Hepatomegaly: A Major Clinical Sign in Some Metabolic Disorders

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Abstract

This study included 18 cases with hepatomegaly referred to the Human Genetics Department, National Research Centre with a suspicion of a metabolic disorder from 2006 to 2008.

The aim of our study was to find out the importance of hepatomegaly as a sign for many metabolic disorders and their frequency among other disorders with hepatomegaly.

All cases were subjected to clinical and biochemical studies. 12 cases, 66%, (10 males 83.4% and 2 females 16.6%) were diagnosed with a metabolic disease. 8 cases with mucopolysaccharidosis (MPS) (3 cases MPS I, 3 cases MPS II, one case MPS III and one case MPS VI); one case with glycogen storage disease (GSD); one case with galactosemia and 2 cases with Niemann-Pick disease type C.

75% of the diagnosed cases showed positive consanguinity and the remaining 25% were three patients with MPS II with an X linked mode of inheritance.

Key Words: Hepatomegaly – Metabolic diseases – Inborn errors of metabolism.

Introduction

HEPATOMEGALY as a clinical sign can reveal metabolic disorders with liver damage. The clinical manifestations of liver involvement which lead to suspicion of inborn errors of metabolism should alert pediatricians to the possibility of metabolic liver diseases [1].

Different etiologies of metabolic liver diseases, with specific enzymes deficiency, can lead to storage disorders e.g. lysosomal and glycogen storage diseases. Hepatocellular necrosis whether acute or subacute e.g. galactosemia which necessitate a rapid diagnosis and treatment and sometimes the manifestations are of cholestatic jaundice e.g. Niemann-Pick disease [2].

Metabolic liver disorders are mostly of autosomal recessive inheritance and other clinical manifestations associated with metabolic liver diseases differ according to the disorder. In mucopolysaccharidosis, the patient usually presents with coarse facieses, skeletal abnormalities, short stature and other features. Niemann-Pick disease may represent by neonatal hydrops or neonatal hepatitis. Other neurovisceral storage diseases, glycogen storage diseases, in addition to metabolic hepatomegaly are associated with ketotic or nonketotic hypoglycemia according to their type. In galactosemia in addition to hepatomegaly, other clinical manifestations as cataract and jaundice may present early in the neonatal period [3].

Patients and Methods

This study includes 18 cases with hepatomegaly suspected to be of metabolic origin (10 males + 8 females). They were selected from cases complaining of hepatomegaly referred to "Clinical Genetics Clinic" at National Research Center, Cairo, Egypt during the last two years (2006-2008). Selected cases had variable clinical signs and symptoms of different metabolic disorders in addition to hepatomegaly. The diagnosed cases included 10 males and 2 females, their ages ranged from 8 months to 5 years.

For each case the following was done:

• Three generations family pedigree analysis including consanguinity and other affected family members.

• Complete history taking with stress on main complaint, developmental history, past history pregnancy and delivery history.

• Detailed clinical examination with special emphasis on dysmorphic features, abdominal examination specially on liver as well as examination of different body systems.

• Anthropometric measurements especially height, weight, head circumference as a routine examination to evaluate the growth parameters of the cases.

• Other investigations especially abdominal ultrasonography to confirm hepatomegaly. Skeletal
survey, blood glucose level, blood cholesterol and MRI brain were done whenever indicated.

Biochemical studies:

Biochemical diagnosis for MPS:

1- Determination of total urinary glycosaminoglycans (GAGS):

Glycosaminoglycans (GAGS) were determined quantitatively, urinary dimethylmethylene blue (DMB) in a reaction that did not require precipitation of the GAGS. The colour was measured immediately at a wave length of 520nm. The DMB ratio was obtained by dividing the urine creatinine with GAGS concentration in mg/dl and the quantity was expressed as mg/mmol creatinine [4].

2- Two dimensional electrophoresis of the GAGS extracted from urine:

Glycosaminoglycans (GAGS) were determined qualitatively by two dimensional electrophoresis to determine possible subtypes of mucopolysaccharidosis [5].

3- Enzyme assay for the various types of MPS to confirm the diagnosis. Fluorometric enzyme assays where done according to the abnormal electrophoretic pattern to confirm the type of mucopolysaccharidosis.

Biochemical assay for the diagnosis of niemann-pick:

- Shingomylinase activity according to Ta-Yan Chang et al., 2005 [7].
- Chitotriosidase activity according to Young et al., 1997 [8].
- β-glucocerebrosidase activity according to Daniels et al., 1980 [9].

