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Craniofacial bone atrophy in Parry Romberg syndrome demonstrated using a Bayesian hierarchical model

Quentin Hennocq [a, *], Arianna Facchini [a], Bothild Kverneland [a], Christine Bodemer [b], Arnaud Picard [a], Roman H. Khonsari [a]

[a] Assistance Publique – Hôpitaux de Paris, Hôpital Necker – Enfants Malades, Service de chirurgie maxillo-faciale et plastique, Université Sorbonne Paris Cité, Université Paris Descartes, Paris, France
[b] Assistance Publique – Hôpitaux de Paris, Service de dermatologie, Hôpital Necker – Enfants Malades, Université Sorbonne Paris Cité, Université Paris Descartes, Paris, France

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ABSTRACT

Purpose: Parry Romberg syndrome (PRS) is a condition characterized by progressive hemifacial atrophy, predominantly affecting the soft tissues. Associated bone retraction is a common clinical feature of PRS but has never been assessed. Here we used 3D imaging and Bayesian statistics in order to demonstrate and quantify bone atrophy in PRS.

Materials and methods: Ten non-operated patients with PRS (4/10 males) and 12 age-matched controls (7/12 males) were included into the study. The average age at CT-scan was 9.67 ± 4.13 years for PRS patients and 12.5 ± 4.37 years for controls. Soft and hard tissue atrophy levels were quantified using computed tomography scans, based on the distances between surfaces of the affected side and the non-affected contralateral side, both for the skin and the bone. We used a hierarchical Bayesian model with clinical priors in order to assess the relationship between hard and soft tissue atrophies.

Results: PRS patients had significant hard tissue atrophy, and atrophy extents were similar for soft and hard tissues. There was a trend for a correlation between the extent of hard tissue retraction and the extent of soft tissue retraction, and we could not demonstrate that the relationship between hard and soft tissue retractions was different in PRS and controls.

Conclusion: Our results indicated that bone atrophy was most probably a primary process rather than a phenomenon secondary to soft tissue retraction. We have provided the first assessment of bone atrophy in PRS patients using Bayesian statistics.

1. Introduction

Parry Romberg syndrome (PRS) is a rare condition characterized by progressive hemifacial atrophy of fat, skin, connective tissue and muscle (Fig. 1). PRS symptoms usually develop during the first 20 years of life, although late-onset forms have been reported (Mendonca et al., 2005). An early onset could be a risk factor for greater severity (Aynaci et al., 2001). The prevalence of PRS is higher in women (Aynaci et al., 2001; Moko et al., 2003; El-Kehdy et al., 2012) and the disease is mostly active in the first and second decades of life, with a slight left predominance (Pichiecchio et al., 2002; Moko et al., 2003; Tollefson and Witman, 2007). PRS is usually slowly progressive but self-limited. In fact, the disease typically "burns out" in 2–10 years and then stabilizes (Rogers, 1964).

Other facial damage in PRS may include tongue atrophy, localized alopecia and skin depigmentation. Dental anomalies such as short roots also occur and are most probably underdiagnosed (Khan et al., 2014). Neurologic abnormalities, such as seizures, migraine, facial pain, Rasmussen encephalitis, sympathetic dysfunction and even mild cognitive impairment may occur in up to 15% of patients. Neuroradiological abnormalities such as intraparenchymal calcifications, cerebral atrophy and intracranial vascular abnormalities have been detected in PRS (Stone, 2003; Yano et al., 2000; Madasamy et al., 2012). Eye anomalies are reported in 10–35% of

* Corresponding author. Service de chirurgie maxillo-faciale et plastique, Hôpital Necker – Enfants Malades, 149 rue de Sèvres, 75015, Paris, France.
E-mail address: quentin.hennocq@aphp.fr (Q. Hennocq).

