Characteristics of Early MRI in Children and Adolescents with Vanishing White Matter

Hannemieke D. van der Lei [1] Marjan E. Steenweg [1] Frederik Barkhof [2] Ton de Grauw [3] Marc d'Hooghe [4] Richard Morton [5] Siddharth Shah [6] Nicole Wolf [1] Marjo S. van der Knaap [1]

[1] Department of Child Neurology, VU University Medical Center, Amsterdam, The Netherlands
[2] Department of Radiology, VU University Medical Center, Amsterdam, The Netherlands
[3] Department of Neurology, Children's Hospital Medical Center, Cincinnati, United States
[4] Department of Neurology/Child Neurology, General Hospital Sint-Jan, Brugge, Belgium
[5] Department of Paediatrics, Derbyshire Children's Hospital, Nottingham, United Kingdom
[6] Bristol Royal Hospital for Children, Bristol, United Kingdom

Address for correspondence and reprint requests Marjo S. van der Knaap, M.D., Ph.D., Department of Child Neurology, VU University Medical Center, De Boelelaan 1117, Amsterdam 1081HV, The Netherlands (e-mail: ms.vanderknaap@vumc.nl).

Neuropediatrics 2012;43:22–26.

Abstract

Objective MRI in vanishing white matter typically shows diffuse abnormality of the cerebral white matter, which becomes increasingly rarefied and cystic. We investigated the MRI characteristics preceding this stage.

Design In a retrospective observational study, we evaluated all available MRIs in our database of DNA-confirmed VWM patients and selected MRIs without diffuse cerebral white matter abnormalities and without signs of rarefaction or cystic degeneration in patients below 20 years of age. A previously established scoring list was used to evaluate the MRIs.

Results An MRI of seven patients fulfilled the criteria. All had confluent and symmetrical abnormalities in the periventricular and bordering deep white matter. In young patients, myelination was delayed. The inner rim of the corpus callosum was affected in all patients.

Conclusions In early stages of VWM, MRI does not necessarily display diffuse cerebral white matter involvement and rarefaction or cystic degeneration. If the MRI abnormalities do not meet the criteria for VWM, it helps to look at the corpus callosum. If the inner rim (the callosal-septal interface) is affected, VWM should be considered.

Keywords
- vanishing white matter
- MRI
- children
- adolescents
- leukoencephalopathy

Introduction

Vanishing white matter (VWM; MIM #603896) is a leukoencephalopathy with autosomal recessive inheritance, characterized by slowly progressive ataxia and spasticity with additional stress-provoked episodes of rapid deterioration after febrile infections, mild head trauma, or even acute fright.[1–3] Although VWM most frequently occurs in children, it affects people of all ages.[1,2,4–7] The disease is caused by mutations in the genes *EIF2B1–5* encoding the five subunits of eukaryotic initiation factor eIF2B. This protein complex is essential in all cells of the body given its pivotal role in protein synthesis and its regulation in stress conditions.[8]

MRI typically shows diffuse and symmetrical abnormalities of the cerebral white matter. Over time the cerebral white matter becomes progressively rarefied and cystic (►**Fig. 1C**).[2,6] Before DNA testing was available, the diagnosis of VWM was made by clinical and MRI criteria.[2,6]

received
October 10, 2011
accepted after revision
December 23, 2011

DOI http://dx.doi.org/10.1055/s-0032-1307456.
ISSN 0174-304X.

