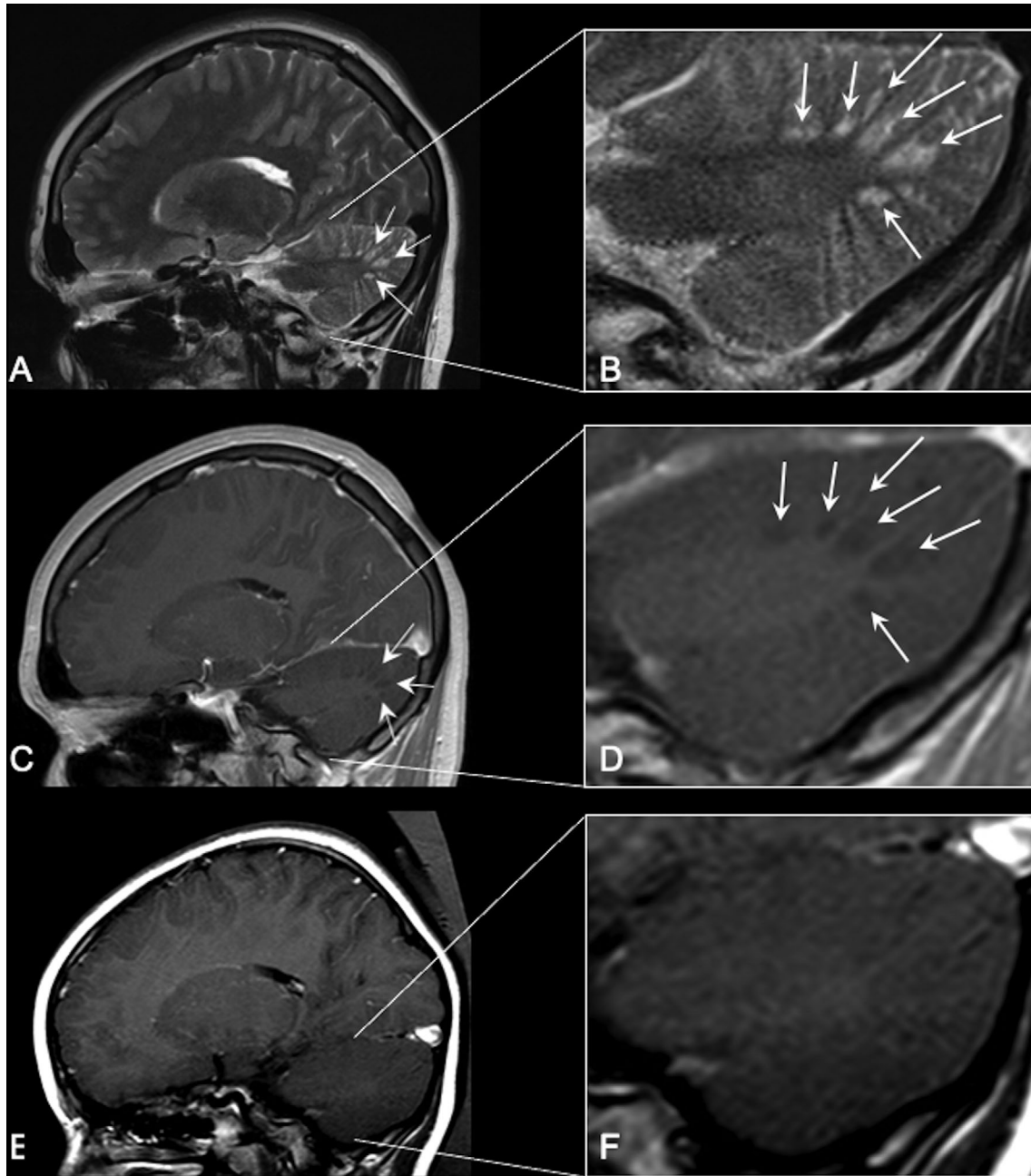
View this article online at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ana.26311). DOI: 10.1002/ana.26311

Received Jan 1, 2022, and in revised form Jan 17, 2022. Accepted for publication Jan 24, 2022.

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[Correction added on February 18, 2022, after first online publication: Benjamin Roeben was updated as one of the Corresponding author.]

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FIGURE

associated disease, particularly in *MT-ATP6*-associated Leigh syndrome, basal ganglia and brain stem lesions, cortical, subcortical and cerebellar atrophy have been reported.<sup>2</sup>

Distinct T2-hyperintensities at the bottom of cerebellar fissures, so-called cerebellar “Bottom-of-Fissure Dysplasias” (BOFD),<sup>4</sup> have been described in pediatric patients without clinical evidence of cerebellar dysfunction.

The striking T2-hyperintense signal changes in our patient are reminiscent of cerebellar BOFD. Importantly, however, here they developed *in the course* of the disease

as evidenced by sequential MRI, unlike *dysplasias* which reflect abnormal *developmental* tissue. By analogy, we termed this novel MRI finding cerebellar “Bottom of Fissure Hyperintensities” (BOFH).

Our case demonstrates that, while the severe clinical phenotype and lesions in locations characteristic for Leigh syndrome can be missing in *MT-ATP6*-associated disease, other intriguing signal changes might be present: a striking MRI pattern of BOFH which expands the spectrum of MRI features in *MT-ATP6*-associated disease. This novel neuroimaging finding illustrates a distinct cerebellar MRI pattern

in mitochondrial ataxia due to *MT-ATP6*-associated disease, which might be easily overlooked on clinical routine MRI.

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## Acknowledgments

We are thankful to the patient and her family.

B.R. receives support through the Clinician Scientist program of the Medical Faculty of the University of Tübingen (grant #478-0-0). This work was supported, in part, by grant 779257 “Solve-RD” from the Horizon 2020 research and innovation program to M.S.

## Author Contributions

B.R. and M.S. contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of data. B.R. and M.S. contributed to drafting the manuscript and preparing the figures.

## Potential Conflicts of Interest

The authors declare that there are no conflicts of interest.

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