Clinical and oral findings in an Afro-Brazilian family with Gorlin-Goltz syndrome: case series and literature review

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Introduction

Despite previous reports of patients presenting similar skeletal, dermatologic and orofacial anomalies, only in 1960, Gorlin and Goltz defined three parameters (the classical triad), which determined the recognition of the disease as a distinct entity: multiple nevoid basal-cell epithelomas, keratocysts in the jaws and bifid ribs. At that time, those authors called it the “multiple nevoid basal-cell epithelium, jaw cysts and bifid rib syndrome,” but several names have been given to this syndrome since then, such as: “Gorlin-Goltz syndrome (GGs),” “nevoid basal cell carcinoma syndrome,” and “basal-cell nevus syndrome.”

Besides the classical triad, further studies have shown a wide spectrum of developmental defects and tumors that can be variably found in individuals affected with GGs. The patient often has a characteristic facies, with frontal and temporoparietal bossing, which results in an increased cranial circumference. The eyes may appear widely separated characterizing hypertelorism with a broad nasal root. Mild mandibular prognathism is also commonly present. Other common findings include: palmar and plantar pits, calcification of the falx cerebri, medulloblastoma, and ovarian fibroma. However, more than 100 minor features have been described for this syndrome.

All the clinical manifestations of GGs do not have to be present for a diagnosis. Current diagnosis generally depends on both the identification of a combination of clinical and histological features, and is heavily dependent on family history. In 1993, Evans et al. proposed diagnostic criteria, which were further modified by Kimonis et al. based on their population study (Table 1). Once diagnosis is made, the treatment of the syndrome is the specific therapeutics for its clinical manifestations.
GGS is inherited as an autosomal dominant trait with a high penetrance and variable phenotype expressiveness associated with mutations in the patched 1 gene (PTCH1). It presents a quite variable estimated prevalence, which varies according to the country where the study has been carried out. Nevertheless, a prevalence of 1 in 60,000 inhabitants is generally accepted, and both men and women are affected in the same way.

The syndrome probably arises in all ethnic groups, but most reports have been of whites. According to Goldstein et al., only 28 cases have been reported in blacks from 1960 to 1994. Additional 22 cases from black individuals were published from 1994 to 2012, including the cases published by Goldstein et al. (Table 2).

The purpose of this paper was to report clinical and oral findings in an Afro-Brazilian family (son, daughter, and mother) with GGS after reviewing the literature with regard to the cases in blacks that have been reported by Goldstein et al. and after their study (until 2012).

### Case series

#### Case 1—Son
A 9-year-old Afro-Brazilian male presented to the Pediatric Dental Clinic at the Federal University of Rio de Janeiro, Brazil, with a painless swelling of the left mandible. Previous medical history included surgery for cryptorchidism. On presentation, he was otherwise healthy.

Intraoral examination revealed a mixed dentition without carious lesions and other alterations, except for an expansion of the alveolar ridge near the left deciduous mandibular second molar. Panoramic radiograph demonstrated a well-defined unilocular radiolucent lesion located in the left mandible associated with unerupted permanent canine and premolars. Therefore, left permanent canine and first premolar were displaced inferiorty near to the basal mandibular region. Root resorption of the left deciduous first and second molars associated with the lesion was noted. Other four unilocular lesions were detected bilaterally associated with unerupted permanent canines in the maxilla and to unerupted permanent second molars in the mandible. On the left side, the mandibular lesion involving the permanent second molar extended to the left ascending ramus (Figure 1A).

Imaging findings were suggestive of odontogenic keratocysts, which were confirmed after surgical decompression and histopathological examination of the cysts wall. The four specimens showed similar features characterized by a wall of regular thickness composed of fibrous tissue relatively free of inflammation and lined by a uniformly thin parakeratinized stratified squamous epithelium (Figure 1B). The epithelial lining showed absence of rete pegs as well as palisading of the nuclei of the basal cells (Figure 1C).

Clinical examination of the skin showed multiple cutaneous nevi in the left periorbital and auricular regions (Figures 1D and E) and multiple palmar and plantar pits (Figures 1F and G).