Biochemical diagnosis of galactosemia:

- Determination of total galactose (galactose and galactose-1-phosphate) in dried blood spot using Quantitative Colorimetric Enzyme-linked immunoassay test.

1- Punch 4mm spots into microtitration plate wells. Pipette 10×1 precipitation reagents into each spot and allow standing at room temperature for 10 minutes.

2- Pipette 100×1 of PBS or saline into each well and incubate at room temperature for 30 minutes.

3- Pipette 40×1 standard/control into designate wells of a clean flat bottom microtitration plate.

4- Transfer 40×1 of the blood spot eluate from the elution plate to the equivalent position of clean flat bottom microtitration plate and add 100×1 working enzyme reagent.

5- Incubate for 30 minutes at room temperature.

6- Add 100×1 colour reagent to each well and read the absorbance at 490/690 (dual wave length) 5 minutes after the addition of the color reagent. The galactose concentration of the patient blood spot is calculated by reference to the absorbance values of the standards. A standard curve is constructed by blotting the absorbance at 490/690nm of the standards of vertical (Y) axis against galactose concentration of the standard curve on the horizontal (X) axis [10].


Biochemical diagnosis of glycogen storage disease:

Debranching activity in RBC according to Shin et al., 1984 [12].

Results

The results of the shown Tables (1-6).

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Consanguinity</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 year</td>
<td>Male</td>
<td>+ve</td>
<td>Mucopolysaccharidosis type I</td>
</tr>
<tr>
<td>2</td>
<td>1 1/12 years</td>
<td>Male</td>
<td>+ve</td>
<td>Mucopolysaccharidosis type I</td>
</tr>
<tr>
<td>3</td>
<td>3 years</td>
<td>Male</td>
<td>+ve</td>
<td>Mucopolysaccharidosis type I</td>
</tr>
<tr>
<td>4</td>
<td>3 3/12 years</td>
<td>Male</td>
<td>-ve</td>
<td>Mucopolysaccharidosis type II</td>
</tr>
<tr>
<td>5</td>
<td>5 years</td>
<td>Male</td>
<td>-ve</td>
<td>Mucopolysaccharidosis type II</td>
</tr>
<tr>
<td>6</td>
<td>2 years</td>
<td>Male</td>
<td>-ve</td>
<td>Mucopolysaccharidosis type II</td>
</tr>
<tr>
<td>7</td>
<td>3 9/12 years</td>
<td>Male</td>
<td>+ve</td>
<td>Mucopolysaccharidosis type III</td>
</tr>
<tr>
<td>8</td>
<td>4 1/2 years</td>
<td>Male</td>
<td>+ve</td>
<td>Mucopolysaccharidosis type VI</td>
</tr>
<tr>
<td>9</td>
<td>1 7/12 years</td>
<td>Female</td>
<td>+ve</td>
<td>Glycogen storage disease type III</td>
</tr>
<tr>
<td>10</td>
<td>1 2/12 years</td>
<td>Male</td>
<td>+ve</td>
<td>Niemann-Pick type C</td>
</tr>
<tr>
<td>11</td>
<td>8 months</td>
<td>Male</td>
<td>+ve</td>
<td>Niemann-Pick type C</td>
</tr>
<tr>
<td>12</td>
<td>1 10/12 years</td>
<td>Female</td>
<td>+ve</td>
<td>Niemann-Pick type C</td>
</tr>
</tbody>
</table>
Table (2): Clinical data of 12 diagnosed cases.

<table>
<thead>
<tr>
<th>Hepatomegaly</th>
<th>Coarse facieses</th>
<th>Cardiomyopathy</th>
<th>Mental retardation</th>
<th>Myopathy</th>
<th>Skeletal abnormality</th>
<th>Delayed milestone</th>
<th>Hypotonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/12</td>
<td>8/12</td>
<td>6/12</td>
<td>8/12</td>
<td>1/12</td>
<td>9/12</td>
<td>11/12</td>
<td>6/12</td>
</tr>
<tr>
<td>(100%)</td>
<td>(67%)</td>
<td>(50%)</td>
<td>(67%)</td>
<td>(8.3%)</td>
<td>(75%)</td>
<td>(92%)</td>
<td>(50%)</td>
</tr>
</tbody>
</table>

