

The role of the dentist and the orthodontist in early diagnosis of Gorlin–Goltz syndrome: a cephalometric and photometric study

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Abstract

Introduction Gorlin-Goltz syndrome (GGS) is an autosomal dominant disease, characterised by basal cell carcinoma, palmar/plantar pits, maxillary and mandibular keratocysts and dental abnormalities.

Aim The aim of this study was to analyse the facial characteristics and the craniofacial morphology in GGS patients in order to enable an early diagnosis.

Methods Nine out of a sample of 24 GGS patients had complete cephalometric and photographic records at an average age of 8.7 years. Cephalometric and photometric analysis were carried out with standard analyses and compared with healthy patients matched for sex and age.

Results and discussion Photometric data: Significantly increased facial convexity, transverse facial dimensions, telecanthus and increased transverse nasal dimensions were found compared to the matched control patients. Cephalometric data: Hyperdivergence of the skeletal bases, skeletal Class III malocclusion associated with retrusion and hypoplasia of the maxilla and increased lower facial height were found in all patients compared to control patients. Patients affected by GGS have a characteristic craniofacial phenotype which clinicians might be able to identify for early diagnosis of developing jaw keratocysts.

Conclusion Early diagnosis of GGS based on clinical features could be useful to identify the presence of keratocysts through x-ray examination proceeding with surgical removal at an early stage, limiting space-occupying damages.

KEYWORDS Gorlin-Goltz syndrome, Cephalometric analysis, Photometric analysis, Craniofacial morphology, Keratocyst, basal cell carcinoma.

Introduction

Gorlin-Goltz syndrome (GGS) is an autosomal dominant condition, described by Gorlin in 1960 [Gorlin et al., 1960], due to Sonic Hedgehog signaling pathway mutations, correlated with Patched PTCH1 gene [Farndon et al., 1992] and, in some cases, with the homologues PTCH2 gene and SUFU gene [Fan et al., 2008; Fujii et al., 2013]. The Sonic Hedgehog signaling pathway regulates embryogenesis, carcinogenesis and tissues repairation process.

GGS clinical features include basal cell carcinoma [Gorlin, 1987; Evans et al., 1993; Pruvost-Balland, 2006], palmar and plantar pits [Gorlin, 1987; Gutierrez et al., 1986; Manfredi et al., 2004], fused or missing ribs [Ratcliffe et al., 1995] and fibromas [Torsten et al., 2006]. Oral and craniofacial manifestations include keratocysts [Lo Munzio et al., 1999; Ozkan et al., 2014], frontal and biparietal bossing, increased occipito-frontal circumference [Kimonis et al., 1997], bridging of the sella turcica [10,13], prognathism, dental abnormalities and cleft lip and palate [Lo Munzio, 1999; Gorlin, 1995; Ruprecht et al., 1987; Soekarman et al., 1991; Meazzini et al., 2011; Leonardi et al., 2009; Maroto et al., 1999; Kimonis et al., 1997; Jawa et al., 2009; Ramesh et al., 2015].

The diagnosis of the majority of GGS patients is based on pre-orthodontic radiological studies that show the presence of keratocysts in the maxilla or mandible [Saccomanno et al., 2022]. The diagnosis is usually made when the keratocysts are of large dimension, need aggressive surgery and some times induce the loss of permanent teeth [Leonardi et al., 2009; Maroto et al., 1999]. The diagnosis at an early age might reduce the severity of complications that include cutaneous and cerebral malignancy, maxillary and mandibular deformation or tooth loss.

The aim of this study was to quantitatively analyse facial and craniofacial characteristics in a sample of GGS patients to increase the awareness of the general dentist, the paedodontist and the orthodontist for an early detection and diagnosis of the syndrome.

Subjects and methods

This retrospective case-control study was approved by the internal review board of our institution. The study follows the current national and international laws and regulations governing the use of human subjects (Declaration of Helsinki II). Informed consent was obtained from all the participants included in the study.

The study population consisted of 24 patients (14 F and 10 M) with a diagnosis of GGS. Of these patients, 9 had cephalometric and photographic records retrospectively collected at an average age of 8.6±0.5 years (range 7.9–9.3) prior to any orthodontic or surgical treatment.

