Int. J. Oral Maxillofac. Surg. 2004; 33: 117–124
doi:10.1054/ijom.2003.0435, available online at http://www.sciencedirect.com

International Journal of
Oral & Maxillofacial Surgery

Invited Review Paper
Clinical Pathology

Nevoid basal cell carcinoma syndrome: a review of the literature

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M. Manfredi, P. Vescovi, M. Bonanini, S. Porter: Nevoid basal cell carcinoma syndrome: a review of the literature. Int. J. Oral Maxillofac. Surg. 2004; 33: 117–124.

Abstract. The nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin–Goltz Syndrome is an autosomal dominant disorder principally characterized by cutaneous basal cell carcinomas, multiple keratocysts, and skeletal anomalies. The present report reviews current knowledge of this disorder that has profound relevance to specialists in Oral and Maxillo-Facial Surgery, Oral Medicine and Radiology.

Key words: basal, carcinoma, nevoid, oral, syndrome

Accepted for publication 16 April 2003

The nevoid basal cell carcinoma syndrome (NBCCS) was first reported by Jarish in 1894[33] who described a patient with multiple basal cell carcinomas, scoliosis and learning disability. Howell & Caro in 1959[32] were the first to associate the basal cell nevus with other cutaneous disorders and anomalies, while in 1960 Gorlin & Goltz[24] defined the condition as a syndrome comprising the principal triad of multiple basal cell nevi, jaw keratocysts, and skeletal anomalies[32]. A spectrum of other neurological, ophthalmic, endocrine, and genital manifestations[24,74,75] are now known to be variably associated with this triad[60,64].

Epidemiology and genetics

The Nevoid Basal Cell Carcinoma Syndrome prevalence has been variously estimated from 1 in 57 000[17] to 1 in 164 000[65], but there is now general agreement that the prevalence is about 1 per 60 000[28]. NBCCS probably arises in all ethnic groups, but most reports have been of whites. Males and females are equally affected, the clinical features of NBCCS arising in the first, second or third decade[14,35]. This disorder has an autosomal dominant mode of inheritance, but can arise spontaneously, or can have a variable phenotypic penetration[7,24,26]. Indeed almost 60% of patients with NBCCS have no known affected family members, 35 to 50% of these representing new mutations[27]. The causative gene of NBCCS is on chromosome 9q (22.3-q31) and has no apparent heterogeneity[7,19]. This defect also occurs in relevant sporadic tumours such as basal cell carcinoma, medulloblastoma and trichoepithelioma[19,27].

The genetic mechanisms that underlie NBCCS have received considerable attention in recent years. The principal causative mutations occur in the human equivalent of the Patched (PTCH) gene, this functioning as a tumour suppressor gene as well as having other roles[9,17,20]. In *Drosophila* the Patched (PTC) gene functions as a component of the Hedgehog signalling pathway. Hedgehog (HH)[34] is a diffusible protein that binds to, and inhibits PTC. In the absence of this HH-induced inhibition PTC acts to inhibit smoothened (SMO), an adjacent transmembrane protein. When activated, SMO causes the activation of Cubitus interruptus (CI), a transcription factor that activates transcription of wingless, rotated and decaentaplegic, and represses transcription of HH[11]. The human equivalent of the Patched gene (PTCH) likewise interacts with a hedgehog signalling system. In vertebrates Sonic hedgehog (SHH) is the member of a family of hedgehog signalling proteins essential in development. Of relevance to NBCCS the Sonic Hedgehog signalling pathway is expressed during early murine tooth development and *in vitro*, the addition of exogenous SHH protein into and adjacent to early tooth germs results in abnormal epithelium invagination—hence demonstrating that the SHH/PTCH system has an essential role in odontogenesis[30]. There is evidence that mutations in PTCH account for the development

