Vanishing White Matter Disease with Macrocephaly

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ABSTRACT

Vanishing White Matter Disease (VWM) is one of the most common childhood leukencephalopathies. It commonly presents with spasticity, microcephaly, gradual cognitive decline, and characteristic episodes of acute deterioration following an inciting event. However, we present a case of a three-year-old girl with confirmed VWM who also developed severe macrocephaly, a rare and unique manifestation of the disease.

Our patient initially had a clinical course consistent with VWM, including progressive neurologic decline and pathognomonic magnetic resonance imaging (MRI) changes. In addition, genetic testing confirmed the diagnosis of VWM and showed a homozygous mutation of the eukaryotic initiation factor 2b protein 5 (EIF2B5) gene. However, in her third year of life, our patient was also found to have an accelerating macrocephaly. Her head circumference was last noted to be above the 99th percentile (>3 SD). This case demonstrates the extent of the phenotypic variability in this disease. More research is needed to better prognosticate a disease course for known genetic mutations.

INTRODUCTION

Vanishing White Matter Disease is one of the most commonly inherited leukencephalopathies, but its exact incidence is unknown.¹ It classically presents between the ages of one and five, and death generally occurs a few years after diagnosis.² However, the age of onset and severity of the disease can vary widely.¹² In 1997, van der Knaap¹ coined the name Vanishing White Matter Disease and provided comprehensive diagnostic criteria that included clinical presentation, MRI findings, and pathology. Furthermore, with the advent of genetic technology in the late 1990s, VWM was found to be a recessive genetic disorder. Mutations in any of the 5 genes encoding for the eukaryotic initiation factor 2b protein (EIF2B) result in a clinical presentation consistent with VWM.²

According to van der Knaap’s description of the clinical presentation,³ afflicted children are initially developmentally normal. Onset of neurologic symptoms is gradual, and patients slowly develop ataxia, spasticity, mild cognitive decline, and variable optic atrophy. However, the hallmark of the disorder is episodes of acute deterioration precipitated by fever, infection, trau-
Table 1: Van der Knaap’s MRI criteria for diagnosis of VWM

**Obligatory:**

I. Cerebral white matter shows either diffuse or extensive signal abnormalities; the immediate subcortical white matter may be spared.

II. Part or all of the abnormal white matter has a signal intensity close to or the same as cerebrospinal fluid on proton density or FLAIR images, suggestive of white matter rarefaction or cystic destruction.

III. If proton density and FLAIR images suggest that all cerebral white matter has disappeared, there is a fluid-filled distance between ependymal lining and the cortex, but not a total collapse of the white matter.

IV. The disappearance of the cerebral white matter occurs in a diffuse “melting away” pattern.

V. The temporal lobes are relatively spared, in the extent of the abnormal signal, degree of cystic destruction, or both.

VI. Cerebellar white matter may be abnormal, but does not contain cysts.

VII. There is no contrast enhancement.

**Suggestive:**

1. Within abnormal white matter there is a pattern of radiating stripes on sagittal and coronal T1-weighted or FLAIR images; on axial images dots and stripes are seen within the abnormal white matter as cross-sections of the stripes.

2. Lesions within the central tegmental tracts in the pontine tegmentum.

3. Involvement of the inner rim of the corpus callosum, whereas the outer rim is spared.

ma, or even severe fright. During these exacerbations, patients acutely present with any combination of hypotonia, loss of motor function, irritability, vomiting, seizures, and altered mental status.

Although patients usually recover, they generally do not fully return to their previous baseline. As the disease progresses, most children develop microcephaly, epilepsy, and dysphagia. They also eventually become non-ambulatory. In addition, life expectancy is variable. Some patients can have a rapid course with death within one to five years, whereas others can survive for one to two decades.

