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Diagnosis and Dental Management of a 5 year old child with Freeman-Sheldon Syndrome: A Case Report Study

Gandhali Malgaonkar Joshi [1], Sayali Belsare[2] , Alok Patel [3], Shweta Jajoo[4]
[1] Post-Graduate Student, Department of Paediatric and Preventive Dentistry, Bharati Vidyapeeth DeemedToBeUniversity DentalCollegeAndHospital, Pune, India
[2] MDS, Department of Paediatric and Preventive Dentistry, Bharati Vidyapeeth Deemed To Be University Dental College And Hospital, Pune, India
[3] Head of the Department, Department of Paediatric and Preventive Dentistry, Bharati Vidyapeeth DeemedToBeUniversity DentalCollegeAndHospital, Pune, India
[4]Assistant Professor, Department of Paediatric and Preventive Dentistry, Bharati Vidyapeeth DeemedToBeUniversity DentalCollegeAndHospital, Pune, India

Corresponding Author: Dr. Gandhali Malgaonkar Joshi
Paediatric & Preventive Dentistry
Bharati Vidyapeeth Deemed To Be University Dental College And Hospital, Pune
Pune, Maharashtra, 411046, India
Tel: +91-90045-12886
E-mail: dr.gandhali.dm@gmail.com
ORCID ID: 0000-0002-9420-4391

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Abstract:
A 5-year-oldfemale patient reported to the department of Pediatric Dentistry with a chief complaint ofinability to eat due to multiple carious teeth in the mouth. Various intra oral as well as extra oral features pointed towards a clinical diagnosis of Freeman Sheldon syndrome (FSS) and hence a genetic testing was advised. An exome based analysis for relevant genesindicated absence of any alleles of clinical relevance. This suggests that the patient belongs to the minority group of close to 7% subjects that present clinical features of FSS without genetic defect in the related genes. Due to the multiple treatment procedures needed, a full mouth rehabilitationwas carried out for the patient successfully, under general anesthesia.
Keywords: Freeman- Sheldon Syndrome, Freeman Burian syndrome, full mouth rehabilitation, rare diseases

Introduction:

Freeman-Sheldon syndrome (FSS) also known as 'whistling face syndrome' or Freeman-Burian syndrome (FBS) is an extremely rare congenital disorder that primarily affects craniofacial muscles, which also forms the basis of its diagnosis; the severity is graded based on involvement of other joints of the hands or feet.[1,2]It's exact prevalence is largely unknown but it is estimated to be about 1 per one million.[3]Since the diagnosis is primarily based on the combination of certain extra and intra-oral features, dentists have an important role in aiding the diagnosis of FSS syndrome.Due to the paucity of literature with respect to the dental management of
patients with FSS, reporting and documentation of dental treatment of such cases is important.
The present case report summarizes clinical features, genetic testing and dental management of
a child patient with FSS.

Case-Report:A five-year-old, female patient reported to the department with a chief complaint of pain in the upper and lower right and left posterior regions of the jaw. On examination, multiple carious teeth were noted. Medical history revealed she had delayed developmental milestones.The patient also presented with multiple features like nasolabial creases,brachycephaly, pursed lips, whistling mouth, v shaped chin and low set ears**(Figure 1).** Further, the child and had undergone multiple investigations, namely MRI spine and chromosomal array. While the MRI showed systemic scoliosis and hemivertebrae,there was no significant finding from the chromosomal array. On enquiring about the patient's personal history for a possible syndromic diagnosis, it was noted that these features were congenital; however, none of the parents showed their presence. Intra-oral examination revealed features like microstomia, high arched palate, ankyloglossia and missing lower anterior teeth.Oral Pantograph (OPG) investigation showed multiple carious teeth that needed endodontic treatment and confirmed oligodontia in mandibular incisor teeth(absence of permanent tooth buds)**(Figure 2).**On basis of the above findings(combination of oral and other physical congenital anomalies) the patient was clinically diagnosed to be a case of Freeman Sheldon Syndrome.

The patient's behaviour could be classified as Frankl Grade 1(definitely negative). Multiple attempts were made to treat the patient chair-side using different behaviour management techniques in subsequent visits, but there was no change in her behaviour. Hence, after a thorough pre-anaesthetic evaluation, the patient underwent a successful full mouth rehabilitation under general anaesthesia. Briefly, pulpectomy was done for 61,62, 74,75,85; stainless steel crowns with 54,64,65,74,75,85; space Maintainer with 84 regions and GIC restorations with 53,63 **(Figure 3)**

Discussion:

It is important to note that FSS is diagnosed primarily thorough physical examination and medical history. The appearance of the following features can primarily lead to a diagnosis of the syndrome. a) microstomia, b) whistling-face appearance (pursed lips), c) H or V-shaped chin defect, and d) prominent nasolabial folds. Other features associated with FSS include enopthalmos, small nose, high arched palate, midface hypoplasia, dental crowding, ulnar deviation of wrists and fingers, overlapping fingers or toes, camptodactyly, and hypoplasia or absence of interphalangeal creases. In addition to this, there must be two or more body areas with limited movement of joints, frequently the hands or feet and ankles.[4]

