Chapter 29
Gorlin-Goltz Syndrome (Nevoid Basal Cell Carcinoma Syndrome)

Christos P. Panteliadis and Reinhard E. Friedrich

Contents

Introduction

Epidemiological analyses estimate the incidence of GGS to be 1 per 50,000–150,000 in the general population. The causative gene is the analogue to the patched (PTCH) gene of the fly.

Drosophila. PTCH1 maps to chromosome 9q22.3–31 [1]. In addition to the mutations of PTCH1, mutations in the genes PTCH2 [2] and suppressor of fused (SUFU) [3] were also detected in GGS patients. There are differences in the phenotype of the GGS patient in relation to the site of mutation [4]. Therapy is symptomatic.

C. P. Panteliadis (✉)
Department of Paediatric Neurology and Developmental Neurology, Aristotle University of Thessaloniki, Thessaloniki, Greece
e-mail: cpanteliadis@hotmail.gr

R. E. Friedrich
Division of Paediatric Neurology, Aristotle University of Thessaloniki, Thessaloniki, Greece

Department of Oral and Craniomaxillofacial Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
e-mail: r.friedrich@uke.de

C. P. Panteliadis et al. (eds.), *Neurocutaneous Disorders*,
https://doi.org/10.1007/978-3-030-87893-1_29

History. In the late nineteenth century, Jarisch and White made the first descriptions of patients with findings corresponding to the current diagnostic criteria of GGS [5, 6]. Gorlin and Goltz coined their names to the condition in 1960 after presenting an accurate description of the hereditary nature of the disease, phenotype, and main clinical characteristics [7]. Soon after the description of the syndrome, Satinoff and Wells described two Egyptian skeletons of the Dynastic Period with skeletal anomalies compatible with findings recorded in GGS. The skeletons (Istituto di Antropologia, University of Turin) showed mandibular cysts and multiple bony cavities in maxilla, bifid ribs, os sacrum with incomplete fusion of the caudal laminae, and slightly enlarged sella turcica [8].

Terminology. GGS is mislabelled at times as "basal cell nevus syndrome" [9, 10]. The term "nevus", however, is a misnomer in terms of describing the biological quality of the syndrome's skin lesions because the cutaneous lesions frequently represent aggressive basal cell carcinoma (BCC) as seen in GGS, rather than a benign lesion as the term "nevus" implies. According to Gorlin, the general term "nevoid basal cell carcinoma syndrome" describes more precisely the potential risk of the affected patients from skin neoplasms [11]. GGS patients are at risk of more non-cutaneous neoplasms than the general population, so the medical assessment of the patient must include many functions and organs. Patients with this rare syndrome often have anomalies in multiple organs, many of which are subtle.

Clinical Characteristics

General characteristics. General characteristics in GGS are BCC, jaw keratocysts, and cerebral calcifications [12, 13] (Fig. 29.1a, b, c). However, general body characteristics are often of decisive importance for the first examination of patients in order to establish the diagnosis, in particular in young individuals [14–18]. The main visible facial feature frequently is a "coarse face" with an enlarged head, frontal bossing, hypertelorism, and broad nasal root [16, 19, 20]. About 70% of patients with this syndrome have some degree of craniofacial anomalies. GGS patients are often tall in relation to their next of kin. This finding is often noticed already in childhood.

Skin

Whereas life expectancy in NBCCS is not significantly different from average, the neoplastic alterations can be a dominant burden in the patient's life. The patients usually bear pronounced skin sensitivity to ionizing radiation, including ultraviolet light [21, 22]. They have an increased rate of BCC compared to the general population. BCCs may appear as early as 2 years of age, but the first manifestations usually appear between puberty and 35 years of age [23]. The majority (90%) of GGS

