athshala पाठशाला MHRD Govt. of India

Paper : 05 Metabolism of Lipids
Module: 27 Lipids: In Born Errors of Metabolism I

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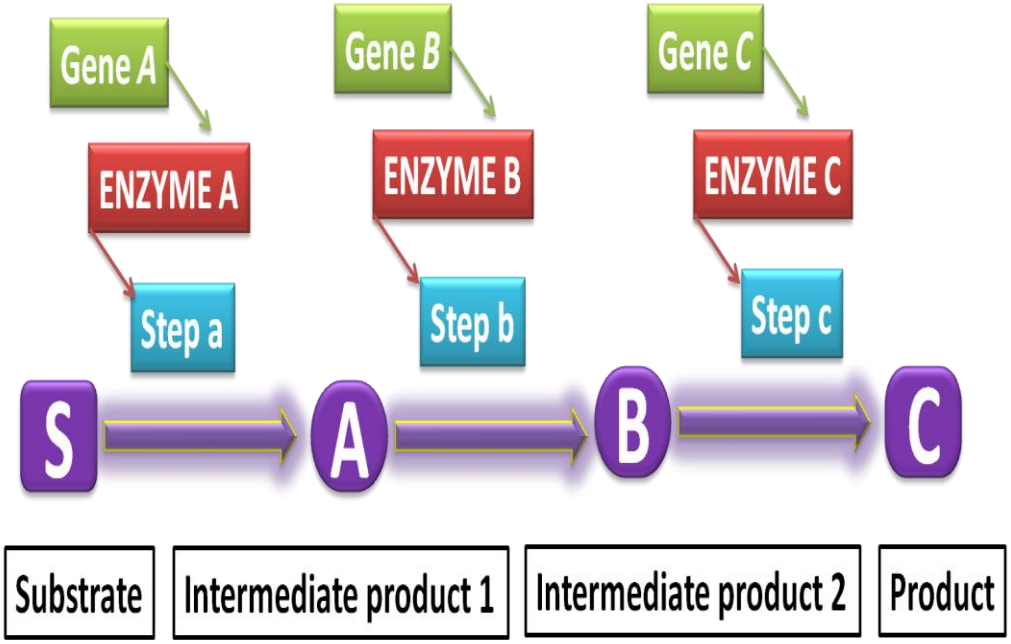
DESCRIPTION OF MODULE	
Subject Name	Biochemistry
Paper Name	05 Metabolism of Lipids
Module Name/Title	27 Lipids: In Born Errors of Metabolism I

1. Objectives

- To understand what is inborn error (s) of metabolism
- What are the plausible causes of inborn error (s) of metabolism
- How the error can be identified and corrected

2. Concept Map



Representation of a metabolic sequence for producing the final product C from a particular substrate (S) in step wise manner controlled by three enzymes. Each enzyme is in turn regulated by an individual gene.

3. Description

After the rediscovery of Mendel`s experiments in 1900, Sir Archibald Garrod (1908) was the first to propose about the fact that certain disease were occur due to IEM (inborn errors of metabolism). He delivered lectures at the Royal College of Physicians about the four metabolic errors i.e. Alkaptonuria, Albinism, Cystinuria and Pentosuria. He investigated the cause of the diseases and established the fact that they occur due to some defects in the biochemical reactions of the essential physiological pathways.

The name 'inborn' error signifies that the symptoms of disorders/defects can be detected in child after birth. He pointed out that there are certain features in common in all these disorders like it occurred with high frequency among the offspring of consanguineous marriages; the symptoms appeared mostly to early days or weeks of neonatal life with familial occurrence in substantial number of cases with overall benign conditions. The original four metabolic disorders have now been amplified to many disorders. Thus, dysregulation of developmental and homeostatic metabolic networks commonly known as 'Inborn errors of metabolism' comprises an important increasing group of genetic disorders. Therefore, it may be defined as an enzymopathy and genetotrophic disease which is genetically based biochemical problem where an enzyme defect obstructs a defined metabolic pathway accumulating the substrate causing disastrous pathologic effect at birth (e.g phenylketonuria) or afterwards in life (e.g. diabetes mellitus). The main four consequences of inborn errors of metabolism are depicted in the following Figure 1.

