Gorlin-Goltz syndrome: Clinicopathologic aspects

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Abstract

Gorlin-Goltz syndrome, also known as nevoid basal cell carcicoma syndrome, comes into being due to a genetic alteration produced by a mutation in the "Patched" tumour suppressor gene, and it is inherited in a dominant autosomal way, though sporadic cases have been found. This syndrome shows a high penetrance and variable expressiveness. It is about a multisystemic process that is characterised by the presence of multiple pigmented basocellular carcinomas, keratocysts in the jaws, palmar and/or plantar pits and calcification of the falxcerebri. Together with these major features a great number of processes considered as minor features have also been described. The latter include numerous skeletical, dermatology related and neurological anomalies among others. In some occasions, the presence of very aggressive basocellular carcinomas has been described as well as other malignant neoplasias. Due to the importance of oral maxillofacial manifestations of this syndrome, it is fundamental to know its characteristic in order to make a diagnosis, an early preventive treatment and establish right genetic advice. In this work the main clinicopathologic and the therapeutic aspects related to the syndrome under consideration have been revised and updated.

Key words: *Gorlin-Goltz, basocellular carcinoma, odontogenic keratocysts, pits.*

Introduction

Gorlin-Goltz syndrome is an infrequent multisystemic disease that is inhereted in a dominant autosomal way, which shows a high level of penetrance and variable expressiveness (1-7). This syndrome has received several names throughout the times such as "basal cell nevus syndrome" (8,9), "nevoid basal cell carcinomas syndrome" (1,2,4-7,10), or the most complex name of "multiple basal epithelioma, jaw cysts and bifid rib syndrome" (11).

In 1894 Jarisch and White (12,13) made the first descriptions of patients with this syndrome, highlighting the presence of multiple basocellular carcinomas. Later, in 1939, Straith (14) described a familiar case in which multiple basocellular carcinomas and cysts appeared. In 1953 Gross (15) presented a case suggesting additional signs such as synostosis of the first left rib and bilateral bifurcation of the sixth ribs. On the other hand, Bettley (16) and Ward (17) were the first to relate the presence of palmar and plantar pits with the syndrome. Nevertheless, it was not until 1960 when Gorlin and Goltz (18) established a classical triad that characterises the diagnosis of this syndrome (multiple basocellular epitheliomas, keratocysts in the jaws and bifid ribs). This triad was later modified by Rayner et al. (19), who established that for giving the diagnosis at least cysts had to appear in combination with calcification of the falxcerebri or palmar and plantar pits.

The Gorlin-Goltz syndrome presents a quite variable estimated prevalence, which goes from 1 in 57.000 (5) to 1 in 256.000 inhabitants (20). This frequency varies according to the country where the study has been carried out. For

instance, in a study in England (21) the frequency is of 1 in 55.6000. In Italy, on the other hand (20), is of 1 in 256.000 and in Australia a study showed a prevalence of 1 in 164.000 (22). Nevertheless, it is generally accepted a prevalence of 1 in 60.000 inhabitants (2).

This syndrome probably presents itself in all ethnic groups, although a few cases have been published in certain human races, and it affects both men and women in the same way.

During the lasts years very important advances have been taking place in the knowledge of the genetic characteristics of this syndrome, existent clinicopathologic variants and its different manifestations (8,10,23). This piece of work attempts to update the clinicopathologic knowledge of the syndrome under consideration.

Genetic aspects

Gorlin-Goltz syndrome is an autosomal dominant inherited disorder with high penetrance and variable fenotype expressiveness which can manifest itself spontaneously (1-7,9,23,24). It is considered that between the 30% and 50% of patients who suffer from this syndrome do not know if any of their family members has had it.

The tumour suppressor gene called *Patched* (PTCH) , located in the 9q22.3 cromosome, has been identified as the cause of Gorlin-Goltz syndrome (2,5-7,23-25). This gene is composed of 23 exons and codifies a transmembrane glucoprotein composed of 1447 amino acids and 12 domains (5,6,24,25). This protein can be found in the *Hedgehog* signalling pathway. This signalling cell route regulates a great variety of processes such as the embriogenesis, homeostasis mantainance in the old tissues, tissue repairing during the persistent cronic inflammation and carcinogenesis. (26-28).