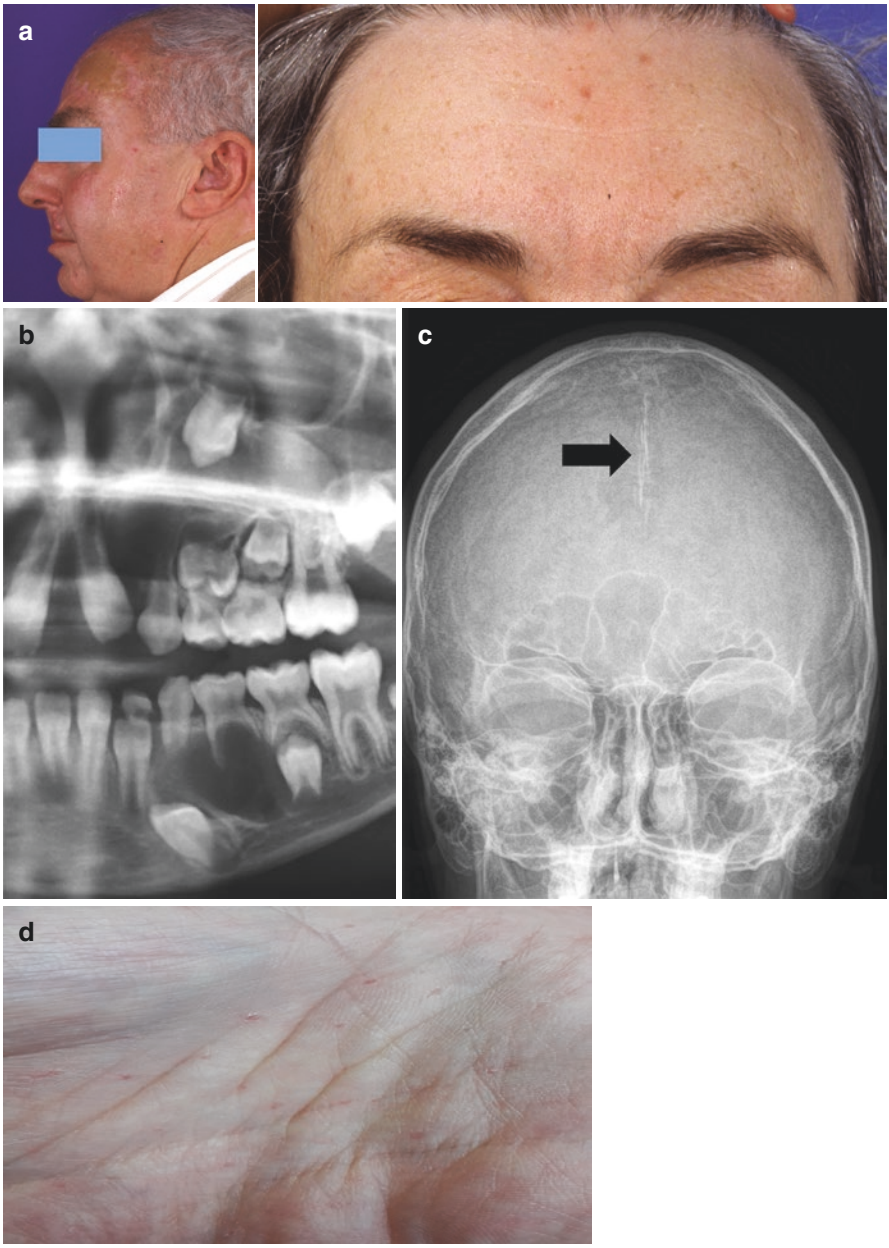

Fig. 29.1 (**a**) Left: Profile of a patient with GGS. Multiple scars and skin transplant resulting from uncounted surgical procedures for BCC excision. Note two scabbing ulcerations of pinna. Right: Frontal bossing and multiple nevi in a patient with GGS. (**b**) Orthopantomography of jaws of a young patient with GGS (cropped image, left body side). Note multiple cystic lesions in both jaws and retained permanent teeth. All cystic lesions proved to be odontogenic keratocysts (OKC). While the X-ray findings of solitary keratocysts are ambiguous, syndromic lesions mostly present as multiple OKC. (**c**) Posterior-anterior skull radiograph of a child with GGS. Note bilamellar ossification of falx cerebri (arrow). (**d**) Palmar pits in a GGS patient

