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Research Letter

Rodriguez lethal acrofacial dysostosis syndrome with ambiguous genitalia

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Dear Editor,

The acrofacial dysostosis syndromes (AFDs) involve a group of disorders characterized by mandibulofacial dysostosis and limb anomalies [1,2]. They are classified into two major groups according to the type of limb defects; Nager type and Genee–Wiedemann type. The Nager type and Genee–Wiedemann type resemble each other in terms of facial findings. However, Nager AFD is characterized with preaxial limb anomalies, while postaxial limb anomalies are typical for Genee–Wiedemann AFD. Pattern of inheritance is mostly autosomal dominant for most AFDs and the majority of cases are likely to ensource from a new mutation [3]. Rodriguez type acrofacial dysostosis syndrome is an extremely rare form of AFD, characterized by Nager- like facial dysmorphisms. Whether Nager type and Rodriguez type are distinct entities or represent variants of the same condition is obscure [4]. The inheritance of Rodriguez type of AFD is autosomal recessive unlike other AFD syndromes [5]. The Rodriguez type of AFD is associated with mandibulofacial dysostosis, preaxial and postaxial upper and lower limb anomalies, shoulder/pelvis girdle hypoplasia, as well as cardiac and central nervous system (CNS) malformations [6]. As far as we know, 10 cases of this type of AFD syndrome have been previously reported up to now. In this case report, we describe an additional case of Rodriguez type lethal AFD with ambiguous genitalia and severe upper and lower limb deformities.

The newborn was born to nonconsanguineous, healthy, Caucasian parents and the ages of the mother and father were 29 years and 34 years, respectively. The family history was remarkable for a dead fetus with phocomelia and uncertain sex in the first pregnancy. Other than this, the family had a 4-year-old healthy daughter. The pregnancy initially seemed to be uncomplicated and there was no history of vaginal bleeding, infection, skin rash, hypertension, diabetes mellitus, any medications, teratogenic agents, and radiation exposure. In the first trimester screening, serious increased nuchal translucency (7 mm) and extremity anomalies were observed in sonography. The family did not approve the amniocentesis and refused termination of pregnancy, then the pregnancy was followed-up until term. In the second and third trimester ultrasonographic examination multiple arachnoidal cysts in the brain, hypoplastic chest, aplasia of the left kidney, and generalized edema in the neck and whole-body was determined. Finally, a fetus of 1480 g was delivered at term. The fetus died 1 hour after birth. In addition to severe growth retardation, there was tetraphocomelia, facial anomalies, and ambiguous genitalia. Discrimination of gender could not be made by observation of external genitalia (Figure 1). There was facial dysmorphism including, a large anterior fontanelle, absence of palpebrale fissure, broad nasal root with a prominent nose, microstomia, and

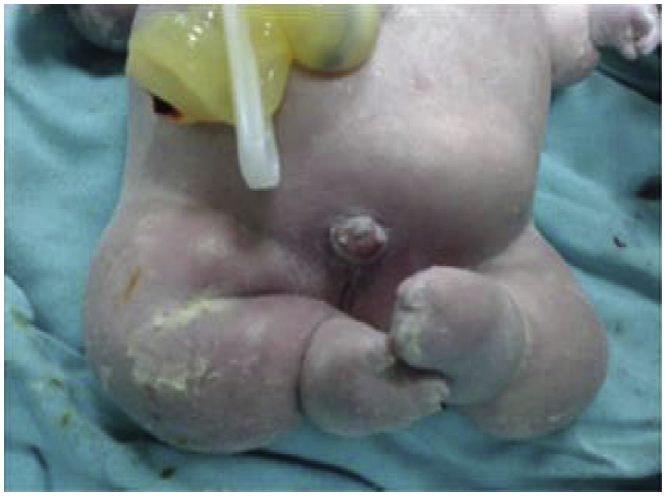

Figure 1. Ambiguous genitalia detected at the observation of external genitalia.

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micrognathia. Both ears were low-set, posteriorly rotated and the auricles were small, abnormal in shape, and the external auditory meati were absent (Figure 2). The upper limbs showed short proximal arms, absent forearms, and only three fingers on each hand. The lower limbs showed absence of fibula and three toes on each foot (Figure 3). The family did not approve autopsy and we could not examine the genetic analysis of the fetus.

Rodriguez type AFDs have typical facial anomalies such as severe mandibulofacial dysostosis, absence of auditory canals, and cleft palate, preaxial and postaxial hand and foot defects with more prominent preaxial involvement, anomalies of pelvic bones, and hypoplasia or agenesis of fibulae, a variety of CNS abnormalities (arrhinencephaly, callosal agenesis), lung (hypoplastic/hypolobated lungs), heart, and urogenital system anomalies [3]. Our patient had short proximal arms, absent forearms, oligodactyly, and lower limb defects including absence of the fibula. The likelihood of variability in the manifestations and the internal organ abnormalities necessitates increased awareness for correct diagnosis of Rodriguez type AFDs. In our case multiple arachnoidal cysts, aplasia of left kidney, and pulmonary hypoplasia were observed.

