Contribution of a better maxillofacial phenotype in Silver–Russell syndrome to define a better orthodontics and surgical management

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Contribution of a better maxillofacial phenotype in Silver Russell Syndrome (SRS) to define a better orthodontics and surgical management

Abstract

Introduction: Maxillofacial phenotype for SRS is incompletely described in literature. The aim of this study was to describe a maxillofacial phenotype for SRS, to determine a better treatment.

Materials and methods: A retrospective study was conducted including 37 patients with SRS. 24-control patients had been included and appareled. The subjective clinical examination included analyzes of SRS defined criteria. Frontal and lateral photographs had been reviewed, according to Farkas analysis; dental photographs had been examined for the deep-bite and the crowding severity. Radiologic cephalometric analysis had been reviewed.

Results: Maxillofacial examination showed protruding forehead (55%), anteverted ears (55%) and low set ears (16%), small triangular face (48%); retrognatia (29%) and micrognathia (13%). SSR patients presented a lower forehead transverse growth, forehead height, and higher sagittal and transverse mandibular growth than control patients. Deep-bite was present in 21 patients of patient, and crowding in 17 patients. Cephalometric analysis showed 18 patients with the skeletal class II. We did not note a correlation between sleep apnea and retrognatia, neither between genetic anomalies and craniofacial phenotype.

Conclusion: In this study we showed new SRS characteristics: small forehead, small mandible, skeletal class II and a dental phenotype, leading to a specific maxillofacial and orthopedic management.

Key words: Silver Russell syndrome; maxilla-facial phenotype; retrognatia

Introduction

In 1953 Silver et al.[1] described a syndrome associating congenital hemihypertrophia, shortness of stature and elevated urinary gonadotropins. One year later Russell[2] published five cases associating craniofacial abnormalities and severe intra-uterine growth retardation. Subsequently, Black[3] and Rimoin[4] defined Silver Russell Syndrome (SRS), as the combination of intrauterine and/or postnatal growth retardation, a facial dimorphism and asymmetry of members. SSR is an extremely rare disease with an incidence estimated at 1-30/100 000 per birth [5]. SRS is a heterogeneous condition based on the identification of clinical features. Recently, molecular genetic anomalies associated to SRS had been identified, from 35 to 50% of individuals with SRS presents a hypomethylation of the paternal imprinting center 1 (IC1) of chromosome 11p15.5 (region regulation IGF2/H19 locus) and 10% have maternal disomy for chromosome 7 (mUPD7) [6-9]. SRS is considered as an imprinting disease. A new clinical scoring system (sensibility = 98%) for the detection of patients with molecular anomalies associated SRS had been recently described [10]. Diagnosis of SRS imposed prenatal growth retardation associated to three of this five following criteria: post natal growth retardation (>2DS), relative macrocephaly, prominent forehead, and body asymmetry, feeding difficulties during early childhood. This score described 2 craniomaxillofacial features whereas SRS initial definition included a facial dimorphism. A new Consensus Statement summarizes recommendations for clinical diagnosis, investigation and management of patients with Silver-Russell syndrome [11]. Although the definition of SSR includes facial dimorphism, craniomaxillofacial characteristics of SRS are not precisely described in literature [9, 10].

Otherwise, micro-mandible associated syndromes are often responsible of obstructive sleep apnea [12, 13], moreover, in other short stature imprinting disease, as Willy-Prader syndrome, central and obstructive sleep apnea had been identified [14, 15]. Sleep apnea syndrome had never been explored in SRS condition.

The aim of this study was to describe and define a maxillofacial phenotype for Silver Russell syndrome, to study its association with sleep apnea troubles, and finally to propose a guideline for orthodontic and maxillofacial management.

Materials and methods

Patients

We conducted a retrospective study from 2009 to 2015, including 37 patients with SRS syndrome before growth hormone therapy registered in the database of the French reference centre for rare maxillofacial disease.

All patients had a genetic examination to seek for a molecular diagnosis.

Patients were evaluated at the age of their first consultation in the reference centre.

Control patients

We included 24 control patients, apparelled to SSR patient according to their civil age, dental age and gender. Control patient were included from non-rare disease patient database of the same centre. Patients with facial malformation, genetic diseases, facial trauma, protruding ear, and central or obstructive apnea were excluded.

