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GORLIN-GOLTZ SYNDROME: A REVIEW ON ITS CLINICOPATHOLOGICAL ASPECTS

Oral Pathology

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ABSTRACT

Gorlin-Goltz syndrome is an uncommon multisystemic disease with an autosomal dominant trait, with complete penetrance and variable expressivity, though sporadic cases have been described. The pathogenesis of Gorlin-Goltz syndrome is attributed to abnormalities linked to long arm of chromosomes 9 and loss or mutation of human patched gene. It is characterized by multiple Odontogenic Keratocyst of the jaws, multiple basal cell carcinoma and various skeletal deformities. Diagnosis is based on the various major and minor criteria. Here we present a detailed review article on the various clinicopathological aspects of this syndrome.

KEYWORDS

Gorlin-Goltz Syndrome, PTCH Gene, Odontogenic Keratocyst and Basal Cell Carcinoma.

INTRODUCTION

Gorlin & Goltz syndrome, is an uncommon autosomal dominant inherited disorder, which is characterized by numerous basal cell carcinoma, multiple keratocyst and mucoskeletal malformations. It is also known by various names Basal Cell Nevus Syndrome, Nevoid Basal Cell Carcinoma Syndrome, multiple basal epithelioma, Jaw cyst and Bifid rib syndrome. This syndrome is known to be caused by mutations in tumour suppressor called PTCH found on the chromosome arm 9q.[1]

This syndrome was first reported by Jarisch and White in 1894 and later it was reported by Binkely and Johnson in 1951.[2] Howell and Caro in 1959 suggested a relationship between basal cell epithelium and developmental malformations. Robert J. Gorlin and Rober W. Goltz described this unique syndrome with multiple OKCs, Basal Cell Carcinomas, Jaw cysts and Bifid Ribs.[3]This syndrome with its distinguishable features is quite rare. Diagnosis is based on the established major and minor clinical and radiological criteria and ideally confirmed by deoxyribo nucleic acid analysis. The radiographic finding of this syndrome is easily identifiable on Orthopantomogram, chest X-ray and computed tomography scans. These investigations prompt an early verification of the disease, which is very important to prevent recurrence and better survival rates from the co-existent diseases. In this review paper we discuss the clinical manifestations of this syndrome along with the diagnostic aspects.

History

This syndrome existed during Dynastic Egyptian times, as shown by findings compatible with the syndrome in mummies dating back to 1,000 B.C. Though this syndrome was first reported in the year 1894 by Jarisch and White in patient with multiple BCCs, scoliosis and learning disabilities.[4][5] Later in the year 1939, Straith described a case with multiple basocellular carcinomas and cysts.[6]Binkely and Johnson in 1951 and Howell and Caro in 1959 observed a relationship between basal cell epitheliomas and developmental malformations.[7][8] Gross in 1953 presented a case with additional signs such as synostosis of the first left rib and bilateral bifurcation of the 6th ribs.[9]

In 1960, Robert James Gorlin and William Goltz discovered the classical triad that established the diagnosis of this syndrome. The triad comprised of multiple basocellular epitheliomas, Odontogenic Keratocyst of the jaws and bifid ribs.[10] Later on this triad was modified by Rayner et al., who established that cysts had to appear simultaneously, either with the calcifications of flax cerebri, or with palmer and plantar pits, in order to disembark at a diagnosis.[11] The association of palmar and plantar pits with syndrome was first described by Bettley and Ward.[12][13]

Prevalance rate

Farndon et al. reported a minimum prevalence of 1 in 57,000 people.[14] In the year 1994 Shanley had reported that the prevalence of NBCCS has been estimated from 1 in 57,000 to 1 in 164,000 , but later Gorlin (1999) reported the prevalence to be about 1 per 60,000.[15][16]A prevalence from 1/57000 to 1/256,000, with a male to female ratio of 1:1 has been described.[17][18] It is considered to be both a sporadic and familial incidence.[14] Though these syndrome are seen in younger age group, they are commonly expressed between the ages of 17 years and 35 years.[19]

