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Consensus statement on preventive and symptomatic care of leukodystrophy patients

Keith Van Haren [a,*], Joshua L. Bonkowsky [b], Genevieve Bernard [c], Jennifer L. Murphy [d], Amy Pizzino [d], Guy Helman [d], Dean Suhr [e], Jacque Waggoner [f], Don Hobson [g], Adeline Vanderver [d,h,i], Marc C. Patterson [j], on behalf of the GLIA Consortium

[a] Department of Neurology, Lucile Packard Children's Hospital and Stanford University School of Medicine, Stanford, CA, USA
[b] Department of Pediatrics and Neurology, University of Utah School of Medicine, Salt Lake City, UT, USA
[c] Departments of Pediatrics, Neurology and Neurosurgery Montreal Children's Hospital/McGill University Health Center, Montreal, Canada
[d] Department of Neurology, Children's National Medical Center, Washington DC, USA
[e] MLD Foundation, USA
[f] The Hunter's Hope Foundation, Buffalo, NY, USA
[g] The PMD Foundation, USA
[h] Department of Integrated Systems Biology, George Washington University School of Medicine, Washington DC, USA
[i] Center for Genetic Medicine Research, Children's National Health System, Washington DC, USA
[j] Departments of Neurology, Pediatrics and Medical Genetics, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

Leukodystrophies are inherited disorders whose primary pathophysiology consists of abnormal deposition or progressive disruption of brain myelin. Leukodystrophy patients manifest many of the same symptoms and medical complications despite the wide spectrum of genetic origins. Although no definitive cures exist, all of these conditions are treatable. This report provides the first expert consensus on the recognition and treatment of medical and psychosocial complications associated with leukodystrophies. We include a discussion of serious and potentially preventable medical complications and propose several preventive care strategies. We also outline the need for future research to prioritize clinical needs and subsequently develop, validate, and optimize specific care strategies.

1. Introduction: lack of a cure should not result in a lack of care

Leukodystrophies are degenerative neurogenetic disorders whose primary pathophysiology involves abnormal deposition or disruption of brain myelin. These disorders are individually rare, but collectively common, affecting roughly 1 in 7500 individuals and covering the full spectrum of age, gender, and ethnicity [1].

Recently, a small number of genetic and stem cell therapies have finally achieved promising results in human trials for leukodystrophies [2–4]. Although tantalizing, in most cases these therapies are still many years away from widespread use and have limited relevance to patients suffering from debilitating symptoms in the present day. In this context, the more distant hope of technological "cures" may undermine the immediate relevance of routine and preventive care.

Improved medical care and quality of life for leukodystrophy patients need not, should not, and must not await the arrival of technological "cures". Few other genetic disorders have exemplified this principle as dramatically as cystic fibrosis, where average life expectancy has rocketed from 30 days to 30 years without the benefit of a genetic "cure" [5]. Rather, these gains in longevity were derived from incremental improvements in the approach to "routine and preventive care" (e.g. aggressive physiotherapy, antibiotics) and the establishment of expert centers. These expert centers monitored outcomes and used the data to publish and refine management guidelines [5]. Clearly, this

Abbreviations: X-ALD, X-linked adrenoleukodystrophy; ADLD, Adult onset autosomal dominant leukodystrophy; AGS, Aicardi–Goutières syndrome; AxD, Alexander disease; CER, Comparative effectiveness research; CT, Computed tomography; CTX, Cerebrotendinous xanthomatosis; GLIA, Global Leukodystrophy Initiative; MLD, Metachromatic leukodystrophy; Pol III, Polymerase III; UTIs, Urinary tract infections; VWM, Vanishing white matter disease

* Corresponding author at: Department of Neurology, Stanford University School of Medicine, 750 Welch Rd, Suite 317, Palo Alto, CA 94304, USA.
E-mail address: kpv@stanford.edu (K. Van Haren).

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astounding progress requires us to consider the possibility that "low tech" solutions to routine care could offer advantages for other genetic disorders still awaiting their definitive "cures".

2. The process of developing a consensus on preventive and symptomatic care

Impatience with the current state of care and a strong desire for progress in all its forms were part of the impetus that prompted a diverse group of leukodystrophy experts, patients, and patient advocates to convene in Washington DC in early 2013 to establish an international leukodystrophy consortium now called the Global Leukodystrophy Initiative or GLIA. The members of GLIA collectively identified four key areas in need of Consensus guidelines: (1) the definition and categories of leukodystrophies, (2) the diagnostic evaluation of suspected leukodystrophies, (3) the approach to leukodystrophy-specific therapies, and (4) the approach to preventive and symptomatic leukodystrophy care. This manuscript summarizes the latter. The remaining guidelines are available in this issue of Molecular Genetics and Metabolism [6–8].