Alongside this evolution of symptoms, MRI imaging shows progressive radiographic changes. Table 1 outlines van der Knaap’s list of pathognomonic MRI findings. Imaging characteristically reveals symmetric and diffuse cystic degeneration of myelinated tissue. These changes are gradual and progress in a predictable stepwise manner. Additionally, MRI spectroscopy and pathology studies have suggested that the vanishing white matter is replaced with CSF. Moreover, genetic testing serves as a confirmatory test for presumed VWM. A confirmed genetic mutation in the EIF2B gene is found in up to 90% of clinically diagnosed cases. The extent of protein dysfunction is thought to determine the age of onset and the severity of the disease. However, there is no clear genotype-phenotype correlation due to the variability in phenotype and penetrance amongst patients with the same mutations.
This case describes a 3-year-old girl who has infantile onset VWM due to a homozygous EIF2B5 mutation. All features of her clinical presentation were initially consistent with the well-established diagnostic criteria. However, she later developed progressive macrocephaly. Although microcephaly is more common, there have been a few documented examples of the former. The genetics behind macrocephaly in VWM has not yet been explored in the medical literature, and its cause remains unclear. Nonetheless, this particular case is a cogent example of both the genetic and phenotypic variability of VWM.

CASE PRESENTATION

The patient is a three-year-old girl who was born full term to non-consanguineous Mexican parents following a normal pregnancy. Both of her parents and her older brother are healthy. However, her family history is notable for a deceased paternal uncle who suffered from an undiagnosed severe childhood neurologic disease.

The patient had achieved all age-appropriate developmental milestones and was in good health until the age of seven months, when she developed *E. coli* urosepsis. At time of diagnosis, she presented with lethargy, inattentiveness, hypotonia, and hyperreflexia. Her subsequent 3-week hospitalization was complicated by respiratory failure requiring intubation, progression of hypotonia with non-purposeful movements, worsening mental status, and new onset dysphagia.

A non-contrast head CT showed symmetric hypodensity of the white matter, which suggested a disease of incomplete myelination. A subsequent MRI revealed diffuse and symmetric hyperintense signal abnormalities in the cerebral white matter, brainstem, and cerebellum, which were also consistent with a leukodystrophy (Figure 1). MRI spectroscopy indicated low lactate, glucose, and creatinine—a spectrum that is more consistent with cerebral spinal fluid (CSF). Additionally, electroencephalogram (EEG) showed diffuse background slowing with rare bilateral sharp/slow discharges but no overt seizures. Laboratory and lumbar puncture workup was unremarkable.

At twelve months of age, the patient had a similar hospitalization when she presented with three days of vomiting, hypotonia, irritability,
During the five months following her second hospitalization, the patient was noted to have a gradual decline in her neurologic status, particularly with worsening motor and speech delay. She was also noted to be hypotonic, hyperreflexive, and microcephalic (43 cm: <3%, < 3 SD), but remained alert, attentive, and interactive. At the age of seventeen months, following an atraumatic fall from her bed, the patient presented with generalized limb shaking, upward gaze deviation, and altered consciousness. This was later confirmed on EEG to be multifocal generalized seizures. During her complicated 1-month hospitalization, she was treated for medication-resistant status epilepticus. She also had severe spasticity, respiratory failure, and dysphagia. Repeat MRI showed progressive T2 prolongation in the cerebral white matter and corpus callosum with newly documented cystic changes and parenchymal volume loss (Figure 2).

Upon discharge, the patient’s baseline had significantly deteriorated. She was spastic in all extremities, unable to stand without assistance, had limited purposeful movements, and was inattentive with the environment. Unfortunately, the patient was then lost to follow-up for about 2 years. She was next seen at the age of three following a referral for evaluation of macrocephaly and possible hydrocephalus.

and altered mental status. A repeat MRI showed progressive T2 prolongation of the cerebral white matter without subcortical cystic changes.

