CHAPTER 3

Characteristics of early MRI in children and adolescents with vanishing white matter

H. D. W. van der Lei
M. E. Steenweg
F. Barkhof
T. J. de Grauw
M. D’Hooghe
R. E. Morton
S. Shah
N. I. Wolf
M. S. van der Knaap

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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.
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.4,8,19 Although VWM most frequently occurs in children, it affects people of all ages.1,2,4,8,9,13 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.12 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).8,9 Before DNA testing was available, the diagnosis of VWM was made by clinical and MRI criteria.8,9 Some patients, however, undergo MRI in the presymptomatic or early symptomatic stage and their MRIs may not fulfill the criteria.2,8,9,16 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.
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 (C, F), both FLAIR images show extensive cerebral white matter abnormalities and with rarefaction of the white matter (arrows).

The inclusion criteria for the present study were:
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 MvdK). 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 T₂-hyperintensity. White matter rarefaction was defined as T₂-hyperintense white matter with low signal on FLAIR images, but not as low as cerebrospinal fluid. Cystic degeneration was defined as T₂-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 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) (figure 1,2). 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 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 (figure 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, page 83). Over time, there was a shift from predominant involvement of the periventricular and bordering deep white matter towards 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 pre-symptomatic 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.
Chapter 3

Figure 2 | Early MRI in adolescent. Axial T2-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, sagittal FLAIR image (D) shows more extensive abnormalities and rarefaction of the white matter (arrow).

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.\textsuperscript{8,9,16} We were aware of the fact that these MRI criteria are not suitable to diagnose VWM in the earliest stages of the disease.\textsuperscript{8,16} 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 (figure 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 (figure 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 (figure 2).\textsuperscript{16} 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.\textsuperscript{5}

Consistent with earlier observations\textsuperscript{8,9}, 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\textsuperscript{8,9,16}, 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.\textsuperscript{16} 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\(^6\) and variable lesions in white as well as grey matter in encephalitis.\(^7\) In both conditions one may find contrast enhancement and prominent diffusion restriction of the affected areas, unlike in VWM.\(^6,7\) In VWM the diffusion restriction is seen in the relatively spared areas.\(^17\) 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.\(^3\) Additionally, mitochondrial disorders are usually associated with lactate elevations in body fluids and MR spectroscopy, which is not the case in VWM.\(^3\)

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.\(^15\) A hint towards 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.\(^2,14\) 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.\(^11,18\)
REFERENCES


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y, year(s); WM, white matter; CTT, central tegmental tracts; aalmost completely spared except for small areas
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