Child Neurology: Hypotonia and Delayed Teeth Eruption in a 2-Year-Old Female

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Abstract

POLR3-related disorders are rare hypo-myelinating leukodystrophies associated with hypodontia. We present a female patient, who was referred to pediatric neurology at 2 years of age for tremor, low tone, and motor delays. Additionally, she was noted to have a delay in her teeth eruption and myopia. Neurological examination was significant for ataxic features and global developmental delay. Laboratory workup was unrevealing. MRI imaging was significant for hypomyelination. Genetic testing confirmed a pathogenic variant of POLR3B. POLR3-related leukodystrophies should be considered in patients who present with hypotonia, ataxia and hypodontia. There are many different subtypes of POLR-related leukodystrophies each with distinguishing phenotypic and radiographic features. Although, MRI can be helpful in initial evaluation genetic testing is needed for confirmatory diagnosis and to guide prognosis.

Case Presentation

We present a female patient, who was referred to pediatric neurology at 2 years of age for tremor and motor delays. Review of early milestones, reveals that she was able to sit at 6 months, crawled at 9 months, and was cruising by 12 months of age. By 2 years of age, fine motor and language delays as well as a prominent tremor were apparent. She has had intermittent follow up to 5 years of age. With the help of therapy, she has continued to progress gaining the ability to stand for less than 5 seconds and to ambulate with a walker. She never developed independent walking and her language remained delayed. There has been no developmental regression reported to date.

Her medical history was essentially benign. She was the product of a term uncomplicated pregnancy and delivery with a birth weight of 2.86 kg. Medical history was significant for
low muscle tone and motor delay noted on evaluations by physiatry and orthopedics. X-rays of the hips were negative for hip dysplasia. Of interest, she did have a delay in her teeth eruption. An ophthalmology assessment revealed myopia, but no cataracts, nystagmus or optic nerve abnormalities.

Her initial neurology examination was notable for low muscle tone, global developmental delays, and ataxic features including dysmetria and truncal titubations. Functionally, she was able to generate good strength, had no sensory deficits, and displayed intact reflexes. There were no cranial nerve abnormalities. Exam findings prompted several investigations. Laboratory studies included: CPK, free T4, TSH, free and total carnitine levels, acylcarnitine profile, very long chain fatty acids, lysosomal enzymes, karyotype, and microarray which were all unrevealing. Initial lactate was elevated at 2.8mmol/L but the repeat was in a normal range.

An EEG was performed and showed slowing, disorganization, and mild bi-hemispheric dysfunction however, no epileptiform discharges were noted. Further evaluation at age 2 included a brain MRI that revealed an abnormal pattern of myelination for the patient’s age. There was a marked paucity of age-appropriate cerebral white matter T2 signal intensity with small areas of T2 signal hypointensity- visualized within the posterior limbs of the internal capsules, within the ventrolateral thalami, and along the optic radiations (Figure 1A). There was also limited normal age-appropriate cerebral white matter T1 signal hyperintensity, particularly within the frontal lobes (Figure 1B). Posterior fossa abnormalities were present which included delayed cerebellar myelination (Figure 1C) as well as vermian atrophy that disproportionately affected the anterior aspect (Figure 1D). At this time, genetic testing (duplication/deletion and sequencing) was initiated due to the concern for a hypomyelinating leukodystrophy. This included POLR3A gene testing which was negative. She was referred to a leukodystrophy
specialist who pursued POLR3B and POLR1C testing, revealing a pathogenic variant in POLR3B.

A follow up visit was conducted at age five. At that time, she was receiving occupational, physical, and speech therapy. She showed advancements in her skills with the ability to walk with a walker for a few steps, speak in 3 to 4-word sentences, feed herself, and assist in dressing. Based on her subtype prognosis, some continued improvement in her language and motor skills would be expected. Although most leukodystrophies manifest as progressive disorders, the clinical course of patients with RNA polymerase III (POLR 3)-related leukodystrophies can vary. The exact reason for this variability is unclear. Currently, it is postulated that genetics and age of onset play a role. Most patients diagnosed as infants show some improvement, but ultimately do not have the age appropriate characteristics.

Discussion

Early recognition of a concise pattern in analyzing hypotonic patients is essential. In evaluating hypotonia there are five main groupings to consider: 1) central nervous system 2) lower motor neuron 3) nerve 4) neuromuscular junction, and 5) muscle. Within these categories, a pattern of global developmental delay is most likely “central” hypotonia, localized to the brain. Initial evaluation of a patient presenting with hypotonia should include a thorough history—including prenatal history, delivery, development, and physical examination. Workup to further guide diagnosis includes CPK, CBC, CMP, and thyroid testing. If a central etiology is suspected, a brain MRI should be obtained. Screening metabolic evaluations may include a lactate, ammonia, serum amino acid profile, urine organic acids, acylcarnitine profile, as well as free and
If there is evidence to support a possible leukodystrophy based on neuroimaging and clinical features, such as in this case, additional laboratory studies include very long chain fatty acids, lysosomal enzymes, and specific gene testing.

