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REVIEW ARTICLE

Lysosomal Storage Disorders in the Newborn

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ABSTRACT

Lysosomal storage disorders are rare inborn errors of metabolism, with a combined incidence of 1 in 1500 to 7000 live births. These relatively rare disorders are seldom considered when evaluating a sick newborn. A significant number of the >50 different lysosomal storage disorders, however, do manifest in the neonatal period and should be part of the differential diagnosis of several perinatal phenotypes. We review the earliest clinical features, diagnostic tests, and treatment options for lysosomal storage disorders that can present in the newborn. Although many of the lysosomal storage disorders are characterized by a range in phenotypes, the focus of this review is on the specific symptoms and clinical findings that present in the perinatal period, including neurologic, respiratory, endocrine, and cardiovascular manifestations, dysmorphic features, hepatosplenomegaly, skin or ocular involvement, and hydrops fetalis/congenital ascites. A greater awareness of these features may help to reduce misdiagnosis and promote the early detection of lysosomal storage disorders. Implementing therapy at the earliest stage possible is crucial for several of the lysosomal storage disorders; hence, an early appreciation of these disorders by physicians who treat newborns is essential. *Pediatrics* 2009;123:1191–1207

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Key Words
lysosomal storage disorders, neonatal, hydrops, enzyme deficiency

Abbreviations
LSD—lysosomal storage disorder
NIHF—nonimmune hydrops fetalis
ERT— enzyme-replacement therapy
MPS—mucopolysaccharidosis
ISSD—infantile sialic acid storage disease
CNS— central nervous system
HCT— hematopoietic stem cell transplantation

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The lysosomal storage disorders (LSDs) are rare diseases with a combined incidence of ~1 in 1500 to 7000 live births.[1,2] LSDs result from the inherited deficiency of 1 or more of the many catabolic enzymes that are located within the lysosome. This group of inborn errors of metabolism encompasses >50 different diseases, each characterized by the accumulation of specific substrates.[3–6] There are many steps necessary for the synthesis and processing of lysosomal enzymes, which makes this system prone to dysfunctions that can result from different mechanisms and at many different steps in the pathway.

LSDs classically have not been considered disorders of the newborn. Generally, clinicians are taught that newborns with LSDs appear normal at birth and that the symptoms develop progressively over the first few months of life or even after many years. However, a portion of these patients can be mildly symptomatic as early as the first few days of life or even before birth, or they may have transient symptoms in the newborn period. Often, these early symptoms evade recognition because they are not considered in the differential diagnosis of disorders of the neonate. Nonimmune hydrops fetalis (NIHF) can be the initial presentation, indicating prenatal involvement.[4] Table 1 lists the different LSDs that have been reported in neonates and the specific enzymes and storage products involved.

It is very likely that the incidence of perinatal manifestations of LSDs is vastly underestimated. Greater physician awareness of these early presentations has important clinical implications. The recent development and availability of enzyme-replacement therapy (ERT) for several of the LSDs makes diagnosis early in the clinical course particularly important. Early diagnosis and intervention is essential for maximizing the potential benefit from some of these therapies and may prevent irreversible organ damage. Early diagnosis can provide parents with realistic information about their child's prognosis and can enable appropriate genetic counseling for future pregnancies. It can also help families avoid the "diagnostic odyssey" that many patients undergo before a diagnosis is made.

The majority of the LSDs are inherited in an autosomal recessive manner, with 3 exceptions: the X-linked disorders Fabry disease, Hunter syndrome (mucopolysaccharidosis [MPS] II), and Danon disease. Ethnicity can also be an important factor when considering the diagnosis of LSDs. Certain ethnic groups have an increased carrier frequency for specific disorders. For example, Gaucher disease, which results from the deficiency of the enzyme glucocerebrosidase, is the most common genetic disorder in Ashkenazi Jews, with a frequency of ~1 in 855 live births.[7] An increased incidence of galactosialidosis is found among individuals of Japanese ancestry.[8] Pompe disease is reported to have an increased frequency in subjects of African or Chinese ancestry.[9] Consanguinity also can be a factor to consider in diagnosis of neonates from isolated communities.

The intent of this review is to describe symptoms of LSDs that can manifest in the newborn period and should alert the clinician to the possibility of inherited lysosomal diseases. The discussion focuses on clinical manifestations that

TABLE 1 LSDs With Neonatal Presentations

Type/Disease	Enzyme	Accumulating Substrate	Inheritance and Gene	OMIM No.
Sphingolipid storage disease				
Fabry disease	α-Galactosidase A	Globotriaosyl-ceramide (ceramide trihexoside)	X-LR; Xq22; *GLA*; manifests in hemizygotes 1 in 40 000	301500
Farber disease	Acid ceramidase	Ceramides	AR; 8p22-p21.3; *ASAH1*	228000
Gaucher disease type 2 (infantile acute neuronopathic)	Glucocerebrosidase, acid β-glucosidase	Glucocerebroside	AR; 1q21; *GBA*	230900, 608013
GM1 gangliosidosis	β-Galactosidase	G_{M1} ganglioside, keratan sulfate	AR; 3p21.33; *GLB1*	230500
Krabbe disease, globoid cell leukodystrophy	Galactocerebrosidase, β-galactosidase	Galactocerebroside, galactosylsphingosine (psychosine)	AR; 14q31; *GALC*	245200
Niemann-Pick disease, types A and B	Sphingomyelinase	sphingomyelin, cholesterol	AR; 11p15.1-p15.4 (*SMPD1*)	257200, 607616
Infantile-onset symptomatic epilepsy	Lactosylceramide α-2,3 sialyltransferase (GM3 synthase)	Lactosylceramide	AR; 2p11.2; *ST3GAL5*	609056
Mucopolysaccharide storage disease				
MPS I, Hurler syndrome	α-L-iduronidase	Heparan sulfate, dermatan sulfate	AR; 4p16.3; *IDUA*	607014
MPS IVA, Morquio syndrome A	Galactosamine-6-sulphatase	Keratan sulfate, chondroitin sulfate	AR; 16q24.3; *GALNS*	253000
MPS VII, Sly syndrome	β-Glucuronidase	Dermatan sulfate, heparan sulfate, chondroitin sulfate	AR; 7q21.11; *GUSB*	253220
Glycogen storage disease				
Pompe disease	α-Glucosidase	Glycogen	AR; 17q25.2-q25.3; *GAA*	232300
Glycoprotein storage disease				
Sialidosis types I and II, mucolipidosis type 1	Neuraminidase 1	Sialic acid	AR; 6q21.3; *NEU1*	256550
Schindler disease	*N*-acetyl-α-D-galactosaminidase	Glycosphingolipids	AR; 22q11; *NAGA*	609241
Complex lipid storage disease				
Wolman disease	Lysosomal acid lipase	Cholesterol esters, triglycerides	AR; 10q24-q25; *LIPA*	278000
Transport and trafficking disorder				
ISSD, sialuria, Salla disease	Sialin (membrane protein)	Sialic acid	AR; 6q14-q15; *SLC17A5*	269920, 604369
Niemann-Pick disease type C	NPC1 and NPC2	Lipids, cholesterol	AR; 18q11-q12 (*NPC1*), 14q24.3 (*NPC2*)	257220, 607625
Multienzyme defect				
Galactosialidosis	β-Galactosidase and neuraminidase	GM3, GM2, GM1, GD1a, lactose ceramide, GA2, and GA1	AR; 20q13.1; *PPCA*	256540
I-cell disease, mucolipidosis type 2	*N*-acetylglucosamine-L-phosphotransferase	Multiple substrate accumulation	AR; 12q23.3; *GNPTAB*	252500
Multiple sulfatase deficiency	Sulfatase-modifying factor 1; affects arylsulfatases A, B, C	Mucopolysaccharides and sulfatides	AR; 3p26; *SUMF1*	272200
Prosaposin deficiency	Prosaposin, SAP A, B, C, D; activators for multiple lysosomal enzymes	ceramide, sulfatide, hexosylceramides, globotriaosyl-ceramide and lactosylceramide	AR; 10q22.1; *PSAP*	176801

OMIM indicates Online Mendelian Inheritance in Man (see www.ncbi.nlm.nih.gov/sites/entrez?db=omim); X-LR, X-linked recessive; AR, autosomal recessive.

affect different organ systems and includes reference tables and an algorithm (Fig 1) to help in the differential diagnosis of these disorders in the neonatal period.