A group of 25 healthy children, from the orthodontic clinic, was used as a control sample. The cephalometric x-rays, photographs and panoramic x-rays of the control children were matched for sex and age and compared to each GGS patient (Figs. 1b and 2b).

3D photographs were not available in our hospital when most of the patients were diagnosed. Therefore, only 2D photographs were analysed while the 2D photogrammetry was adopted to calculate the distances between facial landmarks.

The photographic setup consisted of a 35-mm camera with a 100-mm macro lens. Each subject was positioned beside a vertical ruler divided in 1-cm segments. The scale allowed life size measurements (1:1). The records were taken in frontal and lateral view with head in rest position and lips relaxed. Frontal and lateral photometry were executed by ImageJ®, a software created and used by the National Institute of Health (Rasband, W.S., ImageJ, U. S. National Institutes of Health, Bethesda, Maryland, USA, <https://imagej.nih.gov/ij/>, 1997-2018). The landmarks were identi-

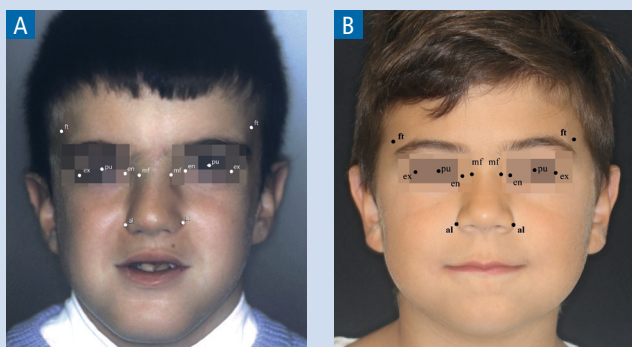


FIG. 1A Photometric measurements on the frontal plane in a 7.9 year-old patient with GGS: Distance between the temporal bones (forehead width) (ft-ft); Distance between the right and left endocanthions (medial canthus the eye) (en-en); Distance between the center of right and left pupils (pu-pu); Distance between maxillo-frontal points (lateral point of the nasal root where maxillo-frontal fissure and nasal-frontal fissure meet) (mf-mf); Distance between Alar points (most lateral limit of the nasal wings) (al-al); Distance between Exocanthion (distal meeting point between superior and inferior eyelid) and Endocanthion (en-ex); Angle between the lines en-en and en-ex (enen[^]enex); **FIG. 1B** same photometric measurements on the frontal plane in patient without GGS.

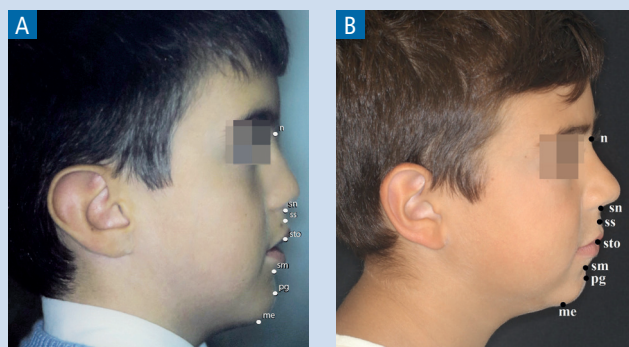


FIG. 2A Photometric measurements on the lateral plane: Distance between Nasion (most posterior point at the level of the frontonasal suture on the soft tissues) and Menton (most inferior point of the chin on the soft tissues) (n-me); Distance between Subnasalis (intersection point between the base of the nose on soft tissues and the upper lip) and Menton (sn-me); Distance between Stomion (most inferior point of the upper lip in closed rest position) and Menton (sto-me); Distance between Nasion and Stomion (n-sto); Angle between Supramental (sm= most posterior point in the anterior concavity of the lower lip) , Nasion and Subspinalis (ss=most posterior point in the anterior concavity of upper lip on the soft tissues, often in the same position of sn) (sm-n[^]n-ss).It corresponds to the soft tissues ANB; Angle between Pogonion (most anterior point of mandibular profile in the mental region of the soft tissues), Subnasalis and Nasion; it is the facial angle with nasal point on soft tissues (pog-sn[^]sn-n); **FIG. 2B** same photometric measurements on the lateral plane in patient without GGS.

fied on the photograph by one trained operator (Figs. 1a and 2a).

