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# Long-term longitudinal evaluation of mandibular growth in patients with Beckwith-Wiedemann Syndrome treated and not treated with glossectomy

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ABSTRACT

*Aim:* This study compares long-term mandibular growth between a group of Beckwith-Wiedemann Syndrome (BWS) patients who underwent glossectomy at an early age and a group of patients not operated.

*Methods:* Cephalometric measurements were performed in BWS patients comparing the data obtained between a group of patients operated at an early age and a group of non-operated patients who declined surgery. Statistics included independent sample T-test.

*Results:* Twenty-four out of 78 BWS patients followed since birth completed longitudinal cephalometric x-rays at age 5, 10 and 15. Eighteen patients needed early surgery. Eleven families accepted glossectomy at 2.3 ± 1.3 years of age; seven declined surgery. No differences in mandibular growth were found between the two groups. Inclination of maxillary incisors results were statistically greater in the non-operated group (operated compared to the non-operated group: 103.58 ± 11.30 Vs 108.98 ± 12.47; p-value 0.0168 at 5; 107.06 ± 7.98 Vs 115.14 ± 7.05; p-value 0.0206 at 10; 109.80 ± 4.68 Vs 116.75 ± 5.28; p-value 0.0233 at 15).

*Conclusion:* Macroglossia has no role in the post-natal mandibular overgrowth in BWS and mandibular overgrowth is part of the syndrome. Therefore, early glossectomy does not change mandibular growth and does not prevent the development of class III skeletal malocclusion in these patients.



## 1. Introduction

Beckwith-Wiedemann Syndrome (BWS) was described for the first time by Beckwith in 1963 (Beckwith, 1963). The estimated prevalence is 1:10000 (Mussa et al., 2016). The syndrome is characterized by a typical triad defined by omphalocele, macroglossia and gigantism to which other signs and symptoms are less frequently associated. Macroglossia is the most common feature in BWS, found in 90–97% of the patients and representing the most sensitive trait for BWS identification (Elliott et al., 1994; Ibrahim et al., 2014).

Previous studies have suggested that macroglossia can cause increased mandibular length (Köle, 1965; Wolford and Cottrell, 1996; Matsudaa et al., 2017). Aside from early indications in infancy, related to breathing or feeding difficulties, a frequent indication for glossectomy is the prevention of mandibular overgrowth (Menard, 1995). Kadouch reported the results of 23 BWS patients operated for tongue reduction with a mean follow-up of 7 years from surgery (Kadouch et al., 2012), but no data were reported on the long-term effect on mandibular growth. In fact very few studies have analysed quantitatively the long term effect of glossectomy on mandibular growth through cephalometric measurements of BWS patients who underwent glossectomy versus those who were not

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operated. Thus there is no evidence that the reduction of the size of the tongue prevents class III malocclusion.

The aim of this study was to compare long-term mandibular growth between patients who were subjected to glossectomy and patients who had been offered surgery, but refused it.

## 2. Material and Methods

### 2.1. Sample

This is a retrospective observational study based on charts and radiographic evaluation of BWS patients followed-up in our clinic from infancy to adolescence. The 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.

Charts of BWS patients followed in our unit since birth who either underwent glossectomy at a younger age or had an indication for surgery but declined it were retrospectively collected. BWS patients, who did not have significant macroglossia, were excluded from this research.

Cephalometric measurements were performed in each patient and the values were compared between the two groups.

### 2.2. Surgical technique

The goal of glossectomy in BWS is to significantly reduce the volume of the tongue, its vertical height, width and length, while preserving the mucosa for specific senses (touch and taste) (Van Der Horst et al., 2010), avoiding blood supply injury and reducing any risk of massive scarring with reduction of body and tip mobility. All patients in the sample were operated by the same surgeon through a Key-hole resection (Morgan et al., 1996) with an anterior wedge excision and a posterior V-shaped drawing, which allows for a consistent debunking of the body and reducing tongue length with preservation of functionality, mobility and cosmetic outcome (Fig. 1).