Although POLR3B is a rare neurological presentation in patients, it is an important consideration in a pediatric patient that presents with hypotonia and hypodontia. Overall, the main presenting symptoms specific for POLR3B are ocular abnormalities, abnormal dentition, endocrine abnormalities, and neurological features. Ocular abnormalities most commonly present as myopia, however strabismus has also been noted in some patients. Abnormal dentition is a key finding within the diagnosis because of its’ uniqueness. In a review by Gauquelin et al., the authors found in POLR3B patients about 70% had dental abnormalities with the most common feature being delayed dentition. Other sources report dental abnormalities occurring in up to 87% of patients. Dental abnormalities can include neonatal teeth, hypodontia, or even abnormal tooth shape. Endocrine abnormalities most commonly present as short stature which is found in 50% of patients, but can also present as hypogonadotropic hypogonadism. Neurological symptoms most commonly present with ataxia, hypotonia, tremor, or motor delay.

When evaluating possible POLR3-related leukodystrophy patients, it is important to identify the most prominent associated features as subtypes vary. Most POLR3-related patients present with hypomyelination, excluding this as a distinguishing feature. Patients that present with predominantly endocrine abnormalities such as hypogonadotropic hypogonadism will most likely have hypomyelination, hypodontia, hypogonadotropic hypogonadism (4H syndrome). Dental abnormalities with absence of endocrine involvement suggest either the ataxia, delayed dentition, and hypomyelination (ADDH) or leukodystrophy with oligodontia (LO) subtypes. The presence of neurological features further differentiates these subtypes. ADDH patients present with ataxia, whereas LO patients do not have predominant neurological signs.
Additionally, ADDH presents with delayed dentition while LO is a leukodystrophy with oligodontia\(^3\). In patients with mainly neurological symptoms, MRI imaging is important to distinguish between tremor-ataxia with central hypomyelination (TACH) and hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (HCAHC) subtypes\(^3\).

Our patient presented with delayed teeth eruption, hypotonia, developmental delay, and atactic features, which prompted the concern for a POLR3- related leukodystrophy. These autosomal recessively inherited disorders are associated with changes in the POLR3A, POLR3B, and POLR1C genes. Genetic testing in this patient confirmed 2 pathogenic POLR3B variants. Based on her presentation, 4H would be unlikely given the absence of endocrine findings. Her dental abnormalities suggest either the ADDH or LO subtype. The presence of ataxia and tremor supports ADDH as the more likely subtype. In POLR3- related leukodystrophy disorders, clinical and radiographic features identify the subtype. Among the genes phenotypic overlap exists, but prognosis varies with POLR3B having the best outcome. Even though patients with POLR3B present earlier, they have a slower disease manifestation compared to POLR3A\(^3\).

When a POL3 related disorder is considered, the main diagnostic study other than genetic testing is a brain MRI that demonstrates hypomyelination (Figure 1B). In the interpretation of pediatric MRI’s, it is imperative to consider the myelination timeline. There is an expected pattern of myelination on MRI, with structures appearing myelinated earlier on T1-weighted imaging compared with T2-weighted imaging. In general, T1-weighted imaging after approximately 10 months of age does not vary and T2-weighted imaging stabilizes after approximately 24-26 months of age\(^5\). With the case presented, the MRI was performed after 2 years of age and clearly presented the hypomyelination.
The utilization of MRI in the evaluation of developmentally delayed hypotonic infants more readily identifies the hypomyelination that can be associated with this type of leukodystrophy. POLR3B hypomyelination commonly presents as hypointensities of the optic radiations, thalami, pallida, and posterior limb of the internal capsule as seen in our patient in Figure 1A. Thalamus and pallidae hypomyelination cause the delay in motor signals, and ultimately the movement dysregulation (tremor) as seen in our patient. Patients may have cerebellar atrophy usually of the vermis (Figure 1D), and hypointensity of the dentate nuclei (Figure 1C) correlating with the ataxic features notable in POLR3B leukodystrophy. Appropriate correlation of clinical and MRI findings can direct the differential for centrally mediated pediatric hypotonia associated with global delays. When a hypomyelinating leukodystrophy is suspected, confirmatory genetic testing is required. There are multiple genes responsible for the POL3 related leukodystrophies, and identification of a specific gene will best guide prognosis.
**Figure 1: MRI T1 and T2 Images** (A) T2 hypo-intensity in the posterior limb of the internal capsule (thickest arrow), along the optic radiations (middle thickness arrow), and within the ventrolateral thalamus (thinnest arrow); (B) Diffuse T1 hypointensity particularly in the frontal lobes; (C) T2 hypointensity in the hila of the cerebellar nuclei black arrow), with absent normal white matter T2 signal hypointensity within the remainder of the cerebellum including the middle cerebellar peduncles; (D) T1 vermian hypoplasia disproportionately affecting the anterior aspect (white arrow).
### Appendix 1. Authors

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