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Nager Syndrome: Report of Clinical and Radiological Findings in an Egyptian Infant

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Abstract

Nager syndrome is an extremely rare genetic condition, that this case is the first reported from Egypt. The affected infant manifested a severe phenotype with growth retardation and congenital heart defect. Limb anomalies are a cardinal sign and, in combination with the characteristic craniofacial features, are diagnostic.

Keywords: Nager syndrome; Acrofacial dysostosis; Branchial arch; Malar and mandibular hypoplasia; Ankylosis of temporo-mandibular joint; Hypoplastic thumb; Absent radius

Introduction

A two-month-old male infant presented with multiple congenital anomalies, feeding problems and failure to thrive. He was the first-born baby to non-consanguineous Egyptian parents. The pregnancy and delivery histories were uneventful. The patient was born at full term via spontaneous labour and his birth weight was 3 kg.

On clinical examination, the patient displayed a characteristic craniofacial phenotype including severe malar and mandibular hypoplasia with retrognathia, down-slanting palpebral fissures with almost absent eyelashes of the lower eyelids, flat supraorbital ridges, extension of temporal hair onto the cheeks, cleft palate, ankylosis of temporo-mandibular joint, a prominent nasal bridge, long philtrum and low-set abnormal ears [A & B]. The patient also showed bilateral upper limb anomalies in the form of hypoplastic thumbs and short forearms with limited elbow extension. On the left hand, an interdigital webbing between the abnormally-inserted thumb and index finger was also noted [C]. Apart from the overlapping toes and widely-spaced big toes, the lower limbs were unremarkable [D]. The growth parameters were all below the 3rd centile (HC: 35.5 cm, Ht: 52 cm, Wt: 3 kg).

Karyotyping, CT brain and US abdomen were free. Hearing assessment revealed bilateral conductive deafness while echocardiography detected atrial and ventricular septal defects. CT scan of mid-face with 3D reconstruction revealed widening sutures of skull notably the metopic suture, which was seen widening till the root of nasal bone with shallow frontal bones and orbits [E]. Plain radiographs of extremities showed absent radii, hypoplastic clavicles and normal lower limbs [F&G].

In the case presented here, the pattern of anomalies strongly suggested the diagnosis of Nager syndrome (OMIM #154400), also called preaxial acrofacial dysostosis (AFD). It is due to aberrations in development of the first and second branchial arches and limb buds, and, thus, it comprises congenital defects involving the limbs and craniofacial region. The limb anomalies are mainly deficiencies mostly affecting the upper limbs, which typically involve the radial ray. The craniofacial manifestations comprise down-slanting palpebral fissures, absent lower eyelashes, malar hypoplasia, microretrognathia, cleft palate, and external ear malformations often associated with conductive deafness. Less frequently, other malformations have also been reported such as costovertebral, renal or cardiac malformations. Most of the affected cases have normal intelligence and have a normal lifespan.

The prevalence of Nager syndrome is unknown, however it's a very rare syndrome; about 110 cases have been published to date. Most cases appear to be sporadic, although autosomal dominant inheritance has been reported. The occurrence of affected siblings with normal parents suggests an additional autosomal recessive form and adds further genetic heterogeneity. Recently, exome sequencing identified mutations in the SF3B4 gene (Splicing Factor 3B, subunit 4) as a major disease causing gene responsible for autosomal dominant Nager syndrome.

In conclusion, Nager syndrome is an extremely rare genetic condition, that this case is the first reported from Egypt. The affected infant manifested a severe phenotype with growth retardation and congenital heart defect. Limb anomalies are a cardinal sign and, in combination with the characteristic craniofacial features, are diagnostic.

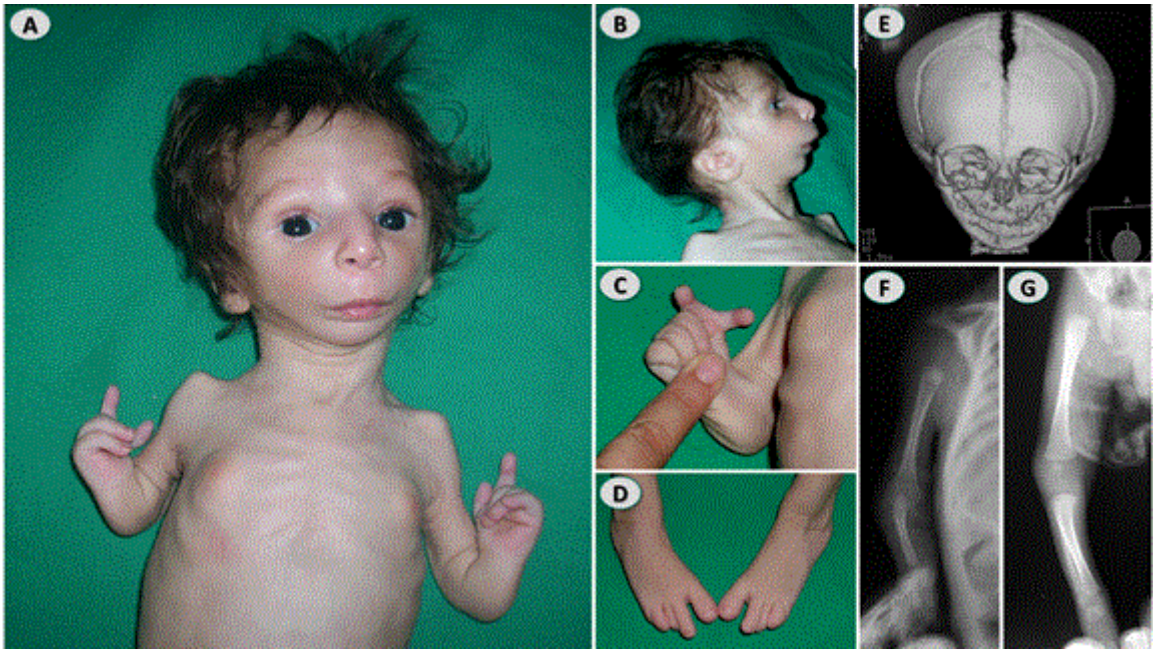

Figure (A-G): Nager Syndrome: Report of clinical and radiological findings in an Egyptian infant.