FREQUENT CLINICAL MANIFESTATIONS IN THE NEONATAL PERIOD

A summary of the major clinical findings encountered among neonates with these inborn errors of metabolism is provided in Table 2. Most newborns with LSDs appear normal at birth, because many of the toxic metabolites cross the placenta during pregnancy and are cleared by the mother during gestation. The interval between birth and the onset of clinical symptoms can range from hours to months (Table 3).

Neurologic Manifestations

Some of the LSDs present with neuromuscular manifestations. Most often these manifestations include hypotonia or weakness caused by toxic effects of accumulating metabolites in the muscles.

Pompe disease, the inherited deficiency of α-glucosidase, also known as glycogen storage disorder type 2, is an uncommon cause of the floppy-infant syndrome and is often overlooked in the early differential diagnosis of

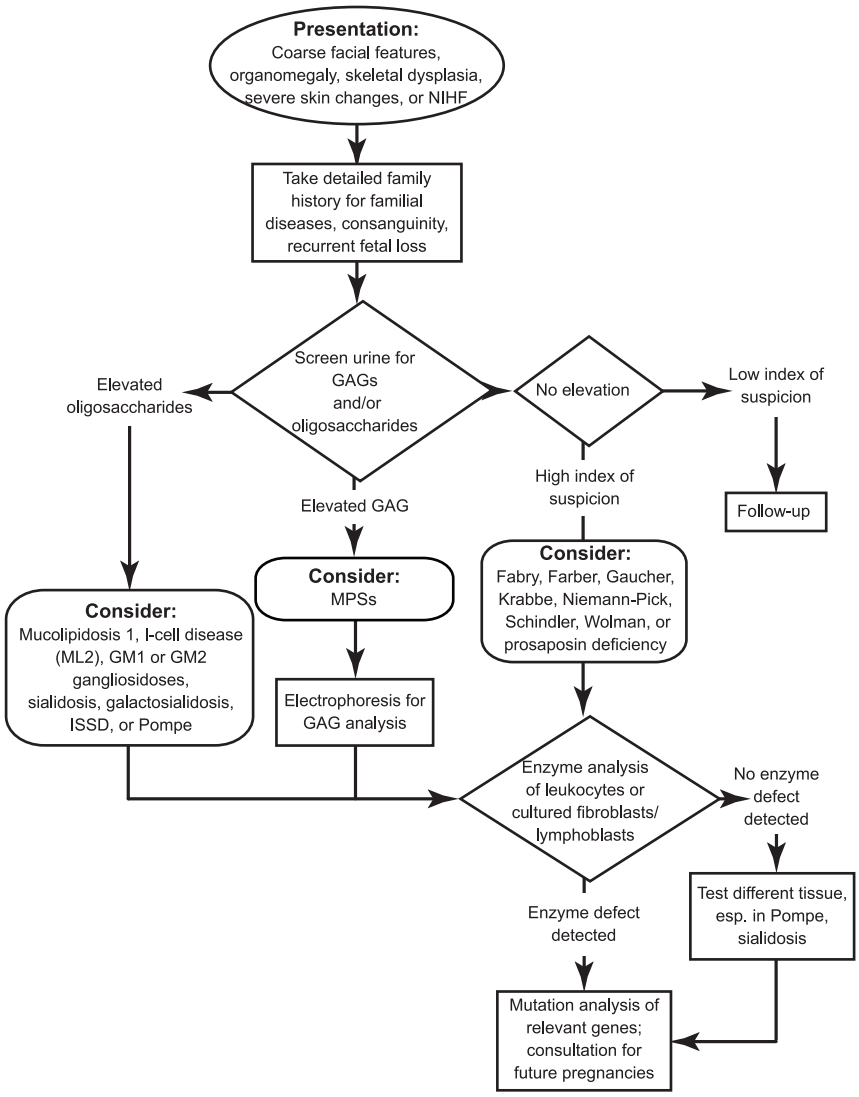

FIGURE 1
Algorithm of the clinical evaluation recommended for an infant with a suspected LSD. GAGs indicates glycosaminoglycans.

such infants.[10] There is a spectrum of clinical presentations of Pompe disease, with the infantile type being the most severe. These infants can have a very striking appearance and little to no spontaneous movements. There have also been descriptions of low "myopathic" carnitine levels in infants with Pompe disease. This can be a form of secondary deficiency that also manifests in the first few months with generalized hypotonia and absent reflexes.[9,11]

Gaucher disease also has a continuum of phenotypic presentations. The acute neuronopathic form, type 2, presents in infancy and has a devastating neurologic course. There is a subset of type 2 disease that manifests in utero or perinatally, with severe neurologic signs including strabismus, trismus, retroflexion of the head, and opisthotonos.[12–14]

Krabbe disease, the deficiency of galactocerebrosidase, is divided into 2 main clinical forms on the basis of the age of onset. The infantile form generally presents at the age of 3 to 6 months with irritability, spasticity, and arrested motor development. However, there are earlier disease manifestations that can be overlooked because of a low index of suspicion. Actually, accumulation of the toxic substrate galactosylsphingosine (psychosine) in tissues has been noted as early as 21 weeks' gestation in a fetus diagnosed prenatally with Krabbe disease.[15] Sahai et al[16] described a newborn who presented at the age of 7 days with irritability that progressed to weakness and seizures at the age of 7 weeks. There was also a description of an asymptomatic infant who developed a peripheral neuropathy at the age of 7 weeks and was subsequently diagnosed with Krabbe disease.[17] Clarke et al[18] reported an extremely rare neonatal variant of Krabbe disease that presented in the newborn with both the typical neurologic symptoms and lung involvement.

