Gorlin–Goltz syndrome: A case series of 5 patients in North Indian population with comparative analysis of literature

Jeevan Lata, Nitin Verma, Amandeep Kaur

Abstract

Objective: In Indian scenario, Gorlin–Goltz syndrome (nevoid basal cell carcinoma syndrome [NBCCS]) has been rarely reported. The clinical, radiological, and histopathological findings and major and minor criteria in five cases of NBCCS in North Indian population have been presented along with a discussion of the role of gene mutation analysis in early diagnosis of syndrome. **Materials and Methods:** The diagnostic findings of Gorlin–Goltz syndrome in 5 patients were compared with other reports in Indian population and with reports of this syndrome in other parts of the world. **Results:** The most common features seen were keratocystic odontogenic tumors (100%), calcifications of falx cerebri (60%), palmar-plantar pits (80%), rib anomalies (80%), macroencephaly (60%), ocular hypertelorism (80%), and frontal bossing (60%) in our series. Retained deciduous teeth seen in 80% patients whose association has not been previously reported has been presented. None of our patients had basal cell carcinoma, syndactyly or polydactyly, pectus deformity, bridging of sella turcica, pigmented nevi, or family history of this syndrome in contrast to such findings in other Indian patients. Medulloblastoma has not been reported in any Indian patient so far compared to this finding in other studies conducted worldwide. **Conclusions:** Combining the features of 48 patients in 38 cases of NBCCS being published in Indian literature with five cases of our series and on comparison with other studies in the world, a wide disparity in different ethnic groups and a wide variation in presentation of syndrome within the same population is suggested.

Keywords: Gorlin–Goltz syndrome, keratocystic odontogenic tumor, literature review, nevoid basal cell carcinoma syndrome

Introduction

Gorlin–Goltz syndrome, also known as nevoid basal cell carcinoma syndrome (NBCCS), is a rare inherited autosomal dominant disorder. The existence of this syndrome dates back to dynastic Egyptian times.[1,2] Although the prevalence of this syndrome varies with different ethnic groups, it is estimated to be 1 in 57,000 to 1 in 164,000.[2] However, in Indian scenario, NBCCS has been rarely reported.[3]

It is characterized by multiple keratocystic odontogenic tumors (KCOTs), multiple basal cell carcinomas (BCC), skeletal, ophthalmic, neurological abnormalities, and facial dysmorphism. Recently, genetic studies suggest markers such as PTCH1, PTCH2, and SUFU to be responsible for the syndrome.[1] Among them, mutation in Patched1 (PTCH1) gene which acts as a negative regulator of hedgehog signaling pathway has been identified as the main cause of NBCCS.[2,4] As the syndrome is a hereditary condition with a 50% chance of inheritance in offsprings of affected patients, genetic screening and counseling of patients and family members become important to screen for familial predisposition of this syndrome.[1] The genetic mapping of individuals would help in early diagnosis and management of suspected disease, thus decreasing the severity of abnormalities. Antenatal diagnosis for pregnancies in increased risk patients is also possible by ultrasound scan and extraction of DNA from fetal cells by amniocentesis. Also, this provides an opportunity for the development of future drugs for treatment or prevention of syndrome in subsequent generations.

The purpose of this present article is to describe, in detail, the clinical, radiological, and histopathological findings in five cases of Gorlin–Goltz syndrome from North India diagnosed in our department, to discuss the role of gene mutation analysis, and to predict the recurrence of KCOTs depending on its histopathologic nature. Also, this article aims to correlate the incidence of the present study's findings

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Access this article online	
Quick Response Code:	Website: www.contempclindent.org
	DOI: 10.4103/0976-237X.166813

How to cite this article: Lata J, Verma N, Kaur A. Gorlin–Goltz syndrome: A case series of 5 patients in North Indian population with comparative analysis of literature. Contemp Clin Dent 2015;6:S192-201.

of Gorlin–Goltz syndrome with cases published in literature in Indian patients and compare the prevalence and frequency of major and minor criteria noted in Indian population with other studies in different parts of the world.

Materials and Methods

This study was conducted in 5 patients of NBCCS diagnosed in our department from September 2013 to October 2014. All 5 patients were females with chief complaint of swelling, pain, or foul fluid discharge on at least one side of maxilla or mandible and a detailed extraoral and intraoral examination was done raising a suspicion of cyst or tumor involvement. It was followed by panoramic radiographs which confirmed the presence of multiple maxillary and mandibular cyst-like lesions [Figure 1].

