Manifestations of Gorlin-Goltz syndrome

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ABSTRACT

INTRODUCTION: Gorlin-Goltz syndrome is an uncommon hereditary condition caused by mutations in the *PTCH1* gene causing a wide range of developmental abnormalities. Multiple basal cell carcinomas, palmoplantar pits and jaw cysts are cardinal features. Many clinicians are unfamiliar with the different manifestations and the fact that patients are especially sensitive to ionizing radiation.

MATERIAL AND METHODS: This was a retrospective analysis of patients with Gorlin-Goltz syndrome seen at the Department of Dermatology and Allergy Centre or at Department of Plastic Surgery, Odense University Hospital, Denmark, in the period from 1994 to 2013.

RESULTS: A total of 17 patients from eight families fulfilled the diagnostic criteria. In all, 14 patients had basal cell carcinomas, 12 patients had jaw cysts and ten patients had calcification of the falx cerebri. Other clinical features were frontal bossing, kyphoscoliosis, rib anomalies, coalitio, cleft lip/palate, eye anomalies, milia and syndactyly. In one family, medulloblastoma and astrocytoma occurred. Traditional treatment principles of basal cell carcinomas were used including radiotherapy performed in six patients. *PTCH1* mutations were identified in six families and none of these mutations had previously been described.

CONCLUSION: The patient cohort illustrates classic and rare disease manifestations. It is necessary to remind clinicians that radiation therapy in Gorlin-Goltz syndrome is relatively contraindicated. Today, mutation analysis can be used for confirmation of the diagnosis and for predictive genetic testing. Patients should be offered genetic counselling and life-long surveillance.

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Gorlin-Goltz syndrome, also known as nevoid basal cell carcinoma syndrome, was first recognised in 1894 when Jarisch and White described the essential phenotypic features of the nevoid basal cell carcinoma syndrome [1, 2]. Almost a hundred years later, in 1960, Dr. Robert Gorlin (Professor of Oral Pathology, University of Minnesota School of Dentistry, US) and Dr. Robert Goltz (Clinical Assistant Professor of Dermatology, University of Minnesota Medical School, US) delineated the different clinical features in their paper on "multiple naevoid basal cell epithelioma, jaw cysts and bifid rib syndrome" [3]. It is a rare syndrome with an estimated prevalence varying from 1/57,000 to 1/256,000 people. Males and females are equally affected [4, 5].

This multi-systemic disease is associated with many different signs and symptoms causing skin, skeletal, craniofacial, neurological, oropharyngeal, genito-urinary and cardiac abnormalities [3-9]. The main clinical features are basal cell carcinomas, odontogenic keratocysts, palmoplantar pits, calcification of the falx cerebri, medulloblastoma and first-degree relative with Gorlin-Goltz syndrome. These six characteristics are considered the major clinical criteria for the diagnosis (**Table 1**) [9]. The diagnostic criteria were originally defined by Evans et al in 1993 and later modified by Kimonis et al in 1997 and Bree et al in 2011 [5, 8, 9].

The most frequent skin signs of Gorlin-Goltz syndrome are basal cell carcinomas. The number of basal cell carcinomas varies from a few to several thousands, most commonly located at the face, back and chest. Most basal cell carcinomas appear between puberty and 35 years of age although they have been reported to occur as early as at two years of age. Odontogenic keratocysts are the main oral sign and occur in the mandible about three times as often as in the maxilla. Palmoplantar pits are another major clinical sign with patients having small 1-2-mm asymmetric palmar and/or plantar pits. The pits are permanent and increase in number with age. When pits are found in a child, they are a strong diagnostic marker [4].

Skeletal abnormalities with skull, rib and vertebral column shape defects are also frequent. Examples are anteriorly splayed, fused, partially missing, hypoplastic or bifid ribs. Kyphoscoliosis is less common [4].

About 2-5% of patients may develop a brain tumour, mostly medulloblastoma, which can be a potential cause of early death [4].

Gorlin-Goltz syndrome is caused by mutations in genes encoding key proteins, especially *PTCH1*, encoding *protein patched homolog 1* in the hedgehog signalling pathway, controlling growth and development of normal tissue [4]. The disease is transmitted as an autosomal dominant trait with complete penetrance and variable expressivity. Data suggest that patched 1 acts as a tumour suppressor. In fact, also sporadic basal cell carcinomas have somatic mutations in *PTCH1* [10, 11].