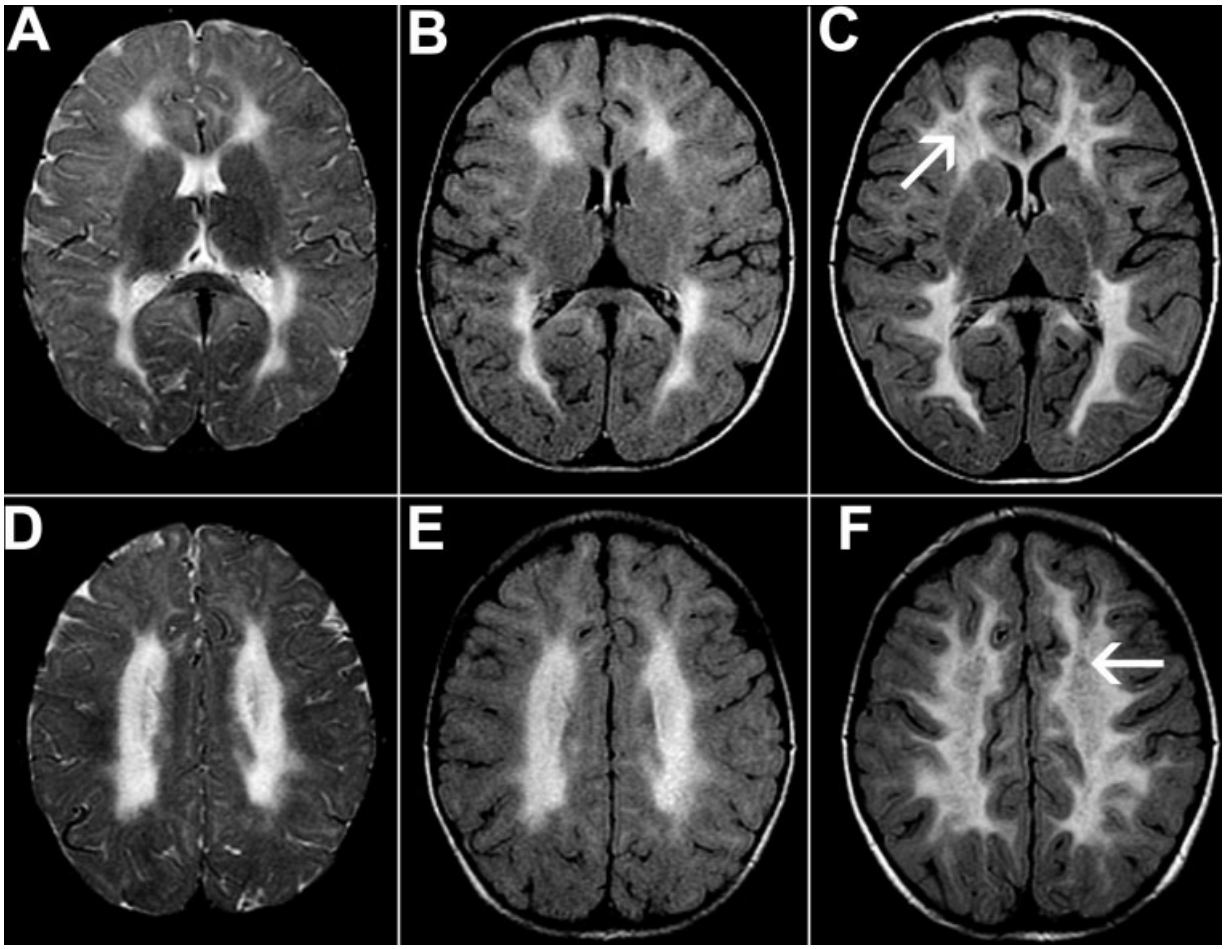

Figure 1 Early MRI with delayed myelination. T_2-weighted images (A, D) in patient 3 at age 1.7 years show abnormal periventricular and bordering deep white matter, while the subcortical white matter is not myelinated, indicative of significantly delayed myelination. On FLAIR (B, E), abnormal but non-rarefied white matter is hyperintense. At age 3.2 years (C, F), both FLAIR images show extensive cerebral white matter abnormalities and with rarefaction of the white matter (arrows).

Some patients, however, undergo MRI in the presymptomatic or early symptomatic stage and their MRIs may not fulfill the criteria.[2,5,6,9] We therefore performed a study on early MRI characteristics in VWM.

Patients and Methods

Study Design

Approval of the institutional review board was received for retrospective analysis of clinical and MRI information with waiver of informed consent.

In this retrospective observational study, we looked at all available MRIs in our database up to February 1, 2011. The database contains MRIs of VWM patients referred for DNA analysis. The inclusion criteria for the present study were the following:

1. Genetic confirmation of the diagnosis VWM.
2. Age at MRI below 20 years.
3. No diffuse cerebral white matter abnormalities on MRI.
4. No MRI signs of rarefaction or cystic degeneration of the cerebral white matter.

If a patient had more than one MRI fulfilling criteria 3 and 4, the first MRI was included. We also looked at follow-up MRIs to document the evolution of the abnormalities. We noted age of onset, age at MRI, disease duration, and clinical signs at time of MRI. Disease duration was defined as time between disease onset and first available MRI.

Evaluation of MRIs

All available MRIs of VWM patients were assessed by consensus of three investigators (HDWvdL, MES, and MSvdK). A previously established scoring list was used to evaluate the MRI studies.[10] Items were scored only as absent or present to minimize the effects of subjective rating.

White matter abnormalities were defined as areas of T_2-hyperintensity. White matter rarefaction was defined as T_2-hyperintense white matter with low signal on FLAIR images, but not as low as cerebrospinal fluid. Cystic degeneration was defined as T_2-hyperintense areas with on FLAIR images a signal as low as that of cerebrospinal fluid.

