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Review Article

Genetic alterations in syndromes with oral manifestations

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ABSTRACT

Ever since Gregor Johan Mendel proposed the law of inheritance, genetics has transcended the field of health and has entered all walks of life in its application. Thus, the gene is the pivoting factor for all happenings revolving around it. Knowledge of gene mapping in various diseases would be a valuable tool in prenatally diagnosing the condition and averting the future disability and stigma for the posterity. This article includes an array of genetically determined conditions in patients seen at our college out-patient department with complete manifestation, partial manifestation and array of manifestations not fitting into a particular syndrome.

Key Words: Down's syndrome, marfan's syndrome, Rothmund Thomson syndrome

INTRODUCTION

Syndrome is the association of several clinically recognizable features, signs, symptoms, phenomenon or characteristics that often occurs together, so that the presence of one feature alerts the physician to the presence of others.

Knowledge of a syndrome and its molecular genetics is essential for primary health care professionals to document dysmorphic features in a child. The entire human lexicon is encoded in approximately 10,000 different genes assembled to constitute the human genome. The first step in understanding the molecular genetics of a syndrome is to identify the "phenotype" followed by "gene mapping."

Understanding the molecular genetics of a syndrome is to identify and positionally clone the gene associated with the malformation, which will improve diagnosis, prevention and therapy. These scientific advances translate into improved health, disease prevention, smarter diagnostics and innovative therapeutic approaches to craniofacial dysmorphogenesis.[1] Sensitivity and specificity of molecular based diagnosis have revolutionized how diseases and disorders are defined.[2]

Craniofacial symptoms may have similar clinical phenotypes that are caused by mutations in a gene. Identical mutations within a gene can cause widely different clinical phenotypes.[3] Mutations in different genes can cause similar clinical phenotype. Molecular based diagnosis has given a way to identify these disorders. Prior to these techniques, syndromes were characterized based on characteristic features. Although the most common can be identified, many clinical characteristics do not readily fit into a particular syndrome or it was uncommon and dentists were unaware of its existence.

In our study, we made an attempt to analyze an array of subjects with complete and/or partial manifestations or manifestations not fitting into a particular syndrome and correlate with the genes responsible by reviewing the literature thoroughly for each syndrome. These phenotypes were correlated genetically. All subjects had reported to College of Dental Surgery, Saveetha University over a period of 2 years. A thorough genetic history and literature review was collected

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and the possible gene mapping was arrived at from literature.

Case 1

A male patient aged 10 years with mental retardation reported to our out-patient department with the chief complaint of decayed tooth. Extraoral examination revealed brachycephaly, oblique palpebral fissure, depressed nasal bridge, short neck, and gap between toes, short broad hands with simian crease and lip incompetence [Figure 1a-c].

Intraoral examination revealed a high arched palate with crowding of teeth [Figure 1d], and macroglossia. These phenotypical features were analyzed and were found to have complete manifestations of Down's syndrome such as abnormal facial and skeletal features[4] and mental retardation.[5]

Discussion

Individual phenotype can often be assigned or mapped to specific regions of the genome. Down's syndrome critical region (DSCR) genes play a critical role. DSCR1 gene on chromosome 21 is a development regulator gene and is involved in neurogenesis. It's overexpression contributes to brain abnormalities.[2] DSCR1 is highly expressed in the brain and heart and it is suggested as the candidate for pathogenesis of Down's syndrome, in particular, for mental retardation and cardiac defects.[6]

Congenital heart disease of patient was identified and candidate gene was mapped as SH3BGR (21q 22.13) in Down's syndrome heart critical region, which has a role in heart morphogenesis.[7-9] Deoxyribonucleic acid (DNA) microarray analysis of gene expression in amniotic fluid cells revealed that GSTT1 glutathione-s-transferase theta-1 (22q 11.23) gene was the only gene

