

Vanishing white matter disease in a child presenting with ataxia

CJ Wilson,¹ JC Pronk² and MS Van der Knaap³

¹National Metabolic Service, Starship Hospital, Auckland, New Zealand, Departments of ²Clinical and Human Genetics, and ³Child Neurology, Free University Medical Center, Amsterdam, the Netherlands

Abstract: Vanishing white matter disease is a recently described leukoencephalopathy that is characterized by chronic and episodic neurological deterioration. These episodes often follow periods of fever or minor head trauma. It frequently presents in childhood with problems of ataxia and tremor. Five genes have been identified for the disease, *EIF2B1-5*, which encode the five subunits of translation initiation factor eIF2B. Mutations in each of the genes may independently cause the disease. The defect in eIF2B results in abnormalities in translation and its regulation, leading to abnormalities in protein synthesis and its regulation. Magnetic resonance imaging of the brain reveals extensive cerebral white matter abnormalities with evidence of white matter rarefaction and cystic degeneration, which has been confirmed pathologically. We report the first confirmed Australasian patient.

Key words: eIF2B; leukoencephalopathy; translation; vanishing white matter.

Concerns regarding child development are common presentations to a paediatric service. Often no underlying cause is found, complex investigations are not indicated and the condition is not progressive. The presence of a positive family history including consanguinity, the suggestion the child is regressing and/or the presence on examination of focal neurological signs or features such as hepatomegaly should alert the clinician to further investigate. A magnetic resonance imaging (MRI) brain scan is usually indicated and additional investigations are often based on these radiological findings. A patient is reported in whom the MRI scan revealed striking abnormalities and led to the diagnosis of a recently described and probably rare novel leukoencephalopathy.

CASE REPORT

A female Caucasian child presented with concerns regarding her motor skills at two and a half years of age. While she had normal developmental milestones her parents felt that since hitting her head following a fall a few months earlier she had been clumsy and had poor balance. Immediately following the fall she had been drowsy for a short period.

The pregnancy was complicated by mild intrauterine growth retardation (IUGR) but the delivery and neonatal period were unremarkable. There was no family history of note. On examination her head circumference was on the 25th centile and there were no localizing neurological signs. She had a mildly ataxic gait and a mild intention tremor. There were no other abnormalities and it was decided to refer to a neurodevelopmental therapist and adopt a 'wait and see' approach. Her creatine kinase (CK) was normal.

At age 3 years, following a series of otherwise unremarkable urinary tract infections, she had developed a more pronounced ataxic gait and had increased tone in her lower limbs with brisk ankle jerks and clonus. She had above average cognitive ability. An MRI scan showed extensive T2 hyperintensity in the cerebral white matter throughout the periventricular and subcortical regions. There was involvement of the cerebellum and of the posterior aspect of the pons and mid brain. It was

thought the changes could be consistent with metachromatic leukodystrophy.

Subsequent normal investigations included white cell lysosomal enzymes, urine glycosaminoglycans, urine oligosaccharides and sulphatides, urine amino and organic acids, plasma VLCFAs, CSF lactate, glucose, cells and protein.

At age three and a half she had continued to make normal cognitive progress but following another fall her gait had worsened. She had significant truncal ataxia and her fine motor skills were more unsteady. She had a moderate intention tremor.

After a review of the initial MRI images it was considered that the changes were consistent with 'childhood ataxia with diffuse central nervous system hypomyelination' (CACH), a condition also known as 'vanishing white matter disease' (VWM).

Repeat MRI (Figs 1 and 2) at 3 years 10 months showed progression of the white matter disease with extensive T2 hyperintensity and, on Fluid Attenuated Inversion Recovery (FLAIR) imaging, areas that were of cerebrospinal fluid (CSF) signal intensity, in keeping with rarefaction and cystic degeneration of large parts of the white matter. Within the rarefied white matter dots and stripes were seen consistent with preserved tissue strands.

Molecular analysis revealed her to be compound heterozygous for two mutations, 1813delC and 338G > A, in the *EIF2B5* gene, thus confirming the diagnosis of VWM. Her parents were carriers and there were no other affected family members. The first mutation leads to a frameshift, the second to an amino acid substitution (at position 113 of the protein arginine is changed into histidine). The latter mutation was not found in 268 control chromosomes, making it unlikely that it is a benign polymorphism.

She has subsequently made good progress. At age 6 years she is a happy child of normal intelligence who enjoys school. She is very unsteady on her feet and requires a motorized wheelchair for mobility. She has a marked tremor and has a lot of difficulty with her fine motor skills. She has normal vision and hearing. The spasticity in her lower limbs has resulted in flexion deformities at the ankles requiring orthopaedic intervention.

