lyosomal storage diseases (LSDs) are a group of genetic disorders that result from defective lysosomal metabolism or export of naturally occurring compounds. Signs and symptoms are variable both within and between disorders depending on the location and extent of storage. Many patients develop neurologic symptoms that become obvious from the newborn period to adulthood. Diagnosis of suspected patients can usually be made by measuring the activity of an enzyme or concentration of a metabolite in easily obtained tissue samples. Based on the considerable diagnostic experience of our laboratory, we aid the physician in selecting the appropriate tests to perform. Hematopoietic stem cell transplantation and enzyme replacement therapy are already available or in clinical trials for a number of LSDs. Early diagnosis is critical, especially since those patients who are treated before significant symptoms arise have the best chance for a positive outcome.

The LSDs are a group of genetic disorders that result from the accumulation of storage products due to a defect in a hydrolytic enzyme, activator protein, transport protein, or enzyme required for the correct processing of other lysosomal proteins. About 40 different genes have been identified as sites for mutations resulting in an LSD. A large number of mutations have been delineated for most disorders, and this contributes to the wide clinical spectra observed in patients with a deficiency of a necessary protein. As a group, LSDs occur in approximately 1 in 5000 to 8000 births in the United States, Europe, and Australia. Therefore, about 500 to 800 people are born each year with an LSD in the United States. While some of these disorders result in purely nonneurologic manifestations (eg, Gaucher disease type 1), many others are characterized by a wide range of neurologic symptoms, with or without somatic features, presenting from birth to adulthood. Owing to the complexity of the storage products and differences in their tissue distribution and rates of accumulation, the disease can cause pathologic changes in multiple organ systems or can be confined to the nervous system. While the genes responsible for almost all of the defined LSDs have been cloned, this information may not be useful for diagnosing a patient initially presenting to the practicing physician. Measurement of a panel of lysosomal enzymes and/or identification of storage products is a more definitive method for diagnosing new patients. As effective treatment for some of these disorders becomes more of a reality, it is critical that patients be diagnosed as early as possible. There are even initiatives to institute newborn screening for LSDs to identify presymptomatic individuals who may be candidates for early therapeutic intervention. However, this may result in additional problems because predicting the clinical course in untreated patients is not reliable, especially in the later-onset forms of most LSDs.

Since 1973, our laboratory has diagnosed an LSD in more than 2600 patients. In this review, we outline some clinical features that should signal a request for testing, with a focus on those diseases requiring special diagnostic attention, discuss the difficulties in making a prognosis in newly diagnosed patients, and present the possibilities for therapy in current use or under development. This re-
view will mainly concentrate on disorders diagnosed in our laboratory.

**CLINICAL FEATURES THAT COULD SUGGEST AN LSD**

The diagnosis of an LSD initially requires a physician to consider whether the patient’s clinical features suggest this possibility. The Table presents some of the initial signs and symptoms of those LSDs with neurologic involvement. Lysosomal storage diseases should be considered among the disorders to be ruled out in any individual experiencing developmental delay, loss of learned skills, ataxia, seizures, weakness, and dementia. This is especially true if the individual is regressing after a period of relatively normal development and the disorder seems progressive. While many features are not specific and could result from genetic or environmental factors,
diagnostic testing should be performed. A systematic study of disease possibilities, including mitochondrial, peroxisomal, and lysosomal, should be considered. The samples required for the study of each group of disorders may be different, and a given diagnostic laboratory usually does not perform tests for all disorders. For those LSDs diagnosed in our laboratory, whole heparinized blood sent at room temperature permits the isolation of leukocytes and plasma to use for screening. Using our considerable diagnostic experience, test selection is based on a patient's clinical history, other test results, and suggestions from the physician.