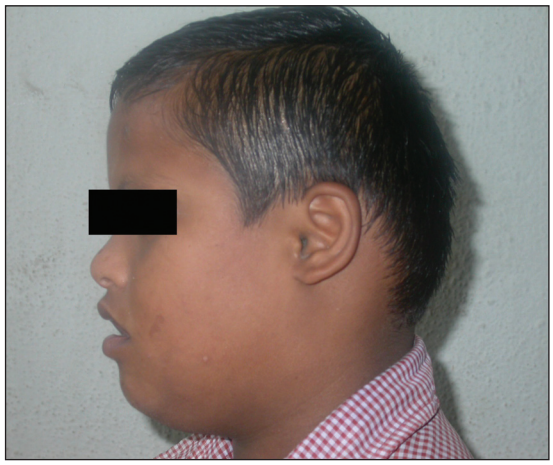

Figure 1a: Lateral profile revealing depressed nasal bridge, lip incompetence and short neck

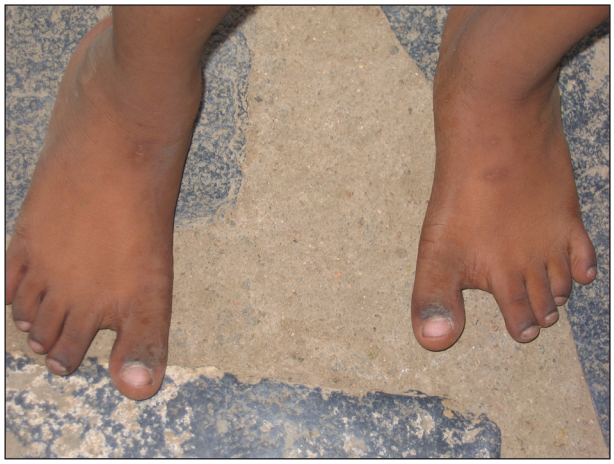

Figure 1b: Picture revealing gap between toes

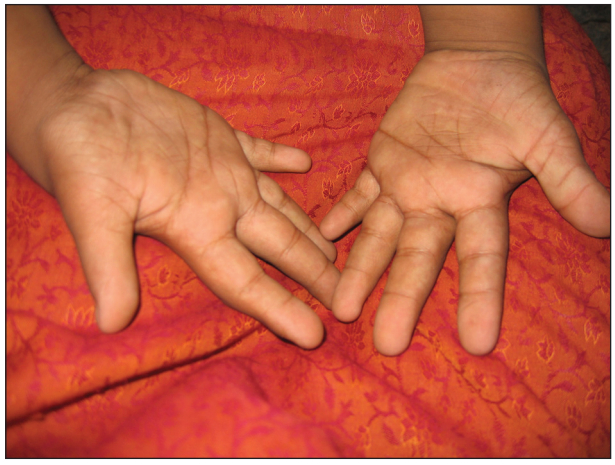

Figure 1c: Picture revealing short broad hands with simian crease

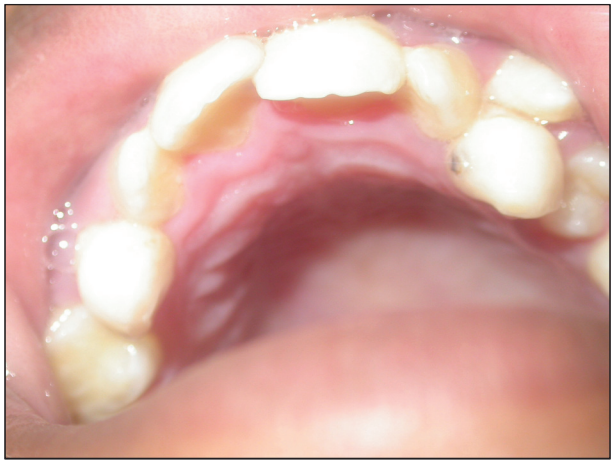

Figure 1d: Intra oral picture showing high arched palate with crowding of teeth

up regulated in Down's syndrome patients.[10] DSCR4 (21q22.12) was identified as nests that map to 1.6MB DSCR and is predominantly expressed in placenta.[11]

