Nevoid basal cell carcinoma syndrome in Indian patients: a clinical and radiological study of 6 cases and review of literature

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Objective. Nevoid basal cell carcinoma syndrome (NBCCS) is rarely reported in the Indian population. We present the clinical and radiological features of 6 cases of NBCCS in Indian patients.
Study Design. The clinical and radiological features of 6 cases of NBCCS were characterized into major and minor criteria and compared with features reported in Indian patients and in patients from other parts of the world.
Results. The most common features seen were presence of multiple keratocystic odontogenic tumors, rib abnormalities, and calcification of falx cerebri. Talons cusp and supernumerary teeth are features not previously reported in association with NBCCS. Basal cell carcinoma was not seen in any patient.
Conclusions. Combining the current series with 17 additional cases reported in Indian patients, it is evident that the frequency of clinical and radiological features in NBCCS in Indian patients differs from other ethnic groups. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:99-110)

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin-Goltz syndrome, is an infrequent multisystemic disease with a spectrum of developmental anomalies and predisposition to a range of neoplasms.[1-3] Its occurrence has been observed even in ancient Egyptian skeletons of the Dynastic period.[4] The first reported literature dates as early as 1894, wherein Jarisch and White described a patient with this syndrome, highlighting the presence of multiple basocellular carcinomas (BCCs). Many additional features associated with this syndrome were reported. Gorlin and Goltz in 1960 first established a classical triad of multiple BCCs, multiple keratocysts of jaws, and bifid ribs as characteristics of NBCCS.[1,5-9] The odontogenic keratocysts associated with NBCCS are usually multiple and of the parakeratinized variety, although a single case of orthokeratinized odontogenic keratocyst has been reported in this syndrome by Bolbaran et al. in 2000.[10,11] The odontogenic keratocyst was first described by Philipsen in 1956 and he renamed it keratocystic odontogenic tumor (KCOT) in the 2005 edition of the World Health Organization's histologic classification of odontogenic tumors. This edition reclassified the parakeratinized odontogenic keratocyst as KCOT and the orthokeratinized variant is now recognized as a separate entity and called an orthokeratinized odontogenic cyst.[12,13] Other clinical manifestations frequently seen are hyperkeratosis of the palms and toes, skeletal abnormalities, intracranial ectopic calcifications, and facial dysmorphism.[1,2,5] Neurological, ophthalmic, sexual, cardiac, and auditory system anomalies have also been reported.

The estimated prevalence varies from 1 in 57,000 to 1 in 256,000, with a male-to-female ratio of 1:1.[1,2] Cases of NBCCS have been reported in different ethnic groups from different parts of the world. Studies on large number of NBCCS cases have been reported from the United Kingdom, Australia, the United States, Italy, Korea, France, and Islamic Republic of Iran, delineating the frequency of clinical and radiological findings that are found in these patients.[3,14-19] The diagnostic criteria of NBCCS were first established by Evans et al.[14] and later modified by Kimonis et al. in 1997.[15] The syndrome is established when at least 2 major or 1 major and 2 minor criteria are present (Table I).[2,5,15]

NBCCS is inherited as an autosomal dominant trait with a high level of penetrance and variable expressiveness, which can manifest itself spontaneously.[1,5] The mutations in tumor suppressor gene called Patched (PTCH 1), located in the 9q22.3–q31 chromosome, has been identified as the cause of this syndrome.[1,5] The oncogenic potential in NBCCS is explained by Knudson's oncogenic theory or 2-hit hypothesis, which

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Table I. Diagnostic criteria in NBCCS[15]

Major criteria	Multiple (>2) BCCs or 1 younger than 20 years
	Odontogenic keratocysts of the jaws proven by histopathology
	Three or more palmar or plantar pits
	Bilamellar calcification of the falx cerebri
	Bifid, fused or markedly splayed ribs
	First-degree relatives with NBCCs
Minor criteria	Macrocephaly after adjustment for height
	Congenital malformation: cleft lip or palate, frontal bossing, "coarse face," moderate or severe hypertelorism
	Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
	Radiological abnormalities: bridging of sella turcica, vertebral anomalies, such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defecta of the hands and feet, or flame-shaped lucencies of the hands or feet
	Ovarian fibroma
	Medulloblastoma

NBCCS, nevoid basal cell carcinoma syndrome.

states that normal cells require 2 mutagenic hits to produce a cancer. Patients with NBCCS have a germ line defect in 1 of the 2 copies of the Patched gene, which is insufficient to cause cancer. If a second injury or if loss of the normal remaining allele occurs at the same locus (the second hit), the cell may become malignant. In NBCCS, various tumors and hamartomas (BCC, KCOT, meningiomas, ovarian fibromas) exhibit loss of heterozygosity. Various physical abnormalities (bifid rib, macrocephaly, palmar/plantar pits) apparently need only one hit. This explains why patients suffering form NBCCS show an important variability in their phenotype.[1,2]

There have been very few cases of NBCCS reported from India. We could find 17 cases of NBCCS reported in Indian patients in the medical literature over a period of 34 years (1977 to 2010).[20-34] We present a series of 6 cases of NBCCS diagnosed and being treated in our institute. The clinical and radiological findings reported in other Indian patients with NBCCS are also presented. The purpose of this article is to present any characteristic clinical or radiological finding that is typically seen in Indian patients with NBCCS and to find out if these are different from those reported in patients from other parts of the world.

