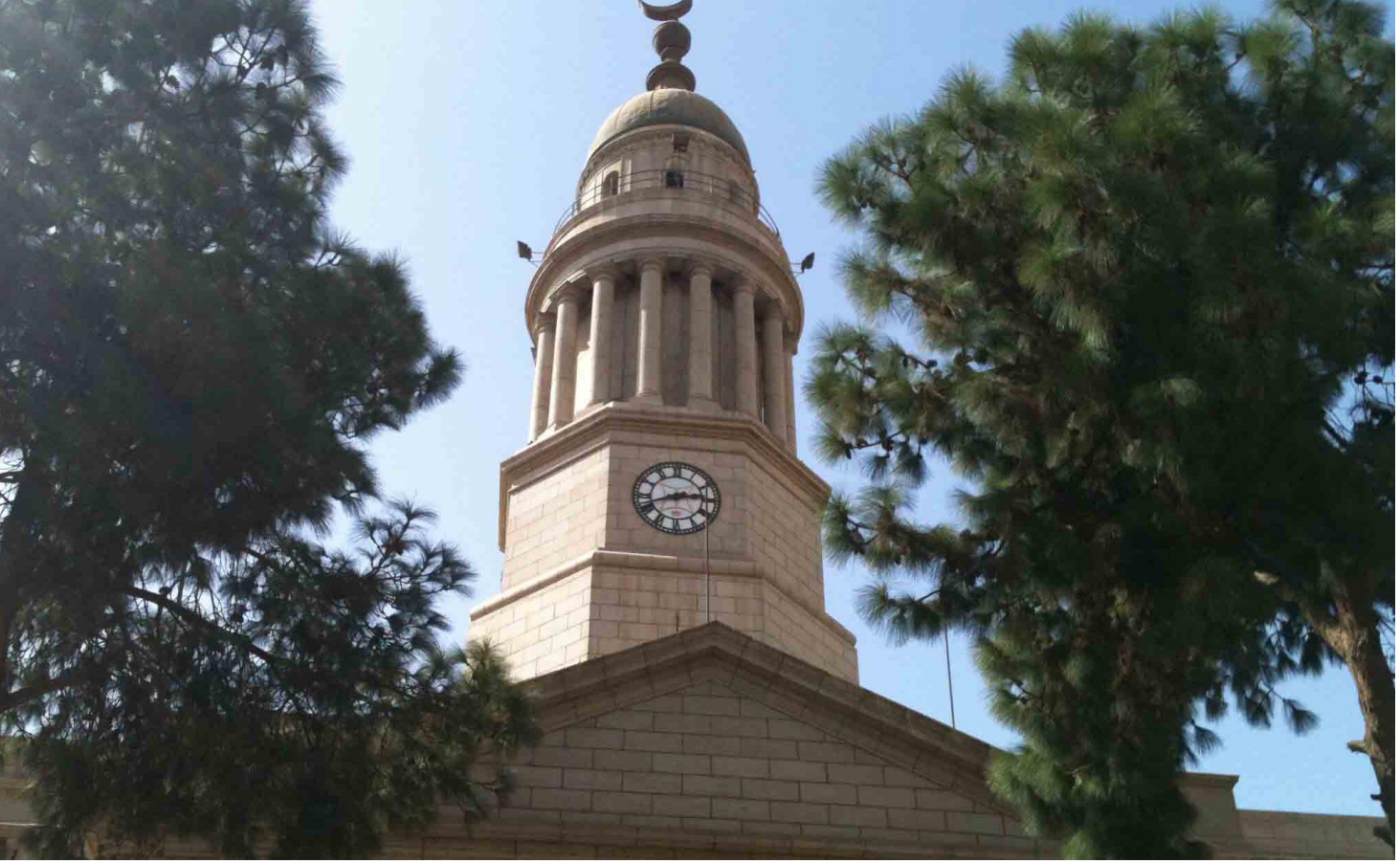
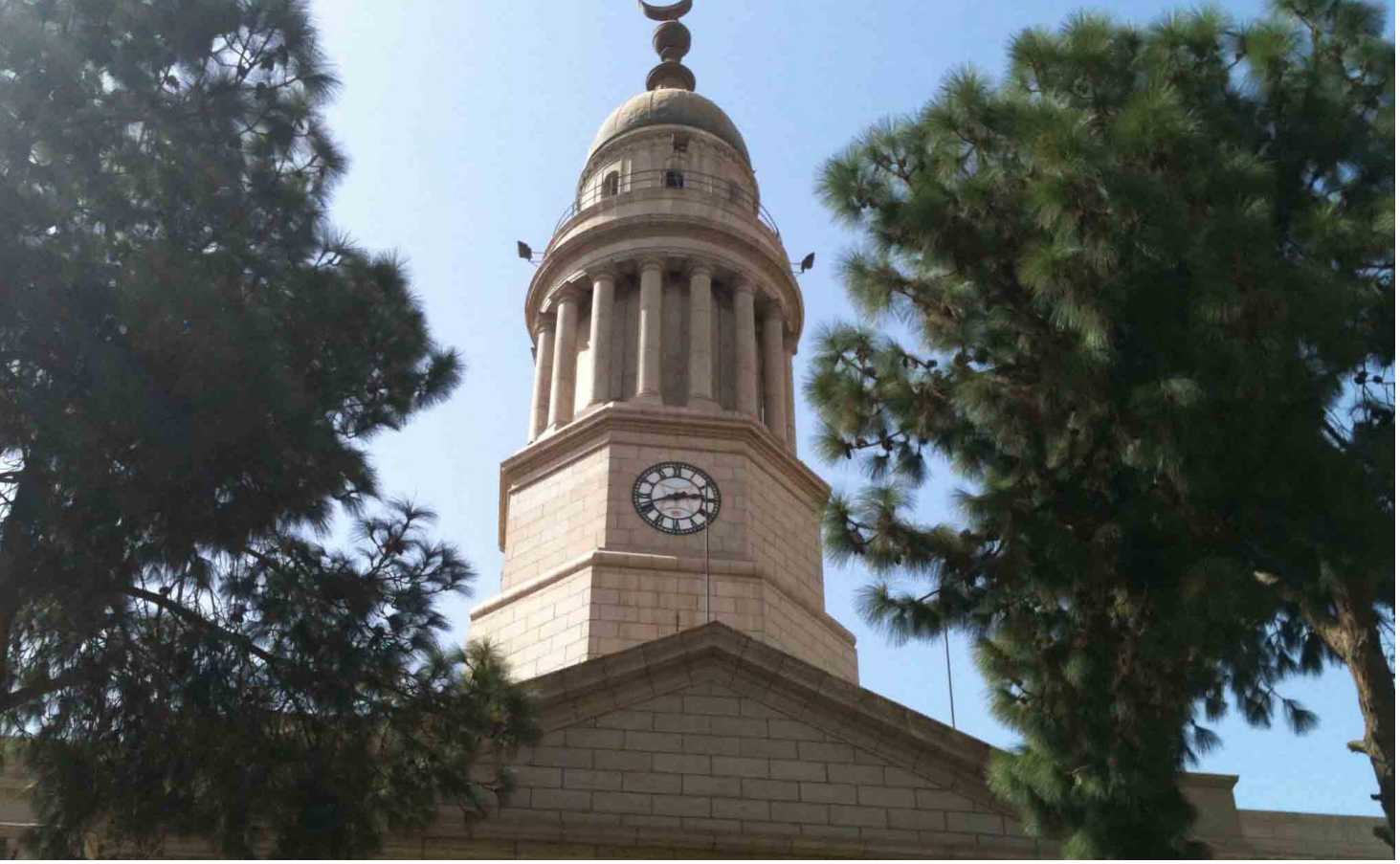


Neurometabolic Disorders



Amr Hasan, MD,FEBN

Associate Professor of Neurology - Cairo University

NEUROMETABOLIC DISORDERS

Different classifications

- Clinical syndrome
- Cellular organelle involved
- Biochemical studies
- Genetic mutation

Clinical Syndromes Suggestive of An Underlying Metabolic Cause

1. Neurologic disorder, including mental retardation, replicated in sibling or close relative.

1. Recurrent episodes of altered consciousness or unexplained vomiting in an infant.

2. Recurrent unexplained ataxia or spasticity Progressive central nervous system degeneration.

3. Mental retardation without obvious cause.

Classification

- Disorders of amino acid metabolism
- Disorders of renal amino acid transport
- Disorders of carbohydrate metabolism and transport
- Carbohydrate-deficient protein syndromes
- Organic acidurias
- Disorders of fatty acid oxidation
- Disorders of purine and pyrimidine metabolism
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Disorders of amino acid metabolism

Disorder	Inheritance	Gene Locus
PKU	AR	12q24
Maple Syrup disease	AR	19q13
		1p31
		6p22

Disorders of amino acid metabolism

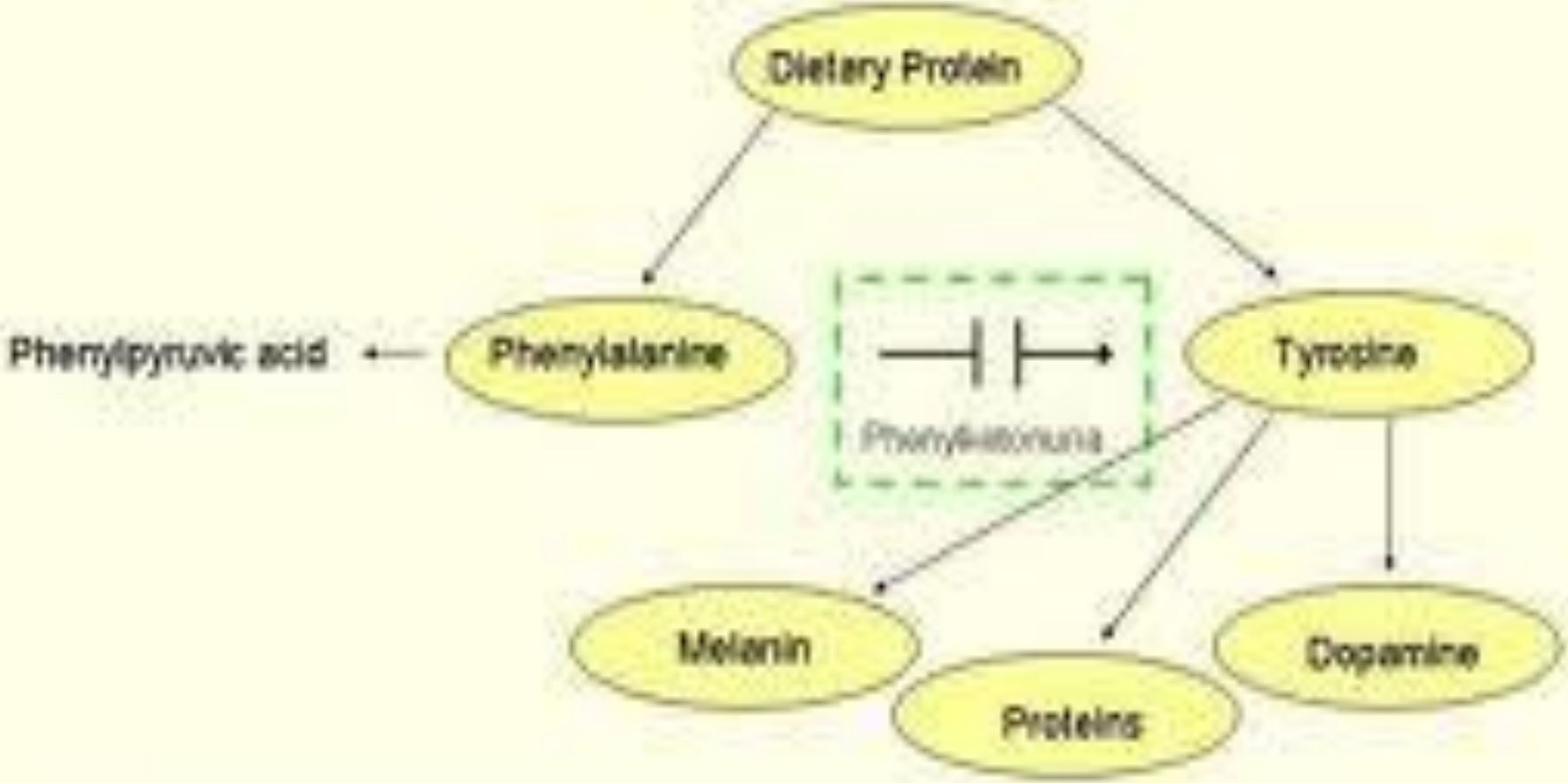
Phenylketonuria:

- AR 12q22.

- a mutation in the gene that codes for phenylalanine hydroxylase (PAH), the enzyme that hydroxylates phenylalanine to tyrosine.

- Phenylketonuric infants appear healthy at birth. In untreated infants, vomiting, which at times is projectile, and irritability are frequent during the first 2 months of life.

Phenylketonuria



- Lack of phenylalanine hydroxylase blocks the transformation of phenylalanine into tyrosine
- Unmetabolized phenylalanine is shunted into the pathway that leads to the formation of phenylketones
- Excess phenylalanine also inhibits the formation of melanin from tyrosine

Disorders of amino acid metabolism

Phenylketonuria:

- By 4 to 9 months, delayed intellectual development becomes apparent
- In the untreated classic case, mental retardation is severe.
- Children in this category have an IQ below 50.
- Seizures, common in the more severely retarded, usually start before 18 months of age and can cease spontaneously.
- During infancy, they often take the form of infantile spasms, later changing into tonic-clonic attacks.

Disorders of amino acid metabolism

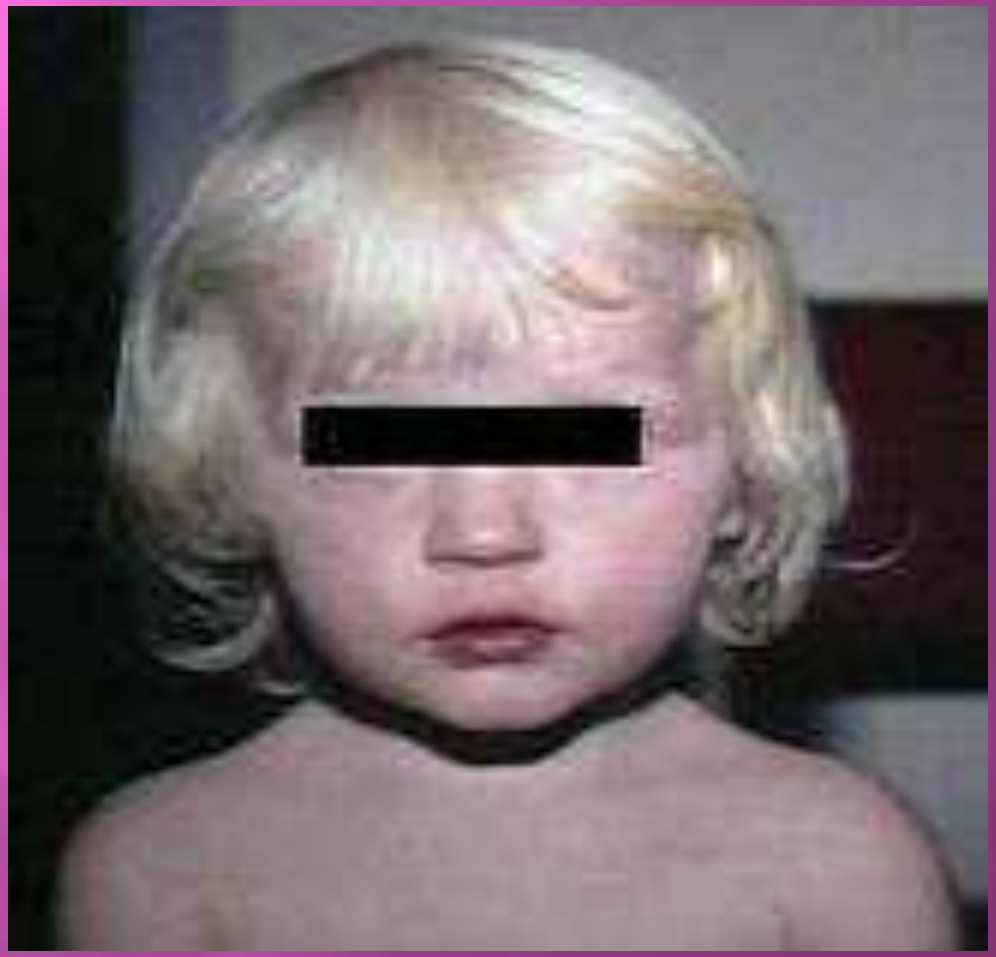
Phenylketonuria:

- Phenylketonuric child is blond and blue-eyed, with normal and often pleasant features. The skin is rough and dry, sometimes with eczema.
- A peculiar musty odor, attributable to phenylacetic acid, can suggest the diagnosis.
- Significant neurologic abnormalities are rare, although hyperactivity and autistic features are not unusual.
- Microcephaly .
- A fine, irregular tremor of the outstretched hands.
- Parkinsonian-like extrapyramidal
- The plantar response is often extensor.

Boy with untreated PKU

Because a child with PKU lacks the normally functioning enzyme necessary to break down phenylalanine (PHE), it accumulates in the blood and body tissues.

This excess PHE can prevent normal brain development and result in mental retardation.



Disorders of amino acid metabolism

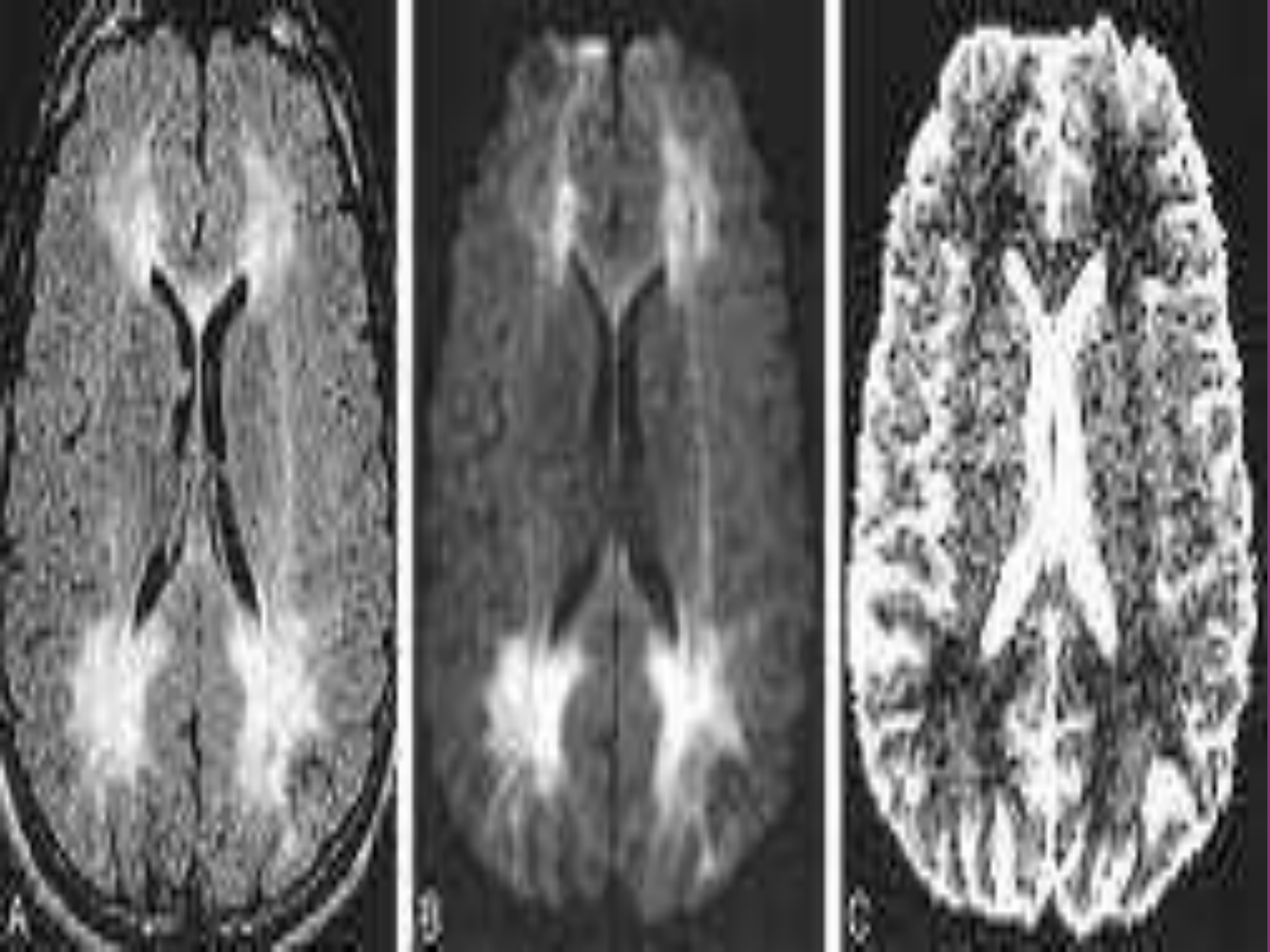
Phenylketonuria:

- A variety of electroencephalographic (EEG) abnormalities has been found, but hypsarrhythmic patterns, recorded even in the absence of seizures, and single and multiple foci of spike and polyspike discharges are the most common.

Disorders of amino acid metabolism

Phenylketonuria:

- T2-weighted imaging, increased signal in the periventricular and subcortical white matter of the posterior hemispheres.
- No signal abnormalities are seen in brainstem, cerebellum, or cortex, although cortical atrophy may be present
- Treatment can improve MRI abnormalities.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Disorders of amino acid metabolism

Phenylketonuria:

- The goal of PKU treatment is to maintain the blood level of phenylalanine between 2 and 10 mg/dl.
- Some phenylalanine is needed for normal growth. This requires a diet that has some phenylalanine but in much lower amounts than normal.
- High protein foods, such as: meat, fish, poultry, eggs, cheese, milk, dried beans, and peas are avoided. Instead, measured amounts of cereals, starches, fruits, and vegetables, along with a milk substitute are usually recommended.
- Phenylalanine free formulas are available for all age groups.


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pku 2

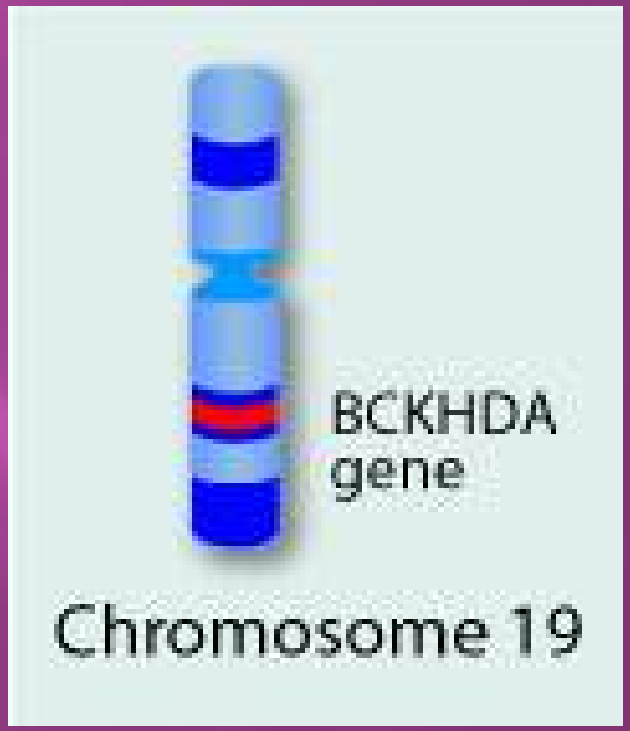
Disorders of amino acid metabolism

Maple syrup urine disease (MSUD)

Deficient enzyme (branched-chain alpha-keto acid dehydrogenase, BCKD) necessary for the breakdown of the amino acids leucine, isoleucine, and valine.

Without the BCKD enzyme, these amino acids build up to toxic levels in the body.

Maple Syrup disease



Disorders of amino acid metabolism

Maple syrup urine disease (MSUD)

Aged 4-7 days

- Poor feeding ,Vomiting
- Poor weight gain
- Increasing lethargy (difficult to wake up)
- Characteristic burned sugar smell to urine
- Changes in muscle tone, muscle spasms, and seizures
- If left untreated, these infants will die with the first months of life.
- Individuals with *intermittent MSUD*, the second most common form of the disorder, develop normally but when ill show the signs of classic MSUD.

