Clinical Report

Neonatal Diabetes Mellitus, Congenital Hypothyroidism, Hepatic Fibrosis, Polycystic Kidneys, and Congenital Glaucoma: A New Autosomal Recessive Syndrome?

Doris Taha,1* Maha Barbar,2 Hassan Kanaan,3 and John Williamson Balfe4

1Division of Pediatric Endocrinology, King Faisal Specialist Hospital and Research Center, Jeddah, Kingdom of Saudi Arabia
2Division of Pediatric Gastroenterology, King Faisal Specialist Hospital and Research Center, Jeddah, Kingdom of Saudi Arabia
3Department of Pathology, King Faisal Specialist Hospital and Research Center, Jeddah, Kingdom of Saudi Arabia
4Division of Pediatric Nephrology, Department of Pediatrics, King Faisal Specialist Hospital and Research Center, Jeddah, Kingdom of Saudi Arabia

We report on two sibs (of 4) with a syndrome of minor facial anomalies, proportionate IUGR, neonatal non-autoimmune diabetes mellitus (NDM), severe congenital hypothyroidism (CH), cholestasis, congenital glaucoma, and polycystic kidneys. Liver disease progressed to hepatic fibrosis. The renal disease was characterized by large kidneys and multiple small cysts with deficient corticomedullary junction differentiation and normal kidney function. The phenotype observed in the two sibs was identical. Although a combination of liver, kidney, and pancreatic involvement has been described in Ivemark syndrome (hepato-renal-pancreatic syndrome), the coexistence of NDM, CH, and glaucoma in both sibs suggests the possibility that this combination of manifestations describes a new autosomal recessive syndrome. Mutation analysis for several candidate genes is warranted.

INTRODUCTION

We describe two sibs with a “new” combination of manifestations including symmetrical intrauterine growth retardation (IUGR), neonatal diabetes mellitus (NDM), severe CH, cholestasis with progressive hepatic fibrosis, congenital glaucoma, and polycystic kidneys. Such a previously undescribed combination presenting uniformly in two children of consanguineous parents may represent a new syndrome.

Clinical Reports

The parents and the grandfathers are first-degree cousins of Saudi Arabian origin. Patient 1 is the firstborn child, a girl, who was delivered at term without any antenatal or perinatal complications. Patient 2 is the 4th child, a boy, delivered at 37 weeks without complications. The second and third born children are healthy. Both parents are healthy. There is no family history of diabetes, liver, kidney, eye, or thyroid disease.

Patient 1

This Saudi Arabian girl weighed 2,200 g at birth at term after an uncomplicated pregnancy and normal vaginal delivery to a gravida 1 mother. She was admitted to the neonatal intensive care unit because of IUGR. On the second day of life, she was noticed to have hyperglycemia and was treated with neutral protamine hagedorn (NPH) insulin 1 unit subcutaneously daily. Newborn thyroid screening showed a markedly elevated thyroid stimulating hormone (TSH) level (TSH, 629 mU/L; normal, 0.3–5.5). The diagnosis of CH was confirmed and the patient was treated with levothyroxine (50 μg daily). She was discharged after 1 week.
At the age of 3 weeks, she developed jaundice; direct bilirubin was 75 μmol/L (normal, 0–8). At age 6 months, her liver disease had progressed; total bilirubin was 254 μmol/L, and liver enzymes were elevated (Table I). She was admitted for investigation. She had a large anterior fontanelle, depressed nasal bridge, and a large umbilical hernia. Liver span was 8 cm. TSH level was markedly elevated and free thyroxine (FT4) level was normal (Table I). The dose of levothyroxine was increased to 75 μg daily. Blood pressure and results of renal function tests were normal. She was noticed to have large hazy corneae; however, intraocular pressures were not documented. Abdominal ultrasound study showed an enlarged liver with increased echogenicity, no focal abnormality, and no evidence of portal hypertension. Both kidneys were enlarged and showing increased echogenicity with absence of corticomedullary differentiation and containing multiple small cysts. A skeletal survey showed no evidence of epiphyseal dysplasia. Computerized tomography (CT) scan of the abdomen demonstrated hepatosplenomegaly with no focal lesions and a small pancreas. Echocardiogram was normal. TORCH titers were unremarkable. Liver biopsy documented portal, periportal, and perisinusoidal fibrosis, proliferation and distortion of bile ducts, and cholestasis predominantly canalicular (Fig. 1). She was maintained on 0.5–1 U of insulin ultralente subcutaneously twice daily, levothyroxine 75 μg orally daily, and vitamins A, D, E, and K. At the age of 14 months, her diabetes was reasonably well controlled, TSH level remained elevated, and liver enzymes continued to rise (Table I). She died at the age of 16 months of pneumonia and respiratory failure. Autopsy was not done.

