Arthrogryposis, renal tubular acidosis and cholestasis (ARC) syndrome: two new cases and review
Omar Abu-Sa’da, Maha Barbar, Naffaa Al-Harbi and Doris Taha

ARC syndrome, the association of arthrogryposis, renal tubular dysfunction and cholestasis, is a rare genetic disorder. We report two Saudi infants from two different families with ARC syndrome. Magnetic resonance imaging of the brain of one of the infants showed lissencephaly, a previously unreported finding in this syndrome. We also review 39 ARC cases reported in the literature using the Medline database from January 1966 to September 2004.

Introduction
The association of arthrogryposis, renal tubular dysfunction and cholestasis, ARC syndrome, is a rare multisystem disorder originally described by Lutz-Richner and Landolt (1973) and by Nezelof et al. (1979). The disorder has been mapped to chromosome 15q26.1 and germline mutations in VPS33B gene were identified in 14 kindreds with ARC. We describe two Saudi infants from two unrelated families with lethal ARC syndrome; one of the patients had lissencephaly, a previously unreported central nervous system (CNS) finding in this syndrome. We also review 39 ARC cases reported in the literature.

Case reports
Case 1
This male infant was born at term by Cesarean section because of breech presentation. His birth weight was 3.1 kg. The parents are first-degree cousins of Saudi origin. The pregnancy was complicated by oligohydramnios and decreased intrauterine fetal movement. Shortly after birth, he developed jaundice, diarrhea and failure to thrive. Physical examination showed mild ichthyosis, high arched palate, hepatomegaly, generalized hypotonia and arthrogryposis in the form of dislocation of hips, talipes calcaneovalgus, and flexion contracture of the knee joints.

Laboratory evaluation revealed serum total and conjugated bilirubin levels of 160 μmol/l and 122 μmol/l, respectively. The serum alkaline phosphatase level was elevated (1620 U/l), while the serum gamma-glutamyl transferase (GGT) level was normal (23 U/l). Liver transaminase enzyme levels, ALT and AST, were 85 and 77 U/l, respectively. Serum albumin level was 26 g/l. Prothrombin time and partial thromboplastin time were normal. A complete blood count (CBC) showed a white blood cell (WBC) count of 14.0 × 10^9/l, a hemoglobin of 70 g/l, and a platelet count of 400 × 10^9/l. The platelets were giant with a mean platelet volume (MPV) ranging between 9.4 and 10.9 fl. The initial electrolyte profile was normal. Both TORCH and metabolic screens were negative. Thyroid function evaluation revealed a free thyroxine (FT4) level of 13 pmol/l (12–23) and a thyroid-stimulating hormone (TSH) of 13 mU/l (0.35–4.3). Sweat chloride test was normal (25 pmol/l), and plasma amino acid profile was normal. Slit lamp examination was normal. A chromosomal analysis showed a normal karyotype (46,XY). An echocardiogram was normal.

At the age of 2 months, he developed Fanconi syndrome with a blood pH of 7.28, bicarbonate of 12 mmol/l, base excess of –12.8, urine pH of 5.5, with proteinuria, calciumia, phosphaturia, and glycosuria with normal serum glucose concentration. His serum phosphate level ranged between 0.52 and 0.78 mmol/l (normal range, 1.36–2.26 mmol/l). Urea and creatinine levels were 9.4 mmol/l and 65 μmol/l, respectively.

An ultrasound of his kidneys revealed nephrocalcinosis (Figure 1). A radionuclide scan of the biliary system (HIDA scan) revealed good uptake of the tracer but no excretion to the bowel after 24 hours. Liver biopsy revealed canalicular and hepatocellular cholestasis, portal fibrosis, minimal hepatocyte giant cell transformation, focal minimal steatosis, and absence of bile duct proliferation (Figure 2).

Neurologically, the baby was hypotonic with marked developmental delay. Brain magnetic resonance imaging
(MRI) showed agyria and loss of sulci suggestive of lissencephaly (Figure 3).

The infant had several admissions with febrile illnesses, dehydration, and metabolic acidosis. At 7 months of age, he developed polyuria (urine output of 15 ml/kg/hr); serum sodium level was 149 mmol/l (ranging between 140 and 160 mmol/l), serum osmolality 309 mOsm/kg, and urine osmolality 109 mOsm/kg. He did not respond to desmopressin, and was diagnosed with nephrogenic diabetes insipidus.

