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Case Report

Possible autosomal recessive inheritance in a neonate with Nager syndrome: Case report

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ABSTRACT

Introduction and importance: Nager syndrome is a rare inherited disorder characterized by craniofacial malformations occurring in association with abnormalities of the thumb and radial parts of the forearm.
Case presentation: We presented a 18-day-old boy with Nager syndrome. The diagnosis based on his clinical presentation. He was born to non-consanguineous healthy parents. He had three deceased siblings who had similar clinical features. This family gave further evidence for autosomal recessive inheritance. Nager syndrome can be detected using prenatal screening ultrasound.
Clinical discussion: The etiology of Nager Syndrome is poorly described. Most cases arise spontaneously, although autosomal recessive and autosomal dominant modes of inheritance have been reported. Nager syndrome is suspected to have an autosomal recessive inheritance pattern, when unaffected parents have more than one affected child.
Conclusion: Treatment required the coordinated efforts of a team of specialists. Many manifestations of the disease can be improved by surgery and other supportive treatments.

1. Introduction

Facial dysostoses can be classified into two types: mandibulofacial dysostoses (MFDs) and acrofacial dysostoses (AFDs). MFDs typically have no limb abnormalities, while AFDs are accompanied with limb defects [1]. At least eight forms of MFDs have been described, with the most common type being Treacher Collins syndrome. At least 18 types of AFDs have been characterized based on the specific patterns of limb malformations. They have been classified into those with preaxial limb defects, those with postaxial abnormalities, and a subset with limb anomalies that cannot be classified into either group [2]. The best defined and most frequent pre-axial AFD is Nager syndrome, while Miller syndrome is the best known and best understood postaxial AFD [3].

We describe the case of a 18-day-old boy with Nager syndrome who had three affected siblings. We are reporting this case because of its rarity. This study aims to contribute toward a greater understanding of Nager syndrome. We are reporting this case to present a further evidence for autosomal recessive inheritance pattern.

All our cases has been reported in line with THE CARE 2017 guidelines [4] and THE SCARE 2020 criteria [5].

2. Case report

A 18-day-old boy was referred to our hospital for clinical evaluation because of his characteristic appearance. The present patient was the fifth child of a non-consanguineous couple a 25- year-old healthy mother and a 40- year-old healthy father. He was born via vaginal delivery at 36 weeks of pregnancy. The pregnancy of the mother was uncomplicated. The mother's history regarding alcohol, smoking, and drug abuse was negative. He had one deceased sister and two deceased brothers who had similar clinical features. He had one normal brother. The child was referred to pediatricians periodically from birth because of his problems. He had feeding difficulties and a history of recurrent aspiration. On examination, craniofacial anomalies present included downward slanting palpebral fissures, bilateral lower eyelid colobomas with absence of cilia of lower eyelids, malar hypoplasia, a broad and high nasal bridge, micrognathia, retrognathia, malformations of auricular pinna, atresia of the auditory meatus of the right ear (Fig. 1). Intraoral examination revealed high-arched cleft palate without cleft lip (Fig. 2). There were

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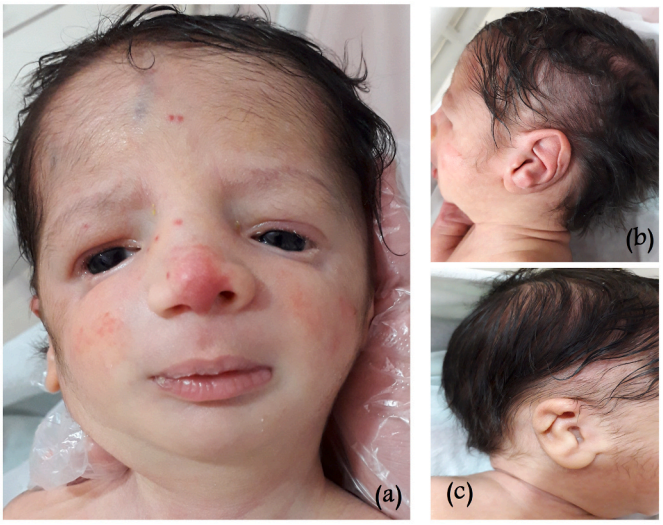

Fig. 1. **(a)** Craniofacial anomalies of the 18-day-old boy with Nager syndrome, **(b + c)** Malformations of the auricular pinna.

