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Use of Brain MRI in Cerebral Adrenoleukodystrophy

International Recommendations for Screening, Monitoring, and Research

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Abstract

Background and Objectives

Cerebral adrenoleukodystrophy (CALD) is a common manifestation of adrenoleukodystrophy (ALD) in men. Early detection of CALD lesions through MRI screening is critical to allow for therapeutic action preventing severe disability and death. While the frequency of brain MRI monitoring has been addressed by international recommendations, no consensus currently exists regarding which MRI sequences should be used in a real-world setting for screening and follow-up of CALD lesions. The aim of this study was to establish guidelines for the MRI protocol in clinical practice and to identify priority sequences for research use, thereby promoting intercenter harmonization.

Methods

A modified Delphi procedure was used to achieve consensus on MRI protocols for ALD screening, lesion monitoring, and research applications among experts with experience in brain imaging in ALD. Questionnaires allowed experts to indicate whether they considered sequences as core, optional, or research, or to express agreement (5-point scale ranging from completely disagree to completely agree) with specific statements. Topics where no agreement was reached were discussed during online consensus meetings.

Results

Thirty experts from 9 countries participated and agreed that the core screening protocol for ALD in adults and children should include at least 3D T1-weighted, spin-echo T2-weighted, 3D fluid-attenuated inversion recovery, and diffusion-weighted imaging (DWI). Postcontrast T1-weighted imaging should be performed systematically in specific clinical scenarios. Experts supported using DWI alongside the Loes score and postcontrast imaging to assess lesion progression. A research protocol was defined, prioritizing diffusion tensor imaging, MR perfusion, and quantitative volumetric analyses.

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Glossary

ALD = adrenoleukodystrophy; **AMN** = adrenomyeloneuropathy; **CALD** = cerebral ALD; **DTI** = diffusion tensor imaging; **DWI** = diffusion-weighted imaging; **FLAIR** = fluid-attenuated inversion recovery; **GIS** = gadolinium intensity score; **GT** = gene therapy; **HSCT** = hematopoietic stem cell transplantation; **MWI** = myelin-water imaging; **SWI** = susceptibility-weighted imaging.

Discussion

This international project harmonizes the ALD MRI protocol, thus offering a practical framework to screen and monitor lesions, which will improve clinical decision making. It also identifies MRI sequences that should be prioritized in future research. Future research on MRI in ALD should focus on topics where no consensus has yet been reached in this project.

Introduction

Adrenoleukodystrophy (ALD) is a neurometabolic disease caused by pathogenic variants in the *ABCD1* gene.[1] Two main disease manifestations are recognized in the CNS. First, all adult men and most women develop a slowly progressive spinal cord disease called adrenomyeloneuropathy (AMN), which results in a debilitating gait disorder for which no curative treatment exists to date.[2,3] Second, a large percentage of male individuals, both children and adults, are at risk of developing a rapidly progressive leukodystrophy called cerebral ALD (CALD),[4,5] with a median survival of 3 years. CALD progression can be halted with allogeneic hematopoietic stem cell transplantation (HSCT) or, in selected cases in the United States, by genetically transduced autologous stem cell transplantation (gene therapy [GT]),[6] although clinical outcomes are dependent on patient condition.[7,8] Recently, leriglitazone, a brain-penetrant peroxisome proliferator-activated receptor-gamma agonist, has shown potential as a novel therapeutic option for CALD.[9-11]

In all male individuals with ALD, regular MRI screening of the brain is necessary to identify CALD at the earliest possible stage,[12] but there is limited consensus on the most appropriate sequences and techniques for this purpose and there is currently no international harmonization of the scanning protocol.[12,13] Previous studies have attempted to establish guidelines, but these have not provided sufficient means for a real-world context, which has led to considerable variability across institutional protocols. As a result, some centers may be better equipped to detect early lesions than others, and those with limited experience in ALD may conduct suboptimal screening. For example, contrast enhancement of the lesion rim on T1-weighted sequences has been identified as the gold standard to assess lesion activity,[14] but the ability to detect enhancement is dependent on the type of pulse sequence used (spin-echo vs gradient-echo, 2D vs 3D scanners) and on the interval between gadolinium administration and image acquisition.[15-17]