When *Hedgehog* is absent, the family of PTCH transmembrane receptors inhibit the protein that emits the Smoothened (SMO) signal. On the contrary, when Hedgehog combines PTCH, SMO signal is released, causing the activation of certain genes such as GLI1, PTCH 1, CCND2, FOXL1 and JAG (29, 30).

Gorlin-Goltz syndrome is produced due to a mutation in this gene, with loss of heterozygosity (4-7,25). This loss has also been observed in basocellular carcinomas without any relation to the syndrome, in the meduloblastoma and in odontogenic keratocysts (6). Nearly 40% of the syndrome cases present as new mutations (4,6,7,25), and they do not seem to represent any polygenetic alteration (7).

Since the discovery of PTCH gene as being the responsible for the Gorlin-Goltz syndrome in 1996 (4), more than 60 germinal mutations of PTCH have been identified and described. Several methods were used to study these mutations in patients` families in the USA, Sweden, Australia, the United Kingdom, Japan, China and France (1,4,24). The mutations are related to a premature truncation of the PTCH gene protein and to some missense, frameshift and nonsense mutations, identified in the transmembrane domains (1,4,24). Nevertheless, missense mutations do not occur with the same frequency as frameshift or nonsense mutations (24)

Patients suffering from Gorlin-Goltz syndrome show an important variability in their phenotype- it has been observed that individuals with the same molecular alterations present very different symptoms (31). The fact that there is no relationship between the genotype and the phenotypein this syndrome suggests the existence of a very complex variability of the phenotype (4). This variation is thought to be originated due to the interaction of genetic and environmental factors (2,24).

Clinicopathologic aspects

In order to make a diagnosis of the Gorlin-Goltz syndrome some diagnosis criteria have to be taken into account.

The most important criteria to make a diagnosis for this syndrome are the presence of pigmented basocellular carcinomas, odontogenic keratocysts, palmar and/or plantar pits and ectopic calcifications of the falxcerebri (1-4,6,8-11,23-25).

Together with these major features more that 100 minor features have been described. The more relevant are the following: cardiac or ovarian fibroma, macroencephaly, bifid ribs, cyphoscoliosis, cleft palate, medulloblastoma (1-2 % is attributed to the syndrome and from 3 to 5 % is the incidence in this syndrome), alterations in the sella tucica, mandibular prognathia, lateral displacement of the inner canthus, frontal and biparietal bossing, imperfect segmentation of the cervical vertebrae, linfomesenteric cysts that tend to calcify, meningiomas, fibrosarcoma, rhabdomyosarcoma, short fourth metacarpal, strabism, ocular hypertelorism, congenital blindness, spina bifida occulta, pectum excavatum, high arched eyebrows and palate, narrow sloping shoulders, immobile thumbs, low-pitch voice in women, renal anomalies and hypogonadism in men (2,3,8,10,11,23). In certain occasions, a tall height and even similar characteristics to acromegaly have been associated with the syndrome (23).

There are two options to make a correct diagnosis of the Gorlin-Goltz syndrome, or two major features and one minor feature (23). In table 1, the main alterations that have been described in relation to this syndrome are presented.

The odontogenic keratocysts represent from 3 to 15% out of the total number of odontogenic cysts (9) and they appear in the 65-75 % of the cases of the syndrome (1,10,11,23). These cysts represent a particular entity that has been of interest, mainly due to biological aggressiveness and to the great amount of recurrence (1,7-11). Recently and based on the intrinsic growth potential of its epithelial coating, they have been re-classified and called odontogenic keratocyst tumours, and they have been included in the odontogenic neoplasias (7,11). Genetically,

Table 1. Anomalies described in Gorlin-Goltz Syndrome.

SKELETAL ANOMALIES	
Bridging sella turcica (60-80 %)	Syndactyly and/or oligodactyly
Scoliosis (50%)	Shortened 4th metacarpal
Bifid rib (40%)	Splayed/fused ribs
Occult bifid rib (cervical, thoracic or both of which 40%)	Cervical ribs
Absent ribs (26%)	Sprengel scapular deformity
Hemivertebrae	*Pectum excavatum, carinatum*
Flatfoot	Pelvic calcification
Polydactyly	Another: arachnodactyly, hallux valgus, cortical defects in long bones.