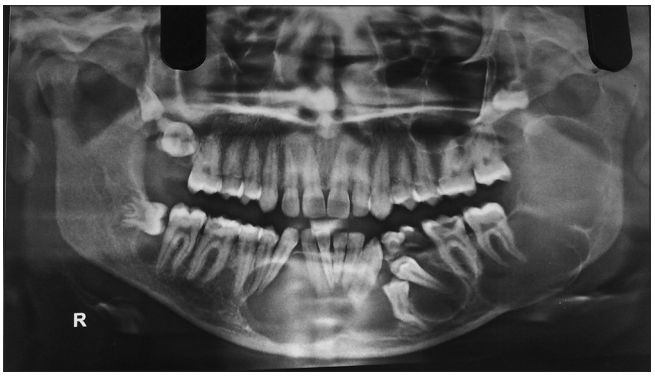

Figure 1: Orthopantomogram of patient (Case 1) showing multiple mandibular and maxillary cyst-like lesions

A detailed clinical examination of head and neck region was done in all patients according to the diagnostic protocol suggested by Lo Muzio[1] which revealed the presence of macroencephaly with increased occipitofrontal circumference (>55 cm), frontal bossing, ocular hypertelorism with increased intercanthal distance (>36 mm), or palmar and plantar pits on systemic examination [Figure 2]. Due to characteristic clinical findings and radiographic presentation of multiple cyst-like lesions, Gorlin–Goltz syndrome was suspected. Aspiration of suspected cystic cavities revealed white keratin-like material in all patients raising suspicion of KCOTs. Further investigations and radiological evaluation of the chest, skull bones, hands, feet, long bones, pelvis, and spine were carried out for all patients. Computed tomography examination of head and face was done in 2 patients to know the extent of cystic lesions. Multisystem evaluation of patients with dermatologic, ophthalmic, cardiac, ear, nose, and throat and neurologic examination was advised for all patients.

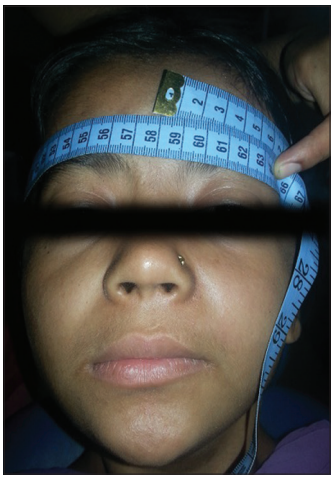

Figure 2: Extraoral photograph of patient showing macroencephaly with increased occipitofrontal circumference and ocular hypertelorism (Case 3)

Incisional biopsy or marsupialization of cystic cavities also revealed keratin-like cheesy material. Histopathological examination showed 5–6 layers of thick stratified squamous epithelium with cuboidal to columnar palisaded basal cell layer with dark-staining nuclei and a corrugated surface with parakeratinization. Prominent daughter cysts containing keratin whorls were found in the thin capsular connective tissue. These features suggested parakeratinized KCOT in all the specimens [Figure 3].

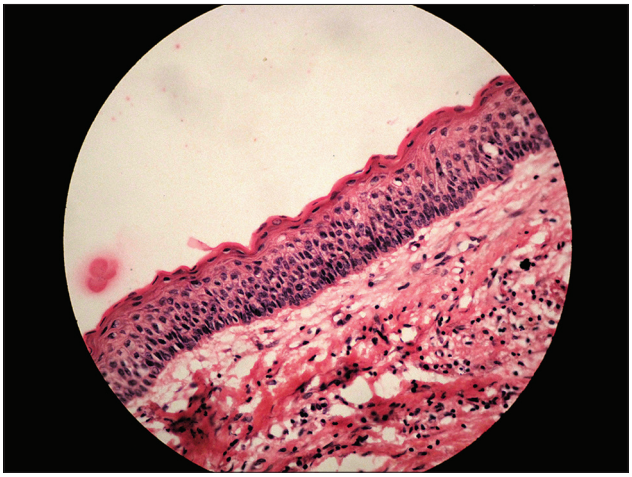

Figure 3: Histopathological examination depicting features of parakeratinized keratocystic odontogenic tumor

The diagnosis of NBCCS was made based on the presence of major and minor criteria as suggested by Kimonis *et al*. (2004).[5] All the patients were enquired about any family history (FH) of cysts and tumors or other features of syndrome and first-degree relatives examined for any positive findings. The detailed clinical and radiographic presentation and positive diagnostic findings of syndrome are presented in Tables 1-3. A search was done of the available literature (PubMed, Google Scholar, Mozilla, and Internet Explorer) on cases of Gorlin–Goltz syndrome reported in India from 1977 to present, which revealed 48 patients in 38 case reports being published. A summary of the diagnostic features of syndrome in these patients is presented in Table 4.[3,6-42] The

