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Leukodystrophy Associated with Mitochondrial Complex 1 Deficiency Due to Mutation in NUBPL Gene—An Unusual Follow-Up Finding

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We report an unusual case of mitochondrial leukodystrophy due to complex 1 deficiency associated with nucleotide-binding protein-like (NUBPL) gene mutation.

A 5-year-old male, born of third-degree consanguineous marriage, presented with complaints of inability to walk without support, involuntary movements involving all four limbs, tremulousness of hands, and delayed development of language milestones for the last 2 years of age. Patient was apparently well till 2 years of age and later developed seizures presenting as involuntary tonic–clonic movements with up-rolling of eyeballs. Each episode lasted for about 2 minutes followed by immediate regain of consciousness. The child was then admitted in a different institute and underwent magnetic resonance imaging (MRI) of brain along with genetic testing. Patient then developed similar tonic–clonic movements in the subsequent 2 months. Patient had difficulty in walking since 2.5 years of age that was insidious in onset and gradually progressive. Patient's mother noticed stiff gait of the child and his difficulty in getting up from sitting posture. The patient also had tremulousness when trying to hold objects and during play. There was also a history of delayed attention of language milestones since 3.5 years of age. The maximum milestone attained was two monosyllables. On examination, the child had spastic gait.

The initial MRI of the brain was done in 2018, after the first episode of involuntary movements, which showed extensive white matter signal abnormalities in the form of symmetrical T2 and fluid attenuated inversion recovery hyperintensities involving bilateral frontal white matter, forceps minor, genu and splenium of corpus callosum (►**Fig. 1**). These regions revealed obvious diffusion restriction (►**Fig. 2**). There was also moderate cerebellar atrophy in the initial presentation with abnormal T2 hyperintense signals.MR spectroscopy was not done.

DNA analysis was done and exome sequencing revealed homozygous missense mutation in exon 6 of the *NUBPL* gene that resulted in the substitution of cysteine for tryptophan at codon 156. While serum creatine phosphokinase, and nerve conduction study was normal, cerebrospinal fluid analysis revealed increased lactate.

The child was referred for follow-up MRI of the brain with contrast at our institute in March 2021 and the study was done in a 3-Tesla MRI system (MAGNETOM SKYRA, Siemens Healthineers, Erlangen, Germany). Standard Institute MRI protocol comprising sagittal T1-weighted, sagittal and axial T2-weighted, three-dimensional SPACE FLAIR, diffusion-weighted, and postcontrast T1-weighted images was done. T2 and FLAIR hyperintensities were noted in bilateral periventricular aspect of frontal region, bilateral peritrigonal areas, genu and splenium of corpus callosum as well as the corticospinal tracts in medulla and pons (►**Fig. 3**). On contrast administration, mild enhancement of pyramidal tracts was noted in anterior pons, midbrain, and medulla (►**Fig. 4**). Cystic encephalomalacic changes were noted in genu and splenium of corpus callosum (►**Fig. 5**). Atrophy of cerebellum and vermis with prominent foliae, predominantly on the left side, was also observed (►**Fig. 6**). On comparison with previous MRI brain done in 2018, follow-up imaging done in March 2021 revealed significant temporal changes with reduction in the FLAIR hyperintensities and relative volume loss in corpus callosum and cerebellum with cystic changes in corpus callosum, which were predominantly confined to the middle layer and enhancement of pyramidal tracts in

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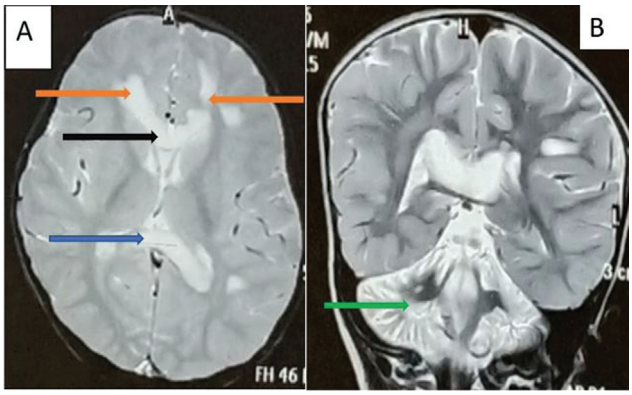

Fig. 1 (**A**) Axial and (**B**) coronal T2-weighted magnetic resonance imaging of brain showing bilateral symmetric hyperintensities involving frontal white matter (orange arrows), fornix, genu (black arrow), and splenium (blue arrow) of corpus callosum as well as both cerebellar hemispheres (green arrow).

