Propranolol-induced gingival hyperplasia with Nager syndrome: A rare adverse drug reaction

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ABSTRACT

Drug reactions are a group of reactionary lesions generally show their manifestations in the oral cavity. The drug reactions may vary from local rashes to well-developed swellings in the oral cavity especially involving the gingiva. Most of the drug reactions are asymptomatic and commonly triggered from the active metabolite of a drug used for a long time. Nager syndrome is a group of acrofacial dysostosis that usually results in craniofacial and limb malformations. The craniofacial defects are very similar to the mandibulofacial dysostosis. A very early intervention is needed for the habilitation of the patient especially when it is concerned with speech and language development. This paper reports a case of a 32-year-old female with craniofacial, limb, and skeletal abnormalities along with a drug-induced gingival hyperplasia.

Key words: Acrofacial dysostosis, gingival hyperplasia, Nager syndrome

INTRODUCTION

There are many syndromes that affect human skeleton and thus, compromising the body function, growth, and development. Nager acrofacial dysostosis (NAD), also known as Nager syndrome, involves facial structures, limbs and also affecting the skeletal morphogenesis. First reported by Slingenberg in 1908, later thoroughly researched by Nager and de Reynier in 1948, NAD shows genetic variability with variation in the penetrance and expressivity. The affected individuals have normal siblings and parents, thus giving an impression of genetic heterogeneity.[1]

Several drug reactions are observed over the different parts of human body in the form of a minor rash to massive hypersensitivity reactions. These drug reactions more actively make their presence over the skin and mucosa by the active drug metabolite present in the drug. The oral cavity shows the side effects of different drugs especially over the buccal mucosa, tongue, floor of the mouth, soft palate, and the gingiva. The knowledge of pharmacology and adverse effect related to the drugs enables the oral physicians to identify the adverse condition.[2]

Oral diagnosis is a science in medicine that provides a logical correlation between the clinical signs and symptoms based on the history and clinical findings, thus helping us to arrive at a particular clinical diagnosis. In this paper, we intend to present a case of Nager syndrome with the oral manifestation of gingival hyperplasia induced by the drug propranolol.

CASE REPORT

A 32-year-old female patient reported to the Department of Oral Diagnosis and Medicine at Al Farabi University...
Hospital with a chief complaint of a growth in her upper and lower gums. The patient revealed that the swelling associated with the gums has been present for 2 years, and has gradually increased to the present size. The patient was known to be hypertensive for the past 6 years and at a younger age was diagnosed with congenital cardiac disease. The patient had refused any surgical treatment and since then she has been on inderal 40 mg tablet (propranolol hydrochloride).

On extraoral examination, the patient presented with short status [Figure 1] and several abnormalities related to the craniofacial and skeletal region. The patient also had problems regarding speech and hearing. She never used any hearing aid but used to respond well with a high-intensity sound unlike normal sound. The patient presented with craniofacial manifestations including downward slanting palpebral fissures, high nasal bridge, and partial deficient lower eyelashes, especially in the medial one-third of both lower eyelids. Hypoplasia of the malar eminence with decreased growth associated with the mandible was noted but was not apparent [Figure 2].

Lower third of the face showed pigmentation [Figure 3]. Hypoplasia with respect to the hands and feet with shortened arms especially the toes was seen [Figures 4 and 5]. Patient’s intellectual capacity was normal, but she had difficulty regarding speech and hearing.

Intraoral examination showed malocclusion, crowding with respect to the lower anterior teeth. Underdeveloped soft palate (malformed velum) with alteration in the morphology of hard and soft palate was also a prominent feature [Figure 6]. Oropharyngeal (velopharyngeal) insufficiency with limited movement of the soft palate was also noted. Moreover, marked gingival hyperplasia of anterior gingiva was observed. The gingiva was pale in color, so to firm in consistency, and with a limited bleeding tendency on probing [Figure 7].

