Consensus-Based Expert Recommendations for Diagnosis and Clinical Management of Vanishing White Matter.

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Consensus-Based Expert Recommendations for Diagnosis and Clinical Management of Vanishing White Matter

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Neurology® 2025;105:e214320. doi:10.1212/WNL.0000000000214320

Abstract

Vanishing white matter (VWM) is a rare disorder, characterized by degeneration of CNS white matter, clinically often exacerbated by stressors such as fever and minor head trauma. VWM is caused by biallelic pathogenic variants in the *EIF2B1-5* genes, causing reduced activity of eukaryotic initiation of translation factor 2B, resulting in dysregulation of the integrated stress response (ISR). New scientific insights and increased clinical trials in experimental therapies highlight the need for clinical guidelines to improve and standardize care for patients with VWM worldwide. Standardized care is important for therapy development, as it lessens clinical variability of trial participants at study entry, enabling more sensitive evaluation of treatment outcomes. The aim of this study was to develop expert consensus-based recommendations for diagnosis and management of VWM. A real-time Delphi process with a multidisciplinary expert panel was conducted to formulate consensus-based recommendations. A literature review was performed to determine the strength of available evidence supporting each recommendation. The consensus yielded 43 recommendations on diagnosis, including genetic and MRI criteria, and on clinical management concerning disease progression, acute and long-term care, and preventive strategies. All known pathogenic and likely pathogenic *EIF2B1-5* variants were identified from the literature and Amsterdam Leukodystrophy Center laboratory. An overview of these *EIF2B1-5* variants was composed to facilitate diagnosis. Clinically used drugs may activate the ISR, posing a risk in VWM, or have no effect on or suppress the ISR, being probably safe in VWM. A second literature search explored the effects of clinically frequently used drugs on the ISR. Drugs were categorized into those likely to activate the ISR, suppress it, and have no likely effects on the ISR. Final judgment was achieved in a consensus meeting of experts. A patient management card was developed with input from clinical experts and patient advocates to provide information on these consensus-based recommendations in lay language and bridge the gap between scientific evidence and expert opinion on one side and the practical needs of clinicians and families on the other side. This study contributes to improving and standardizing VWM care based on scientific and expert insights, while highlighting key areas for future research.

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The Article Processing Charge was funded by the authors.

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Glossary

eIF2B = eukaryotic initiation of translation factor 2B; **ISR** = integrated stress response; **VWM** = vanishing white matter.

Introduction

Vanishing white matter (VWM, OMIM #603896) is a rare (estimated live birth incidence ~1:100.000) leukodystrophy characterized by diffuse cerebral white matter abnormalities with rarefaction and cystic decay.[1,2] Patients can present at any age with chronic neurologic decline and additional subacute episodes of rapid neurologic deterioration provoked by stressors such as febrile infections.[2] Younger age at symptom onset is associated with more severe and rapid disease progression. In all patients, VWM is a devastating disease leading to premature death.[2]

In the past 3 decades, clinical studies, MRI, pathology, and fundamental research have increased understanding of the disease, paving the way for improved disease management. The pathomechanisms are not yet fully elucidated, but a dysregulated integrated stress response (ISR) caused by decreased activity of eukaryotic initiation factor 2B (eIF2B) due to biallelic pathogenic variants in any of the 5 eIF2B subunits drives the disease.[3,4] Currently, there is no curative or disease-modifying treatment for VWM, although multiple therapeutic targets within the ISR have been identified. Two promising compounds, that is, guanabenz (EU Clinical Trials Register identifier: EudraCT 2027-001438-25, CTIS 2023-503320-89-00) and ABBV-CLS-7262 (fosigotifator, ClinicalTrials.gov identifier NCT05757141 and NCT06594016), activating eIF2B indirectly or directly, are currently under clinical investigation.

Emerging scientific insights and the increased implementation of clinical trials increase the need for clinical guidance to improve and harmonize care for patients with VWM globally. A study investigating the impact of VWM on 63 families confirmed this vital need for clear recommendations.[5] Therefore, the aim of this study was to define consensus-based recommendations on the diagnosis and clinical management of VWM.

Methods

In 2019, an international consortium of 9 adult and pediatric neurologists, expert in leukodystrophies, especially VWM, was founded to facilitate diagnosis and therapy development in VWM.[6–8] This clinical expert consortium initiated a real-time Delphi consensus procedure (April 5, 2024–June 1, 2024) to establish agreement on recommendations to guide clinical care in patients with VWM. We used a multistep approach consisting of the following: (1) expert and patient advocate consultation to identify the topics to be discussed in the eDelphi process and to formulate draft recommendations (expert panel and patient advocates), (2) a systematic literature review to collect all available evidence substantiating or opposing the draft recommendations (R.J.v.V. and D.H.S.), (3) execution of the real-time Delphi procedure to agree on the recommendations (expert panel), and (4) agreement on the lay language material including a patient management card (VWM consortium and patient advocates).

Expert Panel

A total of 26 candidate panelists were invited to participate in the eDelphi process, of whom 25 accepted the invitation and 24 participated in voting. The expert panel consisted of the VWM consortium members (n = 9, A.V., J.L.B., I.K.-M., G.B., E.B., A.F., P.V.S., N.I.W., M.S.v.d.K.), supplemented with other pediatric and adult leukodystrophy experts (n = 6, S.G., D.T., C.S., J.L.O.-M., E.S., B.B.) and targeted specialists from relevant medical fields with experience with patients with leukodystrophy, including endocrinologists (n = 3, K.W.t.H., S.E.H., A.M.S.), pediatric gynecologist (n = 1, K.G.H.), geneticists (n = 2, R.v.S., I.T.), pediatric intensivists (n = 2, J.M., M.v.H.), and a complex care pediatrician (n = 1, N.J.). Panelists were asked to give input on the recommendations but could abstain from voting on statements on which they had insufficient expertise. An overview of the voting process is given in eTable 1. Dietitians (n = 3, G.H.H., C.S.B., C.T.) were consulted for the statements on dietary practices. A patient representative advisory board comprised 5 patient advocates representing different patient advocacy organizations, that is, VWM Families Foundation, United Leukodystrophy Foundation, and Vereniging Volwassenen, Kinderen en Stofwisselingsziekten.

Recommendations

This project focused on topics requiring VWM-specific recommendations. The topics and draft recommendations were identified in multiple video meetings and through the expert panel's written input, resulting in 43 draft recommendations. Input from patient advocates was incorporated during the drafting process. Recommendations on general supportive care for children and adults with disabilities were not part of this procedure.