MATERIAL AND METHODS

A retrospective analysis was performed on all patients with Gorlin-Goltz syndrome (diagnosis code Q 82.8 W) seen at the Department of Dermatology and Allergy Centre or at the Department of Plastic Surgery, Odense

ORIGINAL ARTICLE

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TABLE 1

Diagnosis of Gorlin-Goltz syndrome can be made in the presence of: a) 2 major criteria, b) 1 major criteria and molecular confirmation or c) 1 major and 2 minor criteria.

Major criteria

1. Excessive numbers of basal cell carcinomas out of proportion with prior sun exposure and skin type or < 20 yrs of age
2. Odontogenic keratocysts of the jaws prior to 20 yrs of age
3. Palmar or plantar pitting
4. Lamellar calcification of the falx cerebri
5. Medulloblastoma, typically desmoplastic
6. 1st degree relative with Gorlin-Goltz syndrome

Minor criteria

1. Rib anomalies
2. Other specific skeletal malformations and radiologic changes (i.e. vertebral anomalies, kyphoscoliosis, short 4th metacarpals, postaxial polydactyly)
3. Macrocephaly
4. Cleft lip and/or palate
5. Ovarian/cardiac fibroma
6. Lymphomesenteric cysts
7. Ocular abnormalities (i.e. strabismus, hypertelorism, congenital cataracts, glaucoma, coloboma)

University Hospital, Denmark, between January 1994 and June 2013. Medical records were reviewed and the diagnosis was confirmed based on the major and minor criteria described in Table 1 as well as the result of the *PTCH1* mutation analysis. Data on age at diagnosis and first basal cell carcinoma were drawn from the patients' medical files. A total of 17 patients fulfilled the criteria and were included in the study, and the patient data were collected retrospectively from the hospital records. Special focus was given to family history, number of basal cell carcinomas and syndrome-related manifestations and complications.

Trial registration: not relevant.

RESULTS

A total of eight families with 17 affected family members were ascertained in the study period. The average age at diagnosis was 21 years (range: 0-53 years). The patient group included seven males and ten females. The largest family (IV) had six affected family members in four generations (**Figure 1**). The oldest known affected family member died of an astrocytoma and the youngest family member is a one-year-old girl who was diagnosed and treated for a presumed congenital medulloblastoma. Three patients were sporadic cases, and 14 patients (82%) had other affected family members.

Mutation analysis of the *PTCH1*gene was performed in six of the eight families, and a putative disease-causing mutation was identified in all tested families (**Table 2**). Three were frame shift mutations (c.1139_1142 delATGT, c.2287dupG, and c.3673delA), and three were splice site mutations (1603-2A>C, 2703+1G>T, and 2875+2G>T).

Table 2 shows the distribution of Gorlin-Goltz syndrome manifestations in the presented 17 patients and **Figure 2** illustrates some of the characteristic disease manifestations.

Treatment of basal cell carcinomas in our patient cohort consisted of curettage, surgery, cryotherapy, excision, photodynamic therapy, radiation therapy and imiquimod. The 16 patients who remain alive are being followed regularly at the Department of Dermatology and Allergy Centre.

DISCUSSION

In order to make a diagnosis of the Gorlin-Goltz syndrome, the diagnostic criteria have to be fulfilled. The most important clinical criteria required for establishing a diagnosis of this syndrome are the presence of basal cell carcinomas, jaw cysts and palmoplantar pits besides a family history of Gorlin-Goltz syndrome. The diagnostic criteria presented in this article (Table 1) are the most recently published criteria according to a consensus statement from the first international colloquium on Gorlin-Goltz syndrome. These criteria are based on very well-established and original criteria by Evans et al [5], but they have been modernised with the inclusion of molecular confirmation, substitution of the major criterion bifid ribs with medulloblastoma and also some changes in minor criteria which now includes cardiac fibroma. De novo cases can be especially challenging to diagnose according to the diagnostic criteria, but palmar pitting, medulloblastoma or lamellar calcification of the

FIGURE 1

Pedigree showing six affected family members in four generations with Gorlin-Goltz syndrome belonging to family IV.

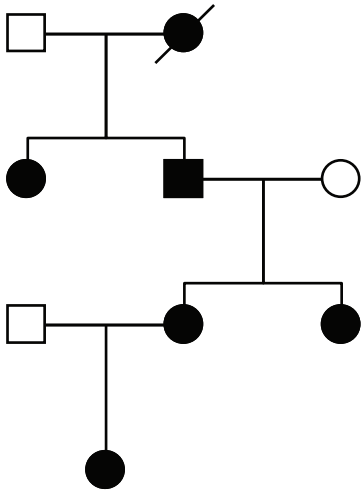


TABLE 2

Characteristics of 17 patients with Gorlin-Goltz syndrome.