Disorders of amino acid metabolism

Maple syrup urine disease (MSUD)

If maple syrup urine disease is suspected based on the physical symptoms, especially the characteristic urine odor, a blood test for amino acids can be done.

If alloisoleucine is detected, the diagnosis is confirmed. Several U.S. states screen newborns at birth for MSUD.

Disorders of amino acid metabolism

Maple syrup urine disease (MSUD)

Treatment:

- The main treatment for maple syrup urine disease is restriction of dietary forms of the three amino acids leucine, isoleucine, and valine. These restrictions must be lifelong. There are several commercial formulas and foods for individuals with MSUD.

- Fortunately, with adherence to the dietary restrictions and regular medical checkups individuals with maple syrup urine disease can live long and relatively healthy lives.

Disorders of amino acid metabolism

Maple syrup urine disease (MSUD)

Disorders of sulpher amino acid metabolism

Homocystinuria

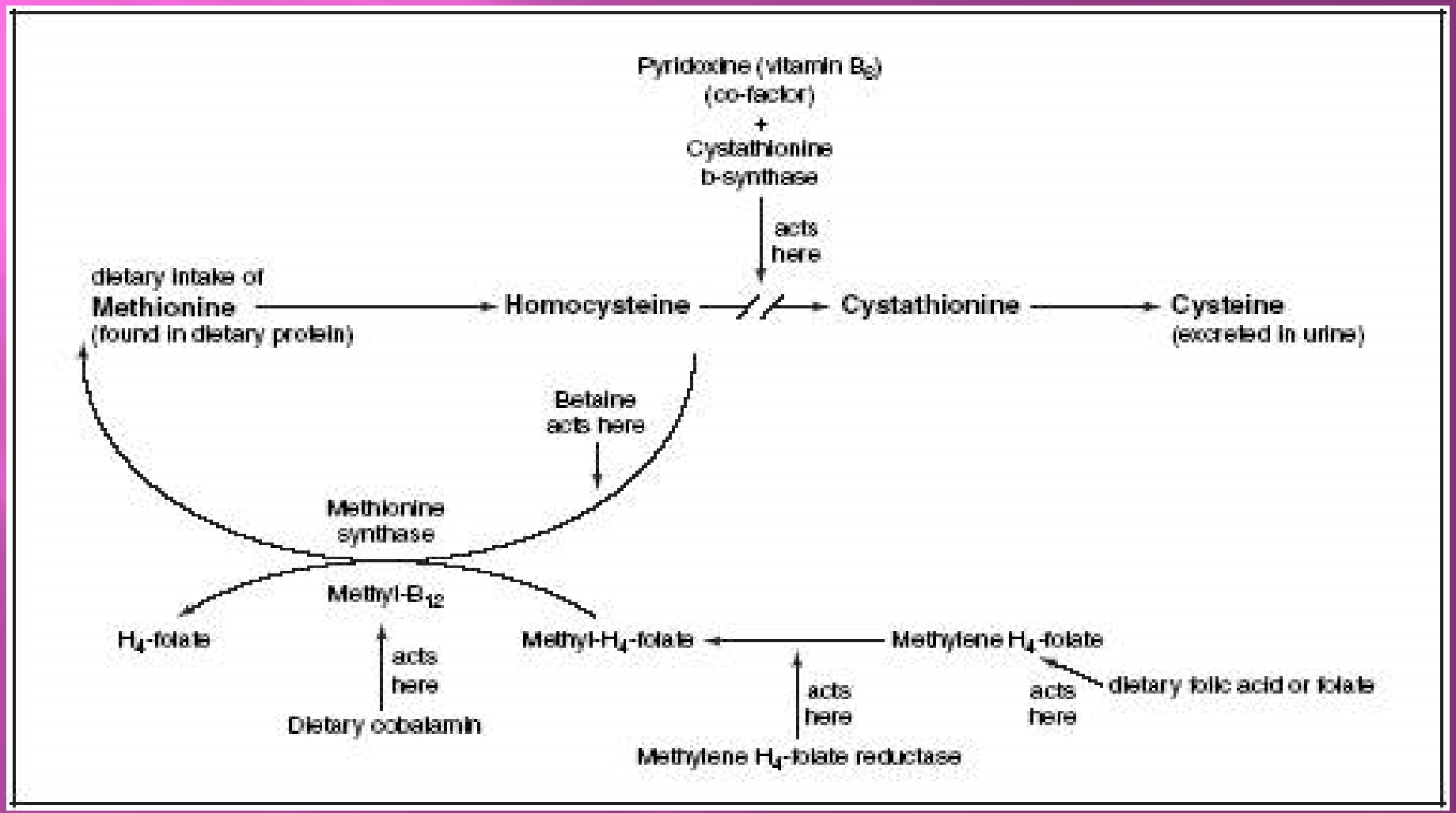
- Homocystinuria can be caused by the deficiency of cystathionine synthase. This is the classic form. The gene for this deficiency is located on band 21q22.3.

- Homocystinuria can be caused by insufficient vitamin B-12 synthesis resulting from a defect in the remethylation of homocysteine to methionine; methylmalonic aciduria is present.

- Homocystinuria can be caused by a deficiency in methylenetetrahydrofolate reductase.

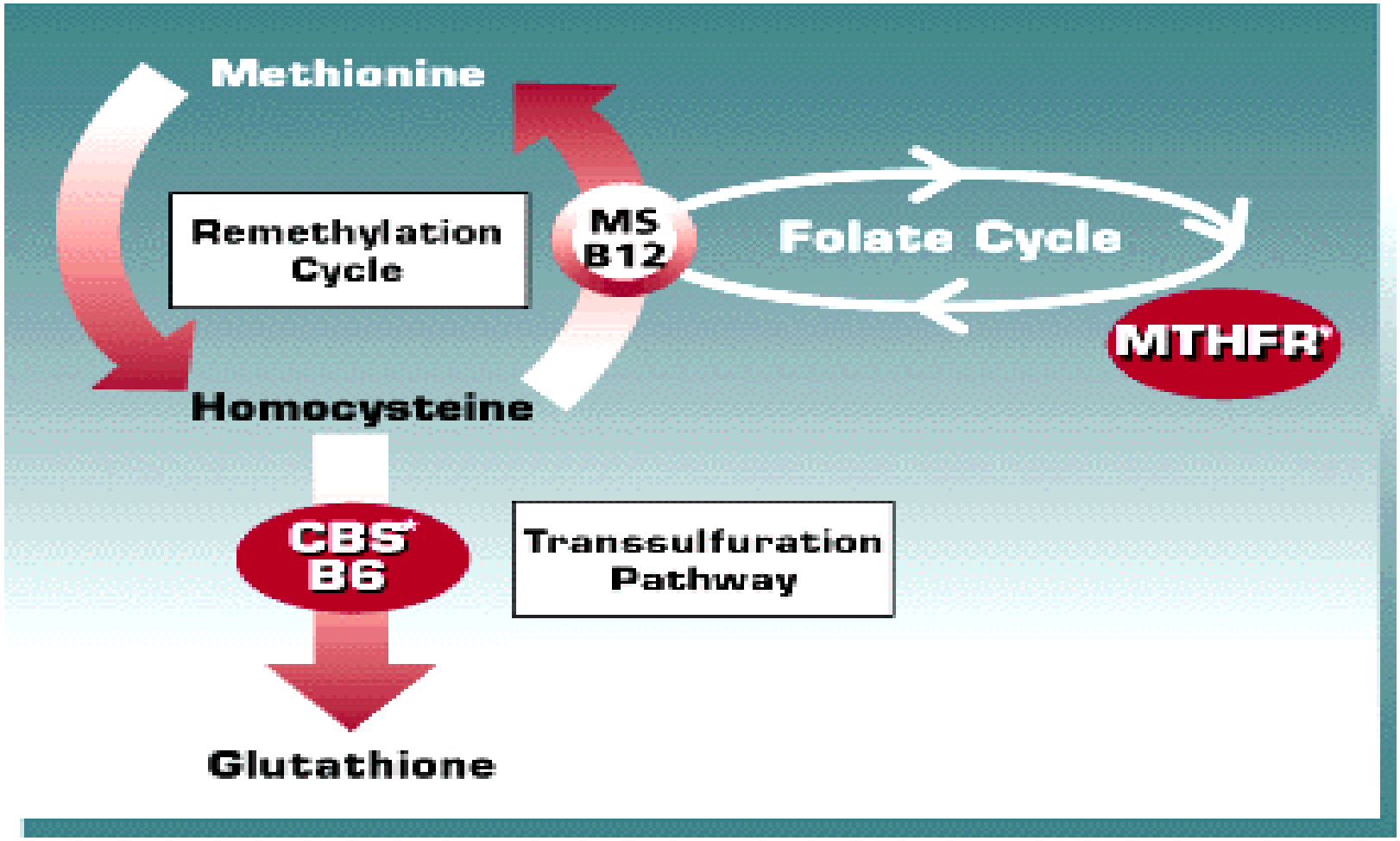
Disorders of sulpher amino acid metabolism

Homocystinuria



Disorders of sulpher amino acid metabolism

Homocystinuria



Disorders of sulpher amino acid metabolism

Homocystinuria

Homocystinuric infants appear healthy at birth, and their early development is unremarkable until

- Seizures.
- Developmental slowing.
- Cerebrovascular accidents occur between 5 and 9 months of age(thromboembolic episodes).
- Ectopia lentis is seen in more than 90% of affected individuals.
- Lenticular dislocation has been recognized as early as age 18 months, but it generally occurs between 3 and 10 years of age.

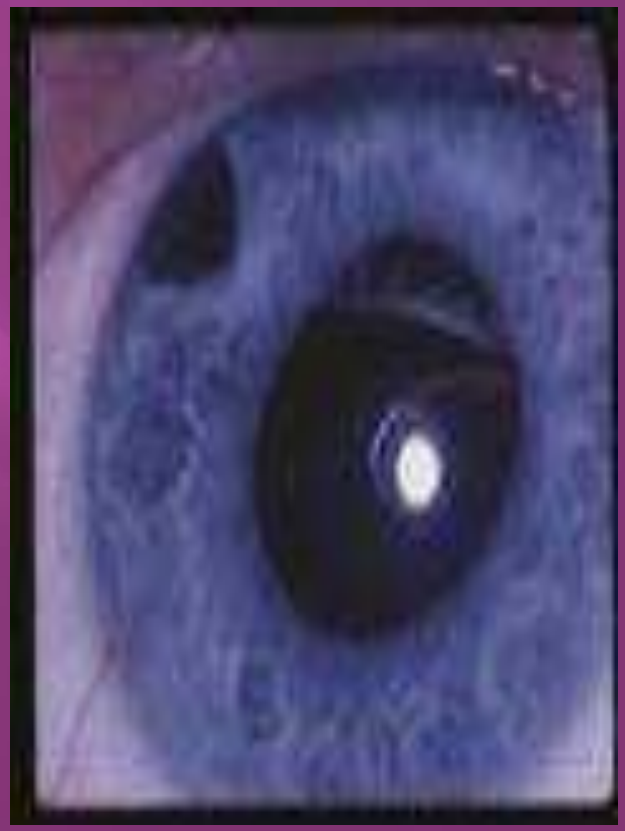
Disorders of sulpher amino acid metabolism

Homocystinuria

- The typical older homocystinuric child's hair is sparse, blond, and brittle, and multiple erythematous blotches are seen over the skin, particularly across the maxillary areas and cheeks.
- The gait is shuffling, the extremities and digits are long, and genu valgum is present in most instances.
- Secondary glaucoma and cataracts are common In approximately 50% of the patients reported, major have occurred on one or more occasions.

Disorders of sulpher amino acid metabolism

Homocystinuria



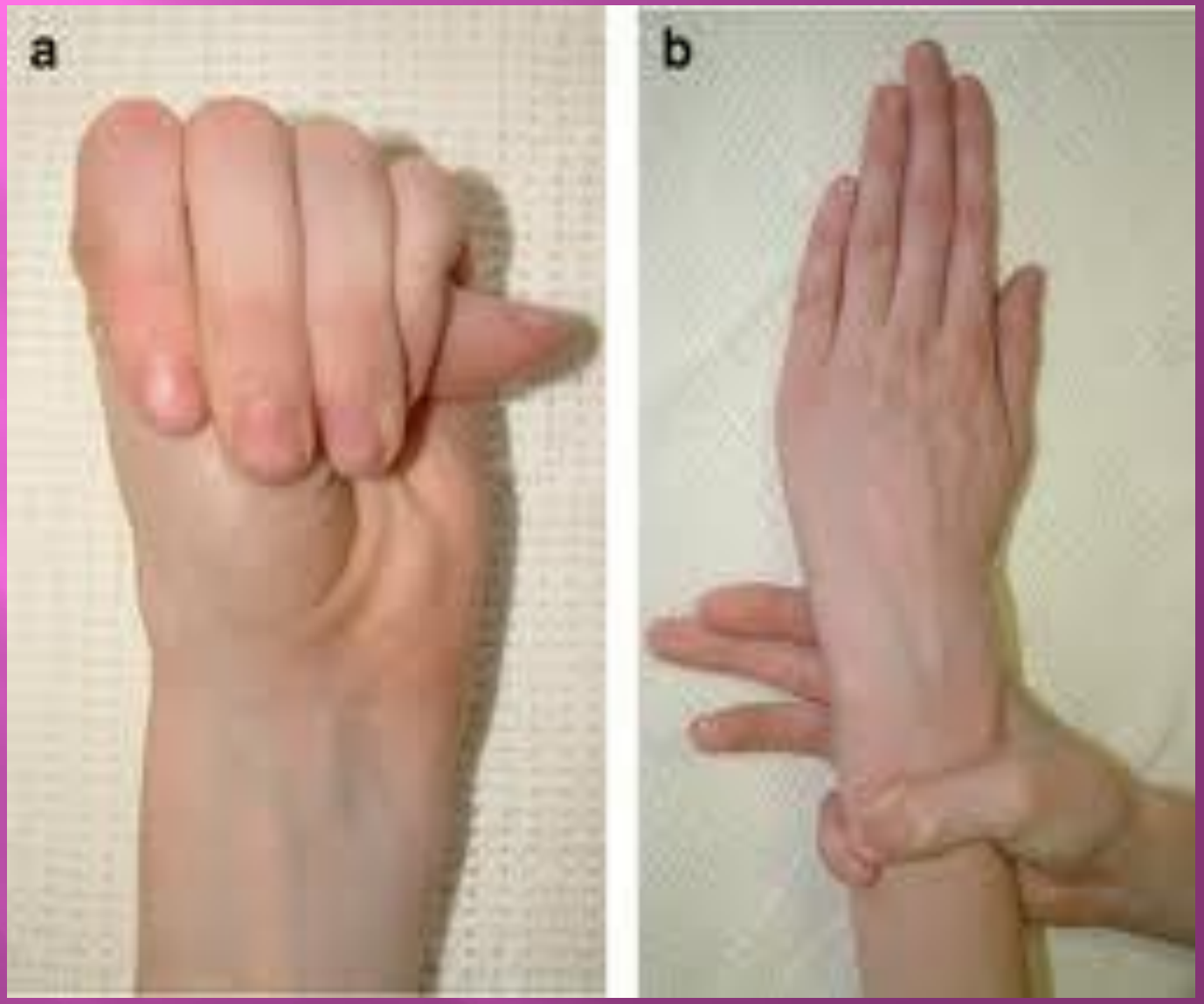

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Table 2. Main diagnostic work-up for Marfan's syndrome

Work-up	Target
Echocardiogram, aortogram, magnetic resonance imaging and computed tomography	Measurement of the aortic root and detection of valve prolapse
Slit lamp examination	Lens abnormalities
X-ray studies on skeletal system	Evaluations of hand, spine, pelvis, chest, foot and skull for characteristic abnormalities
Magnetic resonance imaging	Dural ectasia
Prenatal testing	At approximately 10-12 weeks, using chorionic villus sampling, on a prospective parent who has Marfan syndrome
Genetic testing	Genetic testing may be helpful, but is very costly and time-consuming for different gene mutations

Disorders of sulpher amino acid metabolism

Homocystinuria

- **Imaging Studies**

  With conventional MRI, the brain abnormalities are detected in cobalamin C/D defect and include unusual basal ganglia lesions, hydrocephalus, and supratentorial white matter abnormalities.

Disorders of sulpher amino acid metabolism

Homocystinuria

- Testing for heterozygosity may be valuable.
  - The results can be used to guide the use of preventative measures such as reduced methionine intake and pyridoxine supplementation.
  - Such testing is especially helpful in families of patients with homocystinuria.


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Disorders of amino acid metabolism

Defects in Urea Cycle Metabolism

- Six inborn errors in the urea cycle have been described. Five of these represent a lesion at each of the five steps in the conversion of ammonia to urea .
- These include argininosuccinic aciduria, citrullinuria, hyperargininemia, and two conditions termed hyperammonemia, the more common one attributable to a defect of ornithine transcarbamylase (OTC) and the other the result of a defect in mitochondrial carbamyl phosphate synthetase (CPS).

Disorders of amino acid metabolism

Defects in Urea Cycle Metabolism

- Because most systemic and neurologic symptoms in these diseases are the consequences of hyperammonemia or the accumulation of urea cycle intermediates, clinical manifestations of the urea cycle defects are nonspecific and overlap considerably.

- In their classic presentation, which occurs in some 60% of cases ,the conditions become apparent between 24 and 72 hours of life.

Disorders of amino acid metabolism

Defects in Urea Cycle Metabolism

- When the enzyme deficiency is less severe, hyperammonemic episodes are delayed to late infancy or childhood.
- Patients have recurrent episodes of lethargy, vomiting, and, less often, seizures.
- Hyperactivity, behavioral abnormalities, and moderate to severe mental retardation are common, as is intolerance of protein-containing foods

Disorders of amino acid metabolism

Defects in Urea Cycle Metabolism

Other Problems to be Considered

- Organic acid disorders (eg, isovaleric acidemia)

  Lysinuric protein intolerance

  Transient hyperammonemia of the newborn

  Hepatic insufficiency/dysfunction

  Mitochondrial diseases and pyruvate carboxylase deficiency

  Valproate ingestion

  L-asparaginase ingestion

  Reye syndrome

Disorders of amino acid metabolism

Defects in Urea Cycle Metabolism

- Plasma ammonia level :
  - Obtain this measurement when clinical signs and symptoms are suggestive of hyperammonemia.
  - No other laboratory test can substitute for this measurement, nor does any other test indicate need for it.
- Liver function studies:
- Urinary organic acid profile
- Urine amino acid levels
- Blood lactate levels: This is useful in ruling out mitochondrial diseases.
- Blood gas levels
- BUN level: This is often very low (<3 mg of urea/100 mL) in persons with urea cycle disorders.

Disorders of amino acid metabolism

Defects in Urea Cycle Metabolism

- Dietary therapy greatly depends on the etiologic diagnosis.
- Protein restriction is helpful in most cases, and restriction of specific amino acids may be imperative in treatment of particular entities.
- Dietary treatment of urea cycle disorders is highly specialized and usually requires consultation with a registered dietitian who works in a metabolic disease clinic.

Disorders of amino acid metabolism

Defects in Urea Cycle Metabolism

- Sodium phenylacetate and sodium benzoate (Ammonul)
- Ammonul 10% injection (100 mg/mL):
  Loading: 2.5 mL (250 mg)/kg IV over 90-120 min via central line
  Maintenance: 2.5 mL (250 mg)/kg/d IV over 24 h via central line
  Dilute IV dose in at least 25 mL/kg of dextrose 10% before administration

  >20 kg: Administer as in adults

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Disorders of amino acid transport

Hartnup disease

- AR disorder caused by impaired neutral (ie, monoaminomonocarboxylic) amino acid transport in the apical brush border membrane of the small intestine and the proximal tubule of the kidney.

- The name is that of the family in which it was first detected.

- The first gene to be identified was that for SLC6A19, a sodium-dependent amino acid transporter, on chromosome 5p15.

Disorders of amino acid transport

Hartnup disease

- Photosensitive dermatitis(pellagralike skin eruptions).
- Intermittent cerebellar ataxia.
- Mental disturbances.
- Renal aminoaciduria.

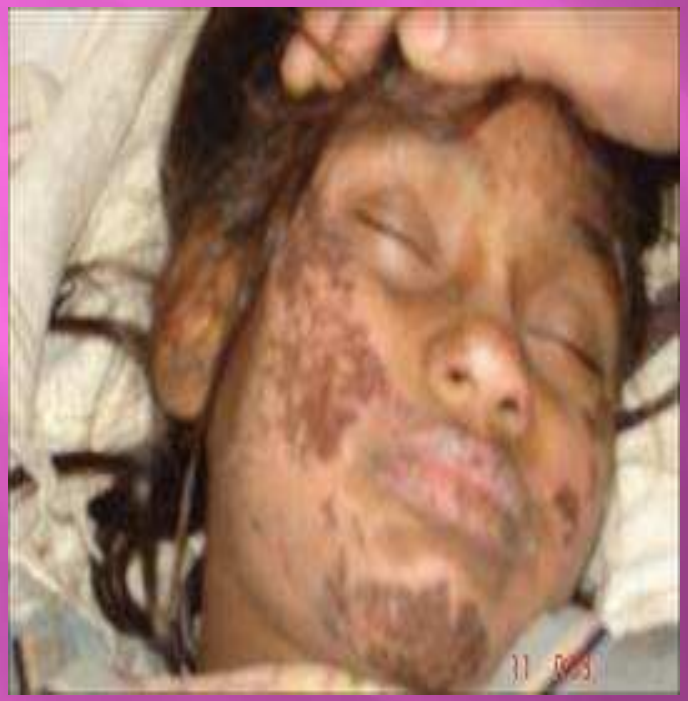
Disorders of amino acid transport

Hartnup disease

- Photosensitivity occurs.
- The skin reddens after exposure to sunlight.
- Further exposures lead to the development of dry, scaly, well-marginated eruptions, sometimes resembling chronic eczema.
- This eruption preferentially affects the forehead, the cheeks, the periorbital regions, the dorsal surfaces of the hands, and other light-exposed areas.

Disorders of amino acid transport

Hartnup disease



Disorders of amino acid transport

Hartnup disease

- A high-protein diet can overcome the deficient transport of neutral amino acids in most patients.

- Poor nutrition leads to more frequent and more severe attacks of the disease, which is otherwise asymptomatic.

Disorders of amino acid transport

Hartnup disease

- Advise all patients who are symptomatic to use physical and chemical protection from sunlight.

- Avoiding excessive exposure to sunlight, wearing protective clothing, and using physical and chemical sunscreens are mandatory.

- Recommend sunscreens with a skin protection factor of 15 or greater.

Disorders of amino acid transport

Hartnup disease

- Nicotinic acid or nicotinamide (50-300 mg/d) provides relief from both the skin manifestations and the neurologic manifestations.

- Administration of tryptophan ethyl ester (a lipid-soluble tryptophan metabolite) in a child with Hartnup disease at a dose of 20 mg/kg every 6 hours resulted in normalization of serum and cerebrospinal fluid tryptophan levels.

Disorders of amino acid transport

Lowe syndrome(OCR)

- **XR**

- The gene responsible for the disorder encodes a phosphatidyl inositol phosphatase located on the trans-Golgi network.

- The substrate for this phosphatase is a phospholipid with an important role in several basic cell processes, including cellular signaling, protein trafficking, and polymerization of the actin skeleton.

