

## RESEARCH LETTER

# Prenatal sonographic diagnosis of Nager acrofacial dysostosis with unilateral upper limb involvement

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Nager acrofacial dysostosis is a rare form of acrofacial dysostosis first described by Nager and de Reynier, 1948. It is characterized by mandibulofacial dysostosis and limb anomalies. Typical craniofacial findings include down-slanting palpebral fissures, malar hypoplasia, micrognathia, abnormalities of the palate including high-arched hard palate, cleft palate or bifid uvula, small, low-set and posteriorly rotated ears, and abnormalities of the external and middle ear. Limb malformations associated with Nager acrofacial dysostosis most often involve the radial aspect of the upper limbs and may result in thumb hypoplasia or aplasia and/or aplasia/hypoplasia of the radius. Findings in a single affected individual are often not symmetrical but both upper limbs are usually involved. Severity can range from mild hypoplasia of the thumb to phocomelia. Radio-ulnar synostosis and abnormalities of the lower limbs have also been reported. Intelligence is typically normal. Congenital bilateral conductive hearing loss, speech difficulties and upper airway obstruction are common secondary to otologic and oral/mandibular abnormalities. A review of reported cases indicates wide variability in manifestations and severity of craniofacial and limb findings (Halal *et al.*, 1983; Hall, 1989; Le Merrer *et al.*, 1989; Danziger *et al.*, 1990; Aylsworth *et al.*, 1991). Cases of Nager acrofacial dysostosis are most often sporadic; however, several cases of autosomal dominant inheritance have been reported (Hall, 1989; Aylsworth *et al.*, 1991). There are also reports of recurrence in children of unaffected parents, suggesting either autosomal recessive inheritance, possible germ line or somatic mosaicism, and, therefore, genetic heterogeneity (Chemke *et al.*, 1988). Diagnosis depends on recognition of the phenotype, most often without a family history.

A 23-year-old G2P0010 female presented for second trimester ultrasound at 20 weeks gestation based

on first trimester ultrasound dating. She underwent a kidney transplant 6 years prior to this pregnancy following trauma and subsequently developed type I diabetes. Hemoglobin A<sub>1C</sub> taken 1 month prior to conception was elevated at 7.2%. The patient took the following medications during pregnancy: CellCept, Cleocin, Humalog, Lantus, Prednisone, Prevacid, Prograf and prenatal vitamins. Significant family history included a brother of the patient who died at 18 months of age due to complications from severe hypoxia at birth. The remainder of the patient's and her partner's family history was unremarkable.

Prenatal ultrasound findings included the following: single umbilical artery; marked micrognathia; abnormal ears, which were thought to be low-set and posteriorly rotated; and short left humerus with more pronounced shortening of the left radius and ulna. The left hand appeared anomalous with abnormal-appearing thumb suspicious for syndactyly of the thumb and index finger. Overall long bone measurements for the right arm were consistent with dating; the right hand was not visualized due to fetal position. Fetal echocardiography revealed normal cardiac structures.

The patient and her partner were informed of the ultrasound findings and were counseled regarding the most likely diagnosis of Nager acrofacial dysostosis as well as differential diagnoses, which included Treacher Collins syndrome, Mohr syndrome, hemifacial microsomia, or, less likely, a chromosome abnormality such as trisomy 18. Treacher Collins syndrome, another form of acrofacial dysostosis, does not exhibit associated limb findings. There is a form of hemifacial microsomia that has been described with associated radial anomalies; however, the facial findings are usually not symmetrical. Findings associated with Mohr syndrome include cleft palate and micrognathia; however, there is often polysyndactyly of both the hands and feet. While fetuses with trisomy 18 may have severe micrognathia and radial anomalies, there are often other associated findings such as heart defects, growth restriction and rocker-bottom feet. After counseling, amniocentesis was declined. The couple elected to undergo early induction

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Figure 1—Postabortal photographs illustrating severe micrognathia, hypoplastic left thumb and type III microtia

of labor for termination of pregnancy with subsequent postabortal autopsy examination. The patient underwent induction of labor at 20 weeks and 4 days of gestation and delivered a 306 g female (41.68 percentile) (Figure 1).

Anatomic pathology exam revealed down-slanting palpebral fissures and shallow orbits. The ocular globes were unremarkable. The nasal root was wide and the mouth was microstomic with severe micrognathia. The palate was intact through the uvula, but forwardly displaced by the tongue, which was herniated into the nasopharynx and folded over the epiglottis. There was type III microtia with external ears consisting of  $2 \times 1$  mm double hillocks. The external auditory canals were absent. The temporal bone morphology was unremarkable as viewed from the interior of the skull. The left arm was hypoplastic with flexion contractures at the shoulder and the elbow. The fingers of the left hand, especially the thumb, were short. By radiograph, the right humerus measured 35 mm, the radius 25 mm and the ulna 25 mm. The left humerus measured 27 mm, the left radius 15 mm and the left ulna 15 mm. The femurs measured 30 mm each. The first left rib was hypoplastic (no sternal articulation) and the sternal-rib articulations were asymmetrical. The lungs were hypoplastic, weighing 4.29 g (0.4 percentile,  $-2.65$  SD). The right kidney was rotated  $90^\circ$  (hilum ventral) with a circumferential groove. Aside from absence of the left umbilical artery, there were no cardiovascular or other visceral anomalies. Brain morphology was appropriate for gestational age. Karyotype was not obtained.

