CASE REPORT

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Oral Manifestations of the Donohue Syndrome: A Case Report

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Abstract

Background and Aim: The Donohue syndrome, also known as leprechaunism, is a rare autosomal recessive genetic disorder of insulin resistance. The severe form of insulin resistance seen in this syndrome is due to a mutation in the insulin receptor gene. This syndrome has symptoms such as delayed growth before and after birth, premature growth, lipoatrophy, hypertrichosis, acanthosis nigricans, and dysmorphic face.

Case Presentation: This report presents oral manifestations (such as macrodontia, severe crowding, supernumerary tooth, etc.) and management of a 10-year-old patient with the Donohue syndrome.

Conclusion: Considering the extensive oral manifestations of the Donohue syndrome, good oral hygiene and regular dental follow-ups are necessary for such patients.

Key Words: Donohue Syndrome; Oral Manifestations; Malocclusion; Tooth, Supernumerary

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Introduction

The Donohue syndrome is a rare autosomal recessive genetic disorder of insulin resistance [1, 2]. The most common forms of diabetes mellitus are due to insulin resistance, and cases of insulin receptor deficiency are rare. The Donohue syndrome is among such cases [3]. This syndrome affects less than one newborn in one billion successful births [4]. It is characterized by symptoms such as delayed growth before and after birth, premature growth, lipoatrophy, hypertrichosis, acanthosis nigricans, dysmorphic face, postprandial hyperglycemia [5], macro-genitosomia, hypertrophy of internal organs, and elfin-like face [2]. In some patients, uremia and polyuria despite normal creatine levels, hypernatremia, and high blood pressure are also observed (5).

This syndrome is caused by a mutation in the insulin receptor gene in the short arm of chromosome 19 [6], (INSR; 19P 13.3.P132) [7]. Mutations in the insulin receptor gene can lead to severe heterogeneous disorders such as the Donohue syndrome or mild disorders such as type A insulin resistance syndrome. Patients with severe disorders usually have homozygous or mixed heterozygous mutations. Homozygous mutations are rarely responsible for this

condition [8]. In such patients, mutations in these receptors lead to functional defects in the function of insulin receptors and affect the ability of insulin to bind to the receptor, which leads to severe hyperinsulinism and fasting hypoglycemia along with severe growth failure despite healthy nutrition. Calorie restriction leads to muscle atrophy, reduction of subcutaneous fat and thick skin. Reduction of chest diameter occurs with an increase in abdominal expansion, which affects the respiratory reserve. Heart disease occurs early in life with hypertrophic cardiomyopathy as a result of hyperinsulinism. The prognosis of this disease is poor, and most patients die in infancy due to sepsis [1].

In some cases, two different mutations are observed in the insulin receptor gene. However, apart from insulin resistance, genetic anomalies responsible for patients' phenotype have not been identified [2]. The diagnosis of this syndrome is based on clinical and genetic assessments. The treatment of this syndrome is often challenging and unsuccessful, and is based on maintaining normal glycemia and avoiding fasting. In some patients, recombinant human insulin growth factor-7 is used for treatment [9].

Considering the rare incidence of this syndrome, its oral manifestations have not been well addressed in the literature. This report describes the oral manifestations and treatment of a 10-year-old boy with the Donohue syndrome.

Case Presentation

A 10-year-old boy was referred to the Endodontics Department of the Faculty of Dentistry of Tehran Azad University with a chief complaint of tooth restoration. When taking a medical history, the parents mentioned insulin-resistant diabetes and the Donohue syndrome, which was confirmed genetically in Germany. The patient was taking empagliflozin (GLORIPA) for insulin-resistant diabetes. Also, the patient's parents had a consanguineous marriage. The parents were completely informed and signed an informed consent form.

Clinical findings:

Extra-oral clinical examination revealed a dolichocephalic facial skeleton, leptoprosopic face, convex facial profile, lip incompetency, lower lip protrusion, short upper lip, flattened nasal bridge, hypertrichosis, hypotrophy of skeletal muscles, and large ears (Figure 1).