Clinical Evaluation

All patients had a clinical evaluation carried out by the one independent senior maxillofacial surgeon.

The subjective and independant clinical examination included the analyse of the following defined criteria: facial dimorphism, a bulging forehead, a small triangular face, retrognathia, micrognathia, bluish sclera, anteverted ears, low-set ears, a thin upper lip, a shrill voice, according to the phenotypic characteristics described in literature (Figure 1.A-D)[10]. Maxillofacial clinical evaluation included occlusal description with the determination of dental Angle class, the vertical, sagittal and transversal anomalies. Furthermore the volume of the tonsils was noted to exclude local cause of obstructive apnea.

Frontal and lateral facial Photographs analysis

At each consultation, one professional photographer had performed frontal and lateral photographs. Frontal and lateral photographs had been analysed, according to Farkas analysis (Figure 1C-D) [16-18] by two different and independent investigators, at the age of the first medical consultation in the reference centre (the values of the measures were weighted to the age of the patient). The transverse forehead growth ((ft-ft/eu-eu) was evaluated by the ratio of the outer canthi distance (from the left exocathion to the right exocanthion: ft-ft) distance and

the width of the head (distance from the left eurion to the right eurion: eu-eu). The height of the forehead (tr-g/eu-eu) is estimated by the ratio of the vertical distance of the forehead (distance from the hair planting line to the glabella: tr-g) and the width of the head. Transverse mandibular growth (go-go/n-gn) was assessed by the ratio of the lower facial width (distance from the left gonion to the right gonion: go-go) and total facial height (distance from the nasion to the gnathion: n-gn). Sagittal mandibular growth (sn-gn/t-gn) was assessed by the ratio of the lower facial height (distance from the subnasal point to the gnathion: sn-gn) and facial depth (distance from the tragion to the gnathion: t-gn) on left profile photography.

For photographic analysis, each patient had been apparelled to two control patients.

Dental Photographs analysis

From dental photographs, we analysed the deep-bite (figure 2.A) (the maxillary incisor overlapped the lower incisive), and the crowding severity (figure 2.B-E): no crowding, light crowding (few crowding was present or/and Bogue's diastema were absent in lacteal denture), moderate crowding (one incisive was lingual positioned or lacteal canine was lost earlier), important crowding (there were no space for one incisive), severe crowding (teeth were arranged in two rows).

Cephalometric Analysis

Frontal and lateral cephalometric X-Ray had been analysed according to Delaire with Orqualceph software (Informer®, France). The following data were analysed: skeletal class, dental class, respective position of the maxillar and the mandibular bone, the position of the hyoid bone, the existence of a tonsil hypertrophy.

Sleep evaluation

An air recording polysomnography evaluation was performed for each patient after the first consultation and before the Growth hormone treatment initiation. Apnea hypopnea per hour index (AHI), desaturation index, snoring index were evaluated. The respiratory rate, the duration of the breathing analysis and the results of cutaneous blood gas were noted for each patient. Obstructive sleep apnea syndrome was defined by an AHI superior to 5 per hour and sub classified into mild obstructive (AHI from 5 to 15), moderate (from 16 to 30), and severe (>30).

Statistical Analysis

Statistical comparisons were made to compare SSR patient to control using Fisher test, with $p<0.05$

being considered significant.

Results

Patients

Among the 37-SRS patients included, 6 had been excluded (absence of photographs n=5, absence of apparelled control n=1). Age of the first maxillofacial consultation in the reference centre varied from 2 to 14 Years-old (average, 6.13 YO). Among the 31 patients analysed, 16 were boys. All patients presented the clinical criteria of SRS[8]. Genetic molecular diagnostics has been tested for all children: 17 had hypomethylation of 11p15 chromosome (ICR1); 6 presented a disomy of chromosome 7 (mUPD7); 2 had 11p15 duplication of maternal material; and no mutation had been identified in 6 cases.

Clinical evaluation (Table 2)

Maxillofacial examination showed protruding forehead in 17 (55%) patients; anteverted ears in 17 patients (55%) and low set ears in 5 patients (16%); small triangular face in 15 patients (48%); retrognatia in 9 patients (29%) and micrognathia in 4 (13%); thin upper lip in 5 patients (16%); and shrilly voice in 2 cases (6%). None presented bluish sclera.

