A Dilemma in Diabetes

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Abstract

A 20 years old girl was suffering from of primary amenorrhoea, polyuria, polydipsia and polyphagia. On investigation patient was found to have congenital absence of uterus, posterior subcapsular cataract transaminitis, very high serum ALP level, diabetes mellitus and strong family history of diabetes mellitus with autosomal dominant mode of inheritance. The raised serum ALP was found to be hepatic in origin though the patient did not have any complaints or physical stigmata of liver disease both in examination and in Radiology. These findings were consistent with a diagnosis of Maturity Onset Diabetes of the Young type 5.

Case Report

A 20 years girl from Southern West Bengal was admitted to the inpatient services of Department of Endocrinology and Metabolism, IPGMER & SSKM Hospital, Kolkata, with complaints of primary amenorrhoea, polyuria, polydipsia and polyphagia. General physical examination of the patient was unremarkable except for short stature. There was no history of any other serious illness prior to present admission except for a birth weight of 1.8 kilograms. On laboratory examination (table-1), patient was found to have very high fasting blood sugar, mild transaminitis and very high serum ALP level. USG abdomen revealed normal hepatic echotexture, normal intra hepatic biliary radicals and absence of uterus. Kidneys were normal in size, shape and echotexture. No other anatomical abnormality was detected. Ophthalmoscopic examination revealed posterior subcapsular cataract. As the patient was already on injectable Insulin treatment endogenous Insulin was not measured. The patient could not afford autoantibody panel for type 1 diabetes mellitus. In view of absence of liver specific signs and symptoms and negative sonographic findings an attempt was made to find out the exact source of high ALP level in serum by heat inactivation analysis according to a previously described method [1]. 0.5 mL serum was incubated at 560 C for 10 minutes in Thermomixer (Eppendorf, Germany). Serum ALP level was measured before and after incubation in DaytonaTM Random Access Autoanalyzer (Randox) by PNPP kinetic method (Coral Clinical Systems). ALP level was found to be 2010 U/L and 820 U/L before and after incubation. Hence the residual enzyme activity of 40.8% pointed towards hepatic origin. This was surprising given the absence of any cholestatic signs or symptoms and normal ultrasound of liver and biliary tree. An attempt was made to give a unifying diagnosis using Occam’s razor (law of parsimony). From a literature search it was apparent that Maturity Onset Diabetes of the Young type 5 was needed to be considered seriously since this condition had the features of Diabetes, mullerian anomaly and elevated liver enzymes. Though the patients parents did not give history of high blood sugar in any of their relatives fasting and postprandial blood sugar was measured which showed her mother was also suffering from Diabetes Mellitus (fasting blood sugar – 176 mg/dL, post prandial blood sugar – 256 mg/dL). Moreover the patient’s maternal grandfather died of renal failure which could be stigmata of Diabetes Mellitus. Hence a history of Diabetes Mellitus in three generations with an autosomal dominant pattern of inheritance and trend towards of earlier age of onset (figure-1) could be elicited. Based on the positive family history, radiology and biochemical findings a working diagnosis of MODY 5 was made. The definitive diagnosis required PCR amplification and sequencing of HNF 1β gene, but the family could not bear the expenses. A decision was made against a liver biopsy as it was unlikely to change the line of management in the index patient.

Discussions and Conclusion

Maturity onset diabetes of the young type 5, first described in 1997 [2,3] is associated with mutation in HNF 1β (TCF 2) gene. HNF 1β is a transcription factor which regulates the development of several organ systems including genitor-urinary system and liver. There are around 40 published cases of MODY 5 most of which are due to novel mutations [4,5]. Interestingly only one case of MODY 5 associated with mullerian agenesis has been reported [4]. The patient had 75 bp deletion in exon 2 (409-483del). Though our index patient did not have biochemical or sonological features suggestive of renal involvement, renal involvement cannot be ruled out since most consistent feature in MODY 5 is interstitial fibrosis [4] which is apparent only on biopsy. Moreover 7.1% of the published cases of MODY 5 did not have apparent
renal involvement [5]. Around 15.26% of published cases had asymptomatic liver enzyme elevation, though Alkaline phosphatase was elevated in only 4.3% of the cases[5].

HNF 1β is thought to regulate expression of liver enzymes on hepatocyte membrane [6]. India is aptly called the Diabetes capital of world with whooping 299.1 million diabetics by 2025 according to WHO estimates. Although no data is available regarding the prevalence of monogenic forms of Diabetes in India, it is likely to represent a sizeable chunk of patients. Hence this case highlights the need to screen all family members of patients with early onset of Diabetes.

References

Illustrations

Illustration 1

Table 1

Biochemical profile of the patient

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
<th>Reference interval</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood sugar</td>
<td>444</td>
<td>70-100</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Sodium</td>
<td>143</td>
<td>135-155</td>
<td>mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.14</td>
<td>3.5-5</td>
<td>mEq/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>95</td>
<td>95-105</td>
<td>mEq/L</td>
</tr>
<tr>
<td>Urea</td>
<td>38</td>
<td>10-50</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.6</td>
<td>0.6-1.2</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>0.7</td>
<td>0.1-1.2</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Direct Bilirubin</td>
<td>0.04</td>
<td>0-0.3</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Total protein</td>
<td>6.7</td>
<td>8-10</td>
<td>g/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.3</td>
<td>3.2-3.5</td>
<td>g/dL</td>
</tr>
<tr>
<td>AST</td>
<td>114</td>
<td>5-34</td>
<td>U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>112</td>
<td>0-31</td>
<td>U/L</td>
</tr>
<tr>
<td>ALP</td>
<td>2010</td>
<td>80-250</td>
<td>U/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>6.2</td>
<td>8-10</td>
<td>mg/dL</td>
</tr>
</tbody>
</table>
Illustration 2

Figure 1

Family pedigree
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