Because of these uncertainties, quantitative MR approaches have been proposed to more accurately assess CALD activity.[18] Diffusion tensor imaging (DTI) has been used in several studies to monitor disease activity and therapeutic response after HSCT in children[19-21] and leriglitazone in adults.[9] Modeling early-stage CALD lesion growth using lesion volumetrics has demonstrated distinct trajectories between patients with progressive and self-stabilizing disease.[22,23] This is important because the most commonly used MRI severity score for this purpose, the Loes score,[24] is insensitive to early CALD progression when HSCT and GT are most effective.[22] Dynamic susceptibility contrast (DSC) perfusion imaging can identify hypoperfusion (defined as a decrease in normalized cerebral blood volume) that precedes blood-brain barrier leakage and contrast enhancement in lesions, allowing for early detection of disease activity.[25] It has also been used as a biomarker to predict clinical outcomes after HSCT.[26] Although promising, the clinical value and practical use of these techniques is often limited by the need for further research.

Using a consensus-based procedure among a large group of ALD and MRI experts, we aimed to establish practical guidelines on the use and interpretation of MRI techniques in ALD for a real-world setting. Intervals between scans for male patients have been established elsewhere (every 6 months between 2–12 years and yearly after 12 years) and are, therefore, not part of this article.[12,13] Our practical guidelines should guide the use and clinical interpretation of MRI to improve treatment opportunities and to monitor CALD dynamics, which is especially important in centers with limited expertise on ALD. In addition, these recommendations can guide MRI research in ALD and in other white matter disorders.

Methods

Modified Delphi Procedure

We used an evidence-based modified Delphi procedure to systematically analyze expert opinion.[27,28] This procedure comprised a literature review to identify relevant topics, which was used to identify core topics and to devise a questionnaire. This questionnaire, together with proof collected by the literature review, was shared with a group of experts to

investigate views on the proposed topics. The first round of questionnaire was followed by an online consensus meeting where respondents were invited to discuss their views publicly based on an anonymized summary of the first questionnaire. Topics were presented by 2 researchers (HY and MG), and participants were given the opportunity to explain their perspectives. Next, a second questionnaire that included questions where no consensus was reached in the first round was disseminated. This provided respondents with the opportunity to change their answers based on the discussion. This procedure was repeated until consensus was reached or it was deemed impossible to reach consensus on specific topics.

International Expert Panel

Experts invited to participate in this project were leaders of national reference centers for ALD and authors of research articles on brain MRI in ALD. Special attention was paid to include researchers from countries outside Western Europe and the United States. Invitees had the opportunity to indicate that they lacked the expertise to adequately respond to specific questions (e.g., adult physicians usually had limited experience with pediatric ALD care).

Topic Identification

A literature search was performed to identify relevant topics using the following search string: (adrenoleukodystrophy OR adrenomyeloneuropathy) AND ("magnetic resonance" OR MRI OR imaging). As of January 2025, this produced 699 records on PubMed, which were screened for relevance by title and abstract. Case studies were excluded. In addition, a small group of experts at the ICM Paris Brain Institute (F.M., D.G., M.G.) was consulted to identify other relevant topics. The following MR techniques and scores were investigated with the survey: T1-weighted imaging, T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR) imaging, T1-weighted postcontrast imaging, susceptibility-weighted imaging (SWI), diffusion-weighted imaging (DWI), DTI, MR perfusion, magnetization transfer imaging, MR spectroscopy, myelin-water imaging (MWI), and their derived scores including Loes score, gadolinium intensity score (GIS), quantitative volumetrics.

Questionnaires and Time Line

Limesurvey was used to disseminate the questionnaire among experts. Two situations were distinguished:

- Screening: concerning patients without known CALD lesions
- Monitoring: concerning patients with identified CALD lesions

For both situations, in children and in adults, we investigated whether experts felt that the proposed techniques should be part of a core, optional, or experimental protocol for ALD, which we defined as follows:

- Core protocol: the minimal set of sequences that should always be used in all centers.
- Optional protocol: an optional set of sequences that should, if possible, be implemented by centers.
- Experimental/research protocol: the set of sequences that should preferably be implemented as core research sequences in centers conducting research in ALD.