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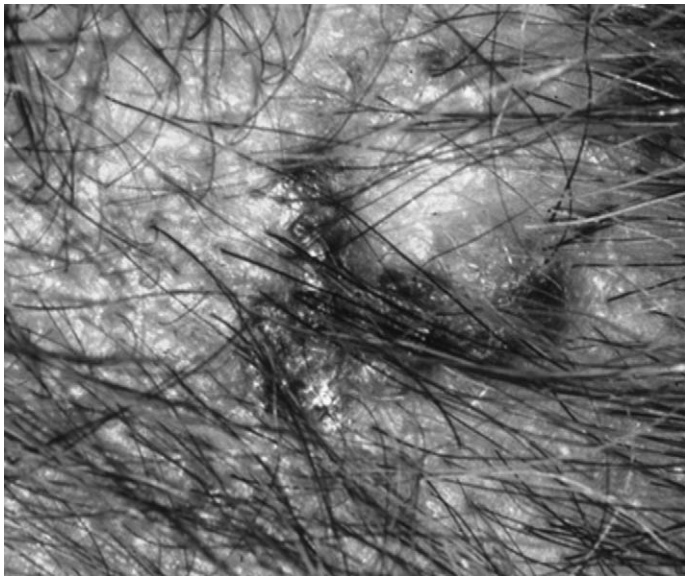

Fig. 1. Basal cell carcinoma of the scalp in NBCCS.

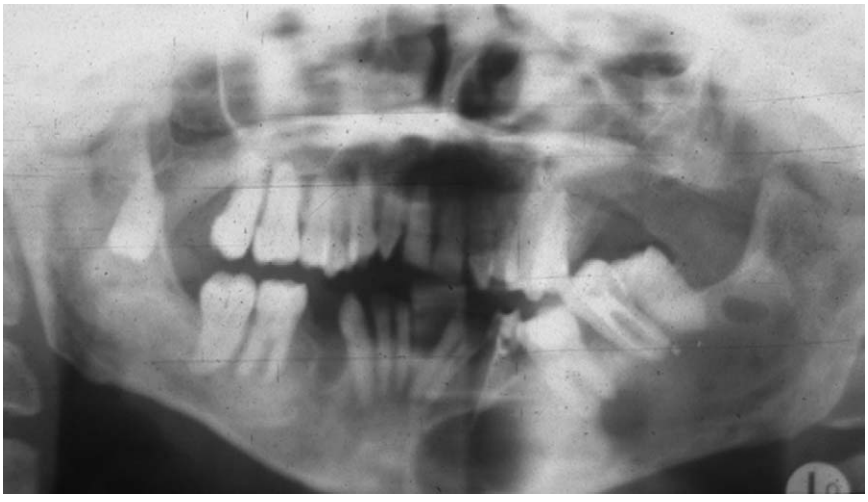

Fig. 2. Radiological features of multiple OKCs and tooth displacement in a patient affected by NBCCS.

of odontogenic keratocysts as well as the tumours associated with NBCCS.

The majority of PTCH mutations so far detected in NBCCS patients lead to premature truncation of PTCH protein[30,34,76–78,82] however, neither mutational hot spot nor apparent genotype–phenotype correlation has been found[82]. Sixty-five PTCH mutations have been reported in association with NBCCS[30], but in a recent study[48] two novel mutations of the PTCH gene, I805X/2395delC and Y93/C297A, were detected in two unrelated Japanese patients. Neither of the two mutations identified has been reported before, although previous studies were mainly of African and Caucasian patients[48].

There is also a second PTCH gene, located at 1p32-p34, but at present there has been only one report of its mutation in an isolated basal cell carcinoma and not in NBCCS[28,70].

Mutations within PTCH occur in sporadic odontogenic keratocysts as well as those associated with NBCCS[41]. It is suggested that a 'two-hit' mechanism may underly the variable expression of NBCCS and sporadic keratocysts. In NBCCS the basal cell carcinomas and keratocysts arise as a consequence of a 'first hit' of allelic loss of PTCH within precursor cells. The development of basal cell carcinomas and keratocysts in the absence of NBCCS reflects two somatic 'hits' in which there are mutations of PTCH within locally susceptible cells that ultimately result in allelic loss. It is also possible that other defects within hedgehog signalling pathways may account for some of the defects of NBCCS, as these would of course affect epithelial proliferation.

The variable phenotypic expression of NBCCS must reflect variations in penetrance, the expression of different mutations within the same gene and/or the effects of modifier genes and environmental factors, thus it would be not unexpected for affected patients and their family members to have a spectrum of different genetic and clinical anomalies[30].

Clinical features

The principal clinical features of NBCCS comprise multiple odontogenic keratocysts (OKCs), basal cell naevi and skeletal anomalies, particularly of the thoracic cavity (Table 1). The diagnostic criteria of NBCCS are summarized in Table 2[4,17,38,64].