Table 1: Diagnostic findings of NBCCS in five cases being reported

Age/sex	Major criteria	Minor criteria	Other findings
15/female	Multiple KCOT's (5) Multiple plantar pits calcifications of falx cerebri and tentorium cerebelli bifid right 6th rib	MC (OFC - 59 cm) FB OHT ICD - (40 mm)	Prognathic mandible operated epidermoid cyst 1-year back high arched palate fused eyebrows hyperpneumatized frontal air sinuses impacted teeth retained deciduous teeth
27/female	Bilateral KCOT's (2) Multiple palmar pits	MC OFC - (60 cm) FB OHT ICD - (37 mm)	Prognathic mandible operated intestinal cyst 11 years back high arched palate impacted tooth
17/female	Bilateral KCOT's (2) Multiple palmar and plantar pits calcifications of falx cerebri bifid right 3rd rib posteriorly and right 4th rib anteriorly	MC OFC - (58 cm) FB OHT ICD - (37 mm) Left hemorrhagic OC	High arched palate Impacted teeth retained deciduous tooth
14/female	Bilateral KCOT's (2) Fused rib	OHT ICD - (36 mm) Operated cleft lip and palate	Impacted tooth Retained deciduous tooth
20/female	Multiple KCOT's (5) Multiple plantar pits calcifications of falx cerebri bifid right 4th rib posteriorly, right 5th rib anteriorly and left 5th rib posteriorly	SD	Scoliosis Fused eyebrows impacted teeth retained deciduous tooth

KCOT: Keratocystic odontogenic tumor; NBCCS: Nevoid basal cell carcinoma syndrome; OFC: Occipitofrontal circumference; ICD: Intercanthal distance; OHT: Ocular hypertelorism; MC: Macroencephaly; FB: Frontal bossing; SD: Sprengel deformity; OC: Ovarian cyst

Table 2: Clinical features associated with KCOT's in five NBCCS patients being reported

Extraoral swelling	Intraoral swelling	Tenderness	Duration	Consistency	Extraoral/intraoral discharge	Aspiration
Mandibular anterior region	Buccal cortical expansion	Absent	6 months	Firm	Present intraorally	Cheesy material
Mandibular anterior region	Buccal cortical expansion	Present	1-month	Hard	Present intraorally extraoral discharging sinus	Cheesy purulent material
Absent	Buccal expansion in right maxillary premolar region	Absent	4 months	Firm	Present intraorally	Cheesy material
	Buccal expansion in left maxillary premolar region	Absent	5 months	Firm	Absent	Cheesy material
Right mandibular body	Buccal cortical expansion	Absent	6 months	Firm	Present intraorally	Cheesy material
Absent	Absent	Present	1-month	Absent	Present intraorally	Cheesy material

KCOT: Keratocystic odontogenic tumor; NBCCS: Nevoid basal cell carcinoma syndrome

frequency of findings in these patients in Indian literature combined with 5 patients in our case series was then compared with studies in different parts of the world and is presented in Table 5.[43-51]

Results

All the 5 patients in this series fulfilled the criteria for NBCCS. Preoperative paresthesia or anesthesia was not noted in any of the patients on clinical examination. All the patients had unilocular or multilocular radiolucent cavities of maxilla or mandible with number of cysts ranging from 2 to 5. The most common site of cystic involvement was mandibular body region followed by mandibular angle - ramus region and maxillary posterior region. Inferior alveolar nerve canal displacement or antrum involvement was seen in all the patients due to large size of cystic lesions. Retained deciduous teeth associated with cystic cavities were found in 80% of the patients though the association of retained deciduous teeth with NBCCS has not been reported in literature so far.

Comparing the findings of the present case series with other reports in Indian literature, none of our patients had BCC, syndactyly or polydactyly, pectus deformity, bridging of sella turcica, pigmented nevi, or FH of syndrome as opposed to these findings in some earlier reports in Indian population. As all the patients reported in this series were from North India, this suggests wide variation in syndrome manifestations within the same ethnic and racial population. Cleft lip and palate had been reported in only one Indian patient with NBCCS previously. The second such finding has been found in one of our patients.

On comparison of diagnostic findings of this syndrome in Indian patients with other parts of the world, the incidence of bifid or fused ribs was found to be higher in Indian patients with a male predeliction. Medulloblastoma (MED) has not been found in any Indian patient in contrast to other studies conducted worldwide. The frequency of pectus deformity was found to be lower in Indian population.

Small unilocular cysts were enucleated and in larger cysts, marsupialization followed by enucleation was done as