Questions either required participants to indicate whether they felt that an MRI technique should be part of the core, optional, or experimental protocol, or asked them to indicate their level of agreement with statements on a 5-point Likert scale ranging from completely disagree to completely agree. Disagreement comprised the responses "completely disagree" and "disagree," and agreement comprised "completely agree" and "agree." Consensus was reached when 75% or more of participants disagreed or agreed with a statement. The responses "neutral" and "not my expertise" were in all cases excluded from the calculations. Participants had the opportunity to leave comments after all questions.

Standard Protocol Approvals, Registrations, and Participant Consents

Approvals and consent were not required because of the nature of the research.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Participants

Thirty experts participated in this project, which included pediatric neurologists (n = 13), adult neurologists (n = 7), radiologists (n = 8), an MR physicist (n = 1) and a bone-marrow transplantation specialist (n = 1). Experts were from Argentina, Brazil, France, Germany, Israel, Italy, the Netherlands, Spain, and the United States. Three rounds of questionnaires were disseminated over a period of 4 months. The results of the first and second questionnaires were discussed online during consensus meetings.

Screening Protocol

Consensus recommendations for the screening protocol were largely consistent across pediatric and adult populations (Table 1, Figure). The results are, therefore, presented together with age-specific nuances highlighted where applicable. Percentages of agreement with recommendations and response rates are presented in eTables 1–3.

First, experts agreed that patients should always be scanned on the same MRI scanner to adequately compare images longitudinally. Second, experts agreed that 3D T1-weighted, spin-echo T2-weighted, 3D FLAIR, and DWI should always be part of the ALD core screening protocol, whereas SWI and 2D T1-weighted imaging were considered optional. It was discussed that SWI could be used in some cases to distinguish

Table 1 Key Screening Protocol Recommendations

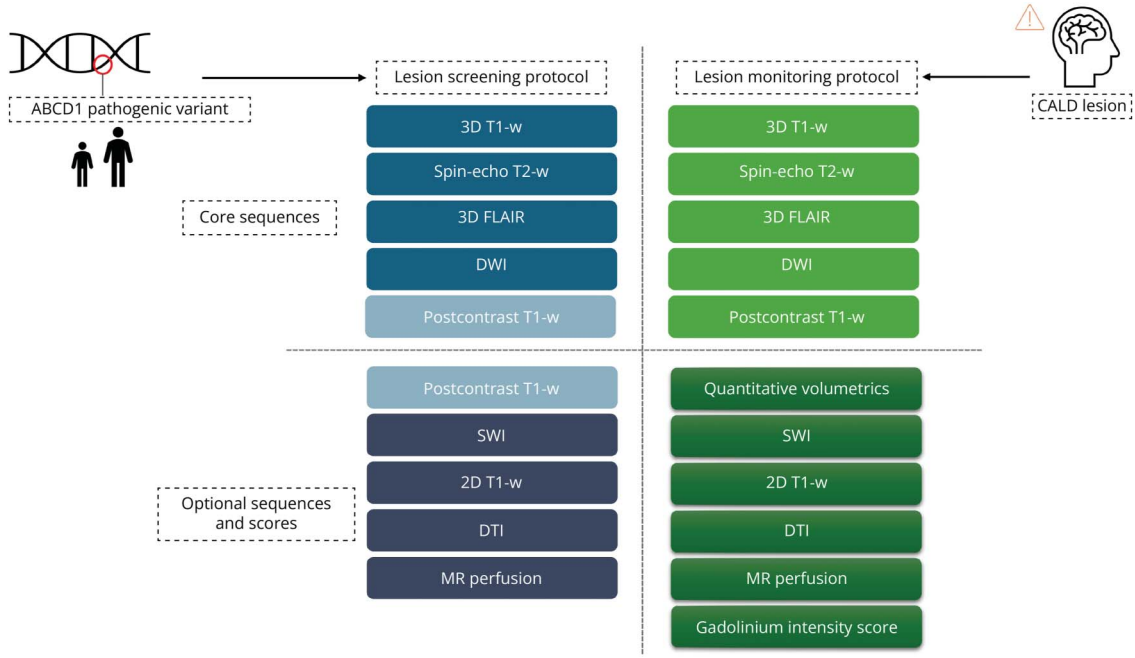
1	Patients should, if possible, always be scanned on the same MRI device
2	The core ALD screening protocol should always include 3D T1-weighted, spin-echo T2-weighted, 3D FLAIR, and DWI
3	SWI and 2D T1-weighted imaging should at least be part of the optional screening protocol
4	The use of postcontrast 3D T1-weighted imaging as part of the core screening protocol should be left at the discretion of the local medical team, except in some specific situations where it should always be acquired
5	Precontrast and postcontrast T1-weighted sequences should be performed with the same parameters
6	The interval between gadolinium administration and image acquisition should be 7–10 min