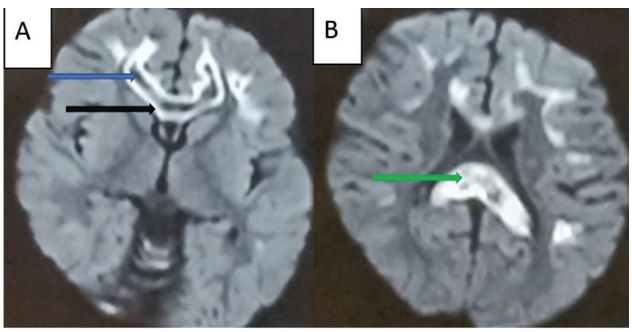

Fig. 2 (**A** and **B**) Diffusion-weighted images showing restricted diffusion in forceps minor (blue arrow), genu (black arrow), and splenium (green arrow) of corpus callosum.

anterior pons (►**Figs. 4** and **7**). There was also severe atrophy of pons in follow-up imaging (►**Fig. 8**).

Pediatric leukodystrophies are rare genetic disorders predominantly involving the white matter of the central nervous system. A subset of leukodystrophies, involving 5 to 10%, is caused by mitochondrial defects.[1,2] The diagnostic process is often challenging and detailed clinical examination combined with laboratory investigations, imaging findings with specific combination of affected structures, and in rare cases genetic analysis help in narrowing down the differential diagnosis.

Mitochondrial diseases comprise a group of disorders with genetic defects in mitochondrial oxidative energy metabolism. While some mitochondrial encephalopathies predominantly manifest with lesions of gray matter structures like mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome, Alpers syndrome, and Leigh syndrome,[3] another category manifests as leukodystrophy.

Recently, next-generation genetic sequencing techniques have revealed that numerous unsolved cases of leukodystrophy have a mitochondrial cause, and MRI patterns of new mitochondrial leukodystrophies were added.

The *NUBPL* gene was first reported as a cause of mitochondrial complex I deficiency in 2010. Kimonis et al[4] in their recent genetic and clinical review of patients with

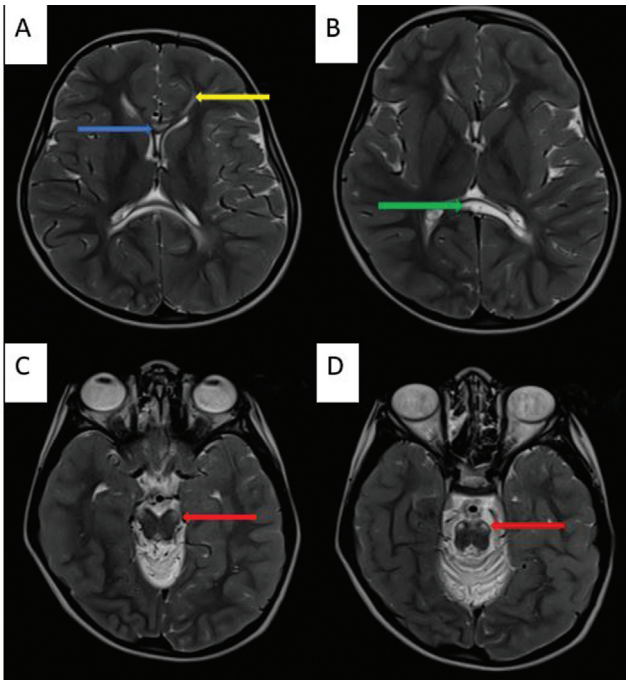

Fig. 3 (**A–D**) Axial T2-weighted images showing hyperintensities involving forceps minor (yellow arrow), genu (blue arrow), splenium (green arrow) of corpus callosum, and pyramidal tracts in pons, and medulla (red arrows).

