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Minireview

Revised consensus statement on the preventive and symptomatic care of patients with leukodystrophies

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Abbreviations: 4H, hypomyelination, hypogonadotropic hypogonadism and hypodontia syndrome; AAC, augmentative and alternative communication; ACTH, adrenocorticotropic hormone; ADLD, adult-onset autosomal dominant leukodystrophy; AGS, Aicardi-Goutières Syndrome; AxD, Alexander Disease; BiPAP, bilevel positive airway pressure; CPAP, Continuous Positive Airway Pressure; CRIES, *C*ry, *R*equires O_2, *I*ncreased Vital Signs, *E*xpression, *S*leeplessness Scale; CT, computed tomography; CTX, cerebrotendinous xanthomatosis; DBS, deep brain stimulation; DEXA or DXA, dual-energy X-ray absorptiometry; EEG, electroencephalogram; FEES, fiberoptic endoscopic evaluation of swallowing; FLACC, *F*ace, *L*egs, *A*ctivity, *C*ry, *C*onsolability Scale; FSH, follicular stimulating hormone; G-tube, gastrostomy tube; GER, gastroesophageal reflux; GJ-tube, gastrojejunostomy tube; GLIA, Global Leukodystrophy Initiative; GMFCS, Gross Motor Function Classification System; LH, luteinizing hormone; MBS, modified barium swallow study; MLC, megalencephalic leukoencephalopathy; MLD, metachromatic leukodystrophy; MRI, Magnetic Resonance Imaging; ODDD, oculodentodigital dysplasia; OSA, obstructive sleep apnea; PedsQL, Pediatric Quality of Life Inventory; PTH, Parathyroid Hormone; QoL, quality of life; SLE, systemic lupus erythematosus; SLP, speech-language pathology; UTI, urinary tract infection; VWM, vanishing white matter disease; X-ALD, X-linked Adrenoleukodystrophy

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ABSTRACT

Leukodystrophies are a broad class of genetic disorders that result in disruption or destruction of central myelination. Although the mechanisms underlying these disorders are heterogeneous, there are many common symptoms that affect patients irrespective of the genetic diagnosis. The comfort and quality of life of these children is a primary goal that can complement efforts directed at curative therapies. Contained within this report is a systems-based approach to management of complications that result from leukodystrophies. We discuss the initial evaluation, identification of common medical issues, and management options to establish a comprehensive, standardized care approach. We will also address clinical topics relevant to select leukodystrophies, such as gallbladder pathology and adrenal insufficiency. The recommendations within this review rely on existing studies and consensus opinions and underscore the need for future research on evidence-based outcomes to better treat the manifestations of this unique set of genetic disorders.

1. Introduction

Leukodystrophies are a heterogeneous collection of genetic disorders that, while individually rare, collectively affect as many as 1 in 7500 individuals [1]. Patients with leukodystrophies, and their families, encounter a wide range of health problems and unique challenges to their care. These patients have a wide variety of issues, ranging from behavioral and sleeping difficulties, to requirements for assisted ventilation, to potential surgical interventions [2,3]. Hospitalizations and related health-care needs account for more than $59 million of health care costs each year in total [4]. For a minority of leukodystrophies, there are curative options, such as hematopoietic stem cell transplantation [5]. However, even in the absence of curative treatment, evidence supports a comprehensive treatment and care plan for all patients with leukodystrophies [6–8]. In addition to significant morbidity, one third of children with a leukodystrophy will succumb to the underlining disease and its complications by the age of 8 years [9].

The general tenets of our approach to the care of children with leukodystrophies are that there are common core symptoms shared among these disorders, that it is important to have a comprehensive approach that encompasses all relevant organ systems and includes the health of the care providers, and, importantly, that all leukodystrophies are treatable.

In this review, we will discuss specific management options for each affected system. We will also address disease-specific concerns, for example the adrenal insufficiency associated with adrenoleukodystrophy and the need for intracranial arteriopathy screening in a subset of patients with Aicardi-Goutières Syndrome. As leukodystrophy-related clinical studies are an area of active need, these recommendations rely primarily on clinical consensus and extrapolated data regarding the management described for other neurologic disorders.

2. Musculoskeletal and skin issues

Dysfunction of the musculoskeletal system is one of the most universal concerns among patients with leukodystrophies. Abnormalities in muscle tone such as spasticity and dystonia can result in secondary medical complications and negatively impact respiratory status, mobility, hygiene, self-care, sleeping patterns, and sexual function. Furthermore, the importance of ambulation for independence, bone and joint health, and emotional well-being cannot be overstated.

2.1. Spasticity

Spasticity is defined as velocity-dependent hypertonia with hyperreflexia that is typically accompanied by weakness [10]. It occurs as the result of injury to the myelin and/or axons of the primary motor pathways (i.e. corticospinal tracts) of the central nervous system and is, anecdotally, one of the most common symptoms reported in patients with leukodystrophies. Patients often have a combination of tone abnormalities, including truncal hypotonia mixed with appendicular hypertonia, dystonia, and other movement disorders, which may change over time [11]. Of importance, a sudden and persistent change in tone should prompt an in-depth assessment to determine the etiology. An acute increase in tone is commonly the result of an intercurrent illness or pain, although it may also be due to new central nervous system pathology.

Clinical assessment of spasticity should include an evaluation by a physical therapist, ideally employing standardized scoring systems to produce quantifiable metrics that can be tracked longitudinally (Table 1). Although these particular scoring systems have not been validated in children with leukodystrophies, they can be applied with caution in this population. In addition to specific scales to measure the severity of the motor dysfunction, the impact of altered tone on quality of life (QoL) can be assessed using standardized scales such as the Pediatric Quality of Life Inventory (PedsQL) [12]. The PedsQL is a self-reported assessment of health-related QoL. The Vineland Scales of Adaptive Behavior Screener can be useful for children that are young or with relatively low functional levels [13]. An important area of future research should be the validation of these scales within the leukodystrophy population, as these unique disorders are typically progressive (unlike cerebral palsy) and may affect a younger population than was used to design the currently available assessment tools.

Abnormal tone can cause significant medical complications, many of which may necessitate medical intervention (Table 2). In milder cases of spasticity without significant axial hypotonia, oral medications such as baclofen or diazepam in combination with physical therapy and daily stretching routines are usually sufficient [14–17]. Chemodenervation with botulinum toxin or intramuscular neural lysis with phenol can be useful to target focal areas of spasticity that impede functional tasks (e.g. adductor muscles to facilitate hygiene, gastrocnemius muscles to improve ambulation) [14–18]. The assessment and administration of chemodenervation can be performed by a variety of specialists, but requires an experienced medical provider with specialized training in this technique. Further guidance, as needed, can be provided by physiatry or orthopedics.

If these initial medical interventions are not effective, or if oral medications are not suitable or tolerated, consideration can be given to more invasive approaches. Intrathecal baclofen enables the use of higher doses of medication with fewer systemic side effects as