Case Report

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Challenges in the Management of Donohue Syndrome: A Case Report

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ABSTRACT

Background: Donohue syndrome (also referred to as Leprechaunism) is an extremely rare and severe genetic disorder. The individuals thus affected are associated with extreme insulin resistance. Most of the diseases present in Donohue syndrome is considered to be due to the insulin receptor binding the insulin like growth factor, regulating the growth of the embryo and the regulation of blood sugar. A case of 13-year-old female having Donohue syndrome is briefly described in this article.

Keywords: Donohue syndrome, Insulin receptor, Growth factor, Genetic disorder, Orofacial features.

INTRODUCTION

Donohue syndrome is an autosomal recessive genetic disorder. The mutations responsible for the disease are found on the short arm chromosome 19 (19p13.2) within the coding sequence of the *insr gene* (insulin receptor) causing the production of inactive receptor molecules [2, 3]. Affected individuals associated with extreme insulin resistance [1]. Due to the lack of complete functional insulin receptor and the receptor produced by the mutant allele is only about 15% as effective as the normal receptor. The beta cells in the pancreas, which make and store insulin and release it on an as-needed basis, are often found to be very large or numerous. Insulin exerts both metabolic and mitogenic effects on its target cells through the insulin receptor [4, 5]. Defects of insulin action result in retarded intrauterine growth and metabolic dysfunction in humans [4, 6]. In addition, infants with leprechaunism characteristically show hirsutism [7]. Despite poor prognosis of this condition and anguishing reports of most patients dying in their first year are present, yet milder forms of the disease are known to have lived longer. However, this variation is unsurprising given the diversity of mutations thus causing this rare disease [2]. Various extraoral, intraoral and ocular manifestations are presented in such syndromes, and many of these manifestations are suggested to be occurring due to the insulin receptor binding the insulinlike growth factor, regulating the growth of the embryo and the regulation of blood sugar [8-9].

CASE REPORT

A 13-year-old female patient reported to us department with a chief complaint of bleeding gums and malaligned teeth. She looks emaciated and week. She further gave a history of weakness, fatigue and occasional loss of appetite. She reported epilepsy at the age of 3 years for which she took medication.

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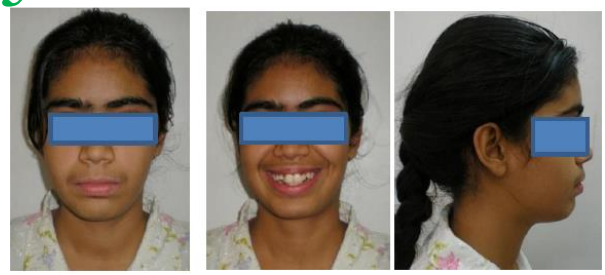

Fig 1: Extraoral photographs.

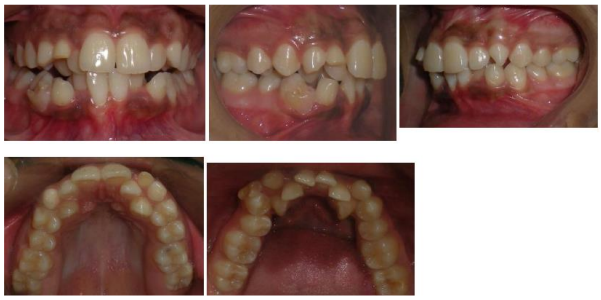

Fig 2: Intra oral photographs.

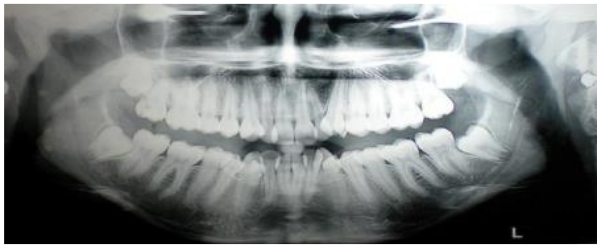

Fig 3a: Panaromic radiograph.