The histopathological, intra-, and extraoral findings led to the clinical diagnosis of GGS and further imaging examinations included chest and skull radiographs to investigate possible skeletal alterations usually present in the syndrome.

Chest radiograph demonstrated a bifid aspect of the third, fifth, and sixth ribs on the left side, and fusion anomaly of the right first and third ribs. Additionally, spina bifida occulta was noted in T1 and T2 (Figure 1H). The posteroanterior skull radiograph demonstrated incipient calcification of the falx cerebri (Figure 1I). These skeletal anomalies confirmed the diagnosis of GGS, which was, therefore, also investigated in his first degree relatives.

The patient is under regular follow-up in order to keep under surveillance the disease evolution and monitor the occurrence of new lesions.

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**Table 1. Diagnostic criteria for Gorlin-Goltz syndrome proposed by Kimonis et al.**

<table>
<thead>
<tr>
<th>Minor criteria</th>
<th>Major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Macrocephaly determined after adjustment for height</td>
<td>1. More than two basal cell carcinomas or one under the age of 20 years</td>
</tr>
<tr>
<td>2. Congenital malformations: cleft lip or palate, frontal bossing, “coarse face,” moderate or severe hypertelorism</td>
<td>2. Odontogenic keratocysts of the jaw proven by histology</td>
</tr>
<tr>
<td>3. Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, and marked syndactyly of the digits</td>
<td>3. Three or more palmar or plantar pits</td>
</tr>
<tr>
<td>4. Radiological abnormalities: Bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet</td>
<td>4. Bilamellar calcification of the falx cerebri</td>
</tr>
<tr>
<td>5. Ovarian fibroma</td>
<td>5. Bifid, fused, or markedly splayed ribs</td>
</tr>
<tr>
<td>6. Medulloblastoma</td>
<td>6. First degree relative with Gorlin-Goltz syndrome</td>
</tr>
</tbody>
</table>