An area of approximately 5MB between loci D21s58 and D21s42 has been associated with mental retardation and facial features. The sub regions D21s55 and MX1, the latter in band 21q22.3, have been associated with several morphological features including oblique eye fissure, gap between toes, short stature and characteristic of dermatoglyphics.[12] SIM2 gene is a transcriptional regulator that operates as an important determinant of the central nervous system and is a candidate gene for mental retardation.[13] DSCR2 was identified between DNA marker D21s55 and MX1, by Vidal-Taboada *et al*.[14]

Oral manifestations

Patients with Down's syndrome may present with delayed eruption of both primary and permanent dentitions. Microdontia or enamel hypocalcification/hypoplasia may also be present. Patients are also more likely to have congenitally missing teeth. Characteristically, patients with Down's syndrome have increased resistance to caries, although they are more prone to gingivitis and periodontitis. V shaped palate, incomplete development of mid-face and soft palate insufficiency may also be noticed. Lips are broad, irregular, fissured and dry. An open mouth with a protruding tongue is observed. The tongue appears relatively large because of the small oral cavity. Occasionally, true macroglossia may be present. Cleft of lip/palate may be present.[15]

Treatment

Management of dental problems in Down's syndrome patients should focus at preventive care through frequent recalls, dietary counseling, topical fluoride application and use of mouth rinses to minimize the incidence of caries and periodontal disease.

Case 2

A female patient aged 14 reported to our out-patient department for painful teeth. On extraoral examination, her physique was abnormal with tall stature [Figure 2a], dolichostenomelia (positive wrist sign) and dolichocephalic face [Figure 2b], arachnodactyly (spidery finger and long digits) [Figure 2c and d]. Intraorally, high arched palate along with decayed tooth was identified.

Cardiac evaluation revealed aortic dilatation. These phenotypical features had partial manifestations of Marfan's syndrome (MFS). Appropriate genes were mapped by reviewing the literature.

Discussion

MFS is an inheritable disorder of fibrous connective tissue, which shows striking pleiotropism and clinical variability. Cardinal features occur in three systems-skeletal, ocular and cardiovascular.[16-20]

All cases of true MFS appear due to mutation in the fibrillin-1 (FBN1) gene, located on chromosome 15.[19,21-23] This statement was supported by observations that the classic Marfan's phenotype co-segregate with intragenic or flanking marker alleles in all families tested and significant mutations identified.[21]

FBN1 is the main component that forms tissues like aortic media with elastic fibers.[23] More than 500 FBN1 mutations have been found in MFS. Buntinx *et al*. described aortic dilatation in a neonate as a feature of MFS.[24]

Dietz *et al*. confirmed the assignment of MFS gene to chromosome 15, but established a centromere location defined by markers d15s25 and D15s1: 15q15-q21.3[25] Sarfarazi *et al*. concluded that the MFS locus was between D15s48 and D15s49.[26] Linkage studies using polymorphic markers within the fibrillin locus demonstrated tight linkage between Marfan phenotype and fibrillin.[27]

Dolichostenomelia and arachnodactyly appear to represent longitudinal growth of tubular bones in limbs and fingers. Unleashing of the normal control of longitudinal growth as a result of a defect in the fibrous elements of periosteum was postulated early by Mc Kusick.[28] Novel mutations were identified in the FBN1 gene by Palz *et al*. and Tiecke *et al*.[29,30]

Westling *et al*. quantified craniofacial morphology through evaluation of dental casts and lateral cephalograms in Marfan's patients and illustrated crowded teeth, high arched palatal vault and overbite.[31] By direct immunofluoresence, Godfrey *et al*. demonstrated deficiency of elastin associated with microfibrillar fibers in Marfan's skin.[32] In cultured dermal fibroblasts treated with recombinant FBN1 Booms *et al*. observed up regulation of matrix metalloproteinases (MMPs), MMP-1 and MMP-3. They suggested that fibrillin fragments themselves might have pathogenic effects by leading to up regulation of MMPs, which in turn might be involved in the progressive breakdown of microfibrils thought to play a role in MFS.[23]