SKIN ANOMALIES	
Basal cell carcinoma (50-97%)	*Milia*, specially in limbs
Palmar and/or plantar pits (60-90%)	Comedones

CRANIOFACIAL ANOMALIES	
Calcification of the cerebral falx (37-79%)	Brachycephaly
Macrocephaly (40%)	*Tentorium cerebellum* calcification
Frontal bossing (25%)	Bridged in sella turcica
Coarse face	Coroidal cysts (3º-4º ventricles)

SEXUAL ANOMALIES	
Uterine and ovarian fibromas (15%)	Supernumerary nipple
Ovarian fibrosarcoma	Hypogonadism and cryptorchidism
Calcified ovarian cysts	Female distribution of the pubis hair, scarce beard in men and ginecomastia.

NEUROLOGICAL ANOMALIES	
Medulloblastoma (3-5%)	Agenesis/ disgenesis of corpus callosum
Meningioma (1% or less)	Schizophrenic personality
Mental retardation	Nervous deafness
Congenital hydrocephalus	Anosmia

OPHTHALMIC ANOMALIES	
Hypertelorism (40%)	Glaucoma
Exotropia	Choroidal and/or optic nerve coloboma
Congenital amaurosis	Congenital blindness and opaque cornea
Ptosis	Cataracts
Internal strabismus (15%) convergent / divergent	Chalazion

OROFACIAL ANOMALIES	
Odontogenic keratocysts (75%)	Palate or maxillary sinus fibroma
High–arched palate or prominent palatine ridges (40%)	Malocclusion (maxillary hypoplasia and mandibular hyperplasia, cleft palate)
Cleft lip and/or palate (4%)	Fibrosarcoma of the jaws
Impacted teeth and/or agenesis. Dental ectopic position.	Ameloblastoma
ANOTHER: Inguinal hernia, renal anomalies, lymphomesenteric cysts, left ventricular fibroma (neonatal) and cardiac fibroma (3%).	

References (2,3,8,10,11,23)

the loss of heterozygosity of the tumour suppression genes that can be found in these lesions, leads to conclude that the keratocysts have a neoplastic origin and that they are not just an anomaly of the cyst development (9). In spite of this discovery this is still a very controversial issue.

These types of cysts manifest themselves for the first time during the first decade in life (8,10,11), and when they present in an isolated way, i.e. without any association with the syndrome, their major incidence is in the second and third decade in life (10,11). There are no sexual differences in isolated keratocysts but still there is a more frequent appearance among men (66%) that have the syndrome (11). The cysts can be found in any part of the maxillar if they are associated with the syndrome whereas isolated keratocysts appear more frequently (65-83%) preferably in the body and upper part of the jaw. Radiographically, they appear in syndrome as multiple uni or multiocular lesions, of variable size with sclerotic borders, and they can be uni or bilateral (9-11, 23) (Figure 1).

Histologicallly speaking, the keratocysts have a well defined scale-like parakeratinised stratified epithelium with an average thickness of 5 to 8 cells, with a basal layer in which cells present themselves fenced up in a corrugated surface and a connective wall rich in mucopolisacarids, without inflammatory infiltration and with a variable number of microcysts and epithelial islets (8-11) (Figure 2). Its high potential of recurrence is justified by the high mitotic epithelial activity, the frequency of satellite cysts, pieces of epithelium and prolific dental sheet, and by the existence of a epithelial coating thicker than in other jaw cysts (7,10,11).

Basocellular carcinomas have different manifestations depending on whether they are associated with the syndrome or not (Table 2). The more frequent skin lesions in the Gorlin-Goltz syndrome are the basocellular carcinomas (10). These tumours are much more frequent in the skin of white people (80%) than in people of black race (38%) (10). Epidemiologic studies have demonstrated that sunlight

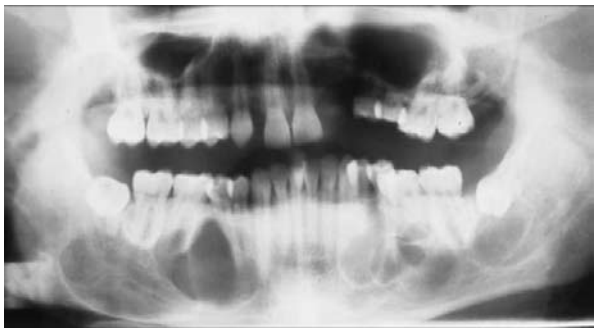

Fig. 1. Radiographic appearance of multiple radiolucent lesions in the jaw for odontogenic keratocysts.