Systematic Literature Review

A systematic literature search was performed to collect relevant evidence for the recommendations. The search strategy included a search string consisting of "vanishing white matter" and its synonyms, focusing on articles written in English and published after 2000. A PubMed search on November 10, 2023, identified 319 hits. Reference screening was performed to identify additional relevant articles. Title, abstract (Tiab), and full-text screening was performed independently by 2 researchers (R.J.v.V. and D.H.S.). The level of evidence was

determined for all included records, using a modified grading scheme [9] because of the limited literature available for VWM (eTable 2). Relevant evidence from the included articles was extracted and organized in draft recommendations. The available evidence was tabulated for each draft recommendation, indicating whether it supported or opposed the recommendation. Eventually, 46 original articles were included. eFigure 1 presents a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of the literature search.

Clinically used drugs may activate the ISR, posing a risk for patients with VWM, or have no effect on or suppress the ISR, being probably safe for patients with VWM. A second systematic literature search was performed to investigate the effect of drugs frequently used in VWM on the ISR. Multiple search strings were combined for this search. The primary search string used the term "Integrated Stress Response" and its key components. This was combined with search strings for various drug classes and their synonyms. eFigure 2 presents details of the literature search using a methodology similar to that described above for the recommendations. Articles were reviewed, and final judgment was achieved in a consensus meeting with the VWM consortium and biomolecular scientists with ISR expertise (T.E.M.A. and S.G.C.). Eventually, 53 articles were included.

Real-Time Delphi Procedure

A real-time Delphi procedure was conducted using the software tool eDelphi 2024.[10] All panelists received an overview of the draft recommendations with available literature evidence. Panelists were invited to indicate their level of agreement or disagreement using a 5-point Likert scale. They were encouraged to provide a rationale for their responses through an anonymous comment section during a 6–8-week period. Weekly reminders encouraged participation.

A plenary discussion with VWM consortium members (n = 8) and leukodystrophy experts (n = 4), held on April 26, 2024, led to the modification of 17 statements. All panelists were provided with the revised statements, minutes from the plenary discussion, and supplementary information regarding the pathophysiology of VWM. The modified statements were reintroduced into the eDelphi platform, and panelists were invited to vote again. Following typical Delphi procedures,[11] the percentage of consensus was calculated based on the agreeing and disagreeing votes (number of votes "strongly agree" + number of votes "agree")/(total number of votes without the votes "neutral"). Neutral votes were interpreted as having no preference and, therefore, did not influence the percentage of consensus. However, if the neutral vote amounted to ≥25% of the total panel votes, this reduced the strength of the recommendations. Statements were strongly recommended (A) if ≥75% consensus was reached for "strongly agree," with votes for "neutral" being <25%. Statements were recommended (B) if ≥75% consensus was reached for "agree" or "strongly agree," with votes for "neutral" being <25%. Statements were suggested (C) if ≥75% consensus was reached for "strongly agree" or "agree," but ≥25% of the panel voted for "neutral."

Statistical Analysis

Descriptive analysis was performed by R.J.v.V. and D.H.S. Percentages of agreeing and disagreeing responses in the eDelphi process were calculated to summarize the distribution of expert opinions.

Patient Management Card

The coordinating researchers (D.H.S. and R.J.v.V.) drafted the lay language material, including a visual representation of the recommendations. The leaflet was further refined based on several rounds of written input from patient advocates and VWM consortium members. The final contents and leaflet design were agreed upon in an online meeting of the VWM consortium.

Variant Update

We listed all known pathogenic and likely pathogenic variants in *EIF2B1-5* genes reported since the 2010 last variant update[12] up to October 2024, supplemented by variants from the VWM database of the Amsterdam Leukodystrophy Center and an extensive literature search using the Franklin Tool.[13]

Standard Protocol Approvals, Registrations, and Patient Consents

This study did not involve human participants or identifiable personal data. Therefore, approval by an institutional review board was not required.

Data Availability

Raw data of the eDelphi voting may, after approval of those involved, be shared at the request of any qualified investigator for purposes of replicating procedures and results.

Results

Table 1 provides an overview of all recommendations. eTable 3 provides their strength, substantiating evidence, and degree of agreement. eTable 4 details the votes in the eDelphi procedure and the resulting classification. The following sections elaborate on the main considerations and points of discussion.

Diagnosis

There was majority agreement that the diagnosis of VWM is based on a combination of clinical features, brain MRI characteristics, and genetic confirmation. MRI characteristics of VWM are listed in Table 2 and illustrated in Figures 1 and 2. Recognizing VWM on brain MRI may be challenging, requiring referral to a leukodystrophy expert center for MRI assessment. In the case of uncertain genotypes, MRI and clinical assessment by a VWM expert were regarded as the best next step to determine whether the patient has VWM. MRI is considered most helpful in determining whether the

patient has VWM if 1 pathogenic or likely pathogenic variant is found in a patient. In patients with a suspected VWM diagnosis based on a typical MRI and a single pathogenic or likely pathogenic variant in a single *EIF2B1-5* gene, attempting to identify a second variant in trans, even if of uncertain significance, was considered necessary, for example, by Sanger sequencing, cDNA analysis, array comparative genomic hybridization, multiplex ligation-dependent probe amplification, and long-read genome sequencing. Most known pathogenic variants are missense, and biallelic null variants have not yet been described. Therefore, if the MRI pattern is consistent with VWM but no pathogenic or likely pathogenic variant in *EIF2B1-5* is found, it is unlikely that the patient has VWM and another diagnosis should be looked for. In this case, mitochondrial leukoencephalopathies constitute the most likely alternative (Table 2). Several diseases may clinically mimic VWM. An overview is provided in eTable 5. A detailed overview of all known genotypes associated with VWM is provided in eTable 6.

Prediction of Disease Course

Full agreement was reached on disease course prediction. Key predictors include age at onset and genotype,[2,17,18] of which age at onset is the strongest predictor. Typically, earlier onset is associated with faster disease progression. A previous natural history study showed that, especially for onset before the age of 4 years, earlier onset was associated with faster disease progression.[2] It is important to note that other factors co-determine the disease course, such as the presence of ISR stressors. With longer disease duration, the occurrence of such factors becomes more likely, contributing to increasing disease variability.[2] It was noted that these stressors constitute a risk of triggering an episode of acute decline, but that such an episode does not always follow. Prediction by genotype is hampered by disease variability, also between siblings, and by the lack of comprehensive information in the case of novel variants, which frequently occur.

Measures to Prevent Episodes of Rapid Decline

Stressors activating the ISR[2,19,20] provoke episodes of acute decline, which negatively affect the disease course and outcome.[2] Therefore, the importance of implementing preventive measures to avoid ISR-activating stress factors was recognized. However, possible constraints on the quality of patients' lives related to preventive measures were also recognized. Therefore, discussing benefits and disadvantages associated with such measures with patients and families in individual cases is essential.

Antipyretics

Fever activates the ISR, and febrile infections are the most common triggers for acute decline in patients with VWM.[2] Most agreed that measures to avoid and treat fever are indicated. The antipyretic of first choice, as potent and safe, would be ibuprofen or naproxen, to be combined with paracetamol/acetaminophen, if necessary. Age-based limitations and other risk factors to the use of these antipyretics in individual patients should be considered, and final antipyretic choices should be made on a case-by-case basis.