Skin lesions

The most frequent skin lesions of NBCCS are cutaneous basal cell carcinomas (BCCs). These may be much more frequent in affected whites (80%) than blacks (38%)[23,35]. Epidemiological studies[20] suggest that sunlight, and particularly UVB radiation, is a strong risk factor for the formation of BCC. The relatively low frequency of these lesions in African-Americans probably reflects the protective action of melanotic pigmentation from ultraviolet light[35]. It has recently been demonstrated that UV irradiation enhances BCC development in mice with PTCH gene mutation[2], thus confirming that BCC development in NBCCS patients is enhanced by UV irradiation. It is therefore important to protect the skin of patients at risk of, or known to have NBCCS, from sunlight, especially in early life, before the expression of clinical manifestations is complete[48].

The basal cell carcinomas of NBCCS have a spectrum of clinical presentations varying from light to brown dark papules, with a smooth surface and hard consistency, to pigmented ulcerative plaques[42] of 1 mm to 10 mm diameter. The number of BCCs may vary from one to thousands. The carcinomas become clinically manifest between puberty and 35 years of age[27] and mostly affect thoracic and cervico-facial skin surfaces. The periorbital areas, eyelids, nose,

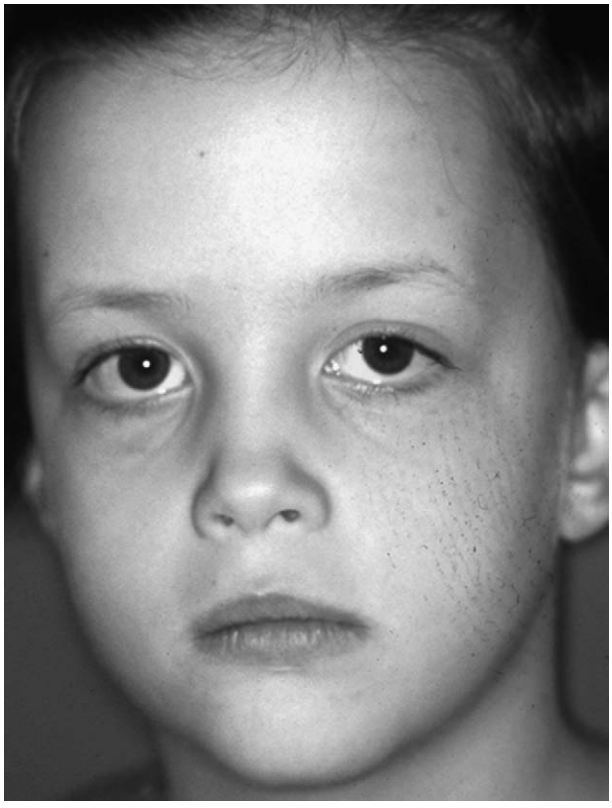

Fig. 3. Mild hypertelorism in a child with NBCCS.

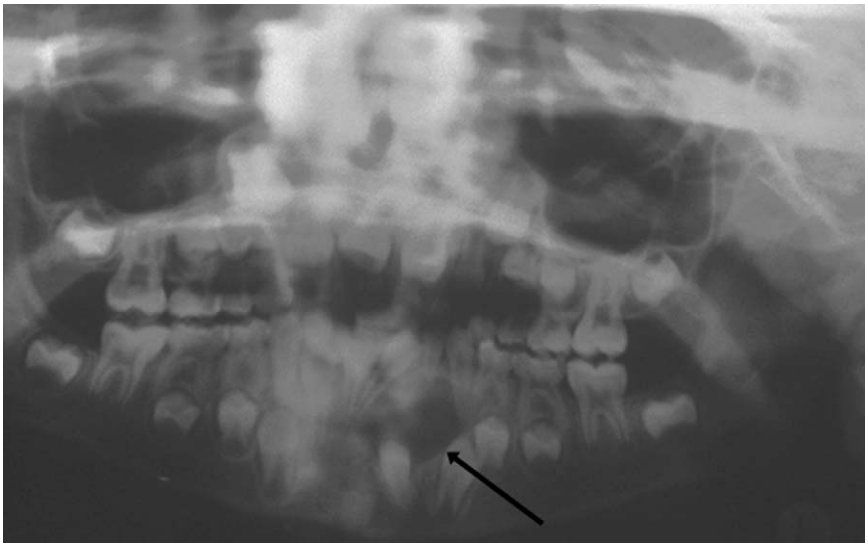

Fig. 4. Radiological features of odontogenic keratocyst in the same child affected by NBCCS.

malar region, and upper lip are the most commonly affected facial sites[26].

