Arthrogryposis, renal dysfunction and cholestasis syndrome

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ABSTRACT

We report for the first time from the Arabian Gulf area 3 patients with arthrogryposis multiplex congenita, cholestasis and renal tubular dysfunction from a Saudi family with 2 other siblings and 3 cousins who possibly died with a similar clinical picture. We also document for the second time in literature other findings in this syndrome including cerebral abnormalities (hypoplastic corpus callosum), congenital heart disease and nerve deafness. We suggest that some of these cases might benefit from ursodeoxycholic acid therapy. We believe that this autosomal recessive disorder is possibly under-diagnosed in this region with a high consanguineous marriage rate.

Keywords: Arthrogryposis, cholestasis.

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The association between arthrogryposis multiplex congenita, cholestatic liver disease, renal tubular acidosis and death in infancy was first reported in 1973.[1] Since then, about 23 children, from 11 families, have now been described.[2] To the best of our knowledge, no similar cases, were published from the Gulf area before. We describe 3 children from a Saudi family on 2 of whom, ARC syndrome, was only suspected retrospectively after diagnosis of case one. Five other children within this family (2 siblings and 3 cousins) died in early infancy with rather similar clinical picture (jaundice, vomiting, joint contractures) but we couldn't find written documentation as they were born elsewhere. The pedigree of this family is shown in Figure 1. We also report the second case in literature with documented cerebral abnormalities, VSD and nerve deafness. We have also observed that one case responded to the ursodeoxycholic acid therapy, suggesting, but not proving, that these patients might have some form of bile acid metabolism disorder.

Case Reports.

Patient 1. A female, the 11th for a first degree Saudi cousin parents, who lost 5 newborns, 2 of whom had proved cholestatic jaundice (patient 2 and 3) and another 2 who died early with vomiting and jaundice. Three of her first degree cousins also died early with jaundice, vomiting and joint deformities. She was born at full term with birth weight of 2.4 kg; Length 45 cm and head circumference of 34 cm (50th centile).

Jaundice was first observed at age of 3 days. At presentation on day 5, liver span was 6 cm with no splenomegaly. Serum bilirubin was 330 μmol/L (0-26) with direct of 320 μmol/L (0-4). Serum transaminases, alkaline phophatase and gamma glutamyl transferase (GGTT) were initially normal but gamma GT and alkaline phosphatase increased at the age of 5 weeks to 78 μ/L (11-50) and 886 μ/L (50-117). Investigations including blood for Tandem

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Mass Spectrometry (TMS), urine for metabolic screen, RBC galactosemia screen, serum long chain fatty acids, phytonic acid, pipicolic acid, (Dr. Ozand, KFSH), serum lactate, serum ammonia, alpha one antitrypsin, copper and caeruloplasmin, sweat test, infection screen for TORCH and syphylis, bone marrow, chromosomes, skeletal survey, T4, TSH, liver ultrasound were normal. HIDA scan (99 mTc-N-substituted-2,16-dimethylphenyl carbamoylethyl aminodiacetic acid) initially showed no excretion but a repeat one at the age of 2 months showed a patent extrahepatic biliary system. Liver biopsy reported by (Dr. Malone, Cleveland Clinic, USA) showed intracellular and intracanalicular cholestasis with paucity of intrahepatic bile ducts. Many hepatocytes showed cytoplasmic granular pigment of indeterminate nature and there was no evidence of metabolic or storage disease. Serum bilirubin remained elevated till the age of 6 weeks when ursodeoxycholic acid 10 mg/kg was introduced. Five weeks later, the serum bilirubin level dropped from 211 µmol/L to 19 µmmol/L (11-18) and alkaline phosphatase to 390 µ/L (50-217). However, she continued to have bouts of diarrhea and no improvement was noticed in her nutritional status inspite of MCT, pregestamil, high fat soluble vitamin therapy.

She was hyptonic with marked generalized muscle wasting, bilaterally dislocated hips, talipes equinovarus deformity and flexion deformities of the knees. By the fifth month she had severe global developmental delay. Ophthalmic evaluation was normal. Brain stem auditory evoked response (BAER) showed severe bilateral sensineural deafness. MRI brain at the age of 150 days showed hypoplasia of the corpus callosum, with insufficient myelination. Electromyography was consistent with muscular atrophy. Muscle biopsy (Professor Weller, Southampton University, UK) was suggestive of neurogenic atrophy. Stains for mitochondria, lipid and glycogen were normal and showed no evidence of metabolic defect or macrophages.

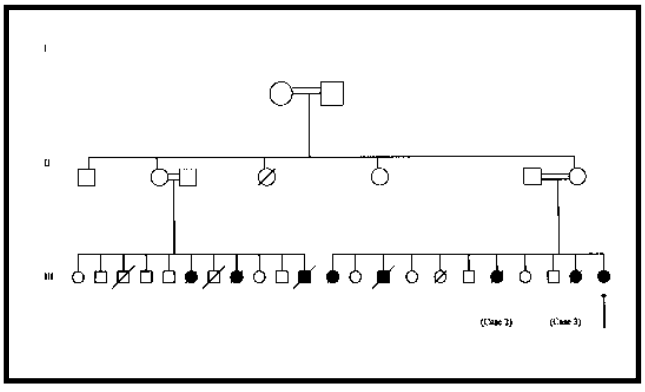

Figure 1 - Family pedigree.