Radiological findings: Anterioposterior view of the skull showed less prominent malar processes, and lateral skull view revealed an increase in the mandibular plane with an increase in gonial angle and short ramus height [Figures 8 and 9].
Based on clinical and radiological findings, a provisional diagnosis of Nager syndrome with drug-induced gingival hyperplasia was given. Differential diagnosis included Treacher Collins syndrome, Millers syndrome, Mohr syndrome, and hemifacial microsomia.

**DISCUSSION**

There are vast groups of Otofacial Mandibular dysostosis such as Treacher Collins syndrome, Pierre Robin syndrome, and Hemifacial microstomia. Nager syndrome also belongs to the otofacial mandibular dysostosis, which is mainly associated with craniofacial abnormalities, hypoplasia of the mandible, earlobe agenesis or hypoplasia, abnormalities with the limbs and other skeletal defects.[3]

A wide range of genetic heterogenicity was noted in this syndrome. Elaborate research done by Halal et al., Meyerson et al., suggest that most of Nager syndrome cases appear sporadic with normal parents of the affected patients. Several cases showed autosomal dominant inheritance. Most of the cases are diagnosed without any family history. Sulik and Dehart reported that the genetic cause for NAD might be an imbalance in the development of the proximal aspect of maxilla and mandibular prominences of the first branchial arch. Zori et al. stated that gene mutation in Nager syndrome may reside on chromosome 9q.[4,7]

Clinically, facial features of NAD include downward slanting palpebral fissures, malar hypoplasia, micrognathia of lower jaw, high nasal bridge, external ear defects, diminished eyelashes, and lower lid colobomas. Hearing loss is the main feature, often occurs bilaterally, conductive in the order of 50–60 dB. The oral findings include probable cleft palate and malformed velum (partial or complete), cleft lip, oropharyngeal insufficiency, temporomandibular joint fibrosis and/or ankylosis.[1,3]

Skeletal abnormalities include short stature, thoracolumbar scoliosis, cervico-vertebral, and rib anomalies. Limb anomalies include preaxial anomalies, proximal radioulnar...
syndactyly, hypoplastic, or missing thumbs, hypoplastic radii, and short humorous bones. Limb defects may occur in combination with the craniofacial defects. Halal et al. stated a correlation between the shortness of the arms and lack of mandibular development.[7]

Nager syndrome may also be associated with genitourinary abnormalities such as unilateral renal agenesis and external genital hypoplasia. Gastrointestinal abnormalities include gastroschisis and Hirschsprung’s disease. Cardiovascular malformations may include tetralogy of fallot and ventricular septal defect. Central nervous system anomalies include microcephaly, hydrocephalus, and polymicrogyria.[1,6]

Gingival hyperplasia usually shows its clinical evidence within 3–6 months of the use of the drug therapy. Most commonly associated drugs with gingival hyperplasia include phenytoin, nifedipine, cyclosporine, diltiazem, verapramil, and amiodipine. Patients taking the drugs for a long period of time as in maintenance phase of drug therapy or as a substitute drug therapy for the immune system and other systemic diseases are prone to get either localized or generalized gingival swellings. These gingival enlargements or hyperplasia with drug therapies can be minimized by either discontinuing the drug or changing the mechanism of action. The gingival enlargements may also be associated with poor oral hygiene with heavy plaque depositions and can be improved by plaque control measures.[8]

Gingival hyperplasia in Nager syndrome has not been reported in any patient with cardiovascular abnormalities. Gingival hyperplasia has been reported by the subjects who generally suffer from chronic diseases such as high blood pressure, osteoporosis, epilepsy, convulsions, and also with kidney or liver transplantations. Drug-induced gingival hyperplasia was noted in our case with a patient taking oral propranolol for a long duration. A nonselective beta blocker propranolol-induced gingival hyperplasia is a very rare oral drug reaction.[9]

According to medfacts.com, the percentage of propranolol hydrochloride patients where gingival hyperplasia was reported as a side effect was 0.2812%. Gingival hyperplasia is a well-known side effect related to the use of calcium channel blockers but with propranolol, it is a very rare oral manifestation.[10]

