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Archives of Dentistry Case Report

Backwards Screening for Gorlin-Goltz syndrome – Does It Make Sense? - A Family Case Report

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Abstract

Introduction: The Gorlin-Goltz syndrome (GGS) is an autosomal dominant disorder characterized by kerato cystic odontogenic tumors (KCOT) in the jaws, multiple basal cell carcinomas and skeletal and ophthalmic abnormities. It also involved in the nervous- and the endocrine system. The prevalence differs from 1:50,000 to 1:150,000. GGS and KCOT do not only appear in an inherited way but also sporadically following mutation of the tumor suppressor gene on chromosome 9 (*PTCH1* or *PTCH2* gene).

Aim: The presented two cases are describing the complex interdisciplinary treatment of a male adolescent patient suffering from GGS and his mother. Initially the mother, who passed the spontaneous new mutation of the *PTCH1* gene to her son, was considered as a carrier without any clinical gene expression. After 10 years she also showed KCOTs. It seems that spontaneous mutations, e.g. the mother, have a late-onset of keratocyst formation compared to autosomal-dominant subsequent generations, which are already conspicuous in adolescence.

Discussion: The subsequent generation seems to be clinically much more conspicuous in cases of a new mutation of *PTCH1* in the parents. That leads to the question, whether it might be useful to derive an indication for a close recall of the until then symptom-free parent generation in the course of a backward screening from a detected GGS case in a juvenile. In the present case, the mother of the boy was only "co-screened" during the active therapy phase of her child in the years 2006-2010, without showing any clinically noticeable findings. Afterwards she was released from the regular recall. The keratocysts discovered 10 years later in the maxillary sinus and the left mandible could have been detected much earlier and treated accordingly, if a close examination had been performed.

Clinical relevance: This case documentation show in line with other publications that early diagnosis of a GGS is important - and not only for the treatment of the affected generation. Rather, the early diagnosis of a CGS in a child or adolescent can also lead to an essential therapy for a parent, who has been clinically inconspicuous until then.

Abbreviations: BCNS: Basal Cell Nevus Syndrome; CBCT: Cone Beam Computertomografy; GGS: Gorlin-Goltz Syndrome; KCOT: Kerato Cystic Odontogenic Tumor; NBCCS: Nevoid Basal Cell Carcinoma Syndrome; OPT: Orthopantomogram; PTCH1: Tumor suppressor gene on chromosome 9

Introduction

The Gorlin-Goltz syndrome (GGS), also referred as Nevoid Basal Cell Carcinoma Syndrome (NBCCS) or Basal Cell Nevus Syndrome (BCNS) was first described by Gorlin et al. in 1960 although it was known for decades before [1]. It is an autosomal dominant disorder characterized by KeratoCystic Odontogenic Tumors (KCOT) in the jaws, multiple basal cell carcinomas, skeletal and ophthalmic abnormities and affects the nervous- and the endocrine system [2]. As epidemiological studies are rare, the prevalence differs from 1:50,000 to 1:150,000. Frequently, the manifestation of the syndrome occurs in the juvenile [3-5].

According to recent findings, the NBCCS and, keratocystic odontogenic tumors, likewise, were described to not only appear in an inherited way but also sporadically following mutation of the *PTCH1* or *PTCH2* [9q22.3] gene [6-9]. Gorlin-Goltz syndrome can be detected by direct molecular genetic evidence of the genetic defect.

Aim of the Case Presentation

The presented two cases are describing the complex interdisciplinary treatment of a male adolescent patient suffering from GGS and his mother. A genetic evaluation of the family including the entire generation of grandparents based on a sequencing of all PTCH1 exons [7] and their intron-exon boundaries was performed. The genetic screening revealed a spontaneous mutation of the *PTCH1* gene in the mother. However, the mother's clinical findings were without pathology so that she - at first - was considered as a carrier without any clinical gene expression.

