Lipid storage disorders

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Introduction

The lysosomal lipid storage diseases are diverse disorders, each due to caused by an inherited deficiency of lysosomal hydrolase leading to intralysosomal accumulation of enzyme enzyme – specific substrate. [1] They are rare , metabolic disorders that can involve any organ of the body. Though ocular involvement in these disorders is rarer as compared to systemic involvement, easy accessibility of eye gives an opportunity to aid in accurate and final diagnosis of these disorders.

Pathogenesis

There is an understanding of many inborn errors of metabolism at biochemical and molecular level s , but the exact pathogenesis remains to be established. With the exception of a few, lipid substrates share a common structure having a ceramide (2-N-acylsphingosine) backbone from which various sphingolipids are derived. Because sphingolipids are an essential component of all cell membranes, the inability to degrade these substances and their subsequent accumulation results in physiologic and morphologic alterations and characteristic clinical manifestations of lipid storage diseases.

The storage of a substrate in a specific tissue is dependent on its normal distribution in the body. Progressive lysosomal accumulation of glycosphingolipid in CNS central nervous system (CNS) leads to neurodegeneration , and in visceral cells it leads to organomegaly, skeletal

abnormalities, pulmonary infiltration and other manifestations. As in other organ systems, the possible mechanism for ocular defects is direct toxic action, errors of synthetic pathways or deficient energy metabolism.

Classification

Lysosomal lipid storage disorders are classified [2] as follows:

1. Neutral glycosphingolipidoses: Gaucher disease, Nieman n – Pick disease (NPD) , Fabry disease
2. Gangliosidoses: GM1 Gangliosidosis, GM2 Gangliosidosis (Tay – – Sachs disease, Sandhoff disease)
3. Leukodystrophy: Krabbe disease, Metachromatic m etachromatic leukodystrophy (MLD)
4. Disorder of neutral lipid: Farber disease

Inheritance of lipid disorders is autosomal recessive except for X- linked recessive Fabry disease.

Diagnosis

The D d iagnosis of affected individual is made through clinical examination, biopsy, genetic testing, molecular analysis of cell or tissue to identify inherited metabolic disease and enzyme assays. [2] Enzyme assays are done by measurement of specific enzyme activity in isolated leukocyte leucocyte s or cultured fibroblasts or lymphoblasts. [1] Genetic testing is helpful in identifying the disease carriers in individuals with family history of lipid storage diseases. It can also determine diseased or carrier f o etus. Prenatal testing is done by chorionic villus sampling and cultured amniocytes. [2]

Neutral Glycosphingolipidoses g lycosphingolipidoses

gaucher G aucher disease

Gaucher disease is the most frequently encountered lipid storage disorder, characterized by h a ematologic abnormalities, organomegaly and skeletal involvement. The disease follows an autosomal recessive inheritance pattern and is more common in Jews (4. 5%). The gene of the enzyme glucocerebrosidase is located on the short arm of chromosome 1. The deficiency of the enzyme glucocerebrosidase (acid β-glucosidase) that is normally present in macrophage lysosome , leads to the accumulation of glucosylceramide in scavenger macrophages and subsequent deposition in the organs of reticuloendothelial system (liver, spleen and bone marrow).

There are the following three clinical subtypes of Gaucher disease depending on the absence or presence and progression of neurologic manifestations : : . 1

- Type 1: Adult, non-neuronopathic form, accounts for 99% of cases
- Type 2: Infantile or acute neuronopathic form , and
- Type 3: Juvenile or sub sub – acute neuronopathic form

The three forms cannot be distinguished from one another biochemically. Gaucher cells are found in the bone marrow of all three variants.

Systemic Features f eatures

Majority of patients with Gaucher disease develop features in childhood. The progressive deposition of lipid results in infiltration of the bone marrow with resultant pancytop a enia, progressive hepatosplenomegaly and skeletal

complications manifesting as bone pain, pathologic fractures and skeletal deformities. [2] Pulmonary involvement is not common , but it can lead to interstitial lung disease and pulmonary hypertension.

Ocular Features f eatures

Classically described ocular and neurologic al associations of this disease include conjunctival pterygia, strabismus and trismus with retroflexion of the neck. [3] Ocular motor defect in Gaucher types 2 and 3 is a progressive , deficient horizontal gaze, especially for voluntary saccades , that simulates those of congenital ocular motor apraxia. [4, 5] Horizontal supranuclear gaze palsy is often one of the first neurologic al signs of neuronopathic Gaucher disease. [6]

Vitreous opacities are seen in this disorder . [7, 8] An incidence of 3% vitreous opacities has been reported in one series. [9] Only those who have undergone splenectomy have the tendency to form vitreous aggregates because more circulating glucosylceramide s is are available. Shrier et al . It has been reported in the literature reported that retinal vascular tortuosity along with very severe vitreous opacities need s ing vitrectomy ’ [3] and the Gaucher cells in the vitreous cavity, while the vitreous gel contain s ed large amounts of glucosylceramide. [10]