### 2.3. Cephalometric method

Lateral cephalometric evaluation was performed for each patient at age 5, 10 and 15 years. The tracings were plotted using Delta dent 2.0 software (Outside Format, Spino D'Adda, Cremona, Italy). For the cephalometric evaluation, the landmarks shown in Fig. 1 were used. Reference planes and angles were constructed for angular measurements. Since the radiographs retrieved had different magnification factors, ratios of linear measurements expressed as a relationship with the cranial base (SN) were reported (Fig. 2). Reference planes of healthy population extrapolated from the Riolo study (Riolo et al., 1974) were applied.

### 2.4. Statistical method

The mean and the relative standard deviation of each measurement at each age were considered and descriptive statistics are reported in Table 1. Mean mandibular growth differences between different age points at 5–10 and 10–15 years old are listed in Table 2.

A Shapiro–Wilk normality test verified that the data obtained for each age group were distributed normally. An independent sample Student's two-tailed T test was carried out to compare the differences between operated and non-operated patients at the different age ranges. Correction for type I error was carried out with a Bonferroni correction and p value was set at 0.025.

Point detection and measurements were performed twice by the same operator at four months interval, which is considered an appropriate interval to assess test-retest reliability. An intra-examiner reliability test was carried out using intraclass correlation coefficients (Cronbach Alpha ICC).

## 3. Results

Records of 78 BWS patients with macroglossia followed since birth in our unit were collected. Among these patients there were subjects with different genetic diagnoses (IC1, IC2 and UDP methylation alterations). Twenty-four out of 78 BWS patients had complete longitudinal cephalometric records from early childhood till adolescence, taken at 5, 10 and 15 years of age. Patients with missing cephalometric records were excluded from the study. Eighteen out of the 24 patients with complete cephalometric records had been suggested surgical treatment for tongue reduction. Eleven families had accepted and their children underwent glossectomy at an average age of $2.3 \pm 0.8$ years (operated group). Seven patients with an indication for surgery decided to decline glossectomy (non-operated group). Given the early age of surgery, no pre and postoperative cephalometric records could be taken in our Department. During the assessments performed every six months since birth, macroglossia was not measured quantitatively but was clinically defined as “tongue not containable in the oral cavity”. None of the patients had any breathing or feeding problems. Therefore none of the patients had any surgical indication during the first year of life. All patients had dental open bite in the deciduous dentition. Systematic speech evaluation was not performed at that time.

The intraclass Correlation Coefficient used to assess consistency of the single rater was 0.926 for single measurements and 0.928 for average measurements, thus providing an indication of excellent

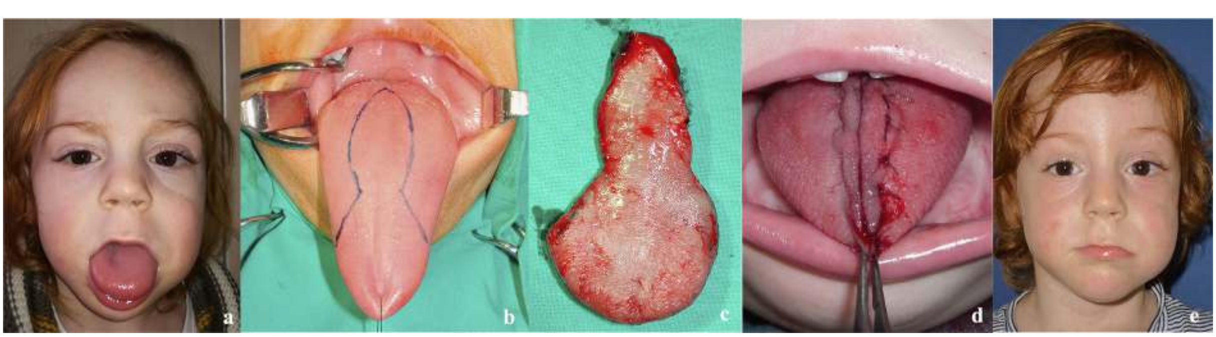


**Fig. 1.** Three year old male patient surgically treated: (1a) frontal image before glossectomy (1b-d) Intraoperative images of the surgical tongue reduction design with Key-hole resection (Morgan et al., 1996). (1e) frontal image after glossectomy.