Few of the BCCs of NBCCS become notably troublesome, the majority remaining localized within the epidermis, often for years, before invading the underlying dermis. The BCCs usually only invade locally[15] and evidence of aggressive transformation is heralded by an increase in size and the development of ulceration, bleeding, and crusting. Histologically BCCs in NBCCS cannot be differentiated from BCCs unrelated to NBCCS.

A spectrum of other cutaneous anomalies can arise, particularly sebaceous cysts (20%)[22] and pits of the palms and soles[13,22,25,56]. The latter arise in 50–65% of patients[13] with NBCCS, are usually 1–3 mm in depth and 2–3 mm in diameter and are caused by localized partial or complete absence of dense keratin[18]. The pits usually develop in the second decade, increase in number with age, and may total more than 500[29].

Odontogenic keratocysts

Odontogenic keratocysts (OKCs) arise in up to 75% of patients with NBCCS[13,41,65]. The OKCs can be the first features of the syndrome (usually during the first decade of life)[12,13,50] and are typically found as incidental radiographic findings, for example at orthodontic assessment, although they may also manifest clinically if they became infected or cause symptoms such as swelling or trigeminal neuropathy[6].

The OKCs in NBCCS usually comprise unilocular and/or multilocular radiolucencies of the posterior body, angle or ramus of the mandible[50] (Fig. 1). The lesions are often bilateral although can be unilateral[13,45]. In young patients, the cysts can cause displacement of the developing teeth (Fig. 4), may be associated with an unerrupted tooth, and occasionally may cause root resorption[26]. The OKCs are locally destructive, spreading within the bone and causing little lateral expansion.

The histologic features of OKCs include a thin parakeratinized or orthokeratinized stratified squamous epithelium (usually five to eight cells in thickness), a well defined basal cell layer generally without rete peg formation, an uninflamed fibrous capsule and a lumen containing desquamated keratin[8,39,72]. The parakeratin lining predominates in up to 97% of OKCs. The connective tissue wall often contains small islands of epithelium and small satellite or 'daughter' cysts.

The cysts previously had a strong tendency (60%) to recur following local resection, possibly reflecting the thin lining and/or presence of satellite cysts within the capsule of the OKCs[1]. Although some authors have reported that OKCs with an orthokeratinized lining have much lower incidence of recurrence than the parakeratinized variants[6,8,10,87], there is little published supporting evidence.

It is suggested that the OKCs may have some premalignant potential[16,49]. Certainly p53 expression[52] may be enhanced in OKCs associated with SCC[44,69,86] and aggressive OKCs with a local behaviour may be associated with cyclin D1 or p53 overexpression[46,86]. Squamous cell carcinoma can arise in

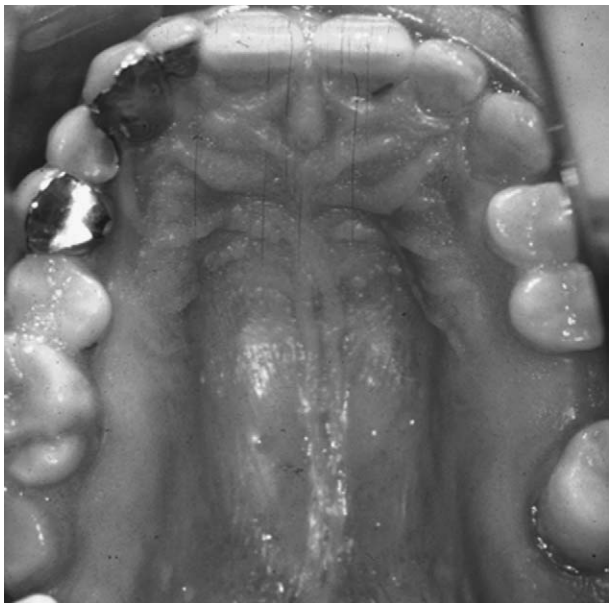

Fig. 5. High arched palate in NBCCS.

