A COMPREHENSIVE REVIEW OF INBORN ERRORS OF METABOLISM IN PAEDIATRIC AGE

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ABSTRACT: BACKGROUND: Inborn errors of metabolism encompass a class of inherited diseases involving disorders of metabolism**.** An understanding of the major clinical manifestations provides the basis for understanding when to consider diagnosis. A high index of suspicion is most important in making the diagnosis. **AIMS AND OBJECTIVES:** To evaluate clinicopathological features of Inborn errors of metabolism and diagnostic workup of the cases. **MATERIAL AND METHODS:** In the present study we evaluated 33 patients with inborn errors of metabolism presenting at Paediatric referral Hospital, Hyderabad from 2006 to 2011. The cases were analysed for clinical presentation, investigations done for clinical evaluation and pathological findings.**RESULTS:** A provisional diagnosis of inborn errors of metabolism was made only in 43% of cases and the final diagnosis was established after confirmatory investigations as Glycogen storage disorders, Gaucher's disease, Niemann-Pick's disease. **CONCLUSION:** Patients especially below 10 years of age born out of consanguineous marriages, few having siblings with similar history or history of early death should arouse suspicion of Inborn errors of metabolism. If these patients present with complaints of delayed milestones, abdominal distension, along with hepatomegaly with or without splenomegaly, differential diagnosis of Inborn errors of metabolism should be considered.
KEYWORDS: Delayed milestones, Hepatomegaly, Splenomegaly, Inborn errors of metabolism.

INTRODUCTION: Inborn errors of metabolism are now referred to as inherited metabolic diseases. The majority are due to defects of single genes that code for enzymes that facilitate conversion of various substrates into products. In most of these conditions problems arise due to accumulation of substances which are toxic or interfere with normal function or due to the effects of reduced ability to synthesize essential compounds.

The British physician, Sir Archibald Garrodis entitled as father of "inborn errors of metabolism" for his pioneering work in revealing the biochemical basis of alkaptonuria in the early 20th century [1]. He coined the term "inborn errors of metabolism"[2].

All inborn errors of metabolism are inherited and have established genetic basis. They are typically transmitted in autosomal recessive or X-linked recessive manner [3].

Usually inborn errors of metabolism are those conditions which are diagnosed incorrectly. Even the manifestations of these disorders are grave and are of a wide range affecting almost all the systems. The usual manifestations are growth failure, developmental delay; central nervous defects; skin abnormalities, dental abnormalities, hematologic abnormalities, renal abnormalities, cardiovascular manifestations like hypotension or hypertension, heart failure, liver manifestations like hepatomegaly, jaundice and endocrine abnormalities.

The diagnosis of inborn errors of metabolism needs a high index of suspicion. History and clinical manifestations often provides valuable clues which comprise positive family history, consanguinity, loss of developmental milestones, siblings with unexplained infant/neonatal death, hepatomegaly and/or splenomegaly, metabolic acidosis, neutropenia and/or thrombocytopenia and unusual odor in urine or sweat [2].

The present study aims to evaluate clinicopathological features of inborn errors of metabolism and diagnostic workup of the cases.

MATERIAL AND METHODS: The cases diagnosed as inborn errors of metabolism during 5 years duration (2006-2011) at a Pediatric Referral hospital, Hyderabad were incorporated in this study. The cases were analysed for clinical presentation, investigations done for clinical evaluation and pathological findings. The sex, age at presentation, family history of the patients and presenting symptoms were documented. Various findings on physical examination were also documented.

Investigations like routine laboratory tests, sickling test, smear for malarial parasite, liver function test, T3, T4, TSH, fundus examination, ultrasound examination and computed tomography as indicated in the individual case were also done. Certain other specific investigations required for definitive diagnosis was also done such as bone marrow study, histopathology and enzyme assay. Based on the above findings a provisional diagnosis and a final diagnosis was made in different cases and compared.