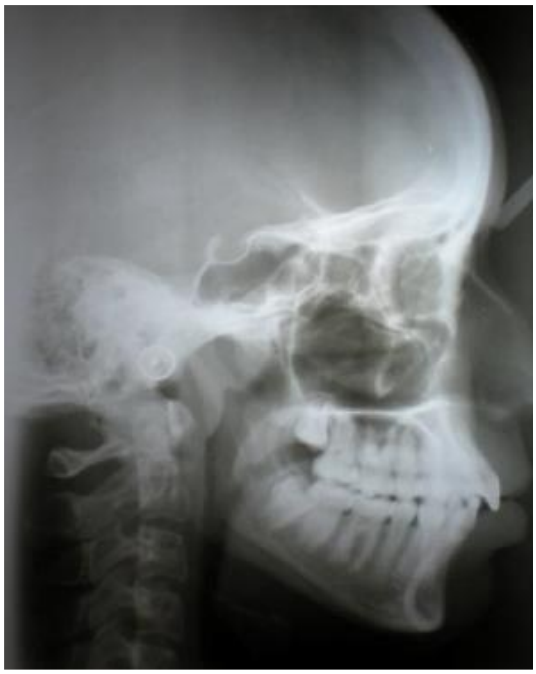

Fig 3b: Lateral cephalogram.

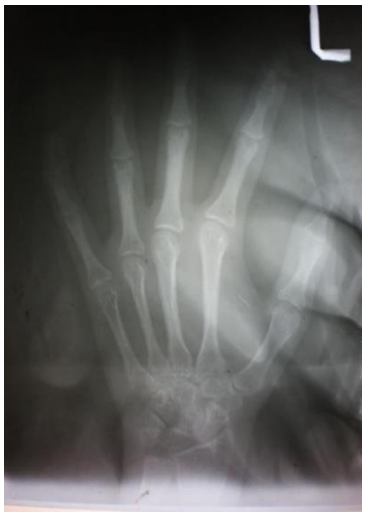

Fig 3c: Hand wrist radiograph.

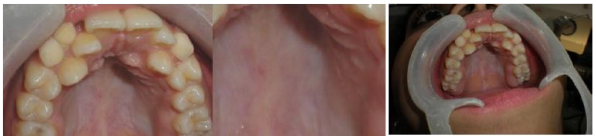

Fig 4: Acanthosis Nigricans (Oral Manifestations).

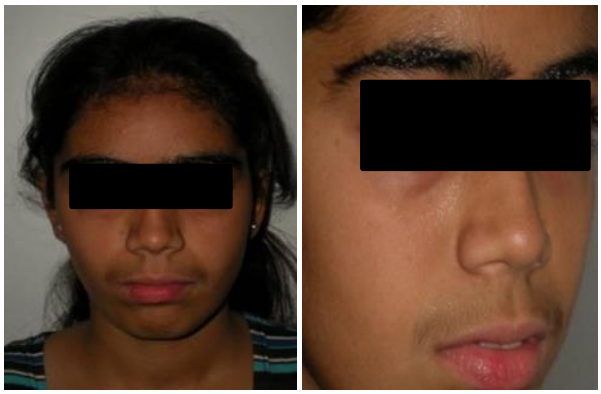

Fig 5: Hirsutism/Hypertrichosis.

The epilepsy was controlled and she continued the medication for 6 years only. Since then she did not developed any history of epilepsy. Family history reveals consanguineous marriage. Her delivery was normal and the milestones of development were late according to the bystanders of the patient. She was unable to walk till two years of her age, and she spoke at the age of 3 years. She also gave a history of various Ayurvedic and Herbal treatment for her facial growth and loose skin for six years.