Results

The database contains the MRIs of 224 DNA-confirmed VWM patients. An MRI of seven patients fulfilled the inclusion criteria. Age, age of onset, disease duration, *EIF2B1–5*

Table 1 Patient and MRI Characteristics

Patient	1	2	3	4	5	6	7
Gender	F	F	F	F	M	F	M
Age at first MRI (y)	1.0	1.5	1.7	3.5	4.4	13.2	15.8
Number/age at follow-up MRI (y)	0/-	1/2.3	2/2.3–3.2	1/8.1	0/-	6/13.4–19.9	2/16.5–19.3
Age at onset (y)	no onset	1.5	1.7	1.0	4.4	13.0	15.0
Disease duration (y)	no onset	0	0	2.5	0	0.2	0.8
Gene mutated	*EIF2B5*	*EIF2B5*	*EIF2B2*	*EIF2B4*	*EIF2B5*	*EIF2B5*	*EIF2B2*
Mutation 1	c.247delC, p.Leu83X	c.338G > A, p.Arg113His	c.599G > T, p.Gly200Val	c.499–1G > C, p.Val167HisfsX47	c.5C > T, p.Ala2Val	c.338G > A, p.Arg113His	c.599G > T, p.Gly200Val
Mutation 2	c.475A > G, p.Ile159Val	c.1208C > T, p.Ala403Val	c.638A > G, p.Glu213Gly	c.626A > G, p.Arg209Gln	c.631A > G, p.Arg211Gly	c.1946T > C,p.Ile649Thr	c.880G > T, p.Val294Phe
Abnormalities on the first MRI							
Periventricular WM	yes	yes	yes	yes	yes	yes	yes
Deep WM	yes	yes	yes	yes	yes	yes	yes
Subcortical WM	no	no[a]	no[a]	no[a]	no[a]	no[a]	no[a]
Cerebellar WM	yes	yes	yes	no	no	no	no
Pons-CTT	no	yes	yes	yes	yes	no	no
Internal capsule-posterior limb	no	no	no	no	no	no	no
External/extreme capsule	no	no	no	no	no	no	no
Corpus callosum-inner rim	yes	yes	yes	yes	yes	yes	yes
Corpus callosum-outer rim	no	no	no	no	no	no	no
Delayed myelination	yes	yes,	yes	yes	yes	no	no

y, year(s); WM, white matter; CTT, central tegmental tracts.
[a]almost completely spared except for small area

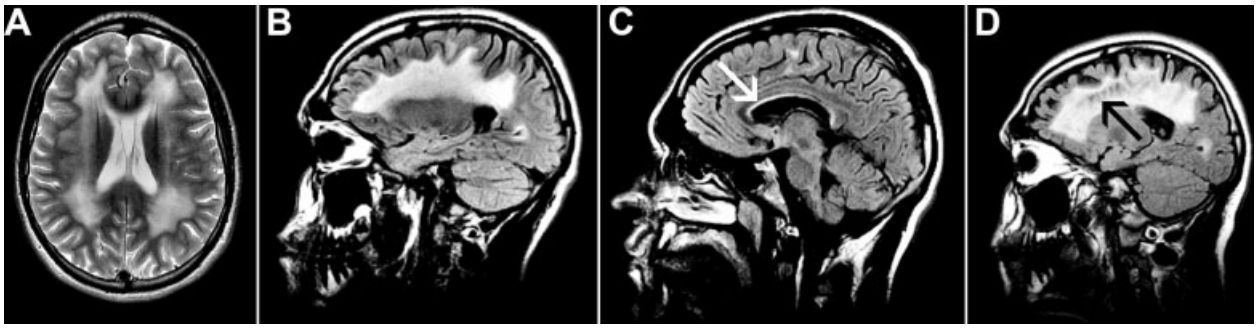

Figure 2 Early MRI in adolescent. Axial T_2-weighted (A) and sagittal FLAIR images (B, C) of patient 7 at age 15.8 years show signal abnormalities in the periventricular and bordering deep white matter and neither delayed myelination nor atrophy. The inner rim of the corpus callosum is affected (C, arrow). At age 19.3 years, sagittal FLAIR image (D) shows more extensive abnormalities and rarefaction of the white matter (arrow).

mutations, and MRI abnormalities are summarized in ►**Table 1**.