MATERIAL AND METHODS

Six cases diagnosed as NBCCS and undergoing treatment at our institute from 2009 to 2011 were included in the study. Ethical approval and patient consent were obtained before commencement of the study. The diagnostic protocol suggested by Lo Muzio[2] was followed. All the patients were asked for any relevant past history or family history of cysts/tumors. Extraoral and intraoral clinical examination was followed by orthopantomogram (OPG) and radiological evaluation of skull bones, chest, hands, feet, long bones, pelvis, and spine. Pelvic ultrasound was obtained for the female patient and echocardiogram was obtained in all patients. Examination for palmar/planter pits and measurement for head circumference and interpapillary distance was done in all patients. Noncontrast computed tomography (NCCT) examination was done in 3 patients who had large maxillary cysts involving the maxillary sinuses. The patients were referred to dermatology, neurology, ophthalmology, cardiology, surgery, and ear, nose, and throat departments for a multisystem evaluation. Routine hematological examination was done in all patients and all cystic lesions in the jaw bones were biopsied and sent for histopathological evaluation. The diagnosis of NBCCS was made based on the presence of major and minor criteria suggested by Kimonis et al.[15] The first-degree relatives of all patients (parents, offspring, and siblings) were called for clinical and radiological examination as per diagnostic protocol to rule out undiagnosed and asymptomatic NBCCS. The clinical and radiographic findings in present case series are presented in Table II. The clinical and radiological details of the KCOT in each case are summarized in Tables III and IV, respectively. A search in medical literature (MEDLINE and others) of reports of NBCCS in Indian patients revealed 17 case reports from 1977 to 2010. A summary of the clinical and radiological findings in these 17 cases (major and minor criteria) is presented in Table V. Combining our case series of 6 patients with 17 additional cases of NBCCS reported in Indian patients, the frequency of clinical and radiological features was determined. A comparison of the major and minor criteria seen in patients with NBCCS from the United Kingdom, Australia, the United States, Italy, Korea, France, Islamic Republic of Iran, and India is presented in Table VI.

RESULTS

A total of 6 cases comprising 5 male patients and 1 female patient in the age range 11 to 38 years are presented. Case 2 was the father of Case 1 and was completely asymptomatic. He was diagnosed incidentally when clinical and radiographic examination was carried out on first-degree relatives of all the 6 diagnosed NBCCS cases. None of the other cases had any first-degree relatives with minor or major criteria of NBCCS. The most common symptom was presence of intraoral and extraoral swelling. The duration of the swellings ranged from 4 to 12 months. The swellings

Table II. Clinical and radiological findings in present case series of Indian patients with NBCCS

Case no.	*Age/Sex*	*Major criteria*	*Minor criteria*	*Others*
1	11/M	Multiple KCOT (5) Calcification of falx cerebri Bifid 4th and 5th rib on R Father affected (Case 2)	Macrocephaly Coarse facies Hypertelorism Scoliosis Polydactyly (Accessory toe L feet) Bridging of sella turcica	Congenital hydrocephalus Frontal bossing Fused eyebrows Malocclusion Unerupted supernumerary teeth* (2 in max incisor, 2 in mandibular incisor region) Impacted teeth (2,15,16,17,18,27,31,32,58,59,74,75)
2	38/M	Multiple KCOT (5) Calcification of falx cerebri Bifid 3rd rib on R Son affected (Case 1)	Macrocephaly Coarse facies Hypertelorism Scoliosis Bridging of sella turcica	Congenital hydrocephalus Frontal bossing Fused eyebrows Impacted teeth (16,17,32)
3	12/F	Multiple KCOT (6) Calcification of falx cerebri Bifid 5th rib on L, prominent anterior end 3rd and 4th rib on R	Coarse facies Hypertelorism Polydactyly (accessory finger R and L hands)	Frontal bossing Fused eyebrows Depressed nasal bridge
4	11/M	Multiple KCOT (4) Calcification of falx cerebri Bifid 5th rib on R	Bridging of sella turcica Macrocephaly Coarse facies Accessory toe with syndactyly L foot Bridging of sella turcica	Impacted teeth (6,15,16,17,23,27,28) Frontal bossing Fused eyebrows Posteriorly angulated ears Depressed nasal bridge Malocclusion Talons cusp* (in 10) Hypospadias Impacted teeth (6,11,16,29)
5	18/M	Multiple KCOT (3) Calcification of falx cerebri Bifid 4th rib on L	Hypertelorism Bridging of sella turcica	Frontal bossing Fused eyebrows Impacted teeth (6,17,32)
6	12/M	Multiple KCOT (4) Fused 1st and 2nd ribs on L and bifid 5th rib on R	Hypertelorism Elongated 5th cervical vertebra	Frontal bossing Fused eyebrows Impacted teeth (1,6,17,18)

NBCCS, nevoid basal cell carcinoma syndrome; *KCOT,* keratocystic odontogenic tumor; *R,* right; *L,* left; *(),* total number of KCOT in each case.
*Findings not previously reported in NBCCS.

Table III. Clinical features associated with KCOT in present series of Indian patients with NBCCS

Case no. (age/sex)	*Extraoral swelling*	*Intraoral swelling*	*Duration*	*Pain*	*Paresthesia/ anesthesia*	*Discharge*	*Aspiration*	*Incidental finding*	*Recurrent lesion*	*Follow-up**
1 (11/M)	Absent	L Max tuberosity	4 mo	Absent	Absent	Absent	Cheesy material	No	No	No recurrence in healed lesions/no new lesions (20 months)
2 (38/M)	Absent	Absent	—	Absent	Absent	Absent	Cheesy material	Yes	No	No recurrence in healed lesions/no new lesions (20 months)
3 (12/F)	R canine fossa	R Max alveolus buccolabial	6 mo	Present	Absent	Present	Cheesy purulent material	No	No	No recurrence in healed lesions/no new lesions (16 months)
4 (11/M)	R canine fossa	R Max alveolus, buccopalatal	5 mo	Absent	Absent	Absent	Cheesy material	No	No	No recurrence in healed lesions/no new lesions (15 months)
5 (18/M)	R Mand angle	R Mand alveolus, retromolar	12 mo	Present	Absent	Present	Cheesy, purulent material	No	No	No recurrence in healed lesions/no new lesions (11 months)
6 (12/M)	L Mand angle, R malar	L.Mand alveolus, retromolar R.max tuberosity	6 mo	Absent	Absent	Absent	Cheesy material	No	No	No recurrence in healed lesions/no new lesions (11 months)

NBCCS, nevoid basal cell carcinoma syndrome; *KCOT,* keratocystic odontogenic tumor; *R,* right; *L,* left; Mand, mandibular; Max, maxillary.
*Undergoing treatment.