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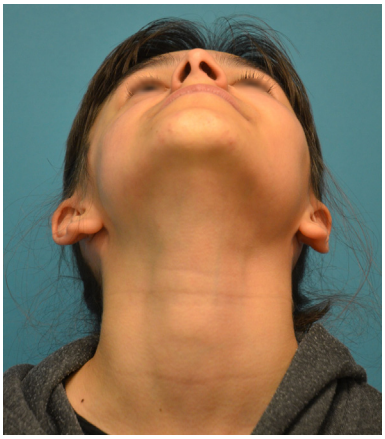

Fig. 1. Fifteen year-old child with Parry Romberg syndrome. Unilateral tissue atrophy with midfacial predominance.

cases and mostly consist of retro-orbital fat atrophy, uveitis, retinitis and optic nerve damage (Aynaci et al., 2001; Yano et al., 2000; El-Kehdy et al., 2012).

There is no generally admitted classification or consensus on diagnostic criteria for PRS. PRS diagnosis is still based on the practitioner's appreciation of the facial atrophy. A classification with four clinical subtypes of increasing severity has been proposed and is based on a subjective opinion on tissue depression: (1) PRS type 1 corresponds to depression only visualized by the patient; (2) PRS type 2 corresponds to skin or cartilage depression; (3) PRS type 3 corresponds to bone damage; and (4) PRS type 4 corresponds to skin tissue directly overlying the bone. Bone retraction in this classification is established based on clinical and/or radiological qualitative appreciation (Guerrerosantos et al., 2007).

PRS is considered by many authors as a form of *en coup de sabre* morphea, a type of localized scleroderma. Morphea is a condition of unknown origin associated with skin thickening secondary to increased collagen production (Blaszczyk and Jablonska, 1999). PRS and *en coup de sabre* morphea seem to be part of a spectrum involving various forms of localized scleroderma (Blaszczyk and Jablonska, 1999). Interestingly, deeper head and neck structures such as bones are usually less involved in localized scleroderma, in contrast to PRS (Khan et al., 2014; Wong et al. (2015)).

Soft tissue atrophy involving the skin and muscles is part of the definition of PRS, but associated bone retraction is reported in only a few cases (Wong et al., 2015; Sommer et al. (2006); Tang et al. (2013)) and has never been assessed quantitatively. The goal of our study was to demonstrate the occurrence of bone atrophy in PRS based on computed tomography (CT) scan data, and then to model the relationship between soft and hard tissue atrophy. For this, we designed a Bayesian model, a rarely used approach in the clinical assessment of craniofacial conditions, with specific advantages adapted to the study of rare diseases.

2. Materials and methods

2.1. Review of the literature

An extensive literature review on PubMed was conducted using with the following MeSH terms: 'Parry Romberg syndrome'; 'bone'.

2.2. Patients, data collection and data processing

We included all patients with PRS and with available CT scans, without previous facial surgery and associated craniofacial anomalies, seen in maxillofacial surgery and dermatology clinics between 2015 and 2018. Age-matched controls with normal craniofacial CT-scans were included from patients seen in neurosurgery for minor trauma. The diagnosis of PRS was based on the clinical assessment of progressive facial atrophy. For each patient, we collected information on age at CT scan, gender, age at the onset of symptoms, affected facial areas, and extra-facial neurological and ophthalmologic symptoms.