Very early developmental arrest is also seen in some LSDs. I-cell disease (mucolipidosis type 2) is a rare lysosomal disorder that presents at birth or in the first few months of life with profound developmental delay and microcephaly.[19] GM1 gangliosidosis type 1, infantile form, can also present with developmental delay. Denis et al[20] described a female newborn who, by the third day

TABLE 2 Symptoms Encountered in Newborns With LSDs

System	Manifestations
Neurologic	Hypotonia
	Floppy-infant syndrome
	Trismus
	Strabismus
	Opisthotonus
	Spasticity
	Seizures
	Peripheral neuropathy
	Developmental delay
	Irritability
	Extrapyramidal movement disorder
	Hydrocephalus
Respiratory	Congenital lobar emphysema
	Impaired cough
	Recurrent respiratory infections
	Hoarseness
Endocrine	Osteopenia
	Metabolic bone disease
	Secondary hyperparathyroidism
	Congenital adrenal hyperplasia
Cardiovascular	Cardiomegaly
	Congenital heart failure
	Arrhythmias
	Wolff-Parkinson-White syndrome
	Cardiomyopathy
Dysmorphology	
Head and neck	Microcephaly
	Enlarged nuchal translucency
	Microstomia
	Micrognathia/microretrognathia
	Long philtrums
Limbs	Bilateral broad thumbs and toes
	Bilateral club feet
	Eversed lips
	Flattened nasal bridge
	Short nasal columella
Oral	Macroglossia
	Molar hypoplasia
	Hypertrophic gums
	Absent nasal septum
	Bilateral epicanthal inferior orbital creases
	Palpebral edema
	Hypertelorism
Facial	Coarse facies
	Low-set ears
Gastrointestinal	Hepatosplenomegaly
	Neonatal cholestasis
Bones and joints	Lytic bone lesions
	Joint contractures
	Dysostosis multiplex
	Hyperphosphatasemia
	Vertebral breaking
	Broadening of tubular bones
	Punctuate epiphysis
	Craniosynostosis
	Painful joint swelling
Skin	Congenital ichthyosis
	Collodion infant
	Hypopigmentation
	Telangiectasias
	Extended Mongolian spots
Ocular	Corneal clouding
	Megalocornea
	Glaucoma
	Cherry-red spots
	Fundi hypopigmentation
	Bilateral cataracts
Hematologic	Anemia
	Thrombocytopenia
Hydrops fetalis	NIHF
	Congenital ascites
Recurrent fetal losses	

of life, was hypotonic with a poor suck but had hyperreflexia. Morrone et al[21] described 5 Italian patients presenting at birth or within 3 months of age who had delayed psychomotor development, hypotonia, and, in 1 case, seizures.

Seizures are a neonatal neurologic presentation in other LSDs. A rare infantile-onset symptomatic epilepsy syndrome, caused by a premature termination in the GM3 synthase enzyme, presents between the ages of 2 weeks and 3 months, primarily with irritability and feeding problems. Infants with this syndrome later develop seizure activity and profound developmental regression.[22] Prosaposin deficiency, a rarely diagnosed storage disease, manifests with rapidly progressive neurologic deterioration characterized by myoclonus and an extrapyramidal movement disorder that proceeds to grand mal epilepsy.[23]

Another neurologic manifestation encountered rarely in the LSDs is hydrocephalus. Hydrocephalus has been described in multiple sulfatase deficiency, presenting at birth or later, and often precedes the actual diagnosis, usually made at ~8 years of age.[24,25] Hydrocephalus can be a manifestation of an atypical variant of Gaucher disease associated with mutation D409H, which also has cardiac valve involvement; however, it usually presents at the age of a few months.[26] Hydrocephalus has also been reported in early infancy in sialidosis and MPS VII.[27,28]

Respiratory Manifestations

Several different LSDs can present with respiratory distress. Respiratory problems can arise in conjunction with hydrops fetalis, which will be discussed later, or can develop in other circumstances.

Niemann-Pick disease type B is known to cause mild pulmonary involvement. Arda et al[29] described the case of a female infant who had massive pulmonary involvement resembling congenital lobar emphysema. She was ultimately diagnosed by a lung biopsy that showed foamy cells, and the diagnosis was confirmed by enzyme analysis. In addition, at least 5 cases of Niemann-Pick disease type C2 have been described who presented shortly after birth with severe respiratory distress.[30]

In Pompe disease, the early respiratory manifestations are attributed mostly to progression of the disease, with muscular weakness leading to low lung volumes, an

TABLE 3 Clinical Manifestations Reported in Different LSDs in the Neonate

Disease	Hypotonia	Irritability	Developmental Delay	Seizures	Movement Disorder	Hyperreflexia	Hydrocephalus	Corneal Clouding	Cherry-Red Spot	Hepatospleno-megaly	Anemia/ Low Platelets	CAH
Pompe disease	X											
Gaucher type 2 disease		X					X			X	X	
Krabbe disease	X	X	X	X								
I-cell disease	X		X	X		X		X		X		
IOSE	X			X								
Prosaposin deficiency				X	X					X		
Multiple sulfatase deficiency							X			X		
Sialidosis							X	X		X	X	X
MPS VII							X			X		
Niemann-Pick type B disease	X											
Niemann-Pick type C2 disease	X						X			X		
Farber disease												
Galactosialidosis									X	X	X	X
Fabry disease												
Sandhoff disease												
GM1 disease	X											
ISSD										X		
Schindler disease												
Wolman disease										X		
Niemann-Pick type A disease												

	Cardiomegaly	Cardiomyopathy	Respiratory Distress	Macroglossia	Hoarseness	Dysmorphic Features	Osteopenia	Joint Contractures	Dysostosis Multiplex	Craniosynostosis	Ichthyosis
Pompe disease	X	X	X	X		X					
Gaucher type 2 disease		X				X		X			X
Krabbe disease											
I-cell disease		X				X	X		X	X	
IOSE											
Prosaposin deficiency											
Multiple sulfatase deficiency						X					X
Sialidosis		X	X								
MPS VII						X					
Niemann-Pick type B disease											
Niemann-Pick type C2 disease			X								
Farber disease					X						
Galactosialidosis		X				X			X		
Fabry disease		X									
Sandhoff disease		X									
GM1 disease		X									
ISSD						X			X		
Schindler disease		X									
Wolman disease											
Niemann-Pick type A disease		X									

CAH indicates congenital adrenal hyperplasia; IOSE, infantile-onset symptomatic epilepsy.

impaired cough, blood gas abnormalities, and sleep-apnea.[9,31] These patients are also at increased risk for aspiration pneumonia. Although most patients with Pompe disease will develop cardiomegaly prior to the significant muscle weakness that leads to respiratory infections, there has been at least 1 description of recurrent neonatal respiratory infections as the presenting sign of Pompe disease. This was explained by hypotonicity of the respiratory muscles.[32] Another important factor that contributes to the respiratory distress seen in Pompe disease is severe macroglossia, which can cause aspiration and uncoordinated deglutition.[33]

Farber disease is known to present at the first few months of life with hoarseness and progressive joint swelling. The hoarseness develops as a result of accumulation of ceramide and development of nodules on the vocal cords. Devi et al[34] described a neonate who presented at the age of 1 month with hoarseness.

Endocrine Manifestations

Unger et al[35] described 3 patients who presented at birth with generalized osteopenia. A review of the literature identified a subset of patients with I-cell disease who presented in the neonatal period with features of "metabolic bone disease" rather than with the common signs of dysostosis multiplex that usually develop later in life. This presentation was accompanied by increased serum parathyroid hormone and alkaline phosphatase activity but normal calcium concentrations.[36–42]

Secondary hyperparathyroidism is a rare diagnosis and is attributed mostly to maternal deficiencies. It is usually transient in I-cell disease,[43] and patients are not diagnosed until later in life, when they develop the typical clinical and radiologic features of the disease. The severe secondary hyperparathyroidism is probably a result of impaired transplacental calcium transport due to the underlying lysosomal disorder. Treatment with vitamin D resulted in a more rapid resolution.[39]

Congenital adrenal hyperplasia (CAH) is occasionally a manifestation of the LSDs. Oohira et al[44] described a patient who presented with CAH as a result of a 21-hydroxylase deficiency associated with sialidosis type 2 (mucolipidosis type 1) that was thought to be due to linkage between HLA and the neuroaminidase gene. Later, Kyllerman et al[45] described another patient with suprarenal masses on computed tomography scans that were likely to represent adrenal changes. At birth the patient had an enlarged clitoris with moderately elevated levels of 17-hydroxyprogesterone and low levels of plasma cortisol, indicating a transient intrauterine dysfunction of the adrenal glands, although inappropriate steroid metabolites could not be demonstrated at 3 weeks of age. This adrenal hyperplasia was most likely secondary to the child's storage disorder, which was diagnosed as galactosialidosis.

