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Case Report

Oro dental manifestations in cases with partial agenesis of corpus callosum-rare phenomena

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ABSTRACT

This article focuses on the associated signs and symptoms of patients with partial agenesis of the corpus callosum. The oro dental manifestations of such cases have been given special weightage which will prove to be of great help to oral physician when encountered with such cases.

Case details: Two siblings, aged 14 and 16 years, reported with a chief complaint of severe crowding of teeth with mouth breathing habit. They were low birth-weight babies and had been born to non-consanguineous parents. The distinguishing features of these children were craniofacial abnormalities, delayed developmental milestones, mild mental retardation and abnormal gait. The nosological features and the clinical manifestations of this syndrome and the plausible autosomal recessive inheritance of this rare syndrome have been elicited. The diagnosis was based on characteristic phenotype, in particular striking craniofacial and skeletal abnormalities and neuroimaging.

Conclusion: It is a challenge for healthcare professionals to help these youths to maximize their potential as human beings and help them achieve a meaningful adulthood. On the other hand, diagnosing such cases can be a challenge to dentistry. A systematic protocol, if adhered, can lead to a more appropriate diagnosis. Managing such cases in a clinical setup involves a multispeciality and interdisciplinary approach.

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1. Article focus:

- This article focuses on the associated signs and symptoms of patients with partial agenesis of the corpus callosum.
- This syndrome involves a multidisciplinary approach to managing such cases.
- The orodental manifestations of such cases have been given special weightage in this article which will prove to be of great help to oral physician when encountered with such cases.

2. Key messages:

- Diagnosing such cases can be a challenge to dentistry.
- A systematic protocol, if adhered, can lead to a more appropriate diagnosis.
- Managing such cases in a clinical setup involves a multispeciality and interdisciplinary approach.

3. Strengths and Limitations:

A detailed workup had been done for this article including FISH and chromosomal analysis despite financial constraints.

1. Introduction

Acrocallosal syndrome is an atypical congenital disorder which was first described by Albert Schinzel in 1979 and may also be referred to as 'Schinzel Acrocallosal syndrome'.¹ The siblings were rare cases of physical and behavioral phenotypes where chromosomal analysis showed normal karyotyping and no interstitial deletions. However, the anatomical and radiological findings closely supported the diagnosis of: "ACROCALLOSAL SYNDROME".

2. Case report

Two siblings, aged 16 and 14 years respectively, had reported to the clinic with a chief complaint of mouth breathing habit and severe crowding of the upper and lower front teeth. They were born at term by normal delivery and history regarding any maternal illness, drug intake or exposure to radiation during antenatal and prenatal period was negative. Both were low birth weight babies; the boy weighed 2200 gm and girl, 2000 gm respectively. After 3 months of age, the mother noticed that both the children had abnormal facies, with delayed developmental milestones like walking and talking, hypophonia and difficulty in keeping up with their peers in school. She also felt pulsations on the top of the head of the male child even after 2 years of age. The respondent also reported extraction of the upper front teeth in the male child by a local dentist in an attempt to relieve crowding of teeth.

Clinical appraisal of both the siblings revealed the following: (Fig. 1)

- Physical and mental growth retardation with delayed developmental and skeletal milestones. Parameters like

Fig. 1 – Anthropometry measurements (NCHC).

height- 139 cm (normal: 160 cm), weight- 23.49 gm (normal: 51.28 kg) were falling below the 3rd percentile.

- Neurological examination revealed borderline mental retardation, moody and irritable behavior. There was scissoring gait due to hypotonicity of the adductor muscles of the lower limbs.
- Urinary bladder and bowel control not achieved.
- No abnormalities were detected in the other systems.
- SMR (Tanner's sexual maturity rate) was 3 with micropenis.
- Anthropometric measurements showed short stature, dolichocephaly (head circumference- 47 cm (normal: 52 cm), frontal bossing and triple hair whorls.
- Limb abnormalities: Dermatoglyphics revealed simian crease in both the cases and clinodactyly of the fifth finger in the girl.
- Pedigree chart analysis revealed that their first cousin had similar features and had died at 6 years of age. (Fig. 2)

The patients exhibited characteristic dysmorphic features like hypertelorism, strabismus, upward slanting and narrow palpebral fissures (with mongoloid slant in the girl) of the eyes. They had broad nasal bridge, short philtrum, incompetency of lips, posteriorly angulated malformed ears and prominent occiput. Malar prominences and mandible were hypoplastic with convex profile. Intra oral examination revealed normal mouth opening, crowding of the upper and lower anterior teeth, anterior open bite, high arched palate and missing 11 and 21. (Fig. 3) Differential diagnosis thought of were Aicardi, Andermann, Shapiro, Greig's

Cephalopolysyndactyly syndrome, Joubert Syndrome and Di-George syndrome.

