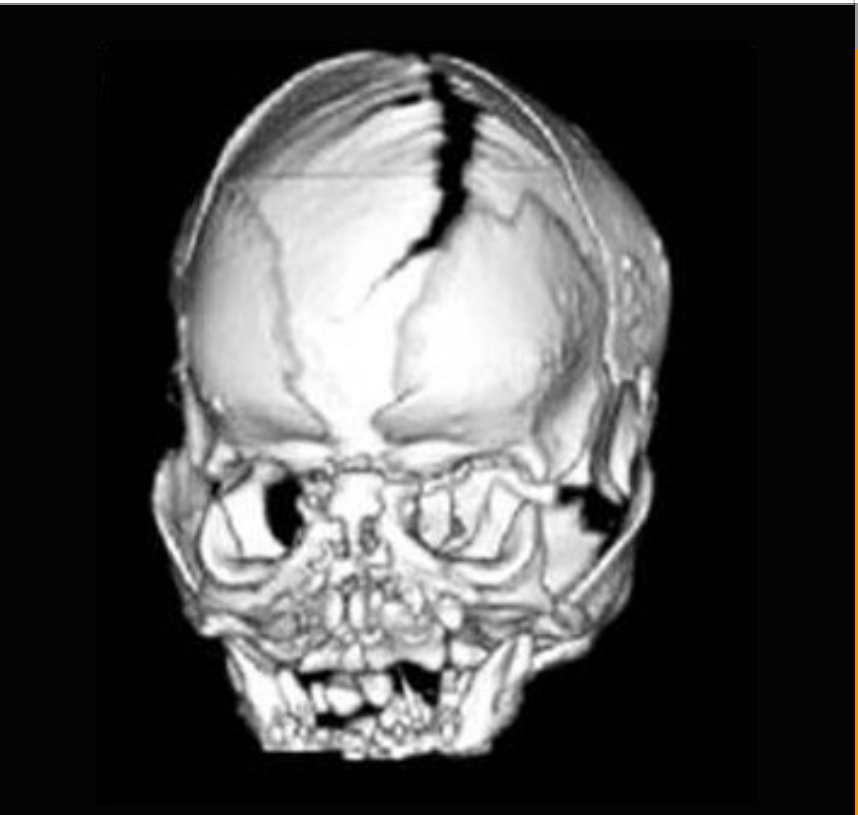
SWISS SOCIETY OF NEONATOLOGY

# Raine syndrome: clinical and radiological features of a case from the United Arab Emirates



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Abu Asbeh J, Bystricka A, Qadir M, Nikolay M, Khan J,
Neonatal Intensive Care Unit, Al-Rahba Hospital, Abu
Dhabi, UAE

This male baby was born at 31 5/7 weeks to a 34-year-old Pakistani G2/P1 by emergency lower segment Cesarean section due to fetal distress. Maternal history was significant for PPROM 24 hours prior to delivery and severe oligohydramnios. Her first pregnancy had ended with preterm delivery at 26 weeks gestation; the baby had gross congenital anomalies and died at 2 hours of age. This baby was born limp and cyanosed, his birth weight was 1785 g (P10), his head circumference 28.5 cm (<P10), and his length 47 cm (>P50). Apgar scores were 4, 6 and 8 at 1, 5 and 10 minutes, respectively.

Physical examination was significant for multiple congenital malformations including dolichocephaly, bulging wide fontanels, narrow prominent forehead, gross bilateral proptosis with chemosis and bilateral corneal opacities, low-set ears, mid-facial hypoplasia, hypoplastic nose with bilateral choanal atresia, and micrognathia/retrognathia (Fig. 1). The mouth was triangular with moderate gingival hypertrophy, a high arched palate and cleft upper gum. There was also bowing of both lower limbs.

Fig. 1

*Characteristic facial features of Raine syndrome: note mid-facial hypoplasia, proptosis, hypoplastic nose, micrognathia/retrognathia, low set ears, and prominent forehead.*

Radiographs of the skull showed increased bone density although overall ossification appeared to be delayed. The skeleton showed generalized increase of bone density. The medullary cavities of the long bones were poorly differentiated from the cortex, and irregular periosteal thickenings were present (Fig. 2-4). Abdominal ultrasound was normal, but head ultrasound showed diffuse periventricular calcifications. This was confirmed on a CT scan of the brain, which showed bilateral subcortical and periventricular cerebral calcifications as well as mild dilatation of the lateral ventricles, and calcification of the basal ganglia and pineal body (Fig. 5). Laboratory investigations upon admission including CBC, liver and kidney function tests, electrolytes were all within normal limits. The baby developed progressive respiratory distress, was mechanically ventilated for almost 2 months and ultimately died of progressive respiratory failure.