OBSERVATIONS AND RESULTS: Of all the cases, 73% were boys and 27% were girls. The male to female ratio 2.6:1 showing male preponderance. In all the 33 cases under the study the age of presentation was below 10 years. Most common age group was 0-2 years (Table 1). Inborn errors of metabolism present with diverse symptoms. In our study, most frequent presenting complaints were abdominal distension, delayed milestones, seizures and fever (Table 2). A history of consanguineous marriage was present in 33% cases and a similar family history was present in 15% of cases (Table 3).

On examination hepatomegaly was present in 100% of cases and splenomegaly in 54% of cases. Other findings like pallor, icterus, coarse facial features and short stature were found in 3%, 2%, 3% and 2% of cases respectively (Table 4). Apart from the regular and routine investigations, a few other investigations were conducted. Of these, bone marrow study was definitive in 36% of cases. Similarly, histopathology was definitive in 72% cases and enzyme assay confirmed the provisional diagnosis in 30% cases (Tables 5, 6).

With the help of the basic investigations, a provisional diagnosis of inborn errors of metabolism was made only in 43% of cases. The others were diagnosed to be hemolytic anaemia, hypothyroidism, pyrexia of unknown origin, hepatomegaly for evaluation, hematologic evaluation and Wilson's disease (Chart 1).

A final diagnosis was made based on the confirmatory investigations as 70% (23 cases) being glycogen storage disease, 15% (5 cases) being Gaucher's disease and the other 15% (5 cases) being Niemann-Pick's disease. (Table 7)

CASES OF INBORN ERRORS OF METABOLISM IN OUR STUDY

Glycogen Storage Disease (23/33-70%)

4 years old boy born of consanguineous marriage, presented with abdominal distension since 1 year. On examination there was hepatosplenomegaly. Liver biopsy was done. Biopsy revealed hepatocytes distended with glycogen. (Figure 1 and 2)

Gaucher's Disease (5/33-15%)

A 2year old boy born of consanguineous marriage presented with fever on and off. On examination there was hepatomegaly. Bone marrow examination showed large cells with crumpled tissue paper like cytoplasm. (Figures 3 and 4).

Niemann-Pick's Disease (5/33-15%)

A 1.5year old boy born of consanguineous marriage presented with fever and delayed milestones. On examination there was hepatosplenomegaly. Fundus examination of the eye showed cherry red spots, bone marrow examination was done and showed sea blue histiocytes with multiple cytoplasmic vacuoles. (Figures 5, 6and 7).

DISCUSSION: In Early 1990s the study of genetic metabolic disorders began with the discovery of the first inborn errors of metabolism, alkaptonuria, pentosuria, cystinuria, and albinism by Sir Archibald Garrod [4].

The current classes of inborn errors of metabolism include disorders of protein metabolism, disorders of carbohydrate metabolism, lysosomal storage disorders, disorders of lipid metabolism, mitochondrial disorders, peroxisomal disorders and trace metal disorders **[5].**The classes and examples of each are depicted in Table 8.

Inborn errors of metabolism that affect the enzyme activity will lead to accumulation of substrate or its derivatives [6]. Lipid storage disorders associated with hepatomegaly and splenomegaly in the first few months of life include GM1-gangliosidosis type I, Gaucher disease, and Niemann-Pick disease [7].

In the present study, all 33 cases presented below 10 years of age. Most common clinical presentation was abdominal distension, followed by delayed milestones, seizure and fever. In a study by Gulati et al (2000). The commonest clinical findings reported were seizures (26%) followed by delayed milestones (18%) **[8]**.

In our study 11 of the cases were products of consanguineous marriage and five had family history of similar complaints. This high rate of consanguinity was attributed to the high incidence of inborn errors of metabolism which is consistent with the available literature.

Kamate et al. (2010) reported that high rate of consanguinity was liable for high incidence of inborn errors of metabolism (2.6%) [8]. Ananth et al. (2009) **[5]** reported consanguinity in 6.9% of the cases he studied.

Our study revealed that of 33 cases of inborn errors of metabolism, 23 cases (70 %) were reported as glycogen storage disorders, 5 (15 %) cases as Gaucher's disease and 5 cases (15 %) Niemann- Pick's disease.

