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Case Report

Antley Bixler Syndrome (ABS), a very rare paediatric syndrome, the first reported case in Sudan

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The Antley-Bixler syndrome (ABS) is a rare multiple congenital anomaly with a high mortality rate. The characteristic manifestations include craniocynostosis, radio-humeral synostosis, mid-facial hypoplasia, joint contractures, genital ambiguity and arachnodactyly (Hosalkar et al., 2001). Femoral arching, ulnar arching, vertebral anomalies, and articular contractures are secondary to synostosis (especially radio-humeral synostosis) (Machado et al., 2001). Antley-Bixler syndrome (ABS) in the scientific literature is genetically heterogeneous with at least two distinct disorders: (1) ABS without disordered steroidogenesis, which appears to be a variant of the autosomal dominant fibroblast growth factor receptor (*FGFR)*–related craniocynostosis syndromes, and (2) ABS with disordered steroidogenesis, which appears to be caused by severe mutations in cytochrome P450 oxidoreductase (*POR)* (Cragun and Hopkin, 2005; McGlaughlin et al., 2010; Reardon et al., 2000; Huang et al., 2005). In addition, a phenocopy of ABS may be seen in infants of mothers treated with fluconazole, an antifungal agent, in early pregnancy (Hosalkar et al., 2001; Reardon et al., 2000). Mortality is as high as 80% in the first months of life. Prenatal diagnosis by mid-trimester ultrasound examination is possible. Fixed flexion of the elbow appears to be the essential diagnostic finding. It needs multidisciplinary team approach in management (Hosalkar et al., 2001).

Keywords: Antley Bixler syndrome, mid-facial hypoplasia, multiple synostoses, joint contracture, Sudan.

CASE REPORT

A 7 months term female baby was outcome of consanguineous marriage delivered by spontaneous vaginal delivery at hospital. She needed no resuscitation. Pregnancy complicated by high grade and continuous fever started at the 2nd month and continued throughout the pregnancy associated with urinary tract infection, albuminuria and LL swelling. She had history of contact with chicken pox at 5th month but no history of skin rash, poly or oligohydromnios. She was the first baby for her parents.

She has developmental delay (no social smile, can't support her head and no cooing). But she can fix light and follow objects. There was no concern about hearing. She was vaccinated up to her age according to new Extended Program of Immunization with BCG scar. There was no family history of similar condition.

On examination: the baby looked ill with mild fever and pallor, not dehydrated or distressed. She was dysmorphic with bilateral proptosis, small head (craniocynostosis and brachycephaly), dysplastic low set ears, pear-like nose and right zygomatic region swelling (5X6 cm) with dilated

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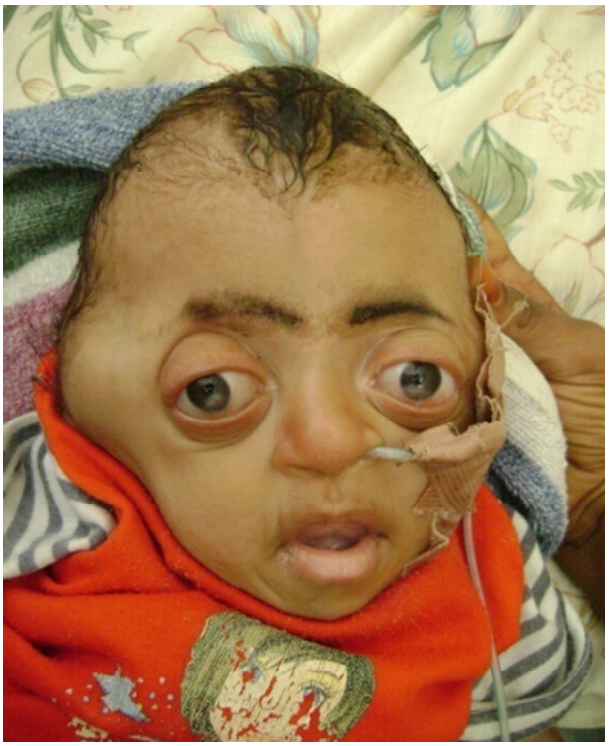