Cephalometric analysis was carried out on lateral cephalometric x-rays, taken with standardised radiographic technique (head positioned according to Frankfurt plane, teeth in centric occlusion and lips at rest). Points of reference, planes and angles were traced manually by an experienced operator, taking midpoints in case of double image of a specific structure (Fig. 3a).

Intra-observer error in landmark identification photometric and cephalometric, were evaluated by performing all measurements twice, at 2-month interval and calculating reliability with an Intraclass Correlation Coefficient (ICC).

STATISTICAL ANALYSIS

After Shapiro-Wilk normality test, descriptive statistics of the data were calculated for the GGS sample. A Student’s t-test was carried out to evaluate the differences of photometric and cephalometric measurements between the GGS sample and the selected matched controls. The p-value was set at 0.05. No correction for multiple measurements was carried out. Statistical analysis was carried out with the Stata 10 software (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP).

Results

Seventy-five percent of GGS patients were referred to our center with a maxillary or mandibular keratocysts found in a panoramic x-ray carried out by the general dentist or orthodontist. Four patients presented extremely large cysts, with delayed eruption and palpable swelling.

Twenty-five percent of the patients had an affected parent and were sent by the genetic department for further studies. Jaw lesions were found in all patients followed.

Photometric study [Farkas, 1994; Sforza et al., 2011; Ferrario et al., 1999]

The photometric results showed increased transversal facial dimensions (Fig. 1a) with frontal distance between the temporal bones (ft-ft) 10.5 mm wider than the control patients (p=0.0007).

Similar findings were observed at the nasal root since the distance mf-mf was 5.8 mm larger on average than control patients, corresponding to a 28.5% differential (p=0.000).

The intercanthal distance (en-en) was increased by 3.8 mm compared to the control group, corresponding to 12.7% differential (p=0.004), indicating the presence of telecanthus. Hypertelorism was observed with an inter-pupillary (pu-pu) distance of 6.2 mm wider than the control group, corresponding to 11% differential (p=0.006).

The facial profile was flat with facial angle (pg-sn[^]sn-n) resulted 9.2° wider than the control group.

The equivalent of the ANB angle on the soft tissues (sm-n[^]n-ss) was 4° smaller than the control group (-48.1% differential; p=0.0001) (Figs. 2a and 2b; Table 1).

CEPHALOMETRIC STUDY

Cephalometric measurements confirmed the presence of a skeletal Class III malocclusion associated to facial concavity. ANB angle was equal to 0.5±0.5°, compared with the 4.5±2.2° observed in the control group (p=0.0078). SNA was 69.2±5.3°, and resulted 12.2° lower than the average control group value (p=0.000) indicating hypoplasia and retrusion of the maxilla. The SN[^]GoGn angle was significantly higher in the GGS patients with an average value of 40.07±6.69°, corresponding to 30% differential compared to the control group (p=0.0206). The gonial angle (GoGn[^]GoPc) resulted 7.4% larger in GGS patients (average value of 135.2±9.2°; p=0.0184). These values demonstrated a mandibular clockwise rotation associated with a hyperdivergence of the skeletal bases. The ratio of the lower-facial height to the total facial height (Sna-Me/N-Me) was 5.7% higher than the control group (p=0.0385) indicating a significantly increased lower-facial height (Fig. 2a; Table 2).

The intraclass correlation coefficient for the average photometric measurements was 0.81, ensuring good intra-examiner

reliability according to Lee et al., although nasal root measurements (mf-mf) were 0.78, which was fair. For average cephalometric measurements, the ICC was 0.94, ensuring excellent intra-examiner reliability [Koo et al., 2016].

Discussion

This study is a retrospective case-control study that aimed to highlight the clinical facial phenotype of GGS patients in order to obtain early diagnosis, reducing the space-occupying damages of mandibular and maxillary keratocysts.

GGS is an autosomal dominant condition, caused by mutations in the PTCH1 gene on chromosome 9q22, the PTCH2 gene on 1p32, or the SUFU gene on 10q24-q25. About 40% of cases represent a de novo mutation [Gorlin, 1982].