Table IV. Radiological features of KCOT in present series of Indian patients with NBCCS

Case no.	*Site as seen in OPG**	*Internal structure*	*Periphery*	*Shape of margin*	*Cortication*	*Buccolingual expansion*	*Displacement/ erosion of lower border of mandible*	*Antral involvement/ displacement of IDN canal*	*Follicle/tooth displacement*	*Root resorption/ dilaceration*	*Associated impacted/ Unerrupted tooth*	*Additional findings in CT scan*	*Total no. of KCOT*
1	L Max tuberosity	Completely radiolucent Unilocular	Well defined	Smooth	Partial	Absent	—	Antral involvement	Yes, 15, 16	Root resorption 14	15, 16	Perforation of medial cortex in R mand ramus region, Calcification of falx cerebri	5
	L Mand molar retromolar	Completely radiolucent Unilocular	Well defined	Smooth	Partial	Absent	Absent	Absent	Yes, 18, 17	Absent	17, 18		
	R Mand molar retromolar	Completely radiolucent Unilocular	Well defined	Smooth	Present	Present	Absent	Absent	Yes, 31, 32	Absent	31, 32		
	R Max tuberosity	Completely radiolucent Unilocular	Well defined	Smooth	Present	Absent	—	Antral involvement	Yes 2	Absent	2		
	R Mand canine	Completely radiolucent Unilocular	Ill-defined	Smooth	Absent	Absent	Absent	Absent	Yes, 27, 75	Absent	27, 75		
2	L Max tuberosity	Completely radiolucent Multilocular	Well defined	Smooth	Present	Absent	—	Antral involvement	Yes, 16	Absent	16	Not done	5
	L Mand canine	Completely radiolucent Unilocular	Well defined	Scalloped	Present	Absent	Absent	Absent	Yes, root displacement 23, 22	Root resorption, 23, 24, 25	—		
	L mand retromolar ramus	Completely radiolucent Unilocular	Well defined	Smooth	Present	Absent	Absent	Absent	Absent	Absent	17		
	R Max tuberosity	Completely radiolucent Unilocular	Ill defined	Smooth	Absent	Absent	—	Antral involvement	Yes 32	Root resorption 31	32		
	R Mand retromolar	Completely radiolucent Unilocular	Ill defined	Smooth	Partial	Absent	Absent	Absent	Absent	Absent	—		
3	R Max canine premolar	Completely radiolucent Unilocular	Ill defined	Smooth	Absent	Present	—	Antral involvement	Yes, root displacement 8, 7, C, 5, 4	Root resorption, 7, C, 5, 4	6	Invagination into and perforation of anterior wall of R max antrum by KCOT in association with 6, Additional cyst like lesion in association with displaced follicle 1	6
	L Max tuberosity	Completely radiolucent Multilocular	Well defined	Scalloped	Present	Absent	—	Antral involvement	Yes, 15, 16	Absent	15, 16		
	L Mand retromolar ramus	Completely radiolucent Multilocular	Well defined	Scalloped	Present	Absent	Absent	Inferior displacement of IDN canal	Yes, 17	Absent	17		
	R Mand canine premolar	Completely radiolucent Unilocular	Well defined	Scalloped	Present	Absent	Absent	Displacement of IDN canal	Yes, 27, 28	Root resorption, 25, 26, R	27, 28		
	L Mand canine	Completely radiolucent Unilocular	Ill-defined	Smooth	Absent	Absent	Absent	Absent	Yes, 23, 22	Root dilaceration 23	23		

Table IV. Continued

Case no.	*Site as seen in OPG**	*Internal structure*	*Periphery*	*Shape of margin*	*Cortication*	*Buccolingual expansion*	*Displacement/ erosion of lower border of mandible*	*Antral involvement/ displacement of IDN canal*	*Follicle/tooth displacement*	*Root resorption/ dilaceration*	*Associated impacted/ Unerrupted tooth*	*Additional findings in CT scan*	*Total no. of KCOT*
4	R Max canine premolar	Completely radiolucent Multilocular	Ill-defined	Scalloped	Partial	Present	—	Antral involvement	Yes, 6. Root displacement 7, 5, 4.	Root resorption C, 5, 4	6	Not done	4
	L Max tuberosity	Completely radiolucent Multilocular	Ill-defined	Smooth	Partial	Absent	—	Antral involvement	Yes, 16. Root displacement 15	Absent	16		
	L Max canine premolar	Completely radiolucent Unilocular	Well defined	Smooth	Present	Absent	—	Antral involvement	Yes, 11. Root displacement 10, 12, 13	Absent	11		
	R Mand canine premolar	Completely radiolucent Unilocular	Well defined	Scalloped	Present	Absent	Absent	Inferior displacement of IDN canal	Yes, 11. Root displacement 28, 30	Root resorption 28, T	29		
5	R Mand molar retromolar	Completely radiolucent Multilocular	Well defined	Scalloped	Present	Present	Absent	Inferior displacement of IDN canal	Yes 29. Root displacement 31	Root resorption 31	32	Not done	3
	L Mand retromolar	Completely radiolucent Unilocular	Well defined	Smooth	Present	Absent	Absent	Absent	Absent	Absent	17		
	R Max canine	Completely radiolucent Unilocular	Ill defined	Smooth	Partial	Absent	—	Antral involvement	Yes, 6	Absent	6		
6	L Mand retromolar ramus	Completely radiolucent Unilocular	Well defined	Smooth	Present	Present	Absent	Inferior displacement of IDN canal	Yes, 18, 17	Absent	18, 17	Additional small cyst like lesion in inter radicular region of 3	4
	R Max tuberosity	Completely radiolucent Multilocular	Ill defined	Scalloped	Partial	Present	—	Antral involvement	Yes, 1	Absent	1		
	R Max canine	Completely radiolucent Multilocular	Ill defined	Scalloped	Partial	Present	—	Antral involvement	Yes, 6	Absent	6		

