Diagnosis and treatment of Metachromatic Leukodystrophy: guideline within ERN-RND

DG/WG
Leukoence-phalopathies

Introduction

Metachromatic leukodystrophy (MLD) is a rare, progressive disease for which no clinical management guideline exists. Care is still mainly symptomatic, while European efforts have advanced knowledge on natural history, imaging markers and indications for stem cell and gene therapy. Yet, clinical practice varies and newborn screening and new therapies are emerging. A harmonized, evidence-based guideline within ERN-RND is therefore essential to standardize diagnosis and care across Europe.

Objective

As a primary objective, we propose to build the first European MLD guideline, combining available data and knowledge on early diagnosis, natural history, management, and treatment of the disease.

Guideline protocol

Months	Tasks	Responsible	
THE CLINICAL QUESTION			
1-4	Definition of PICO questions Identification of outcome parameters Ranking of relative importance	Guideline task force + additional experts + patient representatives	Survey, Delphi
4	Consensus meeting to define PICO critical/important clinical outcomes	Guideline task force + additional experts + patient representatives	Meeting
FIND THE EVIDENCE			
5-12	Systematic review	Coordinator, student assistants, support from EAN statistician	
12	Creation of evidence profile/summary of findings	Coordinator, student assistants, support from EAN statistician	Conference call
GRADE QUALITY OF EVIDENCE			
13-15	Individual grading of quality of evidences	Guideline task force + additional experts + patient representatives	
15	Call to discuss differences	Guideline task force + additional experts + patient representatives	Conference call
DETERMINE DIRECTION AND STRENGTH OF RECOMMENDATION			
16-18	Summary and compilation of quality gradings	Coordinator, student assistants, support from EAN statistician	
18	Consensus meeting	Guideline task force + additional experts + patient representatives	Meeting
WRITING OF GUIDELINE			
19-22	Writing of guideline	Coordinator, Guideline Task Force	
23	Review patient representatives and approval from societies	Patient representatives	
24	Submission for publication to the Journal of Inherited Metabolic Disease	Coordinator	

(according to GRADE and EAN recommendations ([1,2], http://www.gradeworkinggroup.org)

MLD Guideline Task Force (ERN-RND / EAN):
Samuel Gröschel (Germany) and Jean-Marc Burgunder (Switzerland) – Chairs. Carola Reinhard (Germany) – Coordination.
Advisors and EAN representatives: Antonio Federico (Italy), Caroline Sevin (France), Ingeborg Krägeloh-Mann (Germany), Ludger Schöls (Germany), Odile Boespflug-Tanguy (France), Fanny Mochel (France), Francesca Fumagalli (Italy), Enrico Bertini (Italy), Alessandra Biffi (Italy/USA), Anna Ardissone (Italy), Nicole Wolf (Netherlands), Caroline Lindemans (Netherlands), Ettore Salsano (Italy), Valeria Calbi (Italy). Methodological support and coordination: Teia Kobulashvili (Austria). Patient representatives: Tobias Mentzel, Michael Scholz (Germany).

Outlook

- **Guideline task force established** within ERN-RND and EAN, including pediatric/adult neurologists, metabolic specialists, hematologists, transplant experts, methodologists, and patient representatives.
- **PICO questions defined and approved c**overing diagnosis, newborn screening, disease monitoring, supportive care, HSCT, and gene therapy.
- **Systematic literature reviews launched**, following GRADE methodology; data extraction and evidence tables currently in progress.
- **Implementation plans**: dissemination via ERN-RND, EAN and patient networks; creation of quick-reference tools (red flags, care pathways, summaries for non-experts).
- **Challenges**: EAN methodology for rare neurological diseases (limited evidence, heterogeneous care) remains demanding [3], but can be addressed by expert consensus, systematic reviews, involvement of patient organisations, and ERN infrastructure

References
1. Leone MA, Brainin M, Boon P, Pugliatti M, Keindl M, Bassetti CL. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2012. *Eur J Neurol*. 2013;20:410–419.
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3. Aleksovska K, Kobulashvili T, Costa J, et al. European Academy of Neurology guidance for developing and reporting clinical practice guidelines on rare neurological diseases. *Eur J Neurol*. 2022;29:1571–1586. doi:10.1111/ene.15267.

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