Occlusal evaluation showed Angle class 2 in 28 cases (90%), and class 1 in the 3 other patients (10%). Four (13%) patients had hypertrophic tonsils (Table 2).

Patients with hypomethylation of 11p15 chromosome and patient with disomy of chromosome 7 had similar facial phenotype except for the small triangular face that seemed to be more frequent in patients with mUPD7 (Table2). However patients without mutations or with other seemed to present a less pronounced facial phenotype, with principally anteverted ears.

Frontal and lateral facial Photographs analysis (Table 1)

SSR patients presented a significant lower forehead transverse length, forehead height, and sagittal mandibular height than control patients; and a non-significant higher transverse mandibular length than control (figure 3, Table 1).

Dental Photographs analysis

Among the 31 patients analysed, 26 intra oral photographs were available.

Deep-bite was present in 21 patients (80%), and crowding in 17 patients (67%). Crowding was considered as severe in 3 cases (17%), important in 3 cases (17%), moderate in 7 cases (41%), and light in 4 patients (25%).

Cephalometric

A cephalometric X-Ray was performed in 22/31 patients. Cephalometric analysis showed 18 patients with the skeletal class II (81%), 3 with skeletal class I (14%), and 1 with skeletal class III (5%). All the patients with a skeletal class II (n=18) had a mandibular retrognathism with a short ramus and short horizontal branch. Among the patients from the skeletal class I (n=3), 2 presented a hypomaxilly and mandibular retrognathism and 1 patient presented a maxillar and mandibular prognathism. The sole patient with skeletal class III showed a mandibular retromicrognathism associated with hypomaxilly. Almost all patients (n=21/22) displayed a molar dental class II. The hyoid bone was in a normal position in 15 cases, accessioned (from 2 to 4 mm up) in 4 cases, and lowered (from 1 to 9 mm down) in 3 cases.

Sleep apnea

A sleep apnea study was performed on 25 patients, 18 patients presented a mild SAOS (72%), 5 patients presented mild sleep disorders without SAOS, and 2 patients presented a normal polysomnography. Sleep apnea studies were compared to cephalometry analysis (table 3).

Among the 18 patients with mild SAOS, 18 presented a mandibular retromicrognathism, 7 presented an abnormal position of the hyoid bone, 4 showed a tonsil hypertrophy and 2 a long uvula.

Discussion

This study demonstrated the difficulty to describe a typical maxillofacial phenotype in SRS. In this large series, we demonstrated that the facial dimorphism spectrum is often incomplete in SRS patients. However, we showed new SRS characteristics: small forehead, small mandible, skeletal class II and a dental phenotype, leading to a specific maxillofacial and orthopaedic management.

This study represents the largest series of maxillofacial phenotyping published, in our knowledge. Despite the rarity of the disease (incidence: 1-30/100 000) [7], 31 patients had been

included. As previously described by Netchine [9, 10], we confirmed the absence of gender predisposition.

In our study, most patients presented a genetic molecular anomaly, principally a hypomethylation of 11p15 chromosome (ICR1) followed by a disomy of chromosome 7 (mUPD7), these results were consistent with the genetic molecular analysis described in the international literature [7, 11, 19]. In our series, we showed few phenotypic differences between ICR1 and mUPD7 patients; ICR1 patients presented a more typical dimorphism with the small triangular face. However, patient without either ICR1 or mUPD7 mutation displayed a milder phenotype. In a larger series, Eggerman also noticed differences of phenotype according to genotype, but showed the ICR1 patients presented a higher rate of prominent forehead, and a lower rate of microretrognatia than mUPD7 patients [8]. Recently Azzi et al. also showed this milder facial phenotype in patients without the two usual mutations [9].

In our series, diagnosis of SRS had been made late, around 6 year-old. SRS syndrome is a rare disease without pathognomonic sign [1, 2, 11]; indeed its clinical diagnosis is difficult, and often delayed. Since the absence of pathognomonic sign, many clinical scoring had been described[10]. Recently, Netchine et al published the first sensitive scoring system including the following criteria: small for gestational age, birth length and/or weight ≤−2S DS; postnatal growth retardation (height ≤−2SDS), relative macrocephaly at birth, body asymmetry, feeding difficulties and/or body mass index (BMI) ≤−2SDS in toddlers; protruding forehead at the age of 1–3 years [11]. The presence of 4 symptoms predicted the diagnosis of SRS with a 98% of sensitivity. From this study, no typical craniofacial phenotype could be described. All patients have facial dimorphism, principally protruding forehead (55%) and anteverted ears (55%). Most of the SSR patients had a skeletal class 2 (81%). SSR children tend to have smaller forehead (transverse diameter and height) and smaller mandible (transverse and sagittal) compared to control patients.