Kumta. (2005) reviewed 1016 cases of inborn errors of metabolism. Majority were amino acid disorders with 204 cases (20.1%). There were 35 cases (3.4%) of glycogen storage disorders, 24 (2.36 %) cases of Gaucher's disease, 33cases (3.2 %) of Neiman pick's disease **[9].**In comparison our series showed increased incidence of glycogen storage disorders and lysosomal storage disorders**.**

Applegarth et al. (2000) reported the incidence of inborn errors of metabolism with glycogen storage disorders being 2.3 per 100,000 live births and that of lysosomal storage disorders being 7.6 per 100,000 live births [10]. While Coelho et al. (1997) reported the incidence of lysosomal storage disorders to be around 59.8% [11].

History of consanguinity, clinical manifestations and laboratory findings play an important role in diagnosis of inborn errors of metabolism [12]. Hema et al. (2009) [13] reviewed 16 children with inborn errors of metabolism with the mean age of presentation being 11.7±20 months. Consanguineous marriage was reported in 13 cases. The Male to female ratio was 1.2:1. Respiratory distress and developmental delay were commonest clinical findings.

Most of the cases of Niemann-Pick's disease are treated symptomatically. If the patient is having massive splenomegaly, splenectomy should be done. For the Gaucher's disease enzyme replacement therapy is available.

CONCLUSION: Children who present with delayed milestones, short stature, icterus, coarse facies, cherry red spots in the fundus especially below 10 years of age and are born out of consanguineous marriages, few having siblings with similar history or history of early death should arouse suspicion of inborn errors of metabolism. Diagnosis does not require extensive knowledge of biochemical pathways or individual metabolic diseases. An understanding of the major clinical manifestations of inborn errors of metabolism provides the basis for when to consider the diagnosis. Optimal outcome for children with inborn errors of metabolism depends upon recognition of the signs and symptoms of metabolic disease prompt evaluation and referral to Centre familiar with the evaluation and management of these disorders.

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Table 1: Age at Presentation

AGE GROUP	NO. OF CASES
0-2 years	19
2-5 years	9
5-10 years	4
>10 years	1

Table 2: Clinical Presentation

HISTORY	NO OF CASES
Abdominal distension	14
Delayed milestones	9
Fever	9
Generalised weakness	2
Hypoglycaemia symptoms	3
Jaundice	4
Seizure	9
Shortness of breath	3

Table 3: Relevant History

HISTORY	NO. OF CASES	PERCENTAGE
Consanguineous marriage	11	33.33%
Family history of Similar complaints	5	15.15%

Table 4: Physical examination

EXAMINATION FINDINGS	NO. OF CASES
Pallor	3
Icterus	2
Coarse facial features	3
Short stature	2
Hepatomegaly	33
Splenomegaly	18

Table 5: Investigations

INVESTIGATION	NO. OF CASES
Routine tests (CBP, CUE, RBS, Sr. Cr., Blood Urea, chest X-ray)	33
Sickling test	4
Smear for MP	5
Liver function tests	23
T3, T4, TSH	3
Fundus examination	5
Ultrasound abdomen	32
CT scan	3

Table 6: Investigations for Definitive Diagnosis

INVESTIGATION	NO. OF CASES	PERCENTAGE
Bone marrow study	12	36.36%
Histopathology	24	72.72%
Enzyme assay	10	30.30%

Table 7: Final Diagnosis

FINAL DIAGNOSIS	NO. OF CASES	PERCENTAGE
Glycogen storage diseases	23	70%
Gaucher's disease	5	15%
Niemann-picks disease	5	15%

Table 8: Inborn errors of metabolism with examples

Metabolic Disorder	Examples
Disorders of protein metabolism	Aminoacidopathies, Organic acidopathies, Urea cycle defects
Disorders of carbohydrate metabolism	Carbohydrate intolerance disorders, Glycogen Storage Disorders, Disorders of Gluconeogenesis and Glycogenolysis.
Lysosomal storage disorders	Gaucher's disease, Niemann-Pick disease
Disorders of lipid metabolism	Fatty acid Oxidation Defects , Sphingolipidoses
Mitochondrial disorders	Kearns-Sayre syndrome
Peroxisomal disorders	Zellweger syndrome, Adreno leucodystrophy
Trace metal disorders	Menke's Kinky Hair syndrome, Wilson's disease