The prevalence of GGS is estimated as one case every 57,000 [Farndon et al., 1992]. GGS is also called basal cell nevus syndrome since basal cell carcinomas are found in the majority of patients during their life span. In fact, 1/200 of patients consulted with a dermatologist for basal cell carcinoma will potentially have this syndrome. Children under 19 years old with basal cell carcinoma, have an extremely high probability to have GGS.

An early diagnosis associated with high suspicion index of the paediatrician or dermatologist in patients with basal cell carcinoma is therefore important in order to proceed with the search for hidden features such as keratocysts that characterise the syndrome. The role of the dermatologist is even more important in the GGS patients who do not develop jaw lesions.

The results of this study showed that children affected by GGS have quite a typical facial and skeletal characteristics, which may

Photometric Measurements	Matched Control Group (N=25) Mean ± SD	GGS Group (N=9) Mean ± SD	Diff.	P-value
ft-ft (mm)	107.87±5.71	118.33±4.54	Wide forehead (+10.46)	0.0007*
en-en (mm)	29.76±2.41	33.53±2.99	Telecanthus (+3.77)	0.0046*
pu-pu (mm)	58.11±3.4	64.28±1.9	Hypertelorism (+6.17)	0.006*
mf-mf (mm)	20.44±2.06	26.27±3.95	Larger nasal root width (+5.83)	0.0000*
al-al (mm) [23]	31.43±2.57	37.94±2.95	Larger alar base (+6.51)	0.0000*
enen^enex dx (°)[22]	4.52±2.11	3.34±2.39	-1.18	0.2705
enen^enex sx (°) [22]	2.67±2.52	-0.88±4.52	Downward slant (-3.55)	0.0183*
sm-n^n-ss (°) [24]	8.4±1.96	4.36±1.31	Flat face (-4.04)	0.0001*
pg-sn^sn-n (°) [24]	161.4±4.28	170.6±1.85	Increased facial convexity (+9.2)	0.0001*
n-me (mm)	96.53±9.56	105.9±14.64	+9.37	0.0771
sn-me (mm)	58.42±5.76	64.05±8.93	+5.63	0.0795
sto-me (mm)	40.49±4.64	45.33±6.68	+4.84	0.0575
n-sto (mm)	58.83±6.02	62.66±10.03	+3.83	0.2570

Tab. 1 Average photometric measurements of patients affected by Gorlin-Goltz Syndrome and corresponding data matched for sex and age of the control group. (NS = Not significant p-value).