**Patient 2**

This is the younger brother of patient 1, born 7 years later. He weighed 1,500 g at birth after a similarly uncomplicated pregnancy and normal vaginal delivery. He had a 40-day stay in the neonatal intensive care unit where he was diagnosed with diabetes mellitus and CH [TSH of 100 mU/L (0.3–5.5)]. He also had hazy large corneae and was diagnosed with congenital glaucoma. He was treated with levothyroxine 25 μg orally daily and NPH insulin 0.5 U subcutaneously twice daily. He developed jaundice at 1 month. At 2 months, he was admitted to hospital for investigation. His weight was 2.2 kg, length 39 cm, and head circumference 36 cm. Blood pressure was normal. He had bilateral buphthalmos and corneal opacity, depressed nasal bridge, and long philtrum. There was no goiter. The abdomen was distended with an enlarged liver (span around 8 cm), and a small umbilical hernia. Ophthalmologic examination revealed adequate response to light, hazy corneae, round, regular, reactive pupils. The right corneal diameter was 14 mm with intraocular pressure of 47 mmHg; the left corneal diameter was 13 mm with intraocular pressure of 49 mmHg. TSH and FT4 levels were 416 mU/L (0.3–5.5) and 6 pmol/L (12–22), respectively. The dose of levothyroxine was increased to 50 μg daily. The HbA1c concentration was 8.0%. Renal function was normal. Liver enzyme levels were elevated (Table I). Albumin level was low; prothrombin time (PT) and partial thromboplastin time (PTT) were prolonged (Table I). He was treated with vitamins A, D, E, and K and ursodeoxycholic acid. TORCH titers were unremarkable. Karyotype was normal. No anti-thyroglobulin and thyroperoxidase antibodies were found. Thyroid sonogram showed a normal thyroid gland in the normal location. Serum thyroglobulin concentration was 1,016 μg/L (normal, up to 55 μg/L). Islet cell antibodies were absent. A random C-peptide level was 0.25 nmol/L (0.3–1.4). The pancreas could not be visualized by CT scan or by magnetic resonance imaging (MRI) of the abdomen. Hepatitis A, B, and C screen was negative. Anti-kidney, liver, and smooth muscle antibodies (anti-KLM antibodies) were absent. Ultrasound of the abdomen documented an enlarged liver with

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal range</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mU/L)</td>
<td>0.3–5.5</td>
<td>120</td>
<td>280</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>12–22</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.5–6.1</td>
<td>7.4</td>
<td>8.6</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>10–50</td>
<td>156</td>
<td>146</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>10–65</td>
<td>253</td>
<td>308</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>5–55</td>
<td>523</td>
<td>682</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>150–420</td>
<td>1,190</td>
<td>—</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>35–46</td>
<td>—</td>
<td>42</td>
</tr>
<tr>
<td>Tbil (μmol/L)</td>
<td>0–21</td>
<td>254</td>
<td>250</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>10.2–13.3</td>
<td>13.7</td>
<td>12.8</td>
</tr>
<tr>
<td>PTT (sec)</td>
<td>25.0–34.3</td>
<td>43.8</td>
<td>40.6</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>1.5–6.8</td>
<td>7.1</td>
<td>5.8</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>30–62</td>
<td>37</td>
<td>32</td>
</tr>
</tbody>
</table>

