

Case report of familial Gorlin-Goltz syndrome

Relato de caso familiar da síndrome de Gorlin-Goltz

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Resumo

A síndrome de Gorlin-Goltz é uma doença de origem genética que afeta múltiplos sistemas, com herança autossômica dominante, penetrância completa e expressividade variável. Clinicamente, a doença é caracterizada por uma série de manifestações associadas, como queratocistos maxilares e mandibulares e carcinomas celulares basais. Características menos comuns da doença incluem prognatismo mandibular, proeminência frontal e hipertelorismo; malformações de pele e do esqueleto também estão presentes. Este artigo descreve uma família que está sendo acompanhada no Serviço de Genética da Secretária de Estado de Saúde do Distrito Federal em Brasília. A família apresenta manifestações típicas associadas com a Síndrome de Gorlin-Goltz.

Palavras chave: Síndrome de Gorlin-Goltz, genética clínica, síndrome de carcinoma de célula basal nevoide, *PTCH1*

Abstract

Gorlin-Goltz Syndrome is a genetic disease affecting multiple systems. It is an inherited autosomal dominant trait, with complete penetrance and variable expressivity. Clinically, the disease is characterized by a series of associated manifestations such as maxillary and mandibular keratocysts and cutaneous basal cell carcinomas. Less frequent features of the disease include mandibular prognathism, frontal prominence and hypertelorism; skeletal and skin malformations may also be present. This report describes a family currently being treated by the Genetics Service of the Secretariat of Health of the Federal District in Brasília, that presents typical features associated with Gorlin-Goltz Syndrome.

Key words: Gorlin-Goltz syndrome, clinical genetics, nevoid basal cell carcinoma syndrome, *PTCH1*.

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Introduction

Gorlin-Goltz Syndrome, also known as Basal Cell Nevus Syndrome is a multisystemic disease that shows autosomal dominant inheritance, complete penetrance and variable expressivity.^{1,2,3} The prevalence of this syndrome is estimated at around 1:30827 and its incidence is around 1:14923 in the United Kingdom.² However, in Brazil, there is no prevalence or incidence data registered.

The gene most commonly associated with Gorlin-Goltz syndrome is *PTCH1* (patched homolog 1 - *Drosophila*), a 23 exon gene of approximately 70 kb, that is part of a pathway that participates in the regulation of growth and development.² A mutation in one copy of the gene causes the syndrome. The *PTCH1* gene is located on chromosome 9 (9q22.3-q31) and as this is an autosomal dominant disease, 70 to 80% of all patients have an affected parent.⁴ Twenty to 30% of patients have a *de novo* mutation (mutation that neither parent possessed, which occurs during gametogenesis).

The gene product is a transmembrane protein (PTC, or patched) that inhibits the hedgehog signaling pathway by binding a protein called smoothened (SMO). In the presence of the hedgehog ligand (HH), PTC releases SMO, resulting in activation of target gene expression and cell migration, differentiation and division. Inactivating mutations in PTC result in hyperactivation of

the HH pathway and this may explain the tumors seen in Gorlin-Goltz syndrome.^{1,4,6,7} The variable phenotypes seen in Gorlin-Goltz patients reflect variations in gene expression and environmental factors, and patients described in the literature portray a variety of genetic mutations and clinical characteristics.⁸ It should be noted that as well as *PTCH1*, mutations causing this syndrome have been reported in the *PTCH2* and *SUFU* genes, both of which are also elements of the HH pathway.

Clinically, Gorlin-Goltz Syndrome is characterized by a series of associated manifestations divided into major and minor criteria, as described in Table 1. The most common of these are maxillary and mandibular keratocysts and cutaneous basal cell carcinoma.⁹ The presence of any type of soft tissue tumor in patients demands a tissue biopsy to verify and treat cases of sarcoma. Patients with tissue sarcoma, of the subtype angiosarcoma (1% of sarcoma patients), have a poor prognosis because these tumors are fast-growing and have a high chance of metastasis.¹⁰ The minor criteria include coarse syndromic facies characterized by mandibular prognathism, frontal prominence, thick eyebrows, wide bridged nose and hypertelorism; skeletal malformations such as vertebral problems, costal synostosis, bifid ribs; dermoid cysts and lipoma; and presence of ductus arteriosus.⁹ Patients are particularly sensitive to ionizing radiation.

The presence of odontogenic keratocysts is also very frequent in patients diagnosed with the syndrome, and it has been suggested that multiple odontogenic keratocysts alone may be the enough to

confirm diagnosis.¹¹ These calcifying cystic odontogenic tumors may be located centrally or peripherally, and 13% of these cysts are extra osseous in occurrence.¹²

Table 1. Diagnostic criteria of Gorlin-Goltz syndrome (Based on Marcos *et al*⁶)

To be diagnosed with Gorlin-Goltz syndrome: Presence of two major criteria or one major criterion and two minor criteria⁶