We used 3-matic 3.2.71 (Materialise, Leuwen, Belgium) in order to virtually section each PRS and control skull along a mid-sagittal plane. The mid-sagittal plane was defined based on five landmarks: (1) nasion, (2) anterior nasal spine, (3) posterior nasal spine, (4) basion and (5) opisthon. We arbitrarily chose the right side as the affected side for rendering purposes, and mirrored the CT scans of the patients for which the left side was affected. Of note, we did not take into account the potential deformation of the non-affected side due to the attraction of the affected side. We then constructed a series of symmetrical skulls by merging the mirror of the non-affected side with the non-affected side itself. Next we superimposed these constructed symmetrical skulls with corresponding PRS and control skulls for each individual. Skulls were subdivided into 5 regions of interest: (1) bony forehead + (2) corresponding forehead soft tissues, (3) bony midface + (4) corresponding midface soft tissues and (5) bony mandible. We did not consider the corresponding mandibular soft tissues, as the upper limit of this region could not be reliably defined. We computed mean distances between surfaces from the constructed symmetrical skulls and the corresponding individual PRS and control skulls on the right (affected) side for the 5 regions of interest (Fig. 2). This distance was referred to as the "hard tissue index" for hard tissues and as the "soft tissue index" for soft tissues. This distance was computed between the external surfaces of both skull and soft tissues. A positive value corresponded to hard tissue or soft tissue expansion, while a negative value corresponded to retraction. A greater negative value corresponded to more severe bone or skin retraction.

2.3. Statistical analyses

We used a Bayesian mixed linear model, thus implying the choice of informative or non-informative prior distributions for each parameter. Bayesian inference uses probability densities, which optimize the quantity of information when the size of the dataset is limited, as opposed to the single values used in usual frequentist inference approaches (such as the computation of means with standard deviations). Bayesian models seemed adapted to the present study for two reasons: (1) the dataset was small, as PRS is a rare condition; and (2) the clinical opinion of the surgeons on the craniofacial areas affected by PRS was a reliable informative prior. The model was a hierarchical model because a random effect was introduced on the intercept in order to take into account repeated measurements in the same subject on three different craniofacial zones (upper, middle, lower thirds of the face). The posterior distributions of the parameters of interest were plotted, and their probability of including zero was evaluated. Significance was defined as a parameter equal to zero with a probability less than 0.05. The detailed description of the Bayesian model is provided in the Appendix. We then designed another model in order to analyze the relationships between the symmetry of hard tissues and the time elapsed since the onset of PRS. We first assumed a linear dependence of symmetry on the evolution time, and we then postulated a quadratic dependence between these two variables. Statistical analyses were performed using *R v. 3.3.2* (R Core Team, 2016) with *nlme* (Pinheiro et al., 2017), *ggplot2* (Wickham, 2009), *rjags* (Plummer, 2016), *coda* (Plummer et al., 2006) and *ggmcmc* (Fernández i Marín, 2016) packages.

