

Gorlin Goltz Syndrome – Familial Inheritance – A Rare Case Series

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Abstract

Case Report

Gorlin- Goltz syndrome (GGS) is a rare, autosomal dominant syndrome caused by mutations of the patched gene (PTCH) on chromosome 9q (22.3-q31). It has a high level of penetrance and diverse expression, commonly associated with basal cell carcinomas, odontogenic keratocysts, palmar and/or plantar pits and falx cerebri calcifications. Two major findings or one major finding and two minor findings confirm the diagnosis. More than 100 minor criteria are mentioned in the literature for diagnosing GGS [1]. Despite diverse manifestations this syndrome is under reported, three cases of familial inheritance are reported in India till date. Early diagnosis and genetic counseling are essential for managing the syndrome. Total of 65 variants of PTCH mutations have been documented in literature [2], thus it would be not unanticipated for affected patients and their family members to have a spectrum of different genetic and clinical anomalies. There are only 64 cases reported till date since 1977 from India out of which this is the fourth case report showing the hereditary involvement. All the three previously reported cases had only two affected members but this is the first case series reporting three affected of GGS with familial inheritance (mother and both her children). Their diverse manifestation in each are reported here which alerts the clinician and gives an insight for prompt diagnosis and its early management.

Keywords: Gorlin- Goltz Syndrome, Odontogenic Keratocyst, Major Criteria, Minor Criteria.

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INTRODUCTION

Gorlin Goltz Syndrome (GGS) is an autosomal dominant disorder having prodigious penetrance. The syndrome exhibits inconsistent manifestations, caused by mutations in patched tumor suppressor gene (PTCH) [1]. Due to its inherent nature of unpredictable expressivity not all findings are present in each patient. The incidence of this syndrome is estimated to be 1 in 50,000 to 150,000 in general population but professed the may vary according to the geographical regions and is acknowledged to run in families with equal preference to both genders [2]. GGS is same as Nevoid Basal Cell Carcinoma (NBCC), jaw cyst bifid rib basal cell nevus syndrome and nevoid basalioma. The diagnosis is proven by the existence of two major criteria or one major criterion and two minor criteria. More than a hundred minor criteria have been described in the literature for establishing Gorlin-Goltz syndrome. The principal findings include the occurrence of Odontogenic Keratocyst (OKC), basal cell carcinoma, palmar or plantar pits and bilamellar calcifications of the falx cerebri [3]. It was first reported in 1894 by

Jarisch and White. Robert J. Gorlin and Robert W. Goltz described the diverse syndrome, consisting of the presence of multiple nevoid basal cell epitheliomas, jaw cysts and bifid ribs [4]. Despite manifold manifestations this syndrome is under-reported and only a handful of cases with familial inheritance have been reported to date. Early diagnosis, treatment as well as genetic counseling are essential for this syndrome. A case of Gorlin Goltz syndrome with familial inheritance (mother and both her children) and their assorted manifestations in each are reported here. This case report entices the valuable role of a clinician in early diagnosis and prompt management of this syndrome.

Case Report: Patient 1 (Mother)

- A 30 years old female patient visited the Department of Oral and Maxillofacial Surgery, with a chief complaint of pain and swelling on the left side of the lower jaw for 6 months which was slowly progressive. The patient did not affirm any other associated symptoms. Her medical, family, dental and personal histories were noncontributory.