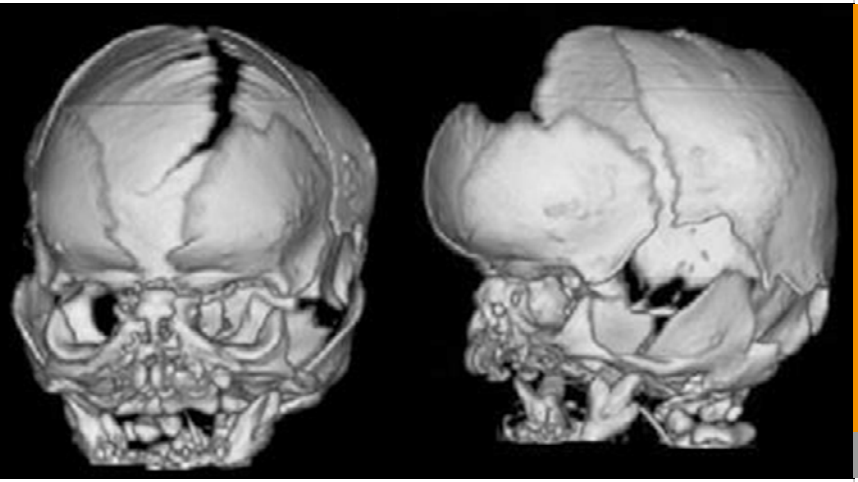

Fig. 2

*CT scan of the head: 3D-view showing wide anterior and temporal fontanels as well as metopic sutures, mid-facial hypoplasia is also evident.*