Routine laboratory investigations (blood, urine, thyroid function) were normal.

- Chest X-ray- normal cardiothorax
- Tanner's Sexual maturity Rating- 4
- I.Q.- moderate
- USG (whole abdomen): no remarkable abnormality

Radiographic findings were as follows:

- PA skull: Dolichocephalism
- Cephalometric analysis: Convex Face Profile, Small chin, Deficit mandible, Marked antegonial notch, Short posterior facial height, Proclined incisors
- Panoramic radiograph: No apparent abnormalities
- Hand-wrist Radiograph: Fifth finger clinodactyly
- Arm-elbow radiograph: No abnormality detected
- CT scan Report (Fig. 4): Partial agenesis of the corpus callosum, Microcephaly with enlarged cerebral ventricles, Hydrocephalus: stenosis at the level of aqueduct of sylvius, Obliteration of sulcus spaces, Dilated lateral and 3rd ventricle with normal size of 4th ventricle, No abnormal intercerebral calcification/focal lesion
- Chromosomal analysis (Fig. 5): Karyotype 46, XY with apparently normal chromosomes.
- Fluorescence in Situ Hybridization (FISH) analysis: (Fig. 6) No deletion observed in 22q 11.2 region.

Thus these were rare cases of physical and behavioral phenotypes where chromosomal analysis showed normal karyotyping and no interstitial deletions. However, the anatomical and radiological findings closely supported the diagnosis of: "ACROCALLOSAL SYNDROME". The diagnosis was based on characteristic phenotype, in particular salient craniofacial and skeletal abnormalities and neuroimaging.

Fig. 3 – Intraoral examination.

3. Discussion

The corpus callosum or the probst bundle is a band of white matter which connects the two cerebral hemispheres. Disturbance in this bundle may occur during the 3rd to 12th week of pregnancy which may lead to rare congenital disorders. The corpus callosum may fail to develop normally leading to its complete (agenesis) or partial (hypogenesis) absence. Sometimes it also can be malformed (dysgenesis) or underdeveloped (hypoplastic). Callosal disorders have been listed under ciliopathies. Ciliopathies are an emerging class of diseases caused by dysfunctional molecular mechanism in the primary ciliary structures of cell organelles of the body. The signs and symptoms of callosal disorders may vary depending on the severity of the disease. Some of the common characteristics include hypotonia, poor motor coordination, delay in motor milestones, delayed toilet training, difficulty in deglutition and mastication and low

Fig. 2 – Pedigree of the patients.

Fig. 4 – CT scan report.

perception of pain. They also have dimorphic head and facial features, cognitive disabilities, social snags and may be mentally handicapped. Though maternal nutritional deficiencies or infections or metabolic disorders have been associated with this disease, no specific etiology has been recorded.²

Aicardi syndrome was first coined by Jean Aicardi in 1965. It is a rare genetic disorder characterized by infantile spasm, corpus callosal agenesis and chorioretinal lacunae. Other features of Aicardi syndrome include microcephaly, polymicrogyria, porencephalic cysts and enlarged cerebral ventricles due to hydrocephalus.³ Although the two sibs did not give a history of infantile spasm or chorioretinal lacunae, features like developmental delay of significant degree, moderate intellectual disability, corpus callosal disturbance, microcephaly and enlarged cerebral ventricles due to hydrocephalus were consistent with our cases.

Andermann syndrome is an autosomal recessive motor and sensory neuropathy with agenesis of the corpus callosum associated with developmental and neurodegenerative defects and dysmorphic features. This syndrome has been reported among sibs-males or females.⁴ Mild mental retardation and mild facial dysmorphism including hypertelorism, short nose, broad nasal root, high arched palate, elongated facies and ptosis were some of the common findings which were consistent with the present case report. However, the sibs had been born to non consanguineous parents.