Table 3: Radiographic findings of KCOT's in 5 NBCCS cases being reported

Number of KCOT's	Site involved	Radiographic presentation	Margins	Antrum involved/ IAN canal displaced	Other findings	Recurrent lesions
5	Mandibular left Ramus, angle and posterior body	Multilocular radiolucent	Scalloped corticated well defined	IAN canal displaced	Retained 7D, 7E	No
	Mandibular left Premolar region	Unilocular radiolucent	Smooth corticated well defined	IAN canal displaced	Impacted 34, 35	No
	Mandibular anterior Region and radiation therapy body till 45	Unilocular radiolucent	Scalloped corticated well defined	IAN canal displaced	Displaced teeth 33, 41, 42, and 43	No
	Mandibular right Molar region	Unilocular radiolucent	Smooth corticated well defined	IAN canal displaced	Impacted 48	No
	Maxillary left Molar and 2nd premolar region	Unilocular radiolucent	Smooth corticated well defined	Antrum involved	-	No
2	Mandibular left Body from 38 till 34	Multilocular radiolucent	Smooth corticated well defined	IAN canal displaced lingual perforation below 36	Displaced 34	No
	Mandibular left Anterior region and right body from 32 to 46	Multilocular radiolucent	Smooth corticated well defined	IAN canal displaced	Displaced 32, 43	No
2	Maxillary right Premolar - molar region	Unilocular radiolucent	Smooth corticated well defined	Antrum involved	Displaced 15 Retained 4C Impacted 13	No
	Maxillary left Premolar - molar region	Unilocular radiolucent	Scalloped corticated	Antrum involved	Displaced 24 Impacted 23, 25	No
2	Mandibular right Body and anterior region from 46 till 31	Multilocular radiolucent	Scalloped cortcated well defined	IAN canal displaced	Retained and root resorption WRT 8E Impacted 44	No
	Mandibular left Body WRT 36, 37 and retromolar region	Multilocular radiolucent	Smooth corticated ill defined	IAN canal displaced	Root resorption WRT 37	No
3	Mandibular right Ramus and posterior body till distal of 47	Unilocular radiolucent	Smooth corticated well defined	IAN canal displaced	Impacted 48	Previous history of cyst enucleat. WRT 35, 36
	Mandibular right Body region WRT 44, 46 region	Unilocular radiolucent	Smooth corticated well defined	IAN canal displaced	Impacted 45 Retained 8C, 8D	Region, 38 Region 44-46, 48 region
	Mandibular left Posterior body region WRT 38	Unilocular radiolucent	Smooth corticated well defined		Impacted 38	23, 24 region, 3 years back

IAN: Inferior alveolar nerve; KCOT: Keratocystic odontogenic tumor; NBCCS: Nevoid basal cell carcinoma syndrome

treatment protocol. In all the patients, enucleation was followed by aggressive curettage and two cycles of liquid nitrogen spray cryotherapy of 1 min each separated by a thaw interval of 5 min. The patients were kept on a strict, regular postoperative follow-up regimen of 1, 3, 6, and 12 months and biannually thereafter to detect early recurrence or for the appearance of any other manifestations of the disease.

Discussion

Gorlin–Goltz syndrome (NBCCS) was first recognized in 1894 by Jarisch and White. Dr. Robert Gorlin and Dr. Robert Goltz (1960) delineated the different clinical features in their study on "multiple naevoid basal cell epithelioma, jaw cysts and bifid rib syndrome." The main clinical manifestations of this syndrome include multiple BCC, KCOTs of jaws, palmer-plantar pits, rib and skeletal anomalies and facial dysmorphism, cleft lip/palate, eye anomalies like cataract, Bitot's spots, etc.). Various low frequency neoplasms such as MEDs, meningiomas, ovarian and cardiac fibromas, epidermoid cysts, and defects of stomatologic system, including mandibular prognathism, high arched palate, malocclusion, impacted teeth, ameloblastoma, squamous cell carcinoma, and odontogenic myxoma, have also been reported.[1] In certain occasions, a tall height has been associated with the syndrome. Very few cases of NBCCS had been reported previously in Indian literature probably representing underrecognition.

Table 4: Total number of NBCCS cases reported in Indian literature along with their diagnostic findings[3,6-42]