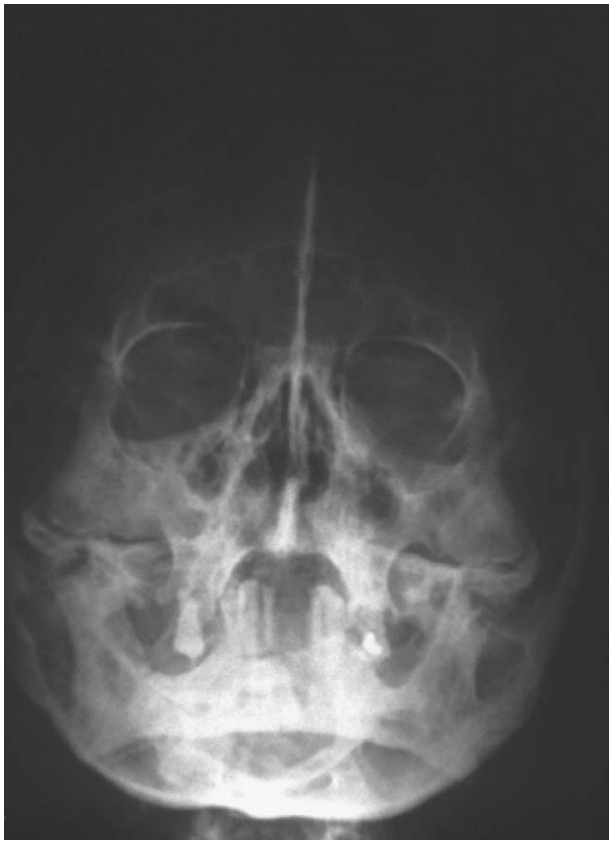

Fig. 6. Radiological features of calcification of the falx in patient affected by NBCCS.

keratocysts in patients with NBCCS following radiotherapy for facial basal cell carcinomas[44,49]. Nevertheless the actual frequency of malignant transformation seems to be low, and the precise oncogenic mechanisms associated with OKCs remain unclear.

Skeletal anomalies

Almost 70% of patients with NBCCS have some degree of cranio-facial anomaly[24,32,33]. This can comprise a high and broad forehead, frontal and parietal bossing, sometimes with highly arched eyebrows[22,35,65]. A broad nasal root is common and may be associated with ocular hypertelorism[22,35] (Fig. 2). The maxilla may be hypoplastic and there may be mandibular hyperplasia with variable prognathism[22,35,54]. Other less common anomalies include a high-arched palate (Fig. 5), cleft palate and lip, malocclusions, impaction and agenesis of teeth[22,35,43,54].

Thoracic cage anomalies are common (43%) particularly bifid and fused ribs[13,35,42]. Vertebral anomalies can arise in up to 31% of patients and can include spina bifida occulta, kyphoscoliosis, fusion defects and hemivertebrae[13,35]. A marked syndactyly of toes and polydactyly may rarely occur (3%)[35,65]. Ectopic calcification (65–92%) of the falx cerebri (Fig. 6), tentorium cerebelli and bridged sella may also be detected radiologically[35,42,65].

Other possible features of NBCCS

A wide range of other clinical anomalies has been reported in patients with NBCCS as summarized in Table 2.

Management and treatment

Although NBCCS has been described as a triad of clinical features, a wide spectrum of other anomalies are now known to be associated with the syndrome. As a consequence of this highly variable clinical presentations patients potentially affected with NBCCS must be evaluated by several relevant specialists to precisely confirm the diagnosis, detect the likely genetic basis, provide appropriate genetic counselling and manage the various clinical manifestations.

The management of affected patients depends clearly on the specific anomalies present. Early diagnosis often enables conservative therapies to be undertaken as opposed to more complex treatment and of course allows patients and their families to be made aware of the likely hereditary risks of the disorder.

Odontogenic keratocysts

The treatment of odontogenic keratocysts in patients affected by NBCCS it is not different from the one proposed for OKCs in patients not affected by the syndrome[5,50]. Early diagnosis and treatment with close clinical and radiological follow-up is as important as the actual surgical treatment[6]. Histopathological examination of the lesional tissue is essential, as the radiological features of keratocysts can mimic other disorders (e.g. ameloblastoma).