The child had polyuria (with urine specific gravity of 1002 and osmolality of 120 mmol/kg) renal tubular acidosis, glucosuria, phosphaturia, hypophosphatemia, hyperchloremia, generalized aminoaciduria and proteinuria. Serum creatinine level and renal sonography were normal. Acidosis was corrected with bicarbonate.

Echocardiography showed muscular VSD with no cardiomegaly or failure. She had repeated attacks of fever with no documented blood or other cultures except terminally when she had Methicillin Resistant Staphylococci (MRSA). Immunoglobulin levels were normal. The patient failed to thrive and died at the age of 5½ months.

Patient 2. This female baby, the sister of case 1, was born at full term with low birth weight (2.46 kg), head circumference 33.5 cm, length 52 cm. The clinical picture was characterized by bilateral hip dislocation, knees flexion and talipes equinovarus. Direct hyperbilirubinemia was noticed at day 2 (serum bilirubin 198 µmol/L (0-26), direct of 128 µmol/L (0-4). Transaminases, gamma glutamyl tranpeptidase and alkaline phosphatase were normal. HIDA scan carried out once showed no excretion. Liver biopsy showed cholestasis with nonspecific parenchymal changes. No comment was made on bile duct. She had hyperchloremic acidosis and glucosuria with normal tandem MS. The child died at age the of 23 days with severe metabolic acidosis and possible necrotising enterocolitis.

Patient 3. This female infant, sister of case 1, was born at full term, birth weight of 2.85 kg, height 51 cm, and head circumference of 35 cm. She was noticed to have flexion deformity of both knees and dislocated right hip at birth. She developed direct hyperbilirubinenia (total 270 µmol/L direct 154 µmol/L) at age of 3 days with normal transaminases, alkaline phosphalase and gamma glutamyl transpeptidase. Liver ultrasound was normal with no excretion on HIDA scan. No liver biopsy was carried out. She had hyperchloremic acidosis with glucosuria and proteinuria with normal urea and creatinine. Developed urinary tract infection due to coliforms and died with clinical picture of sepsis at age of 22 days.

Discussion. All of our 3 patients reported here share similar clinical picture of arthrogryposis, cholestasis and renal tubular dysfunction (ARC). We suspect that most of the other siblings and cousins who died in early infancy possibly had the same problem. The occurrence of affected male and females sibs together with parental consanguinity, suggest autosomal recessive inheritance as has been suggested before.[3,4] One would have expected to see more cases in a country like Saudi Arabia with high consanguinity rate but cases are possibly missed

because of lack of awareness as happened to the rest of our patients on whom this diagnosis was not suspected.

Initially reported cases were divided into 2 separate groups on the basis of hepatic histology. The first group has paucity of intrahepatic bile ducts and giant cell transformation of hepatocytes.[1,5] The second group had pigment deposition in liver cells and marked cholestasis.[3,4,6] However later work up has suggested that they are all variants of the same group.[7] Our cases mainly showed cholestasis with paucity of ducts in patient 1. However neither the absence of pigmentary changes nor the presence of normal intrahepatic biliary ducts exclude the diagnosis.[7] It is interesting that in our first case the initial negative HIDA excretion became positive after 2 weeks ruling out the possibility of extrahepatic biliary obstruction. Most of the previously reported cases had one HIDA study and all showed no excretion.[6,7] No bile acid abnormalities were documented in the previously reported cases though in one report, ursodeoxycholate was attempted unsuccessfully.[7] The dramatic decline in the level of serum bilirubin after deoxycholate in case one suggests, but not necessarily proves that bile acid metabolism disturbance might have a role in the aetiopathogenesis of cholestasis in these cases. Recently, deficiency of 3 β-hydroxy-Δ^5-(27 steroid dehydrogenase deficiency), was reported as a cause of cholestasis in some Asian and Jordanian children.[8] Unfortunately we lost our specimens on shipping and thus were not able to do detailed bile acid studies.

Renal manifestations in our cases were similar to the previously reported cases.[1,6] In a current publication, nephrogenic diabetes insipidus was suggested to be as an additional finding to the triad of this syndrome and one patient responded partially to DDAVP.[2] Our first case had polyuria and occasional bouts of hypernatremia which we attributed to her renal tubular dysfunction and diarrhea. She could as well had nephrogenic diabetes insipidus.

Recently, in one series, 3 patients were found to have absent or hypoplastic corpus callosum, deafness with severe developmental delay among those who lived longer.[2] Our case is the second publication in literature to document these findings and the first to prove nerve deafness through Brain Stem Auditory Evoked Response (BAER). The insufficient myelination or leukodystrophic changes in MRI were not reported before. However one has to take that cautiously as sometimes it is difficult to comment on the myelination status in MRI of newborns and very young infants. However the severe developmental delay observed on those who lived long[2] could be related to cerebral changes other than absent corpus callosum. Unfortunately no comments were made on the MRI findings of the brain white matter of those cases.

There are only 2 case reports in literature showing cardiac involvement in this syndrome, one VSD[2] and one ASD.[7] Our finding of VSD in patient 1 indicates that congenital heart disease is part of the manifestations of this syndrome.

We conclude that this is the first case report of ARC syndrome from the Arabian Gulf area and suggest that this condition is possibly missed in this region with a high consanguinity rate. We have supported the recent finding of absent cerebral corpus callosum in this syndrome but we think that the white matter could also be involved. We have proved nerve deafness using BAER (for the first time) and have documented presence of congenital heart disease. We suggest that some of these cases could possibly benefit from ursodeoxycholic acid therapy.

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