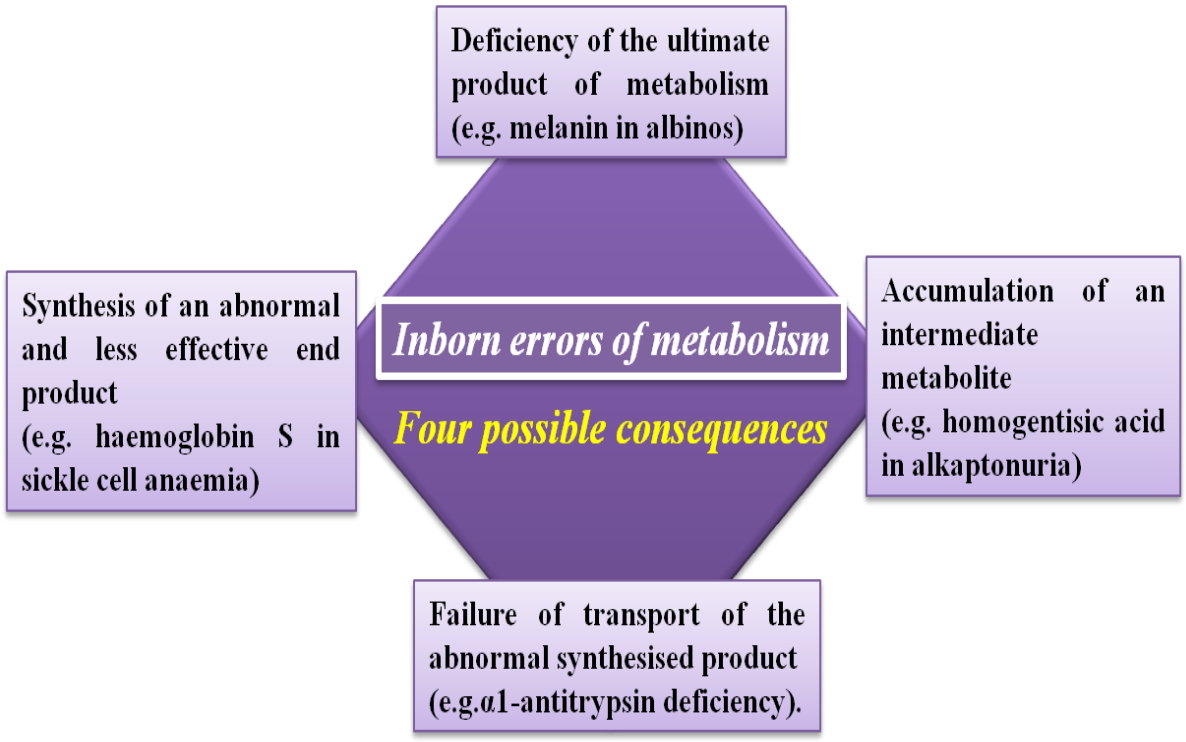


Figure 1. Most Important Possible Consequences of Inborn Errors of Metabolism

An assortment of symptoms include vomiting, diarrhoea, seizures, encephalopathy, hepatomegaly, hypotonia and failure to thrive. The concept of inborn error signifies the aspect of disturbance in the physiological homeostasis. The metabolic pathway is dependent on anabolic (synthetic) and catabolic (degradation) pathway which are balanced. All the pathway-dependent metabolic reactions (endergonic or exergonic) are catalyzed by enzymes. Metabolic abnormality occurs when there is a defect/absence of one particular enzyme of the pathway as given in the Figure 2. These metabolic abnormalities are inherited and leads to most neonatal deaths.