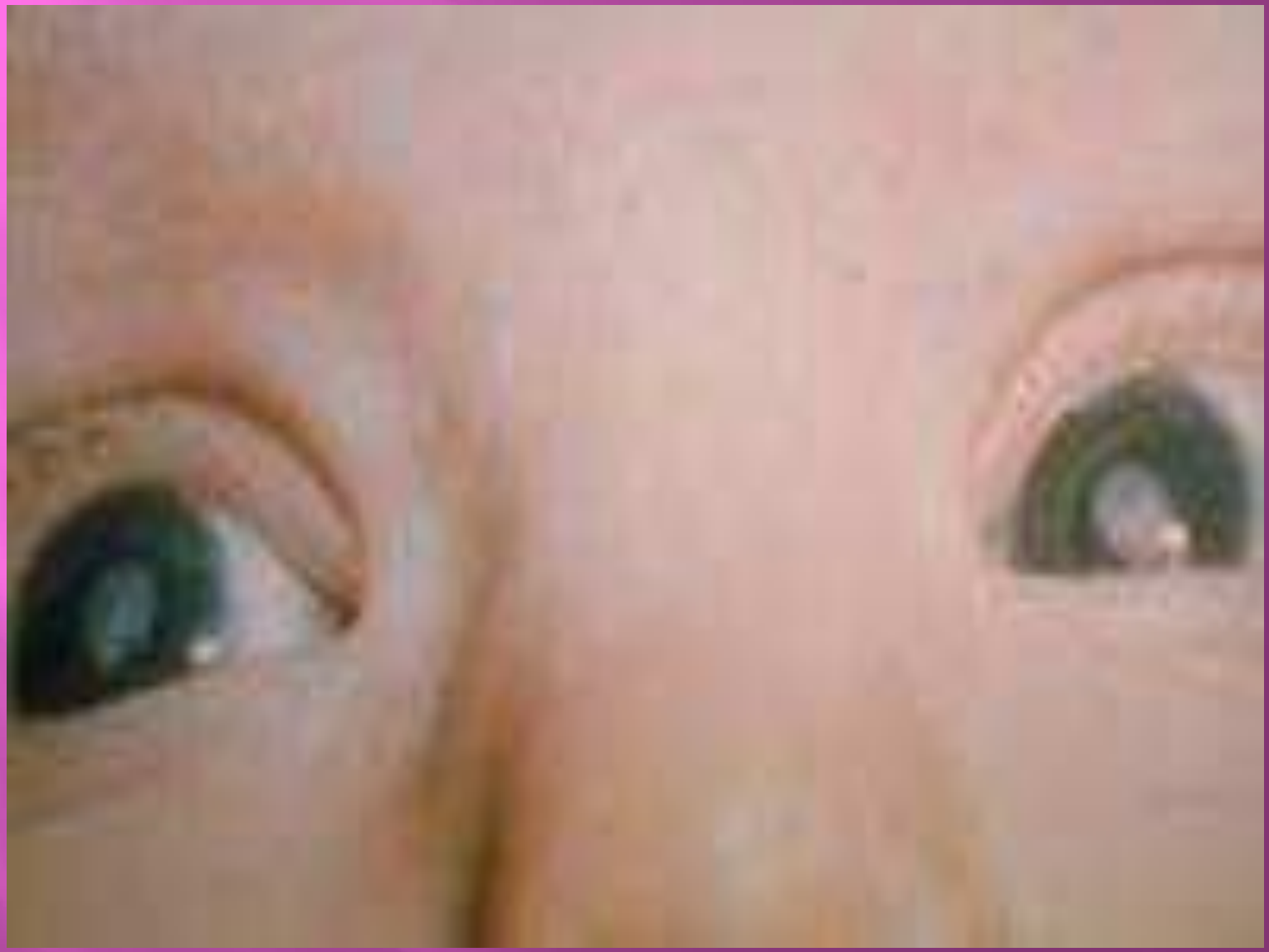
Disorders of amino acid transport

Lowe syndrome:

Oculo: congenital glaucoma or cataract.

Cerebro: severe mental retardation.

Renal: generalized aminoaciduria of the Fanconi type, renal tubular acidosis, and hypophosphatemic rickets



Disorders of amino acid transport

Lowe syndrome

The urinary levels of lysine are more elevated than those of the other amino acids

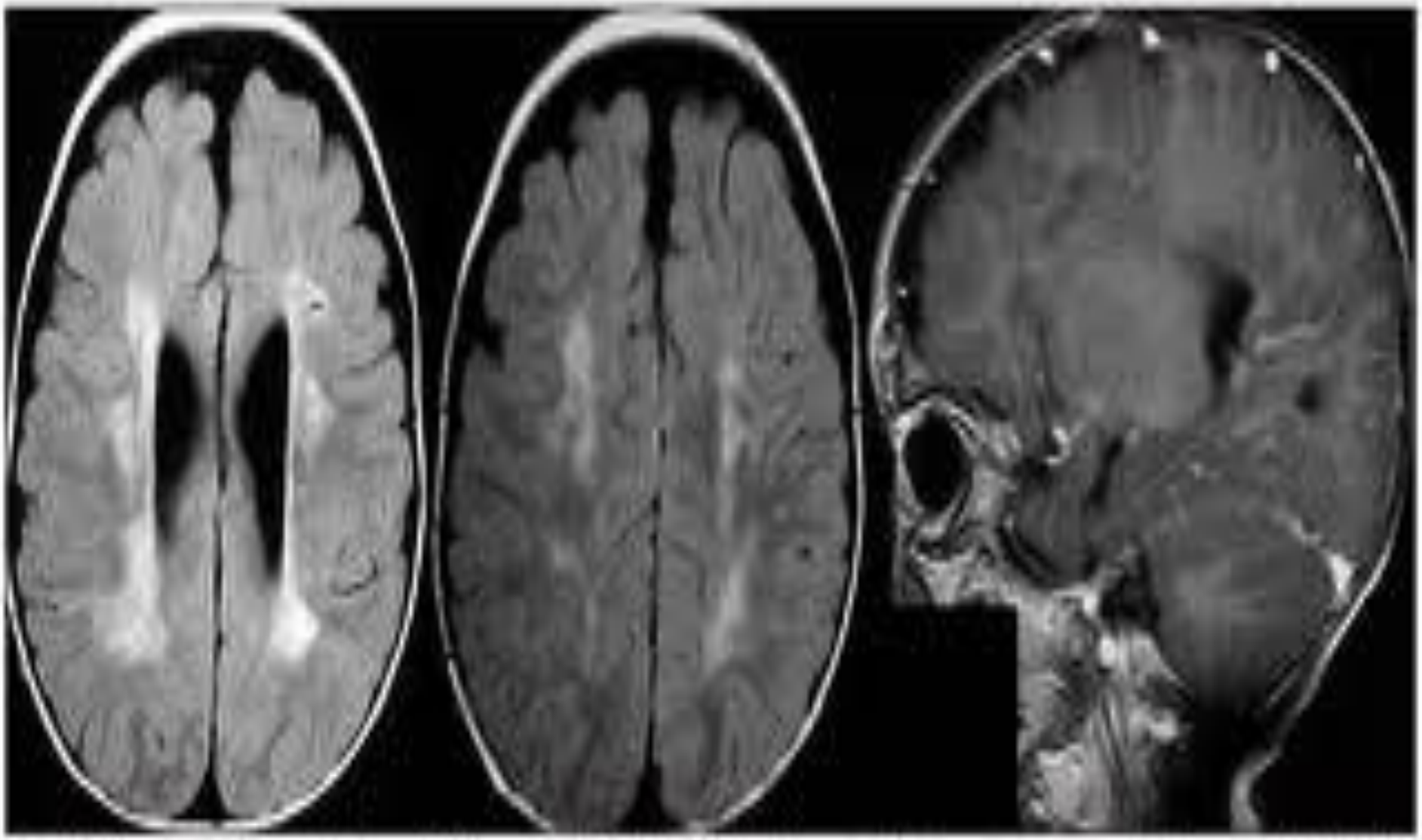


Fig 1. MRI examination at 21 months of age. Axial FLAIR (fluid-attenuated inversion recovery) and sagital T1-weighted post gadolinium (MR contrast agent). T2 weighted images show white matter hyperintensities in the periventricular and centrum semiovale regions.

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Disorders of carbohydrate metabolism and transport

- The most common disorders are acquired. Acquired or secondary derangements in carbohydrate metabolism, such as diabetic ketoacidosis, hyperosmolar coma, and hypoglycemia, all affect the central nervous system.

- Many forms and variants of peripheral nerve disease also are seen in diabetes.

- The remaining disorders of carbohydrate metabolism are the rare inborn errors of metabolism (i.e, genetic defects).

Disorders of carbohydrate metabolism and transport

- AR
- Most of the inherited disorders of carbohydrate metabolism fall into a few broad clinical syndromes, which are classified by age of onset as follows:

Disorders of carbohydrate metabolism and transport

- broad clinical syndromes, which are classified by age of onset as follows:
- Infants and early childhood
  - Episodic lactic acidosis from early infancy, failure to thrive, and hypotonia with or without features that may suggest specific defects
  - Infantile or early childhood mental retardation, hypotonia, failure to thrive, and other features
  - Mental retardation/developmental delay with features that suggest storage disorders
  - Episodic vomiting in infants or young children.

Disorders of carbohydrate metabolism and transport

- Childhood or adolescence
  - Episodic acidosis in childhood or early adulthood, often with features of a specific disorder
  - Intermittent or episodic ataxia in childhood and adolescence

Disorders Of Carbohydrate Metabolism And Transport

- In adults and, more rarely, in adolescents or older children
  - Cramps and weakness, often with some episodes of muscle breakdown and myoglobinuria, during or after heavy anaerobic exercise
  - Symmetrical neuromuscular disease with weakness and wasting of proximal muscles

Disorders Of Carbohydrate Metabolism And Transport

Galactosemia	AR	9p13 17q31 1p36
Fructose intolerance	AR	9q22
Fructose 1,6 diphosphatase Def.	AR	9q22

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Organic Acidemias

- The term "organic acidemia" or "organic aciduria" (OA) applies to a diverse group of metabolic disorders characterized by the excretion of non-amino organic acids in urine.

- Most organic acidemias results from a dysfunction of a specific step in amino acid catabolism, usually due to deficient enzyme activity.

- This leads to the accumulation of organic acids in the biological fluids (blood and urine), which, in turn, produces disturbances in the acid-base balance and causes alterations in pathways of intermediary metabolism.

Organic Acidemias

- Methylmalonic acidemia occurs when the activity of Methylmalonyl CoA mutase is defective in the isoleucine, valine, methionine and threonine degradative pathway.
- Propionic acidemia occurs when the activity of Propionyl CoA carboxylase is defective in the isoleucine, valine, methionine and threonine degradative pathway.
- Isovaleric acidemia occurs when the activity of Isovaleryl CoA dehydrogenase is defective in the leucine degradative pathway.

Organic Acidemias

- Glutaric acidemia type I occurs when the activity of Glutaryl CoA dehydrogenase is defective in the lysine, hydroxylysine and tryptophan degradative pathway.
- 3-Hydroxy-3-methylglutaryl CoA (HMG-CoA) lyase deficiency occurs when the activity of HMG CoA lyase is defective in the leucine degradative pathway.
- 3-Methylcrotonyl CoA carboxylase deficiency occurs when the activity of 3- methylcrotonyl-CoA carboxylase is defective in the leucine degradative pathway.

Organic Acidemias

Clinical Features

- A neonate affected with an organic acidemia is usually well at birth and for the first few days of life.

- The usual clinical symptoms of OA disorders may include vomiting, metabolic acidosis, ketosis, dehydration, coma, hyperammonemia, lactic acidosis, hypoglycemia, failure to thrive, hypotonia, global developmental delay, sepsis and hematologic disorders.

- The non-distinct clinical presentation may initially be attributed to sepsis, poor breast-feeding, or neonatal asphyxia.

Organic Acidemias

- screening test for organic acidemias by tandem mass
- spectrometry (MS/MS). It is a screening test and not a diagnostic test.

Organic Acidemias

Implications for Genetic Testing:

- The disorders included in this screening are inherited in an autosomal recessive manner.
- While a family history of neonatal death should prompt consideration of an organic acidemia, a negative family history does not preclude the possibility.

Organic Acidemias

Treatment

- The cornerstone of treatment is the dietary restriction of the intake of all those affected amino acids to the amounts that are required for growth and no more.
- Other treatment options include low protein diets, carnitine or vitamin supplements and/or avoidance of fasting.

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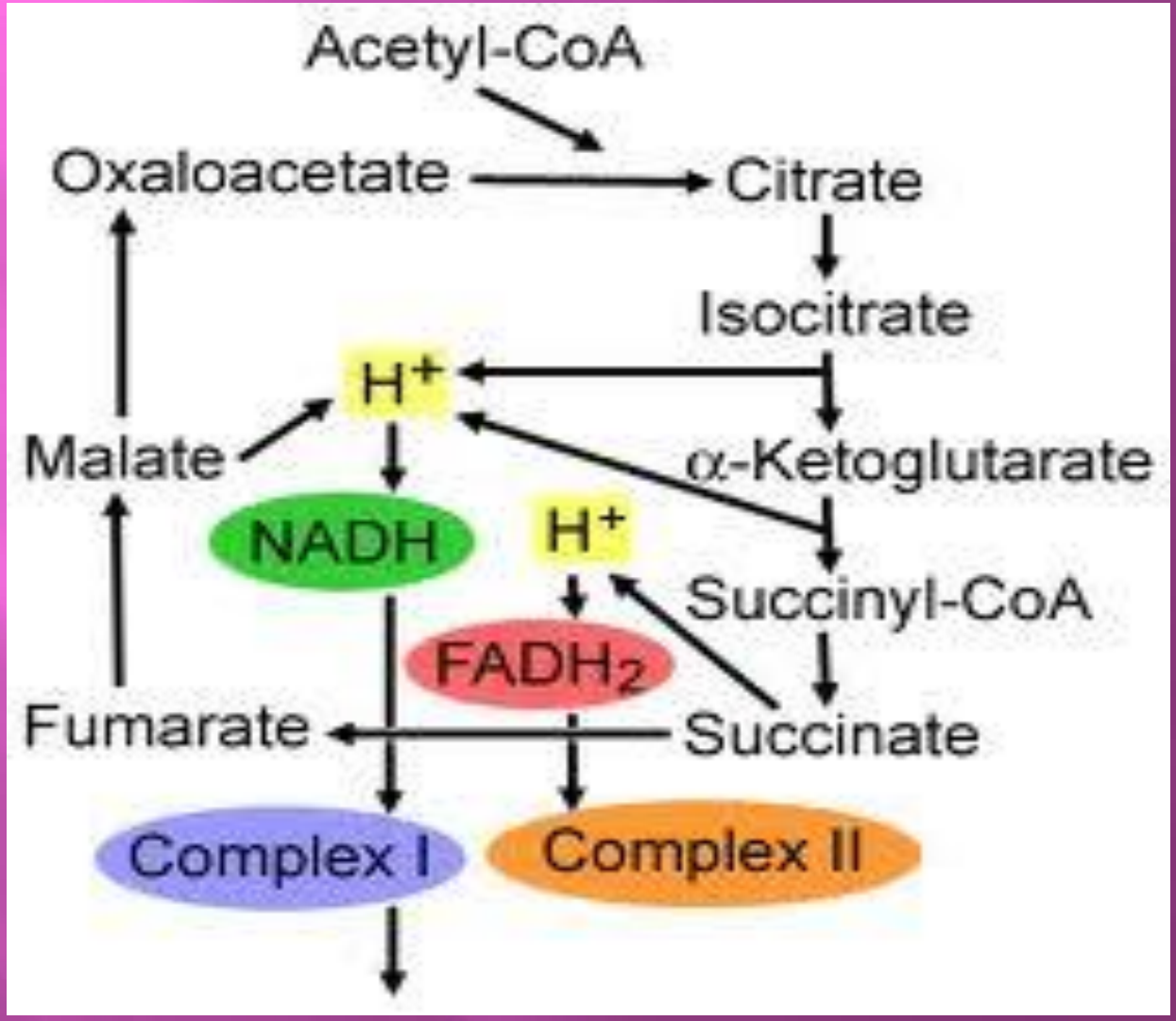
Fatty Acid Oxidation Disorders

- Fatty acid transport and mitochondrial oxidation is a complex pathway that plays a major role in energy production during times of fasting and metabolic stress.

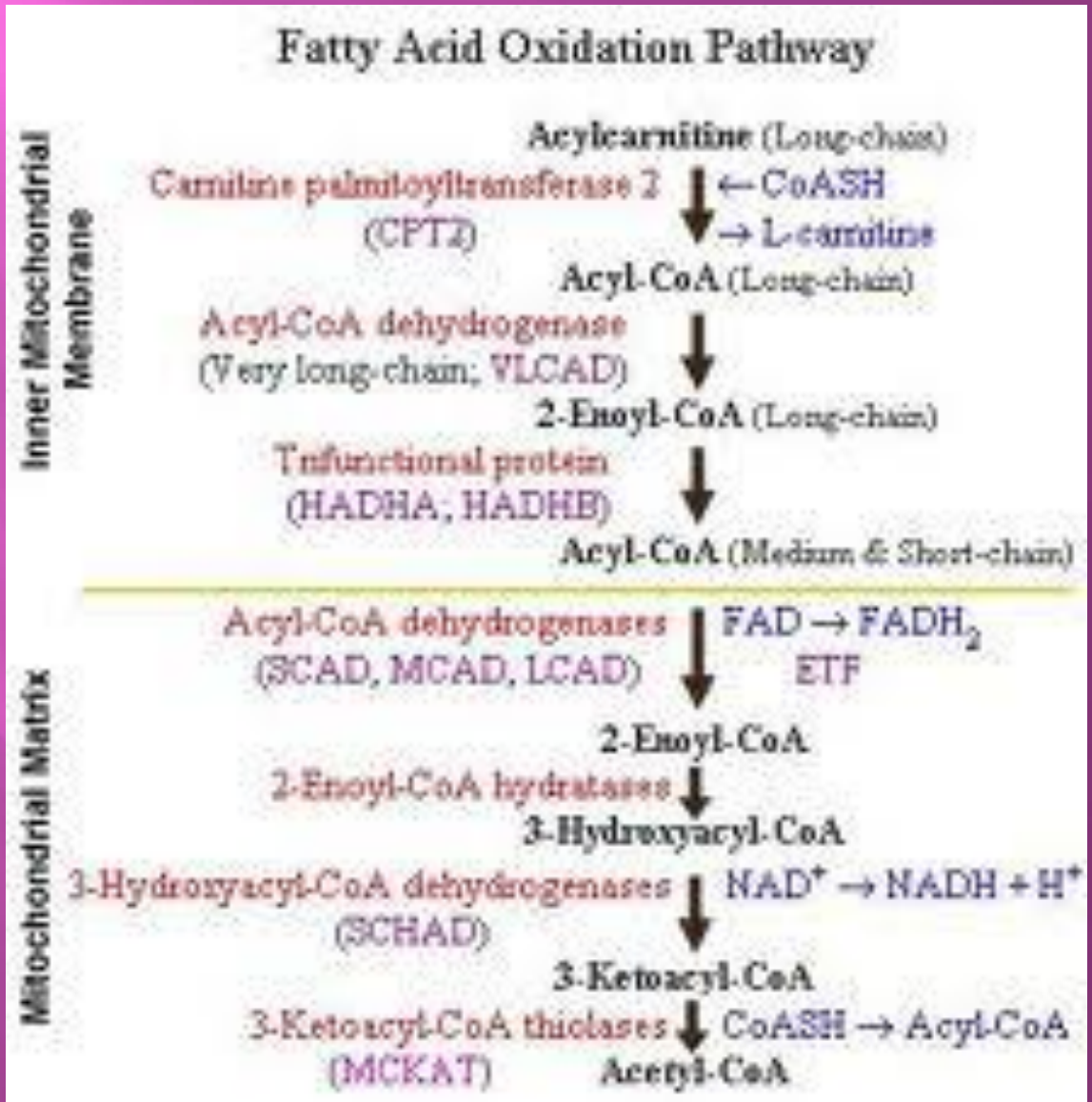
- Once free acids are released into the blood they are taken up by the liver and muscle cells and activated to coenzyme A esters.

- Then they are transported into the mitochondria and oxidized in a cyclic fashion by four sequential reactions that are each catalyzed by one of multiple enzymes.

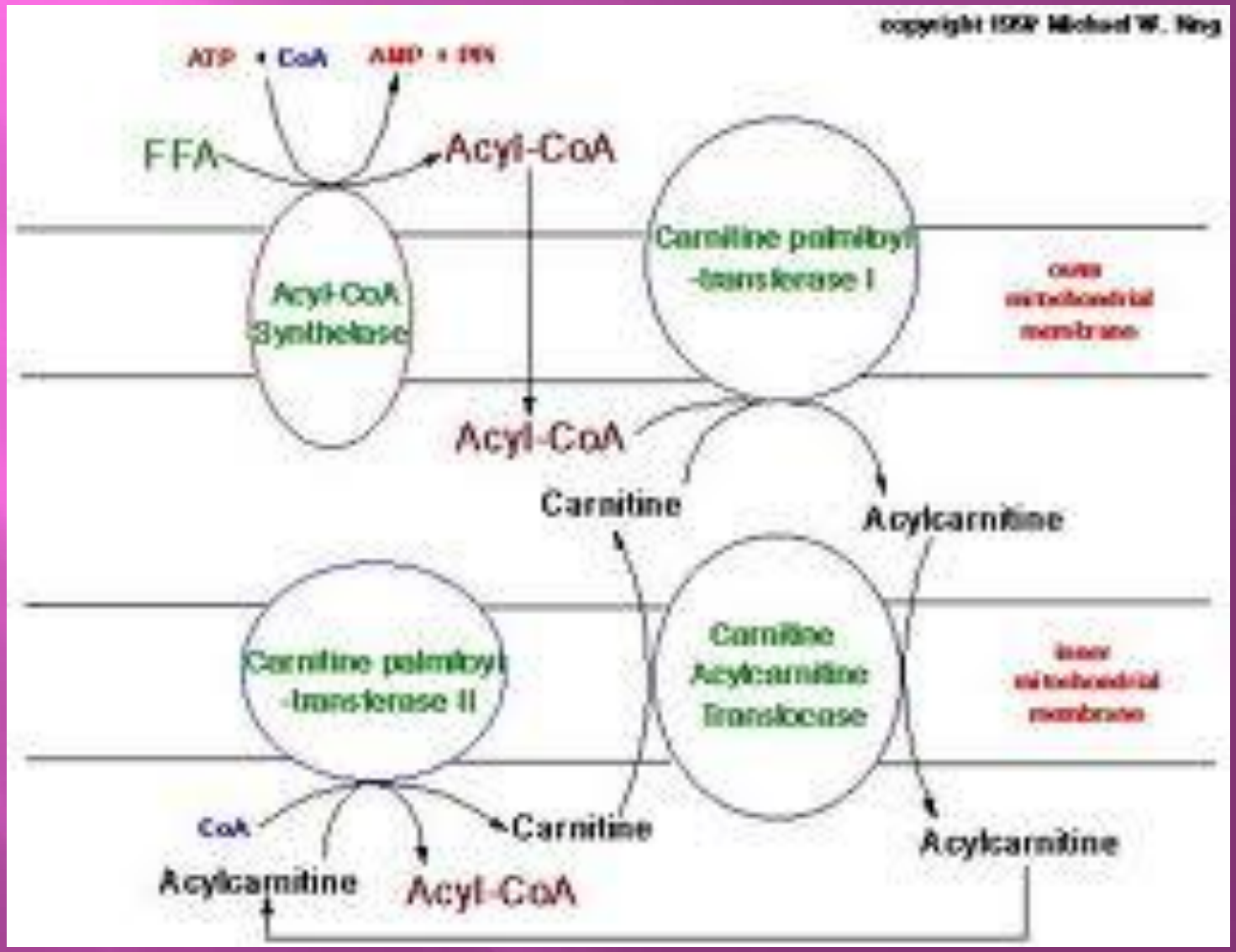
Fatty Acid Oxidation Disorders



Fatty Acid Oxidation Disorders



Fatty Acid Oxidation Disorders



Fatty Acid Oxidation Disorders

- The acyl-CoA dehydrogenases are chain-length specific enzymes.
- Deficiencies or abnormalities in these result in very long chain acyl-CoA dehydrogenase deficiency (VLCAD), long chain acyl CoA dehydrogenase deficiency (LCAD), medium chain acyl-CoA dehydrogenase deficiency (MCAD), and short chain acyl-CoA dehydrogenase deficiency (SCAD).

Fatty Acid Oxidation Disorders

- Any illness may lead to a fasting state that can then lead to the depletion of glucose stores.
- Once this occurs, fatty acid metabolism becomes the dominant energy source. If there is an abnormality in fatty acid metabolism, then life-threatening episodes of metabolic decompensation can ensue.
- Relatively simple dietary management may avoid symptoms.