Diagnosis

Pathologic hallmarks of Gaucher disease are the large glucosylceramide-laden histiocytes , ‘ “ Gaucher cells ’ ” in reticuloendothelial system,

particularly bone marrow. The Presence p resence of intracytoplasmic inclusion gives characteristic ‘ “ wrinkled paper appearance ’ ” to Gaucher cells. The presence of Gaucher cells in marrow aspirate and tissue biopsy is highly suggestive of the disease. Diagnosis is confirmed by the determination of glucocerebrosidase activity in isolated leukocyte leucocyte s or cultured fibroblasts. [1]

Treatment

Symptomatic management of blood cytop a enias, joint replacement surgeries and bisphosphonates for bone mineralization are important supportive therapy therap ies . [2] Enzyme replacement therapy with glucocerebrosidase (Imiglucerase) is the current treatment of choice. Enzyme replacement therapy is effective in type – – 1 (non non – neuronopathic) form of disease ; , however , in type-2 and type-3 forms of the disease the outcomes are disappointing as systemically administered glucocerebrosidase is unable to pass through the blood – brain barrier.

Niemann – – Pick Disease d isease

Niemann – Pick disease NPD is an inborn error of metabolism that results from impaired metabolism of sphingomyelin. The disorder is inherited as autosomal recessive trait with five phenotypic variants , type A through E, based on the age of onset, the severity and type of neurologic involvement and the evolution of the disease. [11] Hepatosplenomegaly and foam cells in the bone marrow are constant features in all variants.

Niemann – Pick disease NPD type A and type B occur due to deficient activity of acid sphingomyelinase (ASM) , and are pathologically characterized by lipid lipid – laden foam cells (Niemann – – Pick cells). In NPD type C, ASM activity is usually normal, the metabolic block in type C is in the intracellular trafficking of cholesterol. The biochemical defects in type D and type E NPD remain undetermined.

Systemic Features f eatures

The Disease d isease is characterized by failure to thrive, hepatosplenomegaly and a rapidly progressive neurodegenerative course that leads to death by 2 – – 3 years of age. Type B NPD is a heterogeneous non-neuronopathic form observed in children and adults. The disease shows hepatosplenomegaly, hyperlipid a emia, interstitial pulmonary disease, variable survival to adulthood and absence of neurodegeneration. NPD type C has a sub sub – acute clinical course and presents in infancy with neonatal hepatitis or later in childhood with moderate splenomegaly and gradual neurologic deterioration. Most patients have seizures and limitation of vertical gaze. The presence of downgaze down gaze paresis and ataxic athetosis is characteristic. NPD type s D and E have slower neurodegenerative course.

Ocular Features f eatures

In NPD-A , the most striking ocular finding is the presence of cherry-red maculae . (Fig. 83. 1 – figure provided is of brao and not cherry red spo t). Occasionally, a macular halo with grey granular appearing macula is observed. Optic atrophy develops over time. Subtle lens opacities and

corneal clouding can occur. Electroretinogram (ER G) G < AQ 2 : Please provide the full form of ERG > is usually abnormal.

In NPD-B , a cherry-red spot is present in a small number of patients , and is not associated with neurodegeneration. [11, 12] Macular halo is a more common finding.

NPD Type t ype C is characterized by ophthalmopl a egia with the limitation of vertical gaze. Horizontal eye movements may be affected with total supranuclear ophthalmopl a egia. There is no macular cherry-red spot or macular halo in type C NPD. There are no ocular abnormalities in NPD type D. Patients with type E variant may have macular cherry-red spot.

The absence of ganglion cells at fovea is responsible for the cherry cherry – red spot. Lipid storage in the macular region appears as a grayish gr e yish – white halo that results from the swelling and loss of transparency of multi – layered ganglion cell ring. When significant lipid accumulation occurs in the ganglion cells, a white ring of lipid-laden neurons encircling the red, ganglion cell – – free fovea can be observed as the characteristic macular cherry cherry – red spot.

Diagnosis

The presence of characteristic NPD cells in the bone marrow aspirate supports the diagnosis of NPD. Confirmation of diagnosis is done The diagnosis is confirmed by measuring acid sphingomyelinase the ASM activity in peripheral leukocyte leucocyte s, cultured fibroblasts or lymphoblasts which shows markedly decreased activity (1 – – 10%) in both type A and type

B NPD. Prenatal diagnosis can be done by measuring sphingomyelinase activity in cultured amniocytes or chorionic villi.

Treatment

Currently , there is no specific treatment for NPD. Enzyme replacement therapy for NPD is under study for therapeutic use.

