Understanding the signs, symptoms and impacts of Metachromatic Leukodystrophy

Patel C[1], de la Motte A[2], Eliasson L[1], Xia A[3], Gervas-Arruga J[3], & Clifford S[2]

[1]Sprout Health Solutions, Pinner, London, UK; [2]Sprout Health Solutions, Los Angeles, CA, USA; [3]Takeda Pharmaceutical Company Limited, Boston, MA, USA

BACKGROUND & OBJECTIVE

Metachromatic leukodystrophy (MLD) is a rare inherited disorder affecting the central nervous system[1] and can be classified into three main clinical subtypes based on age of onset: late-infantile, juvenile (early and late), and adult MLD.[2]

This research reviewed the signs, symptoms and impacts of two paediatric clinical subtypes.

A conceptual model was developed to facilitate the understanding of outcomes of importance to pediatric patients with late-infantile and juvenile MLD and their caregivers.

METHOD

A targeted search was conducted in PubMed and complemented using Google Scholar.

N=256 articles were identified, of which n=13 met inclusion criteria for relevance.[3-14]

RESULTS

The age definitions of MLD subtypes varied among studies. Four studies defined late-infantile MLD as < 2.5 years of age at onset[3-6] and two studies defined late-infantile as < 4 years of age at onset.[7,8] One study defined early-juvenile MLD as 2.5 to < 6 years at age of onset, and late-juvenile MLD as 6 to < 16 years at age of onset.[5]

Late-infantile MLD is characterised by atypical development from 6 to 18 months of age followed by progressive regression presenting first in motor skills.[6] Frequent falls and developmental milestone regressions are early manifestations of the disease.[5,7-11] Patients with late-infantile MLD experience faster decline from initial symptom(s) to first functional loss (as assessed by the GMFC-MLD).[9] Other signs and symptoms (as illustrated by the conceptual model) in late-infantile MLD include deterioration in vision[12] and speech,[5,9] muscle weakness[4] and difficulty eating[9] and swallowing.[9]

Regarding juvenile (early and late) MLD, research showed that patients with these MLD phenotypes exhibit slower disease progression from initial symptom(s) to first functional loss.[6] These patients are characterised by atypical development from 12 to 30 months of age followed by behavioural[8] and cognitive[8,11] changes and impairment of fine motor skills[5] that typically present first.

The signs and symptoms of MLD have significant impacts on the wider family, including caregivers and non-affected siblings.[3,8,9,12]

Initial symptoms

Late-infantile MLD

- Abnormal behaviours
- Frequent falling/walking problems
- Regression of motor skills
- Speech regression
- Strabismus/squint

Juvenile MLD

- Abnormal behaviours
- Clumsy-like falls
- Gait problems
- Decline in school performance
- Psychiatric symptoms
- Problems swallowing
- Bladder accidents/incontinence

Behavioural characteristics

- Irritability
- General behaviour issues
- Disorientation
- Caregiver fixation
- Withdrawn
- Lack of judgement/ responsibility
- Loss of inhibition
- Socially inappropriate behaviour
- Aggression
- Biting

PNS and CNS signs/symptoms

- Ataxia
- Seizures
- Incontinence
- Pain
- Peripheral neuropathy
- Sensory problems
- Muscle weakness
- Muscle tension/stiffness
- Less prominent peripheral neuropathy
- Pyramidal syndrome/rigidity
- Bulbar palsy

Cognitive signs/ symptoms

- Cognitive impairment
- Difficulty understanding and/ or processing information
- Lack of development in speech
- Language decline
- Lack of awareness
- Lack of focus
- Memory loss
- Repetitive behaviours
- Decline in school performance

GMF/FMF signs/symptoms

- Regression in motor skills (never learning to walk, deterioration of balance, loss of trunk control)
- Gait-related changes
- Frequent falling
- Loss of ambulation
- Fine motor skill impairment (movement of the hands, fingers, lips, tongue and eyes)
- Difficulty chewing and swallowing
- Spasticity/muscle spasms
- Strabismus
- Poor vision

Caregiver, sibling and family impacts

- Daily activity limitations
- Social activity limitations
- Emotional/psychological function
- Isolation/confinement to home
- Spousal relationship strain
- Financial strain
- Planning for the future
- Career progression

Signs, symptoms and impacts that **overlap** in late-infantile, and juvenile MLD are indicated **in orange**
LATE-INFANTILE MLD signs, symptoms and impacts are indicated **in green**
JUVENILE MLD signs, symptoms and impacts are indicated **in blue**

CONCLUSION

The results of the targeted literature review showed that the signs, symptoms and impacts of late-infantile and juvenile MLD are heterogeneous. A particular challenge is identifying whether motor or cognitive dysfunction is a cause for the lack of development/regression of developmental milestones. The nature and variability in how MLD symptoms manifest, and their impacts can make it difficult to assess outcomes in paediatric populations, especially in clinical trials. The model presented in this study is preliminary as literature reporting signs and symptoms across MLD subtypes was sparse. Qualitative research is now needed to confirm the validity of concepts included in the draft model. This study aimed to shed light on the diverse patterns of MLD phenotypes, providing valuable insights for future research on aligning COAs with relevant concepts.

ABBREVIATIONS

CNS: Central Nervous System; **COA:** Clinical Outcomes Assessment; **FMF:** Fine Motor Function; **GMF:** Gross Motor Function; **GMFC-MLD:** Gross Motor Function Classification in MLD; **MLD:** Metachromatic Leukodystrophy; **PNS:** Peripheral Nervous System

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