Etiology

Mutations in the human patched gene (PTCH1 Gene), which is part of the hedgehog-signalling pathway, is the molecular basis of this syndrome.[20] This gene was isolated as the human homologue of Dorsophila segment polarity PTCH1 gene, mapped to the long arm of chromosome 9q22.3-q31 with no heterogenecity.[21][22]This gene has been found to play an important role in tumour suppression, embryonic structuring and cellular cycle. Mutation in this gene results in loss of control of many genes playing an important role in organogenesis, carcinongenesis and odontogenesis and thus resulting in Gorlin-Goltz syndrome.[20][23]The PTCH1 gene consists of 23 exons, which spans 34kb. It encodes a transmembrane glycoprotein composed of 1447 ammino acids, with 12 transmembrane domains and two large hydrophilic extracellular loops with Sonic Hedgehog (SHH) ligand binding occurs. However, mutations in other genes such as Patched 2, Smmothened (SMO) and sonic hedgehog (SHH) have reported in isolated cases of basal cell carcinoma and medulloblastoma.[22]

Features

Clinical manifestations of this syndrome can be grouped into the following nine categories.[24][25]

Cutaneous Manifestations includes Basal cell nevus/carcinoma (50-97%), other benign dermal cysts and tumors,(21%) palmar / plantar pitting (90%), palmar and plantar keratosis and dermal calcinosis.

Craniofacial Anomalies – clacification of flax (37-79%), tentorium cerebellum calcification (3%), bridged sella turcica (21%), macrocephaly (40%), brachycephaly, frontal bossing (25%), pearietal and temporal bossing and coarse face (50%)

Skeletal anomalies –Polydactyly (3%), syndactyly, scoliosis(15%), hemi vertebrae or other vertebral defects, flames shaped lucencies of hand and feet, spina bifida (3%), cervical / bifurcated /fused/splayed/absent/ rudimentary ribs (26%), brachymetacarpalism and shortened forth metacarpal (12%) Cardiac fibroma is common.

Opthalmic anomalies- Hyperteloris (40%), dystopia canthorum, congenital blindness (15%), internal strabismus (15%), congenital amaurosis, exotropia, glaucoma (3%), ptosis and coloboma (3%).

Neurological anomalies- Mental retardation (6%), dural calcification, bridiging of sella, agenesis of corpus callosum, congenital hydrocephalus (3%), medullablastoma (3%-5%) Sexual anomalies: Hypogonadism (3%), uterine and ovarian fibromas, calcified ovarian cysts (3%) and supernumerary nipple.

Dentofacial anomalies: multiple Odontogenic keratocyst (75-100%), maxillary Hypoplasia, Mandibular prognathism, high arched palate or prominent palatine ridges (40%), cleft lip or palate, impacted teeth, agenesis, ectopic teeth and malocclusion.

Diagnostic aspects of Gorlin-Goltz syndrome:

As there is variability of expressivity in Gorlin-Goltz syndrome, diagnosis becomes difficult. Early diagnosis of Gorlin-Goltz syndrome is crucial for the affected children and their families, considering the risk of developing malignancies such as medulloblastoma and aggressive skin cancers. [26] A negative family history could hinder the early clinical diagnosis of patients with Gorlin-Goltz syndrome.

The diagnostic criteria for Gorlin-Goltz syndrome has been given by Evans et al (1991)and modified by Kimonis et al (1997). According to Kimonis, diagnosis can be established only when two major, or one major and two minor criteria are present.[15][18]

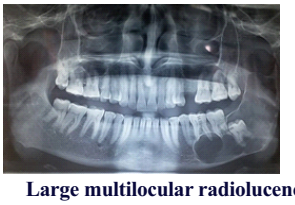
Table – 1: DIAGNOSTIC CRITERIA BY EVANS ET AL. IN 1991

Major Criteria	Minor Criteria
More than 2 BCCS, one BCC in patients younger than 30 years of age or more than 10 basal cell nevi.	Congenital skeletal anomaly (e.g. bifid rib, splayed, fused or missing rib, or bifid wedged or fused vertebra)
Any Odontogenic Keratocyst or Polystotic bone cyst	Occipital-frontal circumference greater than 97 percentile, with frontal bossing
Three or more Plantar or Palmar pits.	Cardiac or ovarian fibromas
Ectopic calcification in patients younger than 20 years of age. (Lamellar or early falx cerebri calcifications)	Lymphomesentric cysts
A positive family history of NBCC	Congenital malformations such as cleft lip/palate, polydactylism or eye anomaly

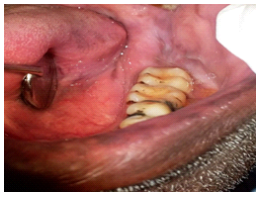
Table - 2: DIAGNOSTIC CRITERIA BY EVANS ET AL. IN 1997

