INBORN ERRORS OF METABOLISM-Present Scenario

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INTRODUCTION

Rare Disease Day®

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It has been found in almost all things ,that what they contain of useful or applicable is hardly *perceived* unless we are *deprived* of them or they become *deranged* in some way.

Taken from Garrod quoting a letter written by William Harvey in 1657—Value of studing human varients

- **<u>Every individual is a deviant</u>** in terms of biochemical individuality- every person has an inherited predisposition to disease in a particular circumstances

- The power of current cellular, molecular and metabolic techniques is that they provide a vast amount of new information.

Williams R.J.Biochemical Individuality.Newyork,Wiley,1956

INCIDENCE

- Individual inborn errors of metabolism (IEM) are rare disorders, most having an incidence of less than 1 per 100,000 births.

- In India, the prevalence of Inborn errors of metabolism (IEM) is one in 2497 newborns

http://www.uptodate.com/contents/inborn-errors-of-metabolism-epidemiology-pathogenesis-and-clinical-features/abstract/8

*www.**indian**pediatrics.net/dec2013/dec-1155-1156.htm*

- In India, the prevalence of Inborn errors of metabolism (IEM) is one in 2497 newborns ; congenital hypothyroidism incidence is **2.1 per 1000** and G6PD deficiency is **2-7.8%** . Worldwide, the incidence of IEM is more than **1/1000** .
- *www.**indian**pediatrics.net/dec2013/dec-1155-1156.htm*

Inborn Error of Metabolism

- The term *inborn error of metabolism* was introduced in 1908 by British physician Sir Archibald Garrod

- He postulated that inherited disorders result from reduced activity / complete absence of enzymes involved in certain biochemical pathways.

Sir Archibald Garrod, around 1910

- Garrod's identification and categorization of inborn errors of metabolism represented an important conceptual advance in 20th-century medical genetics.

- His lectures are perceived today as landmarks in the history of biochemistry, genetics and medicine

- Garrod presented his concept of 'the inborn error of metabolism' in the 1908 Croonian Lectures to the Royal College of Physicians (London); he used albinism, alkaptonuria, cystinuria and pentosuria to illustrate.

IEM-History

- Concepts and evidence were salient primarily among **biochemists**, controversial among **geneticists** and least salient among **physicians** who were not attracted to rare hereditary 'traits'.

- In 2008, at the centennial of Garrod's Lectures phenotype-modifying alleles, a gene product with known structure and function, and altered function in the Mendelian variant was accepted.

- Historical perspective—inborn errors of metabolism were first recognized by Archibald Garrod, whose studies illustrated the dynamic aspects of human biochemistry and how unitary hereditary factors caused variation in the turnover of physiological metabolites derived from dietary components. He proposed that the activity of enzymes involved in human metabolism (e.g. of tyrosine degradation) were subject to control by specific genes, and several of the disorders studied by him were subsequently shown to be the result of block at some point in normal metabolism. He also noted the importance of consanguinity in the clinical expression of rare genetic variants which behave as recessive human disease traits.

Inborn errors of metabolism

- Definition—the inborn errors of metabolism are those inherited diseases in which the phenotype includes a characteristic constellation of chemical abnormalities related to an alteration in the catalytic activity of a single specific enzyme, activator or transport protein.
- About 1500 such disorders have been characterized, with an estimated overall birth frequency of 1 in 4000 live births in non-consanguineous popluation groups. While these are now recognized as belonging to the category of **'rare diseases',** they can also be viewed in an evolutionary context as paradigmatic examples of the interplay between the ***constitutional and environmental aspects*** of disease.
- Sophisticated, and increasingly inexpensive DNA-sequencing technologies, including whole-genome methods, now permit rapid identification of the molecular causation of metabolic diseases occurring in small pedigrees due to rare disabling mutations affecting any of the ~$2x10^4$ expressed human genes.