In our series, we analysed the craniofacial phenotype with objective evaluations; farkas analysis in photography and cephalometric analysis. From Farkas analysis[16-18], we showed that SSR patients tended to present a lower forehead transverse length, forehead height, and sagittal mandibular height than control patients. In our study, whereas subjective clinical evaluation showed a low rate of micrognatism and retrognatism; cephalometric analysis showed that all patients presented a short mandible ramus and horizontal branch. Finally, cephalometric analysis demonstrated that microretrognatism was underestimated. Likewise, in literature, the incidence of microretrognatism is probably unevaluated, since most authors did

not evaluate the cephalometric Xray[12].Kotilainen *et al*[20], also described from a cephalometric analysis a smaller mandible in SRS patient compared to their control.

Our results showed that 18 patients presented skeletal class II with short ramus and short body; only one patient presented maxillar and mandibular prognathism; and one had a class skeletal III but with a hypomaxilly and a microretrognatism. The lower arch may present, in some cases (3 for this study), a severe crowding with a lower lateral incisor being displaced in a lingual position. The dental development is symmetrical with a delayed dental eruption. Class II malocclusion was present in 90% of the patients and supraclusion in 87% cases, which was higher rate than in standard population [21].

In 2003, Bergman and coll. studied the craniofacial characteristics, and the malocclusion characteristics of 16 SRS children. They showed that SRS children had smaller linear facial dimensions and deviations in the facial proportions, maxillar and mandibular repositioning, a high rate of malocclusion and a teeth eruption delay[25].

Therefore, retromicrogratism may be responsible of SAOS [12, 13]. Indeed, in our series, 60% of the patients presented a mild SAOS, probably caused by microretrognatism and majored in some cases by tonsil hypertrophy. However, despite this microretrognatism none presented a severe SAOS.

Conclusion

SRS is extremely rare disease characterized by a polymorphic phenotype. Craniomaxillofacial analysis is often incomplete and subjective in literature. We proposed a systematic and normative evaluation with Farkas and cephalometric analysis in SRS patients in a larger series of SRS patients.

We showed new SRS characteristics: small forehead, small mandible, skeletal class II and a dental phenotype (crowding on the lower arch/ supraclusion), leading to a specific maxillofacial and orthopaedic management.

The orthopaedics, orthodontics and orthognatic surgery treatment can be protocoled as described:

1. For upper crowding: we can propose palatal expansion or rapid palatal expansion, which permit a gradually widens the palate and the upper arch, once the first definitive molars are erupted.

2. For light to moderate lower crowding: we can propose stripping (enamel reduction) or mandibular orthodontic widening

3. For important to severe crowding: dental extraction should be avoided (worsening of the skeletal class2 malocclusion), surgery (symphysal distraction) should be considered.

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Tables

	SRS	Control	p
Forehead transverse growth (ft-ft/eu-eu)	0.72 [0.58-0.84]	0.81 [0.71-0.93]	**6.7×10^{-7}**
Forehead height (tr-g/eu-eu)	0.47 [0.31-0.61]	0.51 [0.34-0.65]	**0.048**
Transverse mandibular growth (go-go/n-gn)	1.13 [0.84-1.4]	1.09 [0.85-1.29]	0.1
Sagittale mandibular growth (sn-gn/t-gn)	0.53 [0.43-0.68]	0.59 [0.47-0.73]	**0.0022**