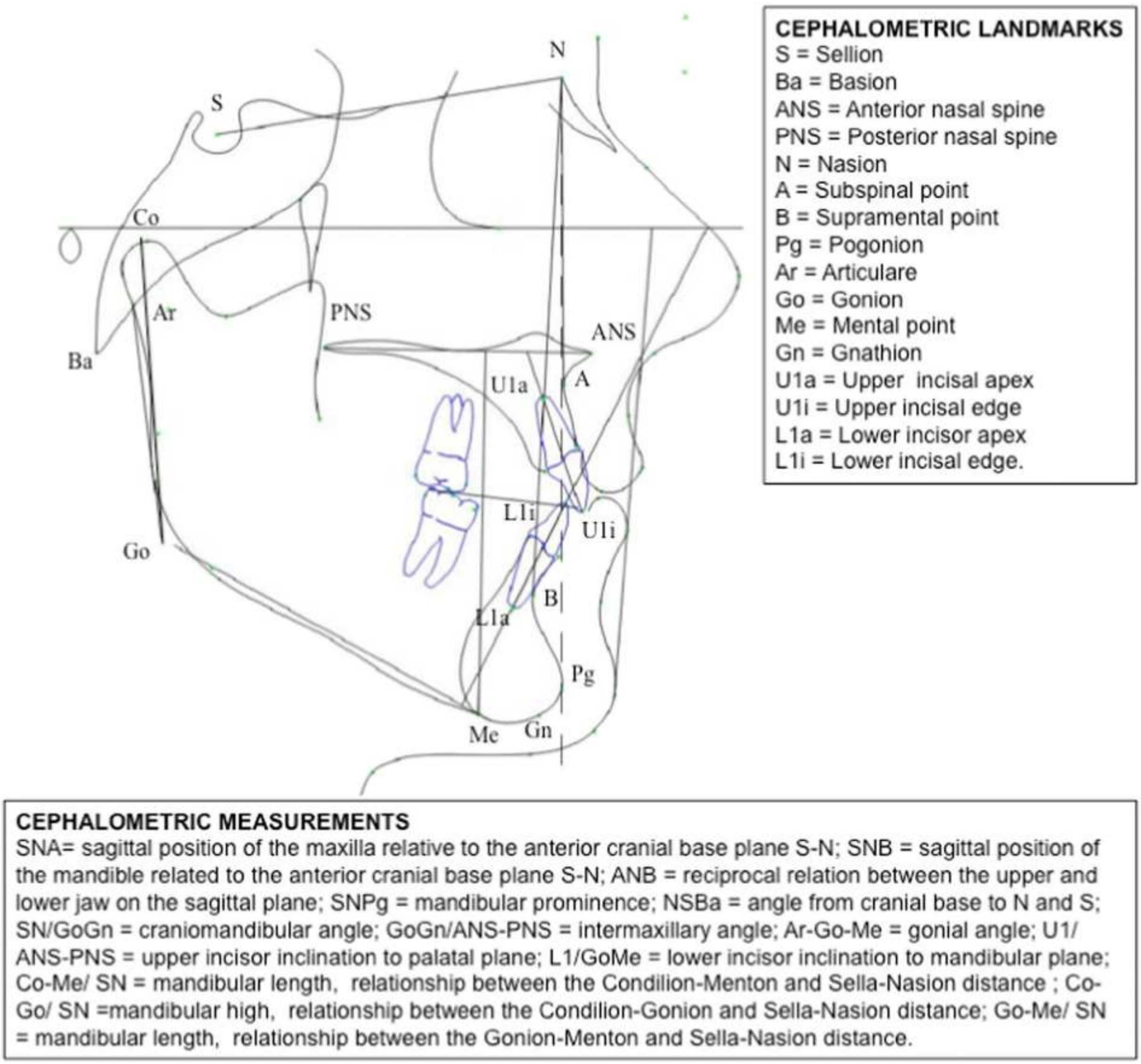


**Fig. 2.** Cephalometric landmarks and measurements.

**Table 1**
Comparison of cephalometric measurements (means ± Standard Deviation) between operated (glossectomy) and non-operated patients affected by BWS at different growth stages. P-value was set at 0.025 with Bonferroni corrections.

| PARAMETERS | OPERATED Mean ± SD | | | NON-OPERATED Mean ± SD | | | p-value | | |
|---|---|---|---|---|---|---|---|---|---|
| | 5 y | 10 y | 15 y | 5 y | 10 y | 15 y | at 5 y | at 10 y | at 15 y |
| SNA | 82.70 ± 4.81 | 82.70 ± 2.91 | 83.35 ± 2.61 | 81.96 ± 5.07 | 82.75 ± 3.81 | 83.82 ± 5.21 | 0.212 | 0.425 | 0.663 |
| SNB | 81.29 ± 4.44 | 81.57 ± 2.09 | 82.08 ± 0.25 | 80.81 ± 3.21 | 80.30 ± 3.61 | 82.38 ± 4.26 | 0.114 | 0.531 | 0.643 |
| ANB | 1.41 ± 2.05 | 1.13 ± 1.91 | 1.27 ± 2.90 | 1.15 ± 2.00 | 1.45 ± 3.08 | 1.54 ± 3.39 | 0.136 | 0.640 | 0.172 |
| SNPg | 81.54 ± 4.04 | 82.83 ± 2.38 | 84.03 ± 1.42 | 81.19 ± 4.05 | 82.27 ± 3.99 | 83.73 ± 4.12 | 0.212 | 0.722 | 0.116 |
| NSBa | 127.72 ± 3.00 | 128.34 ± 5.10 | 129.70 ± 6.16 | 128.76 ± 4.72 | 128.75 ± 6.82 | 129.00 ± 7.51 | 0,2983 | 0,9855 | 0,6350 |
