Nager syndrome associated with 45,X monosomy

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Nager syndrome is a rare malformation complex characterized by facial, limb, and skeletal morphogenesis. The mode of inheritance has not been definitely established. Major karyotypic abnormalities were seldom associated with this syndrome. We report on an infant with Nager acrofacial dysostosis that was associated with 45,X monosomy. This baby was born to a 36-year-old multigravid woman after 37 weeks of gestation and with maternal hydramnios. The baby girl died of airway obstruction due to retruded tongue 3 hours after birth. Phenotypically, this patient had mandibulofacial dysostosis, radioulnar synostosis, hypoplasia and aplasia of thumbs, peripheral edema and apparently normal genital organs. We confirmed that major chromosomal anomaly including 45,X monosomy could be associated with Nager syndrome, although its pathogenetic significance remains unanswered.

Keywords: Acrofacial dysostosis, Nager syndrome, 45,X monosomy

INTRODUCTION

The association of mandibulofacial dysostosis with limb malformations was first described by Nager and de Reynier in 1948 and subsequently at least 78 cases have been reported in the literature (McDonald and Gorski, 1993). This syndrome is accompanied by multiple abnormalities involving facial and extremity bones with minor manifestations of other organ anomalies (Halal *et al.*, 1983; Celeste *et al.*, 1985; Barbara *et al.*, 1977; Aylsworth *et al.*, 1991). In cases with upper airway hypoplasia, respiratory difficulty may occur (Celeste *et al.*, 1985). Careful perinatal monitoring is therefore needed.

A mode of inheritance for Nager syndrome has not yet been definitely established. Although most cases occur sporadically, both recessive and dominant inheritance have been suggested on the basis of reported familial cases (Chemke *et al.*, 1988; Aylsworth *et al.*, 1991). Only two cases of this syndrome with abnormal karyotype have been reported (Wagner *et al.*, 1979; Zori *et al.*, 1993).

We report on a newborn girl with preaxial acrofacial dysostosis (Nager syndrome) who was diagnosed as having 45,X monosomy.

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CASE REPORT

This baby was born after 37 weeks of gestation to a 36-year-old multigravid woman. The pregnancy was complicated with maternal hydramnios. The mother neither smoked nor drank alcohol. Cesarean section was performed and delivery was without complication.

After delivery, the baby had respiratory difficulty and appeared acutely ill. Birth weight was 2.25 kg, height 46 cm, and head circumference 33 cm. Physical examination revealed multiple abnormalities and peripheral edema. The face was dysmorphic, exhibiting micrognathia, maxillary and mandibular hypoplasia, a cleft palate, microophthalmia, choanal atresia, low set ears with preauricular pits (Fig. 1). Reduction deformities of both upper limbs were noted. The right hand had four digits, with absence of thumb. The left thumb was hypoplastic. There was both proximal radioulnar synostosis and elbow contracture (Fig. 2). The baby died 3 hours after birth.

Postmortem examination revealed the absence of the uvula, incomplete posterior cleft palate, and external auditory canal stenosis. The ossicles and other ear structures were normal. The tongue was retruded to obstruct the oropharynx. External genitalia were as in a phenotypically normal female; internal examination revealed nothing remarkable. The brain was unremarkable on both gross and microscopic evaluation.

The chromosome study was conducted utilizing standard Giemsa stain without banding from cultured fibroblasts of buccal mucosa. Only metaphase cells were scored in the analysis. The result was 45,X monosomy (Fig. 3).

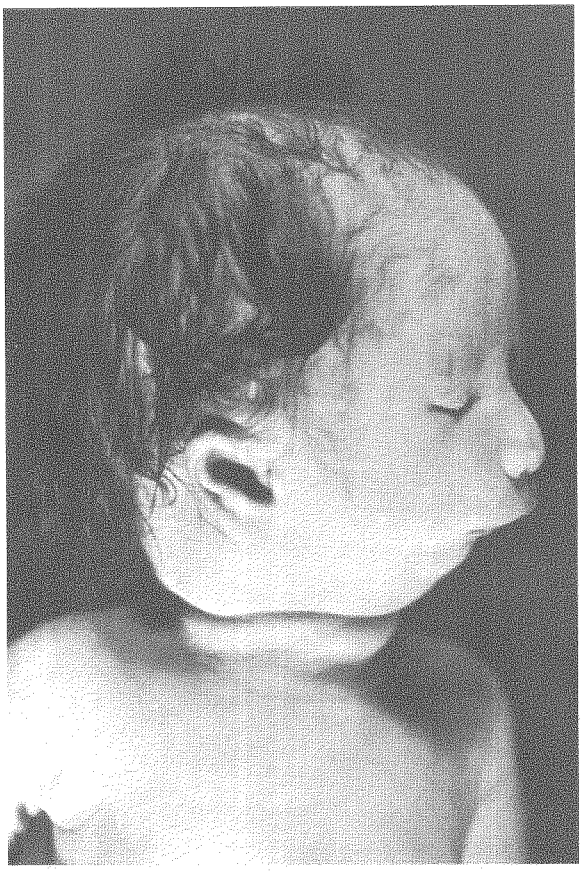

Fig 1. Face of patient with Nager syndrome. This patient shows a severe micrognathia, a relatively small eye and right ear that is low-set and has a preauricular pit.