Table 1 : Farkas analysis. Comparison between SSR patients and their controls

	11p15 ICR1 hypomethylation (n=17)	Disomy Chromosome 7 (n=6)	Other mutations or no mutation(n=8)
protruding forehead	n=11 (65%)	n=4 (67%)	n=1 (12.5%)
small triangular face	n=11 (65%)	n=2 (33.3%)	n=2 (25%)
Clinical retrognathia	n=5 (29.5%)	n=2 (33.3%)	n=2 (25%)
Clinical micrognathia	n=5 (29.5%)	n=1 (16.7%)	n=1 (12.5%)
bluish sclera	n=3 (0%)	n=3 (0%)	n=3 (0%)
anteverted ears	n=9 (52.9%)	n=3 (50%)	n=5 (62.5%)
low set ears	n=3 (17.6%)	n=2 (33.3%)	n=3 (0%)
thin upper lip	n=3 (17.6%)	n=1 (16.7%)	n=1 (12.5%)
talking shrilly	n=3 (0%)	n=2 (33.3%)	n=3 (0%)
skeletal class 2	n=17 (100%)	n=6 (100%)	n=5 (62.5%)
hyoid bone ascension	n=4 (23.5%)	n=3 (50%)	n=2 (25%)
Radiological retromicrograntism	n=17 (100%)	n=6 (100%)	n=8 (100%)
tonsils hypertrophia	n= 2 (11.7%)	n=1 (16.7%)	n=1 (12.5%)

Table 2 : Clinical maxillo-facial phenotype and genetic anomalies

skeletal class	I	II	III
Normal sleep evaluation	0	2	0
Sleeping troubles without SAOS	1	3	1
Mild sleep apnea syndroma	2	15	1

Table 3: Sleep apnea studies and cephalometric analysis

Legends:

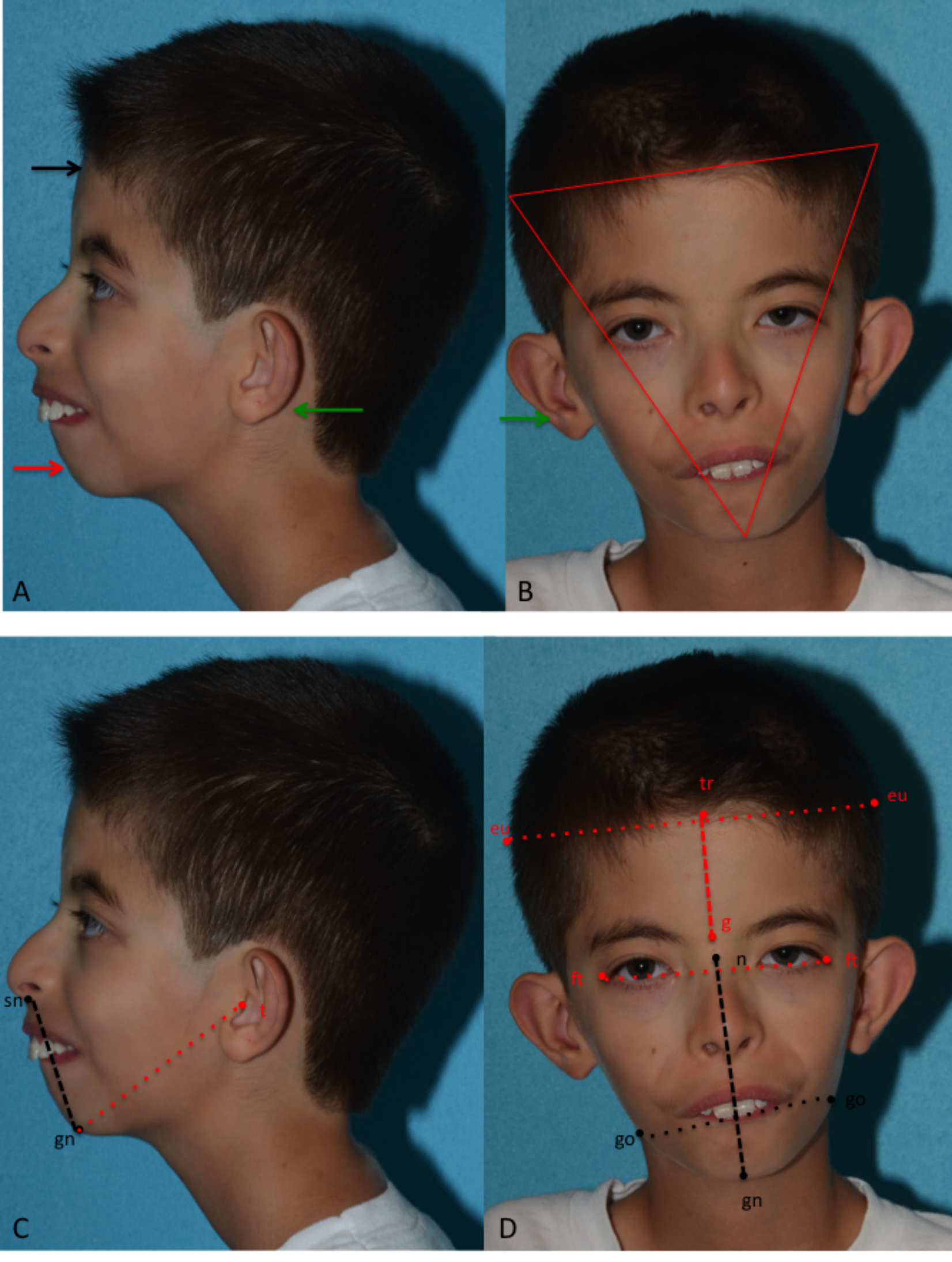
Figure 1: Phenotypic characteristics and Farkas analysis