Patient no.	Family no.	Age at diagnosis/follow-up, yrs	Gender	PTCH1 mutation detected in the family	BCCs, n (age at first BCC, yrs)	Odontogenic keratocysts	Palmo plantar pits	Calcification of the falx cerebri	Rib anomalies	Miscellaneous
1	I	38/30	M	c.2287dupG	> 150 (30)	+	+	Not registered	Not registered	-
2	I	10/0	M	c.2287dupG	> 20 (36)	Not registered	+	+	+	Kyphoscoliosis, coalitio, strabismus, frontal bossing
3	II	53/6	M	Not tested	> 30 (46)	+	Not registered	+	Not registered	
4	III	34/29	F	Not tested	> 90 (39)	+	Not registered	Not registered	+	Cleft lip palate, kyphoscoliosis
5	III	11/29	M	Not tested	1 (11)	+	Not registered	+	+	Cleft lip palate
6†	IV	47[a]/5	F	c.1139_1142delATGT	> 40 (30)	Not registered	Not registered	+	Not registered	Cleft lip palate, milia, astrocytoma
7	IV	26/31	F	c.1139_1142delATGT	> 40 (29)	+	Not registered	+	+	Amblyopia, kyphoscoliosis, strabismus
8	IV	21/30	M	c.1139_1142delATGT	> 90 (21)	+	Not registered	+	Not registered	Kyphoscoliosis, coalitio
9	IV	17/9	F	c.1139_1142delATGT	7 (20)	+	+	+	Not registered	Coalitio, frontal bossing
10	IV	16/2	F	c.1139_1142delATGT	0	+	Not registered	Not registered	Not registered	Strabismus, kyphoscoliosis, coalitio
11	IV	0/0	F	c.1139_1142delATGT	0	Not registered	Not registered	Not registered	Not registered	Medulloblastoma, milia, syndactyly
12	V	21/14	M	c.2703+1G>T	> 175 (21)	+	+	Not registered	Not registered	-
13	V	1/3	M	c.2703+1G>T	0	Not registered	Not registered	Not registered	Not registered	Syndactyly, frontal bossing
14	VI	25/20	F	c.2875+2T>G	> 200 (26)	+	Not registered	+	+	Kyphoscoliosis
15	VI	1/19	F	c.2875+2T>G	12 (8)	Not registered	Not registered	+	Not registered	Cleft lip palate, cataract, frontal bossing
16	VII	13/11	F	c.1603-2A>C	3 (24)	+	Not registered	Not registered	Not registered	Cleft lip palate, kyphoscoliosis, syndactyly
17	VIII	19/45	F	Yes (c.3673delA)	> 50 (21)	+	+	+	+	Kyphoscoliosis

† = dead; BCC = basal cell carcinoma; F = female; M = male.
a) Post mortem.

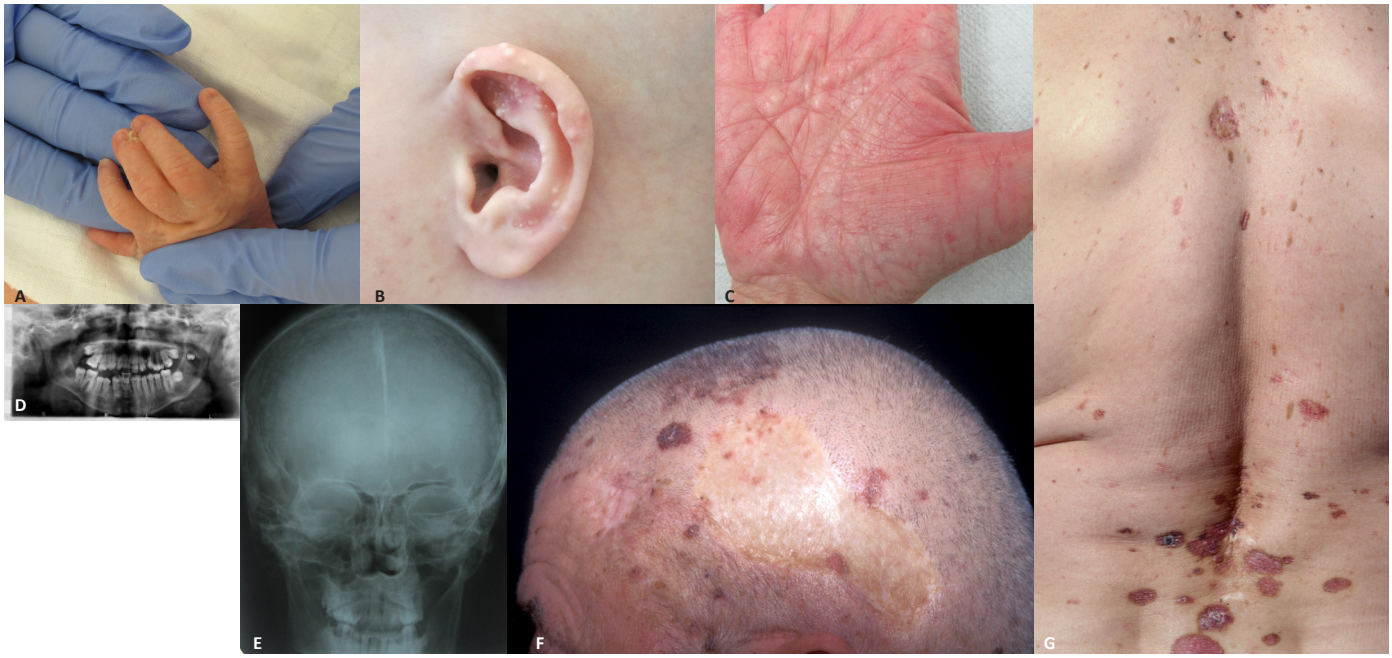
falx cerebri will give the diagnosis with molecular confirmation or two minor criteria such as cleft lip and/or palate, ocular abnormalities, cardiac fibroma or specific skeletal malformations.