patients develop BCC at age 30 years and older [24], which correspond strongly with increased exposure to the sun [25]. Bhattacharjee et al. [26] reported the first primary cutaneous carcinosarcoma associated with NBCCS. Reports on BCC in GGS are predominantly from Western countries. The early development of BCC in Caucasians with GGS is possibly facilitated due to their lower light protection of skin [15]. However, exposure of the skin to sunlight is not mandatory for the frequent development of BCC in GGS [25]. GGS was noted as a rare genetic disorder worldwide [27]. In addition to BCC, other skin findings like basal cell nevus, epidermal cysts [28], facial milia [29], and palmar and plantar pits are typical in GGS (65–80% of patients) (Fig. 29.1d).

Genetics

Epidemiological analyses estimate the GGS incidence to be 1 in 50,000–150,000 [30]. The disorder carries an autosomal dominant trait [14] and has been described equally in number in both sexes. Mutation of a candidate gene was identified on chromosome 9 [30] and finally characterized as the human homologue to the Drosophila patched gene (PTCH) [31]. Patched is part of the highly conserved hedgehog signalling pathway, important in determining embryonic patterning and cell fate in multiple structures of the developing embryo [32–36]. The gene causing GGS in humans is located on chromosome 9q22.3–9q31 and termed "PTCH1" [11, 37–42].

However, recent studies have shown that, in addition to PTCH1, mutations in PTCH2 (chromosome 1) can also cause GGS, although the importance of PTCH2 mutations for the development of the GGS has so far been controversially discussed [43]. Mutations in a third gene, named suppressor of fused (SUFU; chromosome 10 [44]) are relevant in determining the genetic basis of neurogenic tumours in GGS [45]. Apparently, no OKC occurs with mutations of SUFU [45]. There are obviously differences in GGS phenotype depending on the particular mutation [46].

Radiology. Radiological findings in GGS are very numerous and variable [47]. Some findings are of diagnostic relevance; others are also of functional importance. Frequent clinical and radiological manifestations include (multiple) odontogenic keratocysts (OKC; up to 75%), macrocephaly, hydrocephalus, and agenesis of the corpus callosum, bridging of sella turcica, calcification of the falx cerebri (37–79%), skeletal abnormalities such as Sprengel deformity (elevation of the scapula with rotation of its lower angle towards the spine), marked pectus deformity (about 43%), bifid ribs (40%), short fourth metacarpal bone, and syndactyly of the digits. Cleft lip and/or palate occur in 3–8% of the cases [48, 49].

The first radiological indications for a GGS can often be seen on plain radiographs. On radiographs of the thorax and spine, spina bifida occulta, and congenital abnormalities of ribs and of the shoulder(s) were found in a large proportion of patients [50]. A variant of the first cervical vertebra, the ponticulus posticus, was demonstrated by lateral cephalograms to develop in many patients with GGS [51].

However, the diagnostically relevant sella turcica bridge is a much better known radiological sign on lateral cephalometry in patients with GGS [52].

Orbit and Eye

The most frequently reported orbital and ocular findings in GGS are hypertelorism (45.5%), congenital cataract (18%), nystagmus (9%), colobomas (9%) and strabismus (63%), epiretinal membranes (36%), and myelinated optic nerve fibre layers (36%), highlighting the value of ophthalmological investigation in this patient group [53].