Cardiovascular Manifestations

In classical infantile Pompe disease, cardiomegaly, congenital heart failure, arrhythmias such as supraventricular tachycardia, and cardiac arrest during surgery are examples of neonatal cardiovascular manifestations. This disorder is the only glycogen storage disease that is also an LSD, and the effects of glycogen accumulation are very pronounced in the heart. Lysosomal glycogen accumulation results in significant cardiac hypertrophy that may begin in utero and is apparent perinatally or at 4 to 8 weeks of age.[46]

In addition, the insulator effects of glycogen in conduction tissue can result in disruptions to the conduction system of the heart, leading to arrhythmias. Wolff-Parkinson-White syndrome has been reported to occur in Pompe disease as well.[47] These conduction abnormalities, in conjunction with the hypertrophic cardiomyopathy, place affected infants at high risk for sudden death.

Cardiomyopathy may be associated with several other LSDs including Fabry disease, Gaucher disease, Niemann-Pick type A, I-cell disease, GM1 gangliosidosis, Sandhoff disease, sialidosis, galactosialidosis, infantile sialic acid storage disease (ISSD), and Schindler disease, although these generally do not manifest in the newborn.[48,49]

Dysmorphic Features

Several of the LSDs have classic dysmorphic features that can be identified in the newborn (Fig 2). MPS VII, the deficiency of β-glucuronidase, has a spectrum of clinical findings. A review of the literature reveals that some patients present as early as at birth, and have severe involvement, including a characteristic appearance of coarse facies with a depressed nasal bridge and widely spaced eyes.[50] den Hollander[51] also described a patient with MPS VII that presented with an enlarged nuchal translucency in early pregnancy.

The early infantile form of galactosialidosis presents at birth with gargoyle-like features, including bilateral epicanthal inferior orbital creases, absent nasal septum, molar hypoplasia, high arched palate, and micrognathia.[52] Infants with galactosialidosis have also been described with long philtrums and sparse temporal hair.[53]

One of the characteristic features of Pompe disease is severe macroglossia with a protruding tongue, which is also typical of several of the MPSs. The other accompanying features are flattened nasal bridge, facial hair, and coarse facial features.[33]

GM1 gangliosidosis type 1 has been described as presenting in the newborn with a slightly coarse facies and palpebral edema.[20,54] I-cell disease is also characterized by coarse facial features and hypertrophic gums, which are unique to this disease at this age (Figs 2A and 2C).[19]

Several cases of perinatal-lethal Gaucher disease have been described with an unusual facial appearance, including low-set ears, a small nose with a flat nasal bridge, and, less frequently, hypertelorism, microstomia, eversed lips, microretrognathia, and microcephaly.[14,55]

Multiple sulfatase deficiency is not only rare, but also is not usually diagnosed until approximately the age of 8 years. There have been, however, a few descriptions of dysmorphic features seen at birth, including bilateral broad thumbs and great toes, both with angulation deformities, bilateral club feet, and a short nasal columella.[24,25]

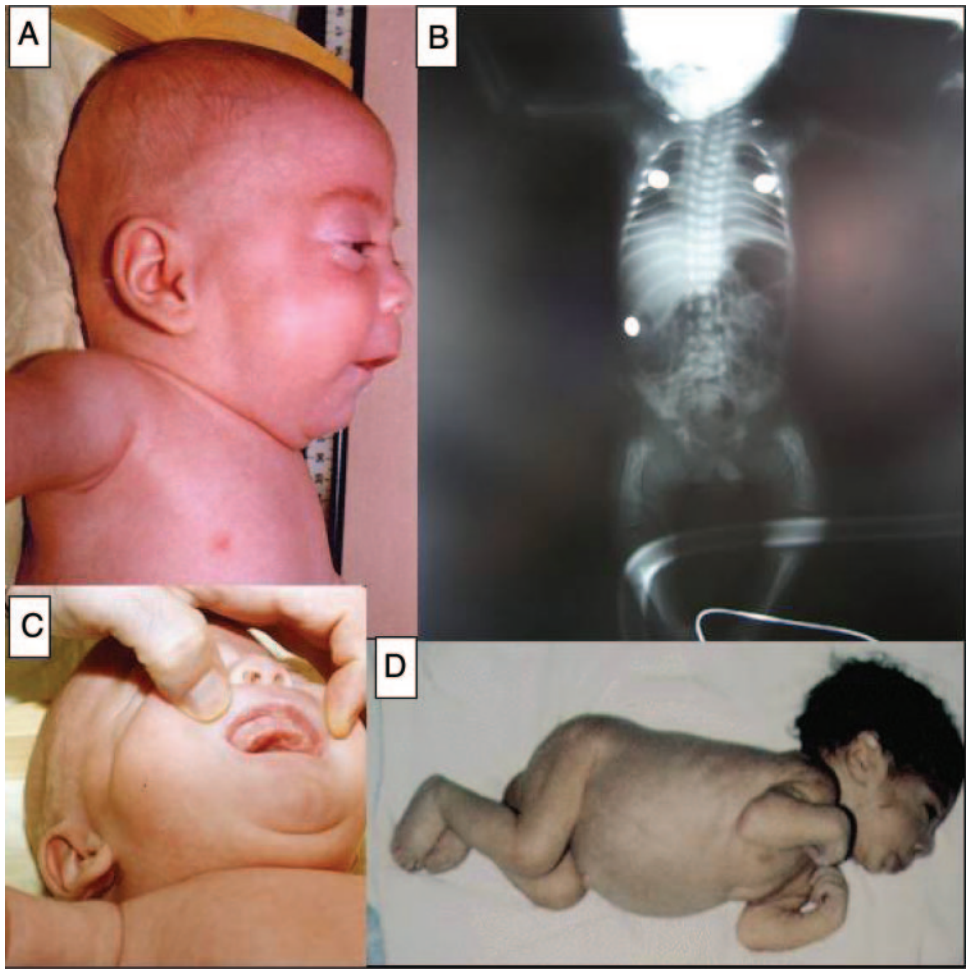

FIGURE 2
Clinical photographs. A, Coarse facial features in a patient with I-cell disease. B, Skeletal survey showing lytic bony lesions in a patient with I-cell disease. C, Gum hyperplasia in a patient with I-cell disease. D, A newborn with perinatal-lethal type 2 Gaucher disease presenting with contractures and hepatosplenomegaly.

Hepatosplenomegaly

The differential diagnosis of hepatosplenomegaly at birth is vast. When a newborn presents with hepatosplenomegaly, the first step is to rule out more common diagnoses such as viral infections, sepsis, and anatomic obstructions. LSDs should be considered in the differential diagnosis, particularly if there are additional manifestations such as coarse facies.