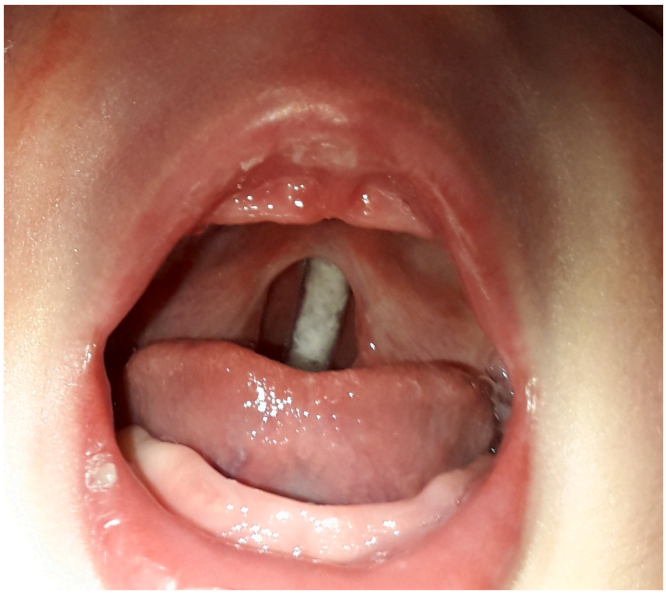

Fig. 2. Intraoral view showed cleft palate.

also anomalies of the upper limbs development. The arms were short and elbow articulation had motion limitations in extension and flexion. On the right hand, he had triphalangeal thumb and an absent thumb on the left hand. In addition, he had overlapping fingers on both hands. Lower limbs anomalies included bilateral dislocation hips and bilateral club feet (Fig. 3). Scrotal examination revealed absence of testicle on the left side. The diagnosis of left side undescended testis was confirmed with ultrasonogram. Brain ultrasound, abdominal ultrasound and echocardiography were normal. Hip ultrasound revealed bilateral dislocated hip. Radiographs of upper limbs showed bilateral radial hypoplasia with the left radius more severely affected than the right. Based on the patient's craniofacial characteristics and the coexisting upper limb preaxial anomalies, a diagnosis of Nager syndrome was confirmed. The treatment required the coordinated efforts of a team of medical professionals, consisted of pediatricians, oral surgeons, plastic surgeons, pediatric otolaryngologists, ophthalmologists, otologists, audiologists, psychologists, and other healthcare professionals may need to systematically and comprehensively plan an affect child's treatment.

