

Acrofacial dysostosis 1, Nager type

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Abstract

Typically Nager acrofacial dysostosis (NAFD) comprises two groups of defects involving respectively the limbs and craniofacial region. The former are mainly deficiencies mostly affecting upper limbs. The latter form a complex indistinguishable from mandibulofacial dysostosis (MFD). The prevalence is unknown; about 70 cases of Nager syndrome have been published. The MFD complex is unmistakable and comprises downward slant of palpebral fissures, ptosis of upper lids, coloboma of lower lids, deficiency of eyelashes of the medial one-third to two-thirds of the lower eyelids, hypoplasia of the malar eminences and zygomata, hypoplasia of maxilla with cleft of secondary palate or highly-arched palate, absence of velum (rarely with chonal atresia), extension of a "tongue" of temporal hair down the sides of the cheeks; clefts of lip are rare. Hypoplasia or absence of thumbs is the most characteristic feature almost invariably associated with radio-ulnar synostosis. Triphalangeal thumbs and index finger are equally characteristic. Most NAFD individuals have normal eyes and intelligence, and after infancy most are healthy and are presumed to have a normal lifespan. All acrofacial dysostosis must be considered as genetic disorders until proven otherwise, and parents deserve careful scrutiny for mild manifestations.

Keywords

Defect of cranial neural crest, defect in upper limbs, hypoplasia/ absence of thumb

Disease name and synonyms

Acrofacial dysostosis (AFD)

Preaxial acrofacial dysostosis

Acrofacial dysostosis, type Nager

Nager AFD, (NAFD)

Catania form of AFD;

Palagonia form of AFD;

AFD syndrome of Kelly, Cooke and Kesler;

AFD syndrome of Reynolds;

AFD type Aarens or Tel Aviv;

the Rodríguez or Madrid form of AFD;

the AFD syndrome of Richieri-Costa *et al.*;

and the Patterson-Stevenson-Fontaine syndrome.

POADS (Postaxial Acrofacial Dysostosis Génée-Wiedemann or Miller syndrome) is also

Excluded Conditions

NAFD belongs to a rather heterogeneous group of genetic disorders comprising defects of cranial neural crest and limb development.

These include the:

excluded, although some affected infants may have pre- and postaxial involvement.

This review focuses on the condition with predominant pre-axial involvement, the Nager syndrome.

Definition

Typically NAFD comprises two groups of defects involving respectively the limbs and craniofacial region. The former are mainly deficiencies mostly affecting upper limbs. The latter form a complex indistinguishable from mandibulofacial dysostosis (MFD). MFD *per se*, also called Treacher-Collins syndrome, is an autosomal dominant condition due to mutations in the *TCOF1* gene at 5q21-q33. To the best of my knowledge, none of the acrofacial dysostosis genes has been mapped.

Prevalence

Pure MFD is not an uncommon condition; however, all AFDs are rare. Their prevalence is unknown; about 70 cases of Nager syndrome and some 40 of POADS have been published.

Clinical description

Craniofacial manifestations

The MFD complex is unmistakable and comprises downward slant of palpebral fissures, ptosis of upper lids, coloboma of lower lids, deficiency of eyelashes of the medial one-third to two-thirds of the lower eyelids, hypoplasia of the malar eminences and zygomata, hypoplasia of maxilla with cleft of secondary palate or highly-arched palate, absence of velum (rarely with chonal atresia), extension of a "tongue" of temporal hair down the sides of the cheeks; clefts of lip are rare. Lateral orofacial clefts are sometimes more common (especially in severely affected individuals) with exposure of upper and lower alveolar ridges and teeth. The combination of micrognathia and microretroglossia with or without cleft of palate is frequently referred to as Pierre Robin "syndrome" (rather sequence) and may cause severe and sometimes lethal respiratory distress. In spite of microstomia such infants may be very difficult to intubate and may also have hypoplasia of larynx and epiglottis. In 6 of 7 patients of Meyerson and Nisbet (1987) tracheostomy was performed; all of them also had ankylosis of the temporomandibular joints. Five of their 7 cases required gastrostomy to maintain adequate nutrition. Ears may be normally formed but posteriorly angulated, or small and malformed, rarely absent. Hypoplasia of parts of or of the whole the auricle is fairly symmetrical in a series of graded severity to which the microtia grading system may be applied. 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 conductive deafness. At times the tympanic membrane may be absent and middle ear ossicles may be deficient or absent. Nose is generally normal, however, with obliteration of nasofrontal angle and later "beaking" and anteversion of nostrils.

Limb anomalies

Hypoplasia or absence of thumbs is the most characteristic feature almost invariably associated with radio-ulnar synostosis. Triphalangeal thumbs and index finger are equally characteristic. Fifth fingers may be short and clinodactylous. Absence of thumbs may be associated with distal hypoplasia or absence of radii with shortness and bowing of ulnae resulting in a radial club hand with or without antecubital webbing. Phocomelia is rare; in such cases the hands appear to be directly attached to the shoulders. The lower limbs may also be involved rarely in a phocomelia-like manner with apparent absence of femora, tibiae and fibulae and hypoplasia of ilia, ischia and pubic rami. Short and/or broad halluces are common, while syndactyly of toes 2 and 3, crowding of toes or oligodactyly with only 3 or 4 toes are less commonly present

Associated anomalies

Universal short stature, occasional genital defects (small penis and/or cryptorchidism, bicornuate uterus), rare renal anomalies (e.g. unilateral agenesis), occasional cervical vertebral and rib anomalies, rare congenital heart defects are observed. Most NAFD individuals have normal eyes and intelligence, and after infancy most are healthy and are presumed to have a normal lifespan. NAFD is not a cancer syndrome.

Management

Neonatal respiratory distress requires immediate attention and frequently tracheostomy. Feeding difficulties are handled most easily with gastrostomy. Repair of cleft palate can be performed. Hearing aids for conductive deafness can be proposed to the patient. Cosmetic surgery, especially for eyelids, can be performed to ensure complete closure of eyelids at night in order to prevent injury of the cornea.

Cause

All AFDs must be considered as genetic disorders until proven otherwise, and parents deserve careful scrutiny for mild manifestations. NAFD appears to be an heterogeneous entity, most cases being sporadic cases, chance isolated cases or due to *de novo* dominant mutations. In cases of sib recurrence with apparently normal parents autosomal recessive inheritance may be postulated (especially if

parents are consanguineous); however, until the molecular basis of the AFDs is elucidated, parental germinal mosaicism with a dominant mutation cannot be excluded. Vertical transmission compatible with autosomal dominant inheritance has been documented in a half dozen cases.

Diagnostic methods

Prenatal diagnosis can be carried out by ultrasonography, while postnatal diagnosis can be established, relying upon clinical and radiological features and with chromosome analysis in syndromal cases.

Genetic counseling

Careful evaluation of parents and sibs is required; if one parent is mildly affected, recurrence risk is 50%; if parents are apparently normal a 25% recurrence risk cannot be excluded

Unresolved questions

Given that in some cases, unilateral pre-axial involvement with contralateral post-axial defect may be present, Nager and Genée-Wiedemann (Miller) syndromes may be variants of the same genetic entity.

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