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Case Report

POLR3-related Leukodystrophy

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ABSTRACT

Pol III-related leukodystrophy is a recently recognized category of leukodystrophy with characteristic clinical presentation and imaging findings. These cases are diagnosed by the combination of typical clinical presentation, brain magnetic resonance imaging findings, and the presence of biallelic pathogenic mutations in three specific genes. We present the case of a 6-year-old girl who demonstrated the classic clinical and imaging features of this disorder. This case report aims to raise awareness of this disorder so that it is easily recognized in the appropriate setting.

Keywords: 4H syndrome, Leukodystrophy, POLR1C, POLR3A, POLR3B

INTRODUCTION

The diagnosis of Pol III-related leukodystrophy is made by integrating classical clinical findings with typical brain magnetic resonance imaging (MRI) features and the existence of biallelic pathogenic mutations. The three classic characteristics of this disorder include hypomyelination, hypodontia, and hypogonadotropic hypogonadism which are variably present resulting in differing phenotypic manifestations.[1-3] Diagnostic MRI of the brain classically demonstrates diffuse hypomyelination with cerebellar atrophy.[1,3,4] Biallelic mutations in three genes POLR3A, POLR3B, and POLR1C have been identified as responsible for this autosomal recessive disorder.[2]

CASE REPORT

A 6-year-old girl born full term presents with abnormal gait, delayed fine motor skills, delayed speech, multiple absent primary incisor teeth, and difficulty with vertical gaze eye movements. As an infant, she had reportedly met all of her early milestones. Yet, her mother began to notice an abnormal gait when she began walking at the age of 18–21 months.

On physical examination, bilateral central and right lateral maxillary incisor teeth as well as the right central and right lateral mandibular incisor teeth were absent. The mother reported that the primary teeth had never erupted in these locations. The patient had an ataxic gait with characteristic wide base, staggering movements, and difficulty with toe, heel, and tandem walking. She also had dysarthric speech, mild head titubation, and difficulty with upward and downward gaze. There was no family history of others with similar problems.

An MRI of the brain with and without IV contrast was performed using the Signa 1.5T HDxt MRI scanner (GE Healthcare, Chicago, IL). This study demonstrated abnormal hyperintense T2, hyperintense fluid-attenuated inversion recovery (FLAIR), and hypointense T1 signal involving

bilateral internal capsules and the white matter of all lobes of both cerebral hemispheres without accompanying cerebral parenchymal atrophy and mild relative T2 hypointense signal within the anterolateral portions of both thalami [Figures 1-3].

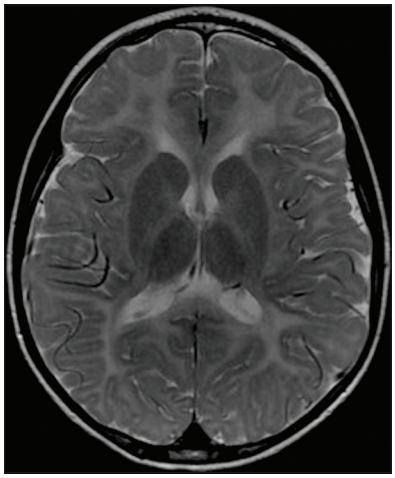

Figure 1: A 6 years old with Pol III-related leukodystrophy who presented with ataxic gait, delayed speech, difficulty with vertical gaze eye movements, and multiple unerupted primary incisor teeth. Magnetic resonance imaging of the brain with axial T2-weighted image at the level of the third ventricle and internal capsule demonstrates abnormal hyperintense T2 signal involving bilateral internal capsules and the white matter of all lobes of both cerebral hemispheres without cerebral parenchymal atrophy. Also noted is mild relative T2 hypointense signal within the anterolateral portions of both thalami.

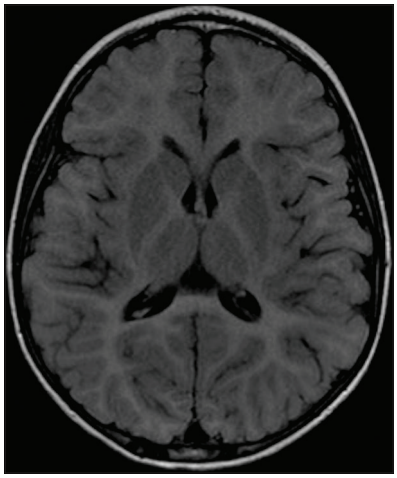

Figure 2: A 6 years old with Pol III-related leukodystrophy who presented with ataxic gait, delayed speech, difficulty with vertical gaze eye movements, and multiple unerupted primary incisor teeth. Magnetic resonance imaging of the brain with axial fluid-attenuated inversion recovery (FLAIR) image at the level of the third ventricle and internal capsule demonstrates abnormal hyperintense FLAIR signal involving bilateral internal capsules and the white matter of all lobes of both cerebral hemispheres without cerebral parenchymal atrophy.