- There was a diffuse swelling in the left lower third of the face with no secondary changes noted over it. On palpation, there was no local rise in temperature; the swelling was not tender, bony hard in consistency causing vestibular obliteration in the region of 36 and 37 extending distally up to the ascending border of the ramus with no history of paresthesia.
- Intraorally, all permanent teeth were present except the third molars in all four quadrants which were clinically missing. Aspiration yielded thick dirty white cheesy fluid. The patient was then subjected to further radiographic examination.
- Orthopantomogram (Figure 1) revealed impacted 18, 28, 48, missing 38 and multiple unilocular well-defined radiolucencies with sclerotic borders located in posterior maxilla and mandible bilaterally. CT scan revealed that the lesion has perforated the buccal and lingual cortical plates of the mandibular ramus and angle region bilaterally.
- The presence of multiple cysts in the jaws, associated with unerupted teeth, raised suspicion of Gorlin Goltz Syndrome and other relevant investigations were done along with a thorough physical examination to look out for other signs.
- Clinical examination revealed multiple palmer and planter pits (Figure 2), macrocephaly (occipitofrontal circumference 61 cm, Figure 3), anteroposterior view radiograph of chest and ultrasonography of the abdomen did not reveal any anomaly. CT scan displayed bifid spine (Figure 4). The patient was then evaluated systemically for other anomalies of the skeletal, cardiovascular or central nervous system, which did not reveal any specific abnormalities.
- Incisional biopsies of the swelling on the left side of mandible and both the sites on the maxilla were done. Histopathological examination was suggestive of odontogenic keratocyst with parakeratinized stratified squamous epithelium.
- Since two major criteria's (multiple odontogenic keratocyst and multiple palmar pits) and two minor criteria's (macrocephaly and bifid spine) were met hence a final diagnosis of Gorlin Goltz syndrome was made. The patient was treated surgically; enucleation of all cysts and peripheral osteotomy was done along with application of Carnoy's solution. The patient is being followed up regularly.
- As Gorlin-Goltz syndrome is an autosomal dominant with high penetrance trait both the children (2 daughters) of the patient were then screened and a full clinical and radiological evaluation was carried out.

Case Report: Patient 2 (Elder Daughter-9 Years)

On general physical examination multiple palmer pits (Figure 5), macrocephaly (occipitofrontal circumference 60 cm, Figure 6) and frontal bossing (Figure 7) were observed along with syndactyly and polydactyly of the left foot digits (Figures 8 and 9). Orthopantomogram revealed multiple radiolucencies in the mandible (Figure 10). CT scan suggested that the lesion has perforated the buccal and lingual cortical plate of the mandibular ramus and angle region.

Incisional biopsy of the mandibular left ramus region was done which was diagnosed as odontogenic keratocyst with similar histopathological features as that of the mother. Further systemic evaluation did not reveal any other anomaly.

Three major criteria (OKC proved histologically, multiple palmer pits and a positive family history of Gorlin Goltz syndrome i.e. her mother) and four minor criteria (macrocephaly, frontal bossing, syndactyly, and polydactyly of the left feet digits) fulfill the major and minor criteria hence confirmed the diagnosis of Gorlin Goltz syndrome.

Case Report (Younger Daughter-4 Years)

On general physical examination, multiple palmer pits (Figure 11) macrocephaly (occipitofrontal circumference 56 cm, Figure 12) with a history of glaucoma (treated). Orthopantomograph revealed a unilocular well-defined radiolucency associated with a developing 43 extending from the base of the mandible to the apices of 83 and 84 (Figure 13). The systemic evaluation did not reveal any other anomaly.

The findings were concordant to that of Gorlin Goltz syndrome. Major criteria being histologically proven odontogenic keratocyst, multiple palmer pits and first degree relatives already have the syndrome (i.e. mother and elder sister). Whereas the minor criteria being macrocephaly and glaucoma.

DISCUSSION

Gorlin Goltz syndrome is indigenous in presentation customarily reported in white, mostly through the first to third decade of life with equal tendencies in both genders [5]. PTCH gene on chromosome 9q (22.3-q31) is the persuasive gene which is a human homolog of the Drosophila segment polarity gene [6]. This disorder is autosomal dominant in nature but can arise intrinsically with or without any phenotypic dissemination [7]. Almost 60% of patients have no known affected family members and 35-50% of these represent new mutations [8, 9].