- A: bulging forehead, retrognathia, anteverted ears
- B: small triangular face, low-set ears
- C: sagittal mandibular growth (sn-gn/t-gn)
- D: transverse forehead growth (ft-ft/eu-eu), height of the forehead (tr-g/eu-eu), transverse mandibular growth

Figure 2: Dental Photographs analysis

- A: the deep bite (the maxillary incisor overlapped the lower incisive)
- B: the crowding severity -no crowding,
- C: light crowding
- D: moderate crowding
- E: important and severe crowding

Figure 3: Phenotypic characteristics such as four Farkas analysis of our population of SSR patients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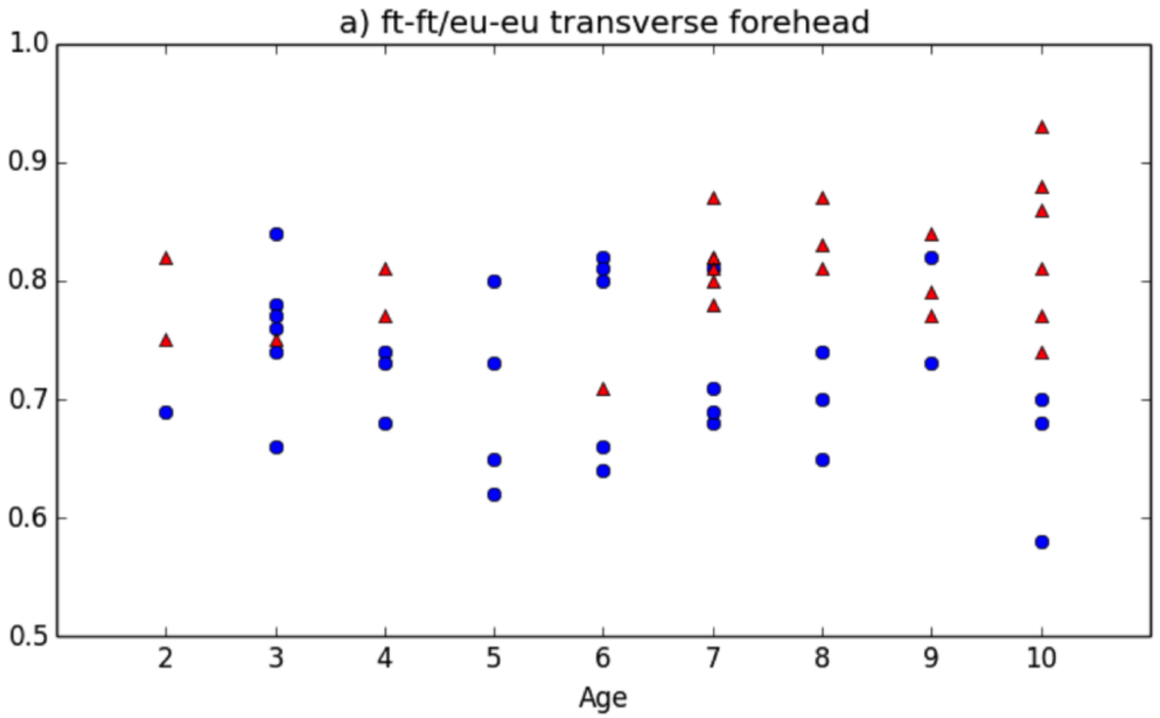
a) ft-ft/eu-eu transverse forehead
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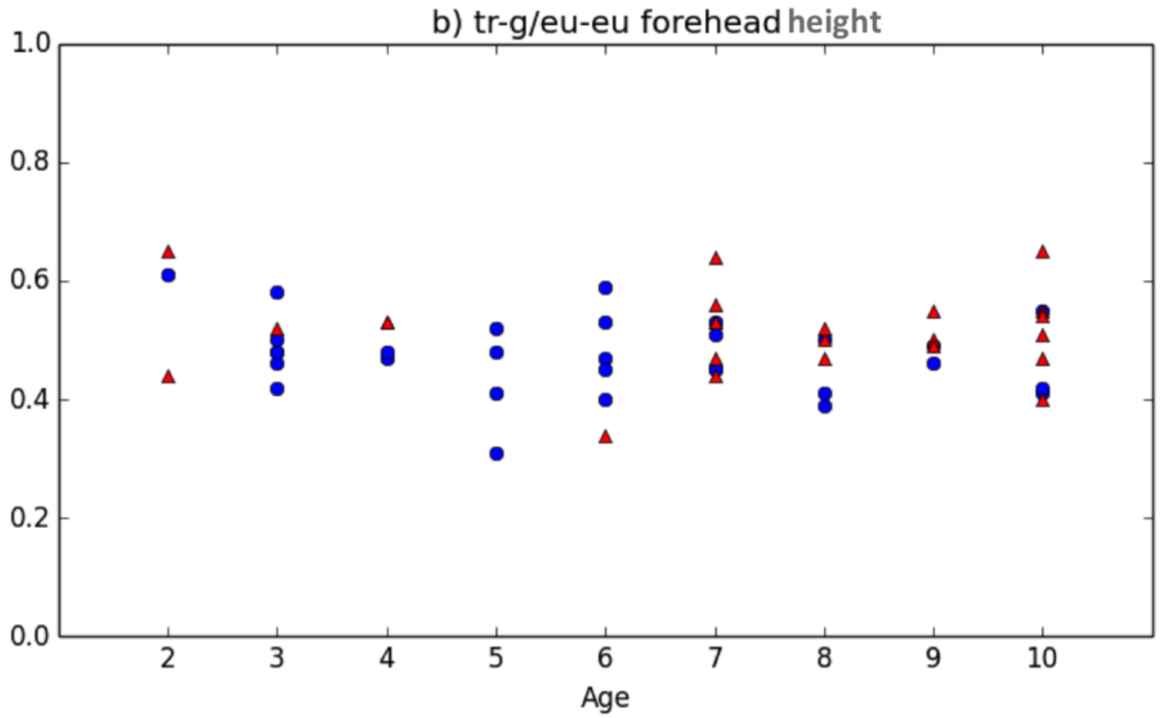
Age