FIGURES

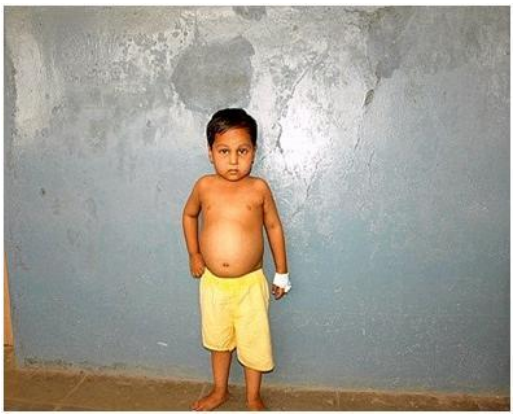

Figure 1: A child with glycogen storage disorder showing distended abdomen.

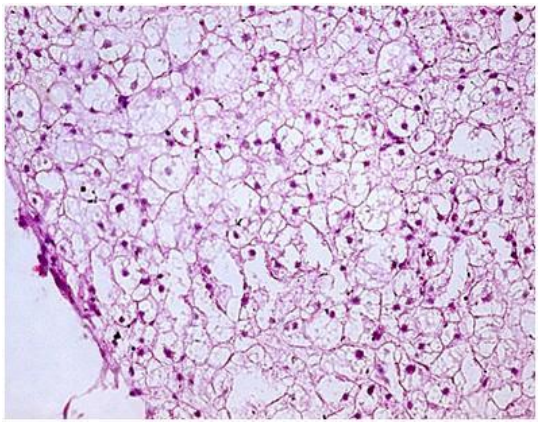

Figure 2: A photomicrograph of liver biopsy showing hepatocytes distended with glycogen (H & E, 40X)

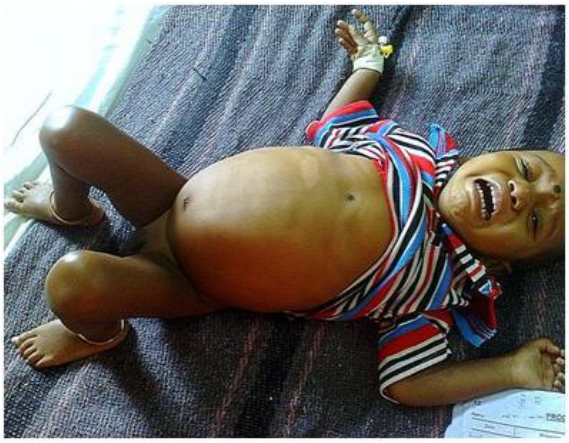

Figure 1: A 3 year old child with Gaucher's disease showing hepatosplenomegaly.

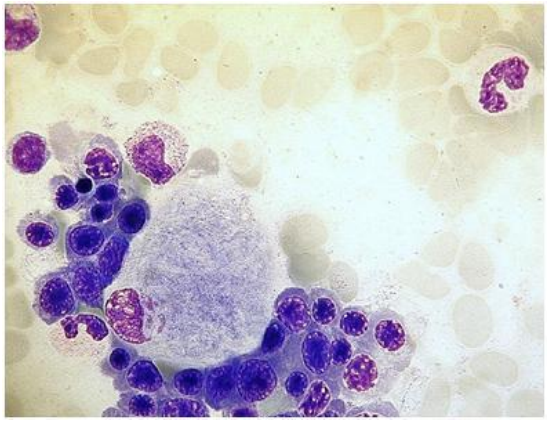

Figure 2: A Photomicrograph of the bone marrow showing cells with crumpled tissue paper like cytoplasm.(H & E, 100 X)