Fabry’s Disease d isease

Fabry’s disease is an X-linked inborn error of glycosphingolipid metabolism due to deficient activity of alpha-galactosidase A. Prevalence is estimated to be 1 in 50, 000 males. Enzyme defect leads to the systemic accumulation of neutral glycosphingolipid, primarily globotriaosylceramide (‘ Maltese cross’ crystals) in plasma and lysosomes of vascular endothelium and smooth muscle cells. This leads to isch a emia, infarction and major disease manifestations.

Disease Disease – related complications can develop in heterozygotic females due to random X- inactivation.

Fabry’s disease is characterized by angiokeratoma (telangiectatic skin lesions), hypohidrosis, acroparesthesias (agonising agoni z ing , burning pain in extremities ‘ “ Fabry crisis ’ ”), vascular disease of kidney, heart and brain with ocular changes.

Ocular Features f eatures

Fabry’s disease can involve cornea, lens and conjunctival and retinal vessels. They correlate with the progressive deposition of glycosphingolipid in ocular

structures. [13] Vortex keratopathy (cornea verticillata) is the most common ocular manifestation reported in the disease and represents high sensitivity and specificity for Fabry's disease. [14] It should be differentiated from amiodarone and chloroquine toxicity. In lens, patients exhibit typical lens opacity with a ' " spoke spoke – like ' " pattern at the level of posterior capsule, referred as ' " Fabry's cataract ' " . Corneal opacities and lenticular changes, observed under slit-lamp examination, are present in affected males and 90% of heterozygotes.

Conjunctival vessels are abnormally dilated. Retinal vessels are tortuous and show aneurysmal dilatation and occlusion. [15] Disruption of vascular architecture is due to substrate accumulation within the vessel wall resulting in endothelial dysfunction, abnormal blood flow and hypercoagulability. Conjunctival and retinal vessel tortuosity may represent a clinically significant marker of diffuse microvascular disorder leading to end organ pathology , and increased vascular tortuosity correlates with severity of systemic disease. Ophthalmological manifestations of Fabry's disease do not result in visual symptoms. [12] Other ocular findings include lid o edema, myelinated nerve fib e r e s, mild optic atrophy, papill o edema, nystagmus , and internuclear ophthalmopl a egia.

Diagnosis

In affected males, diagnosis is made from the history of painful acroparesthesia, hypohidrosis , and characteristic skin, corneal and lenticular lesions. Diagnosis is confirmed by markedly decreased alpha-galactosidase-A activity in plasma, isolated leukocyte leucocyte s, cultured fib r oblasts or

lymphoblasts. Prenatal diagnosis can be done by chorionic villus or cultured amniocytes.

Treatment

Recombinant alpha-galactosidase (Fabrazyme) is a safe and effective enzyme replacement therapy. Medical management of acroparesthesia and renal transplantation in patients of renal failure is done.

Gangliosidoses

Gangliosidoses are inherent disorders of metabolism caused by the defective activity of a lysosomal enzyme , characterized by progressive mental and motor deterioration due to the storage of GM1 or GM2gangliosides in neurons. [16] GMs are classified in to 2 two groups: GM1 and GM2; Gm1 G M 1 has two subtypes, while Gm2 G M 2 has four subtypes.

GM1 G angliosidosis g angliosidosis

- GM $_1$ generalized form: It is caused by the deficiency of isoenzymes A, B , and C β-galactosidase.
- GM $_1$ juvenile form: It is caused by the deficiency of isoenzymes B , and C β-galactosidase.

GM1 Gangliosidosis g angliosidosis is an autosomal recessive disorder due to the deficient activity of beta-galactosidase, characterized by pathologic accumulation of GM1 ganglioside in neural and visceral cells, which is most marked in the brain.

Systemic Features f eatures

GM1 shows hepatosplenomegaly, o edema, skin eruptions (angiokeratoma) and skeletal abnormalities.

Up to 50% of patients show macular cherry-red spot s , which is associated with neurodegeneration. Other ocular manifestations include nystagmus, retinal h a emorrhages, optic atrophy and mild, diffuse corneal clouding.

Diagnosis

Diagnosis is suspected in infants by typical clinical features and confirmed by the deficiency of beta – – galactosidase activity in peripheral leukocyte leucocyte s.

Treatment

Currently , only supportive treatment is available for the disease.

GM2gangliosidosis

GM2 Gangliosidosis g angliosidosis includes Tay – – Sachs disease and Sand h off disease resulting from the deficiency of beta-hexosaminidase activity and lysoso s mal accumulation of GM2 ganglioside , especially in CNS. Beta-hexosaminidase has two isoforms A and B. Beta Beta – hexosaminidase A is a trimeric protein composed of 1 alpha and 2 beta subunits and isoform B has four beta subunits.