The incidence of basal cell carcinomas in Gorlin-Goltz syndrome varies among ethnic groups and is reported in up to 90% of affected Caucasians [4]. In our patient cohort, the average age at diagnosis of first basal cell carcinoma was 26 years (range: 8-46 years) which correlates very well with the literature [4]. Unless the patient has been exposed to radiotherapy, the basal cell carcinomas are unlikely to occur before puberty. The number of basal cell carcinomas in our patients varied between zero and more than 200 in the observation period. In the literature, variation in the number of basal cell carcinomas ranges from a few to several thousand [4]. We used traditional treatment principles for basal cell carcinomas. Most of the basal cell carcinomas resulting from this syndrome do not become invasive and treatment strategies should take this into account [12]. Unfortunately, six patients received radiation therapy against basal cell carcinomas. This is not lege artis, as it is well-described in the literature that patients with Gorlin-Goltz syndrome may develop secondary and aggressive cancers in the radiation field with a much higher rate and shorter latency than the background population [4-9, 13]. It seems that our colleagues in different specialities (dermatology, plastic surgery and oncology) are not fully aware of the damaging effects of radiation therapy in patients with Gorlin-Goltz syndrome. Development of basal cell carcinomas is also enhanced by ultraviolet light, and patients with Gorlin-Goltz syndrome should protect their skin against sunlight.

Odontogenic keratocysts occurred in more than

FIGURE 2

Manifestations of Gorlin-Goltz syndrome: partial syndactyly of fingers (A), milia (B), palmar pits (C), X-ray of odontogenic keratocysts (D), X-ray showing calcification of the falx cerebri (E), basal cell carcinomas and scars after former treatment in a patient with scoliosis (F and G).



80% of our patients older than 20 years of age (11 out of 13). This result confirms earlier observations in the literature [4, 5]. Odontogenic keratocysts were treated by oral surgeons.

Cleft lip and/or palate abnormality was detected in five of the patients (29%), which is significantly higher than the 5% incidence described in the literature [4, 5]. Rib anomalies were reported in six patients (35%), which is in the lower range of data reported in the literature (30-60% of the cases); however, not all of our patients underwent systematic radiological examination for this abnormality.

Kyphoscoliosis was reported in eight patients (47%) and is described in the literature in 10-40% of patients. Tarsal coalitio was described in three patients among our presented cases, and we could find no references on this in the literature among patients with Gorlin-Goltz syndrome besides a publication by Ferrier & Hinrichs, who described a four-generation family with Gorlin-Goltz syndrome and a family member who underwent orthopaedic surgery because of "peroneal spastic flat feet with partial calcaneonavicular coalition" [14].