| SN/GoGn | 33.60 ± 4.12 | 33.90 ± 6.24 | 34.50 ± 7.78 | 36.51 ± 7.21 | 35.86 ± 4.91 | 34.28 ± 4.84 | 0,2906 | 0,3022 | 0,8057 |
| GoGn/ANS-PNS | 27.22 ± 3.99 | 25.32 ± 5.84 | 26.23 ± 9.43 | 28.91 ± 5.63 | 27.06 ± 4.28 | 26.43 ± 6.27 | 0,9970 | 0,2080 | 0,8960 |
| Ar-Go-Me | 135.37 ± 3.79 | 132.92 ± 5.40 | 130.00 ± 4.08 | 135.58 ± 4.93 | 134.03 ± 4.44 | 133.73 ± 2.87 | 0,9230 | 0,2816 | 0,2114 |
| U1/ANS-PNS | 103.58 ± 11.30 | 107.06 ± 7.98 | 109.80 ± 4.68 | 108.98 ± 12.47 | 115.14 ± 7.05 | 116.75 ± 5.28 | 0,0168 | 0,0206 | 0,0233 |
| L1/GoMe | 87.03 ± 8.28 | 85.56 ± 8.20 | 88.67 ± 11.22 | 88.61 ± 9.00 | 87.35 ± 9.62 | 89.30 ± 8.32 | 0,4271 | 0,0654 | 0,1226 |

intra-rater reliability. No significant differences in the sagittal position of the maxilla or mandible relative to the anterior cranial base between operated and non-operated patients were found, at any time point (Tables 1 and 2). Inclination of maxillary incisors (U1/ANS-PNS) at 5, 10 and 15 years was statistically significant, being greater in the non-operated group (operated group mean value (±SD) compared to the non-operated group: 103.58 ± 11.30 Vs 108.98 ± 12.47 at 5 years old; 107.06 ± 7.98 Vs 115.14 ± 7.05 at 10