Jaw Cysts

OKC can be the first finding of the syndrome, which is why the treating dentists are of particular importance when introducing the differential diagnosis of GGS in patients with OKC, especially when young patients are affected without further diagnostically relevant findings being evident. OKC is a locally aggressive osteolytic jaw lesion that occurs sporadically or in association with NBCCS. Indeed, only a few patients with OKC have GGS. Recurrence of OKC is a frequent finding both in sporadic and syndromic lesions. In contrast to cutaneous cysts, the morphological and immunohistochemical profiles of syndromic and sporadic jaw cysts show no significant differences [54, 55]. Sporadic OKC rarely appears in childhood. Careful examination of children and adolescents with OKC is therefore indicated in order to rule out GGS. In a retrospective study of 50 children up to 18 years of age presenting with first diagnosis of OKC and so far not diagnosed as GGS patients revealed a high frequency of new GGS cases. Hence, clinicians should have a low threshold for referral to complete examination or genetic testing in children with even a single OKC [56].

Other Findings

Reports of other findings, particularly dysplasias and tumours, are numerous, for example, ovarian calcification, fibromas of the ovaries (20%) or heart (2%), medulloblastoma (5%), and other tumours [57, 58]. The proportion of syndromic medulloblastomas in a larger case series (n = 129) is less than 10%. Both PTCH1 and SUFU germline mutations were detected in GGS cases (2/129) [59]. In an earlier evaluation of GGS-associated findings, the proportion of patients with medulloblastomas was 3.8% (4/105) and is currently estimated at around 5%. There are assessments of the genotype-phenotype ratio of the GGS that expect a significantly higher risk of medulloblastoma in cases with SUFU mutations (33%) in contrast to PTCH1 mutations (<2%) [60].

Diagnosis

Kimonis et al. [60, 61] have proposed that diagnosis of GGS can be made in an individual suspected of being affected by GGS if two major criteria, or one major and two minor criteria, are revealed.

The major criteria consist of two or more BCC in individuals younger than 20 years; OKC of the jaw (Fig. 29.1b); three or more palmar or plantar pits (Fig. 29.1d); bilamellar calcification of the falx cerebri (Fig. 29.1c), bifid, fused, or markedly splayed ribs; and a first-degree relative with GGS.

The minor criteria comprise macrocephaly, congenital craniofacial malformations (frontal bossing, coarse facies, cleft lip/palate, moderate or severe hypertelorism), Sprengel deformity and other skeletal abnormalities, syndactyly of the digits, ovarian or cardiac fibromas, and medulloblastoma. Genetic diagnostics plays an increasingly important role in differential diagnosis, especially in oligosymptomatic cases.

Imaging techniques may be necessary to establish the diagnosis and in-patient monitoring, such as MRI of the brain, echocardiography, abdominal ultrasonography, dental radiography, and skeletal survey, however, with the goal of minimizing the amount of ionizing radiation rendered at any given period. The rate of meningioma and medulloblastoma may increase post-irradiation in these patients. The combination of clinical, regular skin examinations, imaging, and histological findings is indispensable in identifying patients at risk and establishing diagnosis [61]. Patients suspected of having GGS should have biopsies obtained from several suspicious skin lesions. Obviously, if an infratentorial mass is detected by cranial MRI, it should be biopsied to rule out medulloblastoma.

Therapy and Prognosis

Patients with GGS may need to be treated by a wide range of specialists, including dermatologists, dentists, cardiologists, radiologists, oncologists, and orthopaedic surgeons [62–64]. Frequent clinical and dermatologic surveillance is necessary for individuals with established GGS, and sun protection is an important preventative measure. The colloquium group for NBCCS consists of individuals with research interest in this syndrome and additionally serves as the medical advisory board of the NBCCS Life Support Network [9, 19].

Skin Surgical excision of neoplastic skin lesions is the therapy of choice [65]. In superficial and well-defined lesions, ablative surgery, cryosurgery, laser ablation, and electrocautery successfully may be applied [66]. However, the multiplicity of many lesions and difficult anatomical localizations of the lesions, especially in the face, place considerable demands on surgical therapy. In individual cases, the size and number of tumours may prompt the use of alternative therapies, e.g. cryotherapy or nonsurgical measures [65].