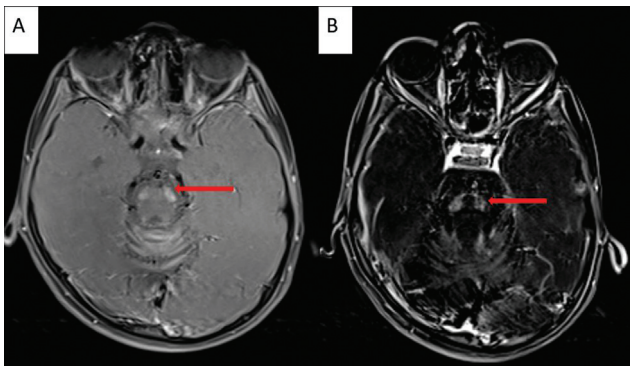

Fig. 4 (**A**) Contrast-enhanced T1-weighted and (**B**) subtracted images showing enhancement of pyramidal tracts in anterior pons (red arrows).

NUBPL mitochondrial disease reported findings in five additional patients. This was in addition to the earlier reports of eight patients with this mitochondrial disorder. Five other patients were also recently reported to have *NUBPL* disease but they had a different clinical picture.[4]

Hereby, we report a case of mitochondrial leukodystrophy due to mutation in *NUBPL* gene. Deficiency of mitochondrial respiratory chain complex 1 is caused by homozygous or compound heterozygous mutations in the *NUBPL* gene. It is the most common enzymatic defect of the oxidative phosphorylation disorders. It causes a wide range of clinical disorders ranging from lethal neonatal disease to adult-onset neurodegenerative disorders. Phenotypes include macrocephaly with progressive leukodystrophy, nonspecific

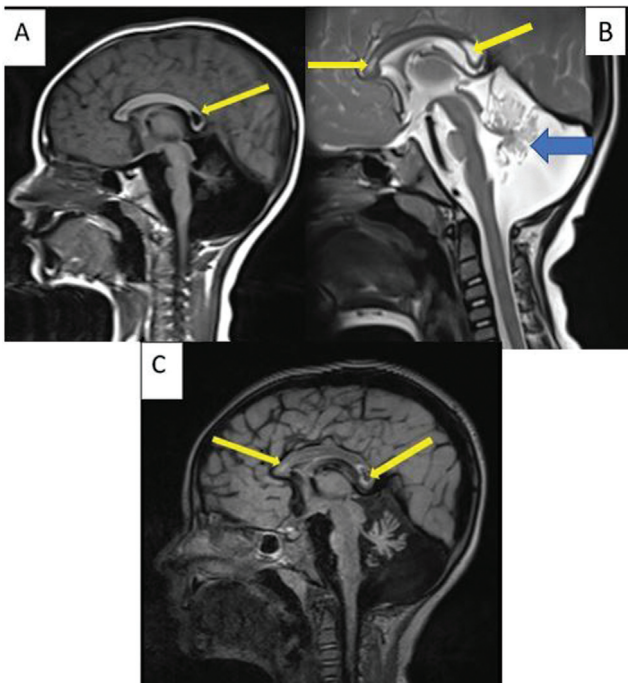

Fig. 5 (**A**) Sagittal T1-, (**B**)T2-weighted, and (**C**) fluid attenuated inversion recovery images showing cystic encephalomalacic changes (yellow arrows) with surrounding gliosis involving genu and splenium of corpus callosum, predominantly involving the middle layer and cerebellar atrophy (blue arrows).

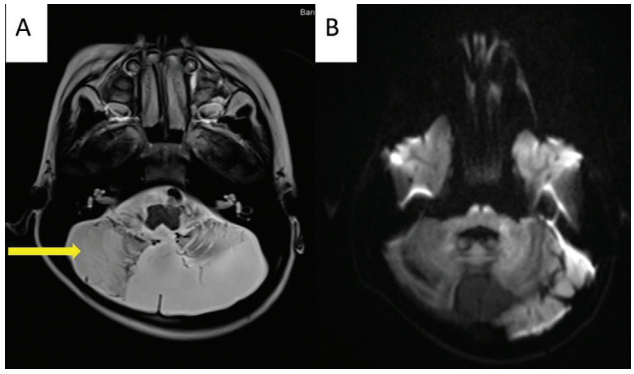

Fig. 6 (**A**) Axial T2-weighted image showing cerebellar atrophy (yellow arrow) with (**B**) diffusion-weighted image showing no diffusion restriction.