NBCCS, nevoid basal cell carcinoma syndrome; *KCOT,* keratocystic odontogenic tumor; *OPG,* orthopantomogram; *R,* right; *L,* left; Mand, mandibular; *Max,* maxillary; *IDN,* inferior dental nerve; *S,* supernumerary.

*Arranged in descending order of radiographic size of KCOT, as seen in OPG of each patient.

Table V. Frequency of major and minor diagnostic criteria for NBCCS reported in Indian patients (1977-2010)[20-34]

	Major criteria						*Minor criteria*						
Author	*Mul KCOT**	*Mul BCC*	*Mul P/P pits*	*CFC*	*RA*	*FH*	*MC*	*FB*	*HT*	*SD*	*S/P*	*BST*	*VA*
Kamath A (1977)	+	+	+	–	–	–	–	–	–	–	–	–	–
Yesudian D (1995)	+	+	+	–	–	–	–	–	–	–	–	–	–
Chavan R (1998)	+	+	+	–+	+	–	–	+	+	–	–	–	+
(3 cases)	–+	+	+	+	–+	–	–	–+	+	–	–	–	–
		+	+			–	–		+	–	–	–	–
Gupta A (2000)	+	+	–	–	–	–	–	–	–	–	–	–	–
Gandage SG (2003)	+	–	–	+	–	–	–	–	–	–	–	+	+
Patil K (2005)	+	–	+	+	–	–	+	–	–	–	–	–	–
Karthiga KS (2006)	+	–	–	–	+	–	+	+	+	–	–	–	+
Rao S (2006)	+	+	+	–	+	–	–	–	–	–	–	–	+
Rai S (2007)	+	–	–	+	+	–	–		+	–	+	–	+
Jawa DS (2009)	+	–	–	+	+	–	–	–	+	–	+	–	–
Kohli M (2010)	+	–	–	–	+	–	–	–	–	+	–	–	+
Guruprasad and Prabhu (2010)	+	–	+	+	+	–	–	–	–	+	–	+	+
Rahman F (2010)	+	+	–	–	+	–	–	–	–	–	–	–	–
Shivaswamy et al. (2010)	+	+	+	+	+	–	–	–	+	–	–	–	+
Baliga and Rao (2010)	+	+	+	–	+	–	–	+	+	–	–	–	–
Total[17]	16	10	10	8	11	0	2	4	7	2	2	2	8

NBCCS, nevoid basal cell carcinoma syndrome; *Mul,* multiple; *KCOT,* keratocystic odontogenic tumor; *BCC,* basal cell carcinoma; *P/P,* palmar/plantar; *CFC,* calcification falx cerebri; *RA,* rib abnormalities; *FH,* family history; *MC,* macrocephaly; *FB,* frontal bossing; *HT,* hypertelorism; *SD,* Sprengal deformity; *S/P,* syndactyly/polydactyly; *BST,* bridging of sella turcica; VA vertebral abnormalities; +, present; –, absent.

*Reports before 2005 have described the lesions as odontogenic cysts/odontogenic keratocyst.

were associated with pain, foul-smelling discharge, and purulent cheesy aspirate in 2 cases, which had become infected. Paresthesia/anesthesia was not associated with the swellings in any of the cases. All the cases had multiple cystic lesions in the jaws as seen in OPG (Figure 1). The number of cysts ranged from 3 to 6 per patient, the most common site being the mandibular retromolar region followed by maxillary tuberosity region, maxillary canine-premolar region, and mandibular canine-premolar region. The most common radiographic findings associated with the cystlike lesions were that they were radiolucent, unilocular, well defined, and corticated; had smooth borders; and were associated with impacted teeth and tooth follicle/tooth displacement. Antral involvement was common in cysts involving the maxillary tuberosity and maxillary canine premolar region. Buccolingual expansion, root resorption, and displacement of inferior dental canal were not commonly seen. Displacement/erosion of the lower border of mandible was not seen in any of the cases. NCCT of jaws was done in cases 1, 3, and 6, which also included the brain in case 1. The CT examination supplemented the conventional radiographic findings and were helpful in preoperative assessment of size and extent of lesions, especially those involving the maxillary antrum. They also showed perforation of cortices and additional small cysts not seen on OPG. All the cases had bifid/fused ribs, the most common rib abnormality being bifid ribs involving the fifth, fourth, and third rib (Figure 2). Frontal bossing and fused eyebrows were seen in all patients. Calcification of falx cerebri (Figure 3), bridging of sella turcica (Figure 4), hypertelorism, and syndactyly/polydactyly (Figure 5) were also frequently seen. Echocardiogram did not reveal any cardiac fibromas in any of the patients and no uterine or ovarian fibromas were detected in the female patient. None of the patients had any history or presence of nevi, basal cell carcinomas, or palmar/planter pits. Other anomalies reported in NBCCS, such as cleft lip/palate, Sprengel deformity, pectus deformity, medulloblastoma, spina bifida, and Albrights sign, were not seen in any of our patients. Supernumerary teeth in case 1(Figure 6) and Talons cusp in case 4 (Figure 7) are manifestations not previously reported in association with NBCCS. All the biopsied cysts were reported as KCOT (Figure 8). All the patients then underwent enucleation of the smaller KCOTs and removal of impacted teeth followed by aggressive curettage and application of Carnoy solution. The larger KCOTs were first marsupialized and subsequently enucleated followed by aggressive curettage and application of Carnoy solution. There has been no recurrence in healed lesions and no new lesions have been detected in any of the cases in a follow-up ranging from 11 to 20 months.