Figure 2a: Picture revealing long stature

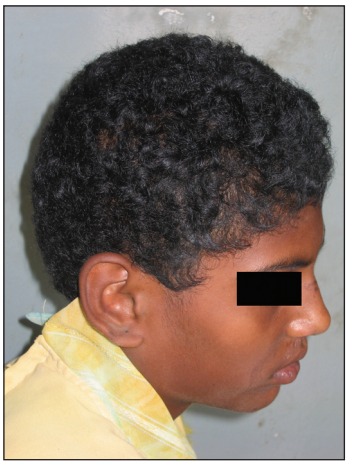

Figure 2b: Picture revealing dolichocephalic face

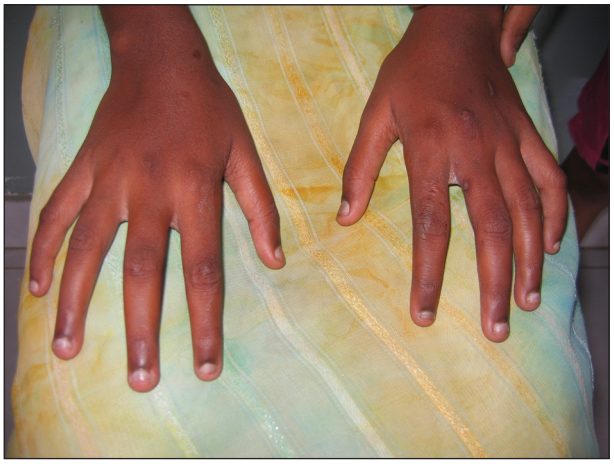

Figure 2c: Picture revealing spidery fingers

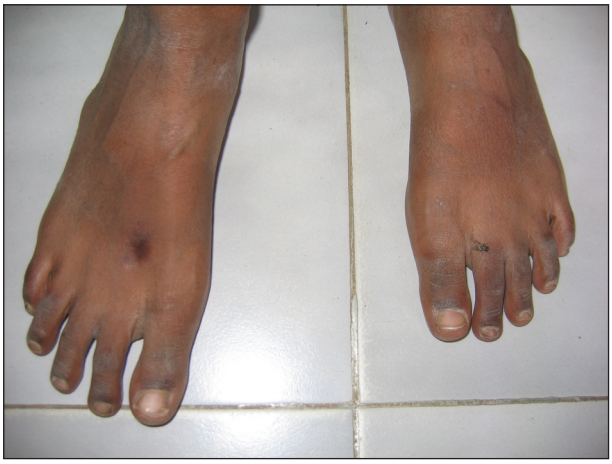

Figure 2d: Picture revealing long digits

Oral manifestations

Patients with MFS tend to show V-shaped palate, which might result in other dental complications such as crowding of teeth, crossbite, etc. Patients are also at a higher risk for developing caries and periodontal disease. Temporomandibular joint problems may also be present. Cleft palate and bifid uvula may be noticed. The teeth have been noted to be long and narrow in many instances.[15]

Treatment

Orthodontic intervention for management of crowding and crossbite is necessary. Carious teeth have to be treated appropriately. Proper periodontal evaluation is essential before opting for dental implants.

Case 3

A male patient aged 23 years, reported to our college with the chief complaint of halitosis. On examination, he had striking clinical features such as exophthalmos, hypertelorism, strabismus [Figure 3a], depressed nasal bridge, hypoplastic maxilla, relative mandibular prognathism, short upper lip [Figure 3b]. Intraorally, high arched palate was present [Figure 3c]. These features showed complete manifestations of Crouzon syndrome. The phenotypic manifestation was correlated with the genotypes collected from the literature. The candidate gene mutation was fibroblast growth factor receptor 2 (FGFR2) with the loci of 10q26.