Photo 1. shows mid-facial hypoplasia and dysmorphic features

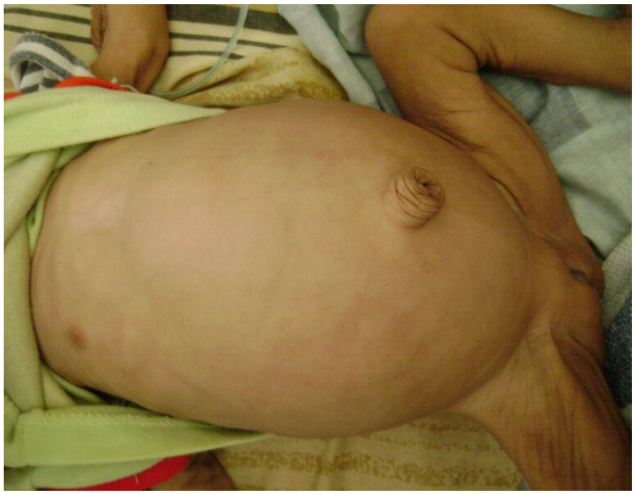


Photo 2. shows abdominal distension and umbilical hernia

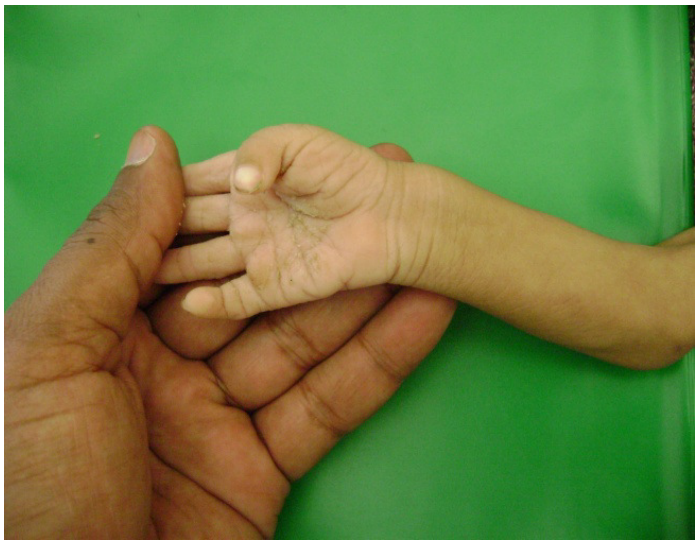


Photo 3. clinodactyly and medially curved thumb.

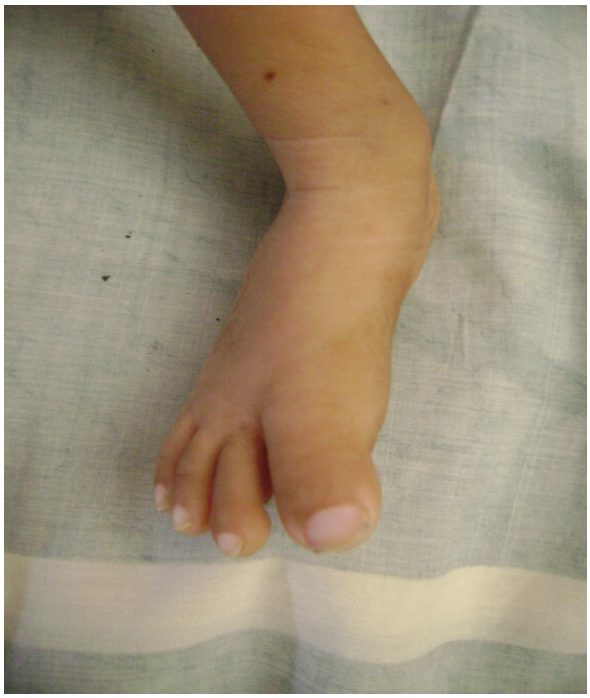


Photo 4. shows medially curved big toe.

veins over it (photo 1). The chest, cardiovascular, nervous systems and the back were normal. The abdomen was distended with umbilical hernia. There was normal female genitalia (photo 2).

Musclo-skeletal examination: emaciated, both wrists showed restricted movements. There is fixed flexion deformity at 30-40º of both elbows with restricted supination pronation movement at radio-ulnar joints. There was overlapping between middle and index fingers with both thumbs curved medially. There is genu-varus bilaterally with metatarsal varus of both big toes (photo 3, 4, 5).