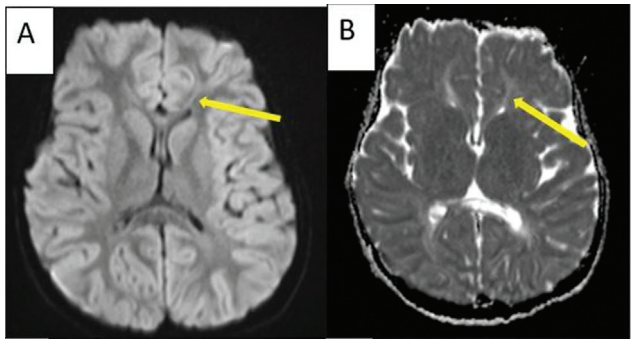

Fig. 7 Diffusion-weighted images showing (**A** and **B**) facilitated diffusion in genu and splenium of corpus callosum (yellow arrows).

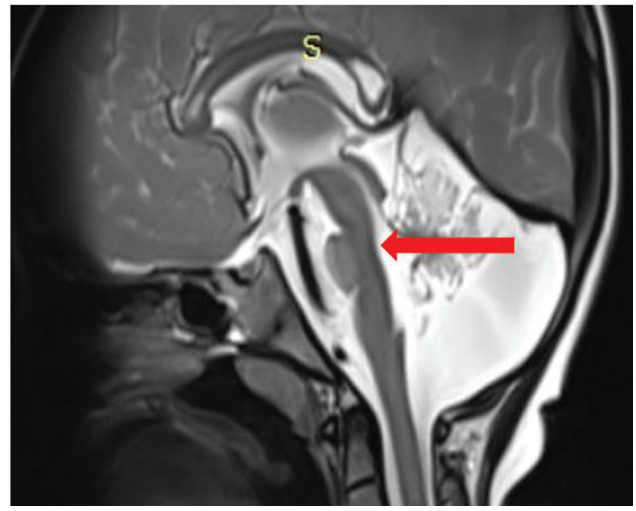

Fig. 8 Sagittal T2-weighted image showing severe atrophy of pons (red arrow).

encephalopathy, hypertrophic cardiomyopathy, Leigh hereditary optic neuropathy, and some forms of Parkinson disease. Literature review shows that NUBPL mutations are associated with a unique, consistent, and recognizable MRI pattern.[5]

Patients with *NUBPL* variants had a unique combination of T2-hyperintense signal of the cerebellar cortex bilaterally and supratentorial white matter abnormalities.

In early stage, the lesions are predominantly seen affecting the cerebellar cortex, deep cerebral white matter, and corpus callosum. On follow-up, the corpus callosum and cerebral white matter lesions improve with progressive cerebellar and brain stem involvement.

Our case had similar findings as earlier described with extensive cerebellar involvement and supratentorial white matter abnormalities, predominantly involving corpus callosum.

Leukodystrophies with involvement of the corpus callosum are unusual. X-linked adrenoleukodystrophy has a characteristic pattern with involvement of the peritrigonal region and splenium of the corpus callosum predominantly and enhancement of the advancing margins having a horse shoe-like appearance.

Recent reports[1] have mentioned certain MRI features suggestive of mitochondrial leukodystrophy. These are selective longitudinal T2 hyperintensity of the middle blade of the corpus callosum, with sparing of inner and outer blades.

However, all layers of the corpus callosum are typically affected in metachromatic leukodystrophy, Krabbe disease, and adrenoleukodystrophy,[6] while in vanishing white matter disease, the inner blade is involved.[7] Marchiafava-Bignami disease[8] and Susac syndrome also selectively affect the middle blade of the corpus callosum. While in Marchiafava-Bignami disease the involvement is in a longitudinal fashion, in Susac syndrome, it is round and multifocal[7].Thus, longitudinal selective involvement of the middle layer should be regarded as a red flag for possible mitochondrial disease.[6]

Other findings described are cerebral white matter rare fraction and cysts with a well-delineated rim, which may

show contrast enhancement and diffusion restriction, symmetric deep gray matter abnormalities, brain stem abnormalities, and symmetric abnormalities in the middle cerebellar peduncle.[1]

The cysts were usually multifocal and well-delineated and mainly located in the periventricular and deep white matter and not in the subcortical regions. Diffusion restriction and contrast enhancement are often specifically involved the rims of the cysts.[1]

Recognition of this unique MRI pattern of FLAIR or T2 hyperintensity of the cerebellar cortex and cerebral white matter involvement should lead one to suspect NUBPL variant of mitochondrial leukodystrophy. However, follow-up imaging in our patient revealed not only cerebellar volume loss with T2 hyperintensities and cystic changes in the corpus callosum but also interesting findings of enhancement involving the pyramidal tract in pons, which were not earlier described.

Conflict of Interest
None declared.

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