Topical therapies, such as 5% imiquimod or 5% fluorouracil, are recommended in patients with low-risk superficial BCC, in cases with nodular BCC possibly combined with phototherapy [65, 67]. In locally advanced and/or metastatic BCC, application of hedgehog inhibitors, e.g. vismodegib or sonidegib, should be considered. However, the rate of dropouts due to drug intolerance is very high in patients with BCC participating in clinical studies. After stopping the medication, further tumour development must be expected [29, 30]. New immunotherapies are currently being tested in clinical studies, e.g. medication with anti-programmed cell death 1 (PD-1) antibodies [65]. However, the study results have so far been unsuitable for developing general recommendations for PD-1 in BCC [68].

Odontogenic keratocyst (OKC) Treatment of OKC is surgical [69]. The use of locally applied toxic agents such as Carnoy's solution to prevent relapses is controversial [70]. In individual cases, conservative treatment strategies have been successful that have reduced the rate of loss of teeth and parts of the jaw [71]. Case reports detailed treatment results with vismodegib for BCC in GGS patients and showed remarkable shrinkage of osseous lesions in some patients with syndromic OKC [72].

Prevention

Adherence to effective measures to protect the skin from light and regular dermatological examinations is essential for patients with GGS. Siblings of GSS patients should be clinically and possibly genetically investigated for evidence of this syndrome. Early diagnosis and therapy may reduce the severity of the long-term sequelae of GGS, including malignancy and oromaxillofacial deformation and destruction. Annual screening for medulloblastoma (in patients younger than 8 years) and orthopantomography of the jaws for OKC (in patients older than 8 years) is recommended. The risk of developing neoplasm in the radiation area has been proven in patients with GGS, so radiation therapy should be avoided whenever possible [73].

References

1. Unden AB, Holmberg E, Lundh-Rozell B, et al. Mutations in the human homologue of drosophila patched (PTCH) in basal cell carcinomas and the Gorlin syndrome: different in vivo mechanisms of PTCH inactivation. Cancer Res. 1996;56:4562–5.
2. Fujii K, Ohashi H, Suzuki M, et al. Frameshift mutation in the PTCH2 gene can cause nevoid basal cell carcinoma syndrome. Fam Cancer. 2013;12:611–4.
3. Smith MJ, Beetz C, Williams SG, et al. Germline mutations in SUFU cause Gorlin syndrome-associated childhood medulloblastoma and redefine the risk associated with PTCH1 mutations. J Clin Oncol. 2014;32:4155–61.
4. Evans DG, Oudit D, Smith MJ, et al. First evidence of genotype-phenotype correlations in Gorlin syndrome. J Med Genet. 2017;54:530–6.