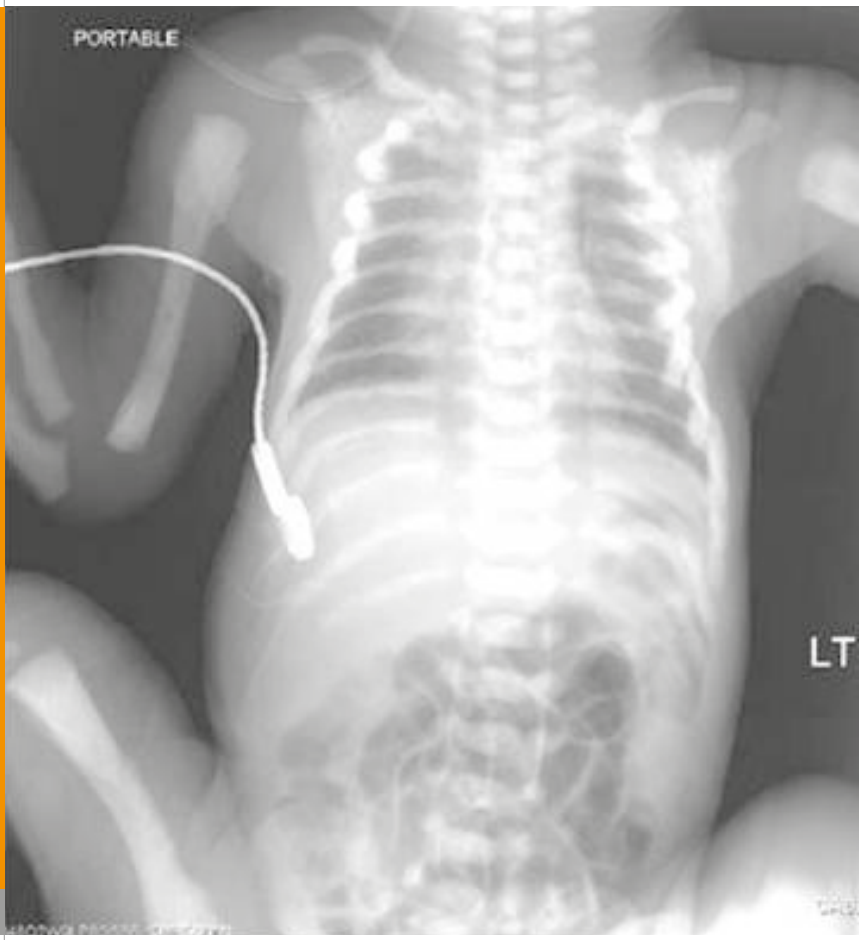


**Fig. 3**

*Babygram: generalized increase in bone density.*

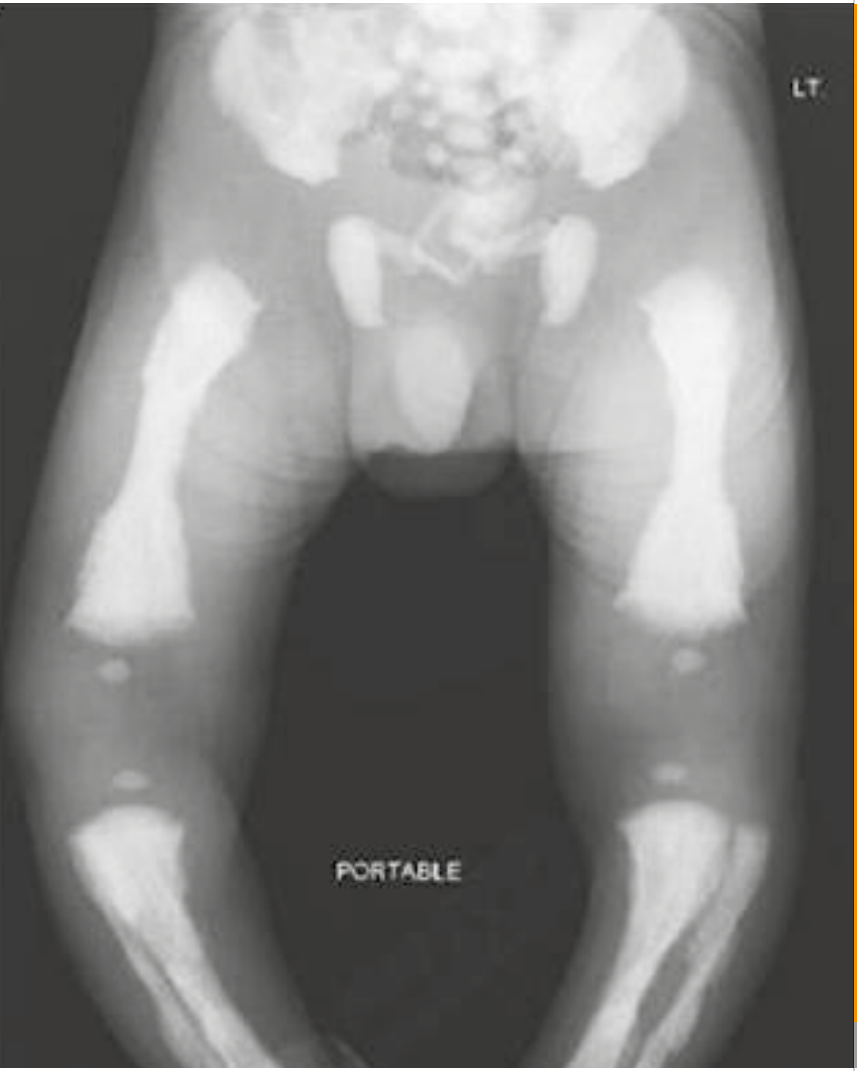


Fig. 4

*X-rays of lower extremities: the medullary cavities of the long bones are poorly differentiated from the cortex and irregular periosteal thickenings are apparent.*