Fatty Acid Oxidation Disorders

- Clinically, individuals with one of the fatty acid oxidation disorders may present with hypoglycemia, liver disease, encephalopathy, myopathy, cardiomyopathy, or sudden death. Symptoms may appear at any age from birth to adult life.
- Children with MCAD are typically normal at birth and develop episodes of hypoketotic hypoglycemia, vomiting, lethargy, and seizures associated with fasting.

Fatty Acid Oxidation Disorders

- The first episode usually occurs between 6 months and two years of age. The plasma acylcarnitine profile is diagnostic and a common gene mutation is found in the majority of patients.
- Urine organic acids in these patients typically show elevations of dicarboxylic acids, glycine conjugates and acylcarnitines.

Fatty Acid Oxidation Disorders

Treatment

- Early diagnosis and treatment is essential for an improved prognosis.
- If left untreated,these conditions may result in significant disability and, ultimately, death.

Fatty Acid Oxidation Disorders

Treatment

- Most of these conditions are chronic, with life-long episodes of hypoglycemia.
- For most fatty acid oxidation disorders, including MCAD, management involves long-term monitoring of serum glucose, a low-fat, high-carbohydrate diet, avoidance of fasting, aggressive support during illness, and carnitine supplementation.
- It is strongly recommended that **infants under age 1 be fed around the clock every 2-4 hours.**

Fatty Acid Oxidation Disorders

Implications for Genetic Testing

- All of the disorders of fatty acid oxidation are autosomal recessive and therefore are associated with a 25% recurrence risk in future pregnancies. If one child is diagnosed
- with a fatty acid oxidation disorder, their siblings should also be tested, even if
- the sibling is asymptomatic.

Classification

- Disorders of amino acid metabolism
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Purine &Pyrimidine disorders

Lesch-Nyhan syndrome	XL	Xq29
Adenosine Deaminase def.	AR AD	8q11 20q13
Xeroderma Pigmentosum	AR	9q22 19q13 3p25

Purine &Pyrimidine disorders

Lesch-Nyhan syndrome (LNS)

- Is a rare, inherited disorder caused by a deficiency of the enzyme *hypoxanthine-guanine phosphoribosyltransferase* (HPRT).

- LNS is an X-linked recessive disease. The lack of HPRT causes a build-up of uric acid in all body fluids

Purine &Pyrimidine disorders

Lesch-Nyhan syndrome (LNS)

- Clinically, patients with HPRT deficiency fall into three groups.

- The most severely affected have all the features of classic Lesch-Nyhan disease, another group has neurologic manifestations and hyperuricemia, and yet a third group has isolated hyperuricemia without neurologic deficits.

Purine &Pyrimidine disorders

Lesch-Nyhan syndrome (LNS)

- In the classic form of Lesch-Nyhan disease children appear healthy at birth, and initial gross motor milestones are achieved appropriately.
- During the first year of life, psychomotor retardation becomes evident.
- Extrapyramidal movements appear between 8 and 24 months of age and persist until obliterated by progressive spasticity.

Purine &Pyrimidine disorders

Lesch-Nyhan syndrome (LNS)

- Seizures occur in approximately 50% of the patients. A curious and unexplained feature of the disease is the involuntary self-destructive biting of fingers, arms, and lips, which becomes apparent by 4 years of age.

Purine &Pyrimidine disorders

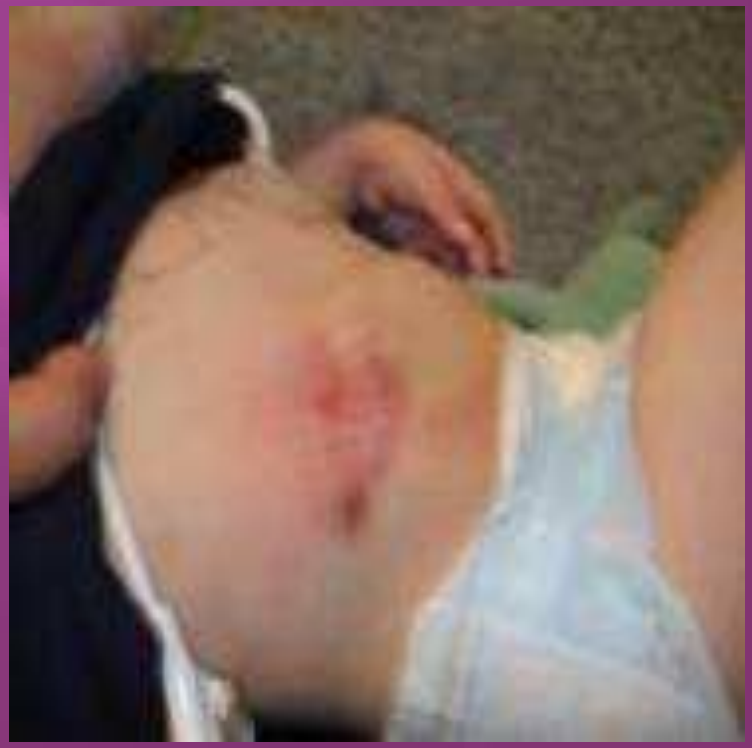
Lesch-Nyhan syndrome (LNS)

- Children are disturbed by their compulsion to self-mutilation and are happier when maintained in restraints. The teeth may have to be removed to prevent damage to the lips and tongue.

- In later years, a large proportion of patients develop vocal tics reminiscent of those seen in Tourette disease.

Purine &Pyrimidine disorders

Lesch-Nyhan syndrome (LNS)



Purine &Pyrimidine disorders

Lesch-Nyhan syndrome (LNS)

- In the second group of patients there is excessive uric acid production, gouty arthritis, and mild neurologic symptoms, most commonly a spinocerebellar syndrome or mild mental retardation, or mild mental retardation, short stature, and spasticity.

- The least severely affected group has defective HGPRT with hyperuricemia

Purine &Pyrimidine disorders

Lesch-Nyhan syndrome (LNS)

- Treatment for LNS is symptomatic. Gout can be treated with allopurinol to control excessive amounts of uric acid.
- Kidney stones may be treated with lithotripsy, a technique for breaking up kidney stones using shock waves or laser beams.
- There is no standard treatment for the neurological symptoms of LNS. Some may be relieved with the drugs carbidopa/levodopa, diazepam, phenobarbital, or haloperidol.

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Disorders of lipid and lipoprotein metabolism

- Globoid cell leukodystrophy and metachromatic leukodystrophy have been shown to result from a disorder in lipid metabolism.

Disorders of lipid and lipoprotein metabolism

Cerebrotendinous xanthomatosis

The defect in cerebrotendinous xanthomatosis has been localized to the mitochondrial sterol 27-hydroxylase → deposition of cholestanol (dihydrocholesterol) within the nervous system.

Disorders of lipid and lipoprotein metabolism

Cerebrotendinous xanthomatosis

- The triad of progressive spinocerebellar ataxia, pyramidal signs, and mental retardation is seen in the large majority of patients with cerebrotendinous xanthomatosis, and mental retardation is seen in more than 90% .
- Cataracts are present in 76% of patients and generally are seen as early as 56 years of age. Seizures are encountered in 40% to 50% of patients and can be the presenting symptom

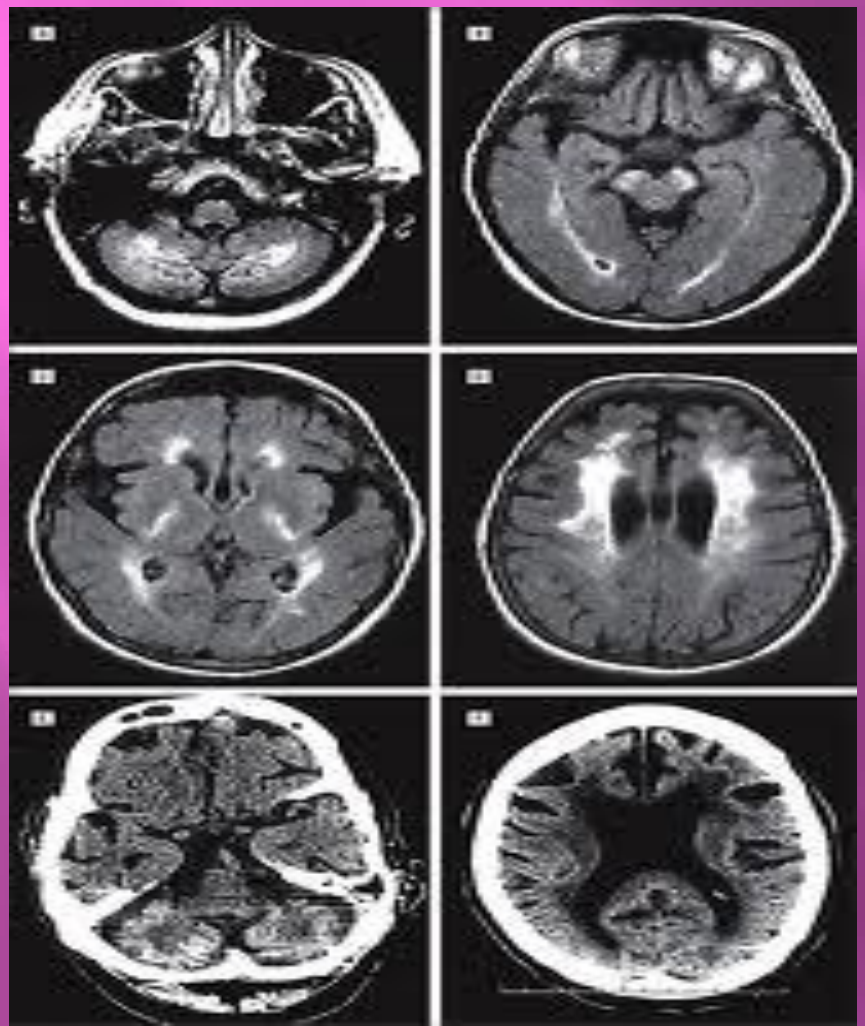
Disorders of lipid and lipoprotein metabolism

Cerebrotendinous xanthomatosis

- Intractable diarrhea can be a major manifestation during childhood (chologenic diarrhea) .
- A sensory and motor neuropathy also has been documented.
- Tendon xanthomas can be apparent in childhood, most commonly over the Achilles and triceps tendons.

Disorders of lipid and lipoprotein metabolism

Cerebrotendinous xanthomatosis



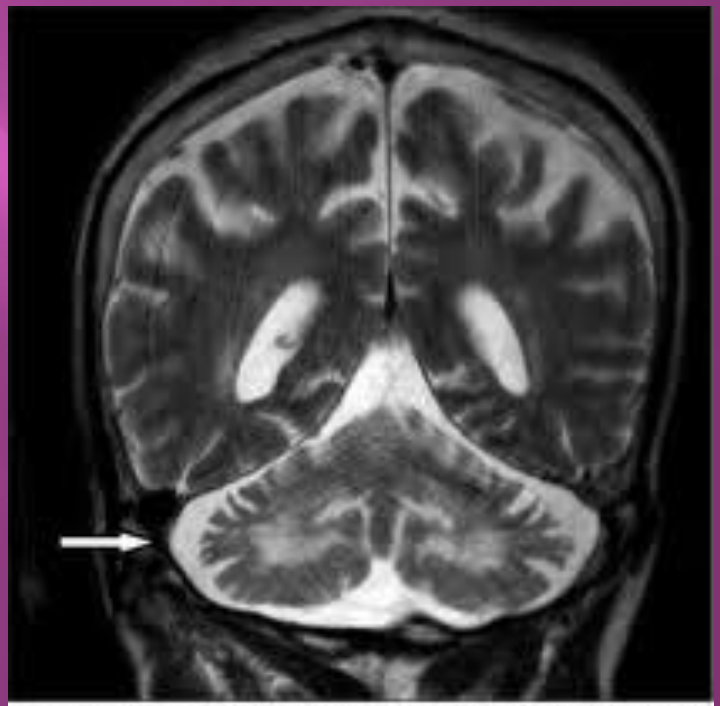
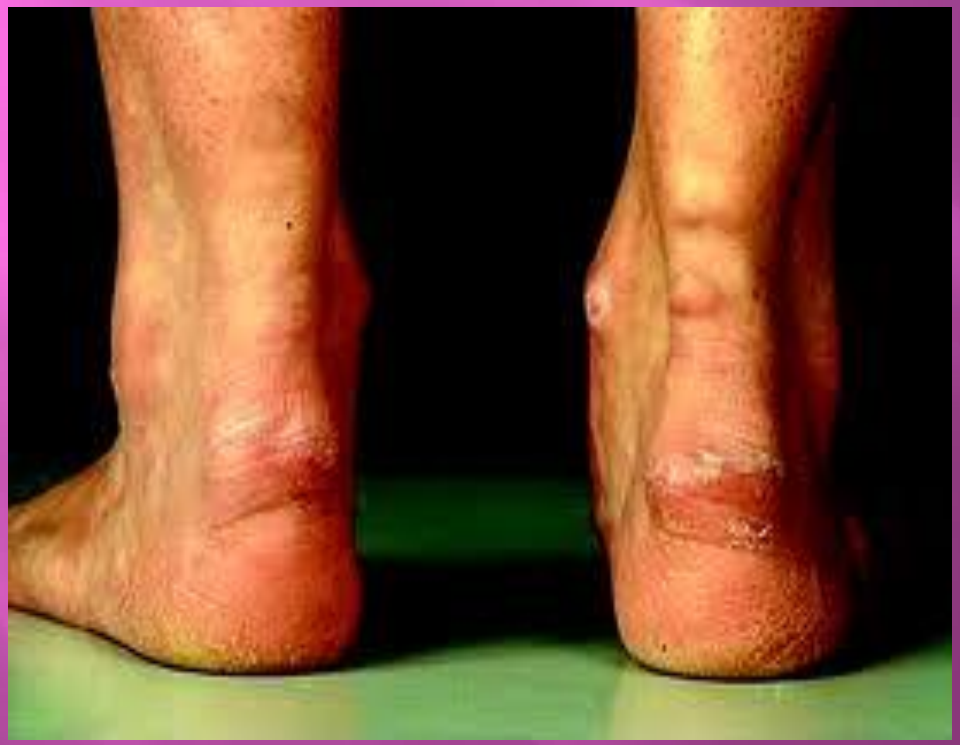


Fig 2. Cerebellar atrophy and hyperintense sign in dentate nuclei and adjacent cerebellar white matter on T2-weight RMI images (arrow), for a patient with cerebrotendinous xanthomatosis.

Disorders of lipid and lipoprotein metabolism

Cerebrotendinous xanthomatosis



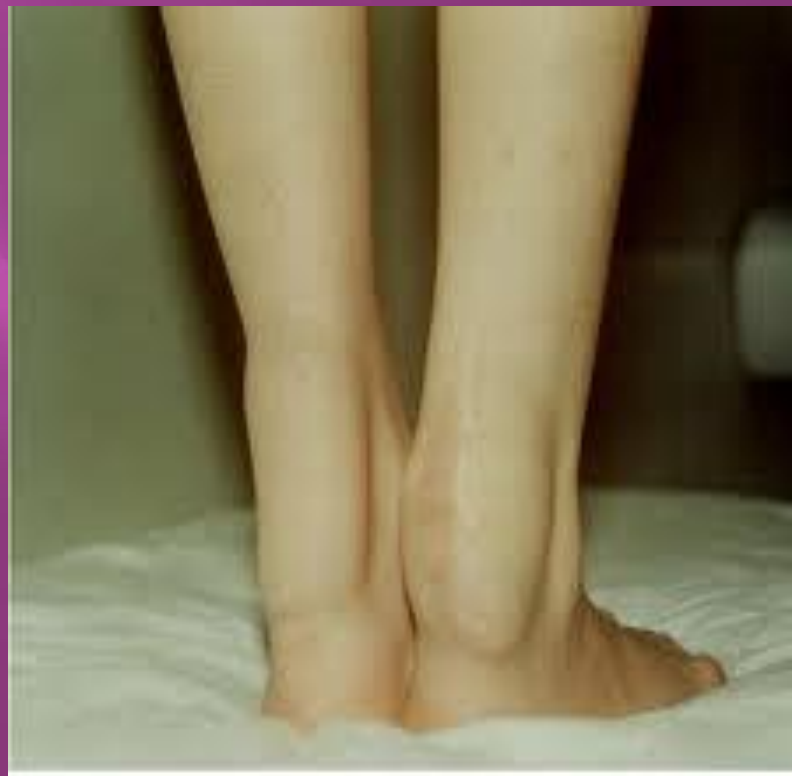
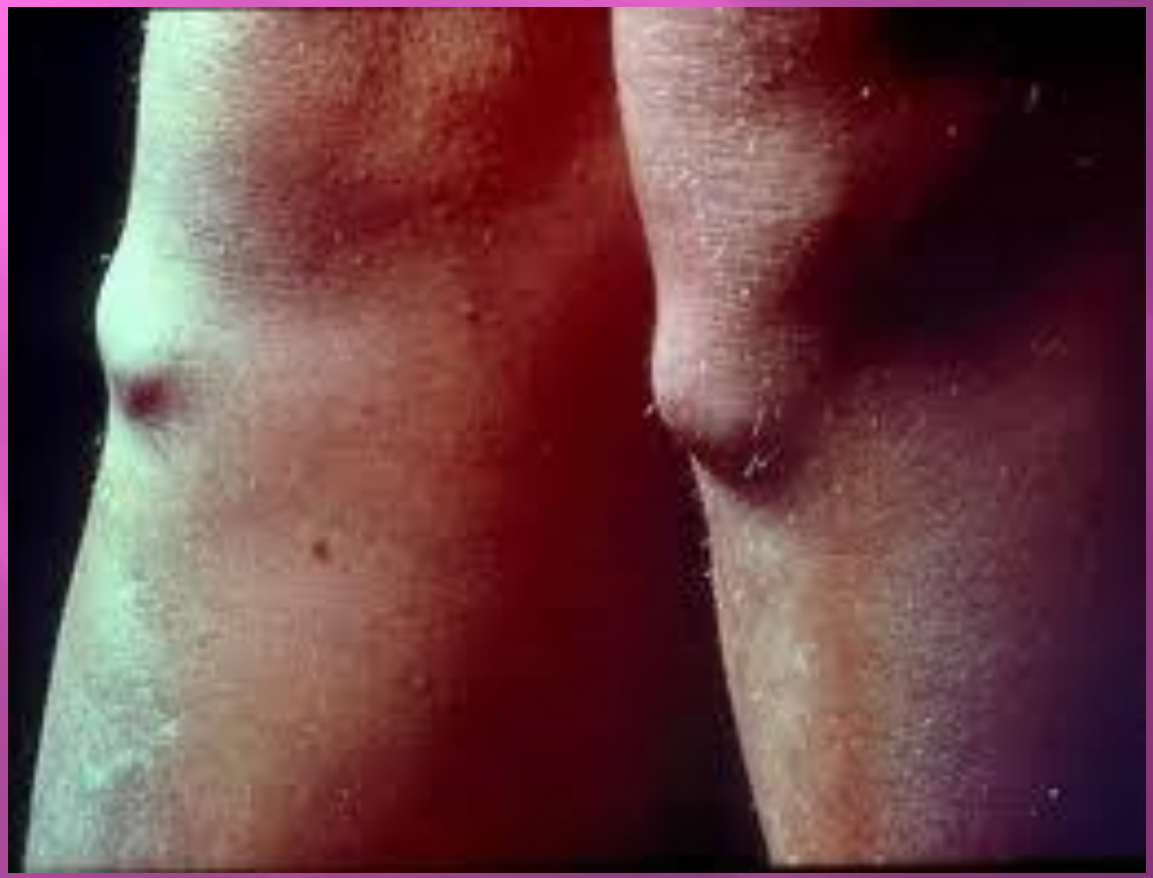


Figure1: Bilateral Achilles Tendon Xanthomas

Disorders of lipid and lipoprotein metabolism

Cerebrotendinous xanthomatosis

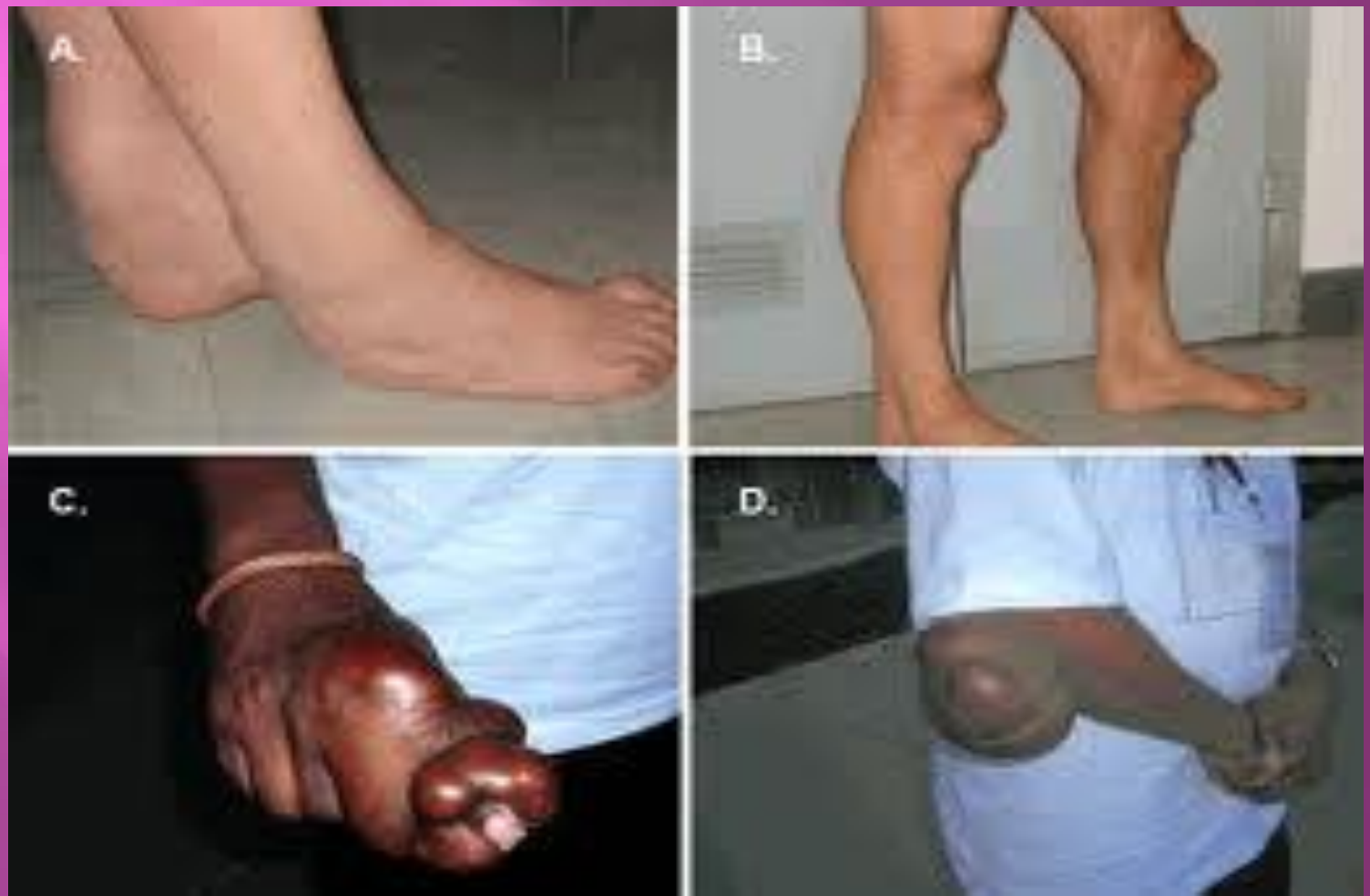


Disorders of lipid and lipoprotein metabolism

Cerebrotendinous xanthomatosis

Disorders of lipid and lipoprotein metabolism

Cerebrotendinous xanthomatosis



Disorders of lipid and lipoprotein metabolism

Cerebrotendinous xanthomatosis:

Serum cholesterol levels tend to be low, and cholestanol concentrations in serum and erythrocytes are elevated .

CT reveals the presence of hyperdense nodules in the cerebellum and diffuse white matter hypodensity. MRI demonstrates atrophy of cerebrum and cerebellum, with occasional atrophy of the brainstem and corpus callosum.

Increased signal is seen on T2-weighted images in the dentate nucleus, globus pallidus, substantia nigra, and inferior olive, extending into the white matter as the disease progresses.