TSH, thyroid stimulating hormone; FT4, free thyroxine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; ALP, alkaline phosphatase; Tbil, total bilirubin; PT, prothrombin time; PTT, partial thromboplastin time.
patent portal vein and no focal lesions. The spleen was normal. Both kidneys showed multiple tiny cysts with poor corticomedullary junction differentiation (Fig. 2); the right kidney measured 5.1 cm × 2.6 cm × 2.7 cm and the left kidney measured 5.3 cm × 2.6 cm × 2.4 cm. Hepatobiliary nuclear (HIDA) scan showed no evidence of biliary excretion to the bowel or gallbladder up to 7 hr post-tracer administration. Liver biopsy showed similar histopathologic findings to those observed in his sister with fibrosis and canalicular cholestasis (Fig. 3). Brain MRI was normal. Skeletal survey showed delayed mineralization and no epiphyseal dysplasia. At the age of 4 months, his weight and length were 2.7 kg and 46 cm, respectively; TSH and FT4 were normal, liver enzymes and bilirubin level were still increasing (Table I). He died at the age of 6 months with *E. coli* sepsis. Autopsy was not done.

**DISCUSSION**

This is the first report of two sibs presenting with IUGR, NDM, severe CH, cholestasis and liver fibrosis, polycystic kidneys, and congenital glaucoma. This combination of multiple organ involvement, not previously described, may represent a new autosomal recessive syndrome. Normal chromosomes in sib 2 excludes major chromosomal aberrations as a cause of this syndrome.

Both sibs were born with IUGR, which suggests the presence of insulin deficiency in utero. Permanent, non-autoimmune, and insulin-sensitive diabetes mellitus
presenting in the first week of life is a component of this syndrome. The early presentation, absence of islet cell antibodies, and radiological evidence of pancreatic hypoplasia point to a genetic defect in pancreatic beta-cell development. NDM is a rare condition usually observed in conjunction with IUGR [Kruger et al., 1997]. Only rarely has NDM been reported in specific syndromes. Wolcott–Rallison syndrome is an autosomal recessive genetic disorder that includes permanent diabetes mellitus, recurrent hepatitis, renal insufficiency, and multiple epiphyseal dysplasia or spondyloepiphyseal dysplasia [Stöss et al., 1982]. The limb abnormalities present in this syndrome clearly differentiate it from other forms of NDM. Our patients did not have the clinical or the radiological evidence of epiphyseal dysplasia.

The two sibs also had severe CH detected by a markedly elevated neonatal TSH level. The absence of autoimmune antibodies such as thyroglobulin and thyroperoxidase antibodies as well as the presence of a normally located thyroid gland of normal size suggests a genetic defect in thyroid hormone metabolism. Such defects occur in 10% of newborn infants with CH and usually are transmitted as autosomal recessive traits. Elevated thyroglobulin concentration occurs in iodide transport, organification, or iodotyrosine deiodinase defects. Even though individuals affected with such defects tend to develop goiter, in many patients development of the goiter is delayed.

The combination of renal dysplasia, pancreatic, and liver fibrosis was first described by Ivemark et al. [1959] and designated “familial dysplasia of the kidneys, liver, and pancreas.” Since then, this dysplasia sequence has been named “renal-hepatic-pancreatic dysplasia (RHPD)” or “Ivemark syndrome.” Cases sharing the involvement of kidneys, pancreas, and liver have been published by other authors with great diversity of the phenotype. Some authors reported cases suggesting the existence of incomplete forms of the RPHD sequence, without hepatic lesions [Crawfurd, 1978; Yeoh et al., 1985]. Others have widened the spectrum of Ivemark syndrome to include other congenital malformations such as situs inversus totalis [Yoshikawa et al., 1981; Pinar and Barton Rogers, 1992], splenic agenesis, and cardiac transposition [Crawfurd, 1978]. It has been suggested that the marked clinical variability between the cases reported may reflect the presence of several overlapping conditions, or more likely, the varying phenotype of a single gene condition [Hurst et al., 2000].