Patients with facial malformations and limited joint mobility in two or more areas of the body are considered FSS Type 1, the Classical FSS. Patients presenting only with craniofacial deformities are considered FSS type 2. Patients with facial malformations plus areas of the body with limited joint mobility are considered FSS type 3, mixed phenotype. Patients with FSS type 2 tend to be the mildest and have few complications, while those with FSS type 1 or 'classic' tend to be the most severely affected and more likely to develop medical complications. Patients with FSS type 3 are intermediate between FSS types 1 and 2.Our patient presented with microstomia, whistling-face appearance(pursed lips), a V-shaped chin defect, and a bilateral nasolabial creases, in addition to scoliosis.Thus, based on this information, we concluded that our patient could be classified as FSS type 2.

FSS can be caused by a change (mutation or allelic variation) in the embryonic myosin heavy chain (MYH3) gene, which is located on band 13.1 of the short arm (p) of chromosome 17. It thus impairs muscle development in the embryo and disrupt muscle function throughout life.Hence the patient was advised to get a mutation analysis of genes associated with FSS.A next generation whole exome sequencing (NGS) panel was run on DNA extracted from peripheral blood sample, using the Illumina platform. This analysis was done at the Genepath Dx Lab, Pune. Bioinformatic analysis was carried out on the MYH3 and NALCN genes which are associated with Freeman-Sheldon syndrome (FSS). However, thestudy did not reveal the presence of any likely pathogenic or clinically relevant variants within the coding regions or along the exon-intron boundaries of the aforementioned genes.The report also highlighted the fact that closeto 7% of subjects with FSS like phenotype do not carry pathogenic allelic variants of the candidate genes.

Management of patients with FSS under general anaesthesia may possess certain anaesthetic issues like difficult intravenous access, difficult airway and postoperative pulmonary complications. An association with malignant hyperthermia has been suggested, but not been confirmed. There have been case reports of managing young children under general anaesthesia for different procedures.[5]Taking these factors into consideration, no muscle relaxant was used and nasal intubation was done with the use of video laryngoscope with microcuff endotracheal tube during general anaethesia**(Figure 4).**

Conclusion:

FSS being a rare disease which is defined by its pathognomic craniofacial findings, it is important for the dental professionals to recognise its features and work towards a dental care with due precautions besides careful follow

ups for preventive measures to preserve the teeth. To that end, while the confirmationof the genetic basis of the observed clinical features in the patient would have aided in better categorization of the patient, the phenotypic features indeed provide adequate indications for an appropriate dental treatment and long term care. This can aid in the early intervention and might help in providing the patient with a better quality of life. Currently, the number of FSS patients tested for genetic defects may be relatively small. With increasing genetic testing, the number of patients negative for pathogenic genetic variations in the two currently identified primary susceptibility genesmay increase which in turn could pave way to, exploration for additional genetic loci for genetic susceptibility to FSS.This in turn could help identify new entities and their role in the development of FSS with potential applications in prenatal testing.

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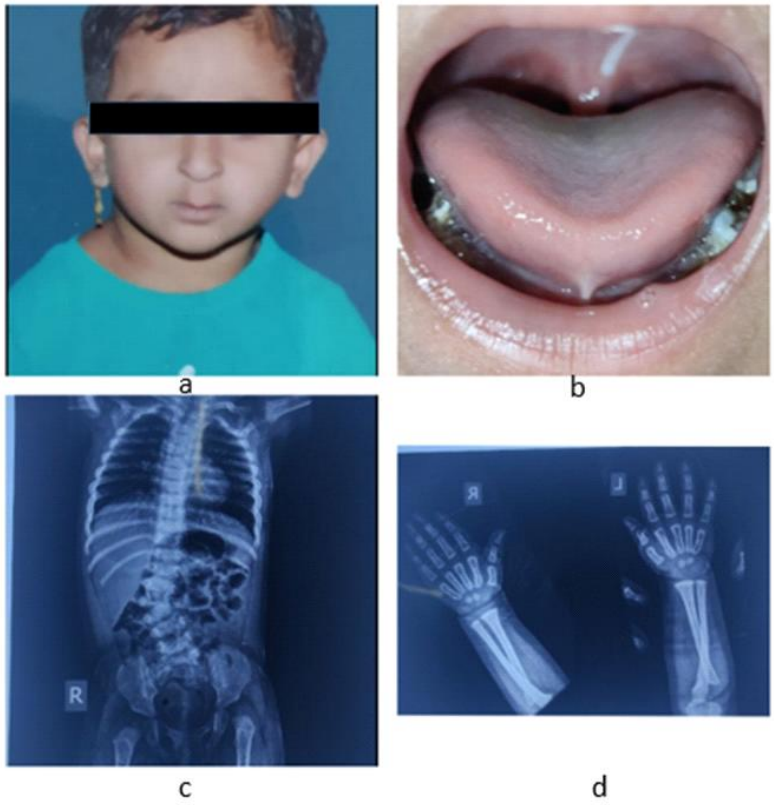