The variable phenotypic expression reflects variations in penetrance, the expression of different mutations within the same gene and/or the effects of modifier genes and environmental factors. A total of 65 variants of PTCH mutations have been documented in

literature [10,11], thus it would be not unanticipated for affected patients and their family members to have a spectrum of different genetic and clinical anomalies just as reported in our cases.

The predominance of GGS is assessed as 1 in 50,000 to 150,000 in the general population [12,13], however Evans *et al.* reported the prevalence as 1 in 560,000 in United Kingdom [14] and Farndon *et al.* reported the prevalence as 1 in 57,000 [15]. In Australia Shanley *et al.* reported the prevalence as 1 in 64,000 and in Italy Lo Muzio *et al.* estimated the prevalence as 1 in 256,000 [16,17].

There are only 64 cases reported to date since 1977 from India out of which this is the fourth case report showing the hereditary involvement. All three previously reported cases had only two affected members but this is the first case series reporting three affected family members [12,18,19].

Woolgar *et al.* in 1987 concluded that the mean age group for syndromic cases is 10 to 30 years and females are more affected than males whereas in the Indian scenario the mean age reported is 23.8 years with a male to female ratio of 1:0.7 [20,21].

Extensive variation in the occurrence of odontogenic keratocysts in GGS patients ranging from 62% to 100% has been reported in the literature [22]. This association was found in 100% of our case series as all the 3 patients had odontogenic keratocysts. In syndromic cases, maxillary molar areas are more frequently affected with a recurrence rate of nearly 63% [20].

Nearly 35%-87% of the syndromic patient's exhibit palmarplanter pits, which is 80% patients, develop by the age of 15 years and by the age of 20 nearly 85% patients exhibit these pits occurring most commonly on the palms than on the soles. These pits arise due to partial or complete absence of dens keratin in sharply defined areas [13]. Palmar pits were found in all the three patients in our cases. Ectopic calcification of falx cerebri was not found in any of the three patients discussed in this case series, despite being reported to have been found in 21.2% to 92% patients worldwide [21].

Macrocephaly with an increased occipitofrontal circumference i.e. greater than 55 cm was found in all the three patients. Relative macrocephaly (occipitofrontal circumference >55 cm in adults) has been reported in 5%-80% of the cases whereas hypertelorism is reported to be found in 6%-78% patient [17] which was evident in only the elder daughter.

Fibroma and ovarian cysts in syndromic females is a finding in 25%-50% of affected patients

with GGS and frequently present bilaterally in almost 75% cases [23]. Bifid, fused, wide, partially missing, or underdeveloped ribs are typical findings in 16%-58% of GGS patients [24, 25]. None of these were consistent with our finding, excluding spina bifida which was seen in the mother.

Of the 3 previously reported cases with familial inheritance in India [12,18,19] odontogenic keratocyst was found in all the cases except in one patient as reported by Nikam B *et al.* [19] where a 28 years male presented with multiple palmer pits, kyphoscoliosis, Sprengel deformity but his 70-year-old father diagnosed with Gorlin Goltz syndrome had multiple OKCs which was a common finding in all the family members in our case report.

Falx cerebri and tentorium cerebri calcification were reported by Chakraborty P *et al.* [18] in a 32-year-old mother and her 12 years old son. Bifid ribs was reported by Hegde S, Shetty SR [12] in a 39 years old father but were not found in her 8-year-old daughter. Calcification of the cerebri and bifid ribs was not seen in any of the three patients in our case.

Evans *et al.* in 1993 enlisted the diagnostic benchmarks for GGS which was subsequently improved by Kimonis *et al.* in 1997 stating that the diagnosis of GGS can be established when two major, or one major and two minor criteria are present as enlisted below in Table 1 [11,13]. Further Lo Muzio *et al.* in 1999 and Manfredi M *et al.* in 2004 mentioned various other diagnostic findings of GGS enlisted in Table 2 [3, 17].