Her investigations showed: normal CBC apart from low haemoglobin (Hb 9.4g/dl), normal ESR. The renal and liver profiles were normal. HIV screening and blood film for malaria were both negative. Urine showed albuminuria (+), Pus cells 9-10/HPF, urine culture: E-coli isolated and sensitive to Gentamycin.

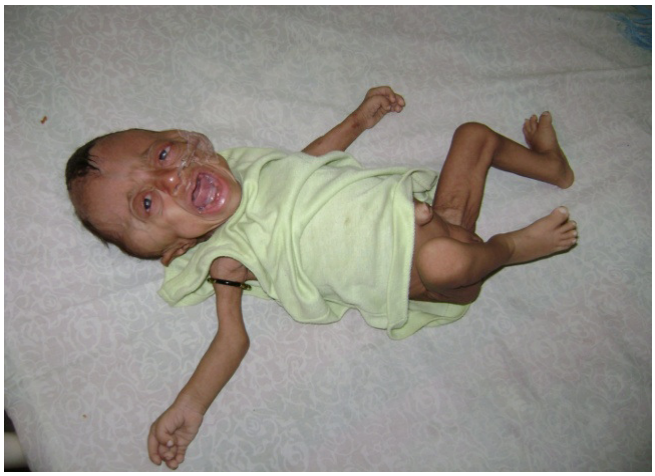
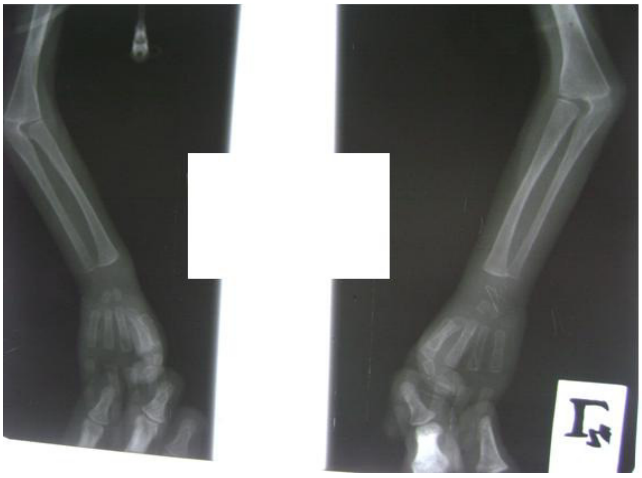
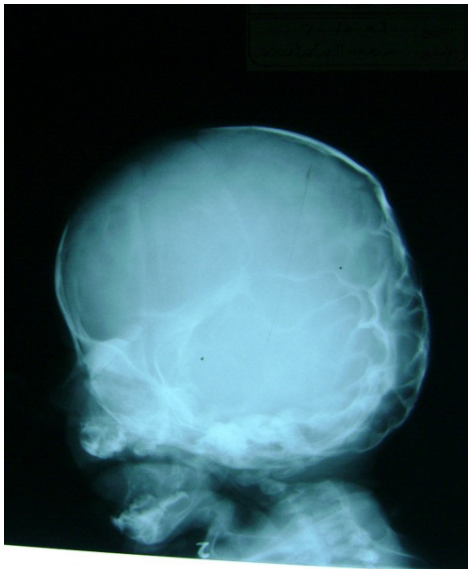


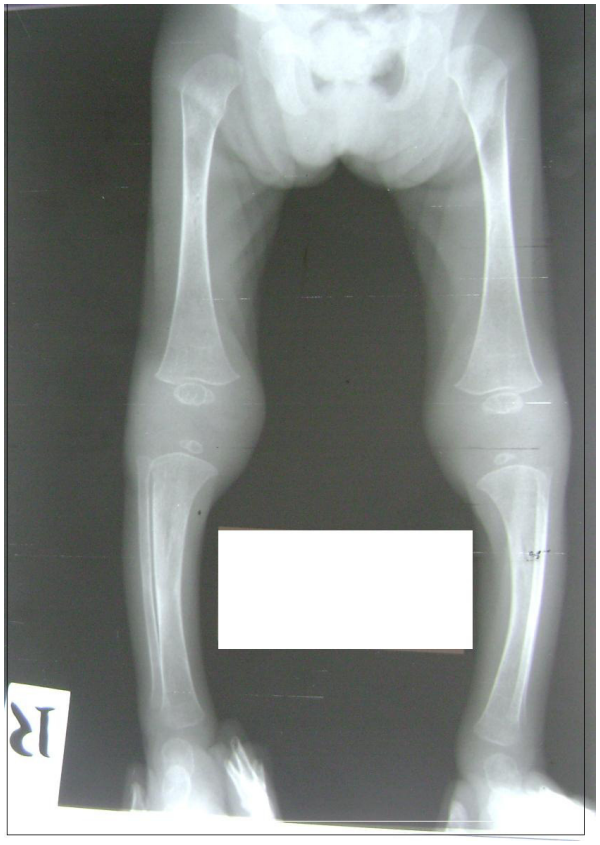
Photo 5. dysmorphic features, muscle wasting and skeletal abnormalities.



