Case Report

Craniofacial ciliopathies: An expanding oral disease spectrum - a review of literature and a case report

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INTRODUCTION

A syndrome can be defined as “a collection of traits, health problems, and/or birth defects in an individual, which usually has a single underlying cause.” Among various syndromes, ciliopathy is classified as a disorder that results from aberrant form or function of primary cilia. They are a group of disorders with desperate symptomatology, including, congenital cerebellar ataxia, retinal blindness, liver fibrosis, polycystic kidney disease, and polydactyly have recently been united under a single disease mechanism called “ciliopathies.” These ciliopathies contribute significantly to the health care burden,\(^1\) manifesting clinically into a broad range of clinical manifestations that ranges from being organ specific to a broadly pleiotropic syndrome. Craniofacial malformations and polydactyly are most commonly reported in ciliopathies. Based on the frequent appearance of craniofacial phenotypes in these diseases, Brugmann et al. in 2010 proposed the term craniofacial ciliopathies.\(^1\)

Earlier midline disorders had been the subject of intense scrutiny. For syndromes associated with midline collapse, no direct correlations between genotype and phenotype were uncovered. Genetic studies have shown these midfacial defects (e.g., hypertelorism) are due to ciliary disorders.\(^2\) Whenever a syndrome with craniofacial ciliopathies are missed, the problems arising might include a combination of physical problems, esthetic problems, learning difficulties, and most importantly occult medical complications.

Polydactyly is a condition in which a person has more than five fingers per hand or five toes per foot\(^4\) which can occur as an isolated malformation or as part of genetic syndromes. Waters et al. showed that mutations in a ciliary protein in the limb mesenchyme resulted in polydactyly.\(^5\) They showed that the polydactyly was due to ciliopathies that affect bone growth in limbs than other genetic defects.

Abstract

For all intents and purposes, craniofacial development is initiated as soon as the anteroposterior axis of an embryo is established. Although the neural crest receives a significant amount of attention, craniofacial tissue has more patterning information than other tissues of the body. New studies have further clarified the contribution of ciliary epithelia as a source of patterning information for the face. In this paper, we review the craniofacial anomalies in patients with ciliopathies, in which orofacial region is a pivotal recognition of the disorder. Also, a case report of a patient with suspected ciliopathy has been presented along with a logical approach for diagnosis of such disorders.

Key words: Ciliary dysfunction, craniofacial ciliopathies, hypertelorism, postaxial polydactyly syndrome

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This paper emphasizes that the dentist must recognize these ciliopathies which is a crucial step in prevention and awareness of medical complications in these patients. Dentists will then be able to offer specialized treatment such as dental rehabilitation, prevention of diseases of mouth and teeth, as well as dental education targeted to parents.

**Classification**

A logical approach is the first step in thorough understanding of ciliopathies. After a thorough review of the literature, a system to the classification of these ciliopathies with particular emphasis on craniofacial malformations has been developed as follows [Table 1].

**Methodology used for classification**

**Craniofacial anomalies**

Minor craniofacial malformations: Involving either upper third, middle third or lower third of the face.

Major-craniofacial malformations: Involving two-thirds or all three divisions of the face.

**Dental anomalies**

- Involving single teeth,
- Involving multiple teeth.

**Polydactyly**

- Mild polydactyly: Polydactyly of single limb
- Moderate polydactyly: Polydactyly of ipsilateral upper and lower limbs
- Severe polydactyly: Bilateral polydactyly of hands/limbs or polydactyly involving more than two upper and lower limbs.