However, the now 57-year-old mother, who passed the spontaneous new mutation of the *PTCH1* gene to her son, also showed KCOTs in a random finding after 10 years. It seems that spontaneous mutations have a late-onset of keratocyst formation, i.e. in the expression of characteristics, compared to autosomal-dominant subsequent generations, which are already conspicuous in adolescence. In the literature there is little reference to this so far. The available publications describe the genetic defects of the parent generations as a predictor for a screening of the offspring. However, since the subsequent generation seems to be clinically much more conspicuous in cases of a new mutation of *PTCH1* in the parents, the question arises whether it might be useful to derive an indication for a close recall of the (until then) symptom-free parent generation in the course of a backward screening from a detected GGS case in a juvenile.

In the present case, the mother of the boy was only "co-screened" during the active therapy phase of her child in the years 2006-2010, without showing any clinically noticeable findings. Afterwards she was released from the regular recall. The keratocysts discovered 10 years later in the maxillary sinus and the left mandible could have been detected much earlier and treated accordingly, if a close examination had been performed.

Case Presentation of the Son

An 11-year-old boy was referred to our clinic for further diagnostic due to the persistence of the lower deciduous molars. The clinical extra-oral examination revealed a kyphoscoliosis accompanied by a pectus excavatum with an age-appropriate habitus. Additionally, a myopia with moderate hypertelorism was obvious.

The intra-oral examination showed a mixed dentition at the beginning of the second dentition phase. The orthopantomogram (OPT) showed a retention of the teeth 33 and 45 at the base of the mandible. In the peri-coronal area of both teeth enlarged radiolucencies with a clearly visible margin in region 33 and 45 were obvious. Additionally, in the area between teeth 46 and 47, a diffuse osteolysis confluent with a peri-coronar osteolysis around the retained 47 was visible. Furthermore, the teeth 35, 34 and 44 were angulated disto-mesially and root resorptions at the teeth 73 and 85 were observed (Figure 1).

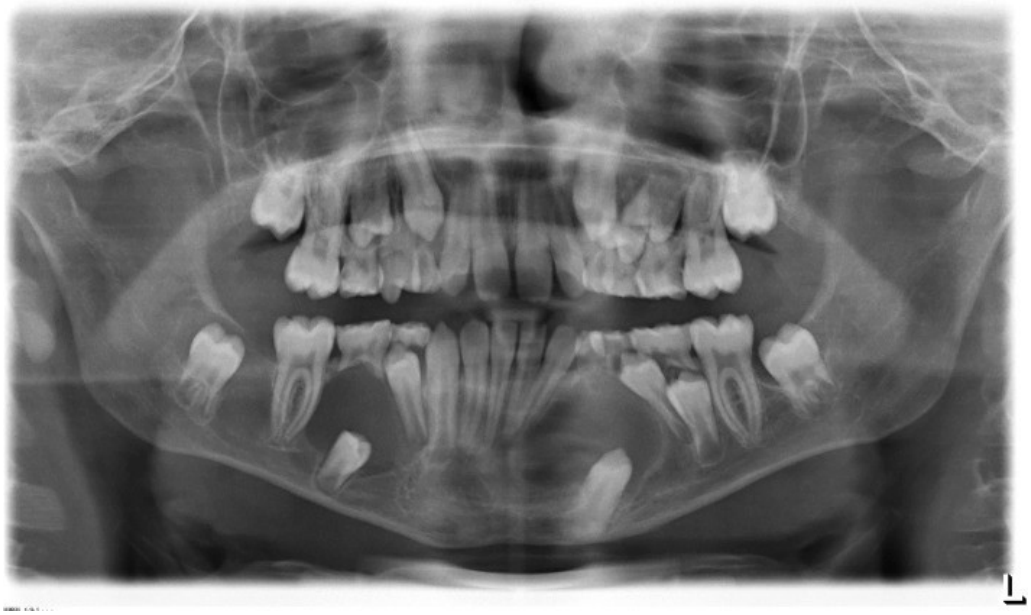

Figure 1: Initial OPT of the boy at the age of 11 years.