b) tr-g/eu-eu forehead height
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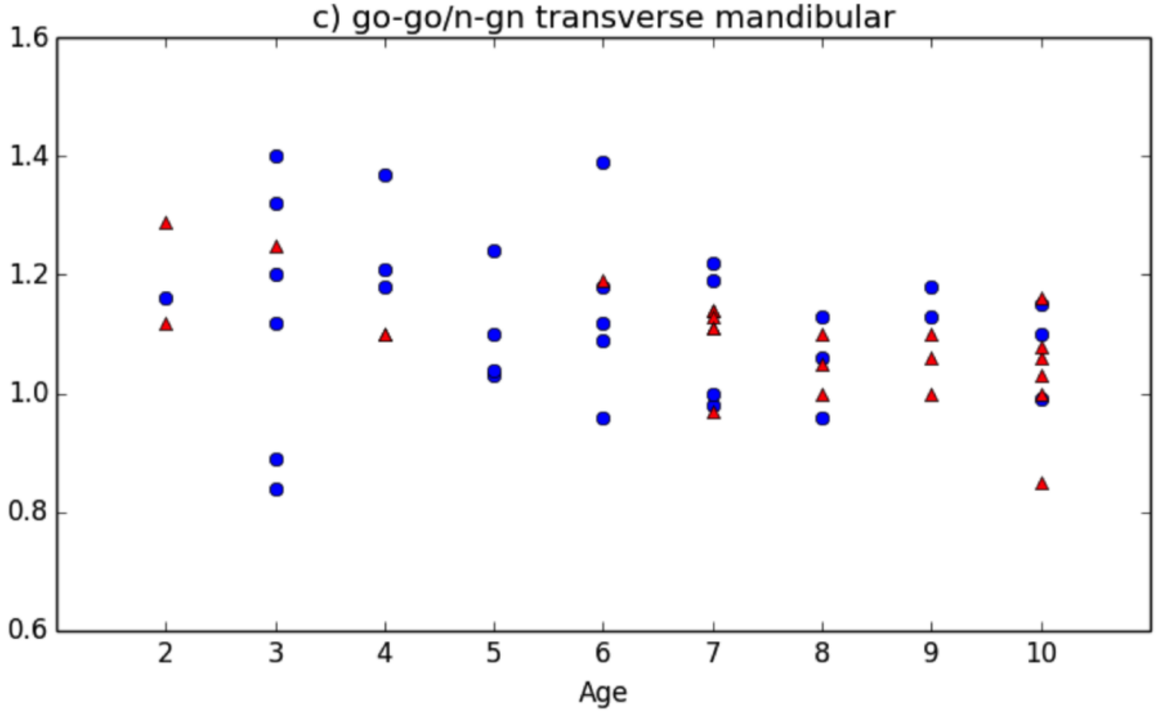
Age


c) go-go/n-gn transverse mandibular
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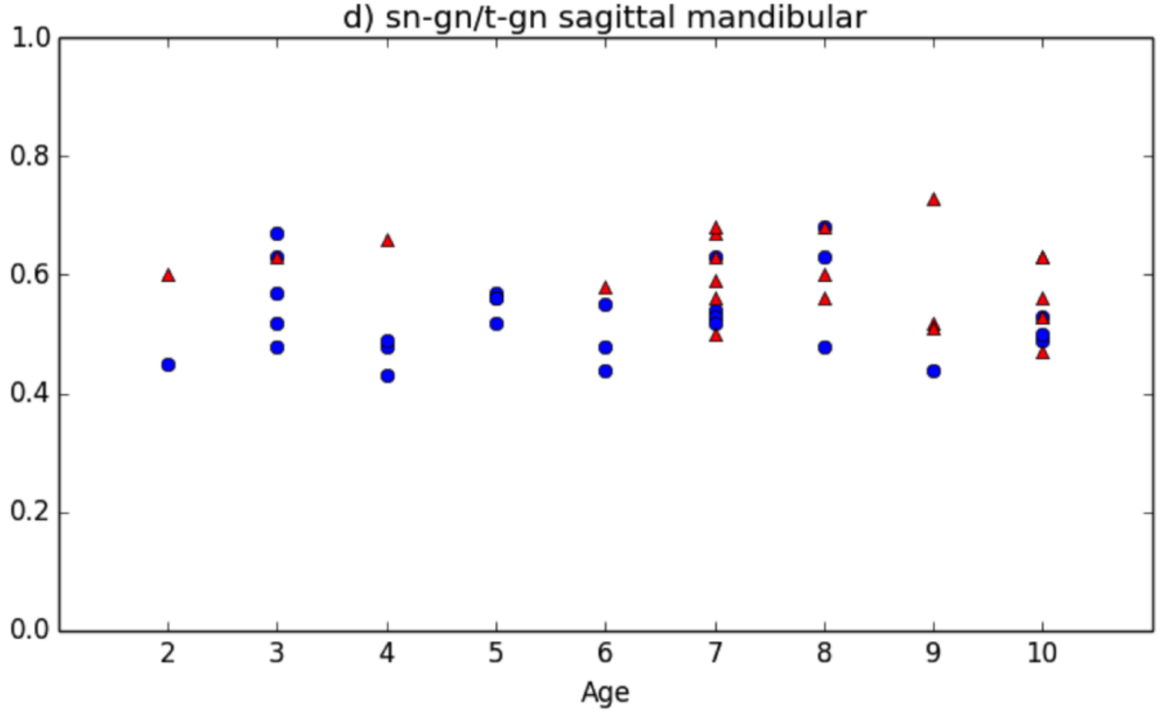
d) sn-gn/t-gn sagittal mandibular
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