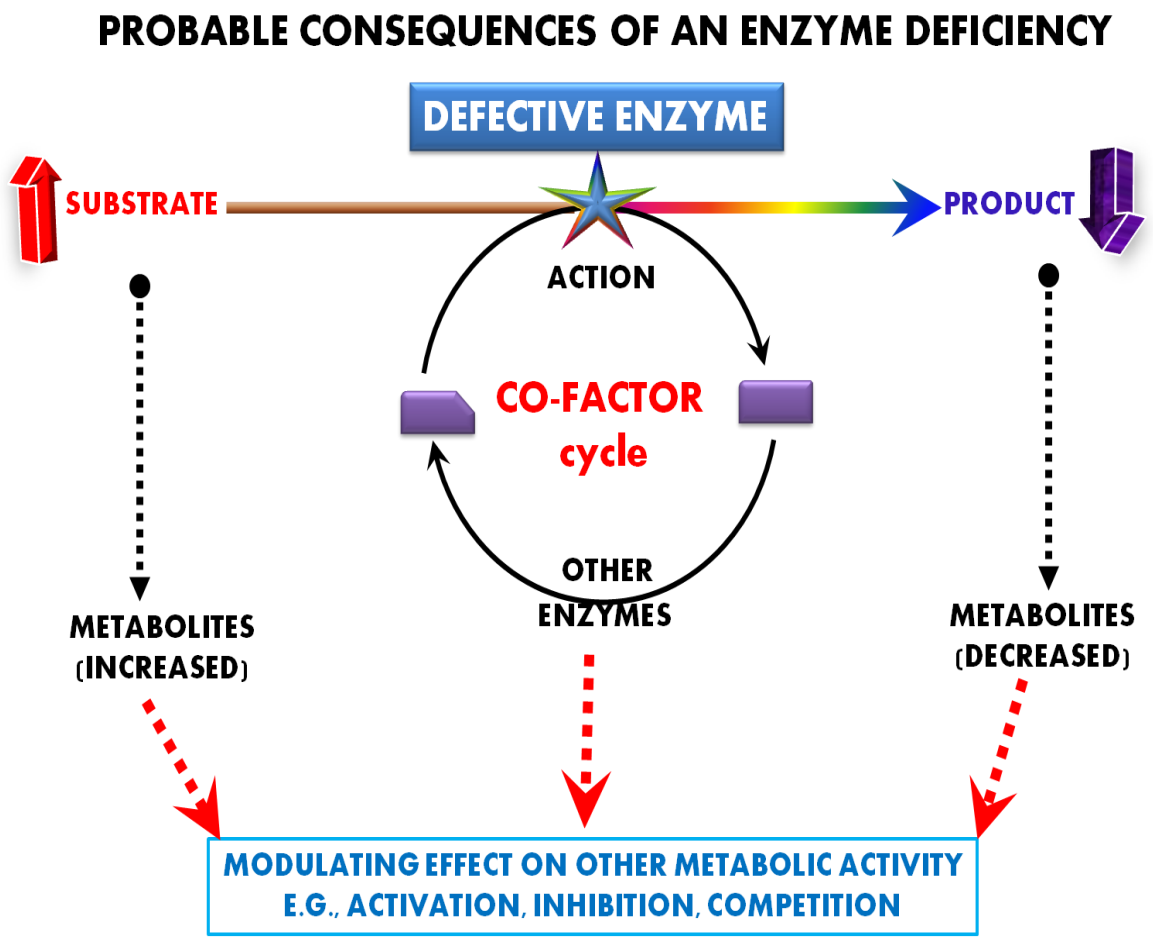


Figure 3. Simplified Representation of Metabolic Effects of an Enzyme Deficiency

The significance of these individually rare yet collectively an important disease can be traced back to the importance of biochemical reactions as it is present in approximately 1 in 2000 births and mostly detectable in childhood.

Basically, there are many ways of classifying the metabolic disorders but when the macromolecules are considered, mainly there are four groups like amino acids, carbohydrates, lipids and others as depicted in Figure 3. In this introductory section, we are primarily concerned with the lipid metabolic disorders.

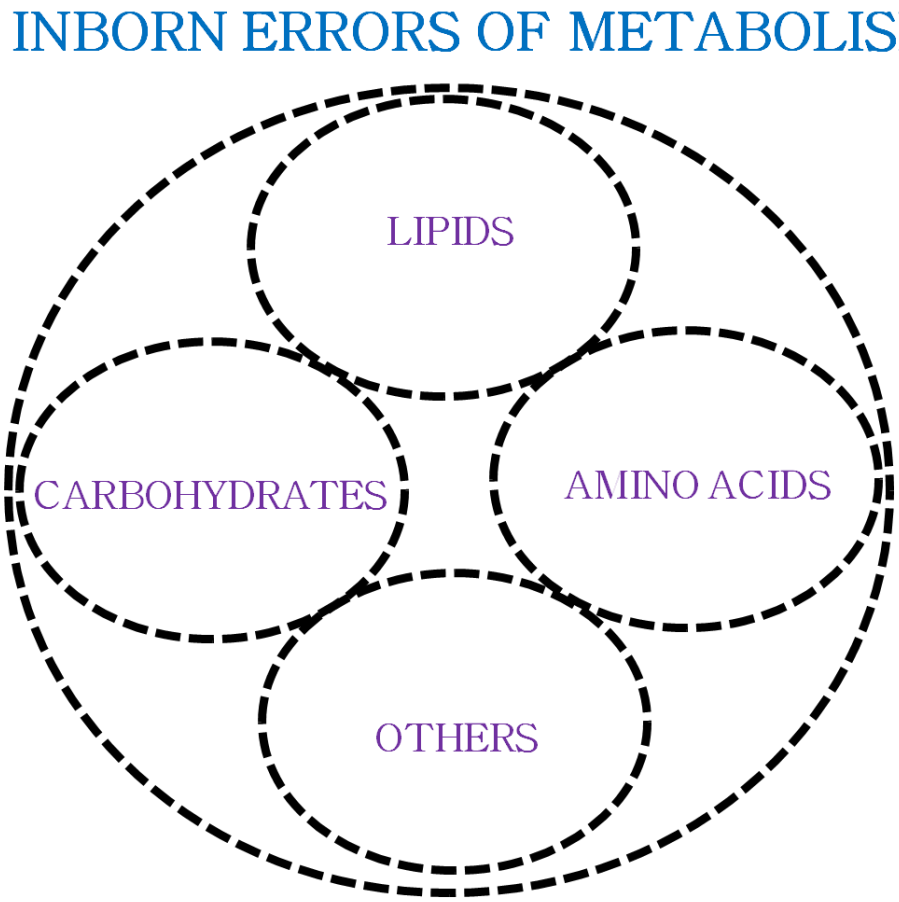


Figure 3. Major Macromolecular System Involved in the Metabolic Syndrome

International Classification of Inborn Errors of Metabolism

The ICD-10 (10th Revision of **I**nternational Statistical **C**lassification of **D**iseases and Related Health Problems) contains 22 chapters (I-XXII) of which chapter (IV or E) contains information about Endocrine, Nutritional and Metabolic Diseases. As classified by WHO (World Health Organization), this system codes these diseases and contains information about abnormal findings, complaints, external causes of injury, signs, symptoms, and or diseases and social circumstances. The IV chapter contains about 90 sub-chapters of which E70-90 contains information about metabolic disorders. In Figure 4, the codes specifically concerned about lipid disorders have been depicted.