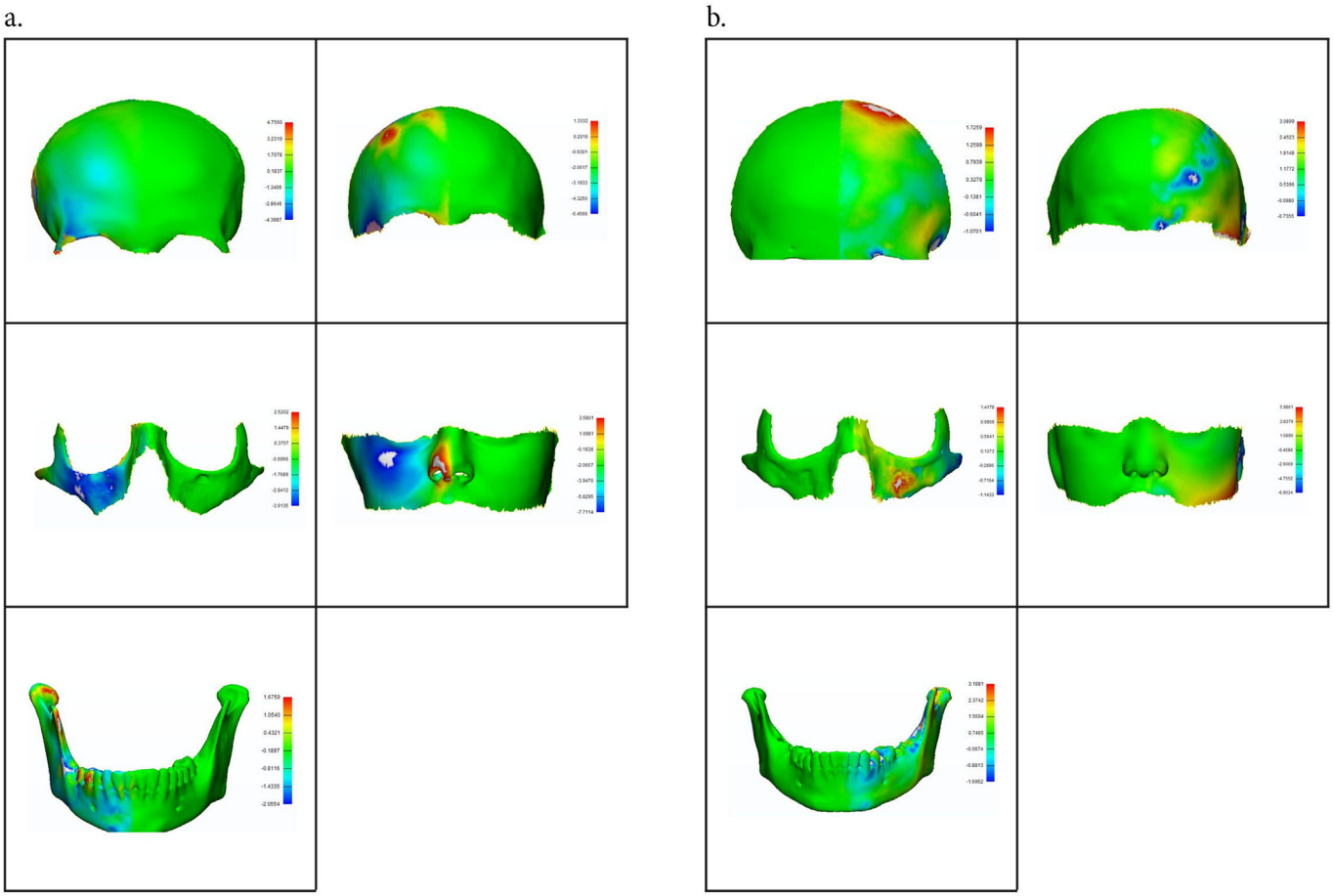

Fig. 2. Image processing: superimposition rendering with color-coded distance maps for (1) a case of PRS with marked asymmetry of the hard and soft tissues in all facial areas and (2) a control case.

3. Results

The literature review yielded 189 articles, and none of them provided a quantitative assessment of bone involvement in PRS.

Ten patients with PRS and 12 controls were included into the study. The average ages at imaging for PRS and controls were similar: 9.67 ± 4.13 and 12.50 ± 4.37, respectively ($p < 0.005$). The average age at the onset of symptoms for PRS was 7.44 ± 4.25 years, and CT scans had been performed on average 2.22 ± 1.97 years after the onset of the disease. The upper and lower thirds of the face were clinically affected in 6/10 patients, and the middle third of the face was affected in 9/10 patients. The mean hard tissue index was −0.012 ± 0.029 for PRS vs 0.080 ± 0.179 for controls; the mean soft tissue index was −0.085 ± 0.381 for PRS vs 0.026 ± 0.163 for controls. Descriptive data are summarized in Table 1.

The coefficient associated with the binary variable β_{PR} (corresponding to a positive PRS diagnosis) was significantly negative: −0.153 (] -∞; −0.027]) as its credibility interval did not contain 0 ($p = 0.010$). This meant that PRS had a significantly lower average hard tissue index (of a relative value of −0.153) for the same soft tissue index value. Smaller, more negative, hard tissue indices corresponded to more bone retraction: our results thus meant that PRS had significantly more bone retraction than controls.

The coefficient associated with the soft tissue index (β_{Soft}) was not significantly positive (0.526 [−0.217; +∞[, $p = 0.069$) but was very close to the significance threshold, indicating that hard and soft tissue indices could vary in the same direction, *i.e.*, that the extent of hard tissue retraction could be correlated with the extent of soft tissue retraction.