(Source: See Ref. (9)).
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Cases (No.)</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Described characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein et al.</td>
<td>1</td>
<td>M</td>
<td>60</td>
<td>Palmar and/or plantar pits, skin cysts, jaw cysts, possible basal cell carcinomas, synophrys</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>F</td>
<td>31</td>
<td>Palmar and/or plantar pits, skin cysts, three basal cell carcinomas, café-au-lait spot, neurofibroma, jaw, cysts, malocclusion, calcification of the falx cerebri, scoliosis, bifid ribs, missing/malformed ribs, Sprengel deformity, hypertelorism, strabismus, synophrys, ovarian fibroma, epicantlal folds, abnormal fundi</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>F</td>
<td>40</td>
<td>Palmar and/or plantar pits, one possible basal cell carcinoma, jaw cysts, malocclusion, calcification of the falx cerebri, scoliosis, short 4th metacarpal, brachycephaly, mandibular prognathism, cortical cysts, synophrys</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>M</td>
<td>38</td>
<td>Palmar and/or plantar pits, three basal cell carcinomas, skin tags, jaw cysts, scoliosis, frontal bossing</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>M</td>
<td>35</td>
<td>Palmar and/or plantar pits, jaw cysts, calcification of the falx cerebri, missing/malformed ribs, short 4th metacarpal, brachycephaly</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>M</td>
<td>30</td>
<td>Palmar and/or plantar pits, skin cysts, one basal cell carcinoma, milia, neurofibroma, jaw cysts, calcification of the falx cerebri, scoliosis, missing/malformed ribs, hypertelorism</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>M</td>
<td>29</td>
<td>Palmar and/or plantar pits, jaw cysts, mandibular prognathism</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>F</td>
<td>61</td>
<td>Palmar and/or plantar pits, skin cysts, hypopigmented areas on skin, jaw cysts, scoliosis</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>F</td>
<td>37</td>
<td>Palmar and/or plantar pits, jaw cysts, calcification of the falx cerebri, mandibular prognathism, slight torus (palate)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>F</td>
<td>17</td>
<td>Palmar and/or plantar pits, polydactyly-bilateral, jaw cysts, calcification of the falx cerebri, scoliosis, short 4th metacarpal, parietal bossing, childhood seizures (onset age 3 years)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>M</td>
<td>14</td>
<td>Palmar and/or plantar pits, one basal cell carcinoma, partial cleft lip; subglotic web/narrowing; skin tag, jaw cysts, calcification of the falx cerebri, scoliosis, bifid ribs, missing/malformed ribs, fusion of ribs, Sprengel deformity, frontal bossing, dolichocephaly, mandibular prognathism, broad nasal root, pectus carinatum, epicantlal folds, childhood seizures (onset age 3 years)</td>
</tr>
<tr>
<td>Shimkets et al.</td>
<td>12</td>
<td>F</td>
<td>15</td>
<td>Macrocephaly, frontal bossing, synophrys, mandibular prognathism, palmar and plantar pits, and scoliosis, spina bifida occulta of T2 and T3 and several bifid ribs</td>
</tr>
<tr>
<td>Korczak et al.</td>
<td>13</td>
<td>M</td>
<td>8</td>
<td>Odontogenic keratocyst, palmar and plantar pits, medulloblastoma, basal-cell carcinomas (areas irradiated for medulloblastoma), frontal bossing, ocular hypertelorism, high-arched palate, slightly large head circumference</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>F</td>
<td>38</td>
<td>Odontogenic keratocyst, extensive calcification of the falx cerebri and dura mater, high-arched palate, large head circumference, small cystic osteolytic lesions of the tubular bones (hands, distal radius, and ulna)</td>
</tr>
<tr>
<td>Hall et al.</td>
<td>15</td>
<td>M</td>
<td>11</td>
<td>Multiple maxillary and mandibular odontogenic keratocysts, palmar and plantar pits, multiple 1 mm fleshcolored papules (nasal bridge, forehead, and preauricular areas), exotropia secondary to an impacted molar displaced into the orbit</td>
</tr>
<tr>
<td>Li et al.</td>
<td>16</td>
<td>F</td>
<td>26</td>
<td>Palmar pits, scoliosis, ophthalmologic abnormalities (cataracts, uveitis, glaucoma, vitreitis), basal cell carcinomas</td>
</tr>
<tr>
<td>Kimonis et al.</td>
<td>17</td>
<td>M</td>
<td>6</td>
<td>Medulloblastoma, flame-shaped lucencies of the hands</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>F</td>
<td>NR</td>
<td>Flame-shaped lucencies of her metacarpal, phalanges, distal radii, and ulna</td>
</tr>
<tr>
<td>Smucker and Smith</td>
<td>19</td>
<td>M</td>
<td>2.5</td>
<td>Macrocephaly, bilateral rib fusion and segmentation anomalies, frontal and biparietal bosselation, hypertelorism, medulloblastoma, mild ventriculomegaly</td>
</tr>
<tr>
<td>Sobota et al.</td>
<td>20</td>
<td>M</td>
<td>19</td>
<td>Medulloblastoma, meningioma, thyroid follicular adenomas with papillary carcinoma, basal cell carcinomas, sinonasal undifferentiated carcinoma, mandibular odontogenic keratocyst, liver fibromyxoid lesion, multiple dural lesions along the tentorium</td>
</tr>
<tr>
<td>Reti et al.</td>
<td>21</td>
<td>M</td>
<td>31</td>
<td>Mild ocular hypertelorism, frontal and temporal bossing, multiple enlarged nevi with regular borders, diffuse dural calcifications of the falx cerebri, tentorium and lateral convexities, maxillary and mandibular odontogenic keratocysts</td>
</tr>
<tr>
<td>Simiyu et al.</td>
<td>22</td>
<td>M</td>
<td>20</td>
<td>Maxillary and mandibular odontogenic keratocysts, multiple basal cell carcinomas, bifid ribs, intracranial calcifications</td>
</tr>
</tbody>
</table>

*The other possible features were not reported. NR= not reported.
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Case 2—Mother

The mother, 39-year old, was called for clinical examination at the Oral Diagnosis Clinic at the same University. Her medical history was uneventful, except for a previous ovarian surgery for cysts' removal.