Diagnostic work-up

In order to clarify the clinical and radiographic findings an incisional biopsy was taken from region 33 and 45 under local anesthesia. The histological examination proved a keratocystic odontogenic tumor in both regions. Due to the diagnosis of bilateral KCOT the clinical suspicion of a GGS arose. Thus, multi-disciplinary consultations including radiology of the head-neck region, a dermatological screening, ophthalmological and orthopedic examinations were initiated.

Treatment

Due to the genetic aberration revealed by the blood test a genetic counseling was recommended to the family. Considering the pathological findings, an interdisciplinary treatment plan for the adolescent patient was created.

- Follow-up of the physical screenings focusing on dermal and ophthalmic anomalies on a regular three-month interval. Radiological follow-up semi-annually focusing on osteolytic lesions in the jaw [3].

- Enucleation of the KCOTs with simultaneous bone grafting.

- Orthodontic treatment to level the dental arches and to maintain space for implant supported oral rehabilitation in region of 33 and the right mandible by distraction.

- Insertion of dental implants and prosthetic restoration after the cessation of the physical growth with 17 years after (proved by hand-x-ray)

Outcome and follow-up period

Regarding the histologically proven KCOTs a three-months radiological control interval was set up during the treatment period until the eruption of the last permanent tooth which was tooth 23 in the presented case. A sharply defined peri-coronal radiolucency around tooth 23 were found at the second control examination. Subsequently, the interval of radiographic examination has been extended to 6 months. To improve bone availability, the right horizontal branch of the mandible was distracted before implantation (Vertical Alveolar Distraction, Type Cologne, Gebrüder Martin & Co KG, Tuttlingen, Germany; Figure 2 Detail).

At the 6-months follow-up after insertion of the prosthetic restorations, OPT, lateral cephalogram and CBCT showed well osseointegrated implants without any sign of bone loss. No recurrence of the surgically removed KCOTs was observed. However, a new cystic lesion in the posterior part of the right sinus maxillaris was found. Tooth 17 was removed due to the close contact to the cystic lesion without complications. Histologic examination proofed another KCOT. At the 12-months follow-up, a lesion in the basal part of the left sinus maxillaris was observed. As the radiographic control showed a rapid progression of the lesion in the left sinus it was surgically removed under general anesthesia. Due to the strong adherence of the cyst to the bone it had to be resected. The resulting oroantral fistula was closed using a titanium supported membrane. Histologic analysis again revealed a KCOT.