Antibiotics

When a patient presents with a febrile condition, efforts should be made to determine whether antibiotics are required. In cases where a bacterial infection is suspected but not confirmed, there was consensus that a lower threshold for initiating antibiotics should be considered compared with patients without VWM. It was, however, emphasized that in cases of frequent infections, consultation with an infectious disease specialist or immunologist could be valuable, and that before considering prophylactic antibiotics, nonantibiotic approaches should be explored.[21]

Vaccinations

There was complete consensus that although vaccinations may sometimes induce acute decline,[2] the risk associated with an infection is much higher than with the respective vaccination. Therefore, routine vaccinations, as well as vaccinations against COVID-19 and influenza, were recommended for patients with VWM. Recommendations for antipyretic use during vaccinations to avoid fever should be based on the type of vaccine, considering the likelihood of inducing fever and the expected duration of such fever.

Head Trauma

It was agreed by all that minor head trauma, the second most common trigger for acute decline in VWM,[2] should be avoided as much as reasonably possible without unduly restraining patients' activities of daily life.

Surgical Procedures

All agreed that surgical procedures in VWM require caution. Noninvasive options are preferred when possible, and the risk of perioperative infection should be minimized.

Behavioral Management

Apart from acute severe fright, psychological stress is not known to provoke acute decline. Avoiding psychological stress may lead to spoiling and cause behavioral difficulties. We, therefore, recommend standard behavioral management.

Medication

Although clinical evidence in patients is unavailable for most drugs, it was agreed that drugs that may activate the ISR should be avoided, if possible, because in VWM, the rapid decline is provoked by ISR activation. Clinical evidence for provoking decline is only present for anesthetics: anesthesia was a provoking factor in 16% of the patients with episodes of acute decline.[2] Inhalation anesthetics, such as sevoflurane, which are most commonly used to induce anesthesia in children, are known to activate the ISR and may pose a risk for patients with VWM (Table 3, eTable 7). It is, therefore, recommended to consider using alternative anesthetic agents, such as propofol, which do not affect the ISR. The risk is more theoretical and not based on clinical evidence for other drugs.

Table 1 Consensus-Based Recommendations

Number	Strength	Recommendation	Agreement (%)
Diagnosis (avoiding false-negative and false-positive diagnoses)			
1.1	A	Genetic confirmation should always be sought after suspected VWM diagnosis based on brain MRI findings	100
1.2	B	If a brain MRI is consistent with VWM (in description), the diagnosis of VWM is confirmed by the presence of 2 pathogenic or likely pathogenic variants or variants of unknown significance in one of the *EIF2B1-5* genes	100
1.3	A	If a brain MRI is consistent with VWM (in description) and a single pathogenic or likely pathogenic variant or variant of unknown significance is found in one of the *EIF2B1-5* genes, we recommend extra efforts to identify a second variant in the same gene	100
1.4	A	If a brain MRI is consistent with VWM and no (likely) pathogenic variants or variants of unknown significance in one of the *EIF2B1-5* genes can be found, we recommend searching for another cause	100
1.5	A	If variants in one of the *EIF2B1-5* genes are found in a patient, we recommend evaluation of a recent brain MRI to help determine a diagnosis of VWM.	100
1.6	A	When an index patient is diagnosed, we recommend genetic counseling to discuss family screening and family planning	100
Prediction of disease course			
2.1	A	Disease course can be predicted for age at onset younger than 4 years based on age at first signs, except for developmental delay	100
2.2	A	Known gene variants can help predict the disease course	100
2.3	A	Episodes of acute decline predict a worse disease course	100
2.4	A	Seizures predict a worse disease course	100
2.5		We suggest counseling families on predicted disease course based on the following statements	
2.5.1	A	A lower age at symptom onset is associated with a faster and more severe deterioration	100
2.5.2	B	Genotype is predictive of the phenotype	100
2.5.3	A	Factors known to precipitate episodes of rapid decline should be avoided because such episodes are associated with a more severe disease course	100
2.5.4	A	Treatment of epilepsy and seizures is important because patients with seizures have a more severe disease course	100
Measures to prevent episodes of rapid decline			
3.1	A	In the case of fever, we recommend the prompt use of antipyretics aiming at normal temperature	94
3.2	A	In the case of a febrile infection, we recommend close follow-up and to consider early use of antibiotics	100
3.3	B	In the case of recurrent and documented bacterial infections, prophylactic antibiotics can be considered in consultation with infectious diseases and/or immunology	100
3.4	B	We recommend vaccination according to the regular national vaccination program, provided that antipyretics are given to avoid fever as much as possible	100
3.5	A	We specifically recommend vaccination against frequent infections, such as influenza and COVID-19	100
3.6	A	We recommend wearing a helmet for daily-life activities associated with enhanced risk of head trauma, such as bicycling	100
3.7	B	We recommend avoiding sports activities associated with enhanced risk of head trauma	100
3.8	A	We recommend balancing the need for major surgical procedures against the risk of anesthesia and physical stress related to the procedure. PEG tube placement is a minor surgery	100
3.9	A	In general, consideration should be given to nonsurgical alternatives for major surgery	100
3.10	A	In general, consideration should be given to alternatives for the implantation of a foreign body enhancing the risk of infection	100
3.11	A	We recommend discussing infection prevention and close monitoring with the surgical and anesthesiology team before surgical procedures	100
3.12	B	We recommend avoiding catabolism	100
3.13	A	We suggest close monitoring after head trauma, surgical procedures, and the use of anesthetics	100

Continued

Table 1 Consensus-Based Recommendations *(continued)*

Number	Strength	Recommendation	Agreement (%)
3.14	A	In the case of previous acute severe decline, we recommend considering hospital admission with high care possibility when a similar stressor occurs	100
3.15	B	Apart from acute severe fright, psychological stress is not known to provoke acute decline; we, therefore, recommend standard behavioral management	100
Medication			
4.1	B	We recommend avoiding drugs that activate the integrated stress response, because they may trigger rapid decline	88
4.2	A	If the drug of choice may activate the integrated stress response and there is no good alternative, the risk of the drug should be weighed against the risk or impact of the problem, which instigated the drug	100
Acute presentation management			
5.1	A	We recommend to start with antipyretics in the case of fever aiming at normal temperature	95
5.2	A	We recommend to consider treatment with antibiotics in the case of fever	89
5.3	A	We recommend to consider hospital admission with high care possibility in the case of acute neurologic decline	100
5.4	C	We recommend considering to start with corticosteroids in the case of acute severe neurologic decline (e.g., reduced level of consciousness and loss of ability to walk), if there is no contraindication	100
Chronic disease management: epilepsy			
6.1.1	A	We recommend to start maintenance anticonvulsant treatment in the case of a (likely) seizure, even after a single event	83.33
Chronic disease management: nutrition			
6.2.1	A	We recommend to maintain a good nutritional status and use (PEG) tube feeding when sufficient oral intake cannot be guaranteed	100
Chronic disease management: ovarian insufficiency and bone health			
6.3.1	A	Because ovarian insufficiency is a common feature in female patients with VWM, we recommend referral to an endocrinologist in the case of primary amenorrhea at the age of 15 or secondary amenorrhea at any age	100
6.3.2	A	We recommend to counsel female patients about the consequences of estrogen deficiency regarding fertility, osteoporosis, and sexual health	100
6.3.3	A	We recommend to monitor risk factors of osteoporosis and refer to an endocrinologist when present	100
Chronic disease management: pregnancy and delivery			
6.4.1	A	We recommend close monitoring of female patients with VWM during pregnancy	100
6.4.2	A	We recommend delivery in a health care setting with obstetrics, neurology and intensive care unit present, and close postpartum monitoring in the case of a pregnant patient with VWM	100