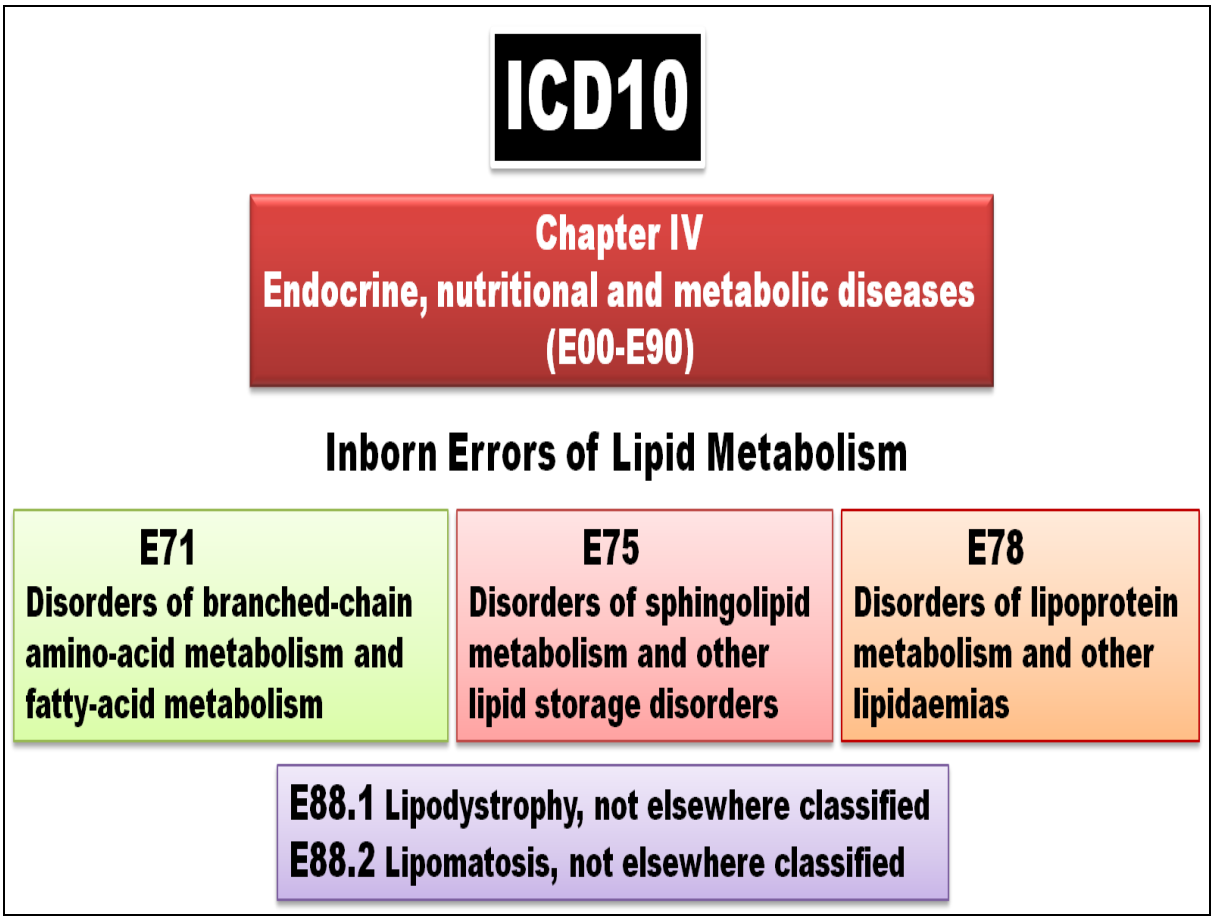


Figure 4. Major Codes of ICD10 Involving Lipid Based Metabolic Disorders

Detail of E75 which involves major lipid storage diseases which are a part of lysosomal storage disease have been depicted in Figure 5 while detail of E78 which involves disorders of lipoprotein metabolism and other lipidaemias is given in Figure 6.