Purely neurologic symptoms in the absence of additional findings, such as coarse facial features, bone abnormalities, and hepatosplenomegaly, signal the need for testing for GM1 and GM2 gangliosidoses, metachromatic leukodystrophy (MLD), and Krabbe disease. The onset of GM1 gangliosidosis (low acid β-galactosidase in both leukocytes and plasma) can occur at any age from birth to adulthood. Patients with the infantile form have initial symptoms related to the storage of GM1 ganglioside in the brain, keratan sulfate in connective tissue, and glycoprotein and oligosaccharides in the liver. Other patients with low β-galactosidase activity can have purely neurologic signs, including dysarthria, and only mild bone and somatic problems, or they may have only severe bone involvement (mucopolysaccharidosis [MPS] IVB, Morquio B). Different mutations in the β-galactosidase gene can result in significant differences in the ability to handle the potential substrates.

Mutations in 3 separate genes can result in patients who are clinically similar to each other and store GM2 ganglioside. GM2 gangliosidosis should be considered in any infant who is losing interest in his or her surroundings and has spasticity, hyperacusis, and macular cherry-red spots. Defining the genetic type is critical for accurate genetic counseling of family members and subsequent prenatal testing. The finding of low hexosaminidase A activity due to mutations in the α-chain of leukocytes and/or plasma confirms the diagnosis of Tay-Sachs disease. While the number of cases of Tay-Sachs disease among the Ashkenazi Jewish community has dropped dramatically since the institution of the carrier testing program in the early 1970s, the number of non-Jewish cases has not declined. Patients with the so-called B1 variant of Tay-Sachs disease have normal hexosaminidase A activity when measured using the heat denaturation method. However, the use of the sulfated derivative of the synthetic substrate for screening will diagnose all patients who have a defect in the α-chain of hexosaminidase A. The finding of low hexosaminidase A and B activity indicates a diagnosis of Sandhoff disease. In addition to the many mutations identified in the α- and β-chains of hexosaminidase A and B, there are infants with similar clinical features who have defects in the GM2 activator protein that is required for the hydrolysis of GM2 ganglioside.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Defective Protein</th>
<th>Presenting Signs and Symptoms</th>
<th>Samples Acceptable For Diagnosis*</th>
<th>Treatment Options†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucolipidosis I†</td>
<td>UDP-N-Ac-galactosaminyl phosphotransferase</td>
<td>Coarse facial features, DD, weakness, DM, gingival hyperplasia, macrocilia</td>
<td>P, F</td>
<td>SC, HSCT</td>
</tr>
<tr>
<td>Mucolipidosis IV</td>
<td>Mucolipin 1</td>
<td>DD, corneal opacities, retinal degeneration, strabismus</td>
<td>F</td>
<td>SC</td>
</tr>
<tr>
<td>Multiple sulfatase deficiency‡</td>
<td>Sulfatase modifier protein</td>
<td>DD, ichthyosis, coarse facial features, deafness, mild DM, PR</td>
<td>L, F</td>
<td>SC</td>
</tr>
<tr>
<td>Neuronal Ceroid Lipofuscinosis 1</td>
<td>Palmitoyl-protein thioesterase 1</td>
<td>Vision loss, motor dysfunction, hypotonia, DD, MR</td>
<td>L, F</td>
<td>SC, HSCT</td>
</tr>
<tr>
<td>Neuronal Ceroid Lipofuscinosis 2</td>
<td>Tripeptidyl peptidase 1</td>
<td>Sz, motor dysfunction, DD, MR, ataxia, dementia</td>
<td>L, F</td>
<td>SC</td>
</tr>
<tr>
<td>Saposin defect, MLD type‡</td>
<td>Saposin B</td>
<td>Similar to JO MLD</td>
<td>F, U</td>
<td>SC</td>
</tr>
<tr>
<td>Saposin defect, Gaucher type‡</td>
<td>Saposin C</td>
<td>Similar to Gaucher disease, type 3</td>
<td>F</td>
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</tr>
<tr>
<td>Saposin defect, generalized type‡</td>
<td>Prosaposin</td>
<td>HSM, DD, motor abnormalities, exaggerated Moro reflex, MR</td>
<td>F</td>
<td>SC</td>
</tr>
<tr>
<td>Aspartylglucosaminuria</td>
<td>Aspartylglucosaminidase</td>
<td>Delayed speech, motor clumsiness, mildly coarse facial features, behavioral problems</td>
<td>L, F, U</td>
<td>SC</td>
</tr>
<tr>
<td>Farber disease‡</td>
<td>Acid ceramidase</td>
<td>Painful and swollen joints, nodules, DD, hoarse cry, hypotonia</td>
<td>L, F</td>
<td>SC, HSCT</td>
</tr>
<tr>
<td>Wolman disease‡</td>
<td>Acid lipase</td>
<td>HSM, vomiting, diarreha, anemia, PR</td>
<td>L, F</td>
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</tr>
<tr>
<td>Schindler disease</td>
<td>α-N-Acetylgalactosaminidase</td>
<td>DD, blindness, Sz, spasticity, PR</td>
<td>L, F, P, SC</td>
<td></td>
</tr>
<tr>
<td>Pompe disease</td>
<td>α-Glucosidase</td>
<td>Hypotonia, DD, cardiac enlargement</td>
<td>F</td>
<td>SC, ERT</td>
</tr>
</tbody>
</table>