Study	Cases	KCOT/OKC	BCC	P/P pits	CFC/TC	RA	FH	MC	FB	OHT	SD	S/P	BST	VA	OF/C	PN	CL/P	PD
Kamath *et al.* (1977)	1	P	P	P	A	A	A	A	A	A	A	A	A	A				
Yesudian *et al.* (1995)	1	P	P	P	A	A	A	A	A	A	A	A	A	A				
Chavan *et al.* (1998)	3	P	P	P	A	P	A	A	P	P	A	A	A	P				
		A	P	P	P	A	A	A	A	P	A	A	A	A				
		P	P	P	P	P	A	A	P	P	A	A	A	A				
Gupta *et al.* (2000)	1	P	P	A	A	A	A	A	A	A	A	A	A	A				
Gandage *et al.* (2003)	1	P	A	A	P	A	A	A	A	A	A	A	P	P				
Patil *et al.* (2005)	1	P	A	P	P	A	A	P	A	A	A	A	A	A				
Karthiga *et al.* (2006)	1	P	A	A	A	P	A	P	P	P	A	A	A	P				
Rao *et al.* (2006)	1	P	P	P	A	P	A	A	A	A	A	A	A	P				
Rai and Gauba (2007)	1	P	A	A	P	P	A	A	A	P	A	P	A	P				
Shakya and Mubeen (2009)	1	P	A	P	P	P	A	A	A	A	P	A	P	P				
Jawa *et al.* (2009)	1	P	A	A	P	P	A	A	A	P	A	P	A	A				
Baliga and Rao (2010)	1	P	A	P	A	P	A	A	P	P	A	A	A	A		P		
Kohli *et al.* (2010)	1	P	A	A	A	P	A	A	A	A	P	A	A	P				
Guruprasad and Prabhu (2010)	1	P	A	P	P	P	A	A	A	A	P	A	P	P				
Rahman *et al.* (2010)	1	P	A	A	A	P	A	A	A	A	A	A	A	A		P		
Shivaswamy *et al.* (2010)	1	P	P	P	P	P	A	A	A	P	A	A	A	P				
Garg *et al.* (2011)	1	P	A	A	P	P	A	A	P	P	A	A	P	A				
Chandra Shekha *et al.* (2011)	1	P	A	A	A	P	A	A	A	P	A	A	A	A				
Dua *et al.* (2011)	1	P	A	A	P	P	A	A	P	P	A	A	A	A			P	
Shobha *et al.* (2011)	1	P	A	A	P	P	A	A	A	P	A	A	A	A				
Gupta *et al.* (2012)	6	P	A	A	P	P	P	P	P	P	A	P	P	P				
		P	A	A	P	P	P	P	P	P	A	A	P	P				
		P	A	A	P	P	A	A	P	P	A	P	A	A				
		P	A	A	P	P	A	P	P	A	A	P	P	A				
		P	A	A	P	P	A	A	P	P	A	A	P	A				
		P	A	A	A	P	A	A	P	P	A	A	A	P				
Joshi *et al.* (2012)	1	P	A	A	P	P	A	P	P	A	A	A	A	A				
Pandeshwar *et al.* (2012)	1	P	A	A	P	P	A	P	P	P	A	A	A	A				
Aggarwal *et al.* (2012)	1	P	A	A	A	P	A	A	P	P	A	A	A	A				
Gosavi and Mundada (2012)	1	P	A	A	A	A	P	A	A	A	A	A	A	A	P	P		
Kiran *et al.*	1	P	A	P	P	P	A	P	A	P	P	A	P	A				
Hegde and Shetty (2012)	2	P	A	A	P	P	P	A	A	P	A	A	A	A				
		P	A	A	A	A	P	A	A	P	A	A	A	A				
Smeeta *et al.* (2013)	1	A	P	P	P	A	P	P	A	P	A	A	A	P	P			
Nikam *et al.* (2013)	2	A	P	P	A	A	P	A	A	A	P	A	A	P				P
		A	A	P	A	A	P	A	A	A	P	A	A	P				P
Sunder *et al.* (2013)	1	P	A	A	P	A	P	A	A	P	A	A	A	A				
Pol *et al.* (2013)	1	P	A	P	P	A	A	P	P	P	A	A	A	A				
Daneswari and Reddy (2013)	1	P	A	P	A	A	A	A	A	A	A	A	A	A				
Mohakud *et al.* (2013)	1	P	P	A	P	P	P	A	A	P	A	A	P	P				
Karagir *et al.* (2013)	1	P	A	P	P	P	A	A	A	P	A	A	A	A		P		
Chopra *et al.* (2014)	1	P	A	A	A	P	A	A	A	P	A	A	A	A				
Saranya *et al.* (2014)	2	P	A	A	A	P	A	A	P	P	A	A	A	A				
		P	A	A	A	P	A	A	P	P	A	A	A	A				

Contd...

Table 4: Contd...

Study	Cases	KCOT/OKC	BCC	P/P pits	CFC/TC	RA	FH	MC	FB	OHT	SD	S/P	BST	VA	OF/C	PN	CL/P	PD
Bijjaragi *et al.* (2014)	1	P	P	P	P	A	A	A	P	P	A	P	A	P				
Mehta *et al.* (2014)	1	P	A	P	P	A	A	P	P	A	A	A	A	A				

KCOT: Keratocystic odontogenic tumor; OKC: Odontogenic keratocyst; BCC: Basal cell carcinoma; P/P pits: Palmar-plantar pits; CFC/TC: Calcifications of falx cerebri or tentorium cerebelli; RA: Rib anomalies; FH: Family history; MC: Macroencephaly; FB: Frontal bossing; OHT: Ocular hypertelorism; SD: Sprengel deformity; S/P: Syndactyly or polydactyly; BST: Bridging of sella turcica; VA: Vertebral anomalies; OF/OC: Ovarian fibroma or ovarian cyst; PN: Pigmented nevi; CL/CP: Cleft lip or palate; PD: Pectus deformity; NBCCS: Nevoid basal cell carcinoma syndrome

Table 5: Comparison of diagnostic criteria with other studies in various parts of world[43-51]

