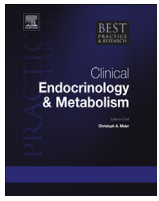
Best Practice & Research Clinical Endocrinology & Metabolism 29 (2015) 173–182

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem



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Non-neuronopathic lysosomal storage disorders: Disease spectrum and treatments

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Keywords:
lysosomal storage disorders
hepatosplenomegaly
cardiomyopathy
dysostosis multiplex

Distinctive facial features, hepatosplenomegaly or cardiomyopathy with or without associated skeletal dysplasia are clinical manifestations that may be suggestive of an underlying lysosomal storage disorder (LSD), However, these features may not be evident in certain subtypes associated primarily with central nervous system involvement. Age at onset can be broad, ranging from infancy to adulthood. Diagnosis may be delayed, as manifestations may be slow to evolve (taking months to years), particularly in those with later (adult-)onset, and in isolated cases (i.e., those without a prior family history). Diagnosis of individual subtypes can be confirmed using a combination of biochemical and molecular assays. In a few LSDs, treatment with hematopoietic stem cell transplantation, enzyme replacement or substrate reduction therapy is available. Symptomatic and palliative measure may enhance quality of life for both treatable and currently untreatable cases. Genetic counseling is important, so patients and their families can be informed of reproductive risks, disease prognosis and therapeutic options. Investigations of underlying disease mechanisms are enhancing knowledge about rare diseases, but also other more common medical conditions, on account of potential convergent disease pathways.

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http://dx.doi.org/10.1016/j.beem.2014.08.005
1521-690X/

Introduction

Lysosomal storage disorders (LSD) are mainly chronic conditions and clinical problems may evolve over years to decades [1]. In contrast to other inborn errors of metabolism due to defects in intermediary metabolism (such as amino acidopathies, organic acidurias and fatty acid oxidation defects), the onset of symptoms in LSDs has no temporal relationship to diet or the fasting state.

Affected individuals may present with clinical signs of tissue storage, such as hepatosplenomegaly or cardiomyopathy, although these may not be evident in those with predominant neuropathic involvement (discussed separately *see Chapter 3*) [2]. Age of onset can be broad, ranging from infancy to adulthood, with not all disorders manifesting severe pediatric sub-types. Diagnosis in late-onset cases may be delayed, particularly when signs and symptoms are limited and disease course is atypical.

Although individually infrequent to rare, collectively the LSDs have a combined prevalence of approximately 1 in 5000 (*see Chapter 2*) [3]. Certain entities are overrepresented in particular populations, such as the Ashkenazi Jews (i.e., those of Central and Eastern European descent) and among Finns, as a consequence of founder effect [4,5].

Clinical findings

In isolation, signs and symptoms of an LSD overlap with more common disorders; thus, diagnosis may not be suspected until the condition has advanced to involve several organ systems and the phenotype more typical. Therefore, it is critical to maintain a high index of suspicion, particularly for those disorders that are treatable [2,3]. Neurologic manifestations are part of the full spectrum of various LSDs; as this topic is covered elsewhere the focus of the current chapter will be on non-neuropathic features (Table 1). In certain cases, neurologic or psychiatric problems may herald an LSD, both in the early- and later-onset forms; unfortunately, these are also cases wherein diagnosis is also often delayed or missed.

Table 1
LSD presentations by age and diagnostic consideration.

Age group	Presenting feature	Diagnosis to consider
Neonate (<1 month)	Non-immune hydrops fetalis	GD, MPSVII, Infantile free sialic acid storage disease (ISSD)
Infancy (≤12 months)	Coarse facies	GM1-gangliosidosis; I-cell disease; Galactosialidosis
	Visual loss	GM2-gangliosidosis, Krabbe disease, NCL
	Hypotonia followed by spasticity	Krabbe disease; TSD; GD type 2
	Cardiomyopathy	Pompe disease, ISSD
Childhood (1–12)	Leukodystrophy	MLD, Krabbe, sialic acid storage disease, fucosidosis
	Hepatosplenomegaly	GD, NPD types A, B and C
	Short stature	MPS
	Joint contracture	MPS
	Acroparesthesia	Fabry disease
	Interstitial lung disease	GD type 3; Niemann-Pick disease type B
	Cytopenia	Gaucher, NPD types B and C
	Angiokeratoma	Fabry disease, Fucosisodosis
Teenage (13–18)	Ataxia	NPC, late-onset TSD
Adulthood (>18 years)	Psychiatric features (Psychosis)	MLD; late-onset (TSD) G_{M2}-gangliosidosis
	Cardiomyopathy	Fabry disease, Danon disease
	Stroke	Fabry disease, fucosidosis
	Interstitial lung disease	Gaucher types 1 and 3, NPD types B and C
	Hepatosplenomegaly	Gaucher, NPD types B and C
	Renal failure	Cystinosis, Fabry
	Cytopenia	Gaucher, NPD types B and C