Basal Cell Carcinoma at Pediatric Age Gorlin-Goltz Syndrome Clinic Experience

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Abstract: The nevoid basal cell carcinoma syndrome is an autosomal dominant inherited disease, associated with PTCH gene mutation. Its presentation is polymorphous, being frequent to appear the clinical triad carcinomas basal cell, odontogenic cysts and skeletal abnormalities. Skin lesions are a very frequent reason for consultation in the paediatric age, being evaluated in most cases in primary care. Sometimes, patients need the intervention of other specialists to deep in a given area. The medical literature shows a fragmented view of the disease, possibly related to the low frequency of appearance of this syndrome, and by the need for intervention of not transversal knowledge specialist, which is why we feel interesting to evaluate the role of specialist who is developing the activity at primary care, with patients who require a multidisciplinary intervention.

Key words: Gorlin-Goltz syndrome, basal cell carcinomas, pediatric age.

1. Introduction

GGs (Gorlin-Goltz syndrome) is a genetic autosomal dominant disease associated with the mutation of the gene PTCH. It has full penetration and variable expression. It produces a multisystem involvement; the estimated prevalence is 1: 50.000 with a 1:1 male/female ratio. It occurs in all ethnic groups with BOP variable [1, 2]. This disease is polymorphous, its form of presentation may vary much from person to person, however, and this syndrome was associated to certain characteristics in 1960, by the physicians Gorlin and Goltz, who described a clinical triad that is very common in this group of patients, the presence of multiple nevoid

basal cell epitheliomas, jaw cysts and bifid rib [3].

1.1 Physiopathology

Mammals have three genes of Hh (Hedgehog family), which are called for: SHH (Sonic hedgehog) Indian hedgehog and DHH (Desert hedgehog). The Hh protein family plays essential functions mainly during embryonic development, but also in the maintenance and regulation of certain stem cells in the adult organism and in the development of many human tumours [5, 6].

The way of the SHH is essential for early embryonic development and participates in the formation of the neural tube, the muscle-skeletal system, hematopoietic system, teeth and skin [4]. Aberrant activation of Hh could contribute to the pathogenesis of the GGS making up-regulating genes,

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which enables the proliferation of different tissue that can cause different neoplasms CBC (carcinoma basal cell), medulloblastomas, rhabdomyosarcomas and meningiomas.

When the PTCH1 tumour-suppressor gene does not present mutations encodes by transmembrane protein whose most important ligand is SHH.

On the GGS mutations occur in the path of the SHH (one of the genes of the HH family) affecting to the suppressor PTCH1 gene located on the long arm of chromosome 9 (9q22, 3) [7-9].

In the absence of ligand, the PTCH1 gene suppresses the activation of (SMO) smoothened protein and this inhibits the expression of growth and cell division genes. On the contrary, when SHH binds to the ligand PTCH1 gene, it inhibits the suppression that PTCH has over SMO and therefore SMO is activated and promotes the activation of transcription factors of the family of the oncogenes associated with glioma (GLI), in particular to the GLI1. Other induced genes include the transforming beta growth factor, to the proto-oncogene anti-apoptotic Bcl-2, Beta-catenin 1, the N-myc (MYCN) proto-oncogene and the morphogenetic protein of bone, all of them are involved in cell proliferation (Fig. 1).

On the GGS, the mutated PTCH1 protein cannot suppress the SMO by causing an unregulated stimulation of the SHH responsible for an abnormal proliferation of tissues and the carcinogenesis [7].

On the other hand there is a wide range of mutations and there is not a place more frequent mutations in the gene that is responsible for the majority of cases, even PTCH1 gene mutations have been found and the SMO is on sporadic CBC [10].

1.2 More Frequent Clinical Manifestations

Skin: CBC is the most common neoplasm. It is usually presented in photo exposed areas, however, patients with GGS have more probabilities to develop these neoplasms in non-exposed areas and surgically difficult to access what determines the aggressiveness of these injuries [1, 14, 16].