**Table 2**
Comparison of mean mandibular growth differences at different age points (age 5–10 and 10–15) between operated and non-operated BWS patients.

| PARAMETERS | OPERATED | | NON-OPERATED | | p-value 5–10 | p-value 10–15 |
|---|---|---|---|---|---|---|
| | 5-10 y | 10-15 y | 5-10 y | 10-15 y | | |
| Co–Me/SN | 11% ± 5% | 4% ± 7% | 13% ± 8% | 9% ± 7% | 0.183 | 0.329 |
| Co–Go/SN | 16% ± 10% | 6% ± 10% | 15% ± 8% | 8% ± 10% | 0.143 | 0.929 |
| Go–Me/SN | 19% ± 9% | 13% ± 6% | 19% ± 8% | 14% ± 8% | 0.645 | 0.462 |

years old; 109.80 ± 4.68 Vs 116.75 ± 5.28 at 15 years old; exact p-value: 0.0168 at 5 years old; 0.0206 at 10 years old; 0.0233 at 15 years old) (Table 1).

The mandibular length (Go-Me/SN) at 5, 10 and 15 years was plotted in a line graph to compare the rate of growth of the mandible in the two groups (Fig. 3). Normal values from Riolo (Riolo et al., 1974) were inserted in the same graph, to have a visual depiction of a normal mandibular growth curve. The lines connecting the different time points were parallel, indicating similar growth rates between operated and non-operated patients. Both groups showed higher values in mandibular measurements compared to the values of the healthy population.

## 4. Discussion

Indications to tongue reduction in children with BWS are multiple. Very early glossectomy is mandatory in selected patients, such as patients who have difficulties in breathing, or when macroglossia is the cause of Obstructing Sleep Apnea Syndrome (Follmar et al., 2014) or feeding (Prendeville and Sell, 2019). It may also be indicated if the size of the tongue induces significant speech difficulties (Van Lierde et al., 2010). In addition, a large tongue may give the impression of cognitive delay, therefore psycho-social impact needs to be considered as a possible indication for surgical management (Kacker et al., 2000; Maas et al., 2016).

Köle first suggested that macroglossia causes mandibular overgrowth (Köle, 1965). Glossectomy reduces bone length and thickness of the lower jaw in animal models (Schumacher et al., 1988; Liu et al., 2008). Matsudaa suggested that patients affected by BWS with macroglossia, even with no acute indication for tongue surgery, should undergo surgery during the period with minimal perioperative risk, before the tongue can influence the growth of the jaw, and strongly recommend that patients undergo surgery between the ages of 2 and 3 (Matsudaa et al., 2017). Similarly, Wolford suggested that an excessively large tongue could cause unfavorable mandibular growth and that reducing it could control the problem (Wolford and Cottrell, 1996). A systematic review analyzing the major indications to surgery revealed that mandibular overgrowth is one of the most frequent indications for surgery in different centers (Kadouch et al., 2012; Simmonds et al., 2018).

However, even though glossectomy is often indicated to prevent excessive mandibular growth (Kadouch et al., 2012), there is no evidence that mandibular overgrowth in BWS is directly correlated with macroglossia.

The attention of this study was on longitudinal variations, especially in terms of rate of mandibular skeletal growth, to estimate whether glossectomy could affect the curve of mandibular growth in time and/or normalize maxillo–mandibular relation. The results of this study suggest that mandibular growth rate does not decrease in the long term in operated patients compared to patients who were at least similar, as they were suggested surgery, but had refused; our data showed that the mandible, despite early glossectomy, continues to grow in height and in length with a similar growth curve, which is steeper than the curve of non-affected children in both operated and non-operated BWS patients (Figs. 3–5). The only significant difference found between the two groups was in the angular inclination of the maxillary incisors, which was higher in the non-operated patients. This might be due to the permanent effect of macroglossia on the dento-alveolar structures, in contrast to the skeletal bases.