Abbreviations: AO, adult onset; CSF, cerebrospinal fluid; CRS, cherry-red spots; DD, developmental delay; DM, dysostosis multiplex; ERT, enzyme replacement therapy; F, fibroblasts; HSCT, hematopoietic stem cell transplantation; HM, hepatomegaly; HSM, hepatosplenomegaly; IO, infantile onset; JO, juvenile onset; LO, late onset; L, leukocytes; MLD, metachromatic leukodystrophy; MPS, mucopolysaccharidosis; MR, mental retardation; NIFH, nonimmune fetal hydrops; P, plasma; PR, psychomotor regression; Sz, seizures; SC, supportive care; U, urine; VSO, vertical supranuclear ophthalmoplegia.

*These are the samples that have been used to diagnose a given disorder by measurement of a biochemical parameter. Molecular studies can be performed on any DNA-containing sample.

†HSCT is not available for all patients with a given diagnosis, and ERT may be in use or only at the stage of preclinical trials. The use of these treatments in a few patients does not necessarily indicate a successful outcome.

‡Diseases diagnosed in our laboratory.

§SC indicates any procedure performed to alleviate pain, discomfort, and seizures and may include splenectomy and kidney transplantation when indicated.
by hexosaminidase A. These rare patients have normal hexosaminidase A and B activity measured with all synthetic substrates, but they can be identified by the accumulation of GM2 ganglioside in cerebrospinal fluid. Additional studies could identify the mutation(s) in the GM2 activator protein gene. While most patients with defects in the lysosomal metabolism of GM2 ganglioside have infantile forms, adolescents and adults with cerebellar ataxia, symptoms resembling amyotrophic lateral sclerosis, and psychiatric problems should have their hexosaminidase levels measured.

Metachromatic leukodystrophy is one of the LSDs causing the most problems with regard to accurate patient identification. Arylsulfatase A (ASA) activity is measured in individuals of any age with evidence of weakness, mental regression, psychiatric problems, or white matter changes on magnetic resonance imaging. Low ASA activity could indicate a diagnosis of MLD. However, owing to the high frequency of the so-called pseudodeficiency (Pd) allele, this diagnosis must be confirmed by additional studies. The major cause of pseudodeficiency is a mutation in the polyadenylation signal that results in only about 10% of the normal amount of ASA messenger RNA. About 1 in 7 individuals in the general population are heterozygous for this polymorphism. Therefore, about 1 in 200 individuals, whether completely normal or with neurologic problems, is homozygous for this mutation and has low (5%-15% of normal) ASA activity. These low ASA values overlap those found in patients confirmed to have MLD (MLD/MLD) and in carriers of MLD who have 1 MLD-causing mutation and 1 Pd allele (MLD/Pd). Further complications arise because MLD-causing mutations have been found on the Pd allele. Since the Pd allele is so common, additional mutations have occurred on the same copy of the ASA gene. However, the accurate diagnosis of suspected patients is not difficult when proper samples are analyzed. First, ASA activity should be measured in leukocytes, and if low, DNA can be isolated from the remaining sample, and the presence of the Pd allele can be determined by polymerase chain reaction–based testing. If the Pd allele is not present and the clinical features suggest a leukodystrophy, the diagnosis of MLD is almost certain. If it is present, MLD must still be considered, and a first morning voiding of urine should be analyzed for sulfatides. If excess sulfatides are being excreted, the diagnosis of MLD is confirmed. It is very important to obtain ASA values from the parents of all patients identified. About 1 in 14 of the healthy parents has ASA activity near that of their affected child due to the frequency of the Pd allele. This is critical to know if the couple requests prenatal testing in subsequent pregnancies. The inheritance of the Pd allele (without an additional mutation) from one parent and an MLD-causing mutation from the other results in low ASA activity in any fetal sample (chorionic villi, cultured trophoblasts, and amniotic fluid cells) received for testing. Having information regarding ASA values and the presence of the Pd allele in the parents results in accurate pregnancy prediction. In addition, patients with multiple sulfatase deficiency have low activity for all sulfatases, including ASA, and excrete sulfatides plus glycosaminoglycans in urine. However, the parents of these patients do not have carrier levels of any sulfatases. It should also be noted that there are some patients who have normal ASA activity but have defects in a sphingolipid activator protein known as saposin B. The few individuals who have been identified clinically resemble those with juvenile MLD. Such patients excrete excess sulfatides in urine, and molecular analysis of the saposin gene can usually identify a mutation(s) in the saposin B region.