	Shanley *et al.* (1994) Australia	Kimonis *et al.* (1997) US	Muzio *et al.* (1999) Italy	Ahn *et al.* (2004) Korea	Provost *et al.* (2006) France	Habibi *et al.* (2010) Islamic Republic of Iran	Titinchi *et al.* (2013) South Africa	Bomfin *et al.* (2013) Brazil	Fujii and Miyashita *et al.* (2014) Japan	Indian literature till date
Major criteria										
Number of cases	118	105	37	33	22	19	15	14	157	53
Mean age	35	34.5	31.4	21.2	44.9	35.4	22.7	31	33.1	23.8
Male:female ratio	1.0:1.3	1.0:1.2	1.0:1.3	1.0:1.1	1.0:1.75	1.0:1.1	2.0:1	1.8:1	1.1:1	1:0.7
KCOT*	75	74	92	91	62	100	100	100	86.3	92.4
BCC*	75	80	30	15	100	43	20	64.3	37.8	22.6
P/P pits*	80	87	35	67	45	74	26.7	35.7	69.2	45.2
CFC*	92	65	70	21	66	89	40	42.8	79.4	58.4
RA*	45	43	32	36	16	58	20	7.1	36.4	67.9
FH*	64	26	7	4	5	1		14.3	48.4	18.8
Minor criteria										
MC*	80	50	NA	NA	27	5	20	28.6	26.5	26.4
FB*	66	27	70	42	18	47	20	35.7	47	43.3
HT*	6	42	78	49	18	53	20	14.3	68.8	66
SD*	4	11	22	NA	NA	NA	NA	NA	2.7	13.2
PD*	23	13	NA	NA	23	NA	NA	7.1	6.1	5.6
S/P*	7	24	5	3	NA	NA	NA	NA	2.1	11.3
BST*	26	68	24	21	NA	NA	0	NA	23.7	18.8
VA*	35	31	14	9	18	5.2	NA	NA	15.1	33.9
OF/OC*	14	17	8	0	13	0	NA	NA	12.5	5.6
MED*	1	4	0	3	13	0	NA	21.4	3.3	0
CL/CP*	4	3	3	9	0	5	0	NA	9	3.7

*In percentage. KCOT: Keratocystic odontogenic tumor; BCC: Basal cell carcinoma; P/P pits: Palmar-plantar pits; CFC: Cacification of falx cerebri; RA: Rib anomalies; FH: Family history; MC: Macroencephaly; FB: Frontal bossing; HT: Hypertelorism; SD: Sprengel deformity; PD: Pectus deformity; S/P: Syndactyly/ polydactyly; BST: Bridging of sella turcica; VA: Vertebral anomalies; OF/OC: Ovarian fibroma or ovarian cyst; MED: Medulloblastoma; CL/CP: Cleft lip or cleft palate; NA: Not available

In order to establish a diagnosis of the Gorlin–Goltz syndrome, the criteria chosen were given by Evans *et al.* (1993),[52] which was later modified by Kimonis *et al.* (2004).[5] The presence of two major and one minor or one major and three minor criteria are necessary to establish diagnosis.[3]

Major criteria[3]

- BCC (multiple or one occurring under the age of 20 years)
- Histologically proven KCOTs of the jaws
- Palmar or plantar pits (three or more)
- Bilamellar calcifications of the falx cerebri
- Bifid, fused, or markedly splayed ribs
- First-degree relative with NBCCS.

Minor criteria

- Macrocephaly (adjusted for height)
- Congenital malformation: Cleft lip or cleft palate, frontal bossing, coarse face, and moderate or severe hypertelorism
- Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, and marked syndactyly of the digits
- Radiological abnormalities: Bulging of sella turcica, vertebral anomalies such as hemi vertebrae, fusion, or elongation of vertebral bodies, defects of the hands and feet, or flame-shaped hands or feet
- Ovarian fibroma
- MED.

In all of our five cases, clinically at least two major and one minor criteria were present. Histopathologically, all the lesions were associated with parakeratinization, intramural epithelial remnants, and satellite cysts suggesting it to be KCOT. Dominguez and Keszler (1988) suggested that all these features were more frequent among NBCCS keratocysts than among solitary keratocysts.[53] Hence, the clinical and histopathological features confirmed the diagnosis of Gorlin–Goltz syndrome for all the five cases.

Donatsky and Hjørting-Hansen reported that the significantly higher occurrence of proliferative epithelial remnants in the connective tissue wall of the cyst might be an explanation for the high recurrence rate of KCOTs seen in patients with NBCCS.[54] As the biological behavior of KCOTs associated with NBCCS is more aggressive and these cysts have higher recurrence rates (82%) compared with solitary keratocysts (61%), treatment by marsupialization or enucleation with adjuvant chemical cautery using carnoy's solution or cryosurgery should be undertaken in these patients. Cryotherapy produces cellular necrosis and destroys the residual cysts and epithelial remnants while maintaining the inorganic osseous framework intact. In our patients, enucleation with or without marsupialization was followed by liquid nitrogen spray cryotherapy (−196°C) for the treatment of cystic cavities.

