

**Objectives:**

For each of the following diseases

- Tay-Sachs disease
- Niemann-Pick disease type A
- Metachromatic Leukodystrophy
- Krabbe Leukodystrophy

the student should be able to:

1. Classify each as a neuronal storage disease (primarily gray matter) or a leukodystrophy (primarily white matter)
2. Describe clinical presentation, course of the disease, criteria for diagnosis, and pathological changes

## I. Introductory Concepts

These disorders are generally associated with specific metabolic abnormalities and result in blockage of amino acid, carbohydrate or lipid metabolism, or deficiency in oxidative phosphorylation. Functional and/or morphologic changes may occur and in some instances may be ameliorated by therapy. In many disorders the carrier state can be identified to permit genetic counseling. Many of these disorders have a clinical expression in children who are normal at birth, but who begin to miss developmental milestones during infancy or childhood.

The three major categories are:

- Neuronal storage diseases – mostly autosomal recessive diseases involving deficiency of a specific enzyme, often a lysosomal enzyme, and accumulation of the enzyme substrate. Gray matter, usually involving cortical neurons, is primarily involved.
- Leukodystrophies –characterized by selective involvement of myelin and white matter involvement. Most leukodystrophies (except for X-linked adrenoleukodystrophy) are autosomal recessive diseases. Diffuse involvement of white matter leads to a variety of clinical expression.
- Mitochondrial encephalomyopathies – disorders involving oxidative phosphorylation and usually resulting from mutations in the mitochondrial genome. They typically involve gray matter and skeletal muscle and are covered with Skeletal Muscle Disorders.

### A. Clinical Expression

The neurological complications of these disorders range from specific focal abnormalities to mental retardation. The precise reason for the mental retardation is not clear. There is marked variation in the age of onset, rate of progression and organ and skeletal involvement among disorders and among variants of each disorder. This is due to factors such as the different isoenzymes involved, solubility of accumulated products for excretion and the specific biochemical reactions occurring in various organs. In general earlier age of onset is associated with a more severe clinical course. The only disorders described below are the early onset forms of a few selected examples

### B. Inheritance Pattern

Almost all of these disorders are characterized by autosomal recessive transmission

### C. Mechanisms of Damage

Functional and pathological damage may be produced by loss of end product of a reaction due to enzyme deficiency, accumulation of substances prior to the metabolic block, or production of toxic metabolites. Almost certainly, indirect effects are also exerted on other metabolic pathways or functional elements.

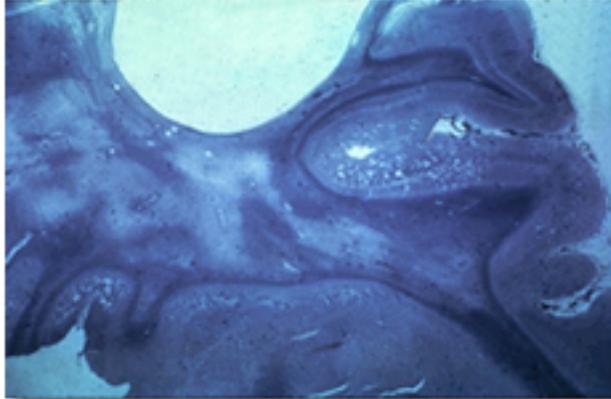
**D. Examples** of Lysosomal Storage Diseases with Neurological Involvement

- Neuronal storage diseases, e.g. Tay-Sachs disease and Niemann-Pick disease type A ---characterized primarily by storage of uncleaved substrate in neurons and other cell types
- Leukodystrophies, e.g. Krabbe disease and metachromatic leukodystrophy --- characterized by impairment of a biochemical process necessary for myelin development or maintenance

**II. EXAMPLES of LYSOSOMAL STORAGE DISEASES** - This table lists characteristics of the infantile form of selected diseases; all of these are autosomal recessive.

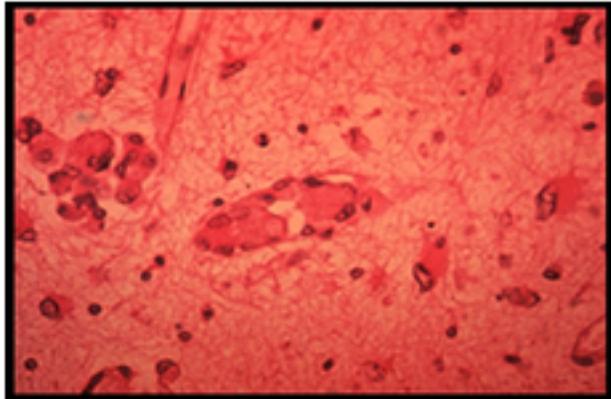
Disease	Enzyme deficiency & accumulated product	Age at Onset	Clinical Signs	Pathology
Tay-Sachs disease	hexosaminidase A; GM2 gangliosides	3-8 mos	psychomotor arrest, exaggerated startle reflex, seizures, retinal cherry-red spot	storage in central & peripheral neurons
Niemann-Pick disease type A	Sphingomyelinase; sphingomyelin	1-6 mos	psychomotor arrent, spleen enlargement, retinal cherry red spot sometimes,	storage in neurons, spleen
Metachromatic leukodystrophy	cerebroside sulfatase; sulfatides	early childhood	progressive mental & motor deterioration, sometimes peripheral neuropathy signs	myelin deficit in CNS & often PNS; storage in glia
Krabbe disease	galactocerebroside $\beta$ -galactosidase; galactocerebroside	3-6 mos	irritability, crying, mental & motor deterioration, seizures	Myelin deficit; globoid cells (large multi-nucleated macrophages)

## Examples of pathology



**IMB 01**

This luxol fast blue-stained section shows hypomyelination in the white matter in Krabbe disease. The lateral ventricle is at the top. The absence of dark blue staining in much of the periventricular white matter indicate the absence of myelin. Note that the U-fibers adjacent to the cortical gyri have normal myelin.



**IMB 02**

This microscopic section illustrates a large multi-nucleated macrophage (globoid cell) in Krabbe disease.

### III. Examples of other leukodystrophies (not lysosomal storage diseases, may be X-linked)

A. Adrenoleukodystrophy – characterized by the inability to properly catabolize very-long-chain fatty acids within peroxisomes. The X-linked form usually presents in the early school years with neurologic symptoms and adrenal insufficiency and is rapidly progressive and fatal.

B. Pelizaeus-Merzbacher Disease – X-linked, fatal leukodystrophy characterized by slowly progressive deterioration resulting from widespread white matter dysfunction. In most cases the gene defect involves proteolipid protein (PLP, a major protein of CNS myelin).

C. Canavan Disease – megalcephaly, severe mental deficits, spongy degeneration of white matter, death by 18 months of age.