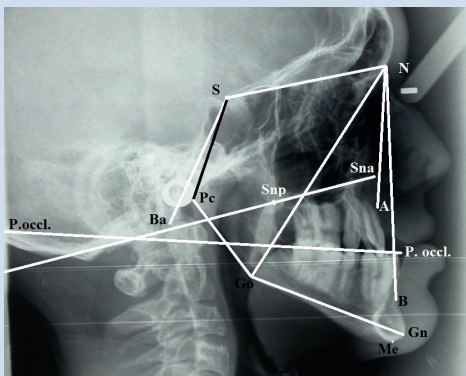


FIG. 3A Landmarks and definitions of the cephalometric measurements: S = Sellion. Midpoint of the fossa hypophysealis (point of intersection between the maximum horizontal diameter and the maximum vertical diameter of the sella turcica); N = Nasion. Most anterior point of the frontonasal fissure.; SN = Cranial base plane; A = subspinalis. Deepest anterior point in the concavity of the anterior maxilla; B = supramental. Deepest anterior point in the concavity of the anterior mandible; Go = Gonion. Point of intersection between the line bisecting the posterior and inferior borders of the mandible and the contour of the chin; Gn = Gnation. Point of intersection between the contour of the chin and the line bisecting the inferior border of the mandible and the line passing through N and Pg; Pg = Pogonion. The most projecting point in the contour of the chin; GoGn = Mandibular plane; Oclp = Posterior occlusal point. Middle point between the mesial cusps of the upper and lower first molars; Coa = Anterior occlusal point. Middle point between the cusps of the upper and lower first pre-molar; Oclp-Coa = Occlusal plane; Me = Menton. Most inferior point of the osseous chin; ANS = Anterior nasal spine. Most anterior point of the antero-posterior profile of the upper jaw; PNS = Posterior nasal spine. Most posterior point of the bony palate defined by the pterygomaxillary fissure; ANS/PNS = Palatal plane; Ba = Basion. Most postero-inferior point of the clivus; Pc= Posterior Condylar point. The intersection of a line along the posterior border of the basal occipital bone; PcGo = Ramus Plane; SNA Sagittal position of the maxilla relative to the anterior cranial base plane SN; SNB Sagittal position of the mandible related to the anterior cranial base plane SN; ANB Reciprocal relation between the upper and lower jaw on the intermaxillary angle; ANS-PNS^GoGn Intermaxillary angle; SN^ANS-PNS Palatal plane angle; SN^P.occl. Angle between cranial and occlusal planes; SN^GoGn Cranio-mandibular angle; SN^SBa Cranial base flexure angle; SN^SPc Sellar angle; SPc^PcGo Articular angle; GoPc^GoGn Gonial angle; GoPc^GoN Upper gonial angle; GoN^GoGn Lower gonial angle; WITS Distance between the orthogonal projection of A and B points on the occlusal plane; (Sna-Me)/(NMe) Ratio of the lower facial height to the total face height; (SGo)/(NMe) Ratio of the posterior facial height to the anterior facial height; **FIG. 3B** panoramic x-ray of an 8 years old patient with GGS and with evident mandibular keratocyst that involves multiple teeth.

Cephalometric Measurements	Matched Control Group (N=25) Mean ± SD	GGG Group (N=9) Mean ± SD	Diff.	P-value
SNA	81.48±2.17	69.24±5.38	-12.24	0.0000*
SNB	77.03±3.16	69.17±5.61	-7.86	0.0030*
ANB	4.52±2.21	0.55±0.25	-3.97	0.0078*
SN ^ GoGn	30.85±5.52	40.07±6.69	+9.22	0.0206*
SN ^ Poccl	18.74±4.45	24.18±7.52	+5.44	0.1010
SN ^ SnaSnp	8.61±2.64	10.47±2.33	+1.86	0.2747
SnaSnp ^ GoGn	23.81±4.64	29.98±6.11	+6.19	0.0613
GoGn ^ GoN	69.41±4.51	77.3±3.74	+7.89	0.0122*
GoN ^ GoPc	56.17±4.01	58.04±5.41	+1.87	0.4936
GoGn ^ GoPc	125.91±4.85	135.18±9.2	+9.27	0.0184*
SNPc	124.62±5.1	128.76±13.95	+4.14	0.3543
SNBa	128.1±6.33	133.84±9.95	+5.74	0.2058
(S-Go)/(N-Me) %	66.37±9.43	61.84±1.38	-4.53	0.4294
(Sna-Me)/(N-Me) %	56.98±1.76	60.2±4.37	+3.22	0.0385*
Wits index (Ao-Bo)	1±2.63	-1.64±2.33	-2.64	0.3327
SNSna	85.54±3.59	78.05±3.03	-7.49	0.0040*
SNPog	77.41±3.43	71.88±3.44	-5.53	0.0214*
A-NPog	3.37±2.32	0.51±1.31	-2.86	0.0582
ANPog	3.57±2.24	0.09±0.68	-3.48	0.0192*
SnaSnp^Ils	116.93±7.84	98.34±6.95	-18.59	0.0016*
GoGn^Ili	97.31±7.88	90.03±2.71	-7.28	0.1413
Ils^Ili	121.95±11.54	141.35±6.39	+19.4	0.0133*

TAB. 2 Average cephalometric measurements of patients affected by Gorlin Goltz Syndrome and corresponding data matched for age and sex of the control group. (NS = Not significant p-value).

justify an early clinical suspicion by the general dentist or by the paediatrician. The main findings regarding the craniofacial morphology already at age 8 years are increased transversal facial dimensions together with a flat midface, mostly associated with a skeletal class III malocclusion. These features are analytically shown by the angles and distances between facial and skeletal landmarks obtained from the photographs and cephalometric x-rays (Table 1 and 2; Figs. 1–3).