Discussion

Crouzon syndrome is an autosomal dominant condition, causing premature fusion of cranial sutures (craniosynostosis). In many reported cases of Crouzon syndrome, mutations were demonstrated in FGFR2 gene.[33-35] FGFR2 is a member of tyrosine kinase receptor super-family, having affinity for peptides that signal the transduction pathways

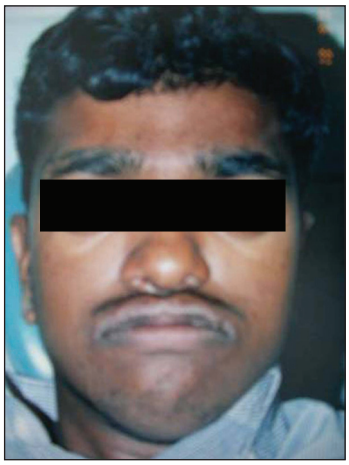

Figure 3a: Picture revealing exophthalmos, hypertelorism and "V" strabismus

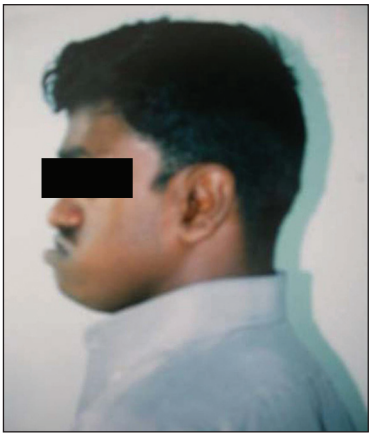

Figure 3b: Picture revealing depressed nasal bridge, hypoplastic maxilla, relative mandibular prognathism and short upper lip

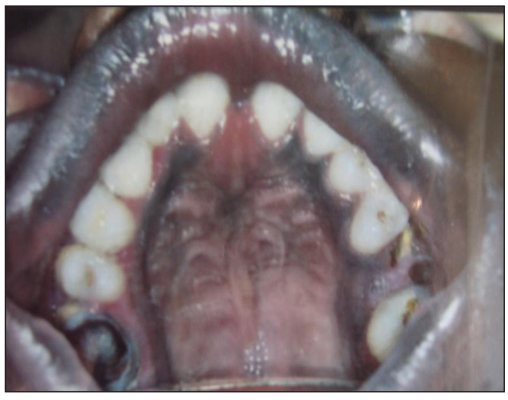

Figure 3c: Intra oral picture revealing high arched palate

for mitogenesis, cellular differentiation and embryogenesis.[36] The gene for Crouzon craniofacial dysostosis has been mapped to the long arm of chromosome 10.[37]

Oral manifestations

Maxillary hypoplasia, narrow high arched palate and cleft lip/palate can be seen in patients with Crouzon syndrome. Dental problems like hypodontia, crowding of teeth may also be present.[15]

Treatment

Multidisciplinary approach involving orthodontic, prosthodontic and surgical planning is essential.

Case 4

A female patient aged 10 years, reported to our college with the complaint of halitosis and decayed tooth. Clinical examination revealed no obvious changes [Figure 4a]. An orthopantomograph revealed unilocular radiolucencies with scalloped margins in all the four quadrants of maxilla and mandible [Figure 4b]. Biopsy was carried out and histopathology showed a cystic lining comprised of parakeratinized epithelium with palisading basal layer along with connective tissue wall [Figure 4c], suggestive of odontogenic keratocyst (OKC).

A diagnosis of multiple OKC was arrived at, based on these findings. However, she did not have any other manifestations relating to a Nevoid Basal cell Carcinoma Syndrome (NBCCS). Chest radiograph did not show any relevant features [Figure 4d]. Gene mutation leading to sporadic OKC was mapped to the Patched (PTCH) gene, a tumor suppressor gene at 9q22.3.