MPS VII commonly presents at birth (or even before birth with hydrops) and is associated with chronic hepatosplenomegaly.[50,56,57] Sialidosis and galactosialidosis have also been described as a cause of hepatosplenomegaly in the newborn.[54,58] Hepatosplenomegaly in the neonate is commonly seen with perinatal-lethal type 2 Gaucher disease[14] (Fig 2D). Pueschel et al[59] described the case of a patient with ISSD who had fetal ascites and chronic hepatosplenomegaly. Likewise, prosaposin deficiency, a very rare progressive LSD, presents with hepatosplenomegaly at birth, with no evidence of ascites.[60,61]

Niemann-Pick type C has been described in at least 3 patients who exhibited hepatosplenomegaly and jaundice in the first 2 months of life, which resolved later in life.[62,63] The disease has also been described as manifesting with fetal ascites.[64] Wolman disease is characterized by hepatosplenomegaly at birth or shortly thereafter.[65,66] Multiple sulfatase deficiency and I-cell disease can present with neonatal hepatosplenomegaly.[24,67–69]

The biliary tract can also be involved in LSDs. Hochman et al[70] described a patient who presented at the age of 9 days with mild jaundice who developed hepatosplenomegaly by the age of 1 month. This was later found to be a result of a bile duct injury that was diagnosed as part of I-cell disease. This case demonstrates that I-cell disease should be in the differential diagnosis of neonatal cholestasis. Neonatal cholestasis has also been described in Gaucher disease.[71,72]

Bones and Joints

Bone and joint involvement has been described occasionally in infants with LSDs. Lytic bone lesions have been observed in type 2 Gaucher disease.[73] Joint contractures have been described in association with Gaucher disease in neonates and fetuses with hydrops fetalis (Fig 2D).[74]

Dysostosis multiplex, which results from abnormal bone formation, is a feature of several LSDs, but it usu-

ally presents later in life. However, it has been described in neonates and fetuses diagnosed with galactosialidosis, GM1 gangliosidosis, and I-cell disease in association with NIHF.[19,75]

Denis et al[20] described a significant hyperphosphatasemia in the first few months of life in neonates with GM1 gangliosidosis who had radiographic evidence of lytic bone lesions. Severe bony changes, including vertebral breaking and broadening of tubular bones, have been described in a few infants with MPS VII.[56] Galactosialidosis has been described in association with precocious calcification, which is also known as punctuate epiphysis.[53]

I-cell disease has been described together with craniosynostosis in the neonate in a few cases. Prenatal development of short femurs has also been seen (Fig 2B) in I-cell disease and must be differentiated from neonatal osteogenesis imperfecta.[76] I-cell disease should be part of the differential diagnosis of significant craniosynostosis in the neonate or prenatal diagnosis of short femurs, especially if coarse facies is seen postnatally.[77]

Farber disease generally manifests after the first few months of life. There was a report of 1 patient, however, who presented with painful joint swelling at the age of 1 month.[34]

Skin Manifestations

Type 2 Gaucher disease can manifest with congenital ichthyosis. Ultrastructural and biochemical alterations are present in the epidermis of infants with type 2 Gaucher disease, even when clinical signs of skin involvement are not. Glucocerebrosidase is abundant in normal epidermis and results in the conversion of glucosylceramide into ceramide, both components of the lipid bilayer that forms the epidermal barrier. In type 2 Gaucher disease, the ratio of glucosylceramide to ceramide is reversed.[78] The clinical spectrum of skin involvement in type 2 Gaucher disease ranges from mild skin peeling and scaling that quickly resolves to a full-fledged "collodion baby" phenotype.[79] Recognition of these skin manifestations is particularly important, because they often precede severe neurologic manifestations in these children.[80–82]

Multiple sulfatase deficiency can present in the neonatal period with variable skin involvement ranging from dry skin to ichthyosis.[24,67,68] Early infantile galactosialidosis has been reported in association with diffuse skin hypopigmentation.[53] There also has been a description of skin telangiectasia associated with this diagnosis.[58]

Another skin manifestation recorded in the literature is extended Mongolian spots. These have been reported in Hurler disease and type 1 gangliosidosis.[83]

Ocular Manifestations

Most of the common ocular manifestations of the LSDs do not present in the neonatal period. However, there can be early presentations. For example, Sergi et al[84] described a Syrian newborn with neonatal sialidosis who was noted at birth to have corneal clouding.

Early eye involvement has also been described with I-cell disease. Of 35 patients with I-cell disease, the most frequent ocular finding was corneal clouding (14 cases), glaucoma (2 cases), or megalocornea (2 cases).[85] There were no descriptions of macular cherry-red spots, a frequent later finding in several of the LSDs. Ultrastructural study of the eyes in 7 affected patients revealed changes in the conjunctival, corneal, scleral, and uveal fibroblasts, whereas other cells were not damaged.

Several ocular manifestations have been described in early-infantile galactosialidosis. These manifestations have included cherry-red spots, cloudy cornea, generalized stroma, and fundi hypopigmentation as well as bilateral cataracts with onset at 3 months of age.[53]

Hematologic Manifestations

Tekinalp et al[86] described a patient diagnosed with galactosialidosis who presented with hydrops and coarse facial features, as well as anemia and thrombocytopenia from birth. There have been additional reports of galactosialidosis associated with anemia.

Gaucher disease and neonatal sialidosis type 2C can also present with anemia and thrombocytopenia in the newborn period.[72,84] In general, thrombocytopenia is a well-recognized feature of Gaucher disease secondary to hypersplenism, due in part to the splenomegaly that develops. Roth et al[72] described a newborn who presented at birth with persistent thrombocytopenia and was subsequently diagnosed with Gaucher disease.

Hydrops Fetalis/Congenital Ascites

Congenital ascites results from a wide range of etiologies including abnormalities of the genitourinary tract or gastrointestinal tract or cardiovascular anomalies, or it can arise secondary to a hematologic disorder. In recent years there has been increased awareness that ascites in the neonate may be a manifestation of 1 of several different LSDs. The event that triggers the accumulation of excessive fluid within the peritoneal cavity in infants with LSDs is a source of considerable controversy in the literature. The mechanism contributing to the development of hydrops in storage diseases may involve the obstruction of venous blood return resulting from organomegaly.[87] Anemia, caused by either hypersplenism or the reduction of erythropoietic bone marrow stem cells caused by infiltrating storage cells, may be a trigger. Hydrops can also result from hypoproteinemia caused by liver dysfunction.[88,89] Other conditions that may trigger ascites in metabolic disease are congestive heart failure and liver cirrhosis.