Abbreviations: COVID-19 = coronavirus disease 2019; PEG = percutaneous endoscopic gastrostomy; VWM = vanishing white matter.
Percentage of consensus is calculated as (number of votes "strongly agree" + number of votes "agree")/(all votes without the votes "neutral").
Statements were strongly recommended (A) if ≥75% consensus was reached for "strongly agree," without counting votes for "neutral," with votes for "neutral" being <25%. Statements were recommended (B) if ≥75% consensus was reached for "agree" or "strongly agree," without counting votes for "neutral" and with votes for "neutral" being <25%. Statements were suggested (C) if ≥25% of the panel voted for "neutral" and, without counting neutral votes, ≥75% consensus was reached for "strongly agree" or "agree."

When choosing medications, it is important to weigh the risks and benefits carefully, consider non-ISR activating alternatives, and base decisions on available evidence and the clinical need for a particular class of drugs in an individual participant.

Acute Presentation Management

It was agreed that antibiotics and antipyretics should be considered in cases of acute neurologic decline, particularly when the trigger is a febrile infection. The use of corticosteroids is controversial, because the available evidence for an ameliorating effect is anecdotal.[22-24] According to the panel, the potential benefits of corticosteroid use may outweigh the potential risks, if their use is limited to a short period. This is the only recommendation with strength C.

Chronic Disease Management

Epilepsy

Adequate treatment of epilepsy is recommended because seizures may trigger rapid deterioration in VWM and have a negative impact on the disease course.[2] In children, careful adjustment of antiseizure medications according to weight is

Table 2 Brain MRI Characteristics

VWM phenotype	MRI characteristics	Differential diagnosis
Neonatal and early infantile VWM (onset ≤1 y of age)	• Cerebral white matter is more hyperintense than unmyelinated white matter on T2W images, without or with little rarefaction or cystic decay • Diffusion restriction, if present, involves relatively spared white matter • The abnormal white matter may look swollen • Gyration may be immature • Often anterior temporal cysts • Sometimes pontocerebellar hypoplasia • Diffusely abnormal cerebral white matter signal intensity that increasingly resembles CSF signal (decreased signal on T1W and T2 FLAIR images, increased signal on T2W images) • Rapidly progressive white matter loss leading to a severely destructed brain white matter • Sometimes, ventricular dilatation occurs with only a rim of white matter under the remaining cortex. May be associated with macrocephaly	• Aicardi-Goutières syndrome: calcifications are often, but not invariably present • Congenital CMV infection: calcifications are often, but not invariably present. Cortical dysplasia may occur. Follow-up MRI looks better • Canavan disease: cerebral white matter is extensively affected but periventricular white matter and corpus callosum are typically spared. Involvement of the globus pallidus and thalamus is seen while caudate nucleus and putamen are spared. Restricted diffusion is present in affected structures
Late-infantile and early-childhood VWM (onset 1–4 y of age)	• Initially swollen aspect of cerebral white matter that is more hyperintense than unmyelinated white matter on T2W images, without or with little rarefaction or cystic decay • Diffusion restriction, if present, involves relatively spared white matter • Diffusely abnormal cerebral white matter signal intensity that increasingly resembles CSF signal, (decreased signal on T1W and T2 FLAIR images, increased signal on T2W images) • Cystic cerebral white matter degeneration is typically diffuse and not well delineated • Radiating stripes, hyperintense within hypointense cerebral white matter on T2 FLAIR and T2W images, due to relatively preserved perivascular tissue strands • Rapidly progressive white matter loss leading to a severely destructed brain • Sometimes, the decayed cerebral white matter looks swollen, with progressive macrocephaly	• Mitochondrial leukoencephalopathy: may be indistinguishable from early-onset VWM with cystic cerebral white matter decay, but the cysts tend to be better delineated, the diffusion restriction occurs often in rims of cysts, and there is multifocal contrast enhancement. MR spectroscopy may reveal (highly) elevated lactate. Additional lesions in basal nuclei and thalami are common • Aicardi-Goutières syndrome: calcifications are often, but not invariably present. Diffuse cystic decay of the cerebral white matter does not occur • Canavan disease: cerebral white matter is extensively affected but periventricular white matter and corpus callosum are typically spared. Involvement of the globus pallidus and thalamus is seen while caudate nucleus and putamen are spared. Restricted diffusion is present in affected structures • Megalencephalic leukoencephalopathy with subcortical cysts: diffusely swollen cerebral white matter with megalencephaly; the corpus callosum is spared. The cysts are subcortical and not related to rarefaction or cystic decay. Diffusion is increased in all affected white matter
Juvenile VWM (onset 4–18 y of age)	• "Classic" VWM MRI with diffuse cerebral white matter abnormality • Progressive cerebral white matter rarefaction and cystic decay • Radiating stripes, hyperintense within hypointense white matter on T2 FLAIR and T2W images in cerebral white matter due to relatively preserved perivascular tissue strands • White matter signal intensity increasingly resembles CSF signal (decreased signal on T1W and T2 FLAIR images, increased signal on T2W images). This rarefaction/cystic white matter degeneration is typically diffuse and there are no well-delineated cysts • Involvement of the inner rim of the corpus callosum • Diffusion restriction, if present, involves relatively spared white matter • Signs of astrocytic gliosis (increased signal on T2 FLAIR and T2W images and mildly decreased signal on T1W images) may be present • Some cerebral white matter atrophy may occur	• Mitochondrial leukoencephalopathies: May be indistinguishable from VWM with cystic cerebral white matter decay, but cysts are typically multifocal, well delineated. Multifocal white matter contrast enhancement and diffusion restriction are frequent. Typically, the middle layer of the corpus callosum is affected. Brainstem abnormalities are common. MR spectroscopy reveals (highly) elevated lactate. Additional lesions in basal nuclei and thalami are common • Metachromatic leukodystrophy: no rarefaction or cystic decay. All layers of the corpus callosum are affected, typically starting with a central splenial lesion. Often a tigroid pattern with radiating hypointense stripes within hyperintense white matter on T2 FLAIR and T2W images reflecting relative preserved perivascular myelin and lipid storage. Diffusion restriction mostly in the stripes • Krabbe disease: no rarefaction or cystic decay. All layers of the corpus callosum affected. Tigroid pattern with radiating hypointense stripes within hyperintense white matter on T2 FLAIR and T2W images reflecting relative preserved perivascular myelin and lipid storage. Diffusion restriction mostly in the stripes. Contrast enhancement of cranial nerves may occur • Alexander disease: predominantly frontal white matter hyperintensities on T2W images. Localized and well-delineated white matter cysts may occur. Signal abnormality of basal nuclei and thalami are frequent. Brainstem lesions occur, typically in the medulla. Contrast enhancement may be seen in localized lesions • Canavan disease: cerebral white matter is extensively affected, but periventricular white matter and corpus callosum are typically spared. Involvement of the globus pallidus and thalamus is seen, but the caudate nucleus and putamen are spared. Restricted diffusion in affected structures • Megalencephalic leukoencephalopathy with subcortical cysts: diffusely swollen cerebral white matter with megalencephaly; corpus callosum is spared. Cysts are subcortical and not related to rarefaction or cystic decay. Diffusion is increased in all affected white matter • Multiple sclerosis: lesions can be cavitary but are typically multifocal, asymmetrical, and located in juxtacortical and periventricular regions