Major Criteria	Minor Criteria
More than 2 BCCs or one BCC in patients younger than 20 years of age.	Macrocephaly
Odontogenic Keratocysts of the jaws (proven by histologic analysis)	Congenital malformation (e.g. cleft lip or palate, frontal bossing, coarse faces and moderate or severe hypertelorism)
Three or more palmar or Plantar pits.	Other skeletal abnormilities (e.g.sprengel deformity, marked pectus deformity and marked syndactyly of digits)
Bilamellar clacification of Flax cerebri	Radiological abnormities (e.g. bridiging of the sella trucica, vertebral anomalies)
Bifid , fused , markedly splayed ribs.	Ovarian fibroma or Medulloblastoma
A first degree relative with NBCCs.	

Asymmetrical face due to swelling in body and ramus of the mandible

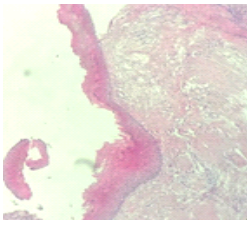


Large multilocular radiolucency with well corticated border and impacted third molar.

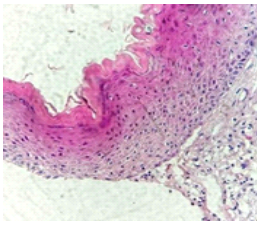


Mild expansion of buccal cortical plate and obliqteration of buccal vestibule.

CBCT shows osteolytic bony lesion and expansion and thining of buccal cortical plate.



Cystic epithelium with variable thickness, surface corrugation and detached cystic epithelium from capsule.



Ortho and parakeratinized corrugated epithelium with variable thickness.

Syndrome associated Odontogenic Keratocyst

These cysts are the constant features present in about 75% of cases with Gorlin-Goltz syndrome. The occurrence of OKC associated with syndrome is approximately a decade earlier than that of OKCs not associated with syndrome. [27]For non syndromic OKC the male to female ration is 1:0.62 while for syndromic OKC exhibits 1:1 ratio.[28]

OKC have found to exhibit greater predilection for mandible (69%) than maxilla (31%). In the mandible, 43% of OKC occur in the molar-ramus region, followed by incisor-canine 18% region followed by 12% in the molar tuberosity region and 3% in the premolar.[29]

In younger patients it has been found to be associated to unerupted teeth and cause tooth displacement along with root resorption. Usually asymptomatic but the most common features being pain, soft tissue swelling, and neurological symptoms such as parestesia of the lip or teeth can cause buccal and lingual cortical plate expansion.

Radiographically most OKCs are unilocular, presenting a well-defined peripheral rim. Multilocular radiolucency can also be observed, generally representing a central cavity having satellite cyst. Occasionally can be associated with an impacted tooth.

The wall of OKC is rather thin unless superimposed by inflammation. The lining epithelium is typically corrugated, rippled or wrinkled, along with remarkable thickness of the epithelium and a prominent palisaded, polarized basal layer of cells often described as having 'picket fence' or 'tombstone' appearance. On comparison with the non-syndromic OKC, syndromic OKC show more number of satellite cysts, solid islands of epithelial proliferating, intramural epithelial remnants, Odontogenic rests within the capsule, increased parakertinization and mitotic figures in the epithelium.

The cystic lining of OKC has been considered to have high mitotic index, hence high proliferative activity suggesting that the greater proliferative potential of epithelial lining leads to increase in the

expansion of the cyst. Various proliferative markers have been found to be positive in the lining of OKC such as Ki-67 and PCNA.

CONCLUSION

Gorlin Goltz syndrome is infrequent multisystem disease that is inherited in a dominant autosomal way, which shows a high level of penetrance and Variable self-expression. This syndrome is manifested by multiple defects involving the skin, nervous system, eyes, endocrine system, bones and oral cavity. Early diagnosis of Gorlin Goltz syndrome is important to reduce the severity of complications, such as skin and brain malignant tumours. Multiple Odontogenic Keratocyst ore one of the most common presentations which are more aggressive in nature along with higher reoccurrences rate in Gorlin Goltz Syndrome. Hence it is essential for the dental practitioner to consider Gorlin goltz syndrome as a possible diagnosis in all patients with multiple OKCs . The patients affected by this syndrome must be evaluated by Multidicipilnary approach.

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