All MRIs showed abnormalities in the periventricular and deep cerebral white matter and the inner rim of the corpus callosum (the callosal-septal interface) (►**Figs. 1** and **2**). All white matter abnormalities were confluent and symmetrical. There was no predominance of white matter abnormalities in frontal, parietal, occipital or, temporal regions. The five youngest patients showed deficient myelination. In four patients, the myelin deficiency was minor, only apparent in mild T2 hyperintensity in directly subcortical and basotemporal areas. In patient 3 myelin deficiency was more prominent and diffuse (►**Fig. 1**). The central tegmental tracts in the pons were involved in four young patients. No gray matter abnormalities were found.

We evaluated the 12 available follow-up MRIs of five patients (for numbers and ages see ►**Table 1**). Over time, there was a shift from predominant involvement of the periventricular and bordering deep white matter toward diffuse white matter abnormalities with more extensive involvement of deep and later subcortical white matter. With time, the classical MRI pattern of VWM with signs of rarefaction of the cerebral white matter was found in all patients. In patient 3 progress of myelination was noted on follow-up. In patients 2 and 4 follow-up MRIs showed diffuse white matter disease, making assessment of progress of myelination impossible.

With respect to clinical findings at time of the first MRI, patient 1 underwent MRI in the presymptomatic stage after her brother was diagnosed with VWM. Patients 2 and 5 had one episode with transient deterioration following a febrile infection or fall, in patient 2 followed by slowly progressive spasticity and ataxia. Patient 3 presented with mild developmental delay, hypotonia, and growth retardation. Patients 4, 6, and 7 had headaches; two had migraines with aura.

Discussion

Central MRI criteria to diagnose VWM are (1) extensive or diffuse cerebral white matter abnormalities and (2) evidence of rarefaction or cystic degeneration of part of or all cerebral white matter.[2,6,9] We were aware of the fact that these MRI criteria are not suitable to diagnose VWM in the earliest stages of the disease.[2,9] In this study, we focused on the MRI pattern in early stages of VWM in patients younger than 20 years.

Young patients with a more severe disease variant (patients 1–5) had signal abnormalities in the periventricular and deep white matter and additionally signs of variably deficient myelination (►**Fig. 1**). On follow-up, the classical MRI picture of VWM with diffuse cerebral white matter abnormalities and white matter rarefaction followed soon. Patients with teenage onset (6 and 7) showed signal abnormalities in the periventricular and bordering deep white matter without signs of deficient myelination. The MRIs of these patients also evolved into the classical VWM MRI picture (►**Fig. 2**).

Independent of age of onset, all patients displayed a gradient in the cerebral white matter signal abnormalities. The periventricular and bordering deep white matter was affected from the beginning. Over time, the rest of the deep and then the subcortical cerebral white matter became affected. In all patients the inner rim of the corpus callosum was involved, which is a known finding suggestive of VWM (►**Fig. 2**).[9] Most young patients showed lesions in the central tegmental tracts. Such lesions are known to occur in VWM, but have also been observed in other conditions and are, in fact, nonspecific.[11]

Consistent with earlier observations,[2,6] we did not find normal or almost normal MRIs in the beginning. Even in the presymptomatic stage, the cerebral white matter already shows extensive abnormalities (patient 1). But in contrast to what was previously thought,[2,6,9] the cerebral white matter abnormalities are not diffuse or almost diffuse from the presymptomatic stage onwards. Initial white matter abnormalities are present in the periventricular and bordering deep white matter and spread out to the directly subcortical white matter.

The differential diagnosis is difficult in the early MRI stages.[9] In patients presenting with rapid neurological deterioration after a febrile infection, disorders to consider are encephalitis, acute demyelinating encephalomyelitis (ADEM), and mitochondrial defects. In contrast to VWM, MRI typically shows asymmetrical multifocal white matter lesions in ADEM[12] and variable lesions in white as well as gray matter in encephalitis.[13] In both conditions one may find contrast enhancement and prominent diffusion restriction of the

affected areas, unlike in VWM.[12,13] In VWM the diffusion restriction is seen in the relatively spared areas.[14] In mitochondrial leukoencephalopathies with rapid deterioration following an infection, MRI may show a picture similar to that of VWM on T2-weighted and FLAIR images, but contrast enhancement and diffusion restriction within the lesions again help in the differentiation from VWM.[15] Additionally, mitochondrial disorders are usually associated with lactate elevations in body fluids and MR spectroscopy, which is not the case in VWM.[15]

In patients with subacute or chronic neurological deterioration mitochondrial leukoencephalopathies, lysosomal storage disorders (especially metachromatic leukodystrophy or Krabbe disease), and peroxisomal disorders are important disorders in the differential diagnosis. MRI features allow distinction from VWM in most cases.[16] A hint toward the diagnosis VWM is the selective involvement of the inner rim of the corpus callosum.