Based on the cephalometric and photometric data, the typical facial features of a GGS patient that should alert the paediatrician, general dentist and orthodontist for an early diagnosis of GGS are wide forehead, broad face and frontal bossing represented by the statistically significant increase of the ft-ft distance compared to the control group. The statistically significant increase of the en-en and pu-pu distances represent hypertelorism and telecanthus. Larger alar base and nasal root width (flat nose) stand for the increase of mf-mf and al-al distances. Flat face (sm-n[^]ss) and increased facial convexity (pg-sn[^]sn-n) are also part of the syndrome feature. Gorlin [1995] described the presence of broad nasal bridge and true hypertelorism in GGS patients. The long face feature observed through the increase of SN[^]GoGn and GoGn[^]GoPc is prevalently due to an increase of the lower facial height (Sna-Me/N-Me). The decrease in SNSna angle and the decrease in the SNPog angle confirm a skeletal class III malocclusion prevalently due to the retrusion and hypoplasia of the maxilla. This later observation should be taken into consideration by the orthodontist and by the maxillo-facial surgeon during the treatment of GGS patients for skeletal class III malocclusion. For our knowledge the only previous cephalometric analysis on a group of GGS patients, was performed by Leonardi et al [2009]. Leonardi's findings are in agreement with our results and demonstrated the presence of hyperdivergence, sagittal hypoplasia of the maxilla, skeletal Class III and increased lower face height.

Only two out of the 24 patients were referred to our Maxillo-Facial Surgery Unit because their mothers were affected by GGS. The remaining 22 patients were referred relatively late due to the presence of an advanced mandibular or maxillary keratocyst. Twenty patients out of the 24 lost at least one tooth during surgery, because of the space-occupying lesion caused by the cyst (Fig. 3b). Fifteen patients needed long and complex ortho-

dontic traction of the teeth ectopically drifted by the cyst after its surgical removal.

Although 10% of GGS patients are reported to have no jaw lesions in the literature [Ahn et al., 2004; Pawlaczyk-Kamienska et al., 2020], jaw lesions were found in all patients referred to our center. This might be a bias because our center is a third level referral center for craniofacial anomalies.

The average increase in the forehead and nasal root width as well as the telecanthus and the other facial dimorphisms found in GGS patients (Tab. 1) are well within the ability of detection, even of a non-expert observer [Haupt et al., 2018]. Evans et al. [2005] found that a dentist or an orthodontist, who have a specialised training in craniofacial growth and morphology might be able to identify and detect these characteristics quite easily during the first general check-up in childhood.

The general and paediatric dentists and the orthodontists are often the first specialists with a specific training on craniofacial growth to see children affected by rare craniofacial anomalies not diagnosed at birth. Early facial recognition might lead the clinician to make an early diagnosis and to identify potentially harm lesions at early stages by a panoramic x-ray. This approach necessary leads to early keratocysts diagnosis and decrease the risk of tooth loss and the need for aggressive surgery [Maroto et al., 1999; Wilson et al., 2008].

In our study 3D photographs were not used since at the time of diagnosis this technique was not yet available in our hospital. Therefore, only 2D photographs were analysed and 2D photogrammetry was adopted to calculate the distances between facial landmarks. This might be considered as a relative limitation of the study. However, obtaining measurements from photographs has the advantage that it provides permanent record of the facial features, which can also be used at a later time to assess reproducibility.

This study suggests that early diagnosis of GGS is important to avoid permanent tooth lesions due to late stages of keratocysts development.

Conclusion

This paper is important to paediatric dentists because dentists

and paediatricians have an active role in early diagnosis of GGS and should be aware of this syndrome since it is easily diagnosed thanks to the typical facial phenotype described in this study. Furthermore, dermatologists' consultants should have a high suspicion index in patients with basal cell carcinoma, especially if the patient is less than 19 years of age.

It is highly recommended to immediately perform panoramic x-rays in this group of patients in order to exclude the presence of related space-occupying lesions by growing mandibular and maxillary keratocysts. This will eventually reduce the risk of tooth lost, pathological jaw fractures and high burden of care for the patient.

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DISCLOSURES

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