Table 1
Characteristics of the population.

	n	PRS	Controls
N	22	10	12
		45.45%	54.54%
Male	20	4/10	7/12
Age at CT in years (sd)	9	9.67 (4.13)	12.50 (4.37)
Minimum		5	5
Maximum		16	18
Age of onset in years (sd)	9	7.44 (4.25)	
Minimum		3	
Maximum		16	
Time since onset in years (sd)	9	2.22 (1.97)	
Minimum		0	
Maximum		6	
Clinically affected facial area	10		
Upper		6/10	
Middle		9/10	
Lower		6/10	
Extra-facial symptoms	10		
Ophtalmological symptoms		0/10	
Neurological symptoms		1/10	
Hard tissue index	49	−0.012 (0.029)	0.080 (0.179)
Soft tissue index	32	−0.085 (0.381)	0.026 (0.163)

Sd: standard deviation.

The interaction parameter $\beta_{PR*Soft}$ was −0.296 (]-∞; 0.497]). This value was not significantly negative ($p = 0.213$). This meant that we could not demonstrate that the relationship between hard and soft tissue retractions was different in PRS and controls.

The posterior distributions of the parameters (Fig. 3) and the linear relationship between the hard and soft tissue indices for each group (Fig. 4) were plotted, and the convergence of MCMC chains was confirmed (Supplementary Figures 1 and 2), thus assessing the validity of the Bayesian model.

A prior sensitivity analysis was performed for β_{PR}, which was the only parameter for which an informative prior was used. β_{PR} values were negative for a varying from 0 to 1: regardless of the level of prior information provided, the estimate thus varied very little and remained significantly negative.

The relationships between the hard tissue index and time since the onset of symptoms were also modelled, and we found a trend towards a positive relationship between the importance of bone retraction and quadratic time (that is, more bone retraction for longer evolution times). These results were nevertheless not significant, most probably due to the small number of cases.

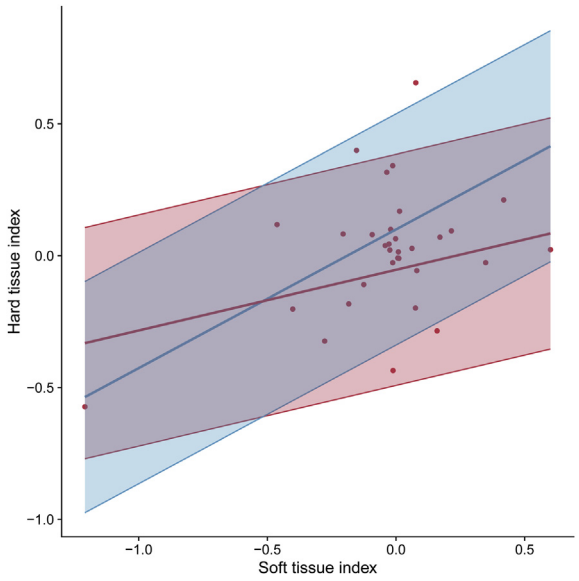

Fig. 4. Linear relationship between hard and soft tissue indices for each group with credibility intervals. Blue: control group; red: PRS.

4. Discussion

Only 1 in 10 patients with PRS had extra-facial anomalies (cortical atrophy with epilepsy). This low prevalence compared to data from the literature (neurological anomalies: up to 15%; eye anomalies: 10–35%) (Aynaci et al., 2001; Stone, 2003; Yano et al., 2000; El-Kehdy et al., 2012; Madasamy et al., 2012) could be explained by the fact that our subjects were young (mean age at CT-scan: 9.67 ± 4.13), even though the dynamics of the extra-facial anomalies in PRS have not been precisely assessed.