Up to the patient's age of 20 years, the follow-up in semi-

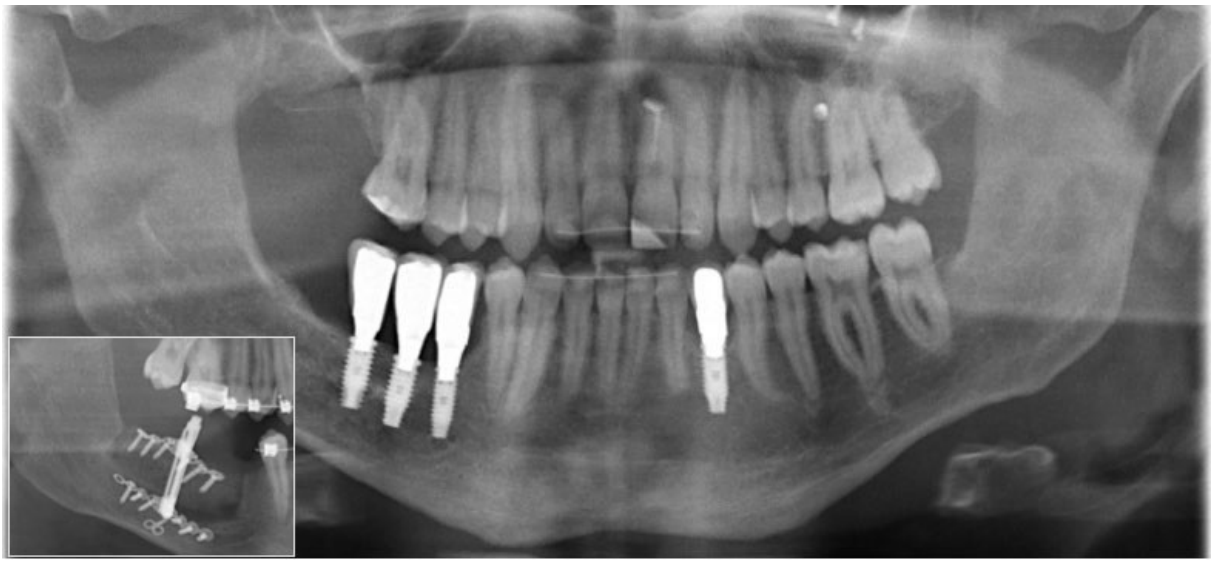

Figure 2: OPT of the boy after therapy at the age of 20 years (Detail: distraction osteogenesis at the age of 17 years ; see text).

annular intervals were without any pathologic finding (Figure 2). Even though the bone was augmented and distracted beforehand, it was not possible to produce an ideal crown/implant ratio.

Case Presentation of the Mother

The 43-year-old mother accompanied her 11-year-old son during the individual therapy steps from 2006 to 2010. The following OPT from 2006 shows her initial radiological findings at a control examination without clinical signs of GGS (Figure 3).

Diagnostic work-up

A spontaneous de novo mutation of c.1347+1G>A (*PTCH1* gene) was detected in the mother; radiology of the head-neck region, a dermatological screening, ophthalmological and orthopedic examinations were performed interdisciplinary.

CT imaging showed an ossification of the falx cerebri, as it is typical for GGS. In 2020, however, cysts were detected in the maxillary sinus and the left maxilla (Figures 4 and 5).

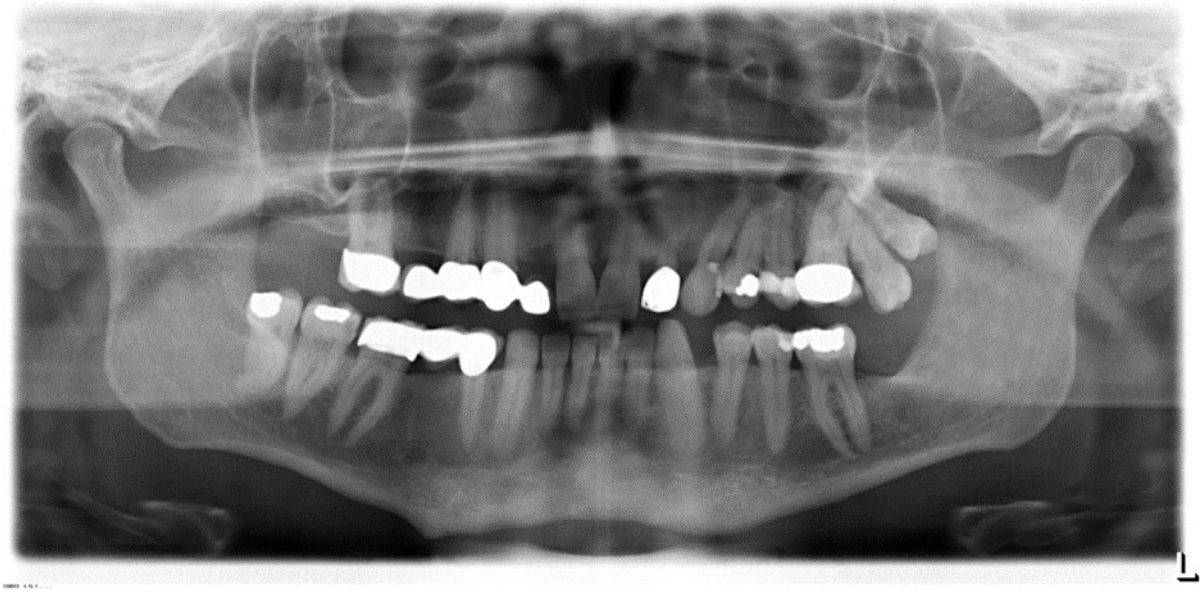

Figure 3: Initial OPT of the mother at the age of 43 years.