Table VI. Comparison of major and minor diagnostic criteria in NBCCS among studies from various countries[14-19]

	Evans et al. UK 1993	*Shanley et al. Australia 1994*	*NIH study USA 1997*	*Muzio et al. Italy 1998*	*Ahn et al. Korea 2004*	*Provost et al. France 2006*	*Habibi A Islamic Republic of Iran 2010*	*Present study India† 2011*
Major criteria								
No. of cases	84	118	105	37	33	22	19	23
Mean age, y	NA	35	34.5	31.4	21.2	44.9	35.4	22.9
Sex ratio M:F	1:1.3	1:1.3	1:1.2	1:1.3	1:1.1	1:1.75	1:1.1	1:0.7
Multiple BCC‡	47	75	80 (38)*	30	15	100	43	43
Multiple KCOT‡	66	75	74	92	91	62	100	95
Palmer/planter pits‡	71	80	87	35	67	45	74	43
Calcification of falx cerebri‡	NA	92	65	70	21	66	89	56
Bifid/fused/splayed ribs‡	NA	45	43	32	36	16	58	74
No. of families with NBCCS‡	29	64	26	7	4	5	1	1
Minor criteria								
Macrocephaly‡	NA	80	50	NA	NA	27	5	21
Cleft lip/palate‡	5	4	3	3	9	0	5	0
Frontal bossing‡	NA	66	27	70	42	18	47	43
Coarse facies‡	NA	NA	54	NA	NA	NA	5.2	17
Hypertelorism‡	NA	6	42	78	49	18	53	52
Sprengel deformity‡	NA	4	11	22	NA	NA	NA	8
Pectus deformity‡	NA	23	13	NA	NA	23	NA	0
Syndactyly/ Polydactyly‡	47	7	24	5	3	NA	NA	21
Bridging of sella turcica‡	NA	26	68	24	21	NA	NA	30
Vertebral anomalies‡	NA	35	31	14	9	18	5.2	39
Ovarian fibroma‡	24	14	17	8	0	13	0	0
Medulloblastoma‡	4	1	4	0	3	13	0	0

NBCCS, nevoid basal cell carcinoma syndrome; *KCOT,* keratocystic odontogenic tumor (studies before 2005 have used terms odontogenic cyst/odontogenic keratocyst); *BCC,* basal cell carcinoma; *NA,* not available.
*American (African).
†Including cases reported in Indian patients with NBCCS.
‡In percentage (%).

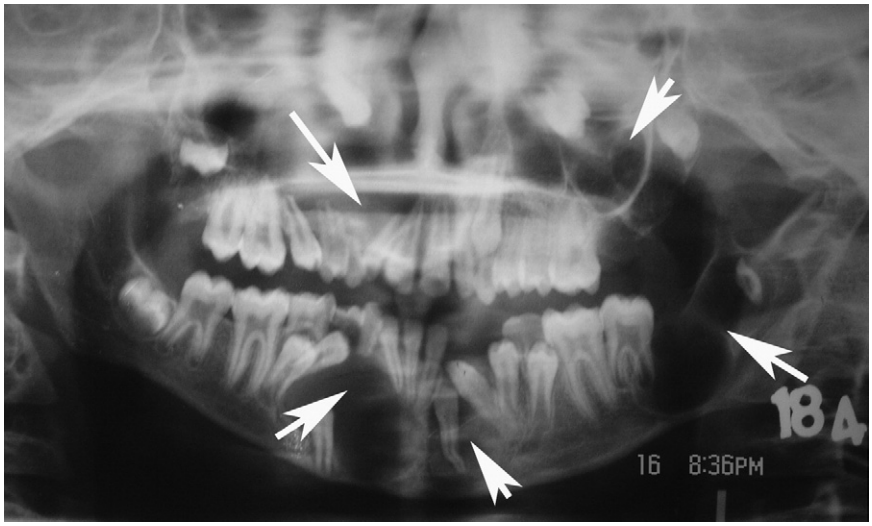

Figure 1. Multiple cystlike lesions of jaws seen in OPG (white arrows indicate 5 lesions in a single patient).

There were similarities in the frequency of the anomalies seen in our patients and other Indian patients reported in the literature (Table V). Most were single case reports except for a series of 3 cases reported by Chavan et al.[22] In the reported cases, presence of multiple KCOTs was the most predominant finding seen in 94% of the patients, whereas calcification of falx cerebri and rib abnormalities were seen in 47% and 64% of the patients, respectively.

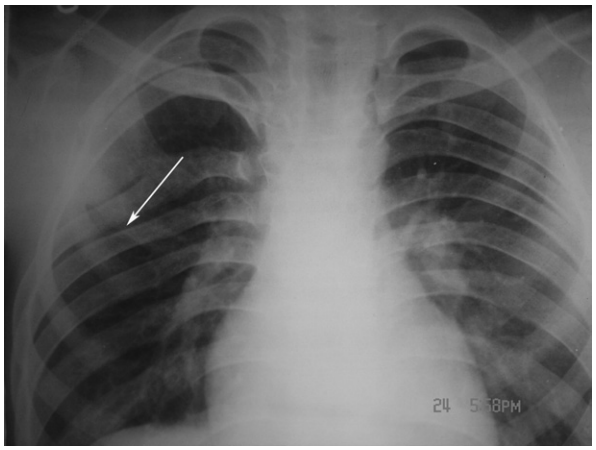

Figure 2. Bifid rib on right side.