Shapiro syndrome, a rare disorder, consists of paroxysmal hypothermia, hyperhydrosis and agenesis of the corpus callosum.⁵

Digeorge syndrome is caused by deletion of chromosome 22q11.2. It is also associated with birth defects such as congenital heart disease, defects in the palate, neuromuscular problems, learning disabilities, mild differences in facial features, and recurrent infections.⁶ Although the sibs had some similarities with this syndrome, FISH ruled out the chromosomal deletion.

Greig cephalopolysyndactyly syndrome is a rare pleiotropic, multiple congenital anomaly syndrome. The primary findings include hypertelorism, macrocephaly with frontal bossing, and polysyndactyly.⁷ The rarity of the disease (1–9/1,000,000), absence of polysyndactyly and central nervous system anomalies helped to exclude this condition.

Acrocallosal syndrome is a rare, heterogenous, autosomal recessive syndrome characterized by corpus callosum agenesis, polydactyly, multiple dysmorphic features, motor and mental retardation and other symptoms.¹ The term acrocallosal refers to the involvement of the acra (fingers and toes) and the corpus callosum. This syndrome has been reported in both males and females. Though the cause of this disorder is unknown, prenatal infections or viruses like rubella, chromosomal abnormalities, toxic metabolic conditions and blockage of the growth of the corpus callosum can interfere with this development. The disruptions in the development of the corpus callosum occur during the 5th to 16th week of

Fig. 5 – Chromosomal analysis.

pregnancy. The major characteristic of this disorder is the hypoplasia or agenesis of the corpus callosum and distinctive malformations of the skull and craniofacial region. This syndrome includes a prominent forehead, occiput, midface hypoplasia, hypertelorism, delayed closure of anterior fontanelle.¹ There is moderate to severe mental retardation with delay of neuromotor development, abnormal gait and speech.^{8,9} Studies involving the affected families have suggested an autosomal recessive pattern of inheritance and that each child will have a 25% risk of being affected.¹⁰ Associated symptoms and findings maybe variable, including among affected members of the kindred.^{11,12} Depending on the pregnancy complications and severity of the disorder the lifespan of the subjects range form stillbirth to relatively normal lives with some percentile of developmental delays.

According to Courtens et al. it was mandatory that a minimum 3 out of the 4 criteria fulfilled the criteria of diagnosis.^{1,6–11,13}

In India, only four cases of acrocallosal syndrome have been reported so far thus making this a rare phenomena. Although the array of clinical manifestations in sibship report was consistent with the spectrum of this syndrome, non-consanguineous healthy parent history contributes to the uniqueness of this case study report.

Fig. 6 – Fluorescence in Situ Hybridization (FISH) analysis (Centre for Genetic Health Care, Mumbai).

4. Conclusion

Disorders of the corpus callosum are not illnesses or diseases, but abnormalities of brain structure. Estimates of the frequency of corpus callosum disorders (particularly agenesis of the corpus callosum or ACC) vary greatly. Prenatal ultrasound or fetoscopy can be attempted to detect duplication of the digits and cerebral malformations which maybe informative for a woman who already had an affected child and has a 25% risk of having another affected child.¹² Orodonal management of such patients involves a multidisciplinary approach. Early recognition and intervention can help in enhancing the quality of life. Genetic counseling is of prime importance. Parent counseling for dental and oral hygiene maintenance, pediatric expert opinion and guidance, ophthalmic and ENT specialists' advice, physiotherapy, speech therapy and child psychologist and psychiatric counseling and periodic follow up is recommended.

Conflicts of interest

All authors have none to declare.

1. The differential diagnosis like ' DiGeorge Syndrome, Aicardi, Anderman (CCA with neuropathy), Shapiro (spontaneous periodic hyperthermia), Greig's Cephalopolysyndactyly syndrome etc have been suitably addressed in detail in the section on discussion.
2. The objective of this article was to facilitate oral physicians to identify such disorders and administer suitable orodental management during their clinical practice. For this a detailed and systematic case history protocol is mandatory in arriving at the closest diagnosis possible.
3. Suitable refinement of the text has been done.
4. Regarding history, the respondent of the sibs had stated that the upper front teeth had been removed earlier in an attempt to correct anterior crowding. Thus examination revealed missing 12 and 21.

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