Discussion

OKC is a benign cystic lesion of the jaws that occurs sporadically or in association with NBCCS. Somatic mutation of PTCH gene is found in sporadic OKCs.[38] The human homolog of drosophila segment polarity gene, PATCHED encodes a transmembrane protein PTCH that is a receptor for the morphogen Sonic HedgeHog (SHH).[39] PATCH acts in opposition to hedgehog signaling and controls cell fate, patterning and growth of numerous tissues including teeth.[38,40] PTCH gene is mapped to chromosome 9q22.3-q.31.[41,42] Loss of heterozygosity (LOH) on chromosome 9q22.3 had been described as a significant factor in sporadic and syndrome associated OKC.[43-45] These reports strengthen the participation of PTCH in the formation of OKC. So, the dysregulation of PTCH/SHH signaling pathway in the interaction between the epithelium and mesenchyme may induce the formation of keratocyst.[38]

The two-hit hypothesis proposed by Knudson *et al*.[46] was substantiated by Levanat *et al*.[45] and Bale[47] to explain the pathogenesis of basal cell carcinoma and

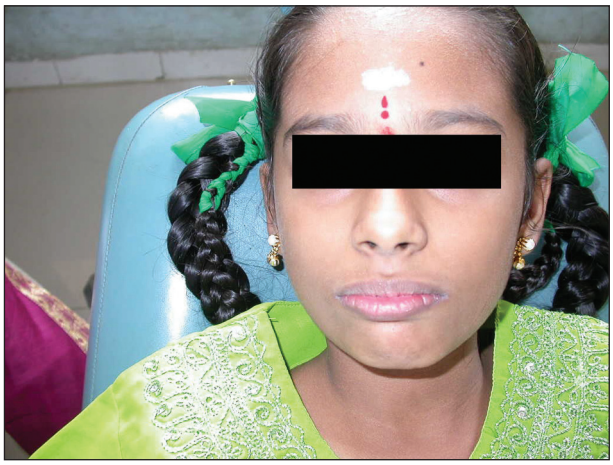

Figure 4a: Clinical picture

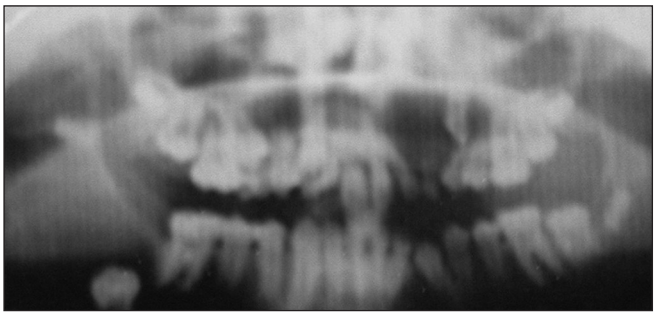

Figure 4b: Orthopantomograph revealing unilocular radiolucencies in four quadrants of maxilla and mandible

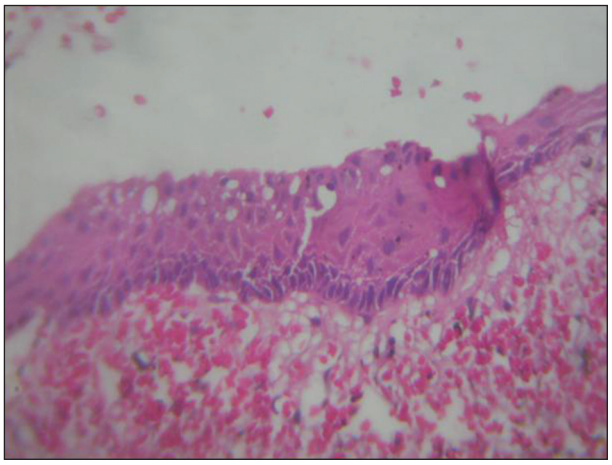

Figure 4c: Histopathology revealing cystic epithelium with palisading basal cells and a connective tissue wall, typical of odontogenic keratocyst (H and E, ×10)