5. Jarisch W. Zur Lehre von den Hautgeschwülsten. Arch Derm Syphilol. 1894;18:162–22.
6. White JC. Multiple benign cystic epitheliomata. J Cutan Dis. 1894;12:477–81.
7. Gorlin RJ, Goltz RW. Multiple nevoid basal cell epithelioma, jaw cysts, bifid rib: a syndrome. N Engl J Med. 1960;262:908–12.
8. Satinoff MI, Wells C. Multiple basal cell naevus syndrome in ancient Egypt. Med Hist. 1969;13:294–7.
9. Bree AF, Shah MR, BCNS Colloquium Group. Consensus statement from the first international colloquium on basal cell nevus syndrome (BCNS). Am J Med Genet. 2011;155:2091–7.
10. John AM, Schwartz RA. Basal cell naevus syndrome: an update on genetics and treatment. Br J Dermatol. 2016;174:68–76.
11. Gorlin RJ. Nevoid basal cell carcinoma syndrome. Dermatol Clin. 1995;13:113–5.
12. Lo ML. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). Orphanet J Rare Dis. 2008;3:32.
13. John AM, Schwartz RA. Basal cell naevus syndrome: an update on genetics and treatment. Br J Dermatol. 2016;174:68–76.
14. Gorlin RJ. Nevoid basal cell carcinoma syndrome. Medicine (Baltimore). 1987;66:98–113.
15. Shanley S, Ratcliffe J, Hockey A, et al. Nevoid basal cell carcinoma syndrome: review of 118 affected individuals. Am J Med Genet. 1998;50:282–90.
16. Kimonis VE, Goldstein AM, Pastakia B, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet. 1997;69:299–308.
17. Díaz-Fernandez JM, Infante-Cossio P, Belmonte-Caro R, et al. Basal cell naevus syndrome. Presentation of six cases and literature review. Med Oral Patol Oral Cir Bucal. 2005;10(Suppl 1):E57–66.
18. Bartoš V, Kullová M, Adamicová K, Paučinová I. Gorlin-Goltz syndrome. Klin Onkol. 2019;32:124–8.
19. Palacios-Álvarez I, González-Sarmiento R, Fernández-López E. Gorlin syndrome. Actas Dermosifiliogr. 2018;109:207–17.
20. Wilding A, Ingham SL, Lalloo F, et al. Life expectancy in hereditary cancer predisposing diseases: an observational study. J Med Genet. 2012;49:264–9.
21. Barton V, Armeson K, Hampras S, et al. Nonmelanoma skin cancer and risk of all-cause and cancer-related mortality: a systematic review. Arch Dermatol Res. 2017;309:243–51.
22. Rayner CR, Towers JF, Wilson JS. What is Gorlin's syndrome? The diagnosis and management of the basal cell naevus syndrome, based on a study of thirty-seven patients. Br J Plast Surg. 1977;30:62–7.
23. Goldstein AM, Bale SJ, Peck GL, DiGiovanna JJ. Sun exposure and basal cell carcinomas in the nevoid basal cell carcinoma syndrome. J Am Acad Dermatol. 1993;29:34–41.
24. Bhattacharjee P, Leffell D, McNiff JM. Primary cutaneous carcinosarcoma arising in a patient with nevoid basal cell carcinoma syndrome. J Cutan Pathol. 2005;32:638–41.
25. Gupta SR, Jaetli V, Mohanty S, et al. Nevoid basal cell carcinoma syndrome in Indian patients: a clinical and radiological study of 6 cases and review of literature. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113:99–110.
26. Tirado M, Ständer S, Metze D. Histologic and immunohistochemical characteristics of cutaneous cysts in Goltz-Gorlin syndrome: clues for differentiation of nonsyndromic cysts. Am J Dermatopathol. 2014;36:892–8.
27. Ogata K, Ikeda M, Miyoshi K, et al. Naevoid basal cell carcinoma syndrome with a palmar epidermoid cyst, milia and maxillary cysts. Br J Dermatol. 2001;145:508–9.
28. Chenevix-Trench G, Wicking C, Berkman J, et al. Further localization of the gene for nevoid basal cell carcinoma syndrome (NBCCS) in 15 Australasian families: linkage and loss of heterozygosity. Am J Hum Genet. 1993;53:760–7.
29. Unden AB, Holmberg E, Lundh-Rozell B, et al. Mutations in the human homologue of drosophila patched (PTCH) in basal cell carcinomas and the Gorlin syndrome: different in vivo mechanisms of PTCH inactivation. Cancer Res. 1996;56:4562–5.