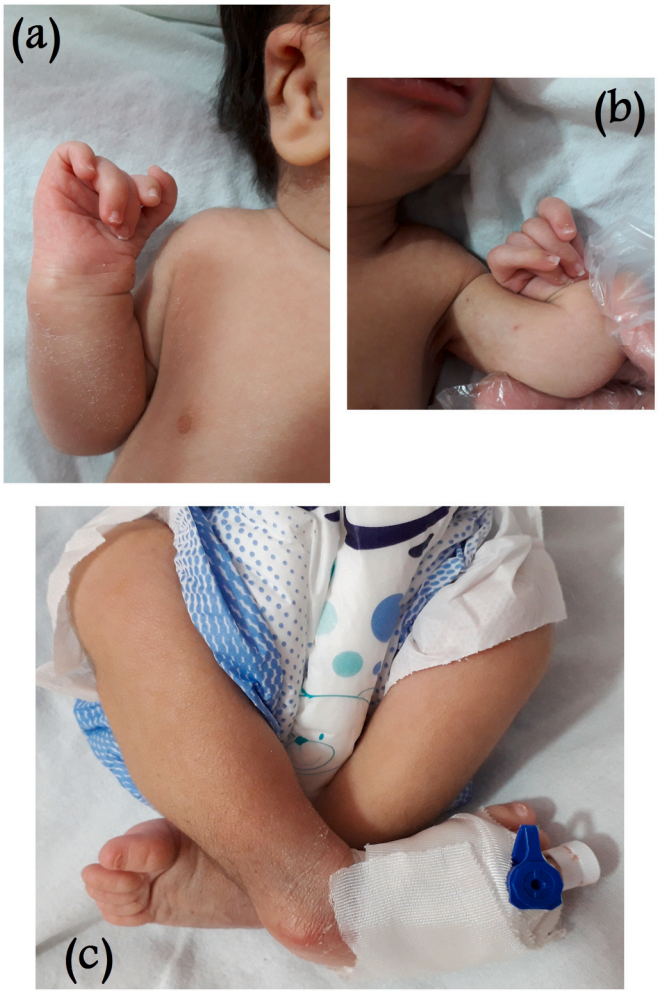

Fig. 3. **(a+b)** The upper limbs anomalies, **(c)** The Lower limbs malformations.

Therefore, the patient was referred to these specialists for further treatment. We recommended genetic counseling for the patient and his family. Psychosocial support for the entire family is essential as well.

3. Discussion

Nager syndrome is an AFD that includes anomalies of faces and limbs. Limb defects affect usually the radial parts of the forelimbs. Nager syndrome encompasses multi-organ malformations and perinatal mortality approaches 20% [1]. Nager syndrome is extremely rare, with fewer than 100 reported cases by 2012 [6]. This condition was first full described as a specific entity by Nager and de Reynier in 1948 [7]. Facial manifestations include downward slanting palpebral fissures, malar hypoplasia, high nasal bridge, micrognathia, and external ear defects. Reduced number of eyelashes, and lower lid colobomas occur less frequently. Hearing loss is a cardinal feature; it is typically bilateral and conductive. The important oral findings include cleft palate and absent soft palate. Limb anomalies are an essential sign. Typical limb abnormalities include pre-axial anomalies like hypoplastic or absent thumbs and radii. Thumb malformations are usually asymmetrical. Duplicated and triphalangeal thumbs have been reported. A variety of lower limb anomalies may occur [8]. Nager syndrome is primarily accompanied with *de novo* mutations, although both autosomal dominant and autosomal recessive mutations have also been reported [9]. Nager syndrome is suspected to have an autosomal recessive inheritance pattern when unaffected parents have more than one affected child. Chemke et al. reported a family in which two siblings are affected by this syndrome,

The sibs were born to healthy, unrelated parents. There was one additional normal daughter. They presented an evidence for autosomal recessive inheritance [10]. Only few autosomal recessive inheritance pattern cases have been published. In this report, we describe the occurrence of Nager syndrome in four siblings of non-consanguineous healthy parents. Nager syndrome can be detected using prenatal screening ultrasound, it has been detected sonographically as early as 16 weeks of gestation. Common detectable abnormalities by ultrasound were severe micrognathia, mandibular hypoplasia, cleft palate, malformed low set ears, hypoplasia of the thumbs, short radial ray and short forearms [11]. In our case, the patient wasn't detected before birth. Other malformations included genitourinary anomalies, gastrointestinal malformations. cardiovascular abnormalities, and central nervous system malformations have been occurred less frequently [8]. Patients with Nager syndrome require a high quality care and treatment, which include both the emergency procedures and scheduled surgeries to correct the developmental malformations. Breathing difficulties may require tracheostomy. multidisciplinary approach is essential for the handling of the diverse problems of these patients [12]. Our patient is on a frequent follow up schedule in our hospital clinics. A well-planned management can reduce disease symptoms and produce good results for complete restoration of the form and function of the patient.

4. Conclusion

Early recognition of Nager syndrome is important, so that the treatment of involved organ anomalies can be initiated and screening for associated malformations performed. Treatment should be tailored to the specific needs of each individual.

Ethical approval

Institutional review board approval is not required for deidentified single case reports or histories based on institutional policies.

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Author contributions

All authors contributed to the development of the manuscript and the care of the patient presented. All authors approved the final manuscript.

Consent

Written informed consent was obtained from the patient's mother for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Guarantor

Dr Rahaf Ibrahim.

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The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102896.

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