Intra-oral clinical examination revealed gingival enlargement with bleeding on probing, dome-shaped palate, V-shaped dental arch, macrodontia, and severe crowding (Figure 2).

Radiographic findings:

Radiographic examination showed multiple caries and supernumerary teeth at the site of tooth #13 (Figure 3).

Therapeutic intervention:

According to the pulp sensibility tests, teeth #21 and #12 were necrotic and endodontic treatment was performed for them. After local anesthesia induction and rubber-dam isolation, the root canals were cleaned and shaped, and subsequently obturated with tricalcium silicate-based cements.

Follow-up:

After 6 months, the patient returned for the follow-up and another panoramic radiograph was obtained, which revealed new carious lesions (Figure 4).

Vital pulp therapy was performed for teeth #22, #44, and #45, and restorative treatment was performed for teeth #36 and #46.

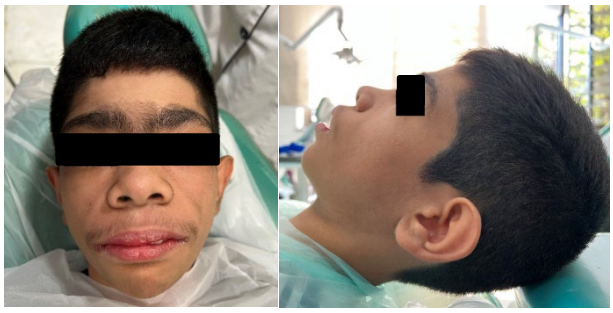

Figure 1. Extraoral frontal-view and profile-view photographs of the patient

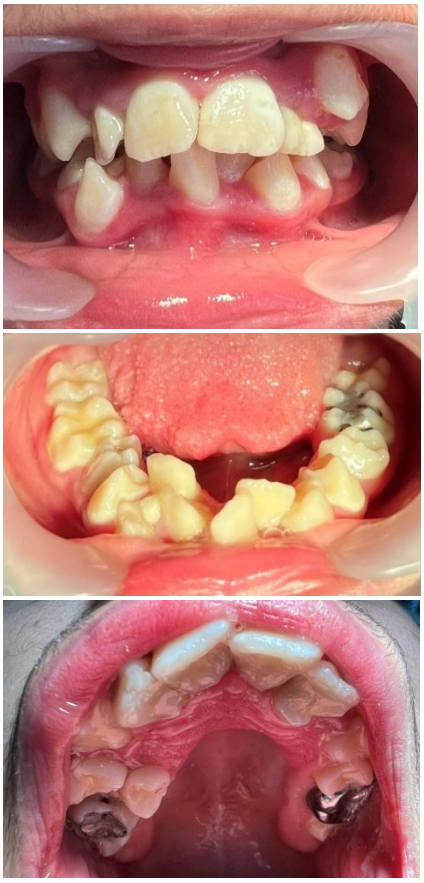

Figure 2. Intraoral clinical examination of the patient

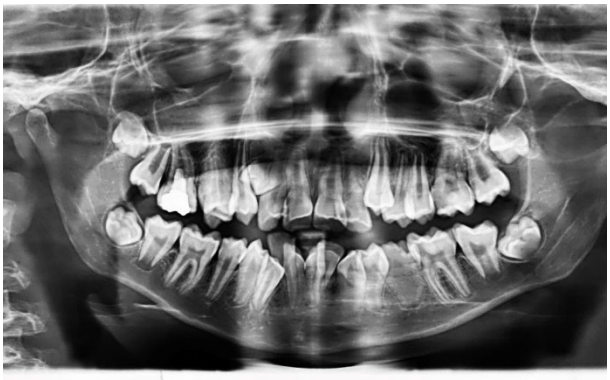

Figure 3. Panoramic radiograph of the patient

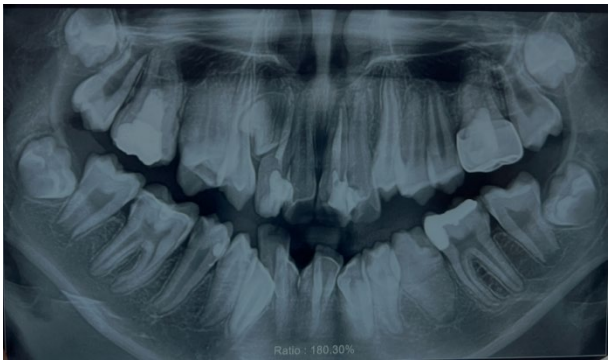

Figure 4. Panoramic radiograph taken at the 6-month follow-up

Discussion

The Donohue syndrome is a rare autosomal recessive genetic disorder of insulin resistance [1, 2]. This syndrome is characterized by symptoms such as hypertrichosis, muscle atrophy, and big ears, among others [5, 10]. Supernumerary teeth are among the most common dental anomalies seen in this syndrome [11]. The teeth or odontogenic structures seen in this syndrome often exceed 20 deciduous teeth or 32 permanent teeth. Mesiodens is the most common dental anomaly observed in this syndrome, which is found at the site of central incisors [12]. The etiology of mesiodens is unclear. Various etiologies such as atavism, dichotomy of tooth bud, dental lamina hyperactivity, and genetic factors have been proposed for mesiodens. Genetics and heredity play a key role in its development, especially in syndromic patients or those with a positive family history [13].

Environmental factors increase genetic predispositions. It is recommended to extract the supernumerary tooth as soon as possible in order to avoid complications such as tooth impaction, delayed eruption, diastema, displacement or rotation, cyst formation, and root resorption of the adjacent tooth [14-16]. In the present case, a supernumerary tooth was found at the site of tooth #13. Macrodontia,