Abbreviations: ALD = adrenoleukodystrophy; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; SWI = susceptibility-weighted imaging.

true parenchymal enhancements from physiologic vessel enhancement. In addition, precontrast and postcontrast 2D T1-weighted imaging can be useful for identifying small enhancing lesions in patients who move during data acquisition because of its greater robustness to motion artifacts compared with 3D sequences.

Spin-echo T2-weighted and 3D FLAIR imaging should both be used to identify hyperintensities as they offer distinct advantages. Lesions can be more prominent on 3D FLAIR than on T2-weighted imaging. However, T2-weighted imaging helps visualize early myelination patterns in children and may be less influenced by certain artifacts than FLAIR. Spin-echo T2-weighted images are mainly acquired in 2D, which is inherently less sensitive to motion artifacts than 3D acquisitions. This makes it a particularly valuable technique in children who may have difficulty staying still for the duration of the examination. Concerning DWI, this sequence provides a means to assess lesion activity as diffusion restriction can be observed in active lesion borders. However, some experts indicated that the significance of diffusion restriction requires further investigation in ALD because no studies have specifically investigated this phenomenon. DWI has the advantages of being fast and noninvasive, which is of particular interest in children.

Figure Recommendations for Screening and Monitoring of CALD



The MRI screening protocol for CALD is described on the left side in blue, and the lesion monitoring protocol once CALD has been identified is described on the right side in green. The upper part of the figure describes core sequences that should always be part of the protocol. The lower part describes optional sequences and scores. Postcontrast T1-weighted imaging should always be part of the screening protocol in centers with limited experience with ALD, in situations where patient follow-up is irregular, and when patients are scanned for the first time, but its use as a core sequence should otherwise be left at the discretion of the local medical team. Quantitative volumetrics, DTI, and MR perfusion should only be performed in centers with sufficient expertise of experimental MR techniques. CALD = cerebral adrenoleukodystrophy; DTI = diffusion tensor imaging; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; SWI = susceptibility-weighted imaging.

Experts agreed that 3D T1-weighted images are essential in the core screening protocol for detecting contrast enhancement and evaluating brain atrophy. However, no agreement was reached on which acquisition technique (i.e., spin-echo vs gradient-echo) should be prioritized. Gradient-echo T1-weighted imaging was suggested as a necessary tool for the evaluation of atrophy because of its excellent contrast between gray and white matter. Moreover, it provides an anatomical reference that can be used in research protocols for postprocessing purposes (such as coregistration). On the contrary, spin-echo T1-weighted imaging was proposed to provide better sensitivity to low-level contrast enhancement, especially in smaller lesions. Experts agreed that, in any case, precontrast and postcontrast sequences should be the same to correctly interpret enhancement, especially because precontrast T1-weighted images can sometimes display hyperintensity in affected areas. The dose of gadolinium-based contrast agent was not discussed by the experts because there is broad consensus on using 0.1 mmol/kg (0.2 mL/kg) as the standard dose in children and adults.