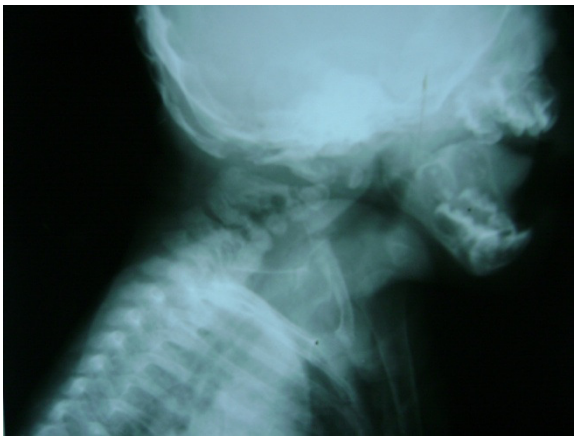
X-ray No 3. ankylosis ulna and radius.



X-ray No 1. lacunar skull



X-ray No 4. genu-varus



X-ray No 2. fused C6-C7

Skull X-ray and cervical spine: There is oxycephaly with lacunar skull, no fracture line and normal pit fossa. C6 - C7 were Fused with patent airways. Chest X ray, Pelvic X ray and Spine X-ray: all were normal. Forearm X-ray: There is bony ankylosis of both ulna and humeral bones (bilaterally). Knee X-rays: showed genu-varus (x-rays 1, 2, 3, 4).

Echocardiography revealed a normal heart anatomically and functionally. Abdomen ultrasound showed hyperechoic mass (12x11mm) in the right lobe of the liver (haemangioma). The kidneys were normal in morphological appearance. CT brain showed premature closure of the coronal sutures. The sagittal suture still unfused. There was no focal parenchymal abnormality. Visual assessment: baby can follow objects. Fundoscopy showed mild bilateral disc oedema.

DISCUSSION

Antley Bixler syndrome (ABS) comprises malformations of cartilage and bone (Bianchi et al., 1991). It is a rare multiple congenital anomalies with high mortality rate particularly in early infancy. Usually it presents in early life with dysmorphic features, skeletal anomalies and ambiguous genitalia. It was first reported by Antley and Bixler in 1975 but the exact aetiopathogenesis of this syndrome is still unknown. Only 41 patients, for the best of our knowledge, are reported worldwide till now. The male to female ratio is believed to be 2:7 (Hosalkar et al., 2001).

Antley Bixler syndrome (ABS) represents the severe end of the spectrum of craniocynostosis. Many such patients have choanal atresia and severe respiratory distress, often resulting in early death. In contrast with most clinically similar forms of syndromic craniocynostosis, which are transmitted in an autosomal dominant manner, Antley-Bixler syndrome has been thought to be an autosomal recessive disorder. This is based upon three reports of affected sibs and the birth of affected subjects to consanguineous parents (Reardon et al., 2000). Antley-Bixler syndrome (ABS) is genetically heterogeneous with at least two distinct disorders (digenic inheritance): (1) ABS without disordered steroidogenesis, which appears to be a variant of the autosomal dominant fibroblast growth factor receptor (*FGFR)*–related craniocynostosis syndromes, and (2) ABS with disordered steroidogenesis, which appears to be caused by severe mutations in cytochrome P450 oxidoreductase (*POR)* (Cragun and Hopkin, 2005; McGlaughlin et al., 2010; Reardon et al., 2000; Huang et al., 2005).

