Case Report

Constipation as an Atypical Sign of ARC Syndrome - Case Report

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ABSTRACT: Background: Arthrogryposis- renal tubular dysfunction - cholestasis (ARC) syndrome is a rare multisystem disorder originally described in 1973 and recently ascribed to mutation in VPS33 B whose product acts in intracellular trafficking. It exhibits wide clinical variability but the constipation isn't a characteristic clinical sign. Case: This girl presented after birth severe contractures of legs. She was admitted at 30 days of age with poor feeding, cholestatic jaundice with normal GGT and failure to thrive . Also we have noted a severe acidosis (pH=7.2) associated with aminoaciduria and glucosuria. At second month of age the girl presented a severe ichtyosis, recurrent fever and constipation. Apart from treatment the constipation has persisted. The baby died of sepsis at 12 weeks of age. Conclusion: ARC syndrome exhibits notable clinical variability. Constipation has not been reported previously on the contrary diarrhea is a frequent clinical sign. Knowledge of this rare condition can benefit the practitioner as well as the patient.

KEYWORDS: *arthrogryposis, renal tubular acidosis, cholestasis*

Introduction

ARC syndrome refers to an association between arthrogryposis, renal tubular dysfunction, and cholestasis . Eleven pedigrees have been reported since the association was first described in 1973 [1-8]. Autosomal recessive inheritance is suggested by the frequency of parenteral consanguinity and recurrence in siblings. Almost half of the patients who underwent diagnostic organ biopsy developed life threating hemorrhage [9]. Gissen et al. recently identified a mutation in VPS33B on chromosome 15q26.1 which involves intracellular protein trafficking [10]

As more patients with ARC syndrome have been identified, it has become apparent that there is notable clinical variability, even within the same family. Affected siblings with and without arthrogryposis have been reported[8]. Renal tubular dysfunction ranges from isolated renal tubular acidosis to complete Fanconi syndrome[7], and hepatic histology shows variable combination of cholestasis , intrahepatic biliary hypoplasia, giant cell hepatitis, lipofuscin deposition ,and fibrosis, ultimately progressing to cirrhosis. Additional features have been reported in some patients , including failure to thrive , nephrogenic diabetes insipidus , neurogenic muscular atrophy (which appears to be responsible for the arthrogryposis), cerebral malformation, and nerve deafness. Most patients die by the age of 7 months, but those surviving longer have shown severe developmental delay [8].

Case presentation

Our patient was a little girl one month old who came at our service from neonatology. This girl was the third child of healthy Albanian parents, without history of consanguinity. During the pregnancy the mother had presented oligohygramnios. The baby had a birth weight 2500g. She was born at term but she was small for gestational age. APGARE score was 8/10. She was discharged at day three but she was admitted in neonatology at age of 20 days because of jaundice, weight loss, feeding problems, failure to thrive and contractures of lower limbs (Fig.1). At age of one month she was transferred at our service of gastrohepatology because of cholestasis. In this moment the girl weight was 2350 g. We decided to feed her by nasogastric tube. The first results of blood analyses had shown cholestasis (direct bilirubine=5,2 U/L; total bilirubine =8,9U/L; ALT=85U/l;AST=66U/L; GGT=30U/L). Abdominal echography has shown important ascites (Fig.2). We had performed a blood transfusion because of severe anemia. In consultation with our neurologist and geneticist the contractures of lower limbs are interpreted as talipes calcaneovalgus (Fig.3). The recent urinary analyses had shown glucosuria ,urinary

ph was basic, aminoaciduria. We found also hyperchloremia and low bicarbonate. This combination of arthrogryposis , cholestasis and renal dysfunction make us to think about ARC syndrome. At the same time we have excluded the most part of pathologies that presents cholestasis like cystic fibrosis,TORCH, a1 antitripsine deficiency, endocrinopathy, Allagille syndrome,some metabolic disorders. Cranial computed tomography was unremarkable. We didn't perform a liver biopsy because of an abnormal prothrombine time. Approximately one month later the girl presented a severe ichtyosis and recurrent febrile episodes despite antibiotic therapy. We have expected that this child will present diarrhea but she presented a severe form of constipation. We treated her with several enema but constipation has persisted .Other part of treatment were ursofalk, vitamine A,D,E,K , sodium bicarbonate and antibiotics. Unfortunately she died at age of three months of septicemia. Permission for autopsy was refused. Three weeks later we had a response of molecular biology that was sent abroad which confirms VPS33B mutation