The literature reports wide variation in the incidence of KCOTs in NBCCS patients ranging from 62%[47] to 100%.[48-50] This association has been found to be 100% in our case series. Usually, multiple keratocysts are found in NBCCS ranging from 1 to 30 in number, average being 5.[1] In our case series, all patients had at least two maxillary or mandibular cysts. The most common site which is usually found is the mandibular molar or ramus region (44%) followed by incisor-canine region (18%).[1] In our case series, mandibular body region was affected in 4 patients (80%), crossing midline, and extending to contralateral side in two (40%) of them. In contrast, the majority of the maxillary cysts occur commonly in incisor-canine region (15%) and molar-tuberosity region (13%).[1] Only a few cysts have been reported in premolar region. The bilateral maxillary cysts in one of our patients were found in premolar - molar region. Palmar-plantar pits usually occur in 35–87% of the syndromic patients and in 80% develop by the age of 15 years and in 85% after the age of 20 years.[1,44,45] Pits were found to be present in 80% of our cases (4 patients). They are usually more commonly found on palms (77%) than on soles (80%), but plantar pits were seen in three of our patients (60%) as compared to 2 patients with palmar pits (40%). Ectopic calcifications of falx cerebri have been found in as low as 21.2% to as high as 92% patients in different reports worldwide whereas in our series, they were found in 60% of the cases [Figure 4].

Relative macroencephaly with an increased occipitofrontal circumference (>55 cm) has been reported in 5–80% of the cases.[43,48] Hypertelorism is usually found in 6–78% of the patients with NBCCS.[43,45] Macroencephaly was found in 60% of our patients with hypertelorism in 80% of them.

Ovarian cysts and fibroma are usually a finding in 25–50% of affected women with NBCCS and often present bilaterally (75%).[1] This is consistent with our finding in only one affected patient (20%) but being present unilaterally. Bifid, fused, wide, partially missing, or underdeveloped ribs are usually found in 16–58% of NBCCS patients.[47,48] Bifid ribs were found in 60% of our patients with fused ribs in 20%.

Epidermoid cysts have been found to occur in 50% of the cases in literature.[1] In our case series, 1 patient (20%) gave a history of epidermoid cyst 1-year back. Cleft lip and palate and Sprengel deformity are rare in this syndrome with 0–9% and 4–22% occurrence. These congenital deformities were found in 20% (1) of our patients. Scoliosis of spine rarely being reported in Indian literature was also found in one of our patients [Figure 5]. Multiple impacted teeth were

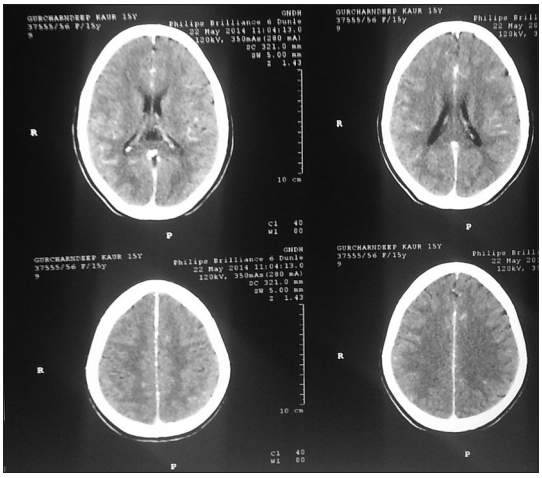

Figure 4: Computed tomography scan showing calcification of falx cerebri and tentorium cerebella (Case 1)

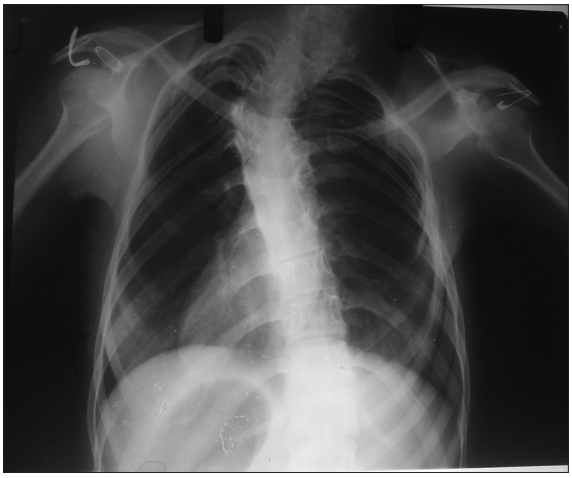

Figure 5: Chest X-ray showing scoliosis of spine, bifid right 4th rib posteriorly, right 5th rib anteriorly and left 5th rib posteriorly

seen in all of these patients with a novel feature of retained deciduous teeth seen in 4 patients (80%) which may be another associated finding with this syndrome not being reported previously.

Molecular genetics

NBCCS is a hereditary condition mostly caused by mutations in the PTCH1 gene which was isolated in 1996 as the human homolog of the Drosophila segment polarity gene PTCH.[1] It is transmitted in an autosomal dominant manner with high penetrance and variable expressivity.[1,2] More than 225 mutations in the PTCH1 gene in Gorlin–Goltz syndrome have been found so far.[55] The PTCH1 gene has been mapped to the long arm of chromosome 9q22.3 located from base pairs 95,442,981 to base pairs 95,516,964.[55] This protein (patched1) can be found in the hedgehog signaling pathway. The PTCH1 gene provides instructions for producing the patched-1 protein, which functions as a receptor. A protein called sonic hedgehog is the ligand for this receptor. Together, they trigger signals that play a role in cell growth, cell specialization, and determining the patterning of different parts of developing body. Mutation in PTCH1 gene prevents the production of patched-1 or leads to the production of an abnormal version of the receptor. An altered or missing patched-1 receptor cannot effectively suppress cell growth and division. As a result, cells proliferate uncontrollably to form the tumors that are characteristic of Gorlin–Goltz syndrome.