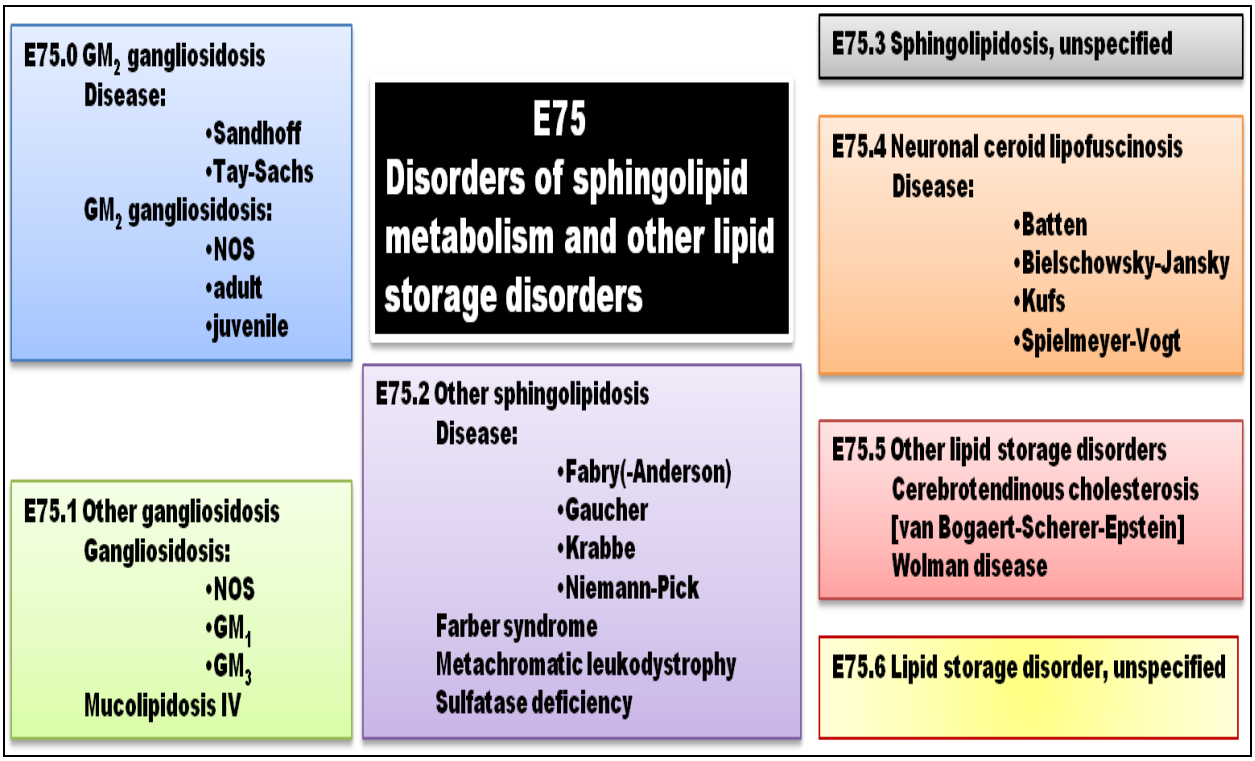


Figure 5. Major Subgroups of Disorders of Lipid Storage Diseases

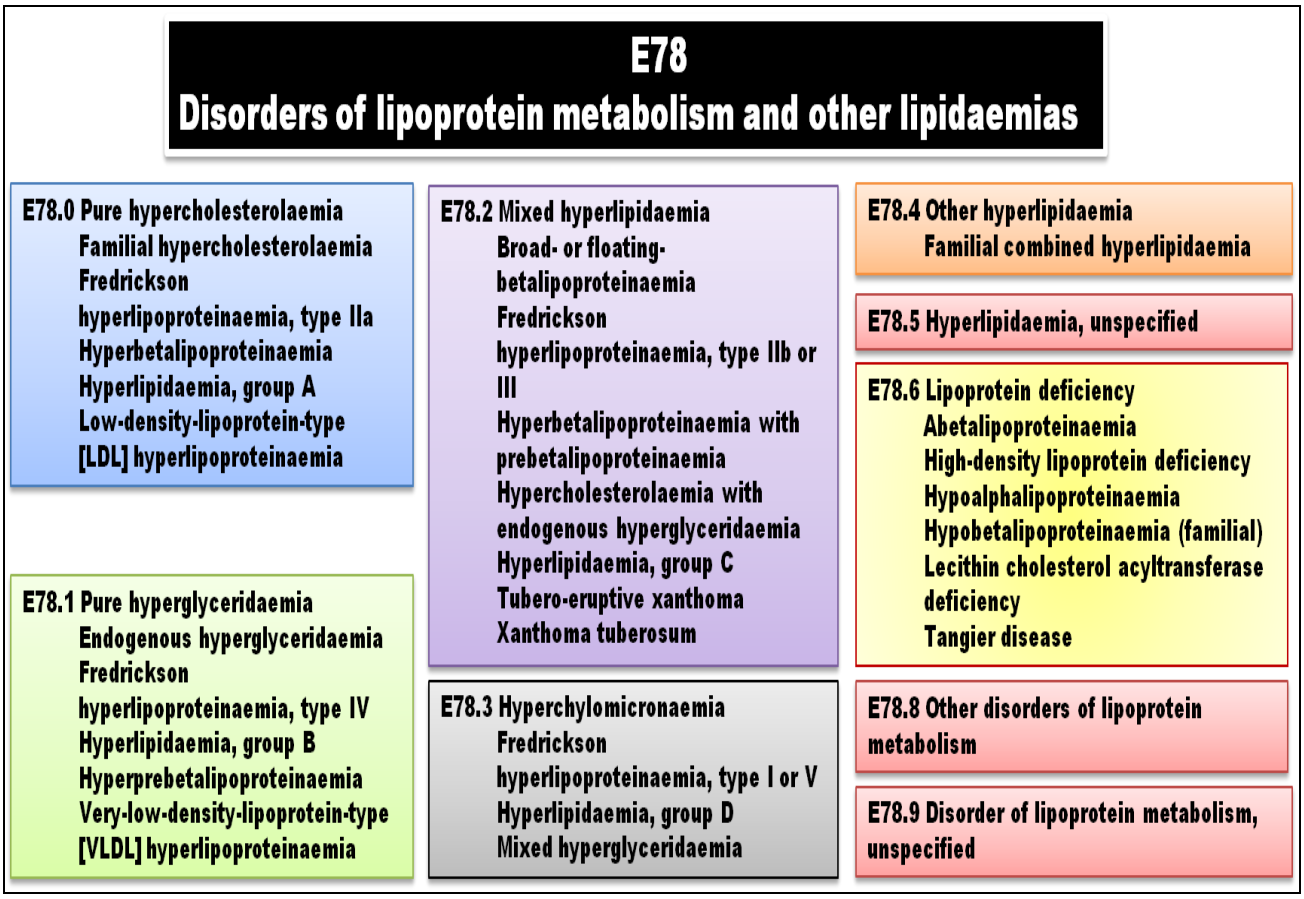


Figure 6. Major Subgroups of Disorders of Lipoprotein Metabolism and Other Lipid Diseases

New Developments

The therapy of IEM is progressively more promising, even though expensive. Enzyme replacement therapy (ERT) emerge to be safe and effectual for peripheral manifestations in patients with Fabry disease, Gaucher disease types I and III, mucopolysaccharidosis I (Hurler, Hurler-Scheie, and Scheie syndromes), mucopolysaccharidosis II (Hunter syndrome), mucopolysaccharidosis VI (Maroteaux-Lamy syndrome), and

Pompe disease. Efforts are underway to extend enzyme replacement alternative for a number of other disorders. Thus far, ERT has been largely futile in improving central nervous system (CNS) expression of the lysosomal storage diseases, putatively due to complexity in piercing the blood-brain barrier. This has vanguarded to lively clinical trials assessing the safety and efficacy of intrathecal enzyme release in numerous lysosomal storage diseases. Accumulated data indicate that for preventing the progression of CNS symptoms in neuronopathic appearance of lysosomal storage diseases, including some of the lipidose, mucopolysaccharidoses, oligosaccharidoses, sphingolipidoses, and hematopoietic stem cell transplantation may perhaps be efficient under best possible (optimal) conditions. Although, longitudinal natural history data are limited, published guidelines are available to assist with decisions related to the pursuit of transplantation and whether to use bone marrow or umbilical cord blood–derived cells. In general, transplantation yields the best results when performed