He was not thriving despite adequate nasogastric tube feeding and treatment with ursodeoxycholic acid, fat-soluble vitamins, sodium bicarbonate, hydrochlorothiazide, potassium chloride, phosphate sandoz, calcium glubionate, one-alpha drops, and L-thyroxine. He died at the age of 7 months with severe dehydration and metabolic acidosis.

**Case 2**

This female infant was born at term in a small local hospital to first-degree cousins of Saudi origin. She was delivered vaginally with breech presentation. Her birth weight was 2.5 kg. Shortly after birth, she was found to have a fracture of the right femur, developmental dysplasia of hips, and severely ichthyotic skin. She also developed metabolic acidosis with Fanconi syndrome, jaundice, and recurrent sepsis. At the age of 3 months, she was transferred to our hospital for further management. On examination, she was febrile, hypotensive, severely dehydrated and ill looking. She had significant
Laboratory evaluation revealed metabolic acidosis with normal anion gap. Arterial blood gas showed a pH of 7.18 (7.35–7.45), PCO2 2.0 kPa (4.67–6.0), PO2 5.7 kPa (10.67–13.3), bicarbonate 9.1 mmol/l, base excess: 21.5 mmol/l. Serum sodium was 158 mmol/l, potassium 2.9 mmol/l, chloride 135 mmol/l, calcium 2.61 mmol/l, phosphate 1.47 mmol/l, urea 25.3 mmol/l, creatinine 171 µmol/l, bilirubin 173 µmol/l, ALT 43 U/l, AST 72 U/l, GGT 42 U/l, and albumin 32 g/l. A CBC showed leukocytosis, and a peripheral smear revealed giant platelets with MPV 10.8 fl (normal, 7.5–9.3). Urinalysis showed proteinuria and glucosuria not associated with hyperglycemia. Urine electrolytes were as follows: Na 26 mmol/l, K 44 mmol/l, Cl 45 mmol/l, Ca 0.46 mmol/l, PO4 13.4 mmol/l, Cr 0.8 mmol/l. Serum immunoglobulin levels were normal for age. Blood culture grew Pseudomonas aeruginosa.

Despite treatment with intravenous antibiotics and resuscitation with fluids and inotropes, she died on the second day of hospitalization with sepsis and irreversible shock. Autopsy was not performed.

**Discussion**

ARC syndrome is a rare multisystem disorder. Arthrogryposis multiplex congenita with renal and hepatic abnormalities was first described by Lutz-Richner and Landolt (1973) and by Nezelof et al. (1979). Since then, a total of 39 cases have been reported (Table 1). Recently, Gissen et al. (2004) mapped the disease to 15q26.1 and identified germline mutations in the VPS33B gene in 14 kindred with ARC syndrome. We report two new patients of Saudi origin with ARC syndrome; one of them has lissencephaly, a previously unreported association in ARC patients. Unfortunately, DNA analysis could not be performed for lack of sufficient tissue for DNA extraction in both patients.

The syndrome is inherited in an autosomal recessive pattern; parental consanguinity and recurrence in siblings are noted in our cases as well as in other cases in the literature. Thirteen of the reviewed cases were of Pakistani origin, and three of Saudi origin, reflecting the high rate of consanguineous marriages among these societies.

Although patients with ARC syndrome might have a variable clinical spectrum at diagnosis, the classic features are arthrogryposis, renal tubular acidosis, and cholestasis.

**Arthrogryposis**

Arthrogryposis is thought to be secondary to neurogenic muscle atrophy. Evidence of denervation was obtained from electromyographic studies as well as from muscle biopsy (Nezelof et al., 1979; Denecke et al., 2000) and autopsy results (Eastham et al., 2001) showing atrophy of
the peripheral muscles, variable size muscle fibers, and alteration of the motor neurons of the anterior horn of the dorsal spinal cord. Arthrogryposis varies in severity and may include talipes equinovarus, talipes calcaneovalgus, radial deviation of the wrists, flexion contracture of limbs, clubfeet, and dislocation of the hips. Although arthrogryposis is a cardinal feature of ARC syndrome, two unrelated patients (Coleman et al., 1997) did not have it.