The incidence of GGS in patients with CBC varies according to the age; at 20 years old is 12% in men and 13.7% in women, and at the fourth decade of life, the incidence rises to 76.5% in women and 80% in men. Although this syndrome can occur in any ethnic group, the incidence of skin neoplasms is higher in Caucasian skin people than in African American patients (incidence at 40 years in patient of African-American patients is 40%) [11].

Fig. 1 Summary of the SHH signaling pathway. **A:** In the absence of SHH, PTCH1 constitutively represses SMO. **B:** Binding of SHH to PTCH1 releases inhibition of SMO, leading to transcriptional activation of GLI proteins and downstream target genes [7].

Palmo-plantar pits macroscopically are small depressions (dimples) that occur more frequently in the heels and the palms of the hands, but can also be seen at the edge of the fingers. They are produced by partial or total absence of the stratum corneum of the skin. This is a fundamental skin lesion at paediatric age due to the early apparition and is presented in 87% of the patients [11].

Dental: For maxillary keratocysts, 75% of patients with GGS presented these Maxillary cysts. In these patients, the behaviour of these cysts tends to be more aggressive and has a high rate of recurrence [13].

Possibly the most common injury in patient suffering from GGS [9, 10] arises from the remnants of dental lamina after odontogenesis is complete. They are usually diagnosed as finding during dental control at paediatric age or when they produce a sign/symptom (dental loss or facial deformity). The mandible tends to be affected more frequently than the upper jaw.

Osseous: Skeletal malformations may be associated with high height, costal and vertebral anomalies. Congenital elevation of one or both scapulae is presented in a variable form and vertebral anomalies frequently consist on hem vertebrae and spinal fusion. Most frequent malformations are bifid ribs, malformation of the anterior costal arch and costal mergers. The thoracic deformity may occur.

Other manifestations include commitment of the central nervous system, ocular, genitourinary and cardiovascular problems [8]. And 5-10% of patients with GGS could develop malignant medulloblastomas, which may be a potential cause of early death.

1.3 Diagnosis

Diagnosis is performed in the presence of two major criteria or one major criteria and two minor criteria [11].

The paediatric age is a challenge when it comes to diagnose this syndrome. It is necessary to keep in mind that the presence of palmo-plantar pits associated with other criteria such as bifid ribs malformation, is enough signs to rule out/confirm the genetically diagnosis. It is essential to prevent or treat complications early [15, 16].

1.4 Clinical Case

Child two years old, carried to consultation by injuries at thorax, hands and feet of a month of evolution.

Personal history: humeral fracture in 2011 and asthma, atopic dermatitis.

The examination showed palmo-plantar pits (Fig. 2, and 3) thorax injuries are difficult to typify macroscopically hypermobile joints.

Table 1 Major and minor criteria stated by first international colloquium on NBCCS [12].

	Major criteria	Minor criteria
1	(BCC) basal cell carcinoma prior to 20 years old or excessive number of BCC out of proportion to prior sun exposure and skin type	Rib anomalies
2	Odontogenic keratocyst of jaw prior to 20 years of age	Macrocephaly determined after adjustment for height
3	Palmer or planter pitting	Other specific skeletal malformation and radiologic changes (i.e., vertebral anomalies, kyphoscoliosis, short fourth metacarpals, past axial polydactyly)
4	Lamellar calcification in the sickle of the brain.	Cleft lip/palate
5	Medulloblastoma, typically desmoplastic	Ovarian/cardiac fibroma
6	First degree in relation to NBCCS	Lymphomesentric cysts
		Ocular abnormalities (i.e., strabismus, hypertelorism, congenital cataract, glaucoma, coloboma)

Fig. 2 Plantar pits.

Fig. 3 Palmar pits.

Fig. 4 Skin biopsy.

Fig. 5 Skin biopsy.

Fig. 6 Orthopantomography.

Plan:

Interconsultation to Dermatology is performed.
Beginning of study due to the suspicion of Gorlin-Goltz Syndrome.

Complementary tests:

Karyotype: Detected a mutation in the gene PTCH: c.3058 > T (p.Q1020X).