Continued

Table 2 Brain MRI Characteristics *(continued)*

VWM phenotype	MRI characteristics	Differential diagnosis
Adult VWM (onset ≥18 y of age)	• Extensive cerebral white matter signal abnormalities, but they may be patchy instead of diffuse • Rarefaction and cystic decay are mild or absent • Signs of astrocytic gliosis (increased signal on T2 FLAIR and T2W images and mildly decreased signal on T1W images) • Increased diffusion • Involvement of the inner rim of the corpus callosum • Progressive white matter atrophy	• Vascular disease, microangiopathy: may be difficult to distinguish from adult VWM. Next to cerebral white matter lesions, typically also lesions in the basal ganglia and brainstem (most helpful distinguishing item). The corpus callosum is typically spared. Microbleeds may occur. Cavitation, if present, is well delineated. Diffusion restriction may occur in fresh infarcts • Metachromatic leukodystrophy: may be difficult to distinguish from adult VWM. Typically, no rarefaction or cystic decay. All layers of the corpus callosum are affected. There may also be cerebral white matter atrophy and gliosis • Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia: cerebral white matter abnormality is typically asymmetrical and patchy with a frontal predominance. Diffusion restriction in small lesions with a steppingstone appearance
Episode of acute decline	• Signal abnormalities in basal nuclei, thalami, and brainstem, in addition to the cerebral white matter abnormalities • If the patient survives, the lesions improve or may disappear • No cystic evolution of these lesions	• Mitochondrial leukoencephalopathies: the combination of cerebral white matter abnormalities and lesions in basal nuclei, thalami, and brainstem may be indistinguishable from VWM. However, in mitochondrial disease, the cysts are typically well delineated and may also affect basal nuclei and thalami. Multifocal white matter contrast enhancement and diffusion restriction are frequent. MR spectroscopy reveals (highly) elevated lactate • Alexander disease: predominantly frontal white matter hyperintensities on T2W images. Localized white matter cysts may occur. Signal abnormalities of basal nuclei and thalami are frequently observed. Brainstem lesions occur, often in medulla. Contrast enhancement may occur in localized lesions

Abbreviations: FLAIR = fluid-attenuated inversion recovery; T1W = T1-weighted; T2W = T2-weighted; VWM = vanishing white matter.
This table is based on Refs. 14–16. More information on the natural history of MRI changes in VWM, including images, can be found in Ref. 14. More information on basal ganglia abnormalities associated with episodes of acute decline can be found in Ref. 15. Horizontal stripe indicates findings typical in early (above) and advanced (below) disease stages.

recommended. It was mentioned that preventive start of anticonvulsants could be considered in patients with severe forms of VWM with onset before 1 year, such as a Cree leukoencephalopathy.

Nutrition

Previous research has shown that amino acid deprivation triggers the ISR in vitro.[19,20] This raises the question whether fasting and/or vomiting could induce an episode of acute decline in VWM through amino acid deprivation. However, studies on basic physiology indicate that short-term fasting does not lead to significant cellular or blood amino acid depletion.[25] During short-term fasting, homeostatic mechanisms, such as muscle protein degradation, provide sufficient amino acids. Clinical observations align with this, as acute episodes of decline in patients with VWM have not been reported after short fasting periods, such as overnight fasting.

With prolonged fasting or malnutrition, systemic levels of various amino acids may decrease,[26] potentially triggering the ISR in patients with VWM. Therefore, maintaining adequate long-term nutritional status is strongly recommended in managing VWM. If oral intake is inadequate, tube feeding with complete formula should be considered. Ensuring good nutritional status is a standard medical practice in both acute and chronic illnesses[27-29] and may be particularly important in VWM to prevent amino acid deprivation–induced ISR activation. There is no evidence to support the administration of additional enteral or intravenous amino acid supplementation.

Ovarian Insufficiency and Bone Health

VWM is frequently associated with ovarian insufficiency in women,[2] and measures to treat and monitor its consequences are recommended. Evaluation of the menstrual cycle at follow-up visits helps to identify ovarian insufficiency. Conforming to established osteoporosis prevention and management guidelines, it was unanimously agreed that all risk factors of osteoporosis such as age, mobility, nutritional status, calcium, vitamin D, and estrogen status should be considered.[30,31] Estrogen deficiency is also known to affect cardiac health, so counseling should be performed as appropriate.[32]

Pregnancy and Delivery

It was agreed that obstetric care deserves specific attention because pregnancy and delivery may trigger acute deterioration peripartum or postpartum.[33-35] Extra attention to potential triggering factors as described in recommendation section 3 is recommended.