At this time, a differential diagnosis based on the progression of MRI findings and clinical symptoms included VWM, other hereditary leukodystrophies, lysosomal storage diseases, mitochondrial disorders, and infectious etiologies. However, the subsequent work-up to include CSF studies for infection and abnormal metabolites was negative. In addition, an encephalitis panel, lysosomal enzyme screen, biogenic amine testing, serum hexoaminidase A/B, and urine organic acids were also within normal limits. Ultimately, genetic analysis revealed that the patient was homozygous for the common variant, EIF2B5 r299h mutation (896G>A), which confirmed a diagnosis of VWM.
Per the patient’s mother and outside hospital documentation, her cranium had accelerated in growth over the course of 5 months. She was non-ambulatory and non-communicative. Additionally, she had developed frequent myoclonic jerks that were inconsistent with seizure activity. On exam, the patient was reactive to painful stimuli, but was severely hypertonic in all extremities. She was able to hold her limbs against gravity, but without purposeful movement. Her head circumference measured at 61.5 cm (>99%, >3 SD). Non-contrast head CT showed interval thinning of the cortical gray matter with minimal residual normal brain parenchyma. The area of white matter had extensive volume loss with a similar density as CSF (Figure 3). A neurosurgical consult was made, but surgical intervention was not indicated.

DISCUSSION

This case’s clinical presentation, imaging, and genetic analysis are all consistent with VWM as defined by van der Knaap, et al (Table 1). The patient had multiple episodes of neurologic decompensation precipitated by illness or fall that was then followed by clinical deterioration compared to her previous baseline status. During these episodes, she had both hypertonia and a loss of motor function. As the disease progressed, she also developed spasticity and seizures.

In addition, as described by van der Lei et al., the progression of her radiographic findings were consistent with previous cases of VWM. Her imaging showed progressive, diffuse, and symmetric dysemelination of cerebral white matter with subsequent development of cystic CSF formations. Additionally, there was early dysmelination of the periventricular area and bordering deep white matter. As the disease evolved, the remaining deep and subcortical cerebral white matter were affected, including the corpus callosum. Furthermore, her MRI spectroscopy showed a pathologic decrease in the white matter’s various metabolites. The new composition was more consistent with CSF and suggests that cerebral fluid is replacing the vanishing white matter.

Although this clinical presentation and imaging could be seen in other dysmyelinating, metabolic, and infectious disorders, the positive genetic testing confirmed the diagnosis of VWM. The patient has a homozygous EIF2B5 mutation at r299h (896G>A), the most common subunit affected in VWM. Furthermore, it is known to have a variable phenotype, as evidenced by this patient’s unique presentation of macrocephaly.

In a case report by Pineda et al., a female patient, who was heterozygous for two EIF2B5 mutations (c.338G>A [p.Arg113His] and c.468G>C [p.Ile156Met]), was unique for her longevity well into her second decade of life, as well as for the development of progressive severe macrocephaly. Her head circumference was reported to be 62 cm or >5 standard deviations. Similarly, imaging showed virtually no cerebral white matter, and spectroscopy confirmed replacement with CSF. Additionally, Passemard et al. describes three cases of genetically confirmed VWM and macrocephaly in patients with heterozygote EIF2B5 mutations R315H/p.F56V (c.944G→A/c.166T→G) and p.R315H/p.F56C (c.167T→G). Their imaging also showed complete loss of white matter and replacement with CSF. However, unlike the previous patient, these children died before reaching their first decade.

Our patient is unique not only for her rare presentation of infantile VWM, but also her homozygous mutation of EIF2B5. Her course is notable for rapid deterioration in her neurologi-
macrocephaly. As in the previous case reports, our patient also had mutations in the EIF2B5 protein, suggesting that this particular allele may be important for development of the rare macrocephaly phenotype. Interestingly, however, unlike the other cases, she had a homozygote mutation. This suggests that heterozygosity is likely not a necessary feature for the development of macrocephaly. Unfortunately, the medical literature has limited information on the genetic causes of macrocephaly in VWM patients, but this case may offer a new perspective. Further research is needed to determine specific genetic predictors of this unusual phenotype.

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**LEARNING POINTS**

1. Vanishing White Matter Disease (VWM) is a common leukodystrophy affecting the pediatric population. It commonly presents with a set of classical clinical and radiologic features. There is also reliable genetic testing to confirm its diagnosis.

2. An interesting feature of the disease is its discrete incidences of clinical deterioration precipitated by some inciting event, such as illness, trauma, or fright.

3. Phenotypic variability is a known feature of VWM. Macrocephaly is an interesting, but rare complication of the disorder.

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