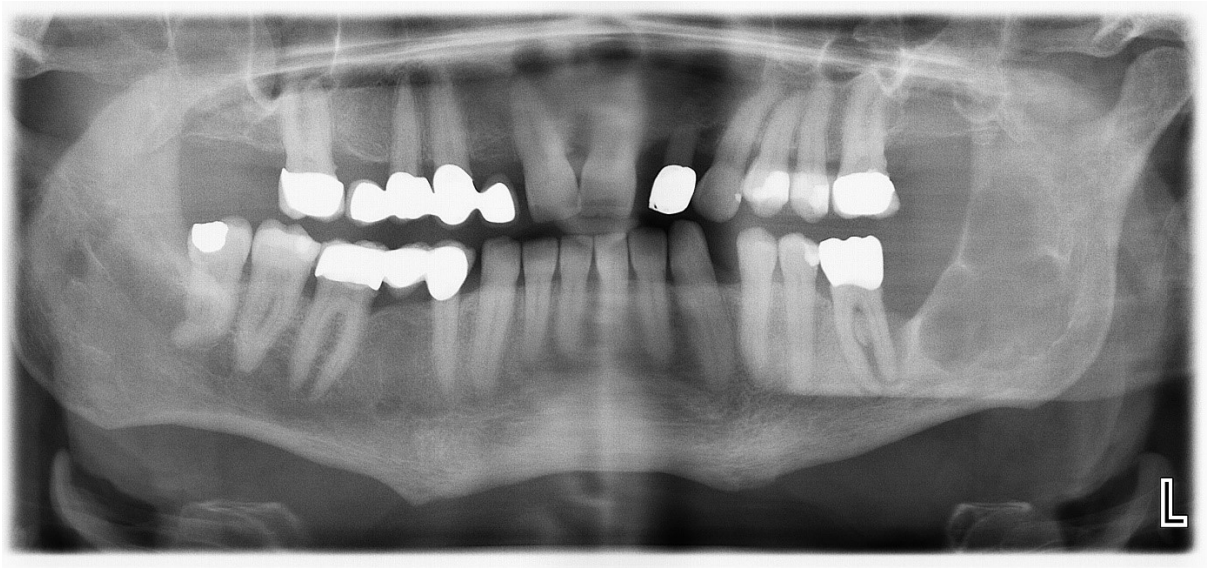

Figure 4: OPT of the mother at the age of 57 years.