30. Wicking C, Bale AE. Molecular basis of the nevoid basal cell carcinoma syndrome. Curr Opin Pediatr. 1997;9:630–5.
31. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. N Engl J Med. 2009;361:1164–72.
32. Tang J, Mackay-Wiggran JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med. 2012;366:2180–8.
33. Tang JY, Ally MS, Chanana AM, et al. Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2016;17:1720–31.
34. Fujii K, Miyashita T. Gorlin syndrome (nevoid basal cell carcinoma syndrome): update and literature review. Pediatr Int. 2014;56:667–74.
35. Farndon PA, Del Mastro RG, Evans DG, et al. Location of gene for Gorlin syndrome. Lancet. 1992;339:581–2.
36. Reis A, Küster W, Gebel E, Fuhrmann W, et al. Localization of gene for the nevoid basal cell carcinoma syndrome. Lancet. 1992;339:617.
37. Compton JG, Goldstein AM, Turner M, et al. Fine mapping of the locus for nevoid basal cell carcinoma syndrome on chromosome 9q. J Invest Dermatol. 1994;103:178–81.
38. Shafei-Benaissa E, Savage JR, Babin P, et al. The nevoid basal-cell carcinoma syndrome (Gorlin syndrome) is a chromosomal instability syndrome. Mutat Res. 1998;397:287–92.
39. Pruvost-Balland C, Gorry P, Boutet N, et al. Clinical and genetic study in 22 patients with basal cell nevus syndrome. Ann Dermatol Venereol. 2006;133:117–23.
40. Bresler SC, Bonnie L, Padwa BL, et al. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). Head Neck Pathol. 2016;10:119–24.
41. Altaraihi M, Wadt K, Ek J, et al. A healthy individual with a homozygous PTCH2 frameshift variant: are variants of PTCH2 associated with nevoid basal cell carcinoma syndrome? Hum Genome Var. 2019;6:10.
42. Stone DM, Murone M, Luoh S, et al. Characterization of the human suppressor of fused, a negative regulator of the zinc-finger transcription factor Gli. J Cell Sci. 1999;112(Pt 23):4437–48.
43. Smith MJ, Beetz C, Williams SG, et al. Germline mutations in SUFU cause Gorlin syndrome-associated childhood medulloblastoma and redefine the risk associated with PTCH1 mutations. J Clin Oncol. 2014;32:4155–61.
44. Evans DG, Oudit D, Smith MJ, et al. First evidence of genotype-phenotype correlations in Gorlin syndrome. J Med Genet. 2017;54:530–6.
45. Moramarco A, Himmelblau E, Miraglia E, et al. Ocular manifestations in Gorlin-Goltz syndrome. Orphanet J Rare Dis. 2019;14:218.
46. Friedrich RE, Scheuer HA, Zustin J. Expression of podoplanin in nevoid basal cell carcinoma syndrome-associated keratocystic odontogenic tumours. Anticancer Res. 2012;32:2125–7.
47. Ruprecht A, Austermann KH, Umstadt H. Cleft lip and palate seldom seen features of the Gorlin-Goltz syndrome. Dentomaxillofac Radiol. 1987;16:99–103.
48. Soekarman D, Fryns JP, Casaer P, Van Den Berghe H. Increased head circumference and facial cleft as presenting signs of the nevoid basal cell carcinoma syndrome. Genet Couns. 1991;2:157–62.
49. Ratcliffe JF, Shanley S, Chenevix-Trench G. The prevalence of cervical and thoracic congenital skeletal abnormalities in basal cell naevus syndrome; a review of cervical and chest radiographs in 80 patients with BCNS. Br J Radiol. 1995;68:596–9.
50. Friedrich RE. Ponticulus posticus is a frequent radiographic finding on lateral cephalograms in nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome). Anticancer Res. 2014;34:7395–9.
51. Leonardi R, Santarelli A, Barbato E, et al. Atlanto-occipital ligament calcification: a novel sign in nevoid basal cell carcinoma syndrome. Anticancer Res. 2010;30:4265–7.
52. Moramarco A, Himmelblau E, Miraglia E, et al. Ocular manifestations in Gorlin-Goltz syndrome. Orphanet J Rare Dis. 2019;14:218.