General physical examination revealed that the patient was moderately nourished with a long, thin body, slightly stooping posture and excessive body hair. Upon further examination; the extraoral

examination (Fig 1) (Fig 5) revealed, Dolichocephalic skull form, Leptoprosopic face, Convex facial profile, Increase lower facial height, Lips were incompetent protrusive lower lip and upper lip is short, Nasolabial angle was normal, Hirsuitism, Depressed nasal bridge. And the Intraoral examination revelled (Fig 2), Permanent dentition with multiple retained deciduous teeth, Malocclusion was Angle class I molar, Canine towards class II, Crowding in the anterior region in the upper and lower arch, Acanthosis nigricans in palate 2 (a soft fibrous band with tiny red points) **(fig 4),** hyperpigmentation of anterior gingiva, marginal gingival inflammation with bleeding on probing. Her Radiological Features (Fig 3A, B, C) showed, Severe crowding, Multiple retained deciduous, Large gonial angle, Decreased overjet, Bone age is slightly less. The Biochemical Findings were Serum insulin growth factor-I 11 (IGF-I) - 156mg/ml.(normal range-250- 340ng/ml) and the Salivary IGF-I-1.9mg/ml.(normal range-3.4-6mg/ml). Her Ocular findings were Prominent eyes**,** Myopia**,** Hypertelorosim. After complete clinical, a radiological and biochemical examination of the patient, she was referred to a paediatrician and an Endocrinologist who individually diagnosed and confirmed that the patient is suffering for **Mild form of Donohue Syndrome.**

DISCUSSION

Donohue syndrome is estimated to affect less than 1 per million people worldwide [20]. It represents the most extreme insulin receptoropathy with an autosomal recessive inheritance which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition[1]. Donohue syndrome results from mutations in the *INSR* gene. This gene provides instructions for making a protein called an insulin receptor, which is found in many types of cells. Insulin receptors are embedded in the outer membrane surrounding the cell where they bind to insulin circulating in the bloodstream, and this binding triggers signalling pathways that influence many cell functions. Hence the mutation of this gene greatly reduces the number of insulin receptors that reach the cell membrane or disrupt the function of these receptors. Although insulin is present in the bloodstream, without functional receptors, it cannot exert its effects on cells and tissues. This severe resistance to the effects of insulin impairs blood sugar regulation and affects many aspects of development in people with Donohue syndrome. Other syndromic forms of insulin resistance include Rabson- Mendenhall syndrome, type A and B insulin resistance, lipodystrophies, and HAIR-AN syndrome [16]. Diagnosis is made on clinical, biochemical, hyperinsulinemia and genetic grounds. Most patients die as a result of intercurrent respiratory tract infection before 2 yr of age in severe forms of the disease [15]. Clinical features in such cases include abnormal facial height, hearing abnormality, high arched narrow palate, hypertelorism, proptosis, thick lower lip vermillion, thick nasal alae, delayed skeletal maturation, hyperinsulinaemia, hirsutism, microcephaly, acanthosis nigricans, hypoglycaemia, gingival overgrowth, large hands, long foot, abdominal detention, cachexia. [13, 14] The present case has shown almost all the above-mentioned features thus described in various literature excepting a few as it is the milder form of the disease and the patient also gives a family history of consanguineous marriage suggesting the possibility of genetic mutation. At present, there is a paucity of evidence for any effective treatment for Donohue syndrome. Management is not standardized but aims to normalize blood glucose. Continuous feeding may be useful. Some have shown beneficial metabolic effects using recombinant human IGF-I [17, 18], whereas others have not [19]. Regarding the use of IGF-I, optimal timing, dosing, and duration of therapy, as well as the relative risks and benefits, have not been properly established [18]. Recently the use of continuous subcutaneous insulin pump therapy has been found to be promising [21].

CONCLUSION

Syndromes of severe insulin resistance such as Donohue syndrome are extremely rare with limited available treatment modality. A however milder form of such syndromes increases the prognosis. The use of insulin sensitizers may delay the development of type 2 diabetes, but ultimately the patient will require insulin therapy. Long term studies are necessary for determining the risks and benefits, thus associated with recombinant IGF-1

therapy and continuous subcutaneous insulin pump therapy. However, the benefits and burden of the treatment have to be made before making a decision on withholding or withdrawing health care service to the patient. Similarly, prenatal testing can help the parents to make an informed decision regarding the pregnancy, which in turn will reduce the incidence of Donohue syndrome.

CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

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