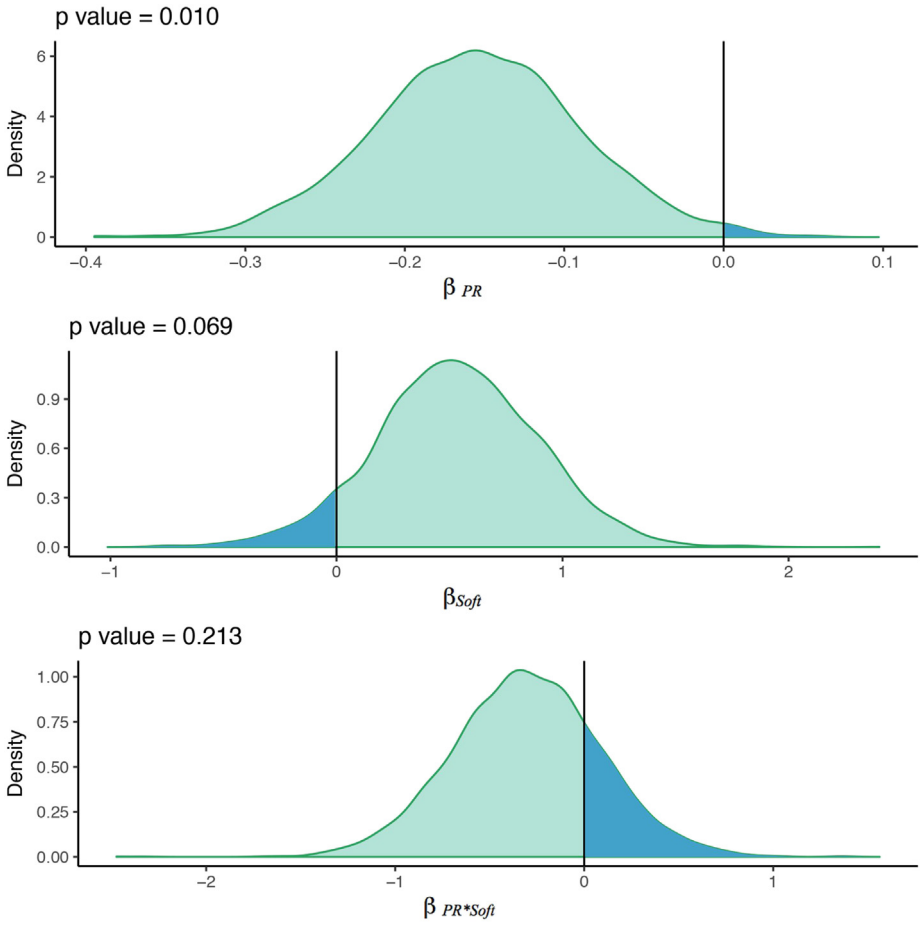

Fig. 3. Posterior distribution of parameters beta (PR), beta (Soft) et beta (PR*Soft). The blue areas corresponded to the probability of rejecting the null hypothesis by mistake, i.e. the hypothesis that the parameter was null. In other words, the blue areas corresponded to the p-value.

Soft tissue atrophy affecting the skin, the subcutaneous fat and muscles are the landmark signs of PRS, but only a few reports of bone atrophy are available in the literature (Wong et al., 2015; Sommer et al., 2006; Tang et al., 2014). Wong et al. (2015) reported 7 cases of bone atrophy affecting the maxilla, the zygoma, the mandible, the orbits and the ethmoid. Tang et al. (2013) reported bone asymmetry in two patients, including one patient with a Tessier No. 3 cleft. Sommer et al. (2006) found bone atrophy in 3 of 12 patients. In all these reports, bone atrophy was based on qualitative appreciation of X-rays and/or CT scans and was not quantified. An extensive review of the literature showed that bone atrophy has not, to our best knowledge, been assessed in PRS.