Contrast administration should always be part of the core screening protocol in centers with limited experience with ALD, in situations where patient follow-up is irregular (i.e., a significantly longer interval between scans than advised),[12] and when patients are scanned for the first time. The choice to acquire postcontrast T1-weighted images should, in all other cases, be left at the discretion of the local medical team. Some of the participating experts indicated that, at their own institution, postcontrast T1-weighted images were only acquired if a clear indication was present (e.g., high suspicion of active CALD), whereas other centers included it systematically in their screening protocol. This decision was often influenced by the expert assessment of harmfulness of gadolinium buildup in the body.[29] One expert stated, "(…) even if the risk is only theoretical, it is still worth minimizing cumulative exposure in pediatric populations," whereas others felt that the risks of gadolinium buildup in the body were negligible or would become less relevant over time because of alternative contrast agents.[30] The interval between contrast administration and acquisition should preferably be 7–10 minutes, although experts indicated that there were insufficient data on this interval. Several participants suspected that the previously suggested >5-minute interval might be too short and could result in missing contrast enhancement in some situations.

Lesion Monitoring Protocol

When CALD lesions have been identified, experts agreed that the Loes score is an appropriate instrument to monitor lesion progression in all age categories (children <4 years, children 4–12 years, children 12–16 years, and individuals >16 years) (Table 2, Figure). The score should preferably be calculated using both spin-echo T2-weighted and 3D FLAIR sequences. In adults, experts did not agree on whether subtle hyperintensities in the corticospinal tracts or other long tracts should be considered when calculating the Loes score, although sufficient consensus was almost reached that they should not be included (74% agreement). Hyperintensities in these tracts can be related to CALD but also to AMN. In the comments, some experts found it difficult to define "subtle," which may have influenced this outcome. Consensus was reached that, in adults, age-related atrophy and nonspecific white matter lesions (e.g., similar in pattern to vascular damage) should not be considered when calculating the Loes score.

Experts agreed that lesions that do not display contrast enhancement can be active, because nonenhancing lesions can still show progression on T2-weighted and FLAIR sequences and weak enhancement signal can in some cases be missed for many reasons (insufficient gadolinium impregnation, sole use of 2D T1-weighted images, and/or gradient-echo ponderation). This illustrates that there is a need for other imaging techniques that are sensitive to activity (e.g., ongoing inflammation in CALD). DWI was considered an important tool to assess lesion activity in addition to postcontrast T1-weighted images and should be part of the core lesion monitoring protocol. Experts also agreed that the GIS, quantitative volumetrics, and DTI should be part of the optional lesion monitoring protocol, although it was stressed that not all centers would have the capacity to adequately collect or analyze the results of these techniques.

Research Protocol

MRI is a key focus in ALD research. Using the current Delphi platform, we gathered expert views on the development of a standardized international research protocol (Table 3). Experts agreed on the need to establish an internationally harmonized research protocol, implying harmonization of technical aspects. Specialized centers would implement these core sequences while retaining flexibility to include additional sequences of interest. When deciding to include an experimental sequence in a clinical scanning protocol, experts agreed that priority should be given to sequences that are relatively easy to process and that have been shown to have good predictive value. Experts identified DTI as the top research priority for lesion screening, followed by MR perfusion. For monitoring lesion progression, DTI and quantitative volumetrics should mainly be prioritized. Experts also supported the exploration of MWI. Regarding the DTI protocol, experts suggested that it should be performed on a 3T scanner, with at least 32 diffusion directions, and that the highest b-value should be at least 1,000 s/mm^2. The number of low b-values was not discussed by the experts, but DTI optimization data from literature indicate that the ratio of high-to-low b-values should be set at 8.[31] No consensus was reached on the method that should be used for quantitative volumetric analysis of CALD lesions, which can be fully manual or semiautomatized. Some experts emphasized that, in children, limited scan duration may restrict the number of sequences that can be included in a research protocol. However, no consensus was reached on acceptable scan times for either children or adults. While experts preferred that all centers

Table 2 Key Lesion Monitoring Protocol Recommendations

1	The Loes score is an appropriate instrument to assess the progression of CALD lesions in all age categories
2	The Loes score should preferably be calculated using spin-echo T2-weighted and 3D FLAIR imaging
3	In adults, age-related atrophy and nonspecific white matter lesions (e.g., likely related to vascular damage) should not be considered when calculating the Loes score
4	DWI should, in addition to postcontrast T1-weighted imaging, be part of the core protocol to monitor lesion activity
5	Quantitative volumetrics analysis and DTI should be part of the optional protocol to monitor lesion dynamics
6	The GIS should at least be part of the optional protocol to assess lesion progression and activity

Abbreviations: CALD = cerebral adrenoleukodystrophy; DTI = diffusion tensor imaging; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; GIS = gadolinium intensity score.

collect the same core sequences, it was proposed that data analysis could be centralized in given expert centers based on their specific expertise.