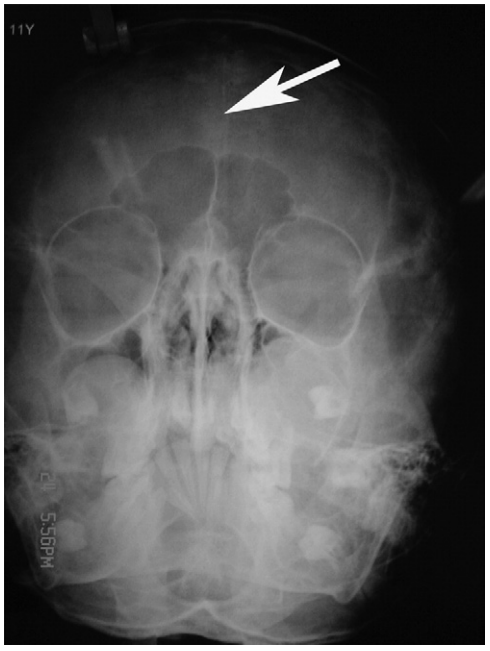

Figure 3. Calcification of falx cerebri seen in PA view of skull.

Multiple BCCs and palmar/planter pits, although not seen in our case series, have been reported in 58% of Indian patients. The other minor criteria have been reported less frequently ranging from 11% to 47%.

On comparing the major and minor criteria seen in patients from the United Kingdom, Australia, the United States, Italy, Korea France, and Islamic Republic of Iran, it is apparent that NBCCS is rare in the Indian population. The earliest age of detection of KCOT (usually the first diagnostic feature) in Indian patients is 11 years (mean age 22.9 years) and there is a slight preponderance of males as compared with females when compared with other populations. Presence of multiple KCOTs is the most common major criteria seen in (22/23) 95% of Indian patients, which is similar to the finding in Italian,

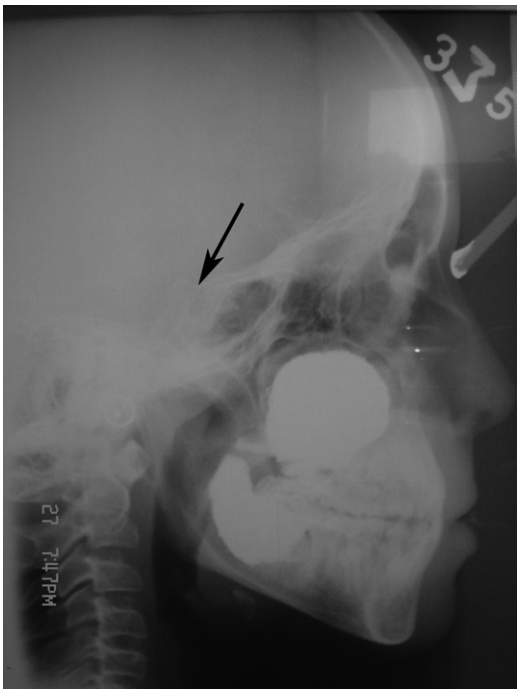

Figure 4. Radio opacities represent the radio opaque dressing material placed in the cystic cavities during marsupialization of mandibular and maxillary KCOT.

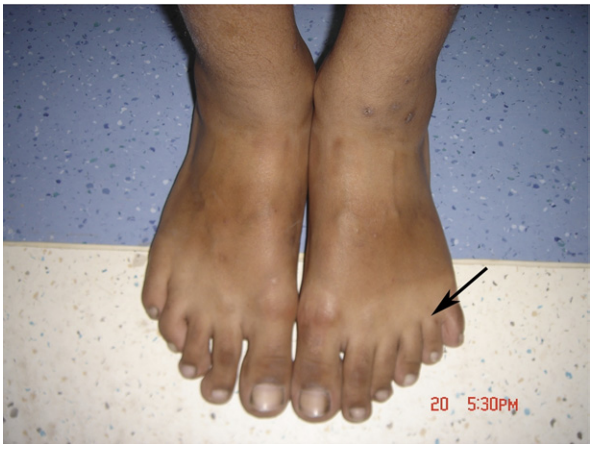

Figure 5. Polydactyly in left foot.

Korean, and Iranian populations. Skin involvement with multiple BCCs and palmar/plantar pits is seen in only (10/23) 43% of Indian patients, which is similar to the findings in Italian patients. Rib abnormalities (fused/bifid/splayed) are seen in (17/23) 74% of Indian patients with NBCCS, which is higher than any of the studies reported so far. Most of the NBCCS cases reported from India are also sporadic in nature. Among the minor criteria, hypertelorism is seen in nearly (12/23) 52% of Indian patients. Cleft lip/palate, pectus deformity, ovarian fibroma, and medulloblastoma have not yet been reported in Indian patients.