The consensus process for symptomatic and preventive care began by designating a core team of seven leukodystrophy clinicians and patient advocates who generated a preliminary outline of care needs and treatment strategies. This outline was subsequently presented to the larger GLIA consortium for discussion and criticism. The consortium members made every effort to incorporate relevant evidence from the medical literature in devising the care guidelines. However, the paucity of research on clinical care strategies in leukodystrophies necessitated that many of our guidelines have been extrapolated from related fields or derived via consensus expert-opinion. The current manuscript represents the outcome of this consensus process and is the first of its kind to provide care recommendations for the full spectrum of leukodystrophy patients.

The basic principles underlying the current clinical guidelines are three-fold:

1. Although currently incurable, all leukodystrophies are treatable conditions.
2. Leukodystrophies share many of the same clinical symptoms, suggesting that a common approach to symptomatic and preventive treatment is reasonable.
3. The emotional vitality and the economic vitality of the caregiving family are important to the patient's health.

3. Establishing a diagnosis is only the first step

Although a genetic diagnosis is not always achievable, a rigorous diagnostic evaluation is important because of its implications for treatment, prognosis, and family planning. Consensus guidelines on defining and diagnosing leukodystrophies are covered separately [7,8]. Delivering the news of a confirmed genetic diagnosis to a family is an important milestone that should include the input of an experienced genetic counselor. The diagnostic disclosure should occur promptly after confirmation and should include the following four topics: diagnosis, prognosis, recurrence risk/reproductive options, and treatment plan. The absence of a genetic diagnosis should not delay the delivery of symptomatic and preventive care.

4. An effective treatment plan requires well-coordinated, multidisciplinary care

The long-term care goals for leukodystrophy patients do not differ from the general population: to enhance the quality and prolong the duration of life. The strategies required to achieve these goals, however, are substantially more complex and require hefty doses of preventive, chronic, and acute care that must evolve as the disease progresses. Leukodystrophy patients invariably require the care of multiple specialists in addition to their primary care physician. In some cases, a dedicated specialist (e.g. geneticist, neurologist or hospital-based pediatrician) may function as the de facto primary care provider or "medical home" for these complex patients. Effective multidisciplinary care delivery requires a strong leader, clear communication, continual reprioritization, and a strong commitment from the patient and family.

An effective treatment plan should address acute, chronic, preventive, and psychosocial needs as outlined herein. However, it is often impractical to devise a complete treatment plan in a single visit. Rather, a thorough treatment plan may take several visits to properly develop and will inevitably evolve as the disease progresses. In order to keep up with these changes, medical visits with the primary care physician should be scheduled at least every 6-months. At each visit, care needs should be reassessed and reprioritized.

Soliciting the patient's and/or caregiver's subjective sense of symptomatic priorities is an invaluable means for identifying treatment strategies in need of refinement. These visit-specific priorities should complement, but not overshadow, the treating physician's assessment of care needs. Consultation with a dedicated leukodystrophy clinic may offer both the referring physician and the family valuable nuances on individualized care strategies and/or clinical trial availability. Lastly, the treatment plan should include a discussion of the family's preferred approach to end-of-life care.

5. Disease-modifying and disease-specific therapies exist for a subset of leukodystrophies

Several leukodystrophies have important disease specific therapies available, most of which require prompt triage and initiation in order to take full effect, adding a level of urgency to an accurate diagnosis and therapeutic knowledge. These disease-specific therapies are covered in a separate GLIA consensus statement [6].

6. Many symptoms and treatments are shared across the spectrum of leukodystrophies

Because all leukodystrophies, by definition, affect brain myelin, these disorders commonly manifest a wide range of overlapping symptoms that allow a degree of uniformity in the approach to care in many cases. Below we highlight several treatable symptoms that appear across the leukodystrophy spectrum and include a brief description of treatment strategies, summarized in Table 1, and common medications, summarized in Table 2.

6.1. Autonomic dysfunction

Autonomic dysfunction or dysautonomia is a frequent source of secondary morbidity in leukodystrophy patients. Clinical manifestations are protean and often subtle, but can be readily uncovered during a comprehensive history and review of systems. Symptoms may affect bowel (e.g. constipation or incontinence), bladder (e.g. retention or incontinence), cardiac (e.g. arrhythmias), vascular (e.g. postural hypotension), and thermoregulation (e.g. diminished sweating). For patients with the adolescent or adult onset phenotypes of Alexander disease, metachromatic leukodystrophy, and adult-onset autosomal dominant leukodystrophy (ADLD), dysautonomia is a prominent feature [9,10]. Although well documented among adult-onset leukodystrophy patients, dysautonomia can also affect younger patients, particularly during the more advanced stages of neurologic progression.

6.2. Cognitive dysfunction and decline

Although some leukodystrophy patients begin life with normal cognitive function, most will eventually manifest some level of cognitive decline. The nature and the severity of cognitive dysfunction are determined by the neural networks affected as well as by the degree of injury.

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