Occasionally hypodensity on T2-weighted images is present in the dentate nucleus, related to deposition of hemosiderin and calcifications

Disorders of lipid and lipoprotein metabolism

Cerebrotendinous xanthomatosis:

- Treatment with chenodeoxycholic acid (15 mg/kg per day) reverses the elevated CSF cholestanol levels and induces a 50% reduction of plasma cholestanol, an increase in IQ, and a reversal of neurologic symptoms.

- Additionally, improvement occurs in the EEG, somatosensory-evoked potentials, and the MRI.

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Disorders of serum lipoproteins

Ceroid lipofuscinosis

The neuronal ceroid lipofuscinoses (NCLs) are characterized by the accumulation of autofluorescent neuronal storage material within neuronal lysosomes, leading to neuronal death and cerebral atrophy.

Traditionally the various NCLs were differentiated according to the age at which neurologic symptoms first become evident and the ultrastructural morphology of the inclusions.

Disorders of serum lipoproteins

- **Infantile Neuronal Ceroid Lipofuscinosis (Santavuori Disease, CLN1) (OMIM 256730)**
- The principal features of the illness include intellectual deterioration that becomes apparent between 9 and 19 months of age (later than the generalized G_{M2} gangliosidoses), ataxia, myoclonic seizures, and visual failure, with a brownish pigmentation of the macula, hypopigmentation of the fundi, and optic atrophy .
- A retinal cherry-red spot is absent, but a pigmentary retinal degeneration is not unusual .
- Head growth ceases early, and in contrast to G_{M2} gangliosidosis, most infants become microcephalic before age 24 months.

Disorders of serum lipoproteins

Late Infantile Neuronal Ceroid Lipofuscinosis (Late Infantile Amaurotic Idiocy, Jansky-Bielschowsky Disease, CLN2)

- The onset of the clinical syndrome occurs later than that of the classic form of G_{M2} gangliosidosis. The condition does not affect Jewish children predominantly, its progression is slower, and patients lack the usual retinal cherry-red spot.

Disorders of serum lipoproteins

- CLN2 is characterized by normal mental and motor development for the first 24 months of life, although in many instances, slight clumsiness or a slowing in the acquisition of speech can be recalled retrospectively.
- The usual presenting manifestations are myoclonic or major motor seizures. Ataxia develops subsequently and is accompanied by a slowly progressive retinal degeneration, which is generally not obvious until the other neurologic symptoms have become well established. Visual acuity is decreased, and a florid degeneration occurs in the macular and perimacular areas.

Disorders of serum lipoproteins

Juvenile Neuronal Ceroid Lipofuscinosis (Juvenile Amaurotic Idiocy; Spielmeyer-Vogt Disease, CLN3)

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Disorders of serum lipoproteins

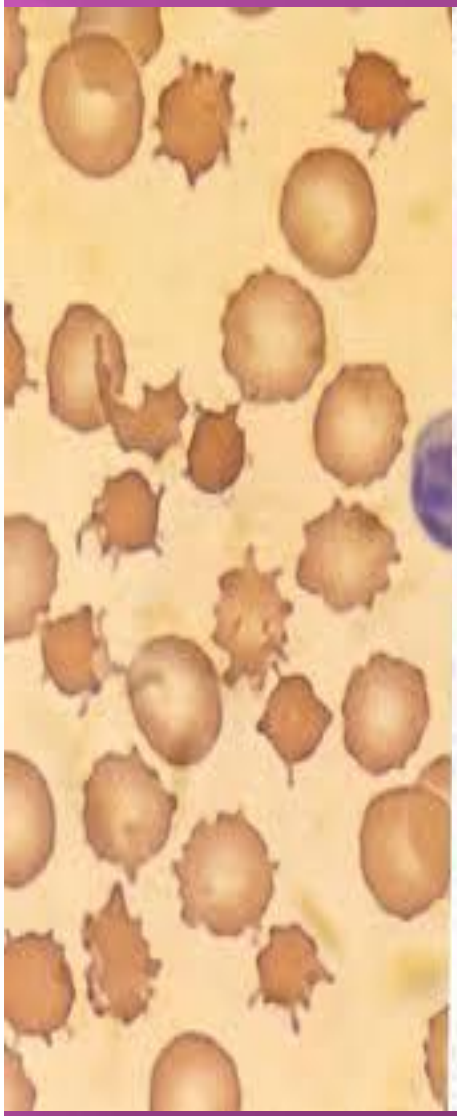
Abetalipoproteinemia

- Abetalipoproteinemia, an unusual disorder, was first described by Bassen and Kornzweig in 1950.
- The main clinical manifestations include acanthocytosis (large numbers of burr-shaped erythrocytes) (which may account for more than one-half of the circulating erythrocytes, hypocholesterolemia, progressive combined posterior column degeneration, peripheral neuritis, mental retardation, retinitis pigmentosa, and steatorrhea.
- AR

Disorders of serum lipoproteins

Abetalipoproteinemia

- In the first year of life, infants develop a typical celiac syndrome with abdominal distention, diarrhea, foul-smelling stools, decreased fat absorption, and, occasionally, osteomalacia. The majority of affected infants are below the third percentile for height and weight. Neurologic symptoms are first noted between ages 2 and 17 years, and 33% of patients are symptomatic before age 10 years.


Disorders of serum lipoproteins

- Commonly, the initial symptom is unsteadiness of gait. This is caused by a combination of ataxia, proprioceptive loss, and muscle weakness.
- Deep tendon reflexes are generally absent, and cutaneous sensory loss is often demonstrable (
- Extensor plantar responses are noted occasionally.
- Mental retardation has been seen in approximately 33% of patients

Disorders of serum lipoproteins

- The retinal degeneration is accompanied by decreased visual acuity and night blindness.
- The ERG and the visual-evoked potentials are often abnormal even in the early stages of the disease.
- Somatosensory-evoked potentials were abnormal in some 40% of patients

- Cardiac abnormalities, including irregularities of rhythm, are common.

Disorders of serum lipoproteins

Tangier disease

- is a hereditary disorder of lipid metabolism distinguished by almost complete absence of high-density plasma lipoproteins, reduction of low-density plasma lipoproteins, cholesterol, and phospholipids, normal or elevated triglyceride levels, and storage of cholesterol esters in the reticuloendothelial system of the liver, spleen, lymph nodes, tonsils, and cornea. T
- he name of the disease refers to an island in Chesapeake Bay where the first two patients were found.

Disorders of serum lipoproteins

Tangier disease

- Symptoms usually are limited to enlargement of the affected organs, notably the tonsils (orange).
- Retinitis pigmentosa and peripheral neuropathy have been observed.

- Peripheral neuropathy was noted in nearly 50% of the reported patients.

Disorders of serum lipoproteins

Tangier disease

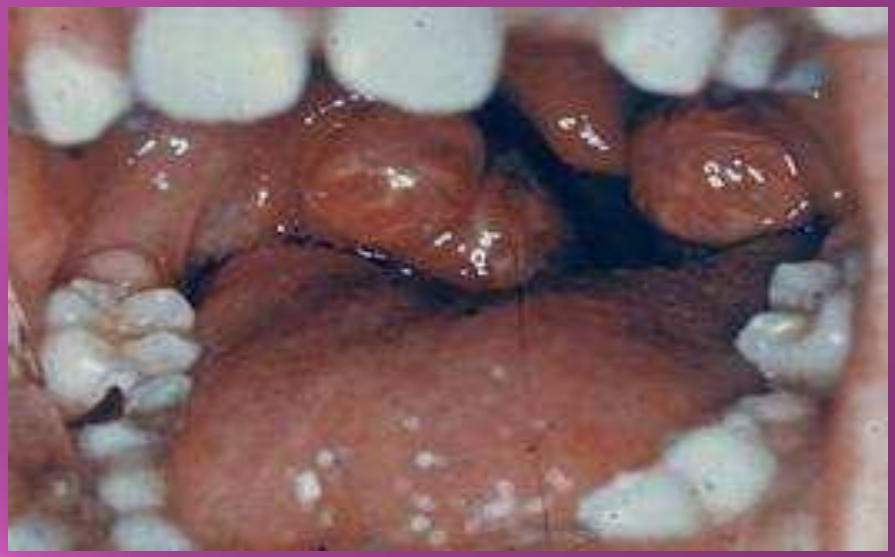
- Nerve biopsy reveals three different types of changes. One group had a multifocal demyelination with large amounts of neutral lipids within Schwann cells, particularly those associated with unmyelinated fibers.

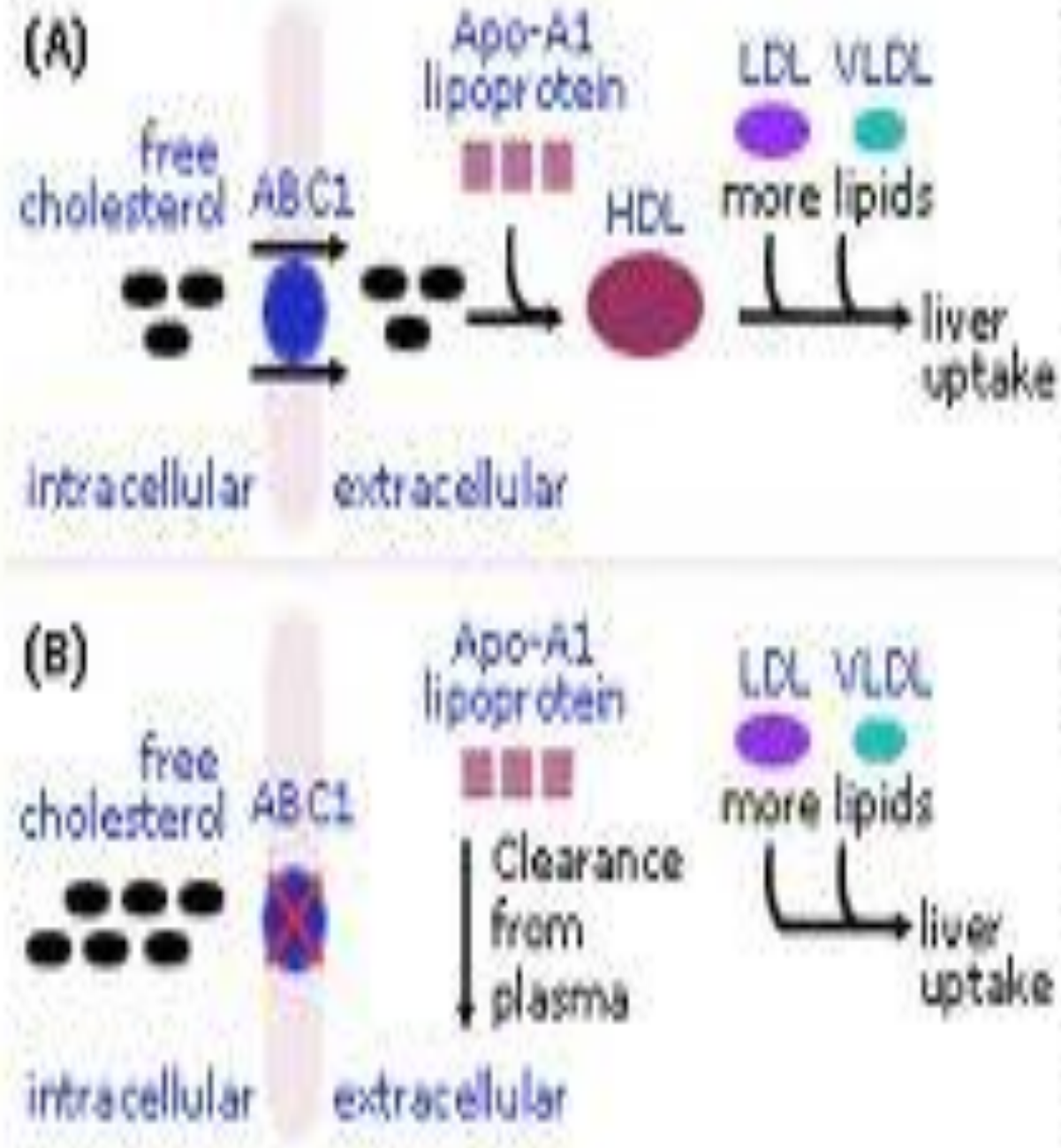
- In another group (whose clinical manifestations include facial weakness, weakness of the small hand muscles, spontaneous pain, and loss of pain and temperature sensations), no demyelination occurs, but lipid is deposited in Schwann cells.

Disorders of serum lipoproteins

Tangier disease

- A third type is a distal sensory neuropathy (862). A syringomyelia-like phenotype has also been encountered.
- The gene has been mapped to chromosome 9q22.
- It codes for ATP-binding cassette transporter 1 (ABCA1), whose function is to bind and promote cellular cholesterol and phospholipid efflux to apolipoprotein I (apoA-I) .





(A) In normal cells ABC1 helps cholesterol exit the cell, where it combines with lipid poor Apo-A1 lipoprotein to form high density lipoprotein (HDL). HDL picks up more lipids from low density (LDL) and very low density (VLDL) lipoproteins and transfers the cholesterol to the liver, where it is processed. **(B)** In Tangier disease, mutations in ABC1 cause cholesterol to accumulate within the cell. [Adapted from Young and Fielding (1999) Nat Genet. Aug;22(4):316-8, with permission.]

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Lysosomal disorders

- Lysosomes are subcellular organelles containing hydrolases with a low optimal pH (acid hydrolases) that catalyze the degradation of macromolecules.

- The lysosomal storage diseases, as first delineated by Hers ,are characterized by an accumulation of undegraded macromolecules within lysosomes. The various groups are named according to the nature of the storage product.

Lysosomal disorders

- They include the glycogen storage diseases (glycogenoses), the mucopolysaccharidoses, the mucolipidoses, the glycoproteinoses, the sphingolipidoses, and the acid lipase deficiency diseases.

- The disease entities result from various single-gene mutations, with each of the enzyme defects induced by one of several different abnormalities on the genomic level.

Lysosomal disorders

GM1-Gangliosidosis	AR	3p21
GM2-Gang. **Taysachs** **Sandhoff,Juv.**	AR	15q23 5q13
Farber disease	AR	8p22

Lysosomal disorders

Niemann-Pick **Type A,B** **Type C**	AR	11p15 18q11
Gaucher disease	AR	1q21

Lysosomal disorders

Refsum	AR	22q11.21 8q21.1
Fabry disease	XL	Xq22

Lysosomal disorders

GM1 gangliosidosis

Deficiency of the lysosomal enzyme β-galactosidase, resulting in accumulation of GM1 gangliosides and other glycoconjugates in the brain and visceral organs.

Lysosomal disorders

GM1 gangliosidosis

There are 3 clinical forms correlating with the degree of residual activity of the mutant enzyme.

The infantile form (type 1) is a severe degenerative encephalopathy presenting between birth and 6 months with coarse facial features, skeletal dysostosis, and hepatosplenomegaly, leading to death within the first 2 years of life.

Lysosomal disorders

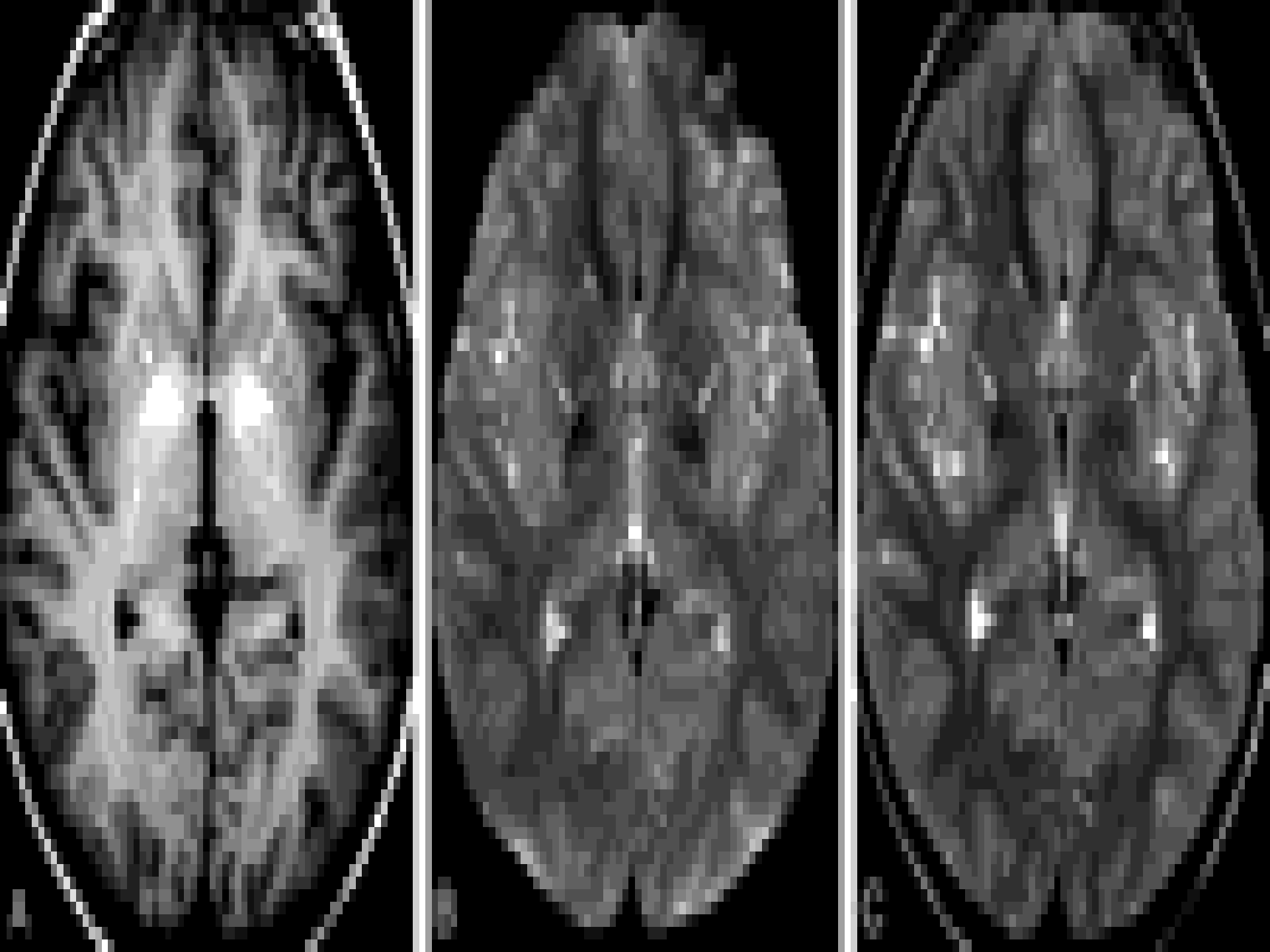
GM1 gangliosidosis

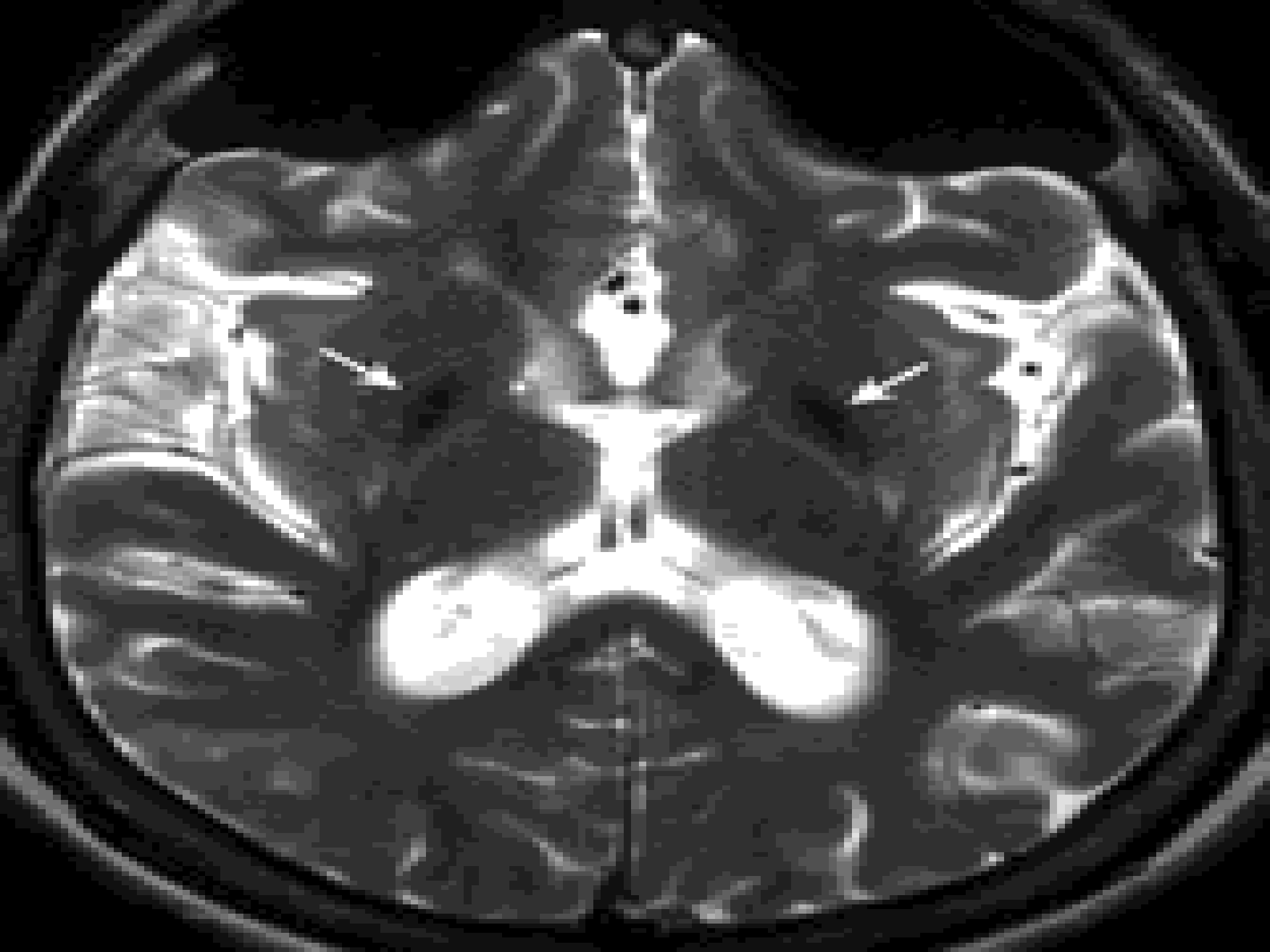
Patients with the late infantile or juvenile form (type 2) present after 1 year of age with motor delay in the absence of dysmorphisms and organomegaly; later, mental deterioration and spastic, cerebellar, and extrapyramidal signs dominate the neurologic picture, probably as a consequence of predominant basal ganglia storage of gangliosides.

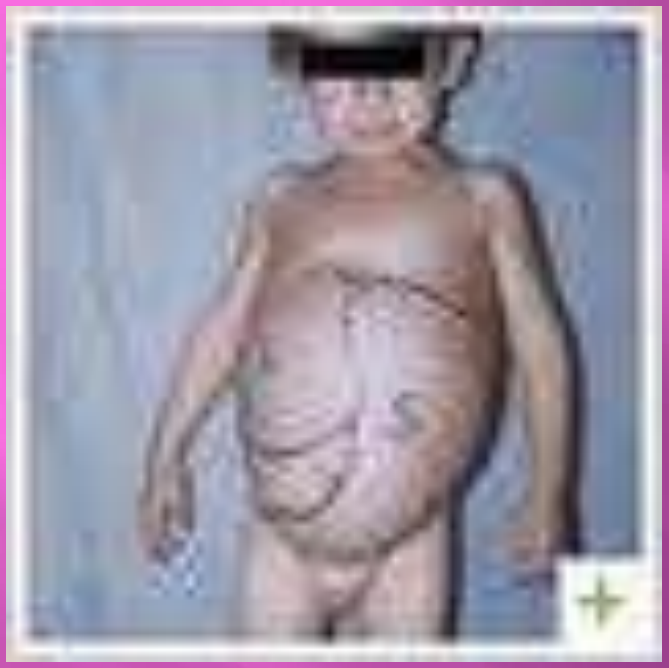
Lysosomal disorders

GM1 gangliosidosis

Reports on the neuroimaging features of the very rare late infantile GM1 gangliosidosis are scant and have mainly included brain atrophy and white matter and basal ganglia abnormalities.