and particularly UV radiation are key risk factors for the basocellular carcinomas development. This explains the low frequency of these lesions in Afroamerican people due to the protection action of the melanin pigmentation (8,10). Experimentation with mice has demonstrated the development of these basocellular carcinomas when they were exposed to UV rays. This exposure produced mutations in the PTCH gene (10), which would confirm that the basocellular carcinomas development in patients suffering from Gorlin- Goltz syndrome would be stimulated by UV rays irradiation (10). That is the reason why it is importat to protect patients` skin from sunshine, especially before clinical manifestations appear.

Basocellular carcinomas that are present in the Gorli-Goltz syndrome vary from one to hundreds and they have a wide spectrum of clinical presentations that go from light to dark papulae of hard consistence and plane surface, to ulcerated pigmented plaques of different size (10). The carcinomas can clinically manifest themselves from puberty to the mid-thirties and they more frequently affect the cutaneous surface of the thorax and the cervicofacial area (10,23). Periocular areas, eyelids, the nose, the malar region and the upper lip are the areas commonly affected. The basocellular carcinomas rarely produce any pain. Most of them are located in the epidermis although, throughout

Table 2. Different manifestations of the basocellular carcinomas depending on whether they are associated to the Gorlin-Goltz syndrome or not.

DATA	Basocellular carcinoma no-assoaciated to the Gorlin-Goltz Syndrome	Basocellular carcinoma associated to the Gorlin-Goltz Syndrome
Number	Only one	50 to 100
Sex	More frequent in men	Equally frequency in both of the sex
Location	Half third facial	Face, neck, back, thorax, abdomen and upper part of the body
Clinical characteristics	Papulae >> central ulceration Variable colour More frequent in white skins	Small papulaes, soft nodule or a plane plaque. Variable colour pink >> brown Any colour of skin
Etiology	Solar radiation	Genetically determinated
Treatment	It depends on the size and the location Surgery	Surgery Risk to develop new injuries

References: (8,10,11,23).

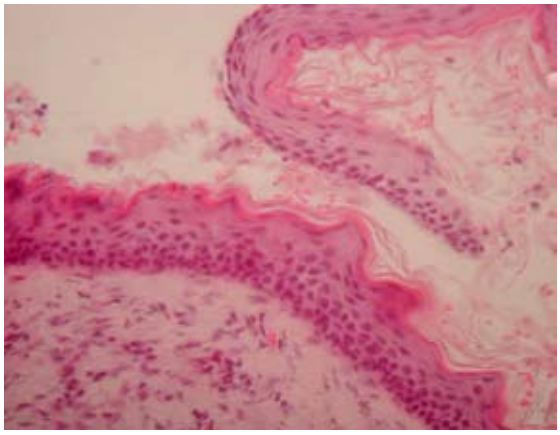

Fig. 2. Characteristic histopathologic aspect of keratinised epithelium of odontogenic keratocyst (H & E 60x).

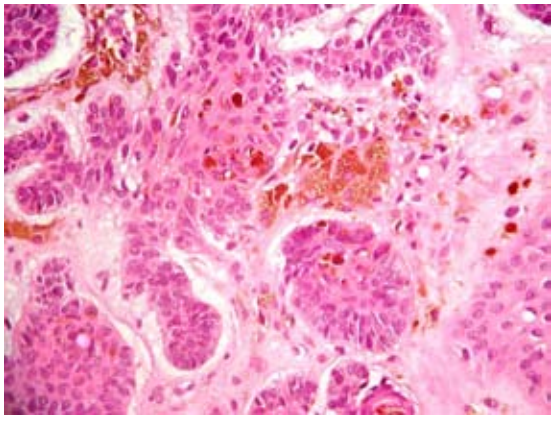

Fig. 3. Histopathologic appearance of basophile epithelial proliferation with melanin pigmentation in a basal cell carcinoma (H & E 50x).

the years, they can invade the dermis. Generally, a local invasion takes place and the evidence of aggressiveness is often preceded by a size growth, ulceration, haemorrhage and scab formation (10). Histologically, the basocellular carcinomas do not show any difference whether they are associated with the syndrome or not, and they have the classical appearance of nets and chains of basophile cells orderly settled, with a great amount of melanin pigmentation in many occasions (Figure 3).