These findings were concerning for a diffuse hypomyelinating process. There were no focal areas of restricted diffusion or abnormal enhancement [Figures 4 and 5]. The MRI images also demonstrated moderate cerebellar vermian and mild cerebellar hemispheric atrophy [Figures 6]. Given the clinical presentation of abnormal wide-based gait and delayed eruption of multiple incisor teeth, Pol III-related leukodystrophy was considered in the differential diagnosis.

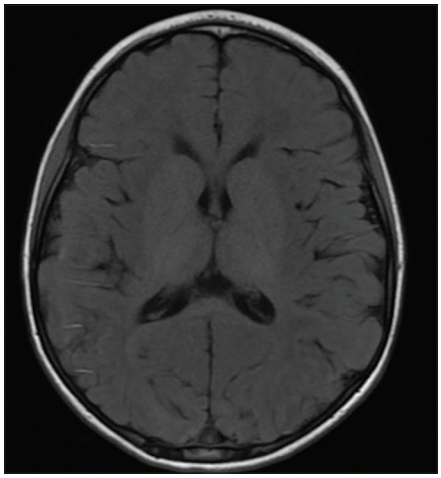

Figure 3: A 6 years old with Pol III-related leukodystrophy who presented with ataxic gait, delayed speech, difficulty with vertical gaze eye movements, and multiple unerupted primary incisor teeth. Magnetic resonance imaging of the brain with axial non-contrast T1 image at the level of the third ventricle and internal capsule demonstrates abnormal hypointense T1 signal involving bilateral internal capsules and the white matter of all lobes of both cerebral hemispheres without cerebral parenchymal atrophy.

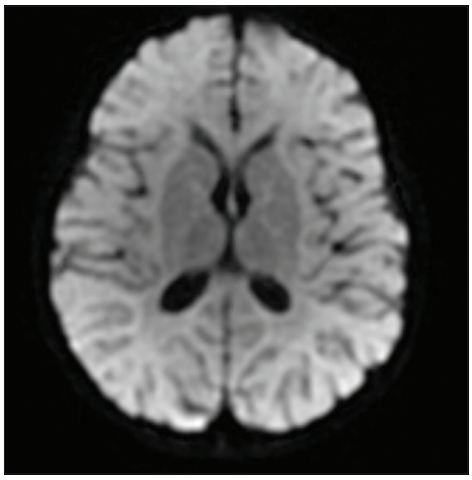

Figure 4: A 6 years old with Pol III-related leukodystrophy who presented with ataxic gait, delayed speech, difficulty with vertical gaze eye movements, and multiple unerupted primary incisor teeth. Magnetic resonance imaging of the brain with axial diffusion tensor image at the level of the third ventricle and internal capsule demonstrates no evidence of abnormal restricted diffusion.

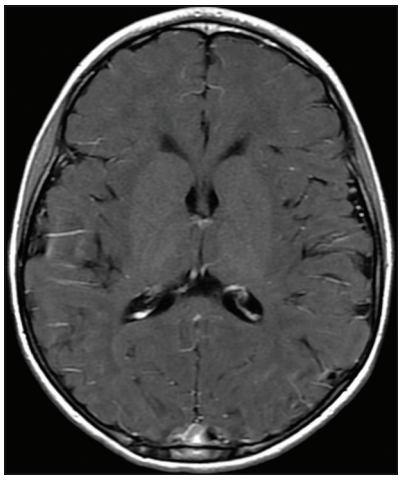

Figure 5: A 6 years old with Pol III-related leukodystrophy who presented with ataxic gait, delayed speech, difficulty with vertical gaze eye movements, and multiple unerupted primary incisor teeth. Magnetic resonance imaging of the brain with post-contrast axial T1 image at the level of the third ventricle and internal capsule demonstrates no evidence of abnormal enhancement.

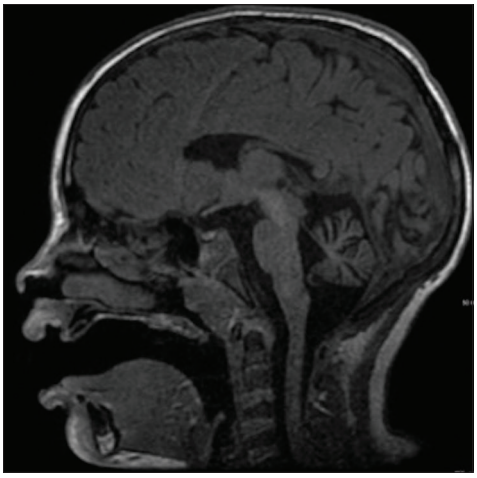

Figure 6: A 6 years old with Pol III-related leukodystrophy who presented with ataxic gait, delayed speech, difficulty with vertical gaze eye movements, and multiple unerupted primary incisor teeth. Sagittal magnetic resonance imaging image through the midline of the brain using non-contrast T1 imaging demonstrates moderate atrophy of the cerebellar vermis.