PRS is often compared to localized scleroderma or *en coup de sabre* morphea, and its origins may be similar. Bone atrophy in scleroderma is well described and affects 10% of cases (Rout et al., 1996). In the craniofacial region, the areas most commonly affected in localized scleroderma are, in decreasing order of frequency: mandibular angles, mandibular condyles, coronoid processes and posterior border of the mandibular ramus (Haers and Sailer, 1995).

Three hypotheses have been proposed in order to explain bone atrophy in scleroderma: (1) atrophy secondary to skin retraction (Pogrel, 1988); (2) atrophy secondary to muscle retraction, predominating at muscle attachment zones (Auluck et al., 2005); and (3) primary bone ischemia due to specific small vessel vasculitis, causing bone damage and atrophy (Ramon et al., 1987). In fact, vasculitis associated with scleroderma often affects the branches of the internal maxillary artery, which vascularizes the mandibular condyle, the coronoid process and the mandibular angle (Ramon et al., 1987), three zones predominantly affected in PRS.

We could not show a significant difference between the extent of soft and hard tissue atrophy in PRS (Fig. 4). Based on the analogy between PRS and scleroderma, this result is in favor of an intrinsic involvement of the bone in the retraction process, and thus in favor of the ischemic hypothesis. The two secondary hypotheses would have de-correlated soft and hard tissue retractions. Furthermore, based on the trends that we report in this study, we could most probably demonstrate the relationship between the importance of tissue atrophy and an early onset of symptoms by extending the number of cases included in the cohort.

Most plastic surgeons focus on reconstructing soft tissue atrophy in PRS (Slack et al., 2012). Some practitioners suggest that soft tissue surgery should be performed after the correction of skeletal facial hypoplasia in order to establish solid foundations before lipofilling, despite the risk of resorption (Longaker and Siebert, 1996; Siebert et al., 1996; Siebert and Longaker, 1997; Myung et al., 2012). Bone surgery in PRS can include a variety of procedures such as bone grafts, orbital osteotomies, facial bipartition, orthognathic surgery and genioplasty (Longaker and Siebert, 1996; Siebert et al., 1996; Siebert and Longaker, 1997; Myung et al., 2012). Our study supports the combined management of soft and hard tissue atrophies.

5. Conclusion

More generally, Bayesian statistics are very useful when analyzing results from studies on rare diseases, that is, in situations in which the use of the maximum amount of available information is crucial. Frequent approaches consist in modelling most distributions using normal laws and thus reduce the available information to the values of the mean and the standard deviation. In the specific case of PRS, as the diagnostic criteria for this condition are not well codified, Bayesian statistics were furthermore particularly relevant as they took into account—and assessed—the qualification of a given facial area as affected vs non-affected. We quantified for the first time the involvement of the craniofacial skeleton in PRS. Furthermore, we found a trend for an increasing linear relationship between the hard and soft tissue indices, *i.e.,* the fact that an important soft tissue retraction would be associated with a larger bone retraction, thus supporting the hypothesis of an intrinsic origin for bone atrophy. Table 2.

Table 2
Bayesian hierarchical model. The intercept corresponded to the mean value of the hard tissue index for controls when the soft tissue index was equal to zero. For example, the mean hard tissue index with a soft tissue index equal to zero for PRS corresponds to beta (cons) + beta (PR) = 0.099−0.153 = −0.054.

Parameters	Mean	Sd	Unilateral CI bound (5%)	p value
Intercept (β_{cons})	0.099	0.167		
Parry Romberg (β_{PR})	−0.153	0.064	] - ∞; - 0.027]	**0.010**
Soft tissues (β_{Soft})	0.526	0.367	[- 0.217; + ∞ [	0.069
Interaction ($\beta_{PR*Soft}$)	−0.296	0.392	] - ∞; 0.497]	0.213
Precision (τ)	22.088	6.108		

Sd: standard deviation; CI: credibility interval.
A p value in bold means a significant result ($p < 0.05$).
A parameter was not statistically significant when its credibility interval contained zero.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2019.03.032.

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