Etiopathogenesis

Its pathogenesis supports the Knudson two-hit hypothesis which states that normal cells require two mutagenic hits (two distinct episodes of DNA damage) to produce cancer. Patients with retinoblastoma, NBCCS, and similar syndromes have a constitutional (germline) defect in the DNA sequence in one of the two copies of a tumor suppressor gene.[1] If a second DNA injury or if loss of the normal remaining allele occurs at the same locus (the second hit), the cell may become malignant.[1] In NBCCS, various tumors and hamartomas (BCC, Odontogenic keratocysts, meningiomas, and ovarian fibromas) exhibit loss of heterozygosity but other lesions, for example, palmar pits do not.[1] Various physical anomalies (bifid rib, macroencephaly) apparently need only one-hit.[1]

BCC have shown an incidence of 40% in black patients and 90% in whites.[1] None of our 5 patients being reported had BCC. This was probably due to a wide variation in the incidence among ethnic groups. Although BCC has a low metastatic potential of 0.0028–0.55%, recently an NBCCS patient had been diagnosed with recurrent BCC with lung metastasis.[56] As cumulative ultraviolet (UV) light is the main risk factor, these patients are warned against prolonged sun exposure.

About 70–80% of the individuals with NBCCS have an affected parent and about 20–30% of the probands have a *de novo* mutation.[1] The risk to a sib of a proband depends on the genetic status of the parents: If a parent of the proband is affected, the risk to the sibs is 50%; when the parents are clinically unaffected probably because the effects being so mild that is, has never been diagnosed, the risk to the sibs of a proband appears to be low.[1] So, genetic counseling involving family members in regular screening appears to be mandatory. In the present case series, the syndrome did not affect the patient's parents or siblings and there were no familial antecedents in any of our 5 patients.

Location of gene for this syndrome by gene mutation analysis offers the possibility that DNA markers can be used in risk estimation and presymptomatic identification of the patients. The most likely position for gene is between DNA markers D9S12 and D9S53.[57] It can also be caused by mutations in PTCH2 gene located on chromosome 1p32. Fan *et al*. (2008) identified a heterozygous germline mutation in PTCH2 gene in affected members of a Chinese Han family with NBCCS.[4,58] However, no PTCH2 mutations were found in 11 cases of NBCCS or in individuals with familial cases of NBCCS who did not have identifiable PTCH1 mutations.[1] An isolated case of Gorlin–Goltz syndrome has been found to have mutation in SUFU gene located on chromosome 10q24.32 in the absence of mutation in PTCH1 gene.[4] As all of these three genes belong to sonic hedgehog pathway, whether mutations in a single gene or a combination of these genes is probably responsible for the various manifestations of NBCCS needs to be further studied. Furthermore, a new treatment strategy based on the understanding and inhibition of the Hedgehog pathway can provide for specific drug treatment of disease in future to suppress tumor growth.

Thus, antenatal diagnosis for pregnancies at increased risk for syndrome is possible by analysis of DNA extracted from fetal cells (obtained by amniocentesis or by chorionic villous sampling) and ultrasound scans.[1] It can thus be helpful in detecting serious fatal developmental malformations such as fibromas of heart. Some fetuses with syndrome may have difficult deliveries due to large heads requiring assistance in delivery by either forceps or caesarean section.[1]

All the 5 patients have been kept on regular periodic follow-ups, and no recurrence of KCOT's or new syndromic manifestations have been found in any patient until date.

Conclusion

Early diagnosis of this syndrome is important for counseling of patients to prevent harmful exposure to UV and ionizing radiations that increase the risk of developing BCC. Regular follow-ups by multispecialists can be offered to prevent substantial morbidity because of complications. Thus, early diagnosis of patients can be used in a preventive multidisciplinary approach to provide a better prognosis. On comparison of our cases of NBCCS with those in Indian literature and with other studies in various parts of the world,

wide variation in manifestations in different ethnic groups and within the same population can be found probably due to genetic or environmental factors. Further, research on mutation of different genes related to syndrome can provide for gene replacement therapy which can be a boon for these patients.

Ethical approval

This study was approved by the Ethical Committee of Punjab Government Dental College and Hospital, Amritsar.

Acknowledgments

We would like to thank Dr. Jaideep Marya and Dr. Vimal Jain, general pathologists for their help in providing histopathological reports and microscopic photographs of the excised specimens.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors have obtained the necessary patient consent forms where the patients have given their approval for participation in the investigation, followed by representation in the concerned article. The patients do understand that the authors will ensure that their identities won't be revealed, however anonymity cannot be guaranteed.

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