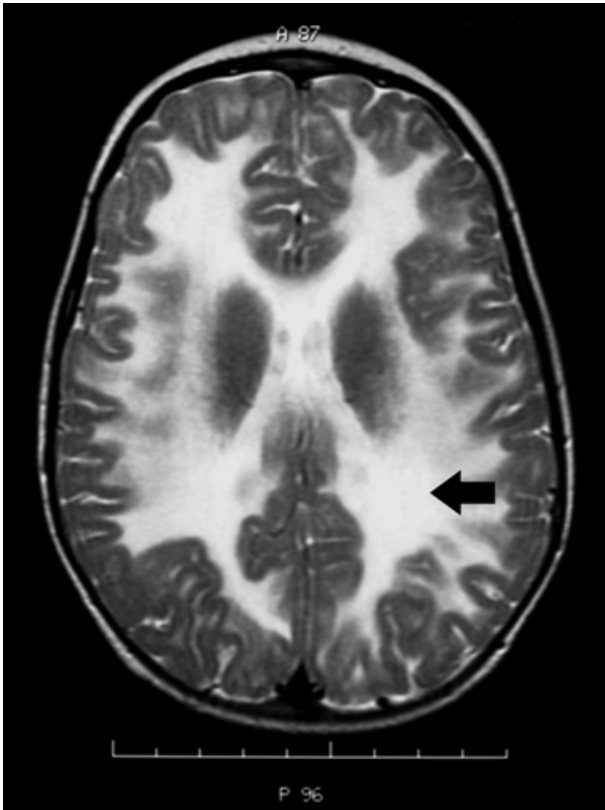


Fig. 1 Axial T2 magnetic resonance image (MRI) at 3 years 10 months showing a severe widespread leukodystrophy with some areas having signal intensity similar to cerebrospinal fluid (CSF) (arrow). The grey matter is preserved and there is no cerebral atrophy.

DISCUSSION

Vanishing white matter disease was first described in 1993 and subsequent reports have revealed a characteristic phenotype of a disease free period followed by a chronic progressive and often episodic deterioration of motor skills in early childhood and yet relatively preserved cognition.¹⁻³ This patient had a history of excessive drowsiness followed by clinical deterioration after episodes of otherwise mild trauma or infection. This is typical for VWM and thus an important clue in the history of patients with developmental regression and/or leukodystrophy. While the condition is classically seen in children, adults with a milder phenotype of late onset deterioration and mild cognitive impairment have been described.⁴

MRI changes are distinctive with extensive cerebral white matter abnormalities, variable cerebellar vermis atrophy and involvement of the pontine tegmentum tracts. The abnormal white matter can have a very characteristic MRI signal intensity signal that is consistent with CSF across a range of images (Figs 1 and 2). This is in contrast to other leukoencephalopathies where the abnormal white matter may have signal intensity similar to CSF on T2 sequences but on proton density and FLAIR images differs. Post mortem examination confirms the extensive white matter disease with widespread cavitation and cystic changes.²⁻⁴ Early in the course of the disease the white matter may not yet be 'vanishing' and repeated radiological investigation may be warranted.

The genes responsible for VWM were described in 2001 and 2002.^{5,6} The majority of patients have mutations in the *EIF2B5*

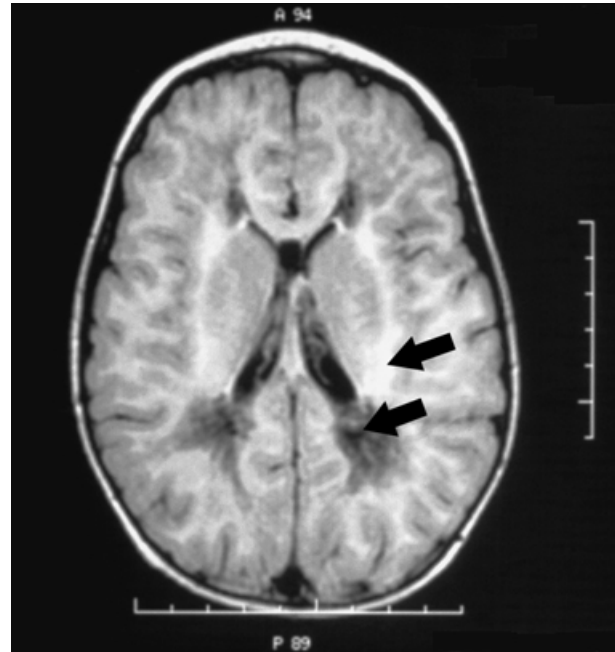


Fig. 2 Axial FLAIR magnetic resonance image (MRI) at 3 years 10 months. There are areas of mildly increased signal throughout the white matter indicating a widespread leukodystrophy (top arrow). There are other areas of 'white matter' that have signal intensity similar to cerebrospinal fluid (CSF) (dark area, bottom arrow). These are typical of vanishing white matter (VWM) disease and are likely to represent areas of cavitation and cystic change.