Major Diagnostic Criteria	Presence in Patients Reported
More than 2 basal cell carcinomas or one carcinoma in a patient over 20 years old	JLS (multiple basal facial nevi); AMC (palpebral basal nevi); AMS (multiple basal facial nevi)
Mandibular and/or maxillary keratocyst (confirmed by histology)	JLS (mandibular and maxillary), AMC (mandibular); AMS (mandibular and maxillary)
Three or more point depressions on palms or soles	Not seen in patients reported
Calcification of <i>falx cerebri</i>	Not seen in patients reported (JLS - small unspecific nodule left of septum pellucid and slight supratentorial ventriculomegaly)
Relative (first degree relation) diagnosed with Gorlin-Goltz Syndrome	Yes, all three family members reported are first degree relatives.
Minor Diagnostic Criteria	Presence in Patients Reported
Macrocephaly (determined after adjustment of height)	Not seen in patients reported
Congenital malformations: cleft lip or palate, face with coarse appearance, presence of frontal prominence	JLS (coarse face); AMC (coarse face); AMS (coarse face)
Skeletal alterations such as Sprengel deformity, pectus excavatum or carinatum, syndactyly of fingers	Not seen in patients reported
Radiological alterations: vertebral anomalies (fused or elongated vertebral bodies, hemivertebrae), hand and foot anomalies, saddle nose	AMC (osteocyte abnormality on T8-T9);
Presence of ovarian fibroma	Not seen in patients reported
Presence of medulloblastoma	Not seen in patients reported

This paper describes a family that presents typical features associated with Gorlin-Goltz Syndrome, first detected during orthodontic treatment. The family is currently being treated at the Department of Clinical Genetics of the Hospital de Apoio in Brasília-

DF. It is imperative to emphasize the importance of the prompt recognition of these features in order to close an early diagnosis and offer the best multidisciplinary care required for patients with Gorlin-Goltz Syndrome.

Case Report

The family in question was referred to the department of Clinical Genetics of the Mother-Child Hospital of Brasília, Brazil (Hospital Materno-Infantil de Brasília - HMIB) by a bucomaxillofacial surgeon, due to the presence of multiple maxillary and mandibular cysts, as well as facial nevi. The affected family members are J.L.S., the proband - 32 years old; his sister A.M.C., 37 years old; and his niece (A.M.C.'s daughter) A.M.S., 11 years old. All family members have signed a free and informed consent form, authorizing the publication of their data and photographs.

J.L.S. had no knowledge of any major occurrences during pre-natal period and development. He reported having learning difficulties and only studied until the equivalent of Brazilian first grade (7 years old). He did not learn to read. The patient reported no major medical conditions and only complained of occupational asthma and hyposmia. Upon physical examination, the patient presented arched and fused eyebrows, prognathism, mandibular and maxillary keratocysts and basal facial nevi (Figure 1). Hematology was normal. Abdominal ultrasound failed to visualize his right kidney.



Figure 1. Patient JMC with arched and fused eyebrows, prognathism, and a characteristic “coarse face”.

A.M.C. did not know if her mother had any pre-natal difficulties but believes she was born post-term. Her twin sister died at birth (the family does not know why). She denied having learning difficulties but reported difficulty reading, which could be due to an educational deficit. She had late development of speech, but was uncertain the

age she pronounced the first words. A.M.C. had five pregnancies resulting in three births and two abortions (both spontaneous, in the first trimester). She denied consanguinity. A.M.C. studied only the lower school level (equivalent of Brazilian third grade) - 9 years old - and is able to read and write. Past surgeries include tubal ligation and

mandibular cyst removal. Upon clinical examination, she had prognathism and palpebral cysts. (Figure 2). Her hematological exams and abdominal ultrasound were

normal; spinal x-ray shows osteocyte abnormality on T8-T9. Her daughter A.M.S. presented similar clinical features.



Figure 2. Patient AMC has a “coarse face”, prognathism and palpebral cysts.

A.M.S., 12 years old, is A.M.C.’s daughter and J.L.S.’s niece. She was born at term and A.M.C. reported repeated infections during the pregnancy, with use of antibiotics. She sat unaided at 8 months and walked at 1 year 5 months. Her mother reported that A.M.S. had difficulty in learning and articulating speech. She is now enrolled in third grade and still has difficulty in reading.

She has a normal social life and plays with children her own age; she is able to have shower, eat and dress herself without help. The patient presented at clinical examination, arched and fused eyebrows, mandibular and maxillary keratocysts and facial nevi (Figure 3). Hematology and abdominal ultrasound were normal



Figure 3. Patient AMS with arched and fused eyebrows, and a characteristic “coarse face”.

Discussion

Gorlin Syndrome is a suspected diagnosis for all three members of the family described. They satisfy more than one major and at least two minor criteria described in literature as the diagnostic breakpoint for this syndrome, described in Table 1.

Gorlin-Goltz Syndrome affects several organs, systems and causes a variety of abnormalities that require early diagnosis and constant clinical management. The phenotype associated with this syndrome can be subtle, and many of the clinical characteristics described in the major and minor criteria for diagnosis of the syndrome are not usually seen in young patients. That makes early diagnosis a much more difficult task. The most consistent and the most reliable finding in Gorlin-Goltz Syndrome is the presence of odontogenic keratocysts which are usually present when the patient is in the first or second decades of life.