On the SGG punctual mutations have been identified, deletions, insertions and modifications at the joints, complete loss of the allele and shift in the

reading frame with premature stops. In our patients, the detected variant results in a premature stop cod (non sense mutation): p.Gln1020Term (p.Q1020X), which has resulted in a protein truncated with 30% less than its amino acids or PTCH1 mRNA decreased due to a deterioration of the same.

This variable has been described in the HGMD database associated with GGS.

Also, they have ruled out mutations of this gene in both parents, so we could be facing a “novo” case.

Blood test: without alterations.

Skin biopsy: Skin structure that presents dermal epithelial neoplasm with solid pattern, constituted by atypical basaloid cells arranged with marginal palisading. This neoplasm does not reach the lateral edges of the sample-solid basal cell carcinoma (Figs.4 and 5).

Orthopantomography: anodontia of upper lateral incisors. There is no evidence of mandibular cystic lesions. (Fig. 6)

Abdominal ultrasound: Normal size and homogeneous morphology liver. Gallbladder and biliary ways within normal limits. Spleen and pancreas without significant findings. Right kidney of 6.7 cm, left kidney of 7.4 cm, both well differentiated, with preserved parenchymal thickness, without ectasias. Bladder without anomaly and without other ultrasound findings. No free liquid.

Magnetic resonance crano-espinal: Skull: grooves and convexity, the cisternae system and the ventricle with normal size and morphology. There are no evidences of significant alterations of the brain parenchyma. There are no signs of intracranial expansive process. Alterations of the brain diffusion are not observed. Intraparenchymal or meningeal pathologies are not observed after the administration of intravenous contrast.

Cervical, dorsal medulla, conomedullary and roots and horsetail present normal signals and morphology. No existence of pathological intramedullary contrast catchment.

Echocardiography: without modifications. Heart is with normal structure.

Tracing: Currently follow-up: paediatric Oncology, Maxillofacial, Dermatology, Ophthalmology, Cardiology and Paediatrics Hospital.

2. Key Points

Skin lesions are health problems posed by a huge uncertainty in the initial assessment. Most of the cases, at the time of the consultation patients usually do not

present a serious clinical impact, being often nonspecific signs of diseases which range goes from trivial to serious.

It is necessary a detailed study to patients that present increased risk factors due to their family history, hard-to-classify lesions, any sign of malignancy and those that are associated with other signs or symptoms.

The paediatric age is a challenge when it comes to diagnose this syndrome. It must be reminded that the presence of palmo-plantar pits associated with other criteria such as bone malformations, are enough signs to rule out/confirm the diagnosis genetically. It is essential to prevent or treat complications as soon as possible.

The first clinical signs will be valued in the majority of cases in primary care, always requiring the intervention of other specialists, so the referral should be done immediately if there is suspicion of this entity. It is also essential that the patient is always “returned” to the primary care paediatrician for a holistic follow-up coordination [16].

3. Conclusions

The field of primary health care is a key pillar for the early detection of chronic diseases, which often require interventions at different levels of care. The treatment of these patients should be multidisciplinary and non-exclusive. The role of primary care paediatrician should be also included after the diagnosis of certainty as integrative part in the different stages of evolution of the disease.

In the case presented, the initial assessment in primary care was essential in the diagnosis, orientation and early detection, but once the diagnosis was confirmed, the specialist that develops its activity in primary care was not included, as part of the multidisciplinary monitoring team.

Clinical/diagnostic tools and the control in primary care for this assessment and an integral check, based on a transverse knowledge in the clinical method

focused on the patient and the evidence-based medicine complement the diagnostic elements, additional tests and interventions done by specialists who develop clinical/surgical tools for deeper knowledge, i.e. it should be considered complementary and not mutually exclusive being this essential, so that these patients can continue receiving a treat focused on the patient and not the disease.

As an opportunity to improve the control of these kind of patients, it is necessary to optimize the communication channels with other specialists, being priority that to cross the hospital barrier.

Conflict of Interest Statement

Authors declare that there are no conflicts of interest.

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