Lysosomal disorders

GM2 gangliosidosis

An accumulation of GM2 gangliosides in neurons and, to a much lesser extent, in other cell types.

Deficiency of hexosaminidase A causes Tay-Sachs disease and late-onset GM2-gangliosidosis.

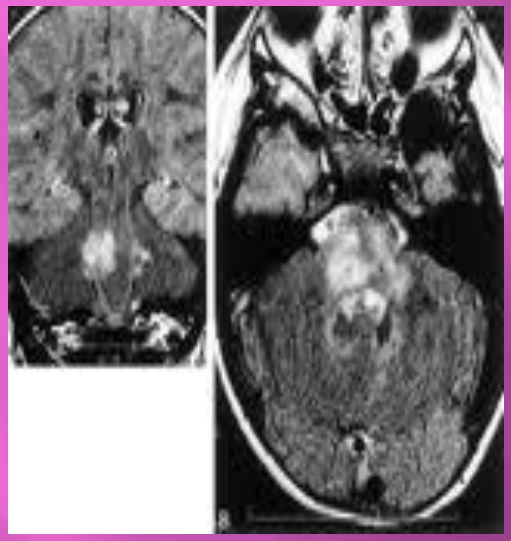
Tay-Sachs disease is the classic infantile form, seen mainly in Ashkenazi Jews.

Lysosomal disorders

GM2 gangliosidosis

The clinical hallmarks include an abnormal startle response and psychomotor deterioration within the first months of life, together with blindness with macular cherry red spots.

GM 2
TAY SACH



Lysosomal disorders

Farber disease

- also known as **Farber's lipogranulomatosis**, **ceramidase deficiency**, "Fibrocytic dysmucopolysaccharidosis," and "Lipogranulomatosis"[is an extremely rare autosomal recessive.
- The clinical features are unique and manifest during the first few weeks of life. The infant becomes irritable, has a hoarse cry, and develops nodular erythematous swelling of the wrists.

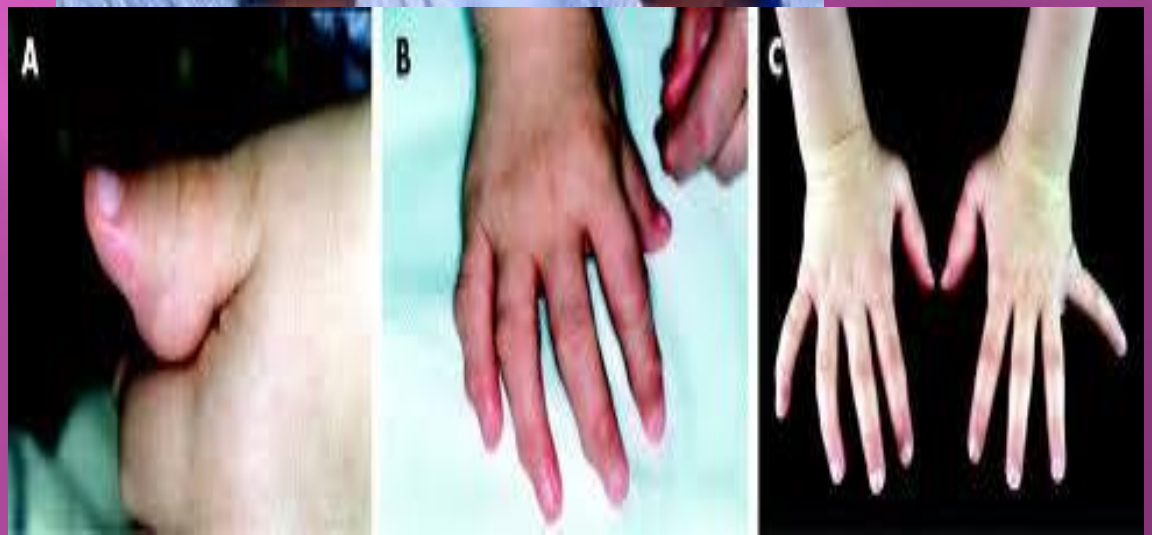
Lysosomal disorders

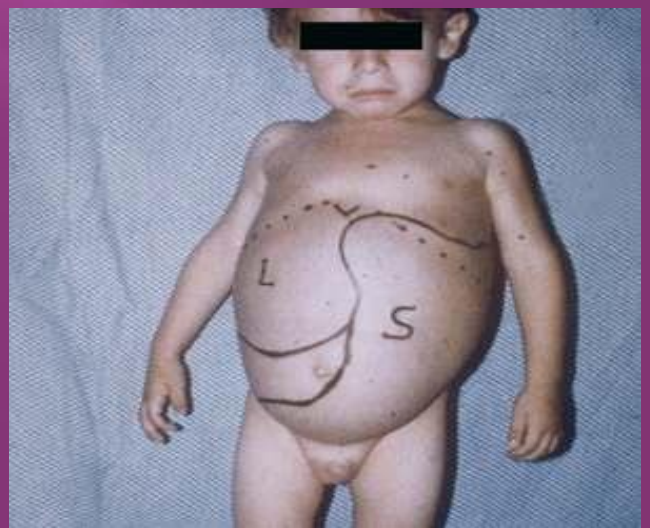
Farber disease

- Over subsequent months, nodules develop in numerous sites, particularly in areas subject to trauma, such as joints and the subcutaneous tissue of the buttocks. Severe motor and mental retardation occur. Hepatosplenomegaly has been seen in approximately 70% of reported cases
- In approximately two-thirds of cases, the disease progresses rapidly, and death usually occurs by 2 years of age.

Lysosomal disorders

Farber Disease





Lysosomal disorders

Fabry's disease

- Fabry's disease is a potentially fatal lyposomal storage disorder which results from deficient activity of alpha-galactosidase A. This multi-system, X-linked recessive disease was first reported in the dermatological literature in 1898.

Lysosomal disorders

Fabry's disease

- A deficiency of the enzyme alpha-galactosidase A causes a build-up of ceramide trihexoside in the kidney and heart vasculature.

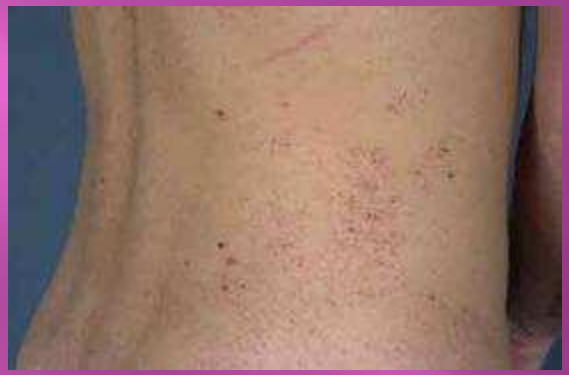
Lysosomal disorders

Fabry's disease

- F; fever
- A angiokeratoma corpus diffusum
- B PN
- R recurrent
- Y young stroke
- S streaks

Fabry disease

This symptomatic female carrior of Fabry's disease shows the classic whorl-like deposits in the basal layer of the corneal epithelium.



A 30-year-old male patient has the distinctive corneal verticillate (whorled streaks) extending to the periphery.

Lysosomal disorders

Fabry's disease

- A galsidase beta (Fabrazyme) has been developed, and seems to be a highly effective therapeutic intervention.

- It is administered IV every two weeks for the life of these affected patients.

Mucopolysaccharidoses

- **Mucopolysaccharidoses** are a group of metabolic disorders caused by the absence or malfunctioning of lysosomal enzymes needed to break down molecules called glycosaminoglycans - long chains of sugar carbohydrates.

- Glycosaminoglycans (formerly called mucopolysaccharides) are also found in the fluid that lubricates joints.

Mucopolysaccharidoses

- People with a mucopolysaccharidosis disease either do not produce enough of one of the 11 enzymes required to break down these sugar chains into simpler molecules, or they produce enzymes that do not work properly.
- Over time, these glycosaminoglycans collect in the cells, blood and connective tissues.
- The result is permanent, progressive cellular damage which affects appearance, physical abilities, organ and system functioning, and, in most cases, mental development.

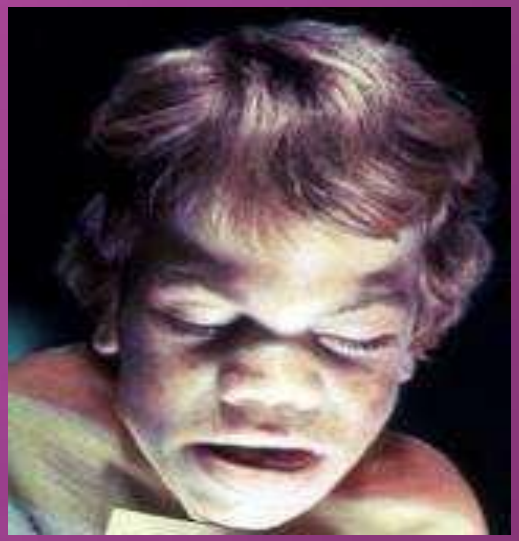
Mucopolysaccharidoses

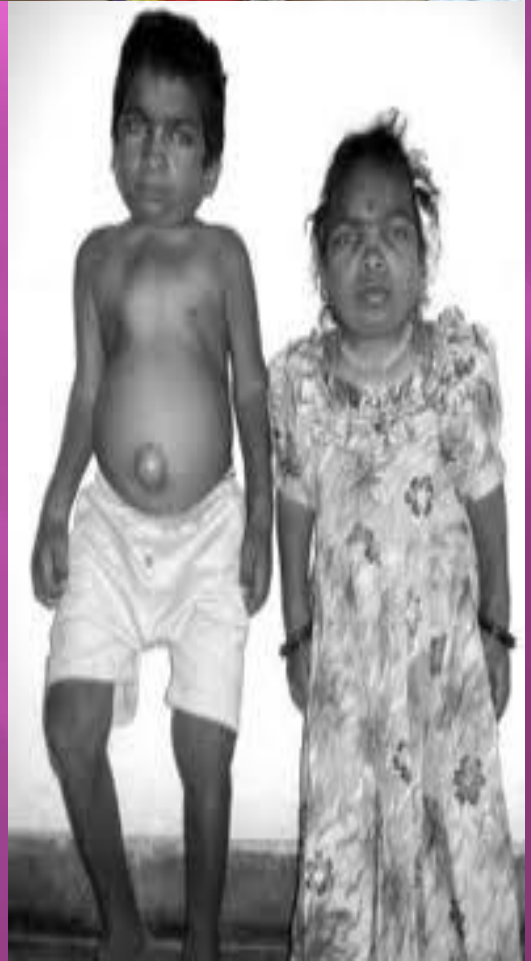
MPS I-H I-S	AR	4p16
MPS II-XR	XR	Xq23
MPS III-A	AR	17q25
MPS III-B	AR	17q27
MPS 1V-A	AR	16q24
MPS V	AR	5q
MPS VII	AR	7q

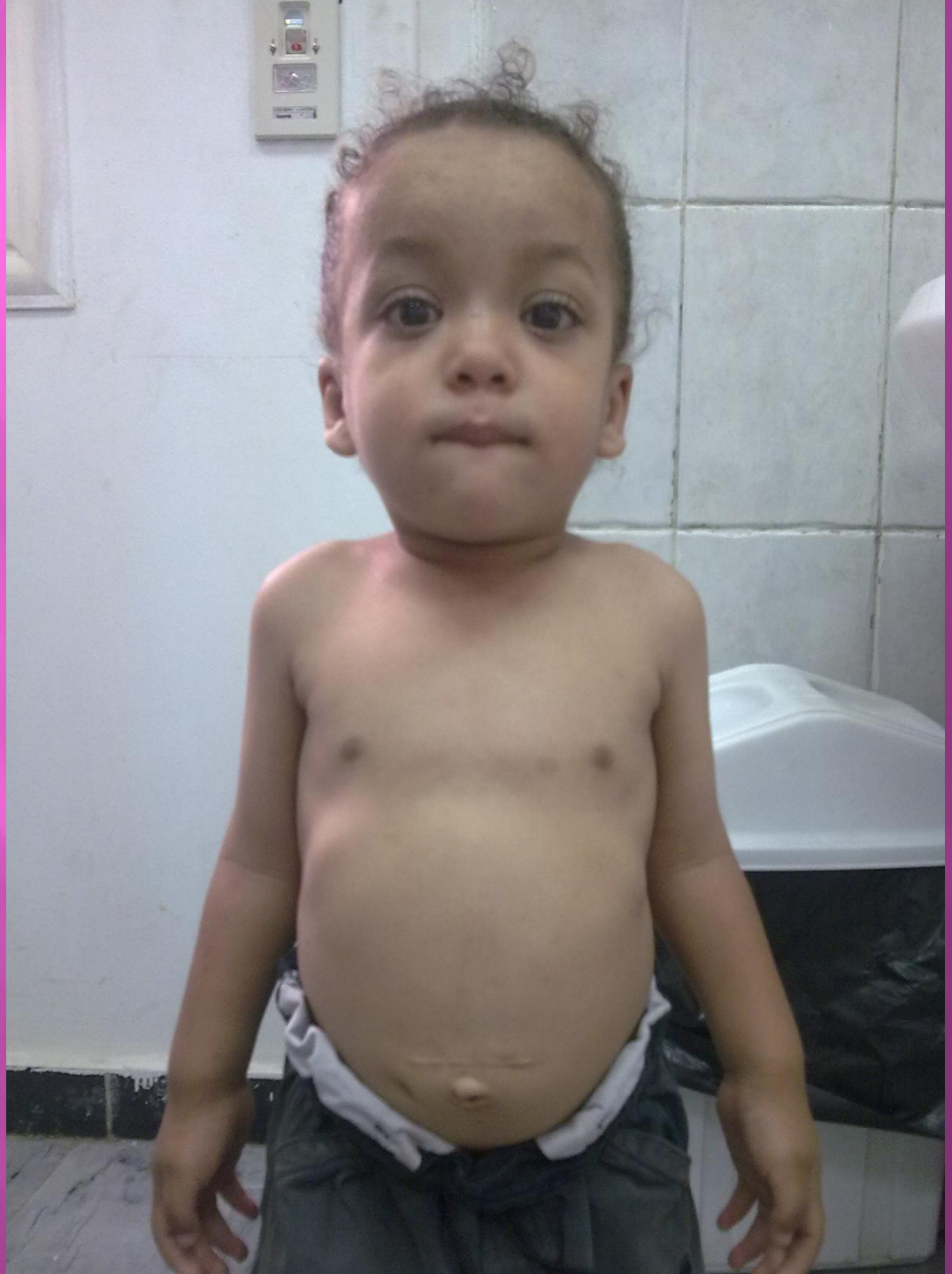
Patients With Maroteaux-Lamy Syndrome (MPS VI).
This inherited disease is estimated to affect about 1,100 people worldwide.

The eyes are widely spaced.
The bridge of the nose is flat
the lips are large.
Corneal cloud
The mouth is open and an almost constant nasal obstruction or upper respiratory infection exists.


醜豆豆 大夢想







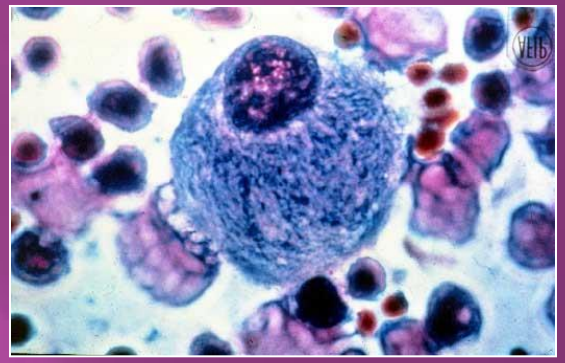
Lysosomal disorders

Mucolipidosis

- Mucolipidoses have the clinical features of both the mucopolysaccharidoses and the lipidoses. At least four mucolipidoses have been distinguished, characterized by MPS storage despite normal excretion of MPS. All of them are rare.

Type	Name	Enzyme Defect	Storage Material	Genetics	Age of Onset
Pelizaeus-Merzbacher Syndrome					
1	Classical	Proteolipid protein	Sudanophilic material	X-linked	Infantile
2	Connatal Seitelberger's disease	Not known	Sudanophilic material	Not known	Birth
3	Transitional disease	Not known	Sudanophilic material	Sporadic	Infantile
4	Adult Lowenberg-Hull	Not known	Sudanophilic material	Autosomal	Adult
5	Variant	Not known	Sudanophilic material	Not known	Variable
Cockayne's Syndrome					
6	Classic	DNA repair	Sudanophilic material	Autosomal	6 to 12 months
Alexander's Syndrome					
7	Classic infantile	GFAP	GFAP	Sporadic	Infants
8	Juvenile	GFAP	GFAP	Autosomal	Children 7 to 14
9	Adult	GFAP	GFAP	Autosomal	Young adults
Canavan's Syndrome					
10	Classic infantile	Aspartoacylase	*N*-acetylaspartate in	Autosomal	Infants
11	Neonatal	Aspartoacylase	*N*-acetylaspartate in	Sporadic	Newborns
12	Juvenile	Aspartoacylase	*N*-acetylaspartate in	Sporadic	Children 5 to teenage
Krabbe's Syndrome					
13	Classic, infantile	Galactocerebroside β-	Galactocerebroside	Autosomal	Infants
14	Late onset	Galactocerebroside β-	Galactocerebroside	Autosomal	Usually childhood,
Metachromatic Leukodystrophy					
15	Greenfield's, classical, or late	Arylsulfatase or SAP-B	Sulfatide	Autosomal	Late infantile 1 to 24
16	Scholz's	Arylsulfatase A	Sulfatide	Autosomal	Juvenile 4 to 10 years
17	Austin's	Arylsulfatase A	Sulfatide	Autosomal	Adult
Adrenoleukodystrophy					
18	Multiple peroxisomal enzyme	Peroxins (1, 2, 5, 6, 12)	Excessive very long-chain	Autosomal	Neonatal
19	Ulrich's disease	Acyl-CoA oxidase	Excessive very long-chain	Autosomal	Neonatal
	Pseudoneonatal adrenoleukodystrophy (NALD)				
20	X-linked Siemerling-Creutzfeldt's	ABC protein	Excessive very long-chain fatty acids	X-linked recessive	Childhood onset is classic

HISTORY OF THE LSDs



Gaucher cell 1882

Ernest GAUCHER (1854-1919)

History of the LSDs

- Symptoms of some LSDs were described as early as the 1880s,
- Many had been described and classified before the lysosome was discovered in 1955 and before their biochemical and genetic basis was fully understood
- This is why they received common names (i.e.: Gaucher disease, name of discovering physician).
- Later, an additional, more clinically descriptive name often came into use (glucocerebrosidase deficiency)

History of the LSDs

- By the 1960s the role of lysosomes in cellular digestion and substrate management was well understood,
- Pompe became the first disease formally recognized as a lysosomal storage disorder.
- By the 1970s scientists had recognized many more LSDs as such and had begun identifying and classifying the specific enzymatic problems.

LSD Sub-Categories

- **When a lysosomal enzyme (or another protein that directs it) is deficient or malfunctioning, the substrate it targets accumulates, interfering with normal cellular activity.**

Healthy cell vs. LSD cell with accumulated substrate

LSD Sub-Categories

- **Sub-categories are based on the type of enzymatic defect and/or stored substrate product.**
- **For example, the mucopolysaccharidoses (MPS) are grouped together because each results from an enzyme deficiency that causes accumulation of particular glycosaminoglycan (GAG) substrates.**

and diseases that fall under them

I - Defective metabolism of glycosaminoglycans " the mucopolysaccharidoses"

MPS I (Hurler, Hurler-Scheie, Scheie)

MPS II (Hunter)

MPS III (San filipo Types A,B,C and D)

MPS IV (Morquio type A and B)

MPS VI (Maroteaux-Lamy)

MPS VII (Sly)

MPS IX (Hyaluronidase deficiency)

Multiple Sulfatase deficiency

II - Defective degradation of glycan portion of glycoproteins

Aspartylglucosaminuria

Fucosidosis, type I and II

Mannosidosis

Sialidosis, type I and II

III - Defective degradation of glycogen

Pompe disease

IV - Defective degradation of sphingolipid components

Acid sphingomyelinase deficiency (Niemann-Pick A & B)

Fabry disease

Farber disease

Gaucher disease, type I, II and III

GM1 gangliosidosis, type I, II and III

GM2 gangliosidosis (Tay-Sachs type I, II, III and Sandhoff

Krabbe disease

Metachromatic leukodystrophy, type I, II and III

V - Defective degradation of polypeptides

Pycnodysostosis

VI - Defective degradation or transport of cholesterol, cholesterol esters, or other complex lipids

Neuronal ceroid lipofuscinosis, type I, II, III and IV

VII - Multiple deficiencies of lysosomal enzymes

Galactosialidosis

Mucolipidosis, type II and III

VIII - Transport and trafficking defects

Cystinosis

Danon disease

Mucolipidosis type IV

Niemann-Pick type C

Infantile sialic acid storage disease

Salla disease

Lysosomal disorders

Mucolipidosis

- As in all other lysosomal disorders, considerable clinical and biochemical heterogeneity exists.
- The clinical and radiologic features of this autosomal recessive disorder are reminiscent of Hurler syndrome, although in distinction, I-cell disease is apparent at birth.
- Features seen in the affected newborn include hypotonia, coarse facial appearance, striking gingival hyperplasia, congenital dislocation of the hips, restricted joint mobility, and tight, thickened skin.

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Lysosomal disorders

Mucolipidosis

- Radiographic changes of dysostosis multiplex develop between 6 and 10 months of age, although periosteal cloaking can occur even prenatally.
- Subsequently, growth failure, microcephaly, and progressive mental deterioration become apparent. Hepatomegaly and corneal clouding are inconstant. Most patients die during childhood.

Lysosomal disorders

Mucolipidosis

- Nonimmune hydrops fetalis can be seen in some pregnancies. Bone marrow transplantation has shown some promise.

Lysosomal disorders

Mucolipidosis

- In ML II and ML III, a number of lysosomal enzymes are elevated markedly in plasma and deficient in fibroblasts. Enzyme levels in liver and brain are normal.
- ML III is a milder form of ML II. In this condition, the defect in the phosphorylation of mannose is also defective, although to a lesser degree than in ML II, and the activity of N-acetylglucosaminyl-1-phosphotransferase is considerably reduced.

Lysosomal disorders

Mucolipidosis

- Symptoms of ML III do not become apparent until after age 2 years, and learning disabilities or mental retardation are mild. Restricted mobility of joints and growth retardation occur. Radiographic examination shows a pattern of dysostosis multiplex with severe pelvic and vertebral abnormalities. Fine corneal opacities and valvular heart disease are occasionally present.

Lysosomal disorders

Mucolipidosis

- The disease can be diagnosed by the presence of elevated lysosomal enzymes in plasma. Prolonged survival is possible but complicated by osteopenia, which may respond to bisphosphonates.

- ML IV is a relatively common disease in Ashkenazi Jews with the estimated heterozygote frequency being 1/100.

Lysosomal disorders

Sialidosis :

- Two clinical forms of sialidosis are recognized. In type I sialidosis (cherry-red spot myoclonus syndrome), the milder form of the disease, neurologic symptoms begin after age 10 years.

- Initially, these include diminished visual acuity (notably night blindness), a macular cherry-red spot, ataxia with gait abnormalities, nystagmus, and myoclonic seizures.
- Neuropathy and punctate lenticular opacities also can be present .
- Patients do not have dysmorphic features or deterioration of intelligence and have a normal life span.

Lysosomal disorders

Sialidosis :

- Type II, the severe, congenital form of primary neuraminidase deficiency with dysmorphic features, is characterized by hepatosplenomegaly, corneal opacifications, dysostosis multiplex, hydrops fetalis, ascites, and a pericardial effusion. The condition is rapidly fatal.

- Pathologic examination of the brain discloses membrane-bound vacuoles in cortical neurons and Purkinje cells and zebra bodies in spinal cord neurons.

- Vacuoles are also seen in the glomerulus and tubular epithelial cells of the kidney and in hepatocytes, endothelial cells, and Kupffer cells of the liver

Lysosomal disorders

Sphingolipidoses

•This group of disorders includes a number of hereditary diseases characterized by an abnormal sphingolipid metabolism, which in most instances leads to the intralysosomal deposition of lipid material within the CNS.