Palmar and plantar pits are specific signs of this syndrome, and they appear as punctiform depressions in the palms and plants skin (8,23). These alterations are caused by the lack of a partial or complete absence of the corneal stratum. They are permanent, unpalpable and asyntomatic, with a depth ranging from 2 to 3 mm. and a diameter that ranges from 1 to 3 mm. (8,23). When the syndrome is present, they manifest in between the 50 and 70% of the patients and they usually get developed in the second decade of life, increasing in the number with the age- they can increase to 500 (10).

More signs are currently being added to the list of components of Gorlin-Goltz syndrome. For instance, Ramaglia et al. (23) showed that an eight-year-old girl was diagnosed with an incomplete fusion of Müller canals with a bicorneal uterous.

Diagnostic and therapeutic aspects

In the case of the Gorlin-Goltz syndrome it is of great importance to make an early diagnosis since severity in complications, such as skin and brain malignant tumours, can be reduced and so can the destruction and secondary oral maxillofacial deformities of the jaw cysts. An early diagnosis is important to give adequate genetic advice.

It is of major relevance to keep track of the family antecedents clinical history and to examine the oral cavity, skin, thorax and cranium in an exhaustive way (3,11). An orthopantomography, a frontal-back thorax radiography and a craniofacial CT must be taken in order to detect osseous morphology aspects that cannot be seen in simple radiographies, and also a MR of the cranium and pelvic ultrasonographies in women.

Patients suffering from the syndrome have to undergo check-ups at least once a year, especially the ones having odontogenic keratocysts (11).

The treatment of Gorlin-Goltz syndrome is the specific therapeutics of its clinical manifestations. In the case of odontogenic keratocysts, there are different treatment techniques to eliminate them and avoid the high rate of recurrence, which can reach up to a 62% of the cases (1,7-10). The therapeutic techniques for the keratocysts vary from simple enucleation with curettage, to the enucleation with peripheral osteotomy or to osseous resection in block (1,10). This last technique is the most aggressive and it logically follows that the recurrence rate decreases (8). There are also more conservative options such as the local parietal therapy with Carnoy solution, with cryotherapy or marsupialisation of the cysts, or decompression followed by a secondary enucleation (9,10). Nevertheless, those methods are not efficient in the long term and their use is considered to be controversial (9,10). In order to decide which technique must be employed, the following factors have to be taken into account: lesion size, lesion extension, location, possible cortical and soft parts damage, the age and whether it is a primary or recurrent lesion (8). It is also important to detect if it is an isolated keratocyst or if it is associated with the syndrome, since in the last case the rate of recurrence is higher as Forsell et al. (11) have suggested- the recurrence rate is of 63% in keratocysts associated to the syndrome, and of 37% in the isolated ones (11).

As well as keratocysts, basocellular carcinomas treatment is also based on conventional surgical exeresis with or without reconstruction, or with other techniques such as CO2 laser (8,10). In primary small and well defined lesions without aggressive behaviour, curettage, electrodissection and cryosurgery techniques have also been used. However, these techniques have the problem of impeding the correct

histopathological estimate of the samples and, hence, the biological estimate and the possible extension to the surgical margins-very usual piece of data in this pathology.

In some plane superficial lesions which do not affect the hair follicle, photodynamic therapy with delta-amino-levulinic acid has been employed, as well as the topical application of 5-fluorouracil to 0,1% (twice a day), or intralesional interferon alfa-2b or the chemotherapeutic paclitaxel agent, etc. (10). Local radiation therapy would not be advisable because of the tumour recurrence risk or because of the possible tumour growth (10).

As a conclusion, it can be said that Gorlin-Goltz syndrome is dominant autosomal genetic process- with the exception of sporadic mutation cases- which is of particular interest for the oral maxillofacial health experts. When a patient has this syndrome is of relevant importance to examine their family to detect possible clinical manifestations and in that way arrive at effective genetic advice. In order to be able to arrive at an early diagnosis of the syndrome, specialists should carry out a clinical radiographic testing in early ages of life. In this way, different health specialists play a key role: paediatricians, specialists in genetics, dentists, maxillofacial surgeons, dermatologists, etc. must have good basic knowledge of the main features of the syndrome to work accordingly in their different health specialities.

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In memorial to:

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