Another relatively common disorder with significant diagnostic problems is Niemann-Pick type C (NPC). This is because the neurologic features are variable, it cannot be ruled out by relatively simple tests performed in leukocytes or plasma, and “variants” have biochemical findings that are difficult to interpret. Testing for NPC is often requested by neurologists who have exhausted other options by more straightforward testing. Patients range in age from neonates with nonimmune fetal hydrops to adults with evidence of dystonia and vertical supranuclear ophthalmoplegia. Many patients with the “classic” form have a history of jaundice at birth, but this can be resolved with phototherapy. They can appear normal until the middle of the first or second decade, when they develop inappropriate behavior and drop in school performance. Some, but not all, have significant hepatosplenomegaly. Diagnosis requires cultured skin fibroblasts for special studies to detect excess free cholesterol using filipin staining and, if positive, to measure cholesterol esterification. Mutations in 2 different genes, NPC1 and NPC2, can cause NPC. DNA analysis is not useful for screening patients, except in suspected cases in the Hispanic population of northern New Mexico and southern Colorado, where one mutation in the NPC1 gene has been identified.

Patients with mild to severe neurologic symptoms who also have evidence of short stature (dysostosis multiplex), coarse facial features, hepatosplenomegaly, corneal clouding, and other more subtle findings (eg, angiokeratomas) usually require a battery of testing to arrive at a definitive diagnosis. Symptoms may be present at birth or become more obvious after a period of relatively normal development. While studies of oligosaccharides and glycosaminoglycans (mucopolysaccharides) in urine may be indicated, it is our opinion that this may only cause a delay in obtaining a diagnosis. Frequent false-negative and false-positive results may influence the tests performed. In most cases, enzymatic or other (eg, sialic acid content) tests are indicated anyway. About 10% of infants born with nonimmune fetal hydrops have an LSD. These include MPS VII, mucolipidosis II, GM1 gangliosidosis, sialidosis, galactosialidosis, Gaucher disease, Faber disease, and NPC. While effective therapy is not currently available for these infants, genetic counseling and prenatal testing can be offered in subsequent pregnancies. However, for other disorders of oligosaccharide and GAG metabolism, early diagnosis could provide an opportunity for treatment, such as hematopoietic stem cell transplantation (HSCT) or enzyme replacement therapy (ERT).

Most LSDs can be diagnosed by measuring the activity of specific enzymes with commercially available synthetic or radiolabeled natural substrates using a blood
The finding of low activity for one enzyme and normal values for others usually results in a definitive diagnosis. On the other hand, patients with mucolipidosis II or III have greatly elevated enzyme values in plasma. The measurement of sialic acid content is useful in screening for 4 genetic disorders. Using a leukocyte sample, sialic acid content is measured in patients with nonimmune fetal hydrops, short stature, coarse facial features, cherry-red spots, and/or myoclonic seizures. If the content of sialic acid is elevated, the test is repeated without acid hydrolysis to determine if it is free or bound. High levels of bound sialic acid are found in leukocytes and fibroblasts from patients with sialidosis and galactosialidosis, and high levels of free sialic acid are found in leukocytes and fibroblasts from patients with sialic acid storage disease or Salla disease and sialuria (not an LSD). Additional studies may be necessary to confirm the diagnosis. Reliable prenatal testing is available for almost all LSDs using chorionic villi samples and cultured amniotic fluid cells.