Basis of IEM

- Every characteristic of human anatomy and physiology is determined by biochemical reactions catalysed by enzymes.

- These in turn are determined by our genetic make-up. If a gene is defective or missing it will result in a defective or missing enzyme—a so-called **Inborn Error of Metabolism.**

- Knowledge of the defective enzyme and its gene(s) may make possible the **rational treatment** of the resulting disease.

- **Newborn screening has dramatically** changed clinical practice for care of children with inborn errors of metabolism (IBEM). For those conditions that are identified by newborn screening, management has moved from a reactive response to one that permits active, early identification.
- In the absence of protocols based on clinical evidence, clinicians caring for patients with very rare disorders are faced with challenging treatment decisions.
- Historically, practitioners have been left to determine how they will treat children with inborn errors of metabolism (IBEM) based on how their mentor approached treatment, what they have read in a manual or text, and what they have learned from their own clinical experience.

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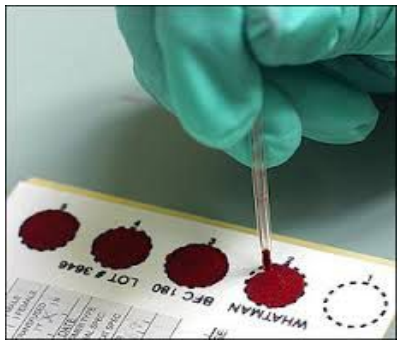
PRESENT MODALITIES



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1.Clinical level-surgical correction and repair

2.Metabolic level-prevent substrate accumulation

3.Protein level-activate/stabilize a protein

4.Cellular level-organ/tissue/cellular transplant

Points to remember…..

- Pre-symptomatic diagnosis of these disorders can minimize the irreversible complications and significantly improve the long-term prognosis, by early treatment.

- This will prevent a lot of anxiety, wastage of time and money for parents and suffering for affected children.

- With only a handful of children diagnosed with inborn errors of metabolism each year in any given state, the lack of controlled studies and evidence-based standards is not a surprising outcome.

REFERENCES

- www.dmd.nl/mutnomen.html
- www.ebi.ac.uk/mutations/recommendations/naming.html
- www.ncbi.nlm.gov/collab/FT/index.html
- Scriver.Beaudet.Valle.Sly.The Metabolic and Molecular Bases of Inherited Diseases.Eighth edn.

Thank you

Inborn Errors of Metabolism

- IEM as a group are not rare: occur 1 in 5000 births collectively
- Often treatable if diagnosed
- Most difficult task for clinician is to know when to consider IEM and which tests to order for evaluation
- Don’t be fooled--other diagnoses like sepsis, ICH, pulm. hem. may accompany IEM
- Clues to presence of IEM may often be found in FH

Incidence of Inborn Errors

Class	No. of Disorders Known	Incidence
Critical, life threatening disorders of infancy	70-80	~1:5,000
Serious disorders compromising health in infants/adults	>300	~1:1,000
Common disorders of any age	>300	~1:50

Metabolic Diseases Which Can Present in Crisis

- Defects of glucose homeostasis (20)
- Defects of amino acids (10)
- Defects of fatty or organic acids (20)
- Defects of Lactate/Pyruvate (20)
- Defects of Peroxisomes
- Others

“Stumbling Blocks” in Diagnosing Inborn Errors of Metabolism

- **Signs and symptoms are often nonspecific**
  - Routine childhood illnesses excluded 1st
  - Inborn errors considered only secondarily
- **Unfamiliarity with biochemical interrelationships/ diagnostic tests**
  - Inappropriate sample collection
  - Inappropriate sample storage

- **Every child with unexplained . . .**
  - Neurological deterioration
  - Metabolic acidosis
  - Hypoglycemia
  - Inappropriate ketosis
  - Hypotonia
  - Cardiomyopathy
  - Hepatocellular dysfunction
  - Failure to thrive

. . . should be *suspected* of having a metabolic disorder