Synostosis of cranial sutures and elbow joints are considered as the minimal diagnostic criteria (Hosalkar et al., 2001). The cardinal features of this condition include craniosynostosis, severe mid-face hypoplasia, proptosis, choanal atresia/stenosis, frontal bossing, dysplastic ears, depressed nasal bridge, radio-humeral synostosis, long-bone fractures and femoral bowing, uro-genital abnormalities and a normal karyotype. Early death was identified in 54% of the reported cases, usually due to respiratory complications (Hassell and Butler, 1994). Varying uro-genital anomalies including ectopic kidneys, ureteric obstruction, hypoplastic uterus, hypoplastic or fused labia majora, large clitoris, small penis or undescended testes are seen in less than 50% of the patients. Congenital heart defects have been noted in about 21 % cases (Hassell and Butler, 1994).

Our patient is a female baby and she was outcome of consanguineous parents and she was the first and only baby of her family. The baby didn't have choanal atresia, renal or genital anomalies. There was no respiratory distress at birth. Other causes of respiratory distress may include laryngeal atresia, laryngeal stenosis and pulmonary hypoplasia (Machado et al., 2001). In contrast, our patient had three unique features not reported in any of the previous cases; namely fused cervical vertebrae C_6-C_7, overlapping of fingers and liver haemangioma. Similarly, There were unique features reported by other authors e.g. Bottero L et al reported 18-month-old girl with imperforate anus which is not reported by any other author (Bottero et al., 1997; Bottero et al., 1997). Crisponi et al and Chabchoub A et al reported a case with elbow joint contracture believed to be due to radio-ulnar synostosis rather than radio-humeral synostosis (Crisponi et al., 1997; Chabchoub et al., 1998).There was no long bone fracture which is similar to our case. Other orthopedic manifestations that may occur are ulnar bowing, camptodactyly, synostoses of carpal and tarsal bones, clubfoot, vertebral body anomalies and advanced skeletal age (Rumball et al., 1999). Interestingly, Feigin et al reported a case of a consanguineous infant with ABS had eosophageal atresia and trisomy 21 (Feigin et al., 1995), Schinzel et al reported a case with vaginal atresia (Schinzel et al., 1983), Luiz Eduardo et al reported a case of ABS with laryngeal atresia (Machado et al., 2001) and Bottero L et al reported a case with imperforate anus (Bottero et al., 1997) together with choanal atresia, suggest the strong association of atresias with Antley-Bixler syndrome.

Prenatal diagnosis: Fixed flexion of the elbow appears to be the essential diagnostic finding (Hosalkar et al., 2001), but the 2D trans-abdominal examination may reveal an abnormally shaped cranium with depression of the frontal bones and brachycephaly suggestive of craniosynostosis, polyhydramnios, and marked craniofacial anomalies, including a flat face, micrognathia, absence of nasal bones, no evidence of communication between the nostrils and the nasopharynx (choanal atresia), a markedly depressed nasal bridge, mid-facial hypoplasia, and exophthalmos, a bell-shaped thorax with hypoplastic lungs. The ultrasonographic differential diagnoses included trisomy 18, Jacobsen syndrome, camptomelic dysplasia, Pena-Shokeir syndrome, Apert syndrome, Carpenter syndrome, Crouzon syndrome, and Pfeiffer syndrome (Machado et al., 2001).

Respiratory distress secondary to choanal atresia or stenosis can be a serious factor for mortality, often requiring intubation, tracheostomy and nasal stents. Craniectomy is performed to treat sutural synostosis to

allow the brain to develop normally and so normal intelligence. Results of resecting the radio-humeral synostosis are not encouraging and surgery may best be avoided. Finger contractures are associated with shortened tendons, which usually improve with physical therapy (Hosalkar et al., 2001).

Survival is closely linked to upper airway obstruction, which also affects (with craniosynostosis) mental prognosis. Association and severity of malformations are variable, and while numerous children have died early from respiratory distress, one third of them are alive, and have had quite satisfactory development (Bottero et al., 1997; Bottero et al., 1997). Prognosis improves with increasing age (Feigin et al., 1995). With early and effective prevention of respiratory complications, and early treatment of craniosynostosis, overall prognosis can be favorable (Bottero et al., 1997; Bottero et al., 1997).

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