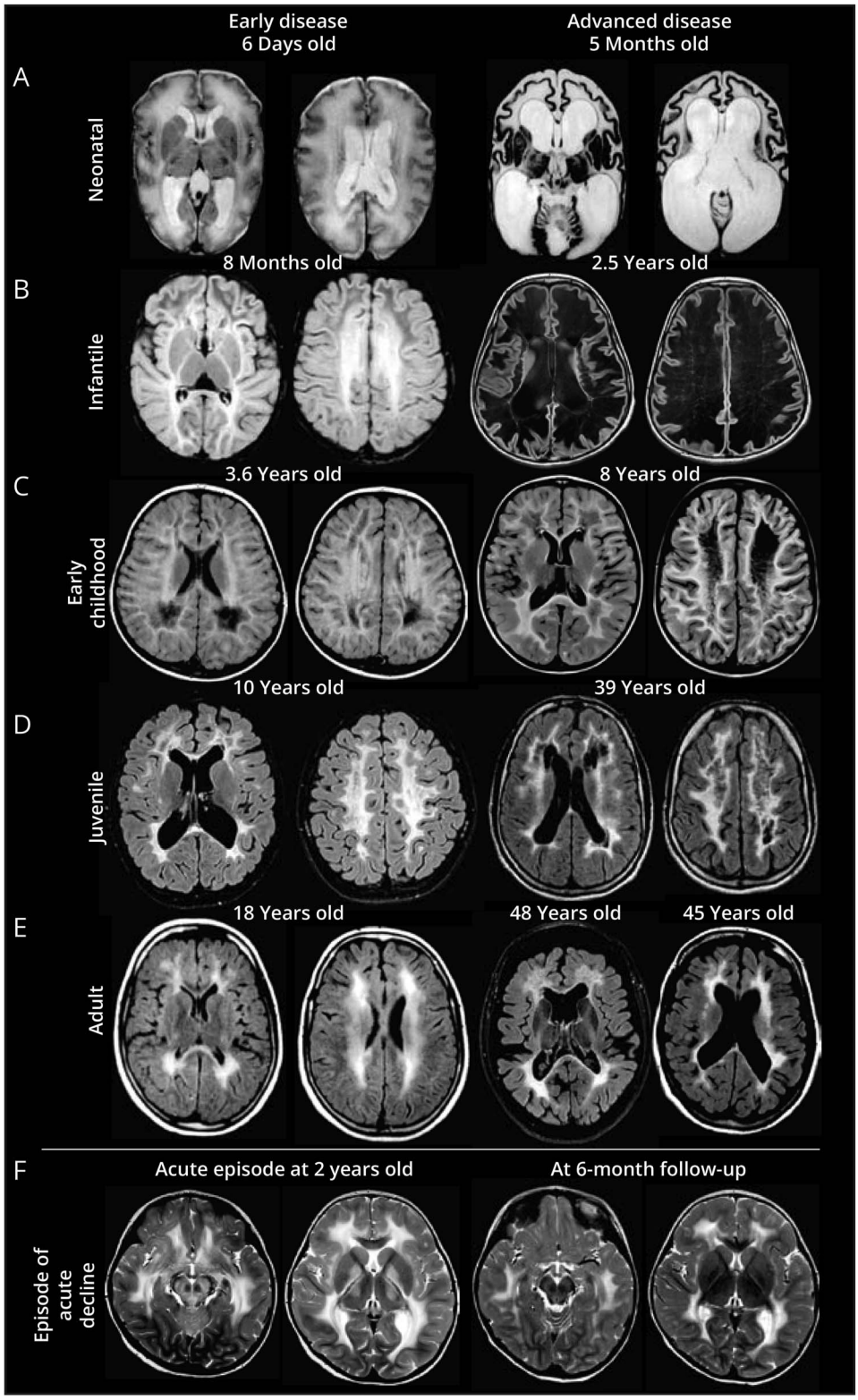
Patient Management Card

A patient management card summarizing the most important recommendations is provided in eFigure 3, A and B.

Discussion

This study provides a consensus-based guideline for the diagnosis and clinical management of VWM according to the latest scientific and expert insights. Using a real-time eDelphi method, we developed recommendations that address key

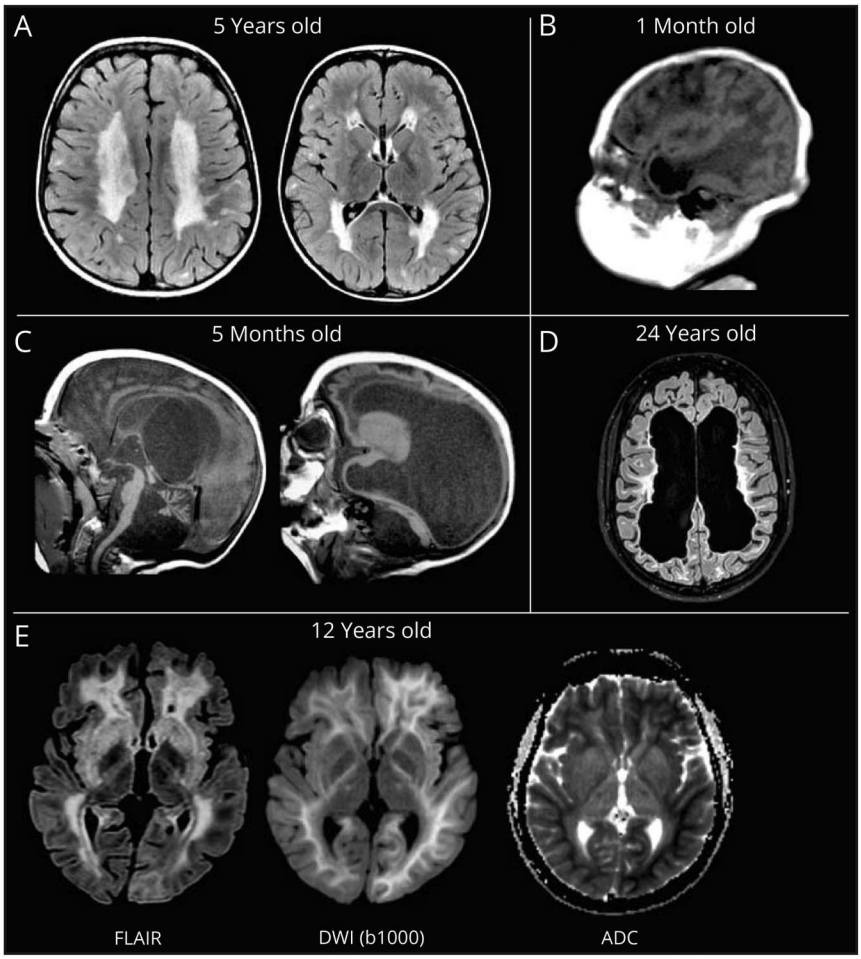
Figure 1 Brain MRI Characteristics



(A–E) Typical MRI findings per VWM subtype (increasing age at onset from top to bottom) and for early disease stage (left panel) or advanced disease stage (right panel) on T2 FLAIR images. A description of the corresponding MRI abnormalities is provided in Table 2. (F) Hyperintensities on T2-weighted images in the midbrain, basal ganglia, and thalami associated with an acute episode (left panel), which spontaneously resolved after 6 months (right panel). FLAIR = fluid-attenuated inversion recovery; VWM = vanishing white matter.

challenges health care providers, patients, and families face. The criteria for recommendations were rather strict: if ≥25% of the votes were "neutral," the strength was a C, even if the majority vote favored the statement. The only class C voting outcome was for using corticosteroids in the case of acute decline. The recommendations on diagnosis stress the importance of combining MRI criteria with genotype information to enhance diagnostic accuracy. The

Figure 2 Unusual MRI Findings in VWM



(A) Presymptomatic patient with bilateral confluent hyperintensities on T2 FLAIR images in the periventricular and deep cerebral white matter and inner rim of the corpus callosum, sparing the subcortical white matter and without rarefaction or cystic decline of the affected white matter. (B) Anterior temporal cysts in a patient with neonatal VWM. (C) Hydrocephalus with ventriculomegaly in a patient with neonatal presentation. (D) Severe atrophy due to loss of cerebral white matter, leading to ventriculomegaly. (E) Extensive diffusion restriction in the cerebral white matter and internal capsule, with high signal on the DWI and low signal on the ADC maps. Only the frontal deep white matter that is mildly rarefied on T2 FLAIR imaging has an increased diffusion. ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; VWM = vanishing white matter.

recommendations for acute and long-term management of VWM guide clinical practice for this disease. The patient management card may support patients and their families during high-stress situations, providing guidance and trust in care management.