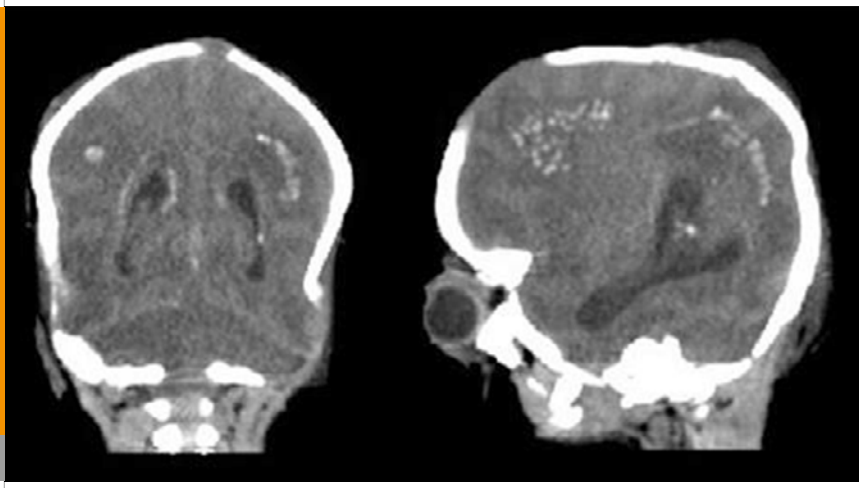

Fig. 5

*CT scan of the head: extensive subcortical and peri-ventricular cerebral calcifications.*

Raine syndrome is a rare autosomal recessive disorder, which was first described in 1989 by Raine et al (1). It is characterized by characteristic craniofacial anomalies and generalized osteosclerosis with periosteal new bone formation. It is considered a lethal disorder usually leading to death during the first few days to weeks of life although survival into childhood has recently been reported by Simpson et al. (2) and Fardin et al. (3). To our knowledge, fewer than 20 cases have been reported in the literature so far.

The facial features of Raine syndrome include a combination of microcephaly, wide anterior fontanel, a narrow prominent forehead, hypertelorism, bilateral eye proptosis with downward eye slant, noticeably low set ears, a hypoplastic nose, severe depression of the nasal bridge, and severe mid-face hypoplasia. Unilateral or bilateral choanal atresia is often also present. Other abnormalities include gum hypertrophy, large protruding tongue, natal teeth, and cleft palate/uvula, microstomia with carp-shaped mouth, and severe micro/retrognathia. Cleft of the maxilla and mandible have been reported by Kan and Kozlowski (4), and the association with a posterior encephalocele has been described by Al Mane et al. (5).

Abnormalities in the urogenital tract have been described in patients with Raine syndrome, including bilateral hydroureters, hydronephrosis, and stenotic ostea of both ureters (6). Pulmonary hypoplasia is a common

associated feature. Cardiomegaly with left ventricular muscular hypertrophy and hypoplasia of the main stem pulmonary arteries have also been reported in association with Raine syndrome (6).

In many reports, the airway compromise in Raine syndrome has been ascribed to choanal atresia, and sometimes to a narrow chest, pulmonary hypoplasia or retrognathia (2, 5). Pyriform stenosis aperture has also been described as a cause of airway compromise and is probably underdiagnosed since the clinical presentation is the same as in choanal atresia (7).

Radiographic findings include generalized increase in density of all bones and a markedly increased ossification of the skull. The increased ossification of the basal structures of the skull and facial bones are responsible for the characteristic facial features. Periosteal bone formation extending over the diaphyses of long bones is also characteristic of this disorder. Widespread focal cerebral calcifications in the periventricular white matter has been described by several authors and was present in our case; calcification of the basal ganglia as well as meningeal calcification have also been demonstrated in some cases. Calcification of the nasal septum was also found in one of the recent cases as well as failure of ossification of the sacrum and cervical bodies C2 to C5 (7).

Raine syndrome is an autosomal recessive disorder. There are reports of recurrence in children born of the same parents, and an increased occurrence in children of closely related, genetically similar parents. A mutation in the gene FAM20C is the cause of the Raine syndrome phenotype. FAM20C stands for "family with sequence similarity 20, member C.". Individuals with Raine syndrome were either homozygous or compound heterozygous for the mutation of FAM20C. FAM20C, located on chromosome 7p22.3, is an important molecule in bone development. Studies in mice have demonstrated its importance in the mineralization of bones in teeth in early development (8). The milder phenotypes of Raine syndrome suggest that missense mutations may not be as lethal as the other described mutations. This is supported by findings from Fradin et al., who reported on children with missense mutations to FAM20C surviving for 1 and 4 years (i.e., much longer than previously reported cases) (3).

Our case presented with the typical clinical and radiological features of Raine syndrome. The early neonatal death of the first sibling with multiple congenital anomalies may have been due to the same syndrome, however, this could not be confirmed as no information was available about the exacte nature of the abnormalities. Genetic confirmation could not be obtained in our case because of financial restraints.

## REFERENCES


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CONTACT Swiss Society of Neonatology
www.neonet.ch
webmaster@neonet.ch