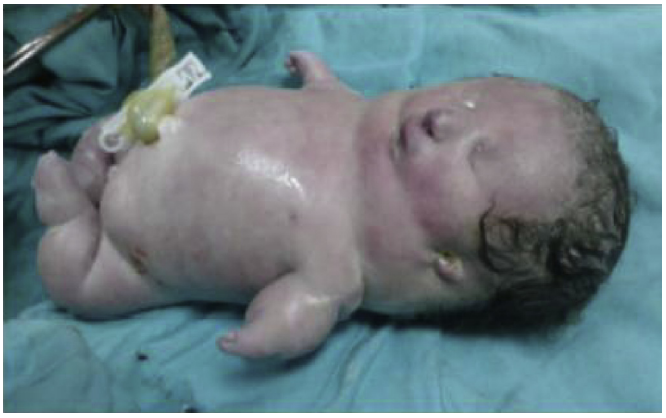

Figure 2. Severe acrofacial dysostosis and tetraphocomelia.

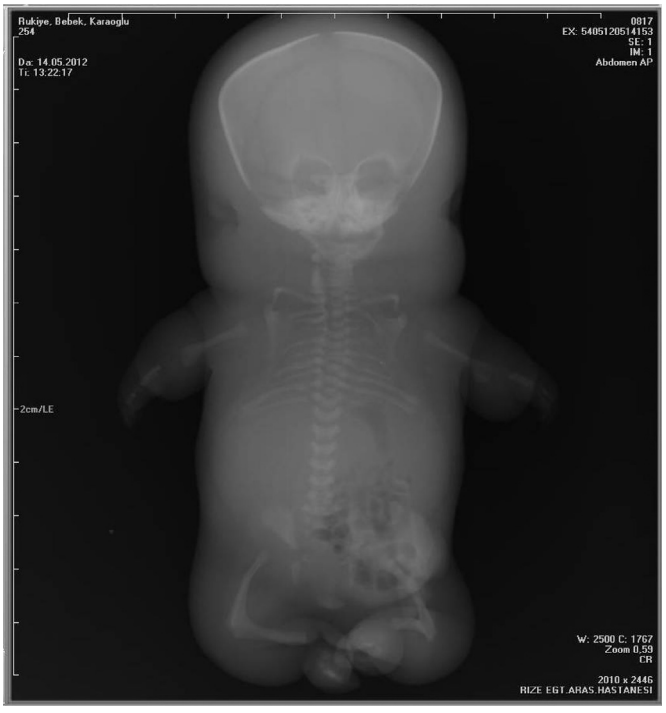

Figure 3. Postmortem radiographs indicating typical defects in upper and lower limbs.

The unique and distinguishing feature of our case is ambiguous genitalia. The external genital examination did not reveal any structures consistent with labia majora or testis, nor urethral meatus could be observed. To the best of our knowledge, only one case of AFD with ambiguous genitalia has been reported [7]. However, as far as we know, there is no data for a Rodriguez type AFD with ambiguous genitalia in the medical literature (PubMed).

The present patient died 1 hour after birth due to respiratory failure arising from pulmonary hypoplasia. Although pulmonary hypoplasia is not essentially a part of Rodriguez type AFD, it may be linked to the fatal course. Severe upper airway obstruction due to severe micrognathia may contribute to the pulmonary hypoplasia [6,8]. In our case, pulmonary hypoplasia was seen but cardiac malformations were not observed.

Since there is no gene specifically linked with this disease, diagnosis is established with respect to physical examination findings. The diagnosis was made postpartum by the severity of the upper and lower preaxial limb defects and the absence of fibula and eyelid coloboma excluded the possibility of other conditions associated with AFD. The absence of fibulae is one important clinical finding to distinguish Rodriguez lethal AFD from Nager syndrome and Genee–Wiedemann syndrome [9,10].

Besides the first report by Rodriguez of this new AFD, there have been only nine other undisputed reports of AFD Rodriguez type in the literature. We present here an additional case of this rare condition. The inheritance of Rodriguez type of AFD is autosomal recessive unlike other AFD syndromes [11]. Apart from Rodriguez et al [11] who reported three affected sibs, Hecht et al [12] reported two sibs with this type of AFD, thus confirming autosomal recessive mode of inheritance. The parents of our patient had a family history of a dead fetus with phocomelia in the first pregnancy. Genetic counseling was made with respect to these data and the family was informed about the recurrence risk.

All in all, we encountered a case of lethal AFD and this case is similar to the literature described by Rodriguez. As far as we know, this is the first Turkish case of Rodriguez type lethal AFD syndrome with tetraphocomelia and ambiguous genitalia. Acrofacial dysostosis Rodriguez type must be considered in the differential diagnosis of newborns presenting with tetraphocomelia and ambiguous genitalia.

Conflicts of interest

The authors have no conflict of interest relevant to this article.

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