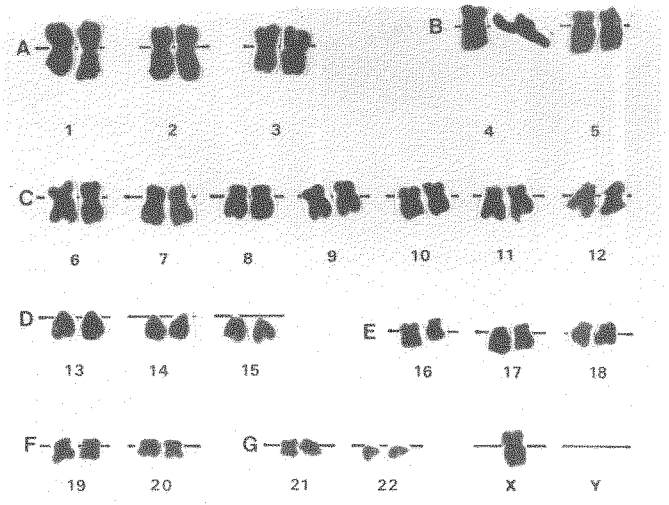

Fig 3. Standard Giemsa stain of chromosome demonstrating 45,X karyotype.

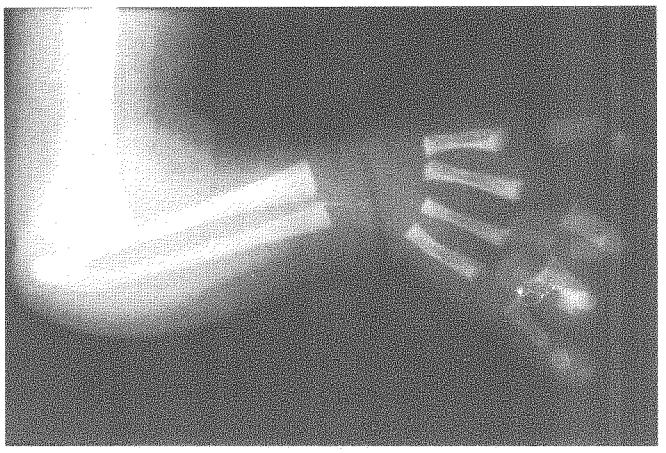

Fig 2. Radiograph of the right arm and hand showing an aplastic thumb and proximal radioulnar synostosis.

DISCUSSION

Nager acrofacial dysostosis is a disorder of mandibulofacial dysostosis and preaxial limb defects. The mode of inheritance is controversial. Several reports suggesting autosomal dominant or recessive have been presented (Chemke *et al.*, 1988; Aylsworth *et al.*, 1991). A review of 78 cases of Nager syndrome by McDonald and Gorski (1993) indicated genetic heterogeneity of this syndrome. Zori *et al.* (1993) suggested that Nager syndrome might be the result of critical breakpoints and/or position effects inducing expression of a gene responsible for the syndrome. Only two cases of this syndrome associated with karyotypic abnormality have been reported (Wagner and Cole, 1979; Zori *et al.*, 1993). One was diagnosed as having an apparently balanced X/autosome translocation (46,X,t(X;9)(p22.1;q32)mat) and the other as exhibiting partial duplication of the long arm of chromosome 2 attached to the long arm of chromosome 15 (46,XY, der(15), t(2;15)(q31;q26)mat).

Chromosomal studies of this infant revealed 45,X monosomy. It is recognized that the 45,X karyotype is one of the commonest observed aneuploidies in humans (Hook and Warburton, 1983), but association with Nager syndrome has not been reported. It is said that 45,X karyotype is associated with a wide variety of clinical phenotypes. These range from early first trimester pregnancy losses to liveborn females whose clinical manifestations are limited to gonadal dysgenesis and short stature. The phenotypic consequences fall into one of 3 patterns. The most common is an early first trimester spontaneous abortion with either no identified fetus or a small macerated embryo. At 15-20 weeks gestation, the diagnosis of 45,X is commonly recognized by the ultrasonographic

demonstration of cystic hygroma and hydrops fetalis. The pregnancy commonly comes to elective termination or stillbirth delivery. Lastly, liveborn infants with 45,X karyotype comprise less than 1% of these conceptions and encompass a phenotype with wide variability (Canki *et al.*, 1988). The mosaicism for 45,X has been postulated as the mechanism that accounts for this phenotypic diversity.

The predominant clinical features seen in our patient include mandibulofacial dysostosis, preaxial limb anomalies including radioulnar synostosis, hypoplasia and aplasia of the thumbs and peripheral edema. The genital organs showed no abnormal findings. The cause of death of this infant was attributed to retruded tongue, which might have obstructed the upper airway. It is known that the presence of peripheral edema due to lymphatic malformation occurs in 60% of patients with 45,X monosomy (Greenlee *et al.*, 1993). While the presence of this syndrome in this patient may be coincidental, the association of karyotypic abnormality should be further studied so that the cause of this syndrome can be examined.

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