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Review Article

Genetically inborn metabolic disorders

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Abstract

Metabolism is the process carried out in the cells of all living organisms converting the food we eat to chemical energy needed for sustaining life. It encompasses allbiochemical processes that occur within any living organism - including humans - to maintain life. These biochemical processes allow us to grow, reproduce, repair damage, and respond to our environment.

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Introduction

Inborn errors in metabolism

Inborn errors of metabolism are rare genetic disorders in which the body cannot properly convert food into chemical energy or any other compound in various metabolic pathways so far investigated. The disorders are usually caused by defects in single or more genes as a result of which specific proteins or enzymes which are required to break down or metabolize compounds are not properly coded resulting in faulty secondary and tertiary structures. A food product that is not broken down properly to give energy or the next compound in metabolic pathways causes significant blockage in the metabolic pathway either by accumulating substrates behind the block or deficiency of the product, resulting in a wide array of symptoms. Several inborn errors of metabolism cause developmental delay if not controlled or rectified. A large number of inborn errors of metabolism have been discovered and elucidated. All inborn metabolic errors are genetically transmitted typically in an autosomal recessive or X-linked recessive fashion. A few of them are highlighted in this chapter.

Disorders of carbohydrate metabolism

Galactosemia, an autosomal recessive inheritable metabolic disorder caused due to mutation in the GALT gene located on the short arm of chromosome 9 coding for the engyme (galactose-1- phosphate uridyl transferase) needed for the proper utilization of galactose into energy yielding pathways. Lactose is the major sugar present in milk and it is digested into glucose and galactose. Further galactose is digested and broken down to yield energy. In the absence of GALT engyme, galactose gets accumulated and elevates blood gulactose level, this build up of galactose causes cellular damage to the liver, eye and brain, and may even cause death to neonates.[1]

Hereditary fructose intolerance, is an autosomal recessive disorder caused by mutation of the Aldo B gene located on chromosome 9q22.3.In the deficieny of Aldolase B engyme, its substrate, fructose-1-phosphate (F1P), accumulates in the liver and kidneys and has a variety of adverse effects. Aldolase B is the only enzyme that breaks down F1P and facilitates its entry into the Kreb's cycle. In the absence of fructose breakdown aldolase B engyme, fructose 1-phosphate is unabsorbed. Fructose osmotically reduces the absorption of water which accumulates in the gut where its breakdown by the normal colonic bacteria (in the gut) to short chain fatty acids and release of the gases hydrogen, carbon dioxide and methane ensues. The abnormal increase in hydrogen can be detected with the hydrogen breath test, one of the techniques employed to assess patients with suspected fructose malabsorption. Symptoms of malabsorption include, bloating, diarrhoea or constipation, flatulence, and stomach pain due to muscle spasms and many more. [2,3,4]

Fructose 1,6-diphosphatase deficiency(FDP-ase), is an autosomal recessive disorder of gluconeogenesis. It converts fructose 1,6 -diphosphate (FDP) to fructose 6-phosphate (F-6-P), which permits endogenous glucose production from gluconeogenic amino acids (eg, alanine and glycine), glycerol, or lactate. Lack of FDPase accumulates intrahepatocellular

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FDP, which inhibits gluconeogenesis and, if intracellular phosphate stores are depleted, inhibits glycogenolysis. The inability to convert lactic acid or glycerol into glucose leads to hypoglycaemia, lactic acidosis, and glyceroluria. [5]

Glycogen storage diseases (GSDs) is another inheritable genetic disorder where storage of excessive glycogen due to lack of specific enzyme which breaks down glycogen to glucose. Glycogen is mainly stored in muscles and liver and when excess storage of glycogen in muscles and in liver remain unmetabolized, it leads to various disease types summarized below:-

The main types of GSDs categorized by number and name and include:

Type I- (Von Gierke disease, defect in glucose-6-phosphatase)—most common type of GSD; accounts for 90% of all GSD cases.

Type II- (Pompe's disease, acid maltase deficiency).

Type III- (Cori's disease, debrancher enzyme deficiency).

Type IV- (Andersen's disease, brancher enzyme deficiency).

Type V- (McArdle's disease, muscle glycogen phosphorylase deficiency).

Type VI- (Hers' disease, liver phosphorylase deficiency).

Type VII- (Tarui's disease, muscle phosphofructokinase deficiency).