The VWM consortium, in collaboration with patient advocacy groups, is working on various projects to improve and harmonize research and care in VWM.[6,7,36] The rarity of VWM requires global collaboration in research studies, so there is a pressing need for uniform clinical standards.[2,7] In a global qualitative and quantitative study about the impact of VWM, families stressed the need for comprehensive clinical guidance.[5] By providing this clinical guidance, consistent management of VWM worldwide can be improved, benefiting both current care and future (therapeutic) studies.

The management of VWM is characterized by efforts to find the individual balance between avoidance of stressors and participation in regular life activities. Preventive measures for an episode of rapid neurologic deterioration may have a huge impact on patients and their families.[5] The panel emphasized the importance of having informed discussions with families to balance quality-of-life goals with the risk of a potential episode of decline. It is important to emphasize that these recommendations serve as recommended and suggested general guidelines, and decisions should always be made on an individual basis. This allows for personalized management strategies that are tailored to the specific needs of each patient and their family.[37]

A significant evidence gap exists regarding medications. The recommendations on using or avoiding certain medications are primarily informed by fundamental research on the ISR, and we acknowledge that supporting clinical evidence is limited.[2] Clinical exposure experiments to determine the risk of provoking an episode of rapid decline in humans would be unethical. The currently available VWM animal models mimic the phenotype of chronic decline, but acute stress-provoked episodes have not yet been modeled,[38-40] hampering research on these episodes. Uncertainty exists about the use of corticosteroids during episodes of acute neurologic decline. Acknowledging these limitations, the panel has classified the recommendation on corticosteroids as level C (suggested

Table 3 List of Clinically Used Drugs That Were Investigated for Their Effect on the ISR

Drug type	Name	Study design	Cell/tissue/organ/species	Effect on the ISR
Anesthetic	Isoflurane[ISR act]	In vivo/in vitro	Rat hippocampus	↑ATF4, CHOP, p-eIF2α
		In vivo	Yeast	↑ATF4, p-eIF2α
Anesthetic	Sevoflurane[ISR act]	In vivo/in vitro	Mice hippocampus	↑ATF4, CHOP, p-eIF2α
		In vivo/in vitro	Mouse pups cerebral cortex	↑ATF4, CHOP, p-eIF2α
Anesthetic	Halothane[ISR act]	In vivo	Rat liver cells	↑p-eIF2α, ↓eIF2B activity
Anesthetic	Lidocaine[ISR act]	In vitro	Neuroblastoma cell line	↑ATF4, CHOP
Anesthetics	Lidocaine[ISR act], ropivacaine[ISR act], levobupivacaine[ISR act], bupivacaine[ISR act], prilocaine[ISR act], chloroprocaine[ISR act]	In vitro	Osteosarcoma cell line	↑ATF4, p-eIF2α
Anesthetic	Propofol + intralipid emulsion[ISR inh]	In vivo	Neuroblastoma cell line, experience in patients with VWM	↓ATF4
Antacid	Omeprazole[ISR quest]			No evidence
Antacid	Esomeprazole[ISR quest]			No evidence
Antibiotic	Azithromycin[ISR act]	In vitro	Rat adrenal gland cell line; fibrosarcoma cell line	↑ATF4, CHOP, p-eIF2α
Antibiotic	Doxycycline[ISR act]	In vitro	Human colon adenocarcinoma cell line; human hepatocytes; breast cancer cell line	↑AFT4, CHOP
		In vitro	Mouse kidney and liver tissue	↑ATF4, CHOP, p-eIF2α
Antibiotic	Minocycline[ISR quest]			Inconclusive results
Antidepressant	Fluoxetine[ISR quest]			Inconclusive results
Antidepressant	Vortioxetine[ISR inh]	In vivo/in vitro	Rat hippocampal and cortical tissues	↓ATF4, CHOP, p-eIF2α
Antidepressant	Trazodone[ISR inh]	In vivo/in vitro	Chinese hamster ovary cell line	↓ATF4, CHOP
Antiepileptic	Carbamazepine[ISR act]	In vitro	Human and mouse primary hepatocytes	↑ATF4, CHOP
Antiepileptic	Valproic acid[ISR quest]			Inconclusive results
Antiepileptic	Phenobarbital[ISR quest]			No evidence
Antiepileptic	Lamotrigine[ISR quest]			No evidence
Antiepileptic	Levetiracetam[ISR quest]			No evidence
Antiepileptic	Vigabatrin[ISR quest]			No evidence
Antihypertensive	Propranolol[ISR quest]			No evidence
Antihypertensive	Valsartan[ISR quest]			Inconclusive results
Antipsychotic	Haldol[ISR quest]			No evidence
Antipsychotic	Olanzapine[ISR act]	In vivo/in vitro	Neuroblastoma cell line; rat hypothalamus	↑ATF4, p-eIF2α
Antipsychotic	Clozapine[ISR act], haloperidol[ISR act], olanzapine[ISR act]	In vivo/in vitro	Immortalized human hepatocyte cell line; rat liver	↑ATF4, CHOP

Continued

Table 3 List of Clinically Used Drugs That Were Investigated for Their Effect on the ISR *(continued)*