CONCLUSION

The inception of Basal Cell Carcinoma (NBCC) or a histologically confirmed odontogenic keratocyst in a patient below the age of 20 years must alert the clinician to explore other diagnostic features, to look for the likelihood of the patient suffering from Gorlin Goltz syndrome. A thorough intra and extraoral inspection and assessment must be done along with appropriate radiographic investigations.

Various authors have recommended the need for neurological examination every 6 months, panoramic radiograph, dermatological and systemic examination once a year, from the age of 7 years, in patients whose first-degree relatives are already diagnosed with the syndrome. This would benefit to detect anomalies in suspected individuals in its initial stages so that prompt management of the detected anomalies is initiated reducing the extent of damage. Prenatal ultrasound to detect CNS and skeletal abnormalities in syndromic mothers along with genetic analysis is recommended to identify carriers.

Early diagnosis, genetic counseling, and treatment are imperative to prevent long term sequelae including malignancy and oromaxillofacial deformation and destruction.

Ethical Approval

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for 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.

Conflicts of Interest

There are no conflicts of interest.

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Table-1: Diagnostic criteria for GGS [3, 7]

MAJOR CRITERIA
More than two basal cell carcinoma or one basal cell carcinoma under the age of twenty years of age or more than ten basal cell nevi.
Any odontogenic keratocyst (proven on histology) or polyostotic bone cyst.
Three or more cutaneous palmar or plantar pits.
Bilamellar calcification of the falx cerebri.
Bifid, fused or markedly splayed ribs.
First degree relatives with nevoid basal cell carcinoma.
MINOR CRITERIA
Macrocephaly determined after adjustment for height.
Congenital malformations: cleft lip or palate, frontal bossing, “coarse face,” moderate or severe hypertelorism.
Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked polydactyly or syndactyly of the digits.
Radiological abnormalities: Bridging of the sella tursica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects or flame shaped lucencies of the hands or feet.
Ovarian fibroma.
Medulloblastoma, eye anomaly (cataract, coloboma, microphthalmus and glaucoma).

Table-2: Other diagnostic findings in GGS [3, 9]

A. SKELETAL ANAOMALIES	
1. Bifid ribs, splayed/ fused ribs, absent/ rudimentary ribs - may be bilateral	4. Flame - Shaped lucencies of hand/ feet
2. Scoliosis	5. Polydactyly
3. Hemivertebrae	6. Syndactyly or both
	7. Shortened 4th metacarpal
B. CRANIOFACIAL ANOMALIES	
1. Frontal bossing (occipitofrontal circumference 60 cms. or > in adults)	8. Heavy fused eyebrows
2. Brachycephaly	9. Broadened nasal root
3. Macrocephaly	10. Low positioning of occiput
4. Coarse face	11. Congenital blindness due to corneal opacity
5. Calcification of the falxes	12. Congenital or precocious cataract or glaucoma
6. Tentorium cerebelli calcification	13. Coloboma of iris, choroids or optic nerve
7. Bridged sella tursica	14. Convergent or divergent strabismus and nystagmus
C. NEUROLOGICAL ANOMALIES	
1. Agenesis / disgenesis of corpus callosum	4. Medulloblastoma (developing in the first two years of life)
2. Congenital hydrocephalus	5. Meningioma
3. Mental retardation	
D. OROPHARYNGEAL ANOMALIES	
1. Odontogenic Keratocysts – (Single or multiple, unilocular/ multilocular cysts)	3. Cleft lip/ palate
2. High arched palate or prominent ridges	4. Malocclusions or dental ectopic position
	5. Impacted teeth and / or agenesis
E. SKIN ANOMALIES	
1. Basal cell carcinoma	2. Palmar and or plantar pits
F. ANOMALIES OF THE REPRODUCTIVE SYSTEM	
1. Uterine and ovarian fibromas	3. Supernumerary nipple
2. Calcified ovarian cysts	4. Hypogonadism and cryptorchidism
G. CARDIAC ANOMALIES	
1. Cardiac fibromas	

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