PROBLEMS IN ASCERTAINING A PROGNOSIS IN A PATIENT WITH AN LSD

Most infants who are diagnosed as having an LSD follow a rather predictable clinical course. The loss of any gained skills and neurologic deterioration continue until the death of the child, usually by infection. Predicting the clinical course in later-onset patients, especially adolescents and adults, is nearly impossible. Accurately predicting the clinical course has important implications not only in selecting candidates for therapy, but also in evaluating the effectiveness of the chosen mode of therapy. There have been a number of methods proposed for determining the clinical course in newly diagnosed patients. While mutation analysis can be useful for predicting the possibility of neurologic involvement in some disorders, the large number of mutations identified coupled with the fact that many patients are compound heterozygotes makes phenotype prediction difficult. For example, finding the N370S mutation in a newly diagnosed patient with Gaucher disease indicates that there will be no neurologic involvement. While knowing the genotype in a newly diagnosed patient may be useful for cataloging purposes and may aid in carrier testing in family members, it is no better than careful clinical evaluation at predicting the clinical course. In our experience, patients with late-onset forms of Krabbe disease can show tremendous clinical variability, even between siblings who have the same genotype for the galactocerebrosidase (GALC) gene. There is a strong suggestion that the onset of symptoms in these patients may occur after a stressful insult, such as an infection or a blow to the head. Also, there is little evidence that measuring residual enzymatic activity or combining this with studies of specific antigen levels in cultured cells aids in making a prognosis.

Recent reports provide evidence that ERT and HSCT can result in a significant improvement in the clinical course if treatment is started when the individual is presymptomatic or only mildly affected. Therefore, there is pressure to obtain a diagnosis as early as possible, especially before neurologic symptoms are significant. This requires educating physicians to recognize the early signs of these disorders and possibly instituting screening methods that identify patients at or near birth before symptoms are present. The screening methods proposed include measuring lysosome-associated membrane proteins 1 and 2 and saposins in small plasma samples, using dried blood spots for enzyme analysis, and using tandem mass spectrometry for measurement of analytes. Additional testing would be required to make a definitive diagnosis. While such testing is theoretically possible, it does present some problems related to the need for expensive or life-threatening therapy in individuals identified without a family history of a disorder. Of the 500 to 800 individuals born each year in the United States with the potential for developing an LSD, some will have very mild disease and may not require treatment, and others will have disease so severe that treatment is not beneficial. However, early diagnosis permits careful clinical evaluation of the individual so that treatment could begin as early as indicated to prevent serious complications.

POSSIBILITIES FOR TREATMENT OF LSDs

There have been recent improvements in the treatment of patients with certain LSDs, even for those disorders that can have significant neurologic involvement. Table presents the treatments that are in use, have been tried in a limited number of cases, or are under development. One treatment that has shown promise in some patients is HSCT in presymptomatic or mildly affected individuals. Many patients with Gaucher disease, MLD, Krabbe disease, and MPS I have undergone transplantation. Some of these patients were identified in utero or at birth because of family history, and others were mildly affected before receiving their transplant. Initially, most of the bone marrow donors for these patients were HLA-identical siblings. However, it is ideal to use noncarrier donors so that the highest level of activity can be supplied by the donor cells. Recently, umbilical cord blood from unrelated donors has been used in transplantation for patients with LSDs. It has been shown in animal studies that donor blood macrophages eventually replace microglial cells in the brain of the recipient. In humans, this can take many months or even years to accomplish. Therefore, HSCT may not be beneficial for those diseases that are progressing rapidly. With successful engraftment of donor HSC, enzyme levels in leukocytes reach those of the donor, progression of the disease slows, and eventually there can be an improvement in certain parameters, such as spinal fluid protein concentration, IQ, and magnetic resonance imaging. A number of patients with purely neurologic LSDs, such as Tay-Sachs disease, have been given HSCT, but more time is needed to determine its effectiveness. While improvement of somatic and hematologic features and stabilization of some neurologic manifestations are usually noted after HSCT, skeletal abnormalities remain difficult to correct.