At clinical examination, she had a large head circumference (Figure 2A), prognathism (Figure 2A), hypertelorism (Figure 2B), scoliosis, polydactyly of the right hand (Figures 2C and D), and palmar and plantar pits (Figures 2E and F).

A panoramic radiograph of the mandible showed two well-defined unilocular expansile osteolytic lesions in the right and left ascending rami of the mandible (Figure 2G). On the left side, the lesion was associated with an unerupted permanent molar. Histological examination of the oral lesions confirmed the hypothesis of odontogenic keratocysts with the presence of satellite cysts (Figure 2H).

The posteroanterior chest radiograph confirmed the scoliosis and demonstrated a bifid aspect of the third ribs on the right and left sides, as well as spina bifida occulta in T1 and T2 (Figure 2I). Similarly to her son, the posteroanterior skull radiograph demonstrated marked calcification of the falx cerebri (Figure 2J).

All the above described features characterized the presence of GGS in the mother too, who did not know about the syndrome until our clinical examination. Therefore, she also started regular follow-up after cysts' removal.

Case 3—Sister

At 15-year old, the boy's sister was also diagnosed as a further case of GGS in the investigated Afro-Brazilian family. Her medical history was unremarkable.

At clinical examination she presented plantar pits (Figure 3A), and a panoramic radiograph revealed two unilocular cystic lesions extended from the retromolar space bilaterally to the right and left ascending rami of the mandible (Figure 3B). Both lesions were associated with unerupted permanent third molars, which were displaced posteriorly. Incisal biopsy of the oral lesions was performed and histopathological...
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examination confirmed the odontogenic keratocysts (Figure 3C).

Regular follow-ups continued to be scheduled in order to monitor probable new or recurrent lesions.

Discussion

In order to make a diagnosis of the GGS some diagnosis criteria have to be taken into consideration as shown in Table 1. Two major or one major and two minor diagnostic criteria have to be present to make a diagnosis of the syndrome. The first two reported cases were very characteristic because they had a remarkable number of associated anomalies. Case 1 presented five major (odontogenic keratocysts, palmar/plantar pits, bifid/fused ribs, calcification of the falx cerebri, and first degree relative with GGS) and one minor criteria (spina bifida occulta), while Case 2 presented five major (odontogenic keratocysts, palmar/plantar pits, bifid/fused ribs, calcification of the falx cerebri, and first degree relative with GGS) and six minor criteria (large head circumference, prognathism, hypertelorism, scoliosis, polydactyly, and spina bifida occulta). The index case's sister (Case 3), on the other hand, proved to be the least affected because it presented only three major criteria (odontogenic keratocysts, plantar pits, and first degree relative with GGS).

Although early reports of GGS implied a higher prevalence among white populations, the syndrome has been reported in other ethnic groups including populations with highly pigmented skin. Such patients have no advantage against developing or inheriting GGS, although a high concentration of melanocytes has been associated with a decreased chance of basocellular carcinoma (BCC) proliferation, presumably owing to protection from ultraviolet radiation. In this case series, only Case 1 had multiple cutaneous nevi, which did not seem carcinomatous, although histological confirmation was prevented because the mother refused to biopsy the lesions.

The lack of BCC formation may further delay diagnosis of early GGS.
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Figure 3. A. Plantar pits (A — magnified view of some pits of the right sole). B. Panoramic radiograph showing two unilocular cystic lesions associated with unerupted third molars (black arrows). C. Typical histological features of an odontogenic keratocyst showing a characteristic thin squamous epithelial lining with a distinct palisaded basal layer and surface parakeratinization (#1) separated from the underlying connective tissue wall (#2; H&E staining, original magnification ×20).

without affording protection from the syndrome's other manifestations. Because most patients with GGS come to clinical attention either because of their BCCs or jaw cysts, black individuals, in whom BCC expression is relatively rare, are less likely to be ascertained. Therefore, GGS seems to be unusual in black persons. Until 1994, only 5% of all case reports involved blacks, who are most commonly diagnosed by asymptomatic odontogenic keratocysts discovered on routine dental or facial radiologic examinations. An exception occurs when oral keratocysts lead to jaw swelling and patients first visit a dental clinic with this chief complaint as happened with our index case. GGS is then, first diagnosed by the dentist in many instances. This report presented a rare GGS diagnosis in an Afro-Brazilian family, which was made by dentists despite the numerous clinical and radiographic characteristics presented by the index case and her mother. Additionally, her diagnosis had not been made until her 39 years and was only possible because of the family investigation proposed by the dental team.