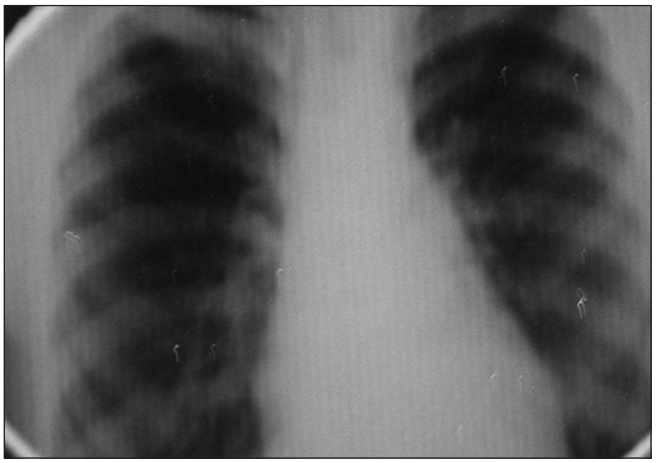

Figure 4d: Chest radiograph did not reveal any abnormality

OKC. Sporadic OKC may arise from susceptible cells in which two somatic hits have occurred, one of which manifests as an allelic loss. Sidransky proposed that PTCH gene might function as a "gatekeeper gene." An activator of gatekeeper gene is required for passing the genetic threshold of the neoplastic process in a given tissue.[48] Mutation inactivation of PTCH leads to overexpression of mutant transcript owing to failure of negative feedback mechanism.[49,50]

Barreto *et al*. suggested that OKC might arise with haplo insufficiency of PTCH.[51] Up regulation of PTCH and Glioma associated oncogene (GLI-1 protein) was demonstrated in both NBCCS and OKC. The pattern of PTCH expression matched the PTCH transcript pattern previously reported in basal cell carcinoma and appears sufficiently characteristic in OKCs to allow differentiation between syndromic and non-syndromic cysts.[52] Studies also suggest that SHH signaling might be involved in the pathophysiology of OKCs. PTCH mutations and disturbed SHH signaling are not only related to syndromic OKCs, but also to sporadic OKCs.[53-55]

Nawshad *et al*., in their study, found that 14% of sporadic OKCs exhibited significant LOH. LOH of the PTCH gene locus supported the view that PTCH may be responsible for OKC development. The authors suggested that the expression of tumor suppressor PTCH and the oncogene SHH might cause loss of PTCH function and lead to OKC development.[56]

Oral manifestations

Multiple OKCs are the most constant and common anomaly in NBCCS, occurring in 65-100% of patients, and usually appearing by the second or third decade of life. OKC development frequently antedates the syndromic basal cell nevi, and occurs more frequently in the mandible. Jaw swelling, dull pain, and intraoral drainage of cystic contents are common signs and symptoms. Recurrence of OKCs is more common,

even after enucleation. Such OKCs associated with NBCCS have been known to transform into ameloblastomas or squamous cell carcinoma. Other oral manifestations in NBCCS include malocclusion, mandibular prognathism, ameloblastoma, cleft lip and/or palate and hyperplasia of the mandibular coronoid process.[15]

Treatment

Early diagnosis and frequent follow-up is essential in patients with NBCCS. Multiple OKCs should alert the dentist to the possibility of this syndrome and trigger a thorough investigation. An annual dental panoramic radiograph has been suggested between the ages of 8 years and 40 years for the potential detection of OKCs.

Case 5

A male patient aged 21 years reported to our institute with the chief complaint of loss of many teeth. Clinical examination revealed features such as brachycephaly [Figure 5a], cataract, skeletal abnormality of the fingers and dermatosis [Figure 5b]. Premature exfoliation of teeth and partial anodontia was present. Radiographs revealed taurodontism [Figure 5c]. An analysis of this array of phenotypic features revealed that the patient had only partial manifestations not fitting into any particular syndrome. The phenotype was correlated with genotype from the literature and the possible mapping was arrived as the RecQ like-protein 4 (RECQL4) gene at 8q24.3.

