Case Reports

Nager's acrofacial dysostosis with hypertrophic cardiomyopathy

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ABSTRACT

Nager syndrome is a rare condition associated with craniofacial malformations such as, micrognathia, zygomatic hypoplasia, external ear malformations, and preaxial limb deformities. This report features a case of Nager syndrome occurring in a one-year-old boy showing microretrognathia, thumb hypoplasia, brachydactyly, hexadactyly, and hypertrophic cardiomyopathy, characteristics not usually encountered in published cases.

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The Nager syndrome is characterized by aberrations in development of the first and second branchial arches and limb buds.[1] The acrofacial dysostoses (AFDs) are a heterogeneous group of disorders characterized by varying degrees of mandibulofacial dysostosis (MFD) with acral limb defects. The word "dysostosis" is used to refer to bone malformations, rather than a skeletal dysplasia. The predominantly preaxial form is called Nager AFD, and the predominantly postaxial form of AFD (postaxial acrofacial dysostosis syndrome [POADS]) is also known as the Genee-Wiedmann or Miller syndrome. Six other previously described forms of AFD include the AFD syndrome of Kelly et al,the Rodriguez or Madrid form of AFD, the Reynolds or Idaho form of AFD, the Arens or Tel Aviv type of AFD, the presumed AFD syndrome of Richieri-costa et al, and the Patterson-Stevenson-Fontaine syndrome.[2,3] A Nager syndrome is the most common form of AFDs. It was first recognized in a patient reported by Nager and de Reynier in 1948, who used the term AFD to distinguish the condition from MFD. Gorlin et al[2] employed the term preaxial (radial side) AFD to separate the disorder from postaxial (ulnar side) AFD or Miller syndrome. Nager syndrome patients have downslanting palpebral fissures, ptosis of upper lids, malar hypoplasia, micrognathia, external ear defects, high nasal bridge, external auditory canal stenosis, bilateral conductive hearing loss, cleft palate, hypoplastic or absent thumbs and radii, proximal radioulnar synostosis, and variable lower limb and toe defects.[3] Major congenital heart malformations occur rarely in this syndrome.[4] To date, no more than 80 cases of Nager syndrome have been reported in the literature.[5] A Nager syndrome is genetically heterogeneous. Most cases are sporadic, although both autosomal recessive and dominant cases have been reported;[3] thus, the mode of inheritance remains unclear. The purpose of this report is to present a case of Nager syndrome exhibiting hypoplastic thumbs, brachydactyly (preaxial anomalies) with ulnar side polydactyly (postaxial anomaly), and major cardiac defects, features that do not usually appear.

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Case Report. A 1-year-old boy patient was referred to the Department of Pediatrics due to difficulty in nursing, respiratory difficulties, and inadequate weight gain. He was born to a 35-year-old $G_3L_3Ab_0$ mother and a 39-year-old father. Family history was unremarkable, and specifically negative for individuals with facial, limb, renal, or cardiac anomalies. The pregnancy was complicated by third-trimester gastroesophageal reflux, treated with metoclopramide and ranitidine. The mother denied using of tobacco, alcohol, and all licit or illicit drugs, including exogenous hormones. There was no known exposure to teratogenic chemicals or radiation. Following a spontaneous vertex vaginal delivery, the baby had Apgar scores of 8 at one minute, and 9 at 5 minutes, and was noted to have facial and limb anomalies. At birth, the weight was 3290 gr (25th-50th centile), the length 49 cm (50th centile), and the head circumference 35 cm (50th centile). During his most recent assessment at the age of one year, his weight 6300 gr (<3rd centile), length 71 cm (<3rd centile) and occipitofrontal circumference was 45 cm (10th centile). Observed facial anomalies (**Figure 1**), included downward slanting palpebral fissures, ptosis of upper lids, extension of a tongue of temporal hair down the sides of the cheeks, deficiency of eyelashes of the lower eyelids, peculiar beaked nose, large low set, and posteriorly rotated ears with narrowed external canals. He also had microretrognathia, bilateral symmetric mandibular, and malar hypoplasia (**Figure 1**), and long upper lip with relatively flat philtrum. The hard and soft palates were intact. The forearms were normal, but there was a slight extension deficit at the elbows, and supination was limited. Both short thumbs were proximally implanted and hypertrophied (**Figure 2**). In addition, there was discrete brachydactyly of 2nd and 3rd fingers (preaxial anomalies). He also exhibited bilateral ulnar side (postaxial) hexadactyly. This rudimentary accessory sixth finger (8 mm), was attached to the first phalanx of the fifth finger and had been removed shortly after birth, but the residue of this appendage can be seen in Figure 2. A bilateral simian crease was found on his palms. The limb radiographs showed marked hypoplasia of the first metacarpals. The forearm bones were normal. Bone age corresponded to chronological age. Anomalies of the lower limbs were not encountered. The chest x-ray showed cardiomegaly (CT ratio = 65%). Two-dimensional and Doppler echocardiography revealed a hypertrophic cardiomyopathy with asymmetric septal hypertrophy (ASH) and systolic anterior movement (SAM), dilated pulmonary artery branches and true tricuspid regurgitation.