Table (3): Clinical data of mucopolysaccharidosis cases.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Hepatomegaly</th>
<th>Coarse facieses</th>
<th>Cardiomyopathy</th>
<th>Delayed milestone</th>
<th>Skeletal abnormality</th>
<th>Mental retardation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I</td>
<td>+ve</td>
<td>+ve</td>
<td>−ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>MPS I</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>MPS I</td>
<td>+ve</td>
<td>+ve</td>
<td>−ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>MPS II</td>
<td>+ve</td>
<td>+ve</td>
<td>−ve</td>
<td>−ve</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>MPS II</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>MPS III</td>
<td>+ve</td>
<td>+ve</td>
<td>−ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>MPS VI</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
</tr>
</tbody>
</table>

Table (4): Clinical data of other metabolic diagnosed cases.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Hepatomegaly</th>
<th>Cardiomyopathy</th>
<th>Myopathy</th>
<th>Delayed milestone</th>
<th>Hypoglycemia</th>
<th>Hypotonia</th>
<th>Cataract</th>
<th>History of jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogen storage disease type III</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>−ve</td>
<td>−ve</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>+ve</td>
<td>−ve</td>
<td>−ve</td>
<td>+ve</td>
<td>−ve</td>
<td>+ve</td>
<td>−ve</td>
<td>+ve</td>
</tr>
<tr>
<td>Niemann-Pick type C</td>
<td>+ve</td>
<td>−ve</td>
<td>−ve</td>
<td>+ve</td>
<td>−ve</td>
<td>+ve</td>
<td>−ve</td>
<td>−ve</td>
</tr>
<tr>
<td>Niemann-Pick type C</td>
<td>+ve</td>
<td>−ve</td>
<td>−ve</td>
<td>+ve</td>
<td>−ve</td>
<td>+ve</td>
<td>−ve</td>
<td>−ve</td>
</tr>
</tbody>
</table>

Table (5): GAGS, glycogen and total galactose levels.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Glycosaminoglycans (GAGS)</th>
<th>Total level</th>
<th>Normal range age related</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- MPS I</td>
<td></td>
<td>58.9 mg/mmol creat</td>
<td>High for age</td>
</tr>
<tr>
<td>2- MPS I</td>
<td></td>
<td>41.7 mg/mmol creat</td>
<td>High for age</td>
</tr>
<tr>
<td>3- MPS I</td>
<td></td>
<td>23.9 mg/mmol creat</td>
<td>High for age</td>
</tr>
<tr>
<td>4- MPS II</td>
<td></td>
<td>86.4 mg/mmol creat</td>
<td>High for age</td>
</tr>
<tr>
<td>5- MPS II</td>
<td></td>
<td>70.6 mg/mmol creat</td>
<td>High for age</td>
</tr>
<tr>
<td>6- MPS II</td>
<td></td>
<td>14.9 mg/mmol creat</td>
<td>High for age</td>
</tr>
<tr>
<td>7- MPS III</td>
<td></td>
<td>16 mg/mmol creat</td>
<td>High for age</td>
</tr>
<tr>
<td>8- MPS VI</td>
<td></td>
<td>22 mg/mmol creat</td>
<td>High for age</td>
</tr>
<tr>
<td>9- Glycogen storage disease type III</td>
<td>Glycogen</td>
<td>38 mg/dl</td>
<td>0-10 mg/dl</td>
</tr>
<tr>
<td>10- Galactosemia</td>
<td>Galactose</td>
<td>47 mg/dl</td>
<td>0-5 mg/dl</td>
</tr>
</tbody>
</table>
Because the liver has a central role in the synthetic, degenerative and regulatory pathways involving carbohydrate, protein, lipid, trace element and vitamin metabolism, many metabolic abnormalities or specific enzyme deficiencies affect the liver primarily or secondarily leading to hepatomegaly with or without liver disease [13]. Hepatomegaly of metabolic origin may arise when absence of an enzyme produces a block in a metabolic pathway, when unmetabolised substrate accumulates proximal to block, when deficiency of an essential substance produced distal to an aberrant chemical reaction develops or when synthesis of an abnormal metabolite occurs [14].

In hepatomegaly of inborn errors of metabolism, clinical and laboratory evidence guide the diagnosis and the evaluation of disorder through qualitative assays which require cooperation of experienced laboratories in addition to proper clinical examination [15].

The present study included 18 patients with hepatomegaly. Twelve cases (66.6%) were diagnosed and classified clinically and biochemically into four different metabolic disorders. All the studied cases showed hepatomegaly as a cardinal clinical presentation. This sign should alert the pediatricians to the possibility of metabolic disorders especially if this finding is associated with other specific clinical signs and symptoms of an inborn error of metabolism.