Discussion

The RECQL4 is a DNA repair gene. The phenotypic and genotypic correlations in our patient pointed us more towards a diagnosis of Rothmund Thomson syndrome (RTS) and hereditary dermatosis. Starr *et al*. emphasized on non-dermatological features such as hypodontia, soft-tissue cataract, proportionate short stature, hypogonadism, anemia and osteogenic sarcoma in RTS.[57] Orstavik *et al*. described a case with poikiloderma on face and extensor surfaces of the limbs, a hallmark symptom of RTS.[58] This feature helps to differentiate RTS from the closely related Rappadilino syndrome. Kitao *et al*. described RTS, also known as poikiloderma congenitale as a rare autosomal recessive genetic disorder characterized by abnormalities in skin, skeleton, juvenile cataracts, premature aging and predisposition to neoplasia.[59]

Cytogenetic studies of cells from affected patients have shown genomic instability, often associated with chromosomal rearrangement causing acquired somatic mosaicism. It has been suggested that the mutation of RECQL 4 at chromosome 8q24.3 is responsible for RTS.[59] Wang *et al*. analyzed a cohort of RTS patients and proposed that it is characterized by poikilodermatous rash starting in infancy, short stature, skeletal abnormalities, juvenile cataracts and

Figure 5a: Clinical picture revealing brachycephaly

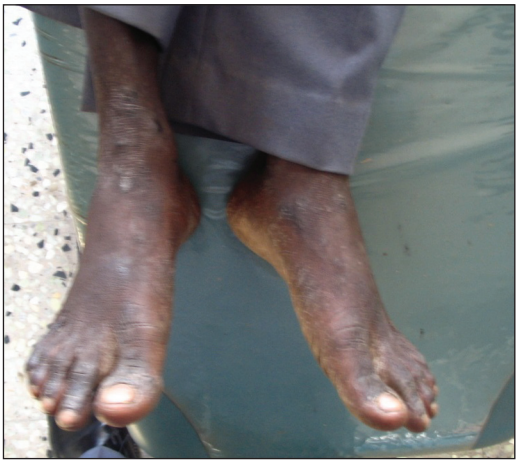

Figure 5b: Clinical picture revealing dermotoses in the legs

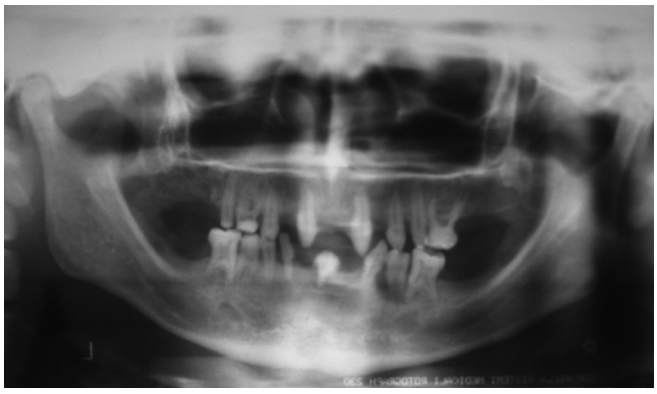

Figure 5c: OPG revealing partial anodontia and taurdontism

pre-disposition to cancer.[60] Hall *et al*. reported that the clinical features of RTS include skin changes, defective nails and teeth, sensitivity to sunlight and juvenile cataracts and emphasized on considering RTS as diagnosis for any patient with extremely short stature, associated with skeletal anomalies with an early onset of typical cutaneous change.[61]

Gangloff *et al*. suggested that defects in RTS may be a consequence of unrestrained recombination due to defects in SRS 2, which encodes another DNA helicase, involved in maintenance of genomic stability.[62] Gene mutations in RTS patients belong to RECQL gene.[63] The RECQL 4 helicase gene is a member of RECQL gene family. The skeletal malformations in RTS patients propose special role for RECQL 4 in bone development.[64] Most RECQL 4 mutations found in RTS patients represent non-sense or frame shift mutation, resulting in a truncated polypeptide.

Oral manifestations

Microdontia, multiple crown malformations, delayed and ectopic eruption, supernumerary and congenitally missing short, conical roots have been reported. It is frequently associated with early onset periodontitis.[15]

Treatment

Since patients with RTS are more prone to develop periodontitis and root resorption, factors such as masticatory stress, fixed prostheses, etc. should be avoided.

CONCLUSION

A careful examination of intraoral findings may reveal striking features, which could be correlated with other clinical findings and thereby used to predict various syndromes affecting the head and neck region. Identification and diagnosis of such syndromes is very essential as it may bear a direct effect on treatment planning for the patient.

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