•Clinically, these conditions assume a progressive course that varies only in the rate of intellectual and visual deterioration.

Lysosomal disorders

Gaucher's disease

Gaucher's disease is the most common of the lysosomal storage diseases.

It is caused by a hereditary deficiency of the enzyme glucocerebrosidase (also known as acid β-glucosidase).

The enzyme acts on a fatty substance glucocerebroside (also known as glucosylceramide).

When the enzyme is defective, glucocerebroside accumulates, particularly in white blood cells (mononuclear leukocytes).

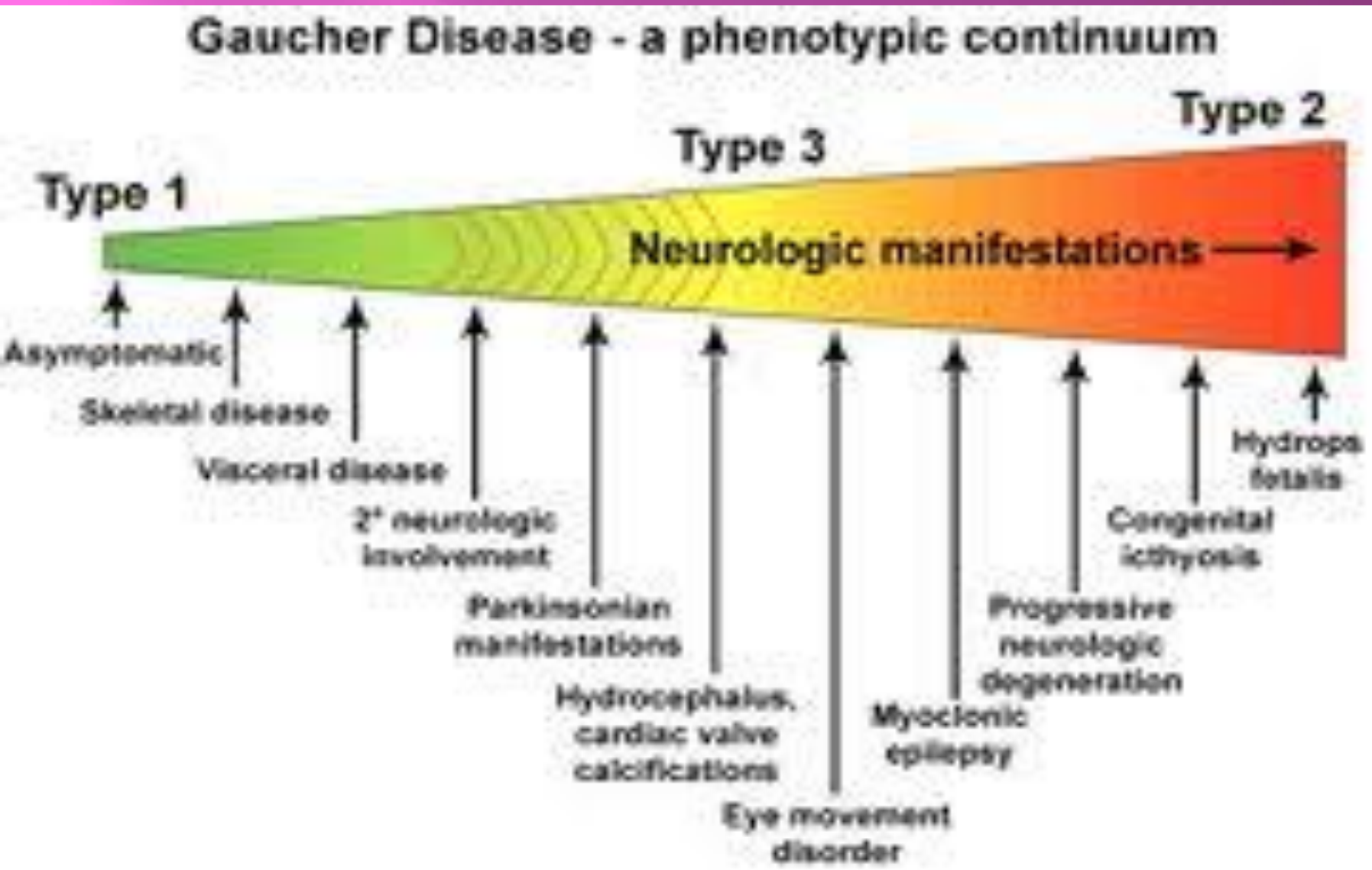
Lysosomal disorders

Gaucher's disease

- Painless hepatomegaly and splenomegaly; the size of the spleen can be 1500-3000 ml, as opposed to the normal size of 50-200 ml.

- Hypersplenism: the rapid and premature destruction of blood cells, leading to anemia, neutropenia and thrombocytopenia (with an increased risk of infection and bleeding).

- Cirrhosis of the liver is rare.



Patients with Gaucher disease can have a spectrum of symptoms, ranging from mild to severe neurological effects. The classic categories of types 1, 2 and 3 have blurry edges along this continuum.

Lysosomal disorders

Gaucher's disease

- Neurological symptoms occur only in some types of Gaucher's (see below):
  - Type II: serious convulsions, hypertonia, mental retardation, apnea.
  - Type III: muscle twitches known as myoclonus, convulsions, dementia, ocular muscle apraxia.
- Osteoporosis: 75% develop visible bony abnormalities due to the accumulated glucosylceramide. A deformity of the distal femur in the shape of an Erlenmeyer flask is commonly described (aseptic necrosis of the femur joint).
- Yellowish-brown skin pigmentation

Lysosomal disorders

Gaucher's disease

- A definitive diagnosis is made with genetic testing. As there are numerous different mutations, sequencing of the beta-glucosidase gene is sometimes necessary to confirm the diagnosis. Prenatal diagnosis is available, and is useful when there is a known genetic risk factor.

Lysosomal disorders

Gaucher's disease

- A diagnosis can also be implied by biochemical abnormalities such as high alkaline phosphatase, angiotensin-converting enzyme (ACE) and immunoglobulin levels, or by cell analysis showing "crinkled paper" cytoplasm and glycolipid-laden macrophages.

- Some lysosomal enzymes are elevated, including tartrate-resistant acid phosphatase, hexosaminidase, and a human chitinase, chitotriosidase. This latter enzyme has proved to be very useful for monitoring Gaucher's disease activity in response to treatment, and may reflect the severity of the disease

Lysosomal disorders

Gaucher's disease:

- For type 1 and most type 3 patients, enzyme replacement treatment with intravenous recombinant glucocerebrosidase (imiglucerase) can dramatically decrease liver and spleen size, reduce skeletal abnormalities, and reverse other manifestations.
- Due to the low incidence, this has become an orphan drug in many countries
- Velaglucerase alfa was approved by the Food and Drug Administration (FDA) as an alternative treatment on February 26, 2010

Lysosomal disorders

Gaucher's disease:

- .
- Miglustat is one of these oral drugs. It was approved for the treatment of this disease in 2003. As of June 2009[update], another oral drug, isofagomine tartrate, is under development.
- bone marrow transplantation cures the non-neurological manifestations of the disease

Lysosomal disorders

Wolman Disease

(Acid Lipase DeficiencyDisease).

- AR,10q23.2.
- Acid lipase deficiency → lack the ability to hydrolyze cholesterol esters entering the cells bound to low-density lipoproteins.

- The clinical manifestations resemble those of NPA and include failure in weight gain, a malabsorption syndrome, and adrenal insufficiency.

Lysosomal disorders

Wolman Disease:

- Lipoproteins and plasma cholesterol are reduced and acanthocytes are evident .

- A massive hepatosplenomegaly occurs, and radiographic examination reveals the adrenals to be calcified. Neurologic symptoms are usually limited to delayed intellectual development.

- Pathologic examination shows xanthomatosis of the viscera. Sudanophilic material is stored in the leptomeninges, retinal ganglion cells, and nerve cells of the myenteric plexus. Sudanophilic granules.

Classification

- Disorders of amino acid metabolism
- Disorders of renal amino acid transport
- Disorders of carbohydrate metabolism and transport
- Carbohydrate-deficient protein syndromes
- Organic acidurias
- Disorders of fatty acid oxidation
- Disorders of purine and pyrimidine metabolism
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Peroxisomal Disorders

- Peroxisomes are ubiquitous organelles containing more than 50 enzymes involved in anabolic and catabolic reactions, including plasmalogen and bile acid biosynthesis, gluconeogenesis, the removal of excess peroxides, purine catabolism, and Î²-oxidation of very long chain fatty acids.

- Peroxisomes do not contain DNA, and peroxisomal matrix and membrane proteins, therefore, must be imported from the cytosol where they are synthesized.

Peroxisomal Disorders

- At least 20 disorders of peroxisomal function have been identified. They can be classified into two groups.
- In group 1, a disorder of peroxisome biogenesis, the number of peroxisomes is reduced and the activities of many peroxisomal enzymes are deficient.
- Zellweger cerebrohepatorenal syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease belong to this group.

Peroxisomal Disorders

- In group 2, peroxisomal structure and function are normal, and the defect is limited to a single peroxisomal enzyme. At least 13 disorders exist in which a single peroxisomal enzyme is defective.

- X-linked adrenoleukodystrophy, in which peroxisomal fatty acid Î²-oxidation is defective, and adult Refsum disease, in which phytanic acid oxidation is deficient, belong to this group.

Peroxisomal Disorders

Zellweger Syndrome

The differentiation of the disorders of peroxisomal biogenesis into Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease is not based on a fundamental genetic difference but on the severity of the disease, with Zellweger syndrome the most severe and infantile Refsum disease the least severe.

Peroxisomal Disorders

Zellweger Syndrome

- All three entities are autosomal recessive disorders, with the Zellweger form having a frequency of 1 in 100,000 births. Several genetic defects cause the disorders of peroxisomal biogenesis.
- Mutations in either one of two adenosinetriphosphatases (ATPases), peroxin 1 (PEX1) and peroxin 6 (PEX6), are common causes of these disorders

Peroxisomal Disorders

Zellweger Syndrome

- The gene for PEX1, which is responsible for about two-thirds of patients with Zellweger syndrome.

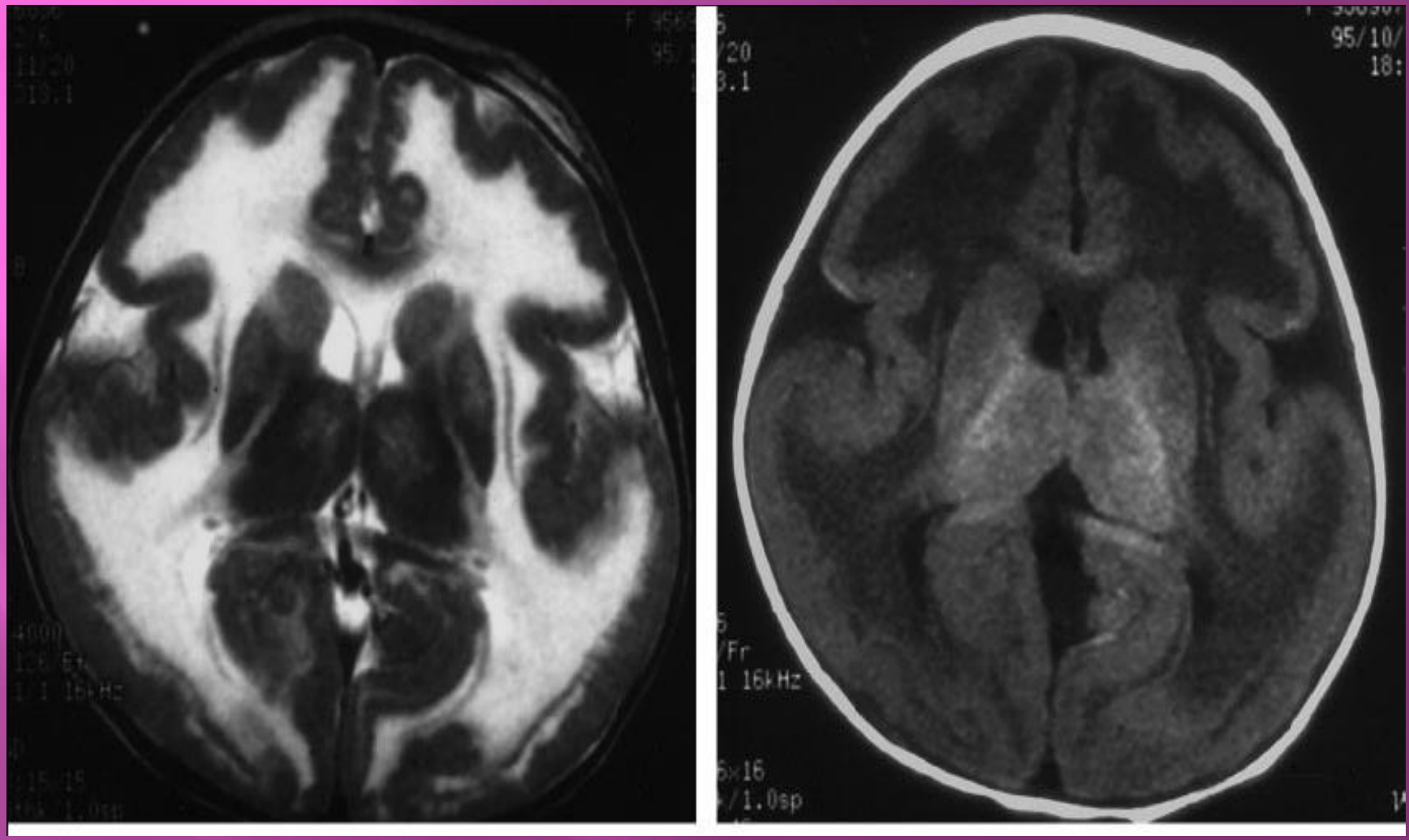
- encodes a 147-kd member of the AAA protein family (ATPases associated with diverse cellular activities), and at least 30 mutations of this gene have been recorded

Peroxisomal Disorders

Zellweger Syndrome

- PEX1 is believed to interact with PEX6, a different member of the AAA protein family, and the two proteins are active in the import of protein into the peroxisomal matrix. At least seven other genetic mutations have been delineated .
- The phenotypic severity of Zellweger syndrome appears to correlate well with the gene defect, in that mutations with the most significant loss of protein function result in the most severe clinical symptoms.

Zellweger syndrome



Peroxisomal Disorders

Neonatal Adrenoleukodystrophy and Infantile Refsum Disease

- These two entities represent less severe expressions of disordered peroxisomal biogenesis. Neonatal adrenoleukodystrophy is an autosomal recessive disease.
- contrast to the X-linked adrenoleukodystrophy of later onset, with symptoms becoming apparent during the first 3 months of life.
- It is marked by dysmorphic features, hearing deficit, hypotonia, hepatomegaly, seizures, and retinal degeneration.

Peroxisomal Disorders

- The clinical features of infantile Refsum disease are similar. They include a sensorineural hearing loss, retinitis pigmentosa, and mental retardation. Facial dysmorphism and hypotonia are less marked, and neonatal seizures are less common than in Zellweger syndrome .
- As in Zellweger syndrome, serum phytanic acid, pipecolic acid, and very long chain fatty acids are present in increased amounts in plasma, and urinary pipecolic acid is elevated

Peroxisomal Disorders

- The diagnosis of these conditions is best made by assay of plasma very long chain fatty acids and can be confirmed by phytanic acid and pipecolic acid determinations in plasma or urine .
- Morphologic examination of established fibroblast cultures or tissue obtained by liver biopsy is also of diagnostic assistance

Peroxisomal disorders

Refsum's disease:

- **Refsum disease**, also known as classic or adult Refsum disease, heredopathia atactica polyneuritiformis, phytanic acid oxidase deficiency and phytanic acid storage disease,[is an autosomal recessive neurological disease that results from the over-accumulation of phytanic acid in cells and tissues.

- It is one of several disorders named after Norwegian neurologist Sigvald Bernhard Refsum (1907–1991).

Peroxisomal disorders

Refsum's disease:

Biological sources of phytanic acid

- In ruminant animals, the gut fermentation of consumed plant materials liberates phytol, a constituent of chlorophyll, which is then converted to phytanic acid and stored in fats.
- Although humans cannot derive significant amounts of phytanic acid from the consumption of chlorophyll present in plant materials, it has been proposed that the great apes (bonobos, chimpanzees, gorillas, and orangutans) can derive significant amounts of phytanic acid from the hindgut fermentation of plant materials.

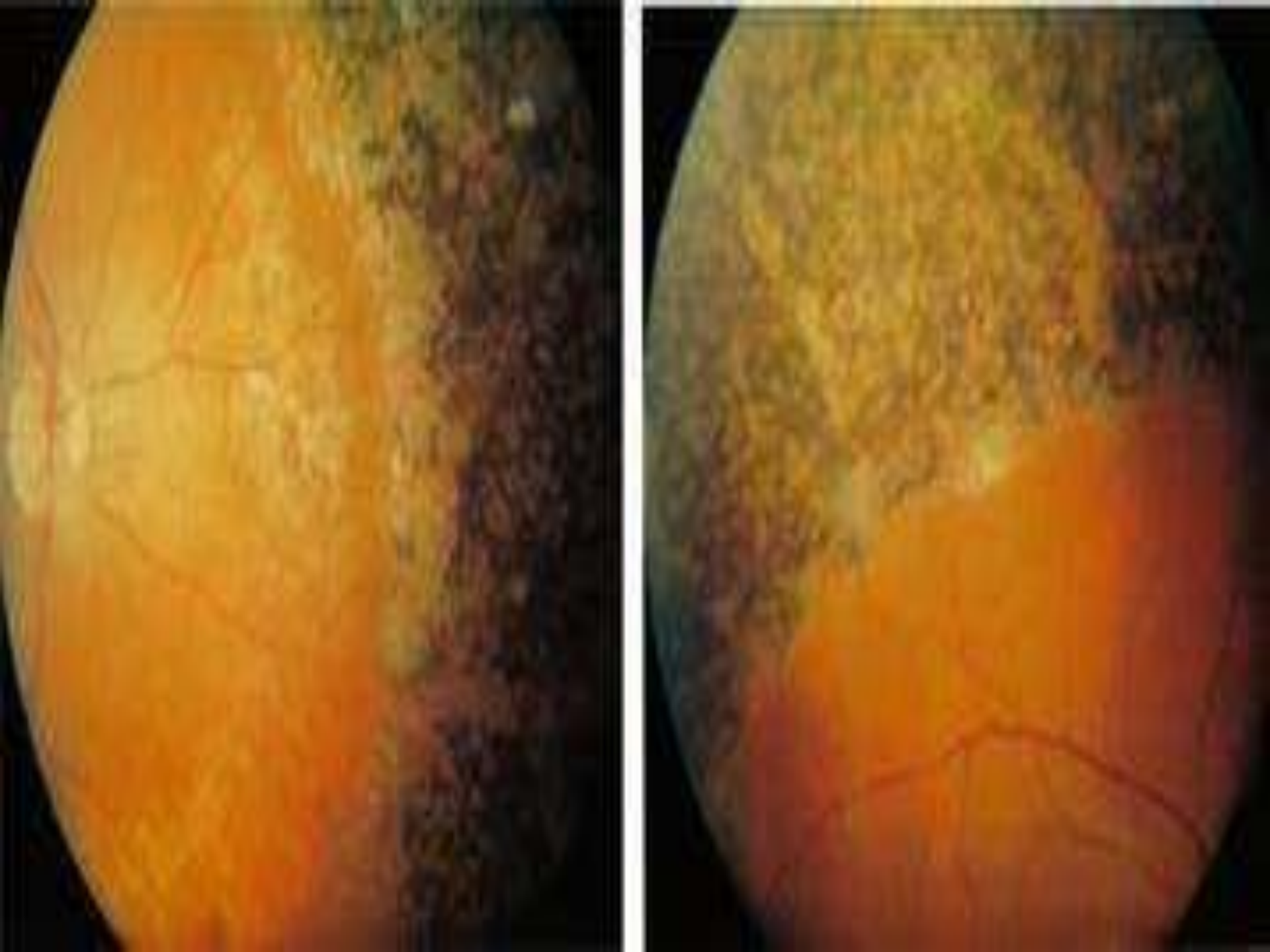
Peroxisomal disorders

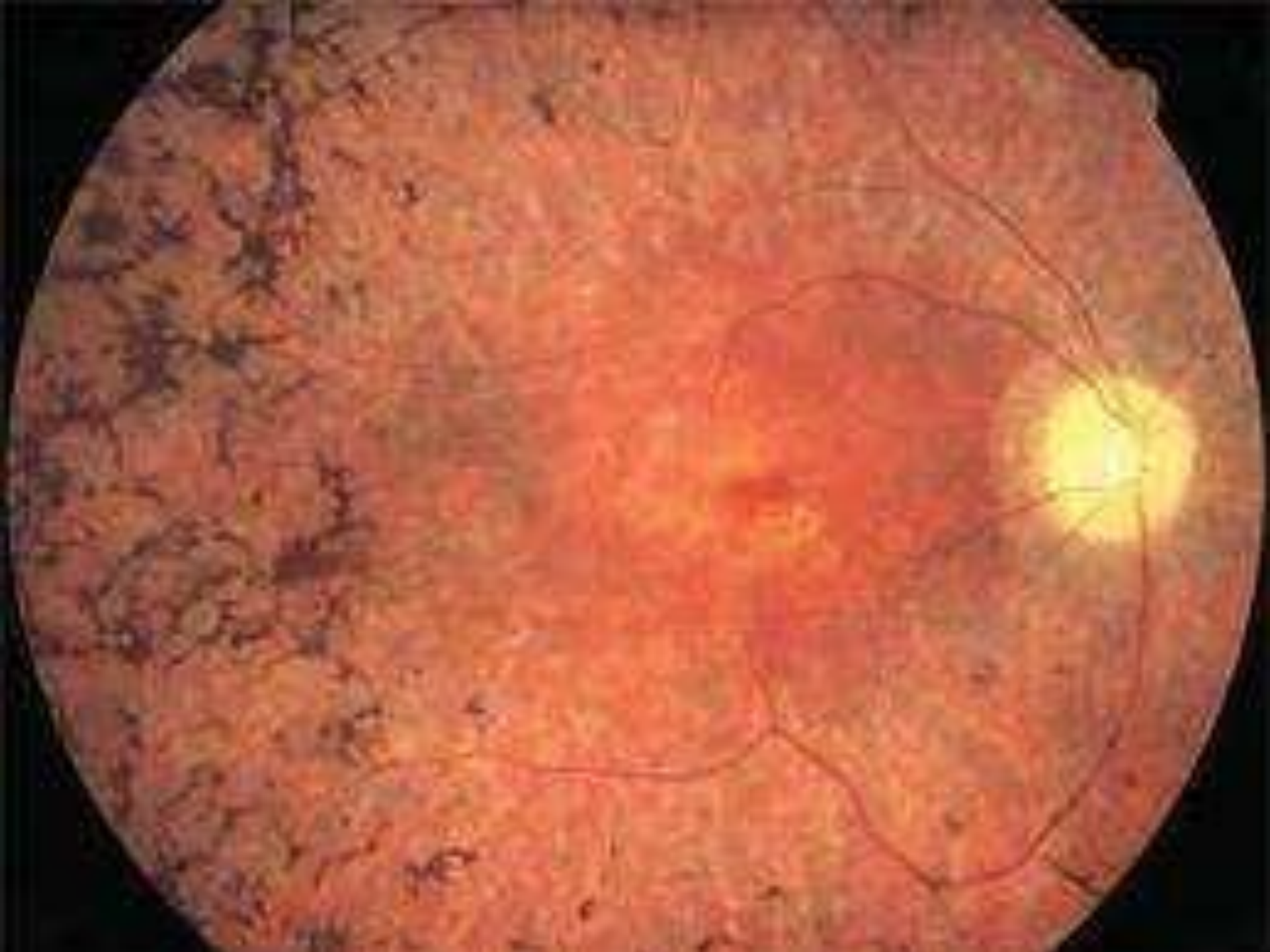
Refsum's disease:

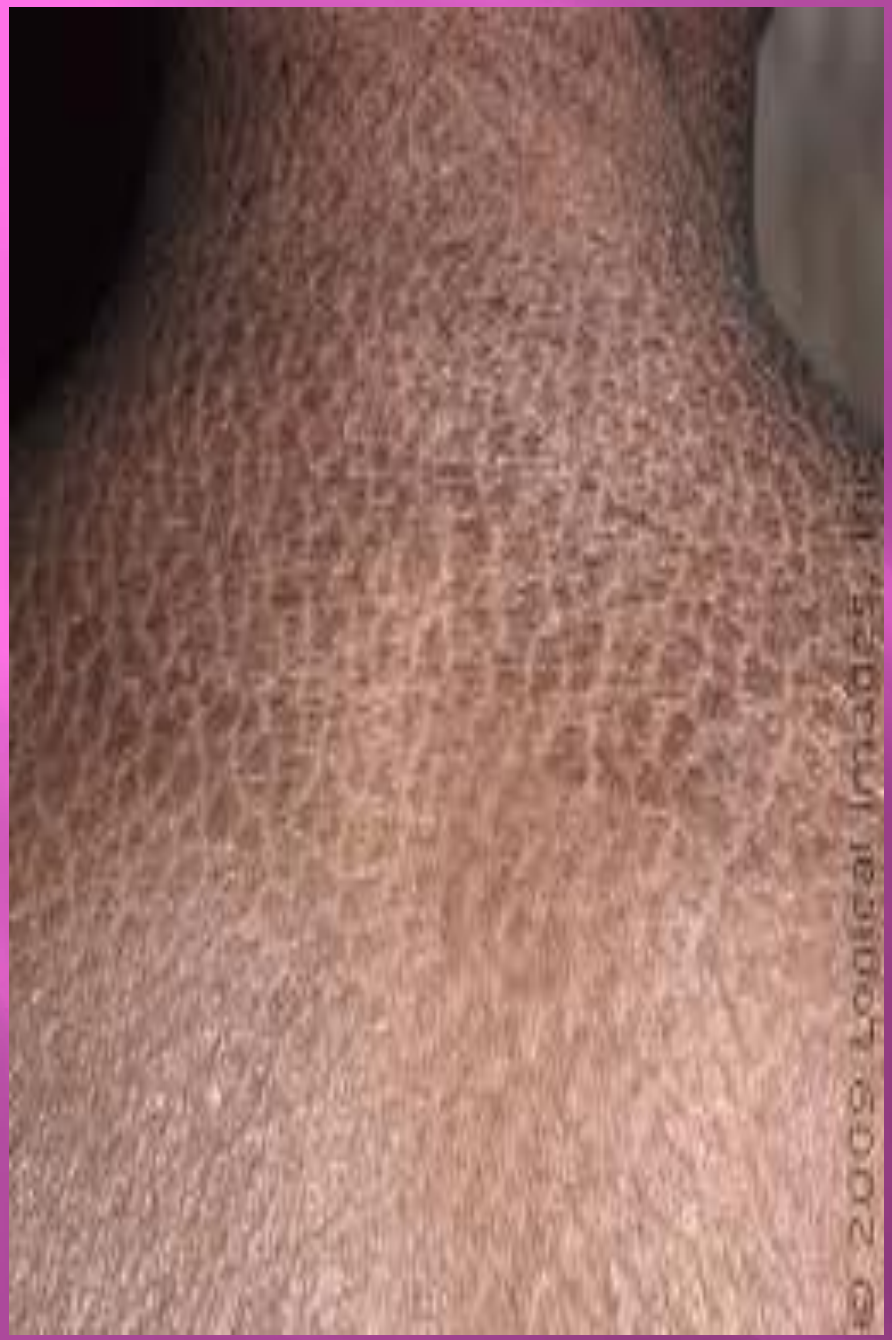
- Individuals with Refsum disease are commonly placed on a phytanic acid-restricted diet and avoid the consumption of fats from ruminant animals and certain fish.