gene on chromosome 3q27. This gene encodes the ϵ -subunit of the eukaryotic translation initiation factor eIF2B. Patients may also have mutations in *EIF2B1*, *EIF2B2*, *EIF2B3* and *EIF2B4*, encoding the α , β , γ , and δ -subunits of eIF2B, respectively. eIF2B plays a key role in the synthesis of protein and its regulation under different conditions. It is required for initiation of translation of mRNA into protein.⁷ Without eIF2B protein synthesis does not occur. Conversely eIF2B also appears to be especially important in the down regulation of mRNA translation and thus protein synthesis under a variety of stress conditions and in the recovery phase that follows.^{8,9} This reaction is part of the so-called 'cellular stress response' or 'heat-shock' response, which is important to avoid the misfolding and coagulation of proteins that can occur in elevated temperatures. It is likely that the defect in eIF2B explains the deterioration of VWM patients under conditions of stress. However, the pathophysiology of VWM is still poorly understood. An important question is why mutations should preferentially affect white matter while the eIF2B genes are expressed in all cells of the body.

Specific pharmacological treatment for the condition is not available. The usual social, educational and occupational supports for children with these forms of disability are important. Immunization for influenza, varicella and measles is probably indicated due to the natural infection would have on an affected child. Caution regarding reactions to the vaccinations must be taken and paracetamol could be given prophylactically. Avoidance of situations that are likely to expose the child to an unnecessary risk of trauma or infection is recommended. In practice however, this is difficult and care must be taken not to interfere too much in the child's quality of life. The prognosis

for VWM is guarded although not predictable. Patients can have long periods of 'remission' but generally there is chronic step-wise progression of the disease. There does not appear to be a clear phenotype/genotype correlation.^{5,6}

To our knowledge this is the first confirmed Australasian case of vanishing white matter disease. A number of small cohorts have been described elsewhere and many patients have been confirmed worldwide (Van de Knapp unpubl. obs.). MRI changes consistent with a leukoencephalopathy are always apparent at the time of symptoms. However, in the initial phase of the disease MRI does not necessarily show evidence of white matter rarefaction. The MRI picture is not specific in those patients, but later in the course of the disease, MRI shows white matter rarefaction and allows a radiological diagnosis.

In general the finding of ataxia and spasticity in a patient with a history of chronic progressive, perhaps episodic, deterioration after being previously well should alert the clinician to the possibility of VWM. The absence of other causes and the presence of suggestive white matter changes make the diagnosis likely and molecular analysis should be sought.

ACKNOWLEDGEMENTS

The authors thank Dr D Jamison, Starship Hospital, Auckland and Dr S Naidu and Dr G Bibat at the Kennedy Krieger Institute in Baltimore, USA for their help in the clinical aspects of this case.

REFERENCES

- 1 Hanefeld F, Holzbach U, Kruse B, Wilichowski E, Christen HJ, Frahm J. Diffuse white matter disease in three children: an encephalopathy with unique features on magnetic resonance imaging and proton magnetic resonance spectroscopy. *Neuropediatrics* 1993; **24**: 244–8.
- 2 Schiffmann R, Moller JR, Trapp BD *et al.* Childhood ataxia with diffuse central nervous system hypomyelination. *Ann. Neurol.* 1994; **35**: 331–40.
- 3 Van der Knaap MS, Barth PG, Gabreels FJ *et al.* A new leukoencephalopathy with vanishing white matter. *Neurology* 1997; **48**: 845–55.
- 4 Van der Knaap MS, Kamphorst W, Barth PG, Kraaijeveld CL, Gut E, Valk J. Phenotypic variation in leukoencephalopathy with vanishing white matter. *Neurology* 1998; **51**: 540–7.
- 5 Leegwater PAJ, Vermeulen G, Konst AAM *et al.* Subunits of the translation initiation factor eIF2B are mutant in leukoencephalopathy with vanishing white matter. *Nature Genet.* 2001; **29**: 383–8.
- 6 Van der Knaap MS, Leegwater PAJ, Konst AAM *et al.* Mutations in each of the five subunits of translation initiation factor eIF2B can cause leukoencephalopathy with vanishing white matter. *Ann. Neurol.* 2002; **51**: 264–70.
- 7 Webb BL, Proud CG. Eukaryotic initiation factor 2B (eIF2B). *Int. J. Biochem. Cell Biol.* 1997; **10**: 1127–31.
- 8 Scheper GC, Mulder J, Kleijn M, Voorma HO, Thomas AA, van Wijk R. Inactivation of eIF2B and phosphorylation of PHAS-I in heat-shocked rat hepatoma cells. *J. Biol. Chem.* 1997; **272**: 26 850–6.
- 9 Scheper GC, Thomas AAM, Van Wijk R. Inactivation of eukaryotic initiation factor 2B *in vitro* by heat shock. *Biochem. J.* 1998; **334**: 463–7.