Enzyme replacement therapy is now available or under investigation for a number of LSDs, including Gau-
enzyme has been shown to greatly improve all aspects of treatment of patients with late-onset forms of MPS I and II to help the somatic manifestations in these patients and to make their management easier for caregivers. Because of the blood-brain barrier, there is little evidence that these enzymes reach the brain. One LSD that could benefit greatly from ERT is Fabry disease. This X-linked X-linked disease, caused by a deficiency of a-galactosidase activity, is characterized by burning paresthesias, kidney failure, strokes, and heart disease in both male hemizygotes and female heterozygotes. Supplying the missing enzyme has been shown to greatly improve all aspects of the disease. Substrate deprivation as an adjunctive treatment for certain sphingolipidoses is receiving attention. Since symptoms in the patients are thought to result from the storage of undegraded substrate, a slower rate of accumulation accomplished by decreasing the rate of synthesis of substrate might be effective. This is especially true in patients with later-onset forms of some LSDs who we suspect have some residual enzymatic activity. If the rate of substrate synthesis was slowed until it was approximately equal to the rate of degradation, little additional accumulation would occur. This theoretically could be accomplished by compounds such as L-cycloserine, which inhibits a very early step in the synthesis of sphingolipids, or N-butyldeoxygalactonojirimycin, which inhibits the synthesis of glycosphingolipids derived from glucosylceramide. Mice with Sandhoff disease treated with N-butyldeoxygalactonojirimycin had delayed onset of symptoms and increased life span. It must be noted that sphingolipids play very important functions in cellular metabolism, including signal transduction, cell adhesiveness, and nerve impulse transmission, and modification of these and other functions by these drugs in a developing child must be carefully tested in animal models before human trials are started. In addition, these drugs also have significant side effects that may limit their use. The amount of enzyme needed in ERT for Gaucher disease or Fabry disease could possibly be lowered if an inhibitor of glucosylceramide synthesis was also provided.

While gene therapy and neural and embryonic stem cell therapy to treat LSDs with neurologic involvement have been under investigation using the large number of available animal models, no protocols in humans are currently in use. Much effort has been expended on the mouse model of MPS VII. A large number of viral vectors containing the human β-glucuronidase complementary DNA have been developed, and when injected into the ventricles or the brain parenchyma of young mice, there is evidence for gene expression and clearing of stored material. In addition, numerous neural stem cell lines have been isolated and characterized. When injected into the developing brain, they have the potential to migrate and differentiate, providing a source of healthy replacement cells and enzymes that can be taken up by neighboring cells. However, before human trials are proposed, issues of safety and effectiveness must be addressed by studies in larger animals for longer periods of time.

In conclusion, the diagnosis of most LSDs is relatively simple using easily obtained tissue samples, such as blood or cultured cells from a skin biopsy specimen. A screen of indicated enzymes can result in a definitive diagnosis within a few days. Molecular analysis to identify the disease-causing mutations may or may not be subsequently performed depending on the disorder. Carrier testing for interested family members is usually available by enzymatic testing. One exception is Krabbe disease, where normal polymorphisms in the GALK gene make a wide carrier and noncarrier range. Prenatal diagnosis using chorionic villus samples and cultured amniotic fluid cells is available for at-risk couples and for other family members concerned about having an affected child. Treatment of presymptomatic individuals and those with mild symptoms is limited to HSCT or ERT for some disorders. The method of choice depends on the availability of a recombinant enzyme or a suitable HSCT donor and whether there is a need to stop or reverse neurologic damage. With effective therapy becoming available for more disorders, it will be increasingly important to recognize the earliest presenting symptoms in patients and seek diagnostic help from a reliable laboratory.

For further reference:
To obtain information about sending samples, please visit our Web site at www.tju.edu/lysolab.

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