Drug type	Name	Study design	Cell/tissue/organ/species	Effect on the ISR
Antipsychotic	Thioridazine[ISR act]	In vivo/in vitro	Mouse colorectal cancer cell line	↑ATF4, CHOP, p-eIF2α
Antipyretic	Acetaminophen[ISR act]/paracetamol[ISR act]	In vivo/in vitro	Luciferase transgenic mice	↑ATF4, CHOP, p-eIF2α in chronic high treatment for 18 days
Antipyretic	Aspirin[ISR quest]			Inconclusive results
Antipyretic	Sodium salicylate[ISR quest]			Inconclusive results
Corticosteroid	Dexamethasone[ISR inh]	In vitro	Human trabecular meshwork cells	↓ATF4, CHOP
Corticosteroid	Methylprednisolone[ISR quest]			No evidence
Corticosteroid	Prednisolone[ISR quest]			No evidence
NSAID	Ibuprofen[ISR quest]	In vitro	Neuroblastoma cell line	Inconclusive results
NSAID	Naproxen[ISR quest]	In vitro	Skin carcinoma cell line	Inconclusive results
NSAID	Diclofenac[ISR act]	In vitro	Human and mouse primary hepatocytes	↑ATF4, CHOP
NSAID	Indomethacin[ISR act]	In vitro	Primary gastric mucosal cell line	↑ATF4, CHOP
NSAID	Indomethacin[ISR act]/diclofenac[ISR act]	In vitro	Colorectal adeno-carcinoma cell line	↑ ATF4, CHOP, p-eIF2α
NSAID	Celecoxib[ISR act]	In vitro	Gastric carcinoma cell line	↑ATF4, CHOP, p-eIF2α
		In vitro	Liver tumor cell line	↑ATF4, CHOP
NSAID	Tolfenamic acid[ISR act]	In vitro	Colorectal cancer cell line	↑ATF4, CHOP
Opioid	Morphine[ISR act]	In vivo/in vitro	Rat dorsal root ganglions	↑ATF4, CHOP
Opioid	Oxycodone[ISR act]	In vivo/in vitro	Rat nucleus accumbens, cortex and brainstem; breast cancer cell line	↑ATF4, p-eIF2α
		In vivo/in vitro	Rats whole brain tissue; breast cancer cell line	↑ATF4, CHOP, p-eIF2α
Opioid	Sufentanil[ISR quest]	In vivo/in vitro	Rat hepatic ischemia/reperfusion model	Inconclusive results
Sedative	Alimemazine[ISR quest]			No evidence
Sedative	Dexmedetomidine[ISR quest]			Inconclusive results
Sedative	Diazepam[ISR quest]			No evidence
Sedative	Clonazepam[ISR quest]			No evidence
Sedative	Clobazam[ISR quest]			No evidence
Sedative	Midazolam[ISR quest]			Inconclusive results
Sedative	Oxazepam[ISR quest]			No evidence
Sedative	Temazepam[ISR quest]			No evidence
Spasmolytic	Baclofen[ISR neutr]	In vitro	Primary rat retinal ganglion cells	↓ATF4, CHOP, p-eIF2α, but does not readily cross BBB

Abbreviations: BBB = blood brain barrier; ISR = integrated stress response; VWM = vanishing white matter; CHOP = C/EBP homologous protein; p-eIF2α = phosphorylated eukaryotic initiation factor 2 alpha; ATF4 = activating transcription factor 4 .
ISR act = ISR activating; ISR inh = ISR inhibiting; ISR quest = ISR effect not investigated or equivocal findings; ISR neutr = neutral. References are provided in eTable 7 online.

practice). Further research is necessary to establish optimal treatment strategies.

Relying on limited evidence and expert opinions is inevitable in a disease as severe and rare as VWM. The real-time eDelphi methodology enabled us to align expert opinions from a diverse international panel. However, inherent to the eDelphi method are potential biases due to panel selection. Panel members have diverse experience with VWM, which may have influenced the outcomes. Nevertheless, similar clinical guidance documents have found to be helpful in other leukodystrophies.[41] Continued international collaboration and expert alignment are crucial until evidence gaps are addressed.[42,43]

In conclusion, this study guides the diagnosis and care of patients with VWM. It helps to bridge the gap between limited scientific evidence and the practical needs of clinicians and families. The consensus-based recommendations are an important step toward harmonizing global care for VWM, which should improve patient outcomes and quality of life.

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Acknowledgment

The authors are grateful to the contributions of all physicians and specialists who provided genetic data on their patients, which facilitated the publication of the genetic variant table.

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Study Funding

This study was funded by the Dutch Research Council (NWO) through the Spinozapremie award.

Disclosure

A. Vanderver receives in-kind support from Affinia, Biogen, Calico, Boerhinger Ingelhiem Eli Lilly, Ionis, Myrtelle, Orchard Therapeutics, Sana Therapeutics, Sanofi, Synaptixbio, and Takeda; and serves on the boards of the European Leukodystrophy Association and the United Leukodystrophy Foundation. S. Groeschel received institutional research support from Shire plc (a Takeda company) and Orchard; and is an advisor and coinvestigator for trials in Metachromatic Leukodystrophy (Shire/Takeda, Orchard). D. Tonduti is a consultant for Orchard Therapeutics, Ionis, Egetis, and Initio Evoke; and served on the scientific advisory boards of the United Leukodystrophy Foundation. C. Sevin reports no disclosures relevant to the manuscript. J.L. Orthmann-Murphey receives or has received research funding from the National Institutes of Health, the National Multiple Sclerosis Society, the Global Leukodystrophy Initiative, the Clayco Foundation, the Simon Foundation, and ITMAT; is a site PI for Vigil Neuroscience; and is a consultant for Vigil Neuroscience and NovoGlia. S.G. Campbell is part of the Leukolabs community, a network for white matter disease research in the United Kingdom; and has received funding in the past from Great Ormond Street Hospital, GOSH Charity. T.E.M. Abbink is listed on patent P112686US00 "therapeutic effects of Guanabenz treatment in vanishing white matter" and on patent P112686CA00 "the use of Guanabenz in the treatment of VWM," both for the Amsterdam University Medical Center, Amsterdam, the Netherlands. P. S. Leferink reports no disclosures relevant to the manuscript. M.S. van der Knaap is coinvestigator for Ionis (Alexander disease trial) and advisor and coinvestigator for Calico and AbbVie vanishing white matter; is listed on patent P112686US00 "therapeutic effects of Guanabenz treatment in vanishing white matter" and on patent P112686CA00 "the use of Guanabenz in the treatment of VWM," both for the Amsterdam University Medical Center, Amsterdam, the Netherlands; and is the initiator and principal investigator of the Guanabenz trial (clinicaltrialsregister.eu/ctr-search/trial/2017-001438-25/NL). Ingeborg Krägeloh-Mann, Enrico Bertini, Nicole Wolf, Samual Groeschel, Caroline Sevin, Ludger Schöls, and Marjo van der Knaap are members of the European reference network for rare neurologic disorders (ERN-RND), project ID 739510. A. Vanderver, J. Bonkowski, A. Fatemi, J. Orthmann-Murphy, and N. Jaffe are members of the Global Leukodystrophy Initiative Clinical Trials Network (U54 NS115052). All other authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology*® March 11, 2025. Accepted in final form October 6, 2025. Submitted and externally peer reviewed. The handling editors were Associate Editor Courtney Wusthoff, MD, MS, Assistant Editor Angela Vidal-Jordana, MD, PhD, and Associate Editor for Editorial Education Bradford Worrall, MD, MSc, FAAN.

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