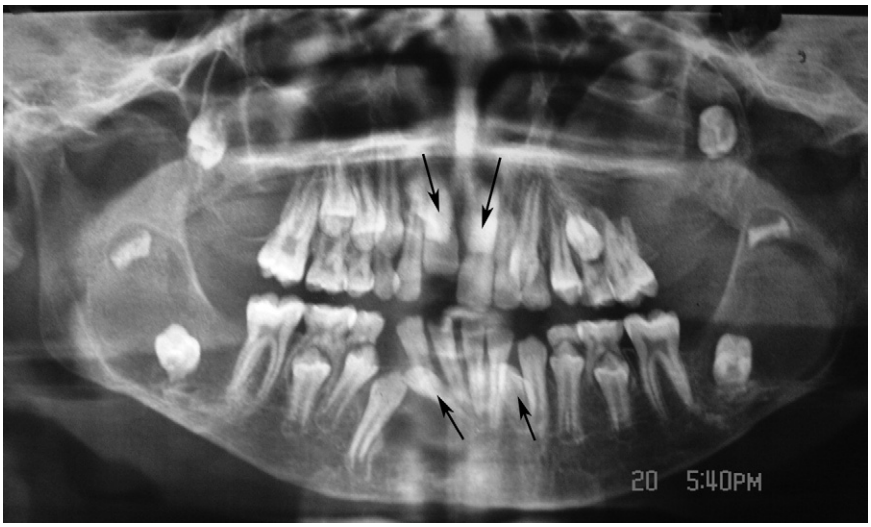

Figure 6. Impacted 4 supernumerary teeth in maxillary and mandibular incisor region.

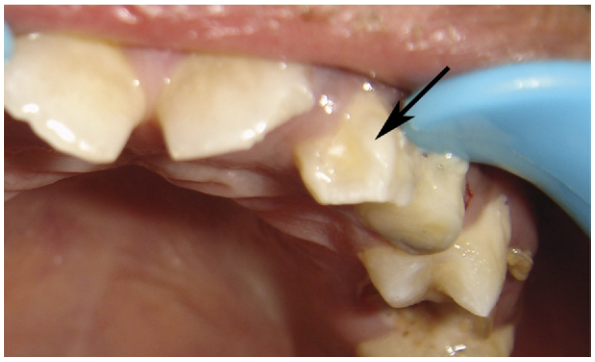

Figure 7. Talons cusp in association with left maxillary lateral incisor.

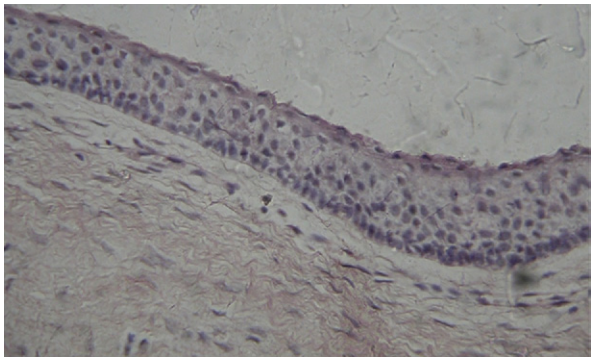

Figure 8. Keratocystic odontogenic tumor. Parakeratinized odontogenic epithelium with tombstone appearance of basal cells (hematoxylin and eosin, ×100).

DISCUSSION

Multiple KCOTs are the most consistent and representative signs of NBCCS in the first and second decades of life.[2] Multiple keratocysts may be present in other conditions, such as orofacial digital syndrome, Ehlers Danlos syndrome, Noonan syndrome, and Simpson Golabi–Behmel Syndrome.[35] The KCOTs seen in NBCCS are multiple, ranging in number from 1 to 30 with an average of 5, occur at an early age, usually in the first decade of life, and have a higher rate of recurrence. Clinically, the most common site is the mandibular molar ramus region and is usually asymptomatic until they reach a large size when they present with swelling, mild pain, and displaced or impacted teeth. Radiographic features include radiolucent lesions, unilocular/multilocular, with smooth/scalloped borders, associated with impacted/displaced teeth and tendency to grow along the internal aspect of the jaws causing minimal expansion.[10] The radiological differential diagnosis for unilocular lesions would include dentigerous cyst, lateral periodontal cyst, and residual cyst, whereas the multilocular variety will have to be differentiated from ameloblastoma, odontogenic myxoma, simple bone cyst, and aneurysmal bone cyst. On CT examination, KCOTs appear as minimally expansile benign lesions, with scalloped borders and high attenuation of contents, which do not enhance with contrast. The high attenuation is because of dense proteinacious material like keratin within the lesion. On magnetic resonance imaging (MRI), the contents of the lesion appear as low to intermediate signal intensity on T1 and high signal intensity on T2 images.[36,37] The clinical and radiographic features of KCOT in this case series of NBCCS were similar to the reported findings. Additionally, CT examination revealed cortical perforation and additional small cysts that were not detected on OPG. KCOTs in NBCCS have a high potential for recurrence (60%) as compared with nonsyndromic KCOT (28%).[2,10] Recurrence has been reported to occur within 2 years to even 25 years after enucleation.[10,37] The friable cyst lining, presence of daughter cysts, and site of involvement have been implicated for the

high recurrence rate; however, factors like surgical accessibility, proximity of lesion to vital structures, surgeon's expertise, and type of surgical procedure used may have a role to play in incomplete removal of epithelial lining and recurrence.[38] In rare instances, they may be associated with development of ameloblastoma and squamous cell carcinoma.[2] They are treated by marsupialization/enucleation/osseous resection en block with adjunctive therapies, such as aggressive curettage, cryotherapy, or application of Carnoy solution. Regular follow-up every year for the first 5 years and thereafter every 2 years has been recommended.[39] The patients in this case series had KCOT in the second decade of life, the total number ranging from 3 to 6 per patient. They are still undergoing treatment, as the larger KCOTs take a longer time for bony healing. Aggressive surgical management has been adopted and more frequent follow-ups are being carried out to detect recurrences earlier, especially during the second and third decades of life. Patients with NBCCS are more susceptible to X-radiation; therefore, low-dose or nonionizing imaging modalities should be selected for surveillance. Follow-up should involve annual conventional radiographic surveillance and supplemented by preferably cone-beam CT or MRI when there is suspicion of recurrence.