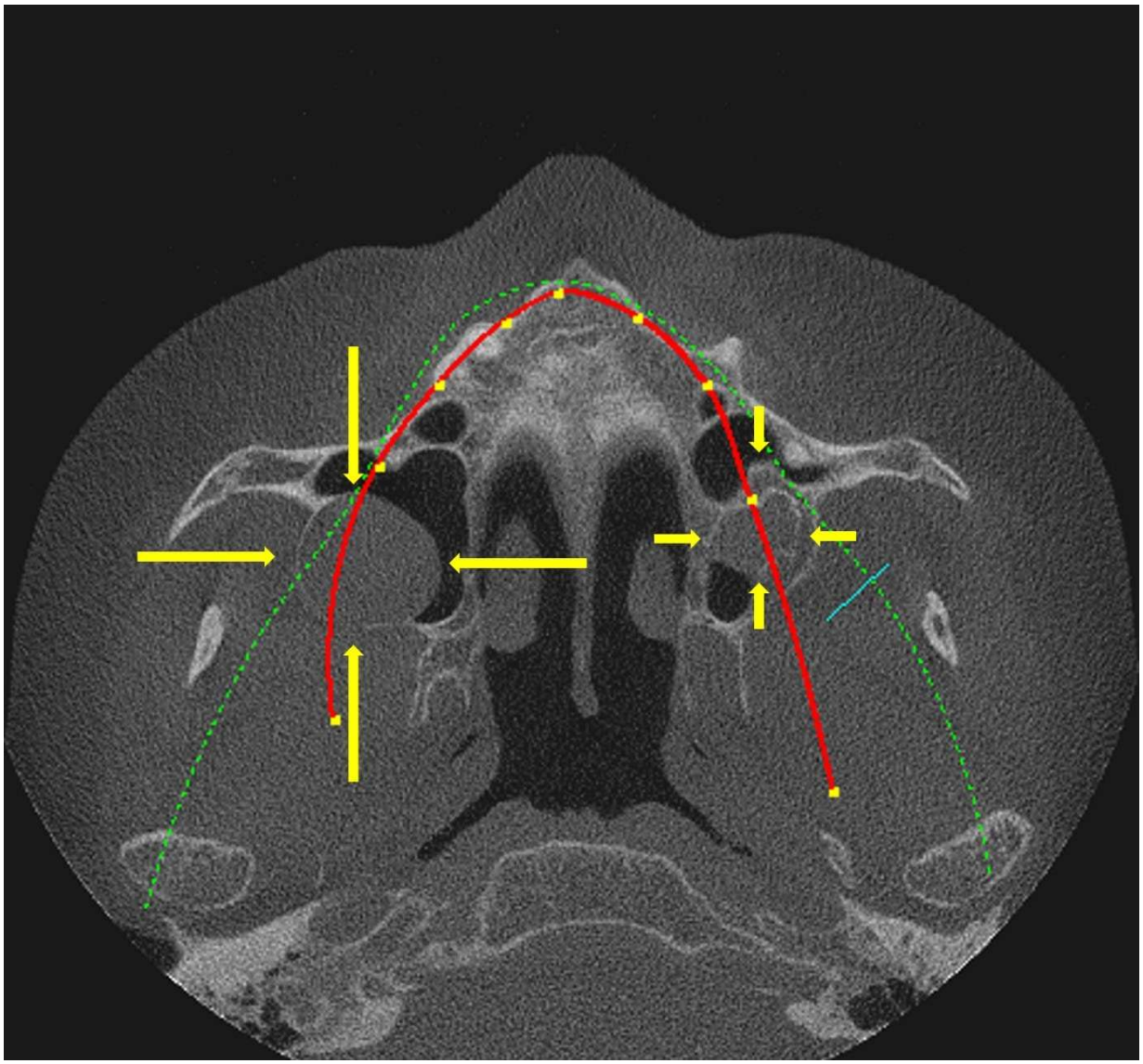

Figure 5: CBCT: Cyst left maxilla basal and right posterior sinus maxillaris.

Treatment

An enucleation of the KCOTs with simultaneous bone grafting was performed. The mother was included in a recall-program with life-long follow-ups at yearly intervals.

Discussion

As shown in the presented case, cystic alterations are frequently diagnosed incidentally. In order to avoid extensive lesions, frequent dental check-ups are recommended [10,11]. A treatment including multiple medical disciplines is necessary for the rehabilitation of patients suffering from tumors [11]. Furthermore, a genetic counseling of the entire family is recommendable due to the dominant inheritance.

During the transitional dentition, radiographical check-ups of the son in intervals of 3 months including the developing tooth germs are recommended to identify potential lesions in an early stage [6,12,13]. As these recommendations would cause a considerable exposure to radiation in our case the radiographical check-ups in three-months intervals were performed until the eruption of the last permanent tooth. Subsequently, the interval was extended to 6 months. Thus, an early detection of translucent lesions in the regions of teeth 17 and 18 as well as 28 was possible. Subsequently, the extraction of 17 and the surgical removal of the wisdom tooth germs was indicated due to the development of another keratocystic odontogenic tumor.