When a patient has GGS is of relevant importance to examine his/her family to detect possible clinical manifestations which can show a familiarity. Interestingly, the clinical expression of the Syndrome varies among individuals within the same family and even more among families, being particularly noted for its extensive interfamilial as well as intrafamilial variability with respect to the manifestation and severity of the phenotype. In our case report, the mother and her daughter were diagnosed only after family investigation and clinical features were variable among the three reported cases, the daughter being the least affected person.

Thorough clinical examination and radiographic investigation remains the diagnostic standard for GGS because molecular genetic testing for mutations in PTCH gene is unable to detect the mutations in all affected individuals. Molecular testing may be considered for confirmation in individuals with atypical findings. In our case series, all clinical and radiological features of the three presented cases were classical signs of GGS, excluding the need for molecular genetic testing.

Odontogenic keratocysts are the most consistent and representative signs of GGS in the first and the second decades of life. They are usually asymptomatic but may cause swelling, loosening or displacement of erupted or developing teeth. They can recur and can be locally invasive causing bone destruction of the jaw. Their proposed origin is from dental lamina or its remnants and their most common site of occurrence is the retromolar region in place of the third molar. They have a unique histologic appearance presenting a thin cyst wall, with a distinctly palisaded basal layer that often separates from the surrounding connective tissue, which is rich in mucopolisacarids, without inflammatory infiltration and with a variable number of microcysts and epithelial islets. Comparisons between syndromic and nonsyndromic keratocysts have shown that keratocysts in GGS are usually multiple and have increased number of satellite cysts and solid islands of epithelial proliferation. Additionally, when compared to solitary keratocysts, GGS keratocysts are more frequently parakeratinized. Our three reported cases presented multiple odontogenic keratocysts with the typical radiographic and histological features previously described. Although asymptomatic, the mother's cyst located in the left mandible assumed such a locally destructive behavior that could cause a pathological fracture of the involved jaw if left untreated.

Other developmental defects proved to be prominent features of GGS and include pits of the palms and soles, spine and rib abnormalities, ectopic calcifications, and macrocephaly. Palmar and plantar pits are specific signs of this syndrome, and they appear as punctiform depressions in the palms and plants skin. These alterations are caused by the lack of a partial or complete absence of the cornal stratum, and they usually get developed in the second decade of life, increasing in the number with the age. They can be considered a very useful diagnostic trait of GGS as pointed out by Kimonis et al., who found palmar pits as the most prevalent sign of the Syndrome in their epidemiological study. In this case report, all the three affected individuals had at least palmar pits, as it was the case of the boy's sister who presented few clinical and radiological features, being the pits one of them.
The age of onset of physiologic falx calcification has not been well established, but is rare in pediatric populations. According to Kimonis et al., the calcification of the falx, often described as bilamellar, is variable and develops with increasing age. Our index case, although being a 9-year-old boy, showed an incipient calcification of the falx cerebri. This feature was much better recognized in his mother as a bilamellar calcification and was not present in his sister until her 15 years.

Spina bifida occulta, marked syndactyly of toes and polydactyly seem to occur with unusual frequency in patients with GGS. However, the first condition was found in this report both in the baby and in his mother. The latter one also presented polydactyly in the right hand.

In conclusion, odontogenic keratocysts in children should alert dental clinicians to look for signs and symptoms that may suggest GGS. And once detected, close relatives should be carefully examined for the Syndrome even if they belong to an ethnic group in which this diagnosis is unusual.

Conflict of interest

All authors declare they have no conflict of interest or financial relationships relevant to this article to disclose.

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References

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