At present, 13 different LSDs are associated with NIHF or congenital ascites.[1,90–92] These LSDs associated with NIHF include cases with type 2 Gaucher disease, sialidosis type II, galactosialidosis, ISSD, Salla disease, MPS types IV and VII, GM1 gangliosidosis, I-cell disease, Niemann-Pick types A and C, Wolman disease, and Farber disease. Often, the patients described had a previous affected sibling who was not diagnosed with such a disorder. For this reason, in cases of familial NIHF, one should consider the LSDs or other inborn errors of metabolism. When there is facial dysmorphism, irregularity

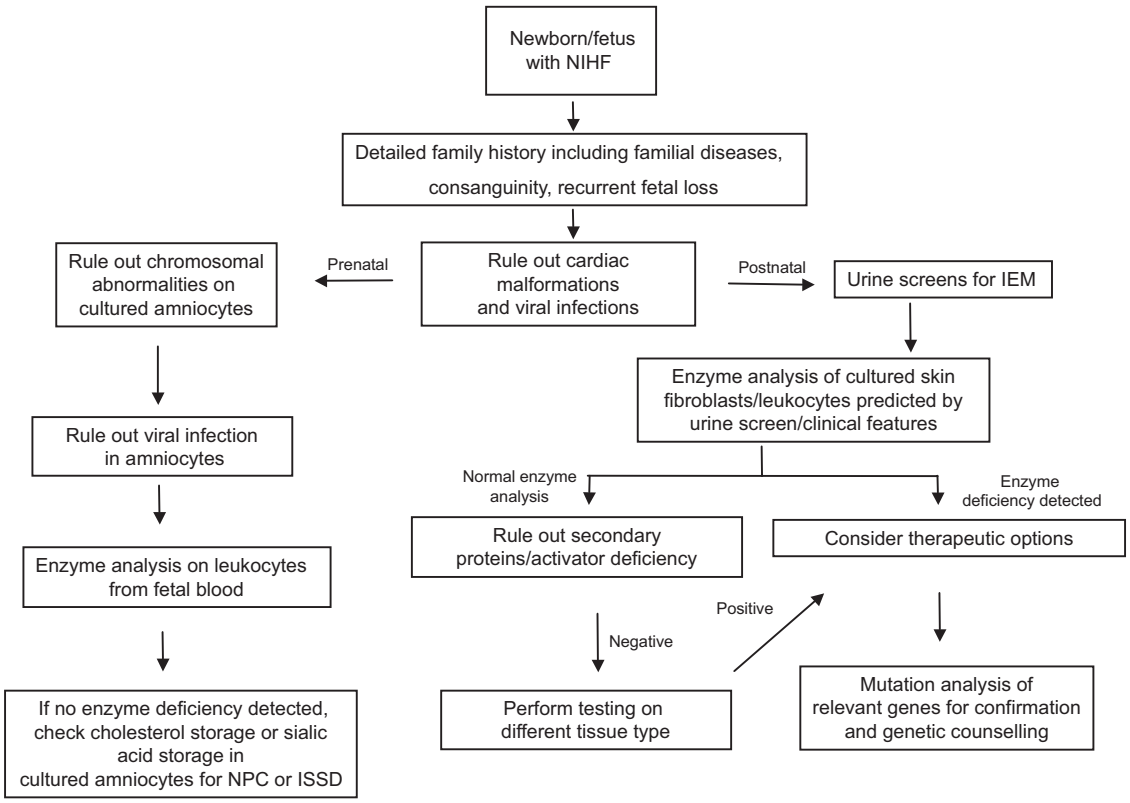

FIGURE 3
Algorithm for the clinical evaluation of a fetus or newborn with NIHF. IEM indicates inborn errors of metabolism; NPC, Niemann-Pick disease type C.

of the epiphyses, and/or coarse trabeculations of the long bones in the presence of congenital ascites, the index of suspicion of a storage disease is even greater.

The relative frequency of the LSDs in the context of NIHF or ascites was 1.4% in a large retrospective series.[93] In 2004, Burin et al[91] searched for LSD in 33 cases of NIHF, including 28 cases in utero and 5 hydropic newborns. They detected 5 patients (15%) with LSD, including 4 diagnosed prenatally (I-cell disease, Niemann-Pick type A, galactosialidosis, and sialidosis) and 1 patient with MPS IVA diagnosed after birth. A recommended algorithm for the evaluation of cases of NIHF is shown in Fig 3.

There are many descriptions of type 2 Gaucher disease presenting with hydrops fetalis and joint contractures. In the majority of cases with this severe phenotype, glucocerebrosidase activity is absent or severely deficient.[13,14,74,78,88,94–99] In general, most patients with Gaucher disease do have some residual glucocerebrosidase activity, with no correlation between severity and the level of residual enzyme activity. Type 2 Gaucher disease is the rarest and most severe type, and untreated patients uniformly die before 3 years of age.

Cases of neonatal sialidosis (sialidosis type 2) presenting as hydrops fetalis or with neonatal ascites have been reported.[27,84,100–108] NIHF has been reported in galactosialidosis.[103,109,110] Claeys et al[111] described a patient who presented prenatally with massive ascites and only after birth was diagnosed as having galactosialidosis. ISSD and Salla disease have been described in patients with massive fetal ascites.[59,101,112–114]

Although MPS IVA is a rare disease, prenatal manifestations of the disease include hydrops fetalis, with confirmation of the diagnosis by chorionic villus sampling or amniocentesis.[115–117] MPS type VII also has been recognized as a cause of NIHF, which is actually the most common presentation of the disease.[1,118,119] However, there is great variability in the associated clinical and biochemical manifestations.[120]

There have been at least 5 descriptions of cases with NIHF or congenital ascites, either transient or persistent, as the presenting symptom of GM1 gangliosidosis 1.[20,75,121–123] Burin et al[91] reported hydrops with I-cell disease and Niemann-Pick type A. Maconochie et al[64] described a patient with severe congenital ascites diagnosed with Niemann-Pick type C, and Meizner et al[124] reported a case of NIHF in which Niemann-Pick type C was diagnosed by electron microscopy. Although Wolman disease is usually accompanied with mild ascites, Uno et al described a case with massive milky ascetic fluid.[65,125] Ben-Haroush et al[125] described another case of isolated ascites that was later diagnosed as Wolman disease. Kattner et al[126] reported a preterm infant with Farber disease and severe hydrops fetalis.

It is very important to examine the placenta carefully in cases where hydrops or ascites are present at birth or detected by ultrasound, even transiently. Placental histology can serve as an early diagnostic clue for a number

of storage diseases, including GM1 gangliosidosis,[20,127] MPS VII,[128,129] ISSD,[130,131] Gaucher disease,[132] galactosialidosis,[133] and Fabry disease.[134] The presence of highly vacuolated cells or cells demonstrating storage should be followed up with enzymatic testing.

Recurrent Fetal Losses

Because most LSDs are autosomal recessive, consanguinity can be an important contributing factor. Many of the case descriptions of the LSDs found in the literature were identified in families with consanguinity, especially cases with NIHF. When taking a medical history, questions regarding previous gestations are very important, because in most families, the diagnosis is made only after previous pregnancies ended as stillbirths or with NIHF. For example, Nelson et al described a case of MPS type VII in consanguineous parents who had 3 previous unsuccessful pregnancies because of recurrent stillbirths.[128] Venkat-Raman et al[135] described a case of MPS Type VII in consanguineous parents who had a previous hydropic pregnancy. Landau et al[109] described a family in which fetal hydrops occurred in 4 pregnancies, and the diagnosis of galactosialidosis was only made after the birth of the fourth affected child. Manning et al[136] described the case of a twelfth pregnancy of a woman who had 4 first-trimester miscarriages and a previous child who died at 4 weeks of age. Ultimately, the diagnosis of Niemann-Pick type C was made.