Our patients appear to resemble the reported cases of Ivemark syndrome in that they had involvement of the liver, kidneys, and pancreas. However, they differ from the RHPD patients in several aspects. Most RHPD patients die neonatally and some presented with Potter sequence. Only one case reported by Neuhaus et al. [1996] was still alive at the age of 6 years after combined liver–kidney transplantation. This patient had no pancreatic involvement. None of the other RHPD patients survived the first year of life. Patients surviving the neonatal period develop cholestasis and liver dysfunction in addition to chronic renal failure [Bernstein et al., 1987; Proesmans et al., 1986]. The renal lesion in RPHD sequence is a true multicystic dysplastic kidney [Carles et al., 1988] or cystic kidney type II [Zerres et al., 1984] with absence of normal structures of any kind. Although kidney biopsy was not performed in our patients, both sibs had normal kidney function that did not deteriorate with time. The presence of enlarged kidneys with multiple small cysts and poor differentiation of the corticomedullary junction, and normal kidney function in both sibs is suggestive of autosomal recessive polycystic kidney disease (ARPKD). ARPKD occurs in 1 in 6,000–1 in 40,000 live births [Zerres et al., 1998]. It is characterized by the combination of renal cystic disease and congenital hepatic fibrosis (CHF). All typical cases of ARPKD are due to mutations of the PKHD1 gene on chromosome band 6p21.1-p12 [Ward et al., 2002]. The clinical presentation of ARPKD is highly variable. ARPKD can present as perinatal, neonatal, infantile, or juvenile-onset disease [Blyth and Ockenden, 1971]. The variability in the age of onset is due to variable expression of mutations of the same gene as well as the effects of modifier genes and environmental factors rather than mutations of different genes [Kaplan et al., 1988]. The liver disease in our patients is not of CHF type. It presented very early in life with progressive direct hyperbilirubinemia and deterioration of liver synthetic function whereas in CHF associated with ARPKD, the liver function is primarily preserved. Children with CHF eventually develop portal hypertension with subsequent hypersplenism and esophageal varices.

Although pancreatic fibrosis is an important component of the RHPD sequence, none of the previously reported cases presented neonatally with NDM. In addition, CH and congenital glaucoma have not been previously reported in association with the RPHD sequence. Hence, our patients differ from the RHPD reported cases in many aspects. Their prenatal course was uneventful except for IUGR, they presented in the neonatal period with NDM, they survived beyond the neonatal period with normal kidney function, and they both had severe CH and congenital glaucoma.
Other syndromes that may involve renal-hepatic-pancreatic dysplasia include Meckel syndrome, Zellweger syndrome, trisomy 8 and 13, and glutaric aciduria type II. In these syndromes, varying degrees of involvement of the central nervous system, skeleton, genitalia, or heart can be detected. Such associated abnormalities did not exist in our patients.

Most infants affected by congenital glaucoma have the autosomal recessive type [Bonaiati et al., 1978]. Two chromosomal regions have been shown to be associated with AR congenital glaucoma (GLC3A; 2p16) and GLC3B (1p36) [Akarsu et al., 1996; Alward et al., 1998]. A gene located in the GLC3A region (CYP1B1) has been identified as the causative gene. The responsible gene located in the GLC3B region has yet to be identified. Mutations in the CYP1B1 gene have been shown to be responsible for the form of congenital glaucoma mapped to chromosome band 2p16 [Stoilov et al., 1997]. Disease associated mutations have been found in Saudi Arabian families [Bejjani et al., 1998].

In summary, we describe two siblings of consanguineous parents with a new combination of congenital organ involvement including NDM, severe congenital hypothyroidism, hepatic fibrosis, polycystic kidneys, and congenital glaucoma. This combination of congenital organ involvement possibly represents a new autosomal recessive syndrome or might constitute another part of the wide spectrum of the RHPD syndrome with a new clinical phenotype. Mutation analysis of several candidate genes is warranted.

REFERENCES


Disease associated mutations have been found in Saudi Arabian families [Bejjani et al., 1998].

REFERENCES