- Recent research has shown that CYP4 isoform enzymes could help reduce the over-accumulation of phytanic acid *in vivo*.

- Plasmapheresis is another medical intervention used to treat patients.



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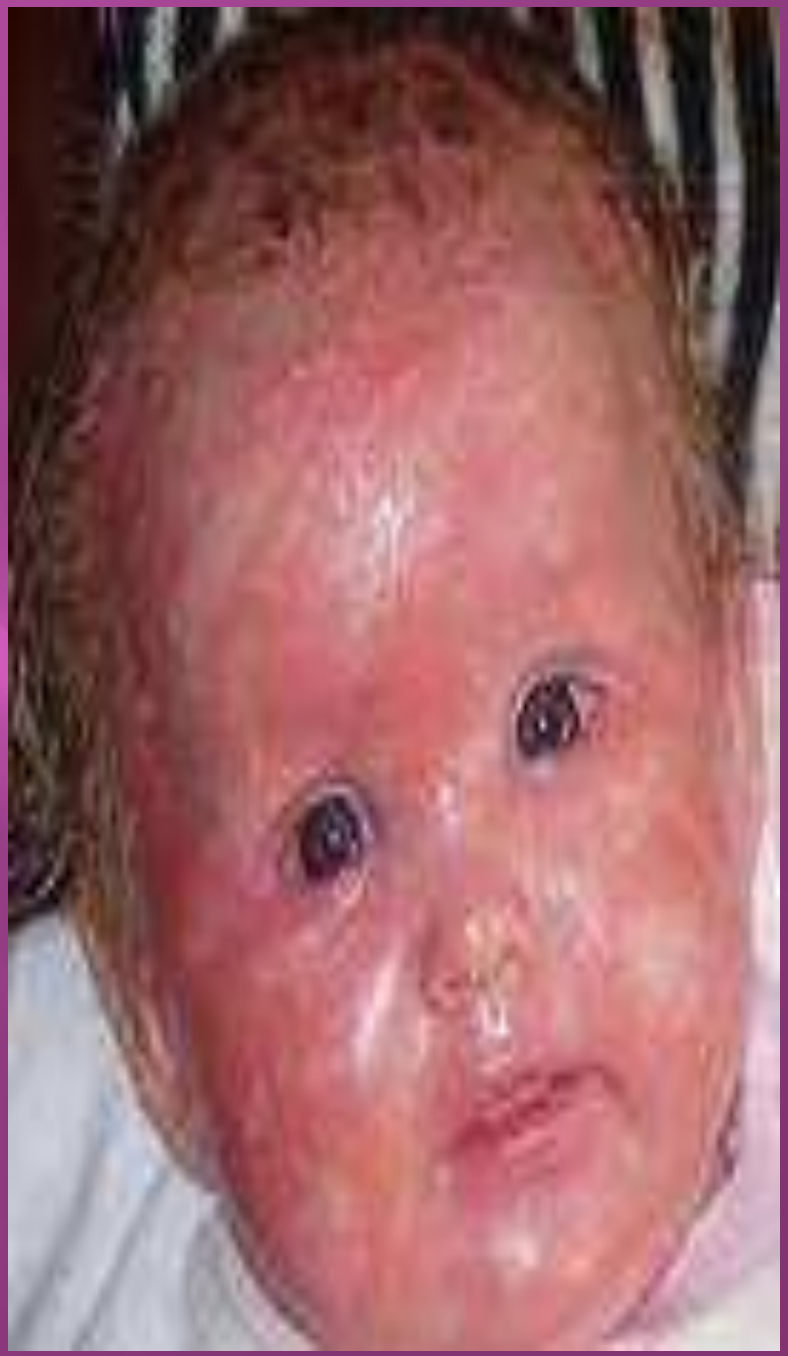

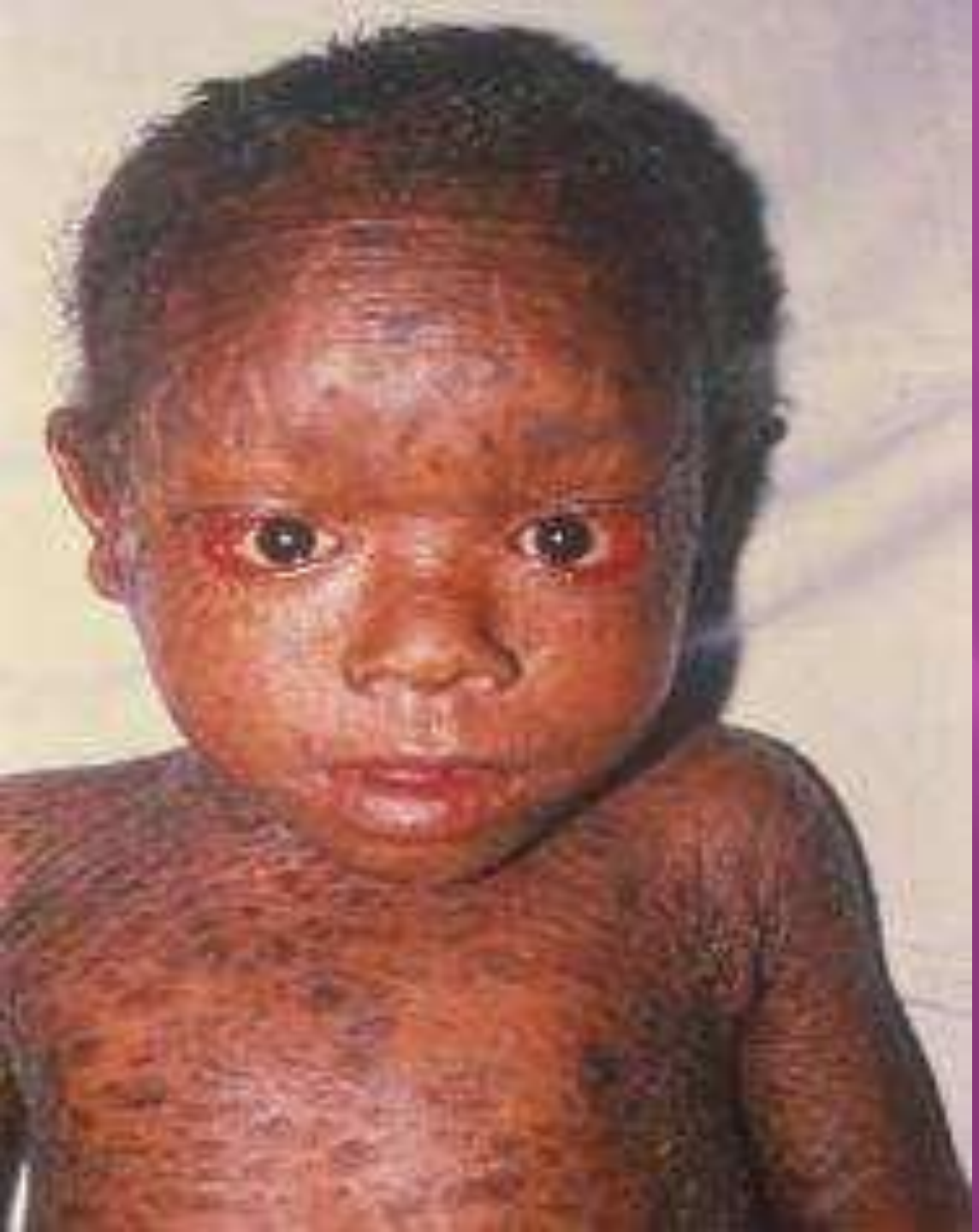

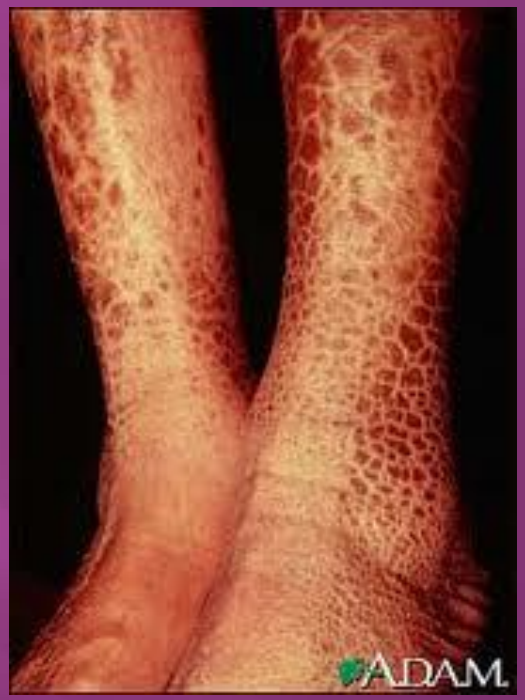
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Disorders Of Metal Metabolism

- **Wilson Disease (Hepatolenticular Degeneration).**
- **Aceruloplasminemia.**
- **Menkes Disease.**
- **Molybdenum Cofactor Deficiency**

Disorders of metal metabolism

Aceruloplasminemia:

- It is due to a mutation in the gene that codes for ceruloplasmin, which acts as a ferroxidase, mediating oxidation of ferrous to ferric iron.
- The clinical picture of aceruloplasminemia is one of dementia, diabetes, ataxia, and extrapyramidal movements.
- MRI and neuropathologic examinations demonstrate iron deposition in the basal ganglia. The condition has its onset in middle age, and to our knowledge has not been reported in the pediatric population.

Disorders of metal metabolism

Menkes Disease :

- (Kinky Hair Disease, KHD)
- This focal degenerative disorder of gray matter was described in 1962 by Menkes and associates (908). It is transmitted as an X-linked disorder.
- KHD is a rare disorder; its frequency has been estimated at 1 in 114,000 to 1 in 250,000 live births

Disorders of metal metabolism

Menkes Disease :

- Patients absorb little or no orally administered copper; when the metal is given intravenously, they experience a prompt increase in serum copper and ceruloplasmin .
- Copper levels are low in liver and brain but are elevated in several other tissues, notably intestinal mucosa, muscle, spleen, and kidney.

Disorders of metal metabolism

Menkes Disease :

- ATP7A, the gene for KHD, has been mapped to Xq13.3.
- It encodes an energy-dependent, copper-transporting P-type membrane ATPase (MNK) .
- ATP7A is expressed in most tissues, including brain, but not in liver. At basal copper levels, the protein (MNK) is located in the trans-Golgi network, the sorting station for proteins exiting from the Golgi apparatus, where it is involved in copper uptake into its lumen

- At increased intra- and extracellular copper concentrations the MNK protein shifts toward the plasma membrane, presumably to enhance removal of excess copper from the cell

Disorders of metal metabolism

Menkes Disease :

- As a consequence of the defect in the transport protein, copper becomes inaccessible for the synthesis of copper-containing enzymes, notably ascorbic acid oxidase, cytochrome oxidase, and lysyl hydroxylase.
- Arteries are tortuous, with irregular lumens and a frayed and split intimal lining
- These abnormalities reflect a failure in elastin and collagen cross-linking caused by dysfunction of the key enzyme for this process, copper-dependent lysyl hydroxylase.

Disorders of metal metabolism

Menkes Disease :

- In the classic form of the illness symptoms appear during the neonatal period. Most commonly, one observes hypothermia, poor feeding, and impaired weight gain. Seizures soon become apparent.

Disorders of metal metabolism

Menkes Disease :

- There also is gingival enlargement and delayed eruption of primary teeth. The optic discs are pale, and microcysts of the pigment epithelium are seen.
- The most striking finding is the appearance of the scalp hair; it is colorless and friable.
- Examination under the microscope reveals a variety of abnormalities, most often pili torti (twisted hair), monilethrix (varying diameter of hair shafts), and trichorrhexis nodosa (fractures of the hair shaft at regular intervals).

Disorders of metal metabolism

Menkes Disease :

- Neuroimaging discloses cerebral atrophy and bilateral ischemic lesions in deep gray matter or in the cortical areas, the consequence of vascular infarctions .
- A progressive tortuosity and enlargement of intracranial vessels also can be shown by MRI angiography.

Disorders of metal metabolism

Menkes Disease :

- Similar changes are seen in the systemic vasculature Asymptomatic subdural hematomas are almost invariable, and when these occur in conjunction with a skull fracture, the diagnosis of nonaccidental trauma is frequently considered .
- EEGs show multifocal paroxysmal discharges or hypsarrhythmia. Visual-evoked potentials are of low amplitude or completely absent.

Disorders of metal metabolism

Menkes Disease :

- The clinical history and the appearance of the infant should suggest the diagnosis. Serum ceruloplasmin and copper levels are normally low in the neonatal period and do not reach adult levels until 1 month of age.

- Therefore, these determinations must be performed serially to demonstrate a failure of the expected increase. The diagnosis can best be confirmed by demonstrating the intracellular accumulation of copper and decreased efflux of Cu from cultured fibroblasts .

Disorders of metal metabolism

Menkes Disease :

- The increased copper content of chorionic villi has been used for first-trimester diagnosis of the disease.

- These analyses require considerable expertise, and only few centers can perform them reliably.

Disorders of metal metabolism

Menkes Disease :

- Copper supplementation, using daily injections of copper-histidine, appears to be the most promising treatment.

- Parenterally administered copper corrects the hepatic copper deficiency and restores serum copper and ceruloplasmin levels to normal.

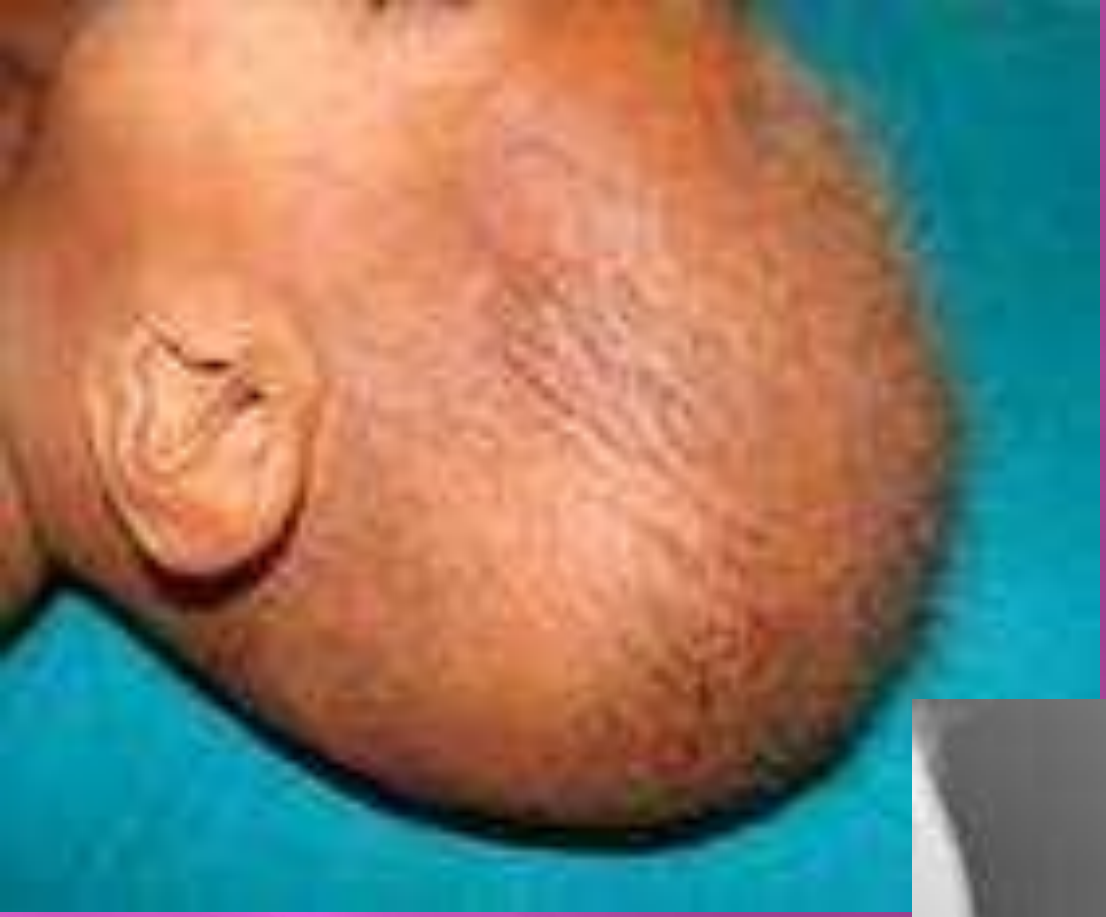
Disorders of metal metabolism

Menkes Disease :

- The effectiveness of treatment in arresting or reversing neurologic symptoms probably depends on

1. whether some activity of the copper-transporting enzyme MNK has been preserved
2. whether copper supplementation has been initiated promptly .


28



Disorders of metal metabolism

Molybdenum Cofactor Deficiency

- Three enzymes require molybdenum for their function: sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. Three genetically distinct disorders result in a defect of the molybdenum cofactor. Each of these represents a defect in one of the four genes involved in the biosynthesis of the molybdenum cofactor.
- Most commonly, one encounters a defect in MOCS1, the gene that codes for the enzyme involved in the formation

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Molybdenum Cofactor Deficiency

- Clinically, all three disorders are autosomal recessive and are marked by intractable seizures, often starting in the neonatal period, severe developmental delay, and multiple cerebral infarcts producing a neuroimaging picture that resembles severe perinatal asphyxia.

- Neuroimaging studies show initial cerebral edema followed by dramatic multicystic leukoencephalopathy.

Disorders of metal metabolism

Molybdenum Cofactor Deficiency

- Molybdenum cofactor deficiency can be suspected by elevated serum lactate levels, low serum and urinary uric acid, and increased urinary sulfite.
- Treatment with dietary restriction of methionine has been attempted
- Dietary therapy of this condition with reduced methionine intake and a synthetic amino acid mixture lacking cystine and methionine has resulted in normal growth and apparently normal psychomotor development

Classification

- Disorders of amino acid metabolism
- Disorders of renal amino acid transport
- Disorders of carbohydrate metabolism and transport
- Carbohydrate-deficient protein syndromes
- Organic acidurias
- Disorders of fatty acid oxidation
- Disorders of purine and pyrimidine metabolism
- Disorders of lipid and lipoprotein metabolism
- Ceroid lipofuscinosis and other lipidoses.
- Disorders of serum lipoproteins
- Lysosomal disorders
- Peroxisomal disorders
- Disorders of metal metabolism
- Porphyrias

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Porphyrias

- Of the various inherited disorders of the heme biosynthetic pathway that result in the accumulation of porphyrin or porphyrin precursors, only congenital erythropoietic porphyria is observed with any frequency during childhood.
- It results in cutaneous photosensitivity and hemolytic anemia but it is not accompanied by neurologic symptoms.

Porphyrias

- Acute intermittent porphyria is transmitted as an autosomal dominant trait with variable, but generally low, penetrance. Symptoms usually begin at puberty or shortly thereafter, and are most pronounced in young adults.

- Prior to that symptoms are vague and of short duration.

Porphyrias

- Manifestations consist of recurrent attacks of autonomic dysfunction, intermittent colicky abdominal pain, convulsions, and a polyneuritis, which usually predominantly affects the motor nerves.

- The upper limbs are generally more involved, and the paralysis progresses until it reaches its maximum within several weeks. Seizures are relatively rare. Mental disturbances, notably anxiety, insomnia, and confusion, are common, but no skin lesions develop .

- Attacks can be precipitated by a variety of drugs, notably anticonvulsants.

Porphyrias

- Decreased activity of porphobilinogen deaminase to 50% of normal has been demonstrated in several tissues, notably in erythrocytes, where the enzyme can be assayed most readily.

- The gene for the enzyme is located on the long arm of chromosome 11 , and more than 100 allelic variants have been documented (976). This heterogeneity is in part responsible for the variable expression of the disease.

Porphyrias

- The pathogenesis of the neurologic symptoms is poorly understood,factors, notably aminolevulinic acid (ALA), which has structural resemblance to GABA, act on the nervous system concomitantly or sequentially.

Porphyrias

- The diagnosis is arrived at by demonstrating increased urinary porphobilinogen and urinary ALA during an attack. Between attacks, the excretion of both metabolites decreases but is rarely normal.
- Clinically silent carriers do not excrete increased amounts of these metabolites.
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Metabolic Causes for Progressive Myoclonic Epilepsy

1. Myoclonus epilepsy with ragged-red fibers (MERRF).
2. Unverricht Lundborg disease.
3. Neuronal ceroid lipofuscinosis (Batten-Spielmeyer-Vogt disease; CLN 3).
4. Lafora disease.
5. Late-onset GM_2 gangliosidosis.
6. G_{M1} gangliosidosis, juvenile type.
7. Niemann-Pick disease.
8. Galactosialidosis.
9. Arylsulfatase A deficiency.


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THANK YOU