Figure 1 - Full face, showing downslanting palpebral fissures, low set ears, and mandibulo malar hypoplasia.

Figure 2 - Left hand - note the short and hypertrophied thumb. The rudimentary accessory sixth finger is attached to the first phalanx of the fifth finger.

Abdominal ultrasonographic examination did not reveal any malformation. Kidneys and urinary system were otherwise normal. Results of brainstem auditory evoked responses (BAERs), and otoacoustic emissions (OAEs) were normal, and no hearing disturbances were recorded. Lymphocyte "high-resolution" karyotype was normal 46, XY. Thyroid function studies, testosterone, leuteinizing hormone, follicle stimulating hormone, serum cortisol, blood urea nitrogen, and serum creatinine levels were normal. His early motor milestones were age-appropriate, but speech development was delayed. Neurological examination was otherwise normal. Our patient was born to phenotypically

Table 1 - Clinical and radiographic features commonly encountered in preaxial acrofacial dysostosis.

Common features	Present case
Maxillofacial area	
Zygomatic hypoplasia	+
Downslanting palpebral fissure	+
Lower eyelid colobomas	
Mandibular hypoplasia	+
Ear involvement	
External ear malformation	+
Conductive hearing defect	
Limbs	
Thumb hypoplasia or aplasia	+
Radial defects	
Others	
Cardiac anomalies	+
Reduced stature	+
Genitourinary abnormalities	

normal, nonconsanguineous parents. The parents are of the same ethnic and religious background. The elder siblings are phenotypically normal. A review of the family history was otherwise unremarkable. There was evidence neither of respiratory disease nor of hormonal disturbance. Based on craniofacial characteristics, and the coexistence of predominantly preaxial anomalies of upper limbs, the diagnosis of the Nager syndrome was confirmed (**Table 1**).

Discussion. The Nager syndrome is a rare disorder, resulting from developmental abnormalities of the first and second branchial arches.[1] The pattern of craniofacial features observed in preaxial acrofacial dysostosis is similar to that seen in Treacher Collins syndrome.[2,3] Mandibular hypoplasia tends to be more severe in Nager syndrome, than in Treacher Collins syndrome,[2] with mandibular malformations and missing joint structures contributing to extreme restriction in jaw movement.[1] Microstomia has been reported, and a cleft palate is common. Despite macrostomia, such infants may be very difficult or impossible to intubate and may also have hypoplasia of larynx and epiglottis. Hypoplasia of the malar eminences is accompanied by underdevelopment of the zygomata (sometimes with bony deficiency), hypoplasia of maxilla with cleft of soft (or soft and hard) palate or highly arched palate, absence of velum, rarely with choanal atresia, and extension of a "tongue" of temporal hair down the sides of the cheeks.[3] Clefts of the lip are rare. Ear involvement consists of varying degrees of external and middle ear malformation.[6] The more severe the involvement of the auricles, the more common is atresia or stenosis of the external auditory meatus, and ear canal with more or less severe conducting deafness.[3] The nose is generally normal, however, with obliteration of the nasofrontal angle and later "beaking" and anteversion of nostrils. The eyes themselves are apparently normal, however, due to difficulty of closure of lids in some severely affected individuals, the corneas are at risk of injury from desiccation and infection. The palpebral fissures are slanted downward; there is ptosis of upper lids with a coloboma defect more commonly of the lower than of the upper lids, deficiency of eyelashes of the medial one-third or two-thirds of the lower eyelids, at times with a defect of the lower orbital rim.[1-3,6] The craniofacial anomalies seem to represent primarily or predominantly a defect of cranial neural crest function or development.[3]