which is also called megalodontia, has an unknown etiology. Genetic and environmental factors play a role in its occurrence [17, 18]. Unlike generalized macrodontia, isolated macrodontia is not accompanied by a syndrome or a systemic pathology [19]. Generalized macrodontia is seen in conditions such as insulin-resistant diabetes, otodental syndrome, and pituitary gigantism [20].

In the present case, generalized macrodontia was seen due to insulin-resistant diabetes. Flattened nasal bridge is another feature that was observed in the present case. Flattened nasal bridge disorders [21] may range from mild to severe. Its mild type includes spondylocarpotarsal synostosis and Larsen syndrome, and its severe type includes atelosteogenesis (type I, III) and Piepkorn type of osteochondrodysplasia. Hypertrichosis [22], which was seen in the present case, is defined as excessive growth of hair anywhere in the body in women or men, which should be differentiated from hirsutism in women, which is excessive growth of terminal hair dependent on androgens. Muscle atrophy [23] is defined as changes in muscles, including shrinkage of myofibers, changes in fiber type and myosin isoforms, loss of cytoplasm and organelles, and total loss of protein.

Muscle atrophy is a direct consequence of protein degradation, which is caused by various pathophysiological conditions such as disuse, immobilization, denervation, aging, sepsis, cachexia, treatment with glucocorticoids, hereditary muscle disorders, cancer, diabetes, obesity, and kidney and heart failure, among others. Big ears, which was also seen in this case, is called macrotia. It is usually seen in children, and is a symptom of other medical conditions. Prominent ears are the most common congenital anomaly in the head and neck region. Prominent ears can cause psychological, social, and educational problems [24].

Due to the scarcity of dental articles about the Donohue syndrome, the prognosis of dental treatments of such patients is uncertain. However, due to the extensive dental problems of such patients including gingival enlargement with bleeding on probing, V-shaped dental arch, macrodontia, severe crowding, etc., these patients often require a multidisciplinary approach involving periodontic, orthodontic, and prosthodontic treatments, among others.

Due to insulin-resistant diabetes in such patients, delayed healing and higher risk of infection are expected in such patients; therefore, follow-ups with shorter intervals should be scheduled for them, and any infection should be treated promptly [25]. Also, a medical consultation is necessary prior to high-risk procedures.

Conclusion

Considering the extensive oral manifestations of the Donohue syndrome, including large dental pulp and high caries rate, good oral hygiene and regular dental follow-ups are necessary for such patients.

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