Table 1. The diagnostic criteria of Nevoid Basal Cell Carcinoma Syndrome[15]

The diagnosis of NBCCS requires the presence of two major, or one major and two minor criteria:

Major criteria:

1. More than two basal cell carcinomas (BCC) or one BCC under the age of 20 years (Fig. 1)
2. Histologically-proven odontogenic keratocysts of the jaw (Fig. 2)
3. Three or more cutaneous palmar or plantar pits
4. Bifid, fused or markedly splayed ribs
5. First degree relative with NBCCS

Minor criteria:

Any one of the following features:

1. Proven macrocephaly, after adjustment for height
2. One of several orofacial congenital malformations: cleft lip or palate, frontal bossing, 'coarse face', moderate or severe hypertelorism (Fig. 3)
3. Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
4. Radiological abnormalities: Bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modelling defects of the hands and feet, or flame shaped lucencies or the hands or feet
5. Ovarian fibroma
6. Medulloblastoma

Table 2. Anomalies in Nevoid Basal Cell Carcinoma Syndrome

Skeletal anomalies
Bifid ribs
Splayed/fused ribs
Cervical ribs
Absent/rudimentary ribs (26%)
Scoliosis
Hemivertebrae
Flame-shaped lucencies hand/feet
Polydactyly
Syndactyly
Shortened 4th metacarpal

Craniofacial anomalies
Frontal bossing (25%)
Brachycephaly
Macrocephaly (40%)
'Coarse face' (50%)
Calcification of falces (37–79%)
Tentorium cerebellum calcification
Bridged sella turcica

Neurological anomalies
Agenesis/disgenesis of corpus callosum
Congenital hydrocephalus
Mental retardation
Medulloblastoma (3–5%)
Meningioma (1% or less)
Schizoid personality

Oropharyngeal anomalies
Cleft lip and/or palate (4%)
High-arched palate or prominent palatine ridges (40%)
Odontogenic keratocysts (75%)
Malocclusion(s) (maxillary hypoplasia and mandibular hyperplasia, cleft palate)
Dental ectopic position
Impacted teeth and/or agenesis

Skin anomalies
Basal Cell Carcinoma (50–97%)
Palmar and/or plantar pits (90%)

Sexual anomalies
Uterine and ovarian fibromas (15%)
Calcified ovarian cysts
Supernumerary nipple
Hypogonadism and cryptorchidism

Ophthalmic anomalies
Congenital amaurosis
Exotropia
Hypertelorism (40%)
Ptosis
Internal strabismus (15%)
Glaucoma
Coloboma
Blindness

Cardiac anomalies
Cardiac fibroma (3%)

There are no detailed studies of the treatment of large series of OKCs associated only with NBCCS. However, as it is known that OKCs in NBCCS are more likely to recur than those in otherwise healthy individuals[12,27,66,72,85], there is a need for effective long term follow-up of patients with NBCCS. In addition there should be a low tolerance for detailed radiological and histopathological investigation of possible new, or recurrent cystic disease in NBCCS.

In view of the lining being thin and friable, and the possible presence of satellite cysts, a solely surgical approach to the treatment of OKCs of NBCCS patients is unlikely to be successful.

As a consequence adjunctive therapies such as cryotherapy or Carnoy's solution are always indicated[62,72,81]. Carnoy's solution is particularly effective and generally safe. It has been reported that the application of Carnoy's solution into the cyst cavity for 3 min after enucleation results in the lowest rate of recurrence (0–2.5%) without damage to the inferior alveolar nerve in OKCs unassociated with NBCCS[79–81,83]. However, the results of a large study suggested that the solution should not be in contact with the exposed nerve for more than 2 min. A strict follow-up protocol (every year into the first 5 years and thereafter every 2 years) to allow early surgical intervention in case of recurrence is essential[73].

More radical surgical resection may be required for large OKCs[1] especially in NBCCS patients but the extensive nature of the surgery may be unacceptable, particularly in young patients. As a consequence more conservative approaches have been also proposed for young patients with large cysts to preserve soft and hard tissues including the teeth. These comprise marsupialization of the cyst or decompression followed by secondary enucleation, but these methods usually do not provide long-term effective care[3].