Characteristics of other true AFDs include;[3] POADS (Genee-Wiedmann, Miller): MFD, vertebral defects, abnormal sternum, cleft palate; genital defects, urinary tract anomalies; Small, not well differentiated, typically protruding ("cupped") ears; Upslanting palpebral fissures; Limb anomalies typically consist of bilateral absence of the fifth ray of hands and feet. As an exception, also the fourth and even the third ray can be affected. Syndactyly may be present. The AFD syndrome of Kelly: intrauterine growth retardation, shortness of stature, mental retardation, hypospadias, cryptorchidism, mild MFD, hearing loss, preaxial limb defects (symphalangism) with facultative radioulnar synostosis. The AFD syndrome of Reynolds or Idaho: mild AFD with mild MFD and hearing loss, and predominantly preaxial limb involvement ranging from thumb duplication to mild hypoplasia of the first metacarpal and first proximal phalanx, normal growth and intelligence quotient. The AFD syndrome of Arens or Tel Aviv: Unusual cri-du-chat like appearance, MFD, postaxial oligodactyly, patent ductus arteriosus talipes, feeding difficulties, death at 2 months. The AFD syndrome of Rodriguez or Madrid: Neonatally lethal syndrome of severe MFD withrespiratory distress syndrome, preaxial limb deficiencies-phocomelia like shoulder/pelvic girdle hypoplasia; cardiac defects and central nervous system malformations. The AFD syndrome of Richieri-costa: MFD with microtia, cleft lip and palate, hypoplastic triphalangeal thumbs. The AFD syndrome of Patterson-Stevenson-Fontaine: mild MFD, cleft of soft palate, abnormal auricles, normal hands, but oligosyndactyly of toes with mental retardation in the French family.

Limb defects, particularly preaxial anomalies, are of diagnostic significance in Nager syndrome, and serve to differentiate this condition from MFD.[1] The most characteristic limb defect is hypoplasia or absence of thumbs, almost invariably associated with radioulnar synostosis.[2,3] However, equally

characteristic preaxial limb defects are hypoplasia of thumbs, triphalangeal thumbs, preaxial polydactyly, such as, almost extensive thumb duplication or syndactyly of thumb, and index finger. In such cases of predominant preaxial involvement, the fifth digit is rarely mentioned as short or clinodactylous, or both, but as described in our case report, this type of coexisting postaxial hexadactyly has not been reported before.[2,3] The radial defect is only believed to occur with concurrent agenesis of thumb. Limitation of elbow extension has also been reported.[2] Defects of the lower extremity also have been described.[6] Well defined reports of congenital heart defects in typical cases of Nager syndrome are scarce. These reported anomalies in typical and atypical cases include; subvalvular muscular obstruction of the right outflow tract,[7] small VSD,[8] tetralogy of Fallot with patent ductus arteriosus,[4] tetralogy of Fallot,[9] and single VSD.[5] Functional impairments encountered in Nager syndrome primarily consist of respiration and feeding difficulties, attributed to mandibular retrusion and severely restricted jaw opening.[1] Various genetic loci have been investigated in attempts to determine the site of genetic alteration responsible. Zori et al[10] suggested that the gene mutation responsible for this disorder might reside on chromosome 9q. Wagner et al has also reported a Nager syndrome with partial duplication of distal 2q. In the sporadic case presented, craniofacial findings included microretrognathia, orbitomalar hypoplasia, downslanting palpebral fissures, external auditory canal stenosis as well as upper limb malformations consisting of hypoplastic first metacarpals, short thumbs, and decreased mobility of the elbow articulation, fulfilling the diagnostic criteria for Nager syndrome (**Table 1**). An interesting feature here is the unusual coexistence of thumb hypoplasia, brachydactyly of 2nd and 3rd fingers, and ulnar side hexadactyly (coexisting predominantly preaxial, and postaxial anomalies). Another finding of note, was the presence of the hypertrophic cardiomyopathy, a condition not encountered in the published cases.[4]

With the available data on clinical variability and heterogeneity in familial occurrence, it is probable that from a nosological point of view, the Nager type of AFD is not a unique syndrome. However, up to now, objective criteria are lacking to start a further subdivision of this syndrome complex.

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