One of the present patients was diagnosed with a medulloblastoma at the age of three months, and it was suggested that the tumour was congenital. She was treated with surgery and chemotherapy. Medulloblastoma is a recognised complication of Gorlin-Goltz syndrome, and it occurs at an average age of two years of age [13]. Her great-grandmother (patient number six) died of an astrocytoma at the age of 47. Astrocytoma is a brain tumour which is not normally associated with Gorlin-Goltz syndrome, but the association has been described in the literature [4, 15]. It is also described that an astrocytoma can appear secondly to radiation therapy [4]. Patient number six had previously received radiation therapy against basal cell carcinomas on the scalp.

In general, medulloblastomas are treated with aggressive resection, chemotherapy and radiation therapy. Patients have been reported to develop myriads of invasive basal cell carcinomas and secondary intracranial and sinonasal tumours after radiation treatment for medulloblastoma [5, 6, 8, 13]. If unavoidable, these patients should receive a treatment field that only includes the posterior fossa with a skin-sparing technique [4, 8]. It is prudent to limit the amount of any type of radiation for these patients [9].

A putative disease-causing *PTCH1* mutation has been identified in six of the eight families (Table 2). None of the mutations have previously been reported. The remaining two families have not been analysed at the molecular genetic level. In the literature, at least 288 different *PTCH1* mutations have been described so far (HGMD Professional 2013.3 – 27. September 2013), but no genotype-phenotype correlations appear to exist.

A few patients have been described with mutations in the PTCH2 or the *SUFU* genes [16]. The hedgehog pathway has been recognised to be a key regulator of cell growth and differentiation during development. It also controls epithelial and mesenchymal interactions in many tissues during embryogenesis [10]. The pathway is typically inactive in adults. Aberrant hedgehog signalling can lead to increased expression of proteins essential for cell proliferation and cancer. Recently, drugs have been developed to block hedgehog signalling, such as the hedgehog pathway inhibitor Vismodegib [11]. The drug is licensed for use in advanced basal cell cancer and there are on-going trials in treatment of medulloblastoma [17, 18].

Management of Gorlin-Goltz syndrome requires a multidisciplinary approach because of the multiple organ-related anomalies. Analysis for Gorlin-Goltz syndrome can be performed in pregnancy by an ultrasound scan with the detection of cardiac tumours, enlarged head or developmental anomalies such as cleft palate [5, 7]. In families with a known *PTCH1* mutation, the diagnosis can be performed in early pregnancy on DNA from a chorionic villus biopsy or an amniotic fluid sample. Some foetuses with Gorlin-Goltz syndrome may need assistance in delivery because of macrocephaly [4]. Early detection of the syndrome makes it possible to minimise the childhood and adult complications related to Gorlin-Goltz syndrome. Furthermore, those who test negative for a known familial *PTCH1* mutation before or immediately after birth can be removed from the surveillance programme in the neonatal period [5]. Patients with a known *PTCH1* mutation should also be informed about the possibility of early prenatal testing and termination of an affected foetus, and about the possibility of preimplantation genetic testing.

Soon after birth, an examination of infants at risk should be performed to reveal any presence of macrocephaly, cleft palate, eye disease or rib and vertebral anomalies. An echocardiogram can reveal cardiac fibromas. A neurological examination and measurement of head circumference is recommended every six months together with annual magnetic resonance imaging (MRI) of the brain until the age of seven years, after which a medulloblastoma is unlikely to appear [5, 8]. Dental screening with an orthopantomogramme of the jaw is recommended from 4-8 years of age until 40 years of age with a view to detecting jaw cysts [5, 7]. A total skin examination should be performed at least annually from puberty, but may need to be done more frequently if rapidly evolving skin lesions are present [4, 5]. Ovarian fibromas can be detected in the first and second decades by an ultrasound scan [7].

If a diagnosis of Gorlin-Goltz syndrome is suspected, it is recommended to refer the patient to genetic counselling. All first-degree relatives of patients with a known mutation should be offered predictive molecular genetic testing [7].

In conclusion, the present case series highlights Gorlin-Goltz syndrome as an uncommon multi-systemic disease, which may be underdiagnosed. It is therefore important that different health specialists have some basic knowledge of the main features of this syndrome and are aware that ionising radiation should be avoided if possible in the treatment of basal cell carcinomas and in the diagnosis of associated disorders. It is a hereditary condition, and all patients should be offered genetic counselling, and their first-degree relatives should be offered clinical examination. If a disease causing *PTCH1* mutation has been identified in the family, predictive genetic testing can be offered to relatives. Patients should be offered a multidisciplinary life-long surveillance programme to reduce morbidity as the syndrome may have potentially lethal complications also in early childhood. Morbidity can be reduced when basal cell carcinomas and keratocysts are treated early to minimise destruction and deformities of skin and bone.

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