Early diagnosis is important because these patients show a tendency towards the development of multiple malignant neoplasms that need to be removed either by surgical excision, laser ablation, photodynamic therapy or topical chemotherapy.¹ The number of neoplasms and age they first manifest cannot be associated with the presence or absence of *PTCH1* mutation or mutation type.¹³ DNA sequencing of the *PTCH1* gene can help in assignment of a definitive diagnosis in patients where Gorlin-

Goltz syndrome is suspected. When there is a known mutation in the family, diagnosis of subsequent cases can be made even earlier, and in the prenatal stage if necessary. In the absence of a *PTCH1* mutation, sequencing of the *PTCH2* and *SUFU* genes may be considered.

It is indicated that the diagnosis and management of Gorlin-Goltz syndrome patients should include a complete and detailed clinical history (including odontologic findings), radiographs (panoramic dental; chest, skull, cervical and thoracic spine, hands and pelvis images), periodic imaging (brain MRI, CT of facial bones for surgical management of lesions, abdominal and pelvic ultrasound, electrocardiogram in search of abnormalities due to fibromas) and patient education about the disease¹⁴, as described in Table 2. Patients are sensitive to ionizing UV radiation and need to avoid radiotherapy and undergo chemoprevention by using vitamin A analogs (retinoids, such as isotretinoin).^{1,3} Five -10% of patients may develop brain medulloblastoma, which could result in early death³; and therefore Gorlin-Goltz patients need to have constant follow-up with a neurologist.¹

Conclusion

Ongoing surveillance and treatment by a multidisciplinary team is required for patients suffering from this syndrome⁷.

Genetic counseling must be made readily available to patients as all siblings and children of patients affected must be clinically and genetically investigated for evidence of Gorlin-Goltz Syndrome due to a 50% risk of inheriting the disease. It is imperative that physicians and dentists know how to promptly recognize the clinical features of this syndrome in order to provide an early diagnosis and proper management of disease. The family described here will be referred for sequencing of the *PTCH1* gene. In the case of a mutation being detected, this information can be used for genetic counseling and early diagnosis of future cases.

References

1. Pandeshwar P, Jayanthi K, Mahesh D. Gorlin-Goltz Syndrome. *Case Rep Den.* 2012; 2012: 247239.
2. Roudgari H, Farndon P, Murray A, Hardy C, Miedzybrodzka Z. Is PATCHED an important candidate gene for neural tube defects? Cranial and thoracic neural tube defects in a family with Gorlin syndrome: a case report. *Clin Genet.* 2012; 82(1):71-6.
3. Lo Muzio L. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). *Orphanet J Rare Dis.* 2008; 3:32.
4. Safronova MM, Arantes M, Lima I, Domingues S, Almeida M, Moniz P. Síndrome de Gorlin-Goltz: Revisão das características neurorradiológicas e maxilofaciais ilustradas com dois casos. *Acta Med Port.* 2010; 23(6):1119-26.
5. Johnson R, Tabin C. Molecular models for vertebrate limb development. *Cell.* 1997; 90(6): 979–90.
6. Marcos JAG de, Dean-Ferrer A, Rodríguez SA, Calderón-Polanco J, Granados FJA, Poblet E. Basal cell nevus syndrome: clinical and genetic diagnosis. *Oral Maxillofac Surg.* 2009; 13(4):225-30
7. Casaroto A, Loures D, Moreschi E, Veltrini VC, Trento CL, Gottardo VD, et al. Early diagnosis of Gorlin-Goltz syndrome: case report. *Head Face Med.* 2011; 7:2.
8. Manfredi M, Vescovi P, Bonanini M, Porter S. Nevoid basal cell carcinoma syndrome: a review of the literature. *Int J Oral Maxillofac Surg.* 2004; 33(2):117-24.
9. Fernández J, Cossío P, Caro RB, Laza LR, García AG, Pérez JLG. R. Basal cell nevus syndrome. Presentation of six cases and literature review. *Med Oral Patol Oral Cir Bucal.* 2005; 10:E57-E66.
10. Penel N, Robin Y-M, Mallet Y, Gauthier H, Vanseymortier L. Association head and neck angiosarcoma and nevoid basal cell carcinoma syndrome (Gorlin syndrome). *Oral Oncology Extra.* 2005; 41(10):289-91.
11. Agrawal A, Murari A, Vutukuri S, Singh A. Gorlin-goltz syndrome: case report of a rare hereditary disorder. *Case Rep Dent.* 2011; 2012: 475439.
12. de Lima A, Kitakawa D, Almeida J, Brandão A, Anbinder A. Peripheral calcifying

cystic odontogenic tumour of the maxillary
gingiva. *BMC Res Notes*. 2012; 5:455.

13. Jones EA, Sajid MI, Shenton A, Evans
DG. Basal Cell Carcinomas in Gorlin
Syndrome: A Review of 202 Patients. *J Skin
Cancer*. 2011; 2011:217378.

14. Kiwilsza M, Sporniak-Tutak K. Gorlin-
Goltz syndrome—a medical condition
requiring a multidisciplinary approach. *Med
Sci Monit*. 2012; 18(9):145-53.