In most VWM patients with an early inconclusive MRI, evidence of white matter rarefaction and cystic degeneration follows soon, allowing an MRI-based diagnosis of VWM. Exceptions are the adult onset variants of VWM. In those patients, the cerebral white matter abnormalities may be slow to become diffuse, may mainly show atrophy and no signs of rarefaction or cystic degeneration for many years after onset, making an MRI-based diagnosis difficult[5,17] For all ages it is true that if the MRI abnormalities do not meet the criteria for VWM, it helps to look at the corpus callosum. If the inner rim is affected, VWM should be considered. If the MRI findings remain inconclusive, it may be worthwhile to assess the known biochemical markers for VWM, such as cerebrospinal fluid glycine and asialotransferrin.[18,19]

Acknowledgments

We would like to thank all patients, families, and colleagues who contributed to our studies. Financial support for our work was provided by the Optimix Foundation for Scientific Research, the Dutch Organization for Scientific Research (ZonMw TOP grant 9120.6002 and ZonMw AGIKO grant 920–03–308), and the Dr WM Phelps Foundation (grant 2008029 WO). The funding agencies had no direct involvement with the contents of the studies in any way.

References

1 Schiffmann R, Moller JR, Trapp BD, et al. Childhood ataxia with diffuse central nervous system hypomyelination. Ann Neurol 1994;35(3):331–340

2 van der Knaap MS, Barth PG, Gabreëls FJ, et al. A new leukoencephalopathy with vanishing white matter. Neurology 1997;48 (4):845–855

3 Vermeulen G, Seidl R, Mercimek-Mahmutoglu S, Rotteveel JJ, Scheper GC, van der Knaap MS. Fright is a provoking factor in vanishing white matter disease. Ann Neurol 2005;57(4): 560–563

4 Fogli A, Schiffmann R, Bertini E, et al. The effect of genotype on the natural history of eIF2B-related leukodystrophies. Neurology 2004;62(9):1509–1517

5 Labauge P, Horzinski L, Ayrignac X, et al. Natural history of adult-onset eIF2B-related disorders: a multi-centric survey of 16 cases. Brain 2009;132(Pt 8):2161–2169

6 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(2):540–547

7 van der Knaap MS, van Berkel CG, Herms J, et al. eIF2B-related disorders: antenatal onset and involvement of multiple organs. Am J Hum Genet 2003;73(5):1199–1207

8 van der Knaap MS, Leegwater PA, Könst AA, 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(2):264–270

9 van der Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. Lancet Neurol 2006;5(5):413–423

10 van der Knaap MS, Breiter SN, Naidu S, Hart AA, Valk J. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. Radiology 1999;213(1):121–133

11 Shioda M, Hayashi M, Takanashi J, Osawa M. Lesions in the central tegmental tract in autopsy cases of developmental brain disorders. Brain Dev 2011;33(7):541–547

12 Tenembaum S, Chitnis T, Ness J, Hahn JS; International Pediatric MS Study Group. Acute disseminated encephalomyelitis. Neurology 2007;68(16, Suppl 02):S23–S36

13 Tunkel AR, Glaser CA, Bloch KC, et al; Infectious Diseases Society of America. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2008;47(3):303–327

14 van der Lei HD, Steenweg ME, Bugiani M, et al. Restricted diffusion in vanishing white matter. Arch Neurol 2012; February 6 (Epub ahead of print)

15 Saneto RP, Friedman SD, Shaw DW. Neuroimaging of mitochondrial disease. Mitochondrion 2008;8(5-6):396–413

16 van der Knaap MS, Valk J. Magnetic resonance of myelination and myelin disorders. 3 rd edition. Springer, Heidelberg, 2005

17 van der Knaap MS, Leegwater PA, van Berkel CG, et al. Arg113His mutation in eIF2Bepsilon as cause of leukoencephalopathy in adults. Neurology 2004;62(9):1598–1600

18 van der Knaap MS, Wevers RA, Kure S, et al. Increased cerebrospinal fluid glycine: a biochemical marker for a leukoencephalopathy with vanishing white matter. J Child Neurol 1999;14(11):728–731

19 Vanderver A, Schiffmann R, Timmons M, et al. Decreased asialotransferrin in cerebrospinal fluid of patients with childhood-onset ataxia and central nervous system hypomyelination/ vanishing white matter disease. Clin Chem 2005;51(11):2031–2042