untimely in the path of the ailment (i.e. in an asymptomatic affected sibling of a child with a lysosomal storage disorder), in centers with experience in performing transplantations to treat inherited metabolic disorders, and in patients healthy enough to tolerate the conditioning and transplantation regimen.

Some evidence indicates that at least in certain disorders, combination ERT and hematopoietic stem cell transplantation together might be superior to hematopoietic stem cell transplantation alone in patients who are appropriate candidates. The accessibility of both ERT and hematopoietic stem cell transplantation has prompted enduring consideration of newborn screening efforts to diagnose and detect lysosomal storage diseases. Although screening for these disorders has not been widely implemented, the potential to treat these disorders is likely to drive further efforts at development.

Manifestations

Although single gene defects typically result in substrate accumulation, the precise causal patho-physiologic mechanisms that lead to clinical symptoms are not wholly lucid. The allocation of accruing material connects with the organs that are affected. Cells of the mononuclear phagocyte system are principally prosperous in lysosomes and accordingly are recurrently exaggerated by lysosomal storage diseases. Glia and neurons are most commonly affected, liable because of the relative paucity of cell turnover in the CNS, yet non-neuronopathic forms of lysosomal storage disease exist. Lysosomal storage diseases may possibly result in a rigorous neurodegenerative phenotype. Milder (typically later-onset or adult-onset) phenotypes have been recognized and are generally associated to the degree of enduring enzyme activity.