Type IX- (liver glycogen phosphorylase kinase deficiency). [6]

Disorders of amino acid metabolism

Phenylketonuria, is an autosomal recessive genetic disorder causing inborn error in amino acid metabolism. This defect occurs due to deficiency in production of hepatic enzyme phenylalanine hydroxy-lase encoded by PHA gene. This enzyme converts phenylalanine to tyrosine. Tyrosine is another amino acid and is one of the main constituents of protein synthesis and further helps in building up the body. In the absence of the enzyme phenylalanine hydroxy-lase, phenylalanine gets accumulated and interferes with brain development and also causes deficiency of tyrosine. The excess of phenylalanine get converted to phenylketone, a bad smelling compound for which the disease is named. This defect resuls in mental disorders and in neuropsychological dysfunctioning [7]

Hereditary tyrosinemia

These are of three types, type 1 Tyrosinemia(also known as Hereditary Infantile Tyrosinemia and Hepatorenal Tyrosinemia), type 2 Tyrosinemia (Oculocutaneous tyrosinemia) and type 3 Tyrosinemia.

Type 1 Tyrosinemia is a genetic metabolic disorder caused due to lack of the enzyme fumaryl lacetoacetate hydrolase (FAH) and p-hydroxyphenylpyruvate hydroxylase. FAH enzyme is needed in the breakdown of the amino acid tyrosine. In the absence of the above enzyme tyrosine gets abnormally accumulated in the liver and results in the liver dysfunctioning. Tyrosine also gets accumulated in the kidney and in central nervous system.

Type 2 Tyrosinemia disorders are inherited autosomal recessive characters, an enzyme defect in hepatic tyrosine amino transferase (TAT) encoded by the gene TAT. This enzyme is one of the enzymes needed for the digestion of tyrosine. [8]

Type 3 tyrosinemia is an inheritable autosomal recessive disorder caused by the deficiency of the enzyme 4-hydroxyphenylpyruvate dioxygenase (4-HPPD) encoded by HPD gene, an enzyme involved in the catabolic pathway of tyrosine. Enzyme deficiency disorder is characterized by elevated levels of blood tyrosine and massive excretion of tyrosine derivatives into urine [9,10]

Maple syrup urine disease [MSUD]: is the inability to metabolise the three branched chain amino acids, leucine, isoleucine and valine. The breakdown products of these amino acids, alpha- keto acids, accumulate and are eliminated through urine. The urine consequently has the odour of maple syrup or burned caramel. This disorder is non-treatable, the infant becomes severely acidotic and may prove fatal.

Nonketotic hyperglycinemia (NKH): is a rare genetic inherited autosomal recessive disorder. This disease is characterized by elevated concentration of glycerine in the body fluids due to molecular disorder in the glycine cleavage enzyme system (GCS). The glycine cleavage enzyme system comprises of four proteins P-, T-, H- and L-proteins, and mutations have been described in the GLDC, AMT and GCSH genes encoding the P-, T-, and H-proteins respectively.[11,12]

Homocystinuria

Cystathionine beta synthase deficiency or CBS deficiency. Inherited autosomal recessive trait, amino acid methionine metabolism disorder and also known as multisystemic clinical disorder. Mutations in the CBS gene cause the most common form of homocystinuria. The CBS gene encodes for production of an enzyme called cystathionine beta-synthase. This disease results in the elevated plasma and urine homocysteine and methionine levels and decreased levels of cystathionine and cysteine because of deficient activity of cystathionine beta synthetase, the enzyme catalyzing conversion of homocysteine to cystathionine.[13,14]

Urea Cycle Disorder or Urea Cycle Defects:

Citrullinemia, is an autosomal recessive urea disorder. It is of two types due to defects in two genes at different locations on chromosomes. Citrullinemia type I (CTLNI) and

Citrullinemia type II (CTLN2), mutations have been reported in the genes ASS and SLC25A13 respectively.[15]

Citrullinemia type I (CTLNI) disorder is a result of improper activity of enzyme arginino-succinate synthetase (ASS) which plays an important role in the urea cycle and in the processing of nitrogen metabolism. Due to mutation in gene ASS the above activities are not performed well and results in disruption in the digestion of nitrogen and this lead to excess accumulation of nitrogen in the form of ammonia and other by-products of the urea cycle in the blood and cause type I citrullinemia.[16]

Citrullinemia type II (CTLN2), is an autosomal recessive disorder caused by a mutation in the SLC25A13 gene, which inhibits the production of enzymeArginino-succinic acid synthetase. Mutation in the above gene results in improper urea cycle and hyperammonemia and elevates citrillin which disrupts the production of proteins and nucleotides.[17]

Ornithine transcarbamylase (OTC) deficiency is an X-linked inherited mitochondrial enzyme (mainly in the mitochondrial matrix of liver cells) that catalyze the synthesis of citrulline from carbamoyl phosphate and ornithine in the urea cycle. Mutation in the OTC gene located at Xp21.1 leads to a single base change (CCG to ACG) in exon 7, leading to the substitution of the amino acid threonine for a proline at position 225. Deficiency in the OTC production leads to hyperammonemic state which is toxic and lethal.[18,19] And otherUrea Cycle Disorders are (c) arginosuccinic aciduria, (d) Carbamoyl phosphate synthetase I deficiency (e) Argininemia and (f) NAGS deficiency.