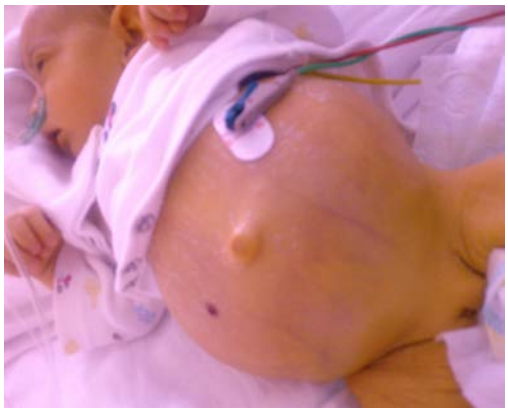

Fig.1.Ascitis , generalized jaundice and severe ichtyosis

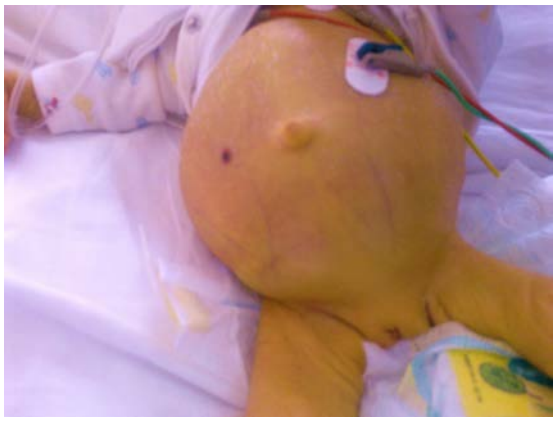

Fig.2.Large abdomen due to important ascitis

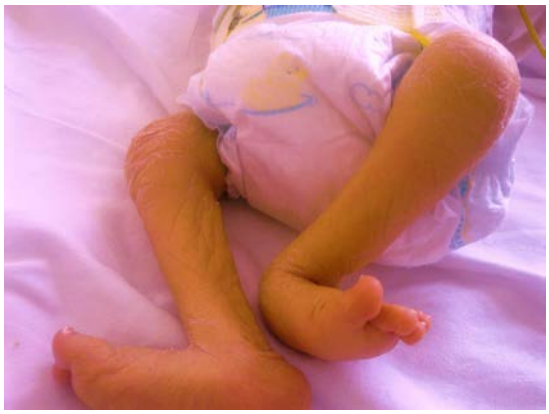

Fig.3.Talipes calcaneo valgus and severe ichtyosis

Discussion

ARC syndrome is a rare autosomal recessive condition. Over recent years it has become apparent that the phenotype is variable; cases may go undiagnosed as not all patients present with the three cardinal features[11] . It has also been recognized that the condition encompasses syndromes originally thought to be distinct [12]. Initially , patient were classified according to their hepatic histology into two groups , characterized either by intrahepatic biliary hypoplasia and giant cell hepatitis or cholestasis with lipofuscin deposition. In 1994, Horslen et al found all the histological abnormalities in a single patient and concluded that both groups of patients had the same condition [10].

The central nervous system manifestations and global developmental delay were described in all reported cases. Other features included sensorineural hearing loss and absence or hypoplasia of the corpus callosum[13].Arthrogryposis is known to be a phenomenon secondary to decreased fetal movement, which is caused by degeneration of the anterior motor neuron cells. As a result, many of these patients are hypotonic. In addition, clubfoot and dislocation of the hip joint are frequently observed[9].

Renal tubular dysfunction has generally been the most striking clinical abnormality and may present in the first few days of life or later around the age of two to three months. Renal tubular dysfunction ranges from isolated renal tubular acidosis to complete Fanconi syndrome. Few patients were found to have diabetes insipidus unresponsive to desmopressin[14] .Kidney ultrasound may show nephrocalcinosis or small dysplastic kidneys[14]. Although nephrocalcinosis was not demonstrated early in

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our case, but was found later when she was almost two months old.

Conjugated hyperbilirubinemia with normal or mildly elevated transaminases is a constant and early feature of ARC syndrome. These patients have normal GGT enzyme levels despite elevated conjugated bilirubin and alkaline phosphatase enzyme levels. However, a few patients had mildly elevated GGT[14].

Ichthyosis has also been reported in association with ARC syndrome in half of the reported instances. It is suspected that the defective lamellar body secretion mediated by the soluble N-ethylmaleimide- sensitive factor attachment protein receptor or SNARE protein pathway in the epidermis might result in the ichthyosiform phenotype[9].

Variable dysmorphic features have been described in association with this syndrome including prominent occiput, flattened nasal bridge, posteriorly angulated and low set ears, up-slanting palpebral fissures, high arched palate, simian crease, beaked nose, small anterior fontanel, lax skin, low implantation of the thumb, and cryptorchidism [15].

A congenital platelet defect similar to the gray platelet syndrome should be suspected in infants and children presenting with a diagnosis or a suspicion of ARC syndrome and platelet morphology should be studied before procedures that may be complicated by significant bleeding [16] . A bleeding tendency was reported in a few cases despite normal clotting studies and platelet count; some patients bled after kidney and liver biopsy, and others had cerebral and gastrointestinal bleeding[16].

Failure to thrive could be secondarily to increased caloric demand because of recurrent episodes of dehydration and sepsis in addition to chronic diarrhea due to fat malabsorption secondary to cholestasis[9].

Conclusion

ARC syndrome exhibits notable clinical variability. Constipation has not been reported previously on the contrary diarrhea is a frequent clinical sign. Knowledge of this rare condition can benefit the practitioner as well as the patient

Acknowledgements

Consent

Consent for publication has been obtained from the parents of patient.

Authors' contribution

VV is the primary author of manuscript. ED, DB and ASH made substantial contributions to acquisition and interpretation of data. PC made substantial contribution to the interpretation of data, revised the manuscript critically, and gave final approval of the version to be published.

Competing interests

The authors declare that they have no competing interests.

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