As detailed previously, up to 60% of NBCCS patients may have recurrence of OKCs.[50]. However, often the development of new cysts in these patients who have shown a considerable tendency to grow new cysts[72] may be confused with recurrence; thus it can be difficult to determine the exact rate of recurrence of these cysts[6]. It has been suggested that the recurrence rate of OKCs in patients with NBCCS may be higher than of OKCs in healthy subjects, probably as these former patients have an inherited tendency within the basal layer of their epithelium to develop new cysts[12,66,85].

Basal cell carcinomas

As a consequence of the large number of lesions, the treatment of BCCs in NBCCS can be difficult[36]. Curettage and cautery/electrodesiccation is probably the most appropriate effective technique for small, well defined primary lesions without aggressive histology[61,67,68,71] although this is generally not recommended[47] for the management of recurrent lesions as well those in 'high-risk' sites[37] such as the nasal, naso-labial and periorbital skin[51,57,58,67]. Cryosurgery may be used to treat solitary and multiple BCCs, but it is less effective for the treatment of recurrent BCCs[57,58].

Microscopically directed excision is particularly useful for thicker concave lesions, and some studies suggest combined use of this with ultrapulse CO_2 laser therapy[36,40]. Mohs' micrographic surgery also offers accurate and conservative removal of recurrent and aggressive BCCs, in high-risk sites. Local radiotherapy is contraindicated[35] in view of the risk of tumour

recurrence or enlargement[42]. Photodynamic therapy (PDT) with topical application of delta-aminolaevulinic acid has been suggested[74] to be useful, but only for the treatment of superficial, flat lesions[36,55,73,84].

Topical application of 0.1% 5-fluorouracil twice daily may be indicated for the management of low-risk, superficial BCCs without hair follicle involvement[21], while intralesional application of interferon alfa-2b has been suggested for the removal of small papular lesions[36]. Oral retinoids may prevent or delay the development and recurrence of BCCs[31]. However, the potential toxicity of these agents at the high dosage required, rules out their long term clinical use[53]. Recently, paclitaxel (Taxol), a chemotherapeutic agent active against a variety of tumours[59] has been proposed as a promising alternative for the treatment of multiple aggressive BCCs, particularly in cases where the location, size and aggressive nature of the tumours are challenging.

Genetic counselling and management of NBCCS families

All siblings and children members of patients with NBCCS must be clinically and genetically investigated for evidence of NBCCS. Objective genetic examination is important to identify unaffected relatives. This should be undertaken early in the neonatal period and all children likely to be carrying the causative gene should closely be evaluated clinically[35,42]. If a family contains more than one affected individual, molecular methods of analysis can be undertaken.

If there is only one affected family member or the diagnosis is in doubt, direct mutation detection can be done. This technique includes PCR amplification of exons encompassing the coding region with flanking regions containing intron–exon junctions. The PCR products are screened for mutations by SSCP analysis, SSCP variants are then sequenced. If no variants are detected, the entire coding sequence with intron–exon junctions is sequenced.

Where there is a family history of Gorlin–Goltz syndrome it is possible to carry out genetic analysis of individual family members to identify carriers. It is also possible to perform this test prenatally by choriocentesis, but only after 10–12 weeks gestation[63].

Contemporary antenatal ultrasonography provides both diagnostic and prognostic information. Indeed a prenatal ultrasound scan at 19 weeks gestation can identify CNS malformations, skeletal anomalies and intracardiac tumours. The detection of these manifestations often gives better estimation of the severity of the condition than DNA analysis[4].

Post-natally it is suggested that children likely to be carriers of the defective gene should have 6 monthly magnetic resonance imaging until the age of 7 to detect medulloblastoma. After this age the risk of development of medulloblastoma is greatly reduced[15,35,42]. Early detection of medulloblastoma facilitates any required complete surgical eradication of the tumour; likewise regular echocardiography permits the early detection of cardiac fibroma[15]. Regular early dental surveillance with appropriate radiology should be undertaken until 40 years of age[15,27,35,42] to detect the possible presence of OKCs. Cutaneous lesions can be detected by regular examination by a specialist dermatologist[27], while ovarian fibromas can be detected by ultrasound scanning in the first and second decades[35].

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