53. Friedrich RE, Scheuer HA, Zustin J. Expression of podoplanin in nevoid basal cell carcinoma syndrome-associated keratocystic odontogenic tumours. Anticancer Res. 2012;32:2125–7.
54. Tirado M, Ständer S, Metze D. Histologic and immunohistochemical characteristics of cutaneous cysts in Goltz-Gorlin syndrome: clues for differentiation of nonsyndromic cysts. Am J Dermatopathol. 2014;36:892–8.
55. Karhade DS, Afshar S, Padwa BL. What is the prevalence of undiagnosed nevoid basal cell carcinoma syndrome in children with an odontogenic keratocyst? J Oral Maxillofac Surg. 2019;77:1389–91.
56. Evans DGR, Ladusans EJ, Rimmer S, et al. Complications of the naevoid basal cell carcinoma syndrome: results of a population based study. J Med Genet. 1993;30:460–6.
57. Scholz TA, Vanderhooft SL, Meyer LJ. What syndrome is this? Pediatr Neurol. 1999;16:403–5.
58. Wang Y, Wu J, Li W, et al. Retrospective investigation of hereditary syndromes in patients with medulloblastoma in a single institution. Childs Nerv Syst. 2020; https://doi.org/10.1007/s00381-020-04885-z.
59. Evans DGR, Farndon PA, Burnell LD, et al. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. Br J Cancer. 1991;64:959–61.
60. Kimonis VE, Goldstein AM, Pastakia B, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet. 1997;69:299–308.
61. Kimonis VE, Mehta SG, Digiovanna JJ, et al. Radiological features in 82 patients with nevoid basal cell carcinoma (NBCC or Gorlin) syndrome. Genet Med. 2004;6:495–502.
62. High AS, Robinson PA. Novel approaches to the diagnosis of basal cell nervous syndrome. Expert Rev Mol Diagn. 2002;2:321–8.
63. Manfredi M, Vescori P, Bonanini M, Porter S. Nevoid basal cell carcinoma syndrome: a review of the literature. Int J Oral Maxillofac Surg. 2004;33:117–24.
64. Hasan A, Akintola D. An update of Gorlin-Goltz syndrome. Prim Dent J. 2018;7:38–41.
65. Peris K, Fargnoli MC, Garbe C, European dermatology forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of cancer (EORTC). Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Eur J Cancer. 2019;118:10–34.
66. Friedrich RE. Diagnosis and treatment of patients with nevoid basal cell carcinoma syndrome [Gorlin-Goltz syndrome (GGS)]. Anticancer Res. 2007;27:1783–7.
67. Strange PR, Lang PG. Long-term management of basal cell nevus syndrome with topical tretinoin and 5-fluorouracil. J Am Acad Dermatol. 1992;27:842–5.
68. Choi FD, Kraus CN, Elsensohn AN, et al. Programmed cell death 1 protein and programmed death-ligand 1 inhibitors in the treatment of nonmelanoma skin cancer: a systematic review. J Am Acad Dermatol. 2020;82:440–59.
69. Silva LP, Rolim LS, Silva LA, et al. The recurrence of odontogenic keratocysts in pediatric patients is associated with clinical findings of Gorlin-Goltz syndrome. Med Oral Patol Oral Cir Bucal. 2020;25:e56–60.
70. Díaz-Fernandez JM, Infante-Cossio P, Belmonte-Caro R, et al. Basal cell naevus syndrome. Presentation of six cases and literature review. Med Oral Patol Oral Cir Bucal. 2005;10(Suppl 1):E57–66.
71. Ally MS, Tang JY, Joseph T, et al. The use of vismodegib to shrink keratocystic odontogenic tumors in patients with basal cell nevus syndrome. JAMA Dermatol. 2014;150:542–5.
72. Wallin JL, Tanna N, Misra S, et al. Sinonasal carcinoma after irradiation for medulloblastoma in nevoid basal cell carcinoma syndrome. Am J Otolaryngol. 2007;28:360–2.
73. Wilson C, Murphy M. Conservative management of multiple keratocystic odontogenic tumours in a child with Gorlin-Goltz syndrome: a case report. Eur J Paediatr Dent. 2008;9:195–8.