Figure 1

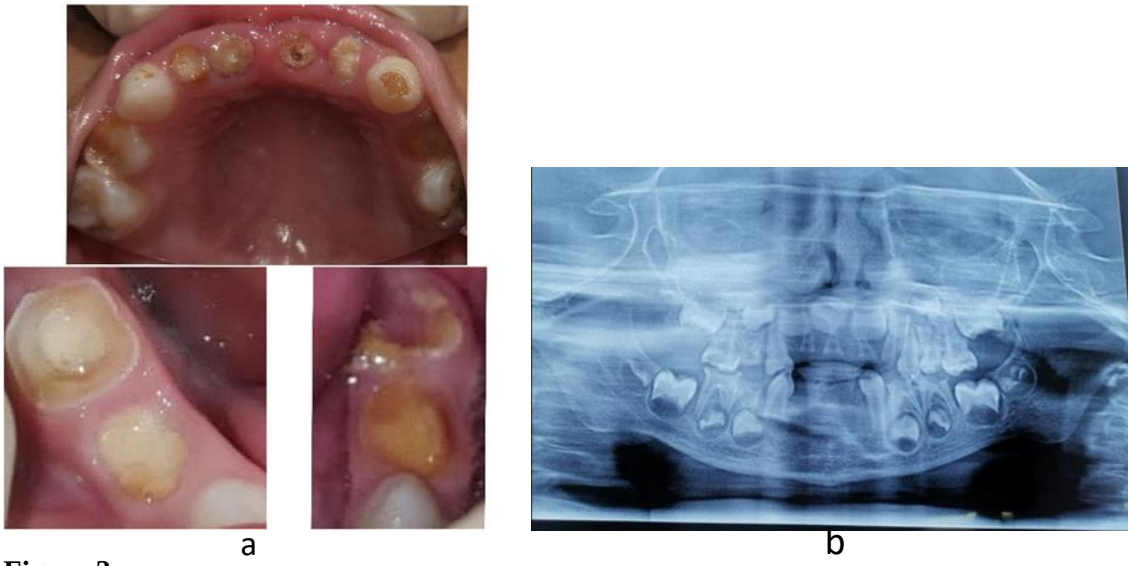

Figure 2

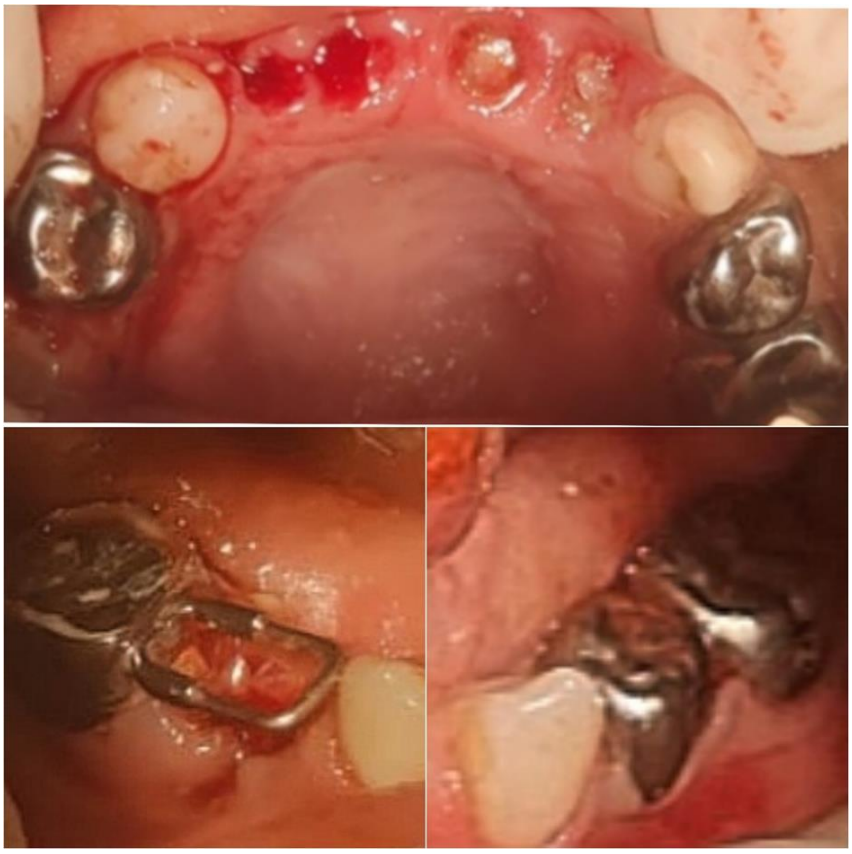

Figure 3

Figure 4

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Figure Legends:

Figure 1:

a. Extra-orally: Bilateral Nasolabial creases, whistling-face appearance (pursed lips), V-shaped chin defect

b. Microstomia, Ankyloglossia

c.Lateral Spinal Curvature(Scoliosis)

d.small 1st metacarpal and deviated phalanges

Figure 2:

a.Intra-oral pre-operative images

b.Pre-operative OPG

Figure 3: Post-operative Full Mouth Rehabilitation of the patient

Figure 4:Nasal intubation with the use of video laryngoscope and microcuff endotracheal tube.