Table (1) shows that 75% of the studied cases were to consanguineous marriage and the remaining 25% were cases with X-linked mode of inheritance. This agrees with many previous studies on metabolic disorders in Egypt were the consanguinity rate was about 80% among the diagnosed patients. This explains the high incidence of such autosomal recessive disorders in our population [16]. Consanguinity was 80% in the study of Shawky et al., 2008 on 16 MPS patients.

In our study the consanguinity reported is 100%, not 75%, as the 25% is to three cases with an X-linked mode of inheritance. Temtamy et al. [17] reported a consanguinity rate of 36.8% among normal Egyptian marriages which help to accumulate deleterious genes in the families.

The studied cases were 10 males and 2 females. If we exclude the three Hunter cases, it will be 7 males to 2 females with autosomal recessive disorders. Male predominance is obvious although we excluded the three X-linked cases. Male predominance has been encountered in other studies of autosomal recessive metabolic disorders. This reflects the oriental culture, which cares more for boys and rushes to manage them and give them special care over girls [16]. Still, other studies on Egyptian patients with autosomal recessive metabolic disorders showed almost 1:1 M/F, like the study of Shawky et al., 2006. Their study included 14 males (46.7%) and 16 females (53.3%) with different types of lipidosis among Egyptian children.

Table (2) shows the clinical findings of the 12 diagnosed cases with four different metabolic disorders. They all (100%) suffered from hepatomegaly.
92% had delayed milestones and 67% were mentally retarded. Cardiomyopathy and hypotonia were present in 50% of the cases and 75% showed skeletal abnormalities.

This wide range of presentation plus the characteristic features of each diagnosed disorder like cataract in galactosemia and the coarse facies in MPS, proves how metabolic disorders, although due to one enzyme deficiency each, affects many systems inside the affected cases leading to multisystem involvement in most of them. This is because the deficient enzyme leads to defective structural protein i.e. MPS and/or accumulation of metabolites which lead to organomegaly.

Table (3) shows the clinical data of the 8 MPS cases. They were three males with MPS I (Hurler disease) 37.5%, three males with MPS II (Hunter disease) 37.5%, one case 12.5% with MPS III (Sanflippo disease) and one case 12.5% with MPS VI (Maroteaux-lamy disease).

These ratios and percentages do not present the MPS distribution among the Egyptian population; they are peculiar to this study and cannot be standardized. There are population differences in the frequency of different types of MPS: MPS type II was the most common type in Israel (1/34,000) and MPS type IV in Northern Ireland (1/840,00) while Sanflippo disease type B is the most prevalent type in Greece and type A in England [18].

Shawky et al., 2008 found in their study that the commonest type among 20 MPS Egyptian patients was type III (35%), followed by MPS I (30%), MPS IV (15%), MPS II (10%) and MPS VI (10%) too. This is a totally different ratio.

A larger group of MPS patients must be studied to find out the distribution of each disorder in our population. It is likely that true incidence of the different types of MPS will become known only when progress in therapy will make it desirable to institute early screening [19].

In the present study all cases of mucopolysaccharidosis patients had hepatomegaly, mental retardation, coarse facies and skeletal abnormalities. Only 50% showed cardiomyopathy and/or valvular diseases. Shawky et al., 2008 [20] reported that cardiac manifestations were found in 40% and hepatomegaly in 75% of their MPS studied cases.

This is different because we choose cases with hepatomegaly. Also, seven of our cases suffered from type I, II and VI which all suffer from enlarged liver as a cardinal sign.

Mental retardation was found in 65% of their cases, while skeletal deformities or abnormalities were found in 70% of the cases of their study. This difference might be attributed to the difference in the types diagnosed in each study. For example we did not include type IV (Morquio disorder), who have normal mentality, while, Shawky et al., 2008 [20] diagnosed two Morquio patients. Regarding the skeletal abnormalities found only in 70% versus 100% among our cases, this is due to the age difference in both studies. Their mean age was 1.37+1.05 years, while the mean age of this study MPS cases was 2.4 years. Our patients are older and accordingly show most of the skeletal abnormalities.

Table (5) All the MPS cases showed biochemically high total level of glycosaminoglycans (GAGS) in urine, electrophoretic separation of GAGS extracted from urine showed different pathologic pattern diagnostic of each type of the disorder.

The specific enzyme assay was done accordingly and showed almost zero activity, Table (6). All MPS suspected cases should be evaluated through, estimation of their GAGS in urine, two dimensional electrophoretic separation of GAGS extracted from urine and determination of the specific enzyme activity according to the abnormal electrophoretic pattern. This is the most accurate and definite diagnosis of MPS.