Some reports seem to confirm the results of our study. Hikita and Van Lierde reported BWS patients subjected to glossectomy at the age of 2–3 years, later requiring surgery (Van Lierde et al., 2010; Hikita et al., 2014). Naujokat evaluated in the long-term 13 operated versus 7 non-operated BWS patients, who had undergone either a conservative or surgical therapy according to the degree of macroglossia. None of the patients in the conservative group developed mandibular prognathism, while 19% of the operated patients showed mandibular overgrowth. The groups compared had a severe selection bias (Naujokat et al., 2018). The strength of our study is that the patients in the two groups had a similar degree of macroglossia (severe) and they were all indicated for glossectomy. Moreover, patient allocation to one group or another was based on the family decision and was not dictated by the surgeon.

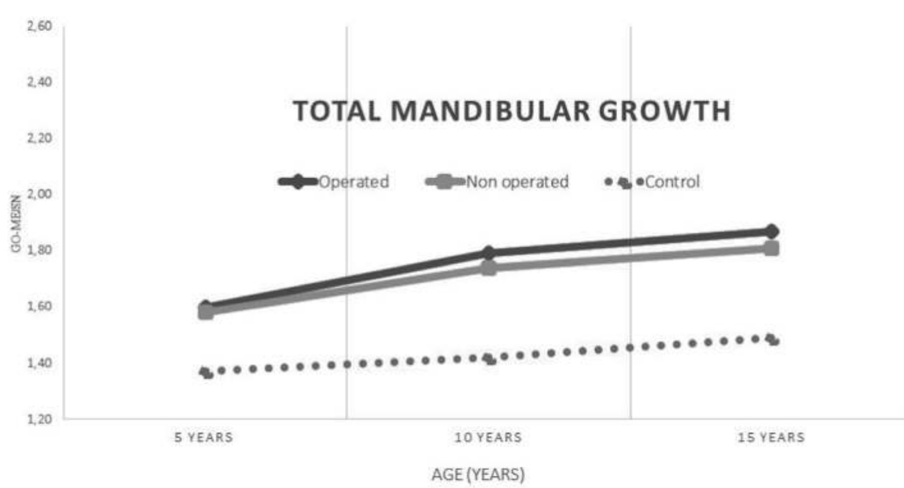


**Fig. 3.** Line graph describing the comparison of the growth curves of the mandible between operated and non-operated patients. The steepness of their growth curves is the same. We have depicted in the same graph a normal mandibular growth curve using published normative data (Riolo et al., 1974).


**Fig. 4.** Lateral cephalometric x-rays of a patient affected by BWS who underwent glossectomy at age 2 years. 3a) Lateral cephalometric x-rays at 5 years. 3b) Lateral cephalometric x-rays at 15 years. Note: This patient was treated with a facial mask for maxillary protraction at age 9 years.