DIAGNOSTIC METHODS

Accurate diagnosis is imperative for genetic counseling for future pregnancies, because most of the LSDs are autosomal recessively inherited. There are many ways to diagnose LSDs (Fig 1). With the development of new treatments for several of the LSDs, the diagnostic requirements are also changing. The efficacy of many of the proposed treatments relies heavily on early detection and initiation of treatment before the onset of irreversible pathology.[137,138]

Although many of the clinical presentations of different LSDs primarily result from substrate storage, these presentations vary greatly depending on the type, quantity, and site of the accumulated storage material. Because there is an overlap of clinical features in many of the LSDs, it is difficult to establish a diagnosis solely on the basis of clinical presentation. Fortunately, different accurate laboratory assays based on detection of the storage product, enzymatic assays, and DNA diagnostics have been developed. There are also biomarkers such as chitotriosidase that, although not optimally specific, can help monitor disease load. For example, in Gaucher disease, chitotriosidase levels decrease after ERT.

Urine screens that test for elevated levels of secreted substrate material are used routinely to examine the pattern of glycosaminoglycans and oligosaccharides in patients suspected of having MPS or disorders that present with oligosaccharidiuria, such as I-cell disease, mucolipidosis type 3, GM1 gangliosidosis, GM2 gangliosidosis type 2, fucosidosis, α-mannosidosis, sialidosis, galactosialidosis, and ISSD. After determining that the level of glycosaminoglycans is elevated, electrophoresis can further support the diagnosis of the MPSs, although the definitive diagnosis is made by enzyme analysis of either leukocytes or cultured skin fibroblasts. Although urine screens are very sensitive, there have been reports of affected individuals with normal urine screens; thus, when there is a strong index of suspicion, normal urine screen results should still be followed by enzyme analysis.[139–141]

Generally, panels of enzyme activity assays are performed on a combination of leukocytes and plasma and predominantly include enzymes involved in the digestion of glycosphingolipids and oligosaccharides. Diseases tested for in these panels include Gaucher disease, Niemann-Pick disease types A and B, acid lipase deficiency, GM1 and GM2 gangliosidosis, Krabbe disease, metachromatic leukodystrophy, mucolipidosis type 2 and 3, fucosidosis, α-mannosidosis, MPS type VII, and Schindler disease. Although measurement of enzyme activity in leukocytes and plasma enables the diagnosis of most LSDs in affected patients, a proportion may not be detected by this method. For example, in sialidosis and Pompe disease, the distinction between the normal and affected range in leukocytes can be very narrow, and the diagnostic analysis should be performed on other tissues or cultured fibroblasts. When leukocyte assays are not reliable, another method of enzyme analysis is to assay individual hair roots that develop from progenitor cells.[138]

A number of the LSDs result from deficiencies in secondary proteins or enzymes where the defect is in the activator protein. In these cases, the diagnosis can be achieved by examining the level of substrate secreted in the urine, or the rate of radiolabeled substrate turnover can be determined in cultured cells by substrate-loading tests. Ultimately, the relevant gene can be evaluated by mutation analysis. One of the examples for secondary protein deficiency is Niemann-Pick type C, which results from defective cholesterol transport in the lysosomal pathway and is diagnosed by analysis of cholesterol processing and accumulation in cultured fibroblasts.

Molecular analysis is rarely used as the primary screening tool for the diagnosis of LSDs. However, molecular analysis plays an important role with respect to carrier and prenatal testing for a variety of LSDs. Mutation data can also enable a rapid and accurate prenatal diagnosis. Because the demand for preimplantation diagnosis is rapidly increasing, it is very important that the causative LSD mutations be identified to enable the implantation of nonaffected fetuses. In a gene with several common mutations, this can be achieved more readily. In other disorders, however, the mutations identified may be novel or very rare. In cases when there is a strong diagnostic suspicion, sequencing of the relevant genes can be used to detect mutations. However, establishing that the nucleotide change identified is pathologic, rather than a mere polymorphism, can be challenging.[138]

Population screening for the LSDs is not performed routinely except for high-risk ethnic groups, for which screening for specific disorders may be appropriate, such as Tay-Sachs disease in the Ashkenazi Jewish popula-

tion. Once a proband is identified in a given family, definitive carrier testing can be performed if the causative mutations are known.

Because of the early presentation of many of the LSDs, and the relative severity of these disorders, prenatal diagnosis is important for future pregnancies. Diseases that can be detected by enzymatic or biochemical changes in cultured cells can be detected using cultured chorionic villous cells or amniocytes for prenatal diagnosis. In many cases, direct analysis of chorionic villous tissue is also diagnostic, providing rapid and accurate results early in gestation. However, because some disorders can have pseudodeficiencies, it is often advisable to perform biochemical analysis on parental cultured cells, as well, to prevent a false-positive diagnosis.[138]

Whenever the causative gene is known, prenatal diagnosis can be made by mutation analysis. It is important that parental DNA is analyzed before prenatal testing to ensure that each parent carries 1 of the known causative mutations and that a corresponding normal allele can be detected also.

There are a few methods for the determination of enzymatic activities that have been developed recently on the basis of elution of the enzyme from a dried blood spot, followed by an assay of the enzyme activity by using fluorescent or radiolabeled substrates. Another alternative is the immune capture of the enzyme before the determination of enzyme activity. In addition, monoclonal and polyclonal antibodies can be used for the immune quantification of specific lysosomal proteins from biological samples, including dried blood spots. These assays provide a convenient and economical means for diagnosis and may have increasing importance as newborn screening for these disorders is considered.[142,143] Electrospray ionization tandem mass spectrometry has been used effectively to investigate stored substrates in a number of the LSDs. This method has great potential and may enable the monitoring of responses to therapy.[144,145] It is important to consider more than 1 type of assay as confirmation in any investigation of a patient suspected of having an LSD.

The decision regarding the advisability of newborn screening for the LSDs is complex. In addition to the requirements for a sensitive and specific assay, there are important ethical, economic, and counseling implications. Because the different LSDs have differing prognoses and therapeutic options, each disorder should be considered individually when deciding whether to implement newborn screening. Currently, screening for Krabbe and Pompe diseases are under discussion because of the therapeutic advances in these disorders, and it is likely that in the near future screening for other LSDs will be explored.

THERAPEUTIC MODALITIES

In the past, the only therapy available for patients affected by LSDs consisted of supportive care and treatment for disease complications. Significant progress has been made during the past few years, and therapies for type 1 Gaucher, Fabry, MPS types I, II, and VI, and Pompe diseases have been approved by the US Food and Drug Administration. Several new treatment modalities are under development for these and other LSDs that are, as yet, untreatable, with the goals of alleviating neurologic manifestations, improving visceral response, and reducing the cost of therapy. However, today the majority of newborns diagnosed with LSDs have an ominous prognosis.

On the basis of the premise that only 1% to 5% of enzyme activity is required to correct many of these metabolic defects, initial efforts were focused on the development of ERT. The prototype treatment was the now widely available ERT for Gaucher disease type 1 (the most common and nonneuronopathic type of Gaucher disease). ERT was approved recently for Fabry disease, MPS types I, II, and VI, and Pompe disease, and clinical trials of ERT in Niemann-Pick disease types A and B are in progress. However, there are limitations to this form of treatment: it does not affect all aspects of the disorder to the same degree, and clinical studies have shown that even after prolonged treatment, many symptoms of LSDs are not reversible. In addition, the extent of response seems to vary from individual to individual.[146]

The efficacy of treatments can be evaluated by close monitoring of clinical manifestations or by using diagnostic or surrogate biomarkers. Other parameters relevant to specific disease entities include tests such as forced expiratory capacity or walking distance in a specified amount of time.