As per the survey done on third September 2015 reported by personalized health information system (eHealthMe), gingival hyperplasia has been observed in patients taking propranolol hydrochloride, especially in older females. The survey which consists of 2552 people taking oral propranolol therapy for systemic illness has been reported by adverse effects. Among them, six patients (0.24%) have gingival hyperplasia, thus giving us an impression of a very low prevalence rate of gingival hyperplasia with patients on oral propranolol therapy.[11]

A study titled, the prevalence of gingival overgrowth secondary to the administration of cyclosporine in liver and kidney transplant pediatric patients done by Allman et al. The researcher has done the systemic evaluation about the medications used by the patients for systemic illness and has shown in a chart with eight patients taking propranolol therapy for cardiovascular illness. Out of eight patients, two show no gingival enlargement, three show mild, two with moderate, and one with severe gingival enlargement.[12]

The role of propranolol has been proven to cause gingival enlargement but until now there is no scientific research evidence regarding its frequency of occurrence. The research facts about propranolol give us a fair description about the drug pharmacology and terms it as a safe drug used for the cardiovascular treatment and chronic migraine. Hence, propranolol stands safe as it has got a very low prevalence rate to cause the gingival enlargement but not as a serious threat.

Treatment and management of Nager syndrome requires a multidisciplinary approach. Most of the cases require surgical intervention for tongue-lip suturing, gavage feeding, gastrostomy, and tracheostomy. In general, a slow development in the speech and language was noted at an early stage when normal surgical procedures such as tracheostomy and gastrostomy were performed. A multidisciplinary team approach with the involvement of a panel of specialists from different medical fields such as neonatology, pediatrics, otolaryngology, plastic surgery, dentistry, reconstructive hand surgery, and genetics, is the best mode of treatment planning for the patients with NAD.[13]
Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. McDonald MT. Syndrome of the mouth. J Med Genet 1993;30:779-82.
2. Jayakaran TG. The effect of drugs in the oral cavity – A review. J Pharm Sci Res 2014;6:89-96.
3. Couyoumjian CA, Treadwell MC, Barr M. Prenatal sonographic diagnosis of Nager acrofacial dysostosis with unilateral upper limb involvement. Prenat Diagn 2008;28:964-6.
4. Sulik KK, Dehart DB. Retinoic-acid-induced limb malformations resulting from apical ectodermal ridge cell death. Teratology 1988;37:527-37.
5. Zori RT, Gray BA, Bent-Williams A, Driscoll DJ, Williams CA, Zawadowski JL. Preaxial acrofacial dysostosis (Nager syndrome) associated with an inherited and apparently balanced X;9 translocation: Prenatal and postnatal late replication studies. Am J Med Genet 1993;46:379-83.
6. Meyerson MD, Jensen KM, Meyers JM, Hall BD. Nager acrofacial dysostosis: Early intervention and long-term planning. Cleft Palate J 1977;14:35-40.
7. Halal F, Herrmann J, Pallister PD, Opitz JM, Desgranges MF, Grenier G. Differential diagnosis of Nager acrofacial dysostosis syndrome: Report of four patients with Nager syndrome and discussion of other related syndromes. Am J Med Genet 1983;14:209-24.
8. Scully C, Bagan JV. Adverse drug reactions in the orofacial region. Crit Rev Oral Biol Med 2004;15:221-39.
9. Hassell TM, Hefti AF. Drug-induced gingival overgrowth: Old problem, new problem. Crit Rev Oral Biol Med 1991;2:103-37.
10. Study of possible correlation between gingival hyperplasia and propranolol hydrochloride: 2014-medic.com.
11. Review: Could Propranolol Hydrochloride Cause Gingival Hyperplasia? Personalized Information System. 2015-eHealthMed.
12. Allman SD, McWhorter AG, Seale NS. Evaluation of cyclosporin-induced gingival overgrowth in the pediatric transplant patient. Pediatr Dent 1994;16:36-40.
13. Bhatia SK. The dental management of a patient with Nager syndrome: A case report. J Disabil Oral Health 2011;12:43-6.

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