It might have been advisable to include the boy's mother in the radiological monitoring. This is supported by the observation that pathological findings in parents and/or siblings were detected in various studies, which would not have been detected without the GGS diagnosis of the adolescent patient – or would have been detected much later.

A case report from India by Sahu et al. [14] describes the case of an 18-year-old girl who presented with a painless swelling of the left half of the face that slowly increased over several months. The clinical examination showed a finding of a cleft lip operated during infancy.

The OPT showed an aplasia of the upper wisdom teeth and impacted lower wisdom teeth. Between 22 and 23 there was a supernumerary tooth germ. In addition, there were multiple well defined unilocular radiolucencies with a radio-opaque border in the maxilla and mandible. An x-ray of the skull showed a calcification of the falx cerebri and another overview of the thorax showed bifid rips. Ultrasound examination of the abdomen showed that both ovaries were filled with multiple subcentrimetric cysts. A genetic analysis also confirmed the initial suspicion of a GGS.

Based on this diagnosis, all close relatives of the patient were advised to undergo the same examination.

During the clinical and radiological examination of the patient's mother, who had been without symptoms until then, a slight facial asymmetry was revealed in the profile. The OPT showed multiple unilocular well-defined radiolucencies with radio-opaque borders on both side of the mandible and a single large well-defined radiolucency bordered by radiopacity in the anterior maxilla. The mother, just like her daughter, had bifide ribs.

After therapy was completed, she was recommended to have a lifelong recall at 6-month intervals, just like her daughter. Both patients were informed about the high risk of recurrence of keratocysts and the development of basal cell carcinoma [14].

Yordanova et al. also described the medical history of a young woman with GGS whose diagnosis led to the detection and treatment of multiple basal cell carcinomas in the facial area and on the arms and multiple oral keratocysts in her 50-year-old mother. Here too, the disease was more pronounced in the daughter generation than in the parent generation [15].

Hedge et al. describe the cases of a 38-year-old father and his 8-year-old daughter. Here, odontogenic keratocytes were diagnosed at the same time and, due to the familial accumulation, induced the discovery and treatment of further lesions typical of GGS in both patients. The authors suspected that in this patient pair the mutation had occurred in the grandparent generation or even earlier. Unfortunately, this could not be determined afterwards [16].

All these case documentations show that early diagnosis of a GGS is important - and not only for the treatment of the affected generation. Rather, the early diagnosis of a CGS in a child or adolescent can also lead to an essential therapy for a parent, who has been clinically inconspicuous until then.

But even within a generation, the early diagnosis of a CGS can lead to a close relative being referred to an early and curative therapy. As an example, Anchlia et al. (2015) report of 18- year-old twin brothers. The therapy of multiple keratocysts of one brother led to examining of the other brother, who until then had no clinical symptoms. Not surprisingly, this young man also showed almost identical signs of GGS and multiple odontogenic keratocysts in urgently need of therapy [17].

Pastorino et al. were able to show in their study that there is no fixed genotype/phenotype correlation in GGS. Rather, individuals with *PTCH1* mutations showed a wide range of clinical variation. The type of mutation and/or the gender of the carrier of the genetic defect had no influence on when the patients developed basal cell carcinoma and/or multiple oral keratocysts. However, there was evidence that the affected individuals developed the disease during their lifetime [18].

Against this background, clinically unremarkable carriers of a *PTCH1* mutation, i.e. often the parent of a sibling with GGS, should also be included in a close monitoring program. This could lead to some detailed information regarding the pathogenesis of the syndrome. This is attributed to variable abnormalities of chromosome 9 and loss or mutations of human patched gene 1. We report two cases of an 11- year-old boy and his 57 years old mother with three major and minor clinical and radiological findings like multiple odontogeneic Keratocysts, basal cell carcinoma, intracranial calcification of the falx cerebri, hypertelorism, skeletal and ophthalmic dysmorphism. The diagnosis prompts an early verification of the disease, which is very important to prevent recurrence and better survival rates of the relatives [19].

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