To our knowledge, this is the third reported case of Nager acrofacial dysostosis diagnosed with prenatal

ultrasound in the absence of a positive family history (Benson *et al.*, 1988; Paladini *et al.*, 2003). The prior reported cases involved bilateral limb findings, unlike the unilateral findings seen in this case. Postnatal diagnosis includes a predominance of bilateral upper limb anomalies although unilateral findings have been described. A review of the available English-language literature reveals that of the 80 reported cases of Nager acrofacial dysostosis, which indicated laterality of upper limb findings, 77 (96%) were bilateral.

There is a known group of acrofacial dysostoses that include a spectrum of findings involving mandibulofacial dysostosis with or without limb anomalies. Animal models of these conditions, which include Nager and Miller acrofacial dysostoses and Treacher Collins syndrome, have suggested that the associated craniofacial anomalies are a result of cell death in the proximal aspect of the maxillary and mandibular prominences of the first visceral arch and in the case of Nager and Miller acrofacial dysostoses in the apical ectodermal ridge of the limb bud (Sulik *et al.*, 1989). Mutations in the TCOF gene on chromosome 5 are responsible for the majority of cases of Treacher Collins syndrome; however, the specific gene mutation(s) responsible for Nager acrofacial dysostosis has not been identified. In the present case, gene testing to rule out Treacher Collins syndrome was not performed since physical findings associated with Treacher Collins syndrome are specifically exclusive of the limbs.

Since varying degrees of severity in affected individuals from the same family have been observed, clinical genetics evaluation of parents of apparently sporadic cases is necessary to provide accurate recurrence risk information. In our case, both parents were evaluated in an adult genetics clinic and were not found to exhibit any characteristics suggestive of Nager acrofacial dysostosis.

This case reinforces the spectrum of findings seen with Nager acrofacial dysostosis. Recognition of the unilateral nature of a portion of cases may improve the ability to accurately diagnose affected fetuses prenatally. Increased willingness of patients to undergo genetic testing prenatally or postnatally could certainly expand our understanding of this spectrum of diseases and ultimately improve our ability to counsel patients.

## REFERENCES

- Aylsworth AS, Lin AE, Friedman PA. 1991. Nager Acrofacial Dysostosis: Male-to-male transmission in 2 families. *Am J Med Genet* **41**: 83–88.
- Benson CB, Pober BR, Hirsh MP, Doubilet PM. 1988. Sonography of Nager acrofacial dysostosis syndrome in utero. *J Ultrasound Med* **7**: 163–167.
- Chemke J, Mogilner BM, Ben-Itzhak I, Zurkowski L, Ophir D. 1988. Autosomal recessive inheritance of Nager acrofacial dysostosis. *J Med Genet* **25**: 230–232.
- Danziger I, Brodsky L, Perry R, Nusbaum S, Bernat J, Robinson L. 1990. Nager's acrofacial dysostosis. Case report and review of the literature. *Int J Pediatr Otorhinolaryngol* **20**: 225–240.
- Halal F, Herrmann J, Pallister PD, Opitz JM, Desgranges MF, Grenier G. 1983. Differential Diagnosis of Nager Acrofacial Dysostosis Syndrome: Report of four patients with Nager syndrome and discussion of other related syndromes. *Am J Med Genet* **14**: 209–224.

- Hall BD. 1989. Nager acrofacial dysostosis; Autosomal dominant inheritance in mild to moderately affected mother and lethally affected phocomelic son. *Am J Med Genet* **33**: 394–397.
- Le Merrer M, Cikuli M, Ribier J, Briar ML. 1989. Acrofacial dysostoses. *Am J Med Genet* **33**: 318–322.
- Nager FR, de Reynier JP. 1948. Das Gehörorgan bei den angeborenen Kopfmissbildungen. *Pract Otorhinolaryngol* **10**: 1–128.
- Paladini D, Tartaglione A, Lamberti A, Lapadula C, Martinelli P. 2003. Prenatal ultrasound diagnosis of Nager syndrome. *Ultrasound Obstet Gynecol* **21**: 195–197.
- Sulik K, Smiley S, Turvey T, Speight H, Johnston M. 1989. Pathogenesis of cleft palate in Treacher Collins, Nager, and Miller syndromes. *Cleft Palate J* **26**: 209–216.