Additional limitations of ERT relate to our incomplete knowledge of the natural history of these rare diseases. Because some of the clinical symptoms are results of secondary processes, ERT might not be expected to be beneficial. Another limitation is the expense of the replacement enzyme. These therapies often cost more than $250 000 per patient per year, and because of the length and chronicity of treatment, the cost can continue indefinitely. In addition, optimal dosing and maintenance doses have not been established definitively for all treated diseases. Because the replacement enzymes do not cross the blood-brain barrier, ERT does not correct central nervous system (CNS) manifestations. Safety studies have indicated that ERT is generally well tolerated. Even in patients who show seroconversion, a decrease in antibody titers occurs over time, and most continue to tolerate the drug. However, antigenicity does seem to impact therapeutic success of ERT for Pompe disease.[146]

Hematopoietic stem cell transplantation (HCT) or bone marrow transplantation, which provides a population of cells with the capacity to produce the missing enzyme, is also used to treat patients with LSD (reviewed in refs 147–150). Initial attempts at treatment of LSDs with marrow transplantation began in the 1980s. The success of marrow transplantation depends on the specific enzyme deficiency and the stage of the disease. Generally, visceral symptoms can be improved, whereas skeletal lesions remain relatively unaffected. HCT has been most successful in Hurler syndrome (MPS I), with improvement in visceral, corneal, and cardiopulmonary symptoms, growth, and developmental delay, especially when attempted before the age of 2 years, but not in

some skeletal or cardiac valve manifestations. Although some improvements have been observed in MPS types VI and VII, HCT has had no effect on the other forms of MPS.[151] The effect on neurologic symptoms varies in different LSDs. Although improvements have been documented in MPS I and Krabbe disease, neurologic disease progression was faster after transplantation in metachromatic leukodystrophy. For LSDs with variable neurologic forms, transplantation early in the disease course is desirable before extensive CNS injury becomes evident. Transplantation of nonallogeneic cord blood has also been performed when a matched bone marrow donor was not available. Encouraging results with this treatment modality have been reported for Hurler syndrome and Krabbe disease.[152,153] The limitations of this treatment modality included nonresponsiveness, immune-related risks, and other complications associated with transplantation. Supplementing engrafted HCT subjects with additional mesenchymal stem cells has also shown promise for some LSDs.[149,154,155]

Another available treatment is substrate-reduction therapy, which aims to partially inhibit the biosynthetic cycle to reduce substrate influx in the compromised lysosome. A number of small molecule inhibitors of ceramide-specific glucosyltransferase, the first enzyme in the biosynthetic pathway that glycosylates ceramide, have been tested as therapeutics. Of these molecules, the one that has been most extensively developed for clinical use is miglustat (*N*-butyl-deoxynojirimycin). Miglustat has been approved for use in patients with Gaucher type 1 in Europe, the United States, and Israel. In Gaucher disease, substrate-reduction therapy is recommended only for adults when ERT is not a possibility or in combination with ERT. For the most part, this treatment modality is still experimental, and so far, results have been reported for only 209 patients enrolled in clinical trials using miglustat as a monotherapy. Of these patients, 108 had Gaucher type 1, 30 had Gaucher type 3, 41 had Niemann-Pick type C, and 30 had GM2 gangliosidosis.[156] In these trials, clinical improvement was documented primarily in type 1 Gaucher disease. Although there have been some anecdotal stories of improvements in other LSDs, there are now ongoing clinical trials for late-onset Tay-Sachs and type 3 Gaucher disease.[146]

Pharmacologic chaperones are also under development as a potential therapy for some of the LSDs. Small-molecule chemical chaperones may be therapeutically useful for LSDs caused by specific mutant, yet catalytically active, enzymes. The hypothesized mode of action of these chaperones consists of reversible binding to the active site of a missense mutant enzyme, correcting protein misfolding and enhancing delivery to the lysosome. In the acidic lysosomal environment and in the presence of substrate, the chaperone would be released and the mutant enzyme would function better. This strategy is being tested in Fabry,[157–159] type 1 Gaucher,[160,161] Pompe,[162,163] GM1 gangliosidosis,[164] and Tay-Sachs and Sandhoff diseases.[165] Large-scale screening of small-molecule libraries has been performed to identify compounds that might serve as improved chemical chaperones for Gaucher disease[166] and Tay-Sachs disease, Sandhoff disease, and GM2 gangliosidosis.[167]

Because of the limited success of ERT in alleviating bone and CNS manifestations, and because of the risk of immune response after long-term treatment, another potential therapy under development is gene therapy. One of the major advantages of gene therapy is the potential for long-term expression of the therapeutic protein. The goal of gene therapy is to provide therapeutic levels of the deficient enzyme to all involved organ systems, which can be achieved by either ex vivo or direct in vivo gene-therapy strategies.[168,169] The ex vivo strategy is to modify cells genetically by using a viral vector carrying the gene for the wild-type enzyme and then to transplant them into an affected patient, where they would express the enzyme and correct the deficiency. Hematopoietic progenitor cells are the primary therapeutic target, and retrovirus, adenovirus, adenovirus associated- and lentiviral vectors have been tested. Experiments using this method seemed promising in animals, but preliminary studies in patients with Gaucher disease demonstrated a poor response, probably because of the viral vector used.[170] The in vivo approach is to inject a gene-transfer vector directly into a tissue or into the circulation. Studies have been performed in animal models of a number of LSDs, with injections administered in utero, neonatally, or in adult animals.[169] Current research is focusing on resolving problems with transient expression of the therapeutic enzyme and severe immunoreaction to the foreign protein. Studies on direct injection into target tissues, including liver, muscle, and CNS, are also being conducted in animal models.[168] Although proof-of-principal experiments in animal models have been promising for some LSDs, these therapies are not yet ready for clinical trials in patients.

CONCLUSIONS

The LSDs are rare diseases that are caused by deficient lysosomal enzyme activity or by a deficient lysosomal protein that interferes with enzyme activity. The accumulation of substrates within the lysosomes of cells is believed to contribute to the disease manifestations. Clinically, these disorders can have multiorgan presentations, resulting from different patterns of substrate accumulation. Because most patients appear normal at birth, it is likely that these disorders are underdiagnosed and their incidence is underestimated. This review highlights the different neonatal presentations of LSDs in order to enhance physician awareness of these disorders in the newborn. LSDs need to be considered in the differential diagnosis of many diverse neonatal symptoms. A high index of suspicion is essential, because treatment, when available, is most likely to be effective when begun early in the course of the disease. Prompt diagnosis may enable both early treatment to prevent irreversible clinical sequelae and timely genetic counseling.

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WEB PASSES PAPERS AS A NEWS SOURCE

"The Internet overtook print newspapers as a news source this year, according to a report by the Pew Research Center for the People and the Press, which asked more than a thousand people where they got 'most of' their national and international news. (Respondents were allowed to name more than one medium.) The change does not represent a decline in the popularity of newspapers, which actually picked up a percentage point over last year. Rather, it represents a near-doubling, from 24% last year, in the number of people naming the Internet as their primary news source.

40: Percentage of Americans who get most of their news from the Internet
35: Percentage who get most of their news from newspapers"

***New York Times*. January 4, 2009**
Noted by JFL, MD

Lysosomal Storage Disorders in the Newborn

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