Our first patient had dislocation of the hips, talipes calcaneovalgus, and flexion contracture of the knee joints and our second patient had developmental dysplasia of the hips.

Renal tubular dysfunction

Tubular dysfunction may present in the first few days of life or later around the age of 2–3 months. Renal tubular dysfunction may manifest as renal tubular acidosis and multiple features of Fanconi syndrome including glucosuria, proteinuria, aminoaciduria, phosphaturia, and bicarbonate wasting. Both our patients had evidence of Fanconi syndrome although the age of presentation differed. Renal tubular dysfunction is seen in most of the reported ARC cases; only one out of six patients reported by Eastham et al. (2001) did not have Fanconi syndrome but that patient did have nephrogenic diabetes insipidus.

Kidney ultrasound may show nephrocalcinosis (Deal et al., 1990; Coleman et al., 1997; Eastham et al., 2001) or small dysplastic kidneys (Eastham et al., 2001). Renal biopsy was only performed in six patients out of the 39 reviewed cases (Deal et al., 1990; Di Rocco et al., 1990; Coleman et al., 1997; Eastham et al., 2001) and showed acute and chronic inflammation of the interstitium, focal multinucleate giant cell reaction, focal segmental or global sclerosis of some glomeruli, tubular distortion, calcification of distal tubules and multicycstic dysplasia. Autopsy findings revealed renal tubular degeneration and nephrocalcinosis (Nezelof et al., 1979; Di Rocco et al., 1990; Di Rocco et al., 1995).

Cholestasis

Conjugated hyperbilirubinemia with normal or mildly elevated transaminases is a constant and early feature of ARC syndrome. Interestingly, patients with ARC syndrome have normal GGT enzyme levels despite elevated conjugated bilirubin and alkaline phosphatase enzyme levels. This finding is noted in two patients and other reported cases (Di Rocco et al., 1990; Di Rocco et al., 1995; Eastham et al., 2001; Howells and Ramaswami, 2002) although a few patients had mildly elevated GGT (Coleman et al., 1997; Abdullah et al., 2000). Liver biopsy was performed on 19 out of 39 cases. The most common histological findings were paucity of bile ducts (Mikati et al., 1984; Papadia et al., 1996; Coleman et al., 1997; Abdullah et al., 2000; Eastham et al., 2001), lipofuscin deposition (Di Rocco et al., 1990; Horslen et al., 1994; Di Rocco et al., 1995), bile plugs, bile duct proliferation, giant cell hepatitis (Mikati et al., 1984; Deal et al., 1990; Di Rocco et al., 1995; Coleman et al., 1997; Denecke et al., 2000; Eastham et al., 2001), and portal tract fibrosis (Coleman et al., 1997; Eastham et al., 2001). One patient progressed to cirrhosis as documented by liver biopsy performed at 3 years of age (Coleman et al., 1997). Pigmentary deposits within the liver had been reported (Nezelof et al., 1979; Di Rocco et al., 1990; Saraiva et al., 1990; Abdullah et al., 2000). Some patients showed only canalicular cholestasis (Di Rocco et al., 1990; Di Rocco et al., 1995; Howells and Ramaswami, 2002).

### Table 1 Features of our patients and other reported cases of ARC syndrome

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S, Saudi; NM, not mentioned; P, Pakistani; O, Omani; T, Turkish; I, Italian; A, Asian; NA, north African; PO, Portuguese; M, male; F, female; DI, diabetes insipidus; FIT, failure to thrive.
variability of the histological findings in the liver biopsies initially led to the thinking that there are two separate forms of the disease but this was later found to represent a spectrum of changes within the same disorder (Horslen et al., 1994).

In addition to the three main features of ARC syndrome, many other associated features have been described in variable severity.

CNS manifestations including hypotonia and global developmental delay were described in all reported cases. Other features included nerve deafness and absence or hypoplasia of the corpus callosum (Coleman et al., 1997; Abdullah et al., 2000). Both of our patients were hypotonic with marked developmental delay. Brain MRI in the first patient revealed lissencephaly. To our knowledge, this finding was not previously reported in patients with ARC syndrome.