Pathophysiology

In general the accumulation of non-degraded substrate is thought to associate to the cellular dysfunction and death that complement lysosomal storage diseases; the precise mechanisms underlying this deterioration are incompletely defined. The pattern of neuronal degeneration in sub-types of lysosomal storage diseases may be surprisingly cell type specific. In some cases, substrate accumulation is also associated with sequestration of important component molecules, leading to a relative deficiency state.

The lysosome dole out as a vital element of the endosomal-lysosomal system. This system is essential for the safeguarding of typical cellular metabolism, operational in conjunction with the chaperone-mediated autophagy and ubiquitin-proteasomal systems. Anomalous function of this system may perhaps lead to ectopic dendritic sprouting (a characteristic quite inimitable to lysosomal storage diseases) and impaired recycling of glutamatergic AMPA receptors. Neuroaxonal spheroid formation is a feature of the ganglioside storage diseases,

Niemann-Pick types A and C, and a-mannosidosis, implicating a shared pathology that leads to the production of these compact accumulations of mitochondria and tubulovesicular bodies.

Testing

The constellation of dysmorphic features (coarse facies, macroglossia), bony abnormalities (dysostosis multiplex), cardiac involvement (arrhythmia or cardiomegaly), hepatosplenomegaly, ophthalmologic signs (corneal clouding or macular cherry-red spot), and neurological features might guide to the irrefutable distrust of a lysosomal storage disease. Symptoms are typically gradually progressive rather than episodic, as occurs with other neurometabolic disorders. Neurological symptoms can include ataxia, developmental delay, epilepsy (complex partial or myoclonic), hypotonia, intellectual disability, peripheral neuropathy and/or spasticity.

Screening can be executed via skeletal radiography to gaze for facts of abdominal ultrasonography to identify hepatosplenomegaly, dysostosis multiplex (observed in numerous lysosomal storage diseases), and echocardiography to assess for the cardiac association. Hearing screening results might be irregular in some cases. Ophthalmologic consultation could be useful in recognizing corneal clouding or cherry-red spot. A peripheral blood smear can reveal white blood cell vacuoles (autophagic vacuoles, fingerprint lipid whorls, granular, zebra bodies) that possibly will provide imperative diagnostic clues. Urine can be examined for prominent excretion of oligosaccharides (oligosaccharidoses) and glycosaminoglycans (mucopolysaccharidoses). Blood chitotriosidase (an enzymatic marker of macrophage activation) may be elevated. State-of-the-art testing is most proficiently executed by enzymatic activity measurement in a reference laboratory, characteristically in peripheral white blood cells (even if skin fibroblasts may also be used). For some disorders, enzyme activity can be measured in dried filter paper blood spots, and, occasionally, enzyme

activity measurement in other tissues such as muscle can have utility. Urine enzyme activity measurements are seldom helpful, although urine substrate excretion can provide useful information (see screening above). In some cases, confirmatory DNA mutation analysis may be indicated.