Discussion

This research describes an in-depth, practical guide on the use of brain MRI in ALD, which increases the chances to correctly identify and monitor CALD at an early treatable stage. Although previous studies have provided recommendations on the use of MRI in ALD,[12,13] international harmonization of the protocol in a real-world context has largely been lacking. This has substantially complicated the use and interpretation of sequences and techniques such as 2D vs 3D scans, gadolinium, DWI, the Loes score, and quantitative MRI, with the clinical consequence that CALD may not be recognized correctly.

During this project, a diverse panel of ALD specialists reached consensus on an internationally useable core screening and monitoring protocol for both children and adults, which will ensure a safer, standardized, diagnostic approach to CALD and can facilitate the discussion of individual patients within the ALD community. The screening protocol should at least include 3D T1-weighted, spin-echo T2-weighted, 3D FLAIR, and DWI and optionally SWI and 2D T1-weighted imaging. The recommendation that both T2-weighted and FLAIR imaging should be used to screen and monitor CALD is particularly helpful for physicians with limited ALD experience. Nonexpert centers are also advised to systematically acquire postcontrast 3D T1-weighted images to provide multiple ways to evaluate lesion activity, which facilitates expert consultation when needed. Unfortunately, no consensus was reached on whether spin-echo or gradient-echo T1-weighted imaging is best suited for this purpose, although spin-echo is historically considered more sensitive than gradient-echo pulse sequence to contrast enhancement.[17,32] Future studies should compare these techniques to determine the most suitable choice. DWI should be used to monitor lesion dynamics in addition to the Loes score and postcontrast imaging. Although not all experts currently include DWI in their protocols, most agreed with this recommendation, suggesting that even expert centers should consider updating their scanning procedures based on the conclusions of this project. This collaborative effort also succeeded in defining a core international research protocol that should at least include DTI, MR perfusion, and quantitative volumetrics. Research centers with adequate expertise are encouraged to include these sequences in their scanning protocol.

Beyond clinical practice, standardizing protocols across expert centers can also improve research collaboration by creating compatible data sets and, therefore, enabling easier pooling of data. Creating a research protocol can help accelerate the evaluation and adoption of MR techniques by focusing on international collaboration. DTI and MR perfusion received more support than other techniques, suggesting that these should be prioritized. Both techniques have been investigated in ALD populations as biomarkers with promising results.[9,19,21,25,26,33,34] The first step in developing a harmonized research protocol has now been taken by defining 3 technical aspects of DTI sequences. Other technical aspects of

Table 3 Key Research Protocol Recommendations

1	An internationally harmonized core research protocol should be established and integrated in all centers that perform research on the use of MRI in ALD
2	Quantitative lesion volumetrics, DTI, and MR perfusion should be part of an international research protocol
3	When deciding to include an experimental sequence in a clinical scanning protocol, priority should be given to sequences that are relatively easy to process and that have been shown to have good predictive value

Abbreviations: ALD = adrenoleukodystrophy; DTI = diffusion tensor imaging.