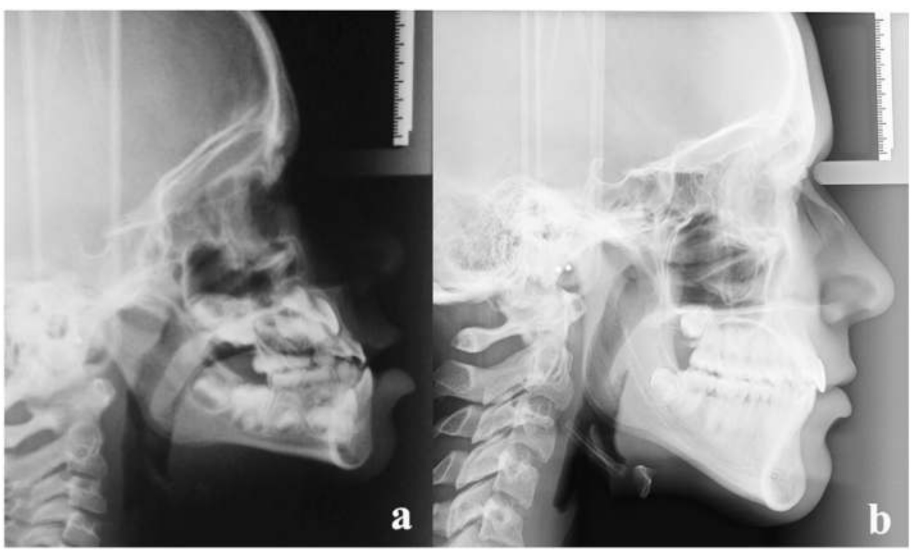


**Fig. 5.** Lateral cephalometric x-rays of patients affected by BWS who did not undergo glossectomy, although it had been offered at the age of 22 months. 4a) Lateral cephalometric x-rays at 5 years. 4b) Lateral cephalometric x-rays at 15 years. Note: This patient was treated with a facial mask for maxillary protraction at age 7 years and subsequently retreated with the Alt-Ramec technique (Meazzini et al., 2019) at age 12.3 y for protraction of the maxilla. The improvement in maxillo–mandibular relation is, therefore, related to maxillary changes and not to mandibular growth. The patient does not need orthognathic surgery.

Interestingly, in the literature, not all patients with mandibular prognathism have increased lingual volumes and not all patients with macroglossia have a class III malocclusion, and these data seem to contradict the hypothesis that a large tongue might stimulate mandibular growth. Yoo and colleagues found no statistically significant differences between the tongue volumes in females with and without mandibular prognathism (Yoo et al., 1996). On the other hand, patients with cerebral palsy, hypothyroidism, and lymphangiomas present as skeletal class II, despite their significant macroglossia (Chung et al., 2012; Gupta et al., 2014; Al Hashmi et al., 2017).

Kawafuji suggested that mandibular overgrowth might be related to a genetic anomaly mediated by Insulin Growth Factor 2, independent from the tongue and therefore a glossectomy to prevent mandibular over-growth does not seem justified (Kawafuji et al., 2011). Therefore, Fig. 2 demonstrates that both BWS samples have higher mandibular length during the period of growth compared to normative data, as one of the main facial features of the syndrome.

While all operated patients were immediately able to contain the tongue (average age 2.3 ± 1.3 years), the sample of patients who refused surgery, demonstrated the ability to keep the tongue in the oral cavity by age 5 in most cephalometric x-rays. This seems to be supported by some authors, who suggest that the tongue during early development tends to reduce its apparent size within the oral cavity (Friede and Figueroa, 1985; Cohen, 2005).

BWS is a collection of various genetic and epigenetic mutations that produce a wide variety of presentations. With regard to macroglossia, considering all BWS patients together as one entity with one protocol does not seem possible.

This study presents some limitations. First, ideally a correlation between glossectomy and class III malocclusion should be investigated with a randomized clinical trial. Given the low prevalence of the disease, however, a retrospective longitudinal case–control study was carried out, with the full awareness of its great limitations, not only in terms of size of the sample, but also in terms of its methodological inability to prove any cause–effect relationship. Second, the sample size is small, given the low prevalence of the disease. Nevertheless, to our knowledge it is the first attempt to compare rate of mandibular growth in BWS patients subjected and not subjected to glossectomy during the same period of growth. The two samples, though not randomized, were matched by the same clinical indication for glossectomy.

## 5. Conclusion

Many BWS patients present progressive mandibular overgrowth from childhood to adolescence and glossectomy does not seem to modify the rate of its growth. Consequently, in the absence of airway obstruction, swallowing problems with failure to thrive, impaired feeding functions and speech problems, based on our data, glossectomy is not recommended in BWS patients for preventing Class III malocclusion.

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## Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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