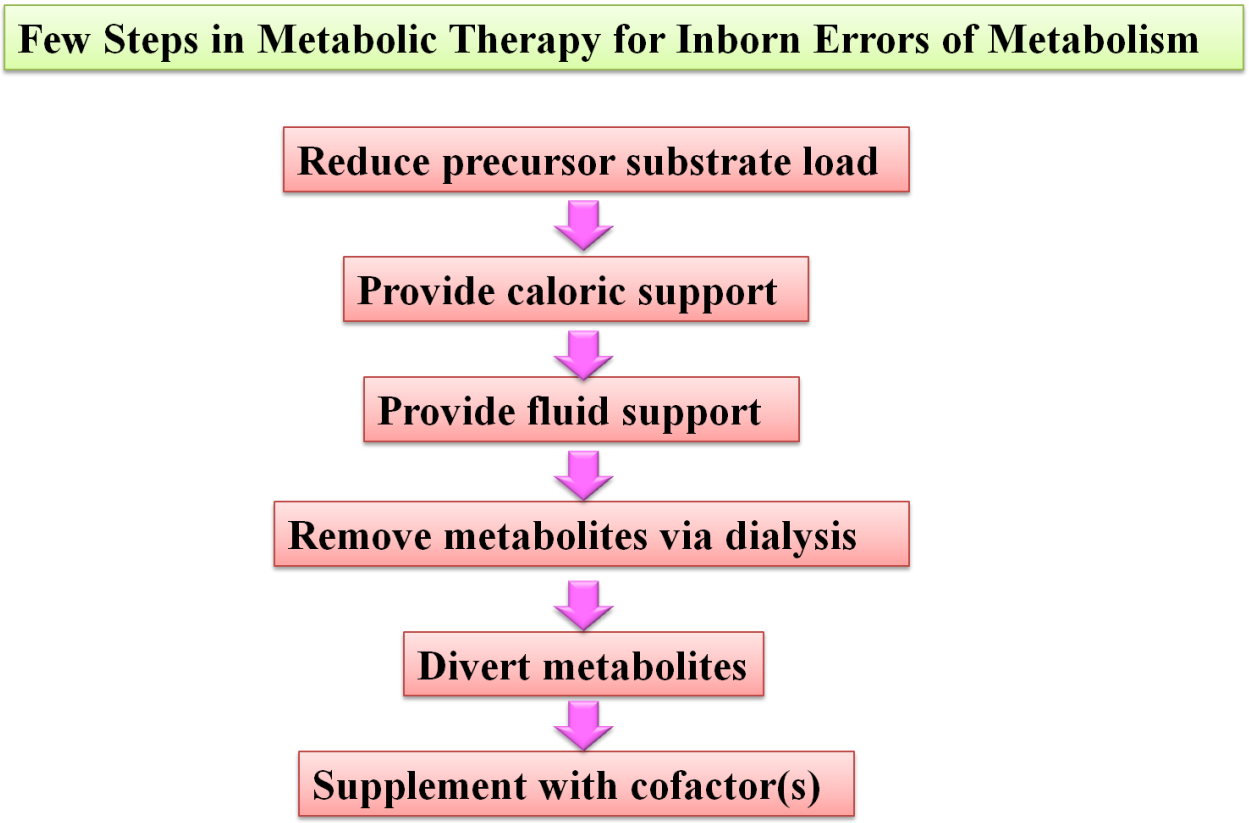


Figure 7. Major Steps in Therapy for Metabolic Diseases

Although inborn error of metabolic disorders arises from mostly one enzyme deficiency yet overall as all the signalling pathways are interlinked, therefore it behave as a complex trait. However, other aspect should also be considered like deficiency of cofactor required for enzymatic activity or hyper-activity of an enzyme or problem in transport process leading to excessive accumulation of metabolite. While within a signaling pathways, the

concept of upstream and downstream metabolite is also crucial as an accrual of upstream metabolite can divert the pathway of this particular metabolic flux to numerous side pathways. The IEM team at the Cochrane Cystic Fibrosis and Genetic Disorders Group declared 28th February as a Rare Disease Day (Figure 8).

Figure 8. Symbol of Rare Disease Day

Regarding the aspect covered in this section can be broadly divided into 4 subgroups which are subsequently described as given in Figure 9.

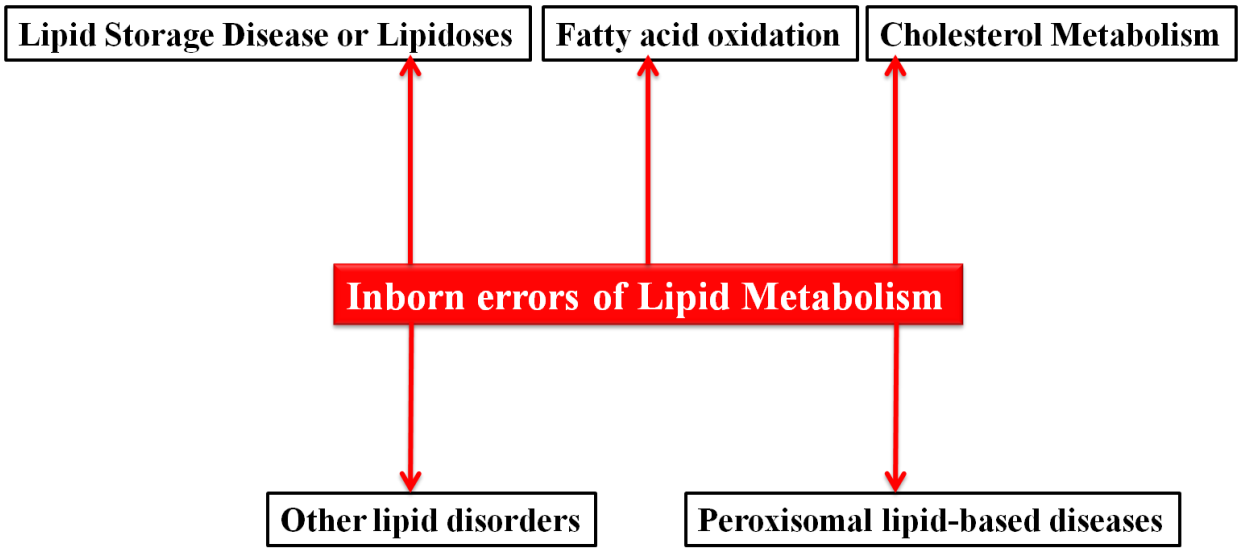


Figure 9. Overview of Lipid Based Inborn Errors of Metabolism

4. Summary

In this lecture we learnt about:

- Inborn errors of metabolism
- Types of Inborn errors of metabolism
- Its Manifestation, Pathophysiology and Testing