DTI where further discussion is needed to harmonize international practice include slice thickness, voxel size, gradient strength, and the use of multishell DWI sequences. Of interest, experts were also positive about MWI, reaching consensus that it should be included in the experimental protocol, although it has been described to a limited extent in ALD.[35]

Although these guidelines offer a standardized approach to scanning patients with ALD and interpreting the results, they do not exclude the use of additional clinical sequences that may be deemed important by institutions. Conversely, when it is not feasible to complete the full scan protocol, including in cases of limited resources, acquiring a subset of the recommended sequences can still support clinical decision making. In cases where scanning time is limited, the optional scanning protocol should not be prioritized. Less investigated imaging techniques aimed at better understanding pathology, such as the GIS, should be used cautiously, because their clinical use still needs to be evaluated in prospective studies.[36]

These guidelines do not address MRI screening in female individuals or imaging of the spinal cord, because neither is currently recommended for routine clinical use because of limited diagnostic value.[4,12] Intervals between scans were not a focus of this research, because current consensus already advises scans twice a year for boys between 2 and 12 years of age and annual scans for those older than 12 years of age.[12]

The modified Delphi procedure enabled experts to articulate the rationale for their decisions but may have introduced bias because dominant views could override minority perspectives. More broadly, Delphi methods are prone to reinforce previously reported findings and to exclude practitioners who have not published on the topic. We chose a 75% cutoff for consensus based on other studies that used a Delphi procedure. Most topics reached agreement levels above 80%, indicating a high degree of consensus. It is important to note that not all participants were experts on all proposed topics, which makes it difficult to compare the level of support, for example, between children and adults. Some participants indicated "not my expertise" for certain items, especially those involving technical aspects of MRI and those for which no consensus was reached. As experts were mainly from Europe and the United States, specialists from other regions may provide additional insights into the use of MRI in ALD in future collaborations. The topics discussed in this project have identified several research priorities that should be further explored. These include the further assessment of the optimal interval between contrast administration and image acquisition and the harmfulness of gadolinium buildup in the body.[29] These guidelines should be updated in case of future technical developments.

Through a collaborative approach, this research has established a set of real-world applicable recommendations for clinicians and researchers working with MRI in ALD. These recommendations will facilitate screening for and monitoring of CALD and can enable clinical decision making. ALD experts and nonexperts should now focus on implementing these recommendations.

Author Contributions

H.A.F. Yska: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M. Golse: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. D. Galanaud: drafting/revision of the manuscript for content, including medical writing for content. H.M. Amartino: drafting/revision of the manuscript for content, including medical writing for content. C. Bergner: drafting/revision of the manuscript for content, including medical writing for content. F. Bruschi: drafting/revision of the manuscript for content, including medical writing for content. F.S. Eichler: drafting/revision of the manuscript for content, including medical writing for content. A. Fatemi: drafting/revision of the manuscript for content, including medical writing for content. À. García-Cazorla: drafting/revision of the manuscript for content, including medical writing for content. M. Gomez-Chiari: drafting/revision of the manuscript for content, including medical writing for content. W. Köhler: drafting/revision of the manuscript for content, including medical writing for content. D. Loes: drafting/revision of the manuscript for content, including medical writing for content. T. Lund: drafting/revision of the manuscript for content, including medical writing for content. E.-J. Mallack: drafting/revision of the manuscript for content, including medical writing for content. M. Moscatelli: drafting/revision of the manuscript for content, including medical writing for content. P.L. Musolino: drafting/revision of the manuscript for content, including medical writing for content. D.R. Nascene: drafting/revision of the manuscript for content, including medical writing for content. J.L. Orthmann-Murphy: drafting/revision of the manuscript for content, including medical writing for content. C. Parazzini: drafting/revision of the manuscript for content, including medical writing for content. P.J.W. Pouwels: drafting/revision of the manuscript for content, including medical writing for content. J. Ribeiro-Constante: drafting/revision of the manuscript for content, including medical writing for content. S.D. Roosendaal: drafting/revision of the manuscript for content, including medical writing for content. E. Salsano: drafting/revision of the manuscript for content, including medical writing for content. P.V. Sgobbi: drafting/revision of the manuscript for content, including medical writing for content. C. Sevin: drafting/revision of the manuscript for content, including medical writing for content. A. Smith Fine: drafting/revision of the manuscript for content, including medical writing for content. D. Tonduti: drafting/revision of the manuscript for content, including medical writing for content. K. Van Haren: drafting/revision of the manuscript for content, including medical writing for content. A. Zerem: drafting/revision of the manuscript for content, including

medical writing for content. M. Engelen: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. F. Mochel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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