On genetic testing, she was found to have compound heterozygous mutations in both alleles of the POL3B gene.

DISCUSSION

White matter disorders can be broadly grouped into four categories: Hypomyelinating (decreased amounts of otherwise normal myelin), demyelinating (loss of previously deposited normal myelin), dysmyelinating disorders (abnormal structure and function of existing myelin), and myelinolytic (myelin vacuolization) diseases.[5] Pol III-related leukodystrophies are a rare group of autosomal recessive hypomyelinating leukodystrophies with slightly more than 100 cases reported in the medical literature.[3,6]

This disorder has four major clinical findings with varying degrees of presentation: (1) Neurologic dysfunction, (2) abnormal dentition, (3) hypogonadotropic hypogonadism, and (4) ocular abnormalities.[1,6] Classic neurological abnormalities seen include slowly progressive, mild-to-severe intellectual disabilities, and prominent cerebellar signs combined with a variable degree of pyramidal and extrapyramidal signs resulting in ataxia and tremors which begin in childhood and progress very slowly over several years.[1] Some patients may have a hypoplastic corpus callosum.[1] Abnormal dentition is characterized by missing or delayed eruption of teeth. Hypogonadotropic hypogonadism is often noted with delayed, arrested, or absent puberty and short stature with or without growth hormone deficiency.[6] Ocular findings often include abnormalities in eye movement, such as progressive vertical gaze palsy, progressive, high-level myopia, cataracts, and optic nerve atrophy.[1,6] Time of manifestations of clinical symptoms can range from early infancy to late childhood.[1] In our patient, the clinical symptoms were first noticed around 18–21 months of age. Before this time, she demonstrated normal age-appropriate development.

Those with Pol III-related leukodystrophy often have varying degrees and combinations of the classic four clinical findings seen with this condition.[1] Before discovering a common molecular basis for these findings, the varied combinations of phenotypic features were originally described as separate disorders with overlapping features. These disorders included ataxia-delayed dentition and hypomyelination, 4H syndrome hypomyelination, hypodontia, and hypogonadotropic hypogonadism, tremor-ataxia with central hypomyelination, leukodystrophy with oligodontia, and hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum.[3,4,6] These previously described separate disorders are now all classified under the category of Pol III-related leukodystrophy.

Within the past 8 years, mutations in three genes POLR3A, POLR3B, and POLR1C encoding the protein subunits of RNA polymerase III were identified as a reason for these overlapping clinical disorders.[2,7-9] RNA polymerase III is a nuclear enzyme essential for the transcription of housekeeping genes required in all eukaryotic cell types including tRNAs and many non-coding RNAs.[10] POLR3A and POLR3B genes encode for the two largest subunits of the RNA polymerase III enzyme complex and POLR1C encodes for a smaller but vital subunit of this enzyme complex.[2,9,10] Mutations in these genes impair either the proper assembly of the RNA polymerase III enzyme or else impair its ability to bind to DNA.[7] Proper

function of the RNA polymerase III enzyme is crucial for the maintenance and development of myelin which if impaired can affect the development and function of many parts of the body.[7,10]

The typical brain MRI findings are characterized by diffuse cerebral hypomyelination manifesting as diffuse hyperintense T2 and FLAIR white matter signal abnormality with varying T1 white matter signal abnormality.[1] There is relative T2 hypointense signal of other brain structures such as the anterolateral nuclei of the thalami, pallida nuclei, dentate nuclei, pyramidal tracts in the posterior limbs of the internal capsules, and optic radiations.[2] Cerebellar atrophy, notably of the vermis, and hypoplasia of the corpus callosum are variably seen as in our patient who had cerebellar atrophy but no callosal thinning.[2,3] However, it should be noted that diffuse hypomyelination is not a mandatory diagnostic imaging feature.[2] Some patients may have selective T2 hyperintense signal abnormality localized to the posterior limb of the internal capsule without additional areas of white matter signal abnormality.[2] Others may have moderate-to-severe cerebellar atrophy with thinning of the corpus callosum or else with scattered focal supratentorial hypomyelination as evidenced by T2 hyperintense white matter signal abnormalities.[2] Many of the MRI imaging features of Pol III-related leukodystrophy such as diffuse cerebral hemispheric hypomyelination, cerebellar or corpus callosal atrophy, and T2 hypointense signal involving pyramidal tracts in the posterior limbs of the internal capsule, anterolateral thalami, pallida nuclei, and optic radiations can be seen occurring separately in other leukodystrophies. However, the presence of these imaging features occurring concurrently is unique to Pol III leukodystrophy.[4]

CONCLUSION

The diagnosis of Pol III-related leukodystrophy is established with the combination of classic clinical findings, typical brain MRI features, and the identification of specific genetic mutations. The suspicion for this rare diagnosis should be raised when classic clinical features and typical brain MRI findings are present. Confirmation is made by molecular genetic testing.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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