Disorders of organic acid metabolism (organic acidurias): Alcaptonuria (**black urine disease**) is a rare inherited genetic disorder of phenylalanine and tyrosine metabolism. This is an autosomal recessive trait the defects of which have been mapped on chromosome 3, between regions 3q21-q23.This disorder results due to a defect in the enzyme homogentisate 1,2-dioxygenase (HGD), which participates in the degradation of tyrosine. The HGD enzyme catalyses the conversion of homogentisic acid (HGA) into 4-maleylacetoacetic acid but due to defect in the gene the enzyme HGD is not encoded as a result, homogentisic acid and its oxide, called alkapton, accumulate in the blood and are excreted in urine in large amounts.[20]

Disorders of fatty acid oxidation

Medium-chain acyl-coenzyme: A dehydrogenase deficiency (often shortened to MCADD) is an autsomal recessive disorder of Beta-oxidation of fatty acid also known as Beta-oxidation defects, are a distinct type of organic acid disorder. Deficiency of MCAD prevents the body from converting certain fats to energy particularly during fasting. This defect occurs due to mutation in ACADM gene, this gene encodes for MCAD. This abnormality leads to hypoketotic hypoglycemia, hyperammonemia, and cardiomyopathy, and may present clinically with Reye's syndrome. Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is among the most common of all inborn metabolic errors and plays significant role in SIDS (sudden infant death syndrome) cases.[21, 22]

Disorders of steroid metabolism: Congenital adrenal hyperplasia (CAH) caused due to mutation in gene encoding for protein/enzyme Steroid 21-hydroxylase. This is an autosomal recessivegenetic disorder and the genes for CAH are located on the chromosome number 6.(Steroid hormones bind to specific intracellular receptors which upon dimerization interact with the DNA in the nucleus. As a result gene activity is modulated and hormone specific response occurs.). [23]

Disorders of mitochondrial function: Kearns-Sayre syndromeis a multisystem disorder caused by rearrangements of mitochondrial genome including various deletions and / or duplications. Symptoms appear before the age of 20 years. External ophthalmoplegia, pigmentary retinopathy, ragged-red fibers on muscle biopsy, progressive degeneration of cardiac conduction system, ataxia and brain abnormalities such as leukoencephalopathy. [24, 25, 26, 27]

Disorders of peroxisomal function: Peroxisomal Biogenesis Disorders (PBD) refers to the disorders in the Zellweger Spectrum and are lethal autosomal recessive diseases caused due to mutation in the PEX gene. PEX gene encodes for the proteins known as peroxins associated in the metabolic pathway of the peroxisome. Zellweger Spectrum includes PBD phenotypes which are three in number i.e, (a) Zellweger Syndrome (ZS), (b) Neonatal Adrenoleuko-dystrophy (NALD) and (c) Infantile Refsum Disease (IRD). There are also two single enzyme peroxisomal disorders: acyl-CoA oxidase deficiency and D-bifunctional protein deficiency and are closely related to PBDs. These are all rare, genetic, metabolic, terminal conditions affecting all major systems of the body. They may present with features similar to the lysosomal storage disorders. Common features of Zellweger syndrome include large fontanel, organomegaly, Down-like facies, seizures and chondrodysplasia punctata. [28, 29, 30,31]

Lysosomal Storage Disorders (LSDs): Most of the LSDs are the results of the defective lysosomal acid hydrolysis of endogenous macromolecules and their consequent accumulation.LSDs are categorised asmucopolysaccharidoses (MPSs), sphingolipidoses, mucolipidoses, glycoproteinoses, oligosaccharidoses, and glycogen storage diseases. These diseases are the results of the mutation in a single gene and are inherited in an autosomal recessive manner, exceptions like Fabry disease and Hunter disease (also called MPSII), which are X-linked recessive diseases. Glycogen Storage Disease (Pompe disease) due to deficiency of protein alpha-1, 4-glycosidase or acid maltase mutation in the gene located at 17q23. Sphingolipidoses (Tay-Sachs) beta-hexosaminidase A (alpha chain) 15q23-q24,(Niemann-Pick A and B) Sphingomyelinase 11p15.1-p15.4, (Fabry) alpha-galactosidase A Xq22, Lipidoses (Wolman) Acid lipase 10q23.2-q23.3,

Glycoproteinoses (Fucosidosis) alpha-fucosidase 1p24 and many more have been identified in modern times due to defective gene functioning, mutations leading to faulty amino acid substitutions, deletions etc. [31]

Doubtless more such disorders of metabolism will be discovered in future as our knowledge increases.

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