All the eight MPS cases were diagnosed at the age between one and five years with a mean age of diagnosis of 2.4/12 years. This is a relatively high age for the diagnosis of MPS. Most of the signs and symptoms of the disease become obvious between 1 to 2 years. The late diagnosis might be due to the low awareness by the pediatrician of the metabolic disorders and the steps of the biochemical diagnosis.

All the eight cases were males, if we exclude the three Hunter cases; the five remaining patients although suffering from an autosomal recessive disorder are males as well. This might be due to the small number of patients.

Shawky et al., 2008 [20] in a study on 20 MPS cases had 12 males and 8 females. If we exclude the two Hunter cases they will be 10 males and 8 females, which also show some male predominance.

Patient number 9 a glycogen storage disease type III, presented only by repeated intermittent attacks of hypoglycemia. Clinical examination showed hepatomegaly, cardiomegaly, delayed mile stones and hypotonia.
Biochemical study showed high level of total glycogen and marked deficiency of amylo-1,6 glucosidase enzyme which confirmed the diagnosis of type III. This disorder is part of a rare group of autosomal recessive disorders affecting the glycogen synthesis and degradation cycle mostly due to deficiency of the glycogen debranching enzyme, amylo-1, 6-glucosidase. This enzyme is critical for both liver and muscles. Deficiency of this enzyme will affect skeletal and cardiac muscles. Mild cases may present only with asymptomatic hepatomegaly. Hypoglycemia may improve with age, although hepatomegaly may convert to cirrhosis and end stage liver disease may occur in small percentage of glycogen storage disease type III [21].

Hepatomegaly in patient number 9 was the clue for the diagnosis of this inborn error of metabolism. Follow-up of the liver dimensions in this patient is of great importance [22]. Fateen et al., 1997 reported in their study that type III is the most common GSD among Egyptian patients. However, the prevalence of type I is not known due to early death of such patients.

Patient number 10 was diagnosed with galactosemia. The patient is 1 2/12 years male presented by hepatomegaly, cataract, delayed milestones and past history of prolonged neonatal jaundice. Biochemical study by enzymatic assay and quantitation of total galactose-1-phosphate confirmed the suspected diagnosis as revealed by the high total level of galactose, with marked deficiency of galactose-1-phosphate uridyltransferase enzyme activity (classic galactosemia). This case of galactosemia is still young. However, follow-up is recommended as long term complications may appear later, as regards liver, cataract and language disorders. Children with galactosemia associated with speech disorder have 4-6 times greater risk for language impairment than children with early speech disorders of unknown origin [23].

Early dietary lactose may increase the risk for cognitive and language impairments [24]. Mass screening program for galactosemia for normal and high risk neonates is of great priority [25].

In this case also hepatomegaly was obvious in addition to cataract that directed us to proceed to the specific investigations.

Biochemical and enzymatic assay for the patients numbers 11 and 12 with hepatomegaly, hypotonia and delayed milestones of development proved the metabolic disorder of Niemann-Pick type C. It is a neurovisceral disorder characterized by progressive hepatosplenomegaly and central nervous system neurodegeneration.

Hepatomegaly was the first sign guiding us to proceed towards metabolic diagnosis. Sheth et al. [26] described a case report of 4 years old girl born to consanguineous parents presented with hepatomegaly and neurological regression. The child had hypotonia, repeated unexplained falls and facial dyskinesia. Bone marrow examination revealed the presence of storage cells suggestive of Gauchers or Niemann-Pick syndrome. Confirmatory study by enzyme assay was normal for beta-glucosidase, normal sphingomylinase activity specific for Gaucher and Niemann-Pick type A or B respectively.

In this study 2 patients with Niemann-Pick type C were diagnosed representing 16.7% of the studied cases. This is a high prevalence of the disorder. Both have organomegaly. The disease is autosomal recessive and is caused by mutations in one of two loci, npc1 and npc2. Mutations in npc1 account for 95% of Niemann-Pick type C. Affected individuals usually die before adulthood.

Both our Niemann-Pick type C patients are to consanguineous parents. One is 8 months of age with sever neurological symptoms and the other is a female 1 years and 10 months of age with less sever neurological affection.

In conclusion, this study revealed that hepatomegaly is considered the main clinical presentation and clue to diagnose suspected metabolic disorders and sometimes elicit rare cases of inborn errors of metabolism. It may be the main guide for further follow-up of the progression of the diagnosed diseases.

References