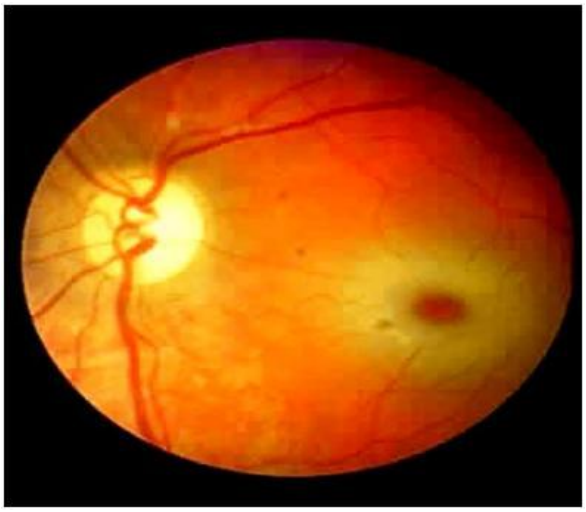

Figure 3: Fundus examination of the eye in a 1 year old boy with Niemann-Pick's disease showing a cherry red spot.

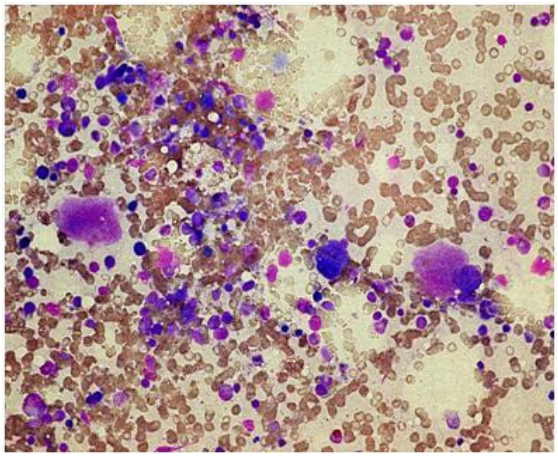

Figure 6: A photomicrograph of bone marrow showing sea blue histiocytes, large cell with multiple small cytoplasmic vacuoles. (H & E, 40 X)

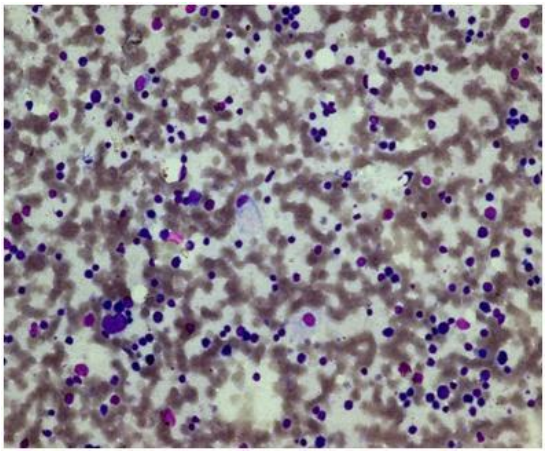

Figure 4: A photomicrograph of bone marrow of a child with Niemann-Pick's disease showing foamy, lipid laden macrophages (H & E, 100X)

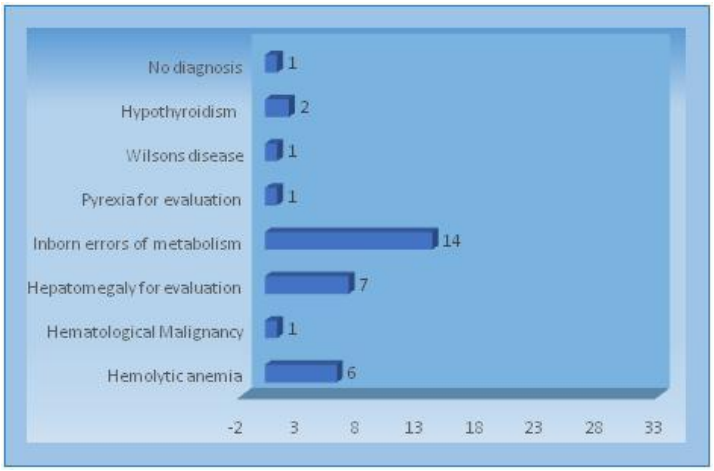

Chart 1: Provisional diagnosis.

ORIGINAL ARTICLE

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