European Journal of Orthodontics 34 (2012) 710–718
doi:10.1093/ejo/cjr101
Advance Access publication 23 September 2011

Growth of functional cranial components in rats with intrauterine growth retardation after treatment with growth hormone

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SUMMARY The goal of this study was to analyse the effect of growth hormone (GH) on catch-up growth of functional facial (splanchnocranial) and neurocranial components in rats with intrauterine growth retardation (IUGR). Wistar rats were divided into the following groups: control (C), sham-operated (SH), IUGR, and IUGR + GH. IUGR was surgically induced and GH was administered between 21 and 60 days of age. Radiographs were obtained at 1, 21, 42, 63, and 84 days of age in order to measure length, width, and height of neurocranium (NL, NW, and NH) and face length, width, and height (FL, FW, and FH). Analysis of variance was perfomed at 1 day of age and a principal components analysis (PCA) at 84 days of age. Neurocranial and facial volumetric indexes were calculated as NVI = $\sqrt[3]{NL \times NW \times NH}$ and FVI = $\sqrt[3]{FL \times FW \times FH}$, respectively, and adjusted by non-linear regression analysis. On postnatal day 1, there were significant differences between SH and IUGR ($P < 0.01$). Also, in both genders, final neurocranial volume was similar between SH and IUGR + GH groups, while the IUGR group had the lower value ($P < 0.01$). Final facial volume was similar among the three groups. In both genders, facial growth rates were SH = IUGR > IUGR + GH ($P < 0.01$). The first axis of the PCA exhibited size effect and the second axis showed shape effect. Reductions of placental blood flow modify cranial growth. The functional neurocranial and facial components in rats with IUGR presented different recovery strategies through modular behaviour, mainly related to modifications of growth rate as response to GH administration.

Introduction

Prenatal growth is a dynamic process determined by the interaction of exogenous (including nutrition, infection, and toxicity) and endogenous (genetics) factors, all of which affect cellular proliferation and differentiation and consequently the formation of tissues and organs. These processes occur more rapidly *in utero* than during any other period of ontogeny, making this stage of development one of the most vulnerable to injury (Godfrey and Barker, 1995; Schneider *et al.*, 1999; Kuzawa and Quinn, 2009). Environmental conditions experienced early in life can profoundly influence the biology and long-term health of an organism (Kuzawa, 2007).

An adequate increase of uterine blood flow throughout gestation is essential for uterine, placental, and foetal growth. Thus, uterine blood flow is inextricably linked to foetal growth and survival (Lang *et al.*, 2003). Most of the cases of intrauterine growth retardation (IUGR) result from restrictions to the placental delivery of nutrients as a consequence of deficiencies in maternal nutrition, reductions in uteroplacental blood flow, and/or malfunctioning of the placenta (Cross *et al.*, 1994; Godfrey *et al.*, 1996).

Two main patterns of foetal growth restriction are observed. When foetal growth is impaired during the first or second trimester, the infant will have symmetric growth restriction. This proportional lack of growth is caused by reduced foetal cellular proliferation of all organs. In contrast, asymmetric growth, in which an infant has smaller abdominal size compared to head size, will occur if the decrease in growth velocity happens in the last trimester. This head-sparing phenomenon is the most common form of IUGR and is attributed to the ability of the foetus to adapt, redistributing its cardiac output to the spleen, adrenal, coronary, and cerebral circulations. Although some overlap can occur, the timing of growth delay is more important than aetiology in determining the pattern of growth restriction (Lin *et al.*, 1991; Brodsky and Christou, 2004).

In addition to being a major factor in stillbirth, IUGR has serious consequences for babies who survive. IUGR is associated with increased risk of premature birth, increased morbidity and mortality among premature neonates, hypoxic brain injury and its long-term sequelae, and the need for respiratory support and chronic lung disease (Garite *et al.*, 2004). In later life, growth-restricted infants are at increased risk of various disorders, including obesity, diabetes, and ischaemic heart disease (Cox and Marton, 2009).

Dentists and orthodontists who treat growth-retarded patients must realize that most of these children have a delay in dentofacial development and in dental maturation and that the facial proportions can be thoroughly different from those of normal patients (van Erum *et al.*, 1997). Studies of craniofacial growth in children with reduced somatic growth because of different origin have shown that several facial structures are smaller, as could be expected. However, growth retardation does not affect all structures to the same extent, which results in an abnormal facial morphology (Kjellberg *et al.*, 2000).

Catch-up growth may be defined as growth velocity above the statistical limits of normality for age and/or maturity during a defined period of time following a transient period of growth inhibition. The effect of catch-up growth is to bring a child towards, or in favourable circumstances, right up to its otherwise normal developmental curve (Williams *et al.*, 1974; Williams, 1981). The use of growth hormone (GH) in IUGR, as evidenced in experimental models, results in catch-up growth observed in total body weight (Guimarey *et al.*, 2003). In growing children, although GH supplementation to augment their stature has become relatively common, the effects of this practice on the growth of the craniofacial complex are not well understood (Singleton *et al.*, 2006; Glen *et al.*, 2008). It is known that in the craniofacial complex, this hormone regulates cartilage formation and accelerates craniofacial growth in children (van Erum *et al.*, 