Multiple BCC is also associated with other conditions like Bazex syndrome, trichoepithelioma papulosum multiplex, and Torres syndrome, but when associated with NBCCS they are mostly seen in younger patients and also involve nonsun-exposed areas of the body.[2] The incidence varies widely among ethnic groups. In whites, they are reported in up to 100% of cases, whereas only about 38% of black patients and 30% of Italian patients manifest BCCs, probably owing to protective skin pigmentation.[1,2,16] Exposure to radiation therapy or carcinogens, such as arsenic, may also predispose the patient to develop BCC at an earlier age. Regular dermatologic surveillance every 2 to 3 months has been recommended. Although multiple BCC was not seen in present case series, they have been reported in Indian patients in older age groups (older than 20 years); hence, precautions, such as sun protection, radiation protection, and regular dermatologic surveillance, should be advised in all patients.

Rib anomalies are reported in 30% to 60% of patients with NBCCS of which bifid ribs are more common, seen in nearly 40% of the cases.[2] All the patients in the current case series had bifid ribs involving either the fifth, fourth, and third rib, which is similar to the finding of Kimonis et al.[40] Bifid ribs may be an isolated incidental finding seen in the general population, but may also be associated with multisystem malformation and childhood malignancies like neuroblastoma.[41,42] A high frequency of rib anomalies (74%) was seen in Indian patients with NBCCS, probably because of genetic and environmental factors.

Calcification of falx cerebri is one of the most frequent radiological features, seen in 37% to 79% of cases with NBCCS.[1] A very high frequency (92%) was reported in the Australian population.[3] Kimonis et al.[40] reported calcification of falx cerebri to be more common in patients older than 20 years. Calcification of falx cerebri was seen in 56% of Indian patients with NBCCS at a mean age of 22.9 years.

Ovarian fibromas and cysts are seen in 25% to 50% of female patients with NBCCS and are often bilateral (75%). They are usually seen in those 16 to 45 years of age and are detected on pelvic ultrasound. They do not reduce fertility but may undergo torsion (twist).[2] Ovarian fibromas were not seen in Indian women with NBCCS, which was similar to the Korean and Iranian studies.

Medulloblastomas (now termed primitive neuroectodermal tumor) are seen in 3% to 5% of patients with NBCCS, usually within the first 2 years of life. They are usually of the desmoplastic subtype and have a better prognosis than medulloblastomas that occur in isolation. Early-onset desmoplastic medulloblastoma may be the first presenting sign of NBCCS in children younger than 3 years, as other major criteria may not be evident at that age. Molecular genetic studies for PTCH1 gene mutations may be helpful in early diagnosis in such cases.[1,2] Radiotherapy should be avoided as a treatment modality for medulloblastomas in patients with NBCCS, as they can develop BCC and other intracranial tumors in the radiation field.[43] Neurological examination, including MRI, is recommended every 6 months until 3 years of age followed by annual follow-up until 7 years of age, after which medulloblastoma is very unlikely.[2] In patients with germ line mutations of PTCH gene in NBCCS, the lifetime risk of developing medulloblastoma is about 4%.[44] Medulloblastomas have not been reported in Indian patients with NBCCS. The patients in the current series were older than the risk group for occurrence of medulloblastoma and did not have any signs or symptoms of the disease. The patients are, however, at risk of developing intracranial tumors in the future, such as meningioma, and, hence, neurological follow-up is recommended.[2]

Once the diagnosis of NBCCS is made, then screening for the syndrome must be carried out in other family members and genetic counseling must be offered. NBCCS is usually a hereditary condition with germ line mutations in the PTCH1 gene reported in members of same family, but 30% to 50% of the cases have also been reported to be sporadic in nature, presenting with new mutations.[1,3] The mutations have been identified as deletions, insertions, and splice-site alterations, and nonsense, missense, and frame-shift mutations. They more often result in the truncation of coded PTCH1 gene protein, which suggests that the developmental

anomalies seen in NBCCS are a result of haplo-insufficiency.[2] Some mutations reported to be shared by families with NBCCS are 244 del CT mutation (Wickling et al.),[45] frame-shift mutation in exon 8 (Boutet et al.),[46] 3169 to 2 A > G mutation (Chung et al.),[47] and 2619C > A mutation (Li et al.).[48] No hot spot mutations or founder effect of PTCH1 mutation has been reported as yet. There is no genotype-phenotype correlation associated with these mutations, and the phenotype variability in NBCCS is a complex event probably arising from genetic and environmental factors.[1,2,45,46] Most of the cases reported in Indian patients are also apparently sporadic in nature, with the exception of cases 1 and 2 (father-son) reported in our case series. Molecular genetic studies for PTCH gene mutations are expensive and not available everywhere. There are no such studies reported in Indian patients with NBCCS at present. Future studies should be directed toward investigating the PTCH germ-line mutations typically seen in Indian patients with NBCCS.

Clinical and radiological criteria will continue to play an important role in diagnosis and screening of NBCCS. New findings are being added to the growing spectrum of clinical and radiological manifestations in NBCCS, such as bilateral coronoid hyperplasia, narrow sloping shoulders, immobile thumbs, low-pitched voice, and others, just like we found supernumerary teeth and Talons cusp.[3,13]

NBCCS is rare in the Indian population or may be underreported owing to lack of awareness about the clinical and radiological manifestations that are commonly seen in Indian patients. Because the clinical and radiological features in NBCCS vary in different ethnic groups, because of either genetic or environmental factors, this study has tried to determine the features that are characteristic in Indian patients. The presence of multiple KCOTs, bifid/fused ribs, and calcification of falx cerebri, often help in diagnosis of NBCCS in Indian patients.

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