**Systemic manifestations of ciliopathies**

The systemic manifestations of few of the above craniofacial ciliopathies are mentioned [Tables 2 and 3].[3,9]

**CASE REPORT**

A 14-year-old female patient reported to the Department of Oral Medicine and Radiology with a chief complaint of discoloration of the tooth since birth. Patient gave a positive history of discoloration with deciduous and permanent dentition, there were no complaints of unusual sensitivity to foods or thermal changes, no systemic symptoms, but because of psychological impact of her appearance and difficulty in mastication, she came to our dental outpatient department for treatment. Past dental history and medical history was not significant. Patient was residing in a fluoridated area since her birth. The subject was the first child of nonconsanguineous and normally developed parents. She has a sister with no congenital abnormalities. Pregnancy of her mother and birth were uneventful. The clinical pictures of the patient are given [Figures 1 and 2]. On general examination, the patient had a mild degree of hypertelorism, postaxial polydactyly with the right hand on the fifth finger, and bilateral postaxial polydactyly on both right and
left foot. Her psychomotor and mental developments were within normal limits [Figure 3].

On intra-oral examination, no soft tissue abnormalities were noted. Salivary ductal orifices were patent and saliva was of normal consistency and flow. On hard tissue examination, she had a normal complement of teeth with clinically missing 42, generalized brownish discoloration of teeth, which was exceeding more than 75% of the tooth structure with pitting and no morphological disfigurement seen. Generalized attrition was also present [Figures 4 and 5].

### Investigations

The hand-wrist radiograph of the right hand showed postaxial polydactyly, carpometacarpal fusion in the fifth finger, and partial fusion between fifth and sixth meta-carpels [Figure 6]. The lateral skull view of the patient showed frontal bossing and increased posterior-anterior dimension of the skull [Figure 7]. The posterior-anterior view of the skull [Figure 8] shows expanded mid-facial structure, one of the common midline facial disorders seen in craniofacial ciliopathies.

### Differential diagnosis

In the present report, patient presents with two

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**Table 3: Other abnormalities seen in craniofacial ciliopathies**

| Phenotype                | LCA | SLS | NPHP | JBTS |
|--------------------------|-----|-----|------|------|
| Cerebellar hypoplasia    | ✓   |     |      | ✓    |
| Encephalocoele           | ✓   | ✓   |      | ✓    |
| Hepatic disease          | ✓   | ✓   | ✓    | ✓    |
| Renal disease            | ✓   | ✓   |      | ✓    |
| Mental retardation       | ✓   | ✓   |      | ✓    |
| Obesity                  | ✓   | ✓   |      | ✓    |
| Polydactyly              | ✓   | ✓   |      | ✓    |
| Retinopathy              | ✓   | ✓   | ✓    | ✓    |
| Sinus inversus           | ✓   | ✓   |      | ✓    |
| Skeletal dysplasia       | ✓   | ✓   | ✓    | ✓    |
| Cleft palate             |     |     |      |      |

LCA: Leber's congenital amaurosis, SLS: Senior-Loken syndrome, NPHP: Nephrolithiasis, MKS: Meckel syndrome, BBS: Bardet-Biedl syndrome, JBTS: Joubert syndrome

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**Figure 1:** The clinical picture of the patient (Frontal view) showing facial asymmetry (mild hypertelorism in relation to eyes)

**Figure 2:** The clinical picture of the patient (Lateral view)

**Figure 3:** The general examination of the patient showing postaxial polydactyly with the right hand on the fifth finger, and bilateral postaxial polydactyly on both right and left foot

**Figure 4:** Maxilla of the patient showing generalized brownish discoloration of teeth, which was exceeding more than 75% of the tooth structure with pitting and generalized attrition
ciliary ectodermal alterations, one is a craniofacial abnormality, that is, hypertelorism, frontal bossing, microdontia, and other polydactyly. Based on the features mentioned above, with a thorough review of the literature, we classified the patient under Type 1 class of craniofacial ciliopathies [Table 1].

CONCLUSION

Recognizing the diverse presentations of the ciliopathies and screening strategies following diagnosis is an important part of the treatment plan of children with cilia-related disorders. Dentists, being health promoters, must be aware of the existence of these ciliopathies and how to treat it from the dental perspective. It is important to deepen the knowledge of these ciliopathies to recognize the type of disability afflicting the patient and offer comprehensive, optimum inter-disciplinary treatment to promote the dental health of patients thus afflicted.

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.
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