Almost all ARC syndrome patients fail to thrive despite maximum enteral caloric intake. Our first patient did not gain adequate weight although he was receiving high caloric nasogastric tube feeding. Failure to thrive could be secondary to increased caloric demand because of recurrent episodes of dehydration and sepsis in addition to chronic diarrhea. Diarrhea may be due to fat malabsorption secondary to cholestasis.

Hypernatremic dehydration and polyuria were reported in many ARC cases as well as in our two cases but only a few patients were proved to have diabetes insipidus unresponsive to desmopressin (Horslen et al., 1994; Coleman et al., 1997; Eastham et al., 2001) as in our first patient. Nephrogenic diabetes insipidus was proved in seven out of 39 cases.

Ichthyosis has also been reported in association with ARC, it varies from mild to severe as seen in our patients. Ichthyosis was described in 12 ARC cases in the literature (Deal et al., 1990; Di Rocco et al., 1990; Di Rocco et al., 1995; Coleman et al., 1997; Franceschini and Barberis, 1997; Eastham et al., 2001; Howells and Ramaswami, 2002). Skin biopsy was performed in two patients (Deal et al., 1990) and showed marked hyperkeratosis with normal dermis and epidermis. Franceschini and Barberis (1997) suggested expanding the acronym from ARC to ARCI, with ‘I’ for ichthyosis. Lax skin especially in the neck was described in six out of the 39 reported cases (Eastham et al., 2001). Mikati et al. (1984) described dry scaly skin in two patients.

Recurrent febrile illnesses were noted in our two patients and in most of the reported cases. Immunological work up was normal in patients who were evaluated for immune deficiency (Deal et al., 1990).

Variable dysmorphic features were described in association with ARC syndrome (Mikati et al., 1984; Deal et al., 1990; Horslen et al., 1994; Coleman et al., 1997; Eastham et al., 2001; Howells and Ramaswami, 2002) including prominent occiput, posteriorly angulated and low set ears, flattened nasal bridge, upslanting palpebral fissures, simian crease, high arched palate, beaked nose, small anterior fontanel, lax skin, low implantation of the thumb and cryptorchidism.

Abnormally large platelets were found in our patients and in other cases in the literature (Deal et al., 1990; Eastham et al., 2001). A bleeding tendency was reported in a few cases despite normal clotting studies and platelet count; some patients bled after kidney biopsy (Eastham et al., 2001), others after liver biopsy (Di Rocco et al., 1990; Di Rocco et al., 1995; Eastham et al., 2001), and others had cerebral (Coleman et al., 1997) and gastrointestinal bleeding (Deal et al., 1990). Two patients died with a hemorrhagic disorder although the clotting studies were not mentioned (Nezelof et al., 1979).

Other manifestations of ARC syndrome include femoral and rib fractures that usually present at birth (Coleman et al., 1997; Eastham et al., 2001). Our second patient had a fracture of the right femur. Hypothyroidism was previously reported in only one patient with ARC syndrome (Eastham et al., 2001). Our first patient had an elevated TSH level with a normal free T4 concentration and was treated with L-thyroxine for subclinical hypothyroidism. Pregnancy-related complications such as oligohydramnios, reduced fetal movements, and breech presentation are also common. Congenital cardiac defects such as ventricular septal defect (VSD) (Coleman et al., 1997; Abdullah et al., 2000) and atrial septal defect (ASD) (Horslen et al., 1994) are seen occasionally.

Death occurs in most of the cases in the first year of life although one patient survived until the age of 3 years (Coleman et al., 1997). Death is usually secondary to sepsis, severe dehydration and acidosis.

Conclusion
ARC syndrome is a rare inherited autosomal recessive disorder. It is not uncommon in societies with high rates of consanguineous marriages. Variable severities of arthrogryposis, cholestatic liver disease and renal dysfunction, in the form of Fanconi syndrome, nephrocalcinosis or nephrogenic diabetes insipidus, are cardinal features of the syndrome. Cerebral malformations such as lissencephaly can be seen in association with this syndrome. Hypothyroidism is another occasional association. Other additional clinical findings include ichthyosis, abnormally large platelets, deafness and facial dysmorphism. Death occurs in first year of life in most cases.
References