Tay–Sachs disease

Tay – – Sachs disease results from the mutation in alpha subunit causing deficiency of beta beta – hexosaminidase A and is the most common storage

disease causing a macular cherry-red spot (Fig. 83. 1). It is autosomal recessive in inheritance and has been classified into infantile, juvenile and adult forms. Infantile form is fatal neurodegenerative disease with microcephaly, loss of motor skills, increased startled reaction associated with neurodegeneration and optic atrophy. Juvenile onset form presents with ataxia, dementia and death by 10 – – 15 years. Adult onset disease shows progressive motor weakness, dysarthria, spinocerebellar and lower motor neuron symptoms.

Sandhoff disease

Sandhoff disease results from mutation in beta subunit causing deficiency of both beta beta – hexosaminidase A and B. Clinical manifestations are similar to Tay – – Sachs disease with the additional presence of hepatosplenomegaly, cardiac abnormality and bone dysplasia.

Ocular manifestations can be in the form of bilateral optic atrophy and a cherry- red spot at macula.

Leukodystrophy

Krabbe disease

Krabbe disease, also known as globoid cell leukodystrophy, is a fatal disorder of infancy. Disease follows the autosomal recessive pattern of inheritance. The D d eficiency of enzyme galactocerebroside β-galactosidase leads to the accumulation of galactosylceramide in the white matter. Galactosylceramide is present exclusively in the myelin sheath causing the affection of both

peripheral and central myelin, leading to the severe degeneration of motor and mental skills.

Clinical Features f eatures

Krabbe disease presents in early infancy with irritability, seizures, hypertonia and death before 3 years of age. Ocular manifestations seen in this disorder are constant wandering eye movements and sluggish pupillary light reflexes. [17] The C c herry-red spot is inconsistent , but optic atrophy is seen very often. [1]

Diagnosis

Diagnosis is established by the demonstration of deficient enzymatic activity in white blood cells or cultured skin fibroblasts.

Treatment

The S s ulphated glycosphingolipid treatment of disease has been reported with umbilical cord blood cell transplantation in newborn and infants.

Metachromatic leukodystrophy

M etachromatic leukodystrophy (MLD) is an autosomal recessive white matter disease caused by the deficiency of liposomal enzyme arylsulfatase arylsul ph atase A (ASA). [1] The enzyme is required for the hydrolysis of sulphated glycosphingolipid. Sulphated glycosphingolipid accumulation in the white matter leads to demyelination and neurodegeneration.

Systemic Features f eatures

Both central and peripheral nervous systems are involved , giving upper and lower motor neurons, cognitive and psychiatric signs. Disease shows infantile, juvenile and adult forms. Infantile form presents between 12 – and 18 months of age with irritability, inability to walk and hyperextension of knee. The Juvenile j uvenile form is seen in late twenties with gait disturbance and mental retardation. In the adult form , emotional difficulties and psychosis are more common.

Ocular Features f eatures

Marked foveal atrophy with chorioretinal atrophy and progressive retinal pigment degeneration has been reported in this condition. The C c herry-red spot is inconsistent. Optic atrophy is seen in all three forms of the disease. [19]

Diagnosis

The diagnosis of MLD in suspected patients is suggested by decreased nerve conduction velocities, increased cerebrospinal fluid protein, metachromatic deposits in sampled segments of sural nerve and metachromatic granules in urinary sediment. The C c onfirmation of the diagnosis is based on the demonstration of reduced activity of ASA in leukocyte leucocyte s or cultured skin fibroblasts.

Treatment

Bone marrow transplantation has been tried, but the clear evidence of clinical efficacy is lacking. Supportive care remains the primary intervention.

Disorder of neutral lipid

Farber disease

This is a rare autosomal recessive disorder that results from the deficiency of the lysosomal enzyme acid ceramidase and the accumulation of ceramide in various tissues, especially the joints. It is also known as Farber lipogranulomatosis.

Systemic Features f eatures

The onset of Farber disease is typically in early infancy , but may occur later in life and is characterized by painful joint swelling and nodule formation, breathing difficulties, failure to thrive and moderate central nervous system CNS involvement.

Ocular Features f eatures

The most common ophthalmic manifestation is the cherry red-spot at the macula , but it is not as striking as seen in the Niemann – – Pick and Tay–Sachs diseases.

Cogan and co-workers have demonstrated accumulated lipid-like material with inclusions in the ganglion cells of macula and mid – periphery of retina. 20 Patients may have decreased visual acuity.

Diagnosis

The diagnosis of this disorder should be suspected in patients who have nodule formation over the joints but no other findings of rheumatoid arthritis. In such patients, ceramidase activity should be determined in cultured skin fibroblasts or peripheral leukocyte leucocyte s.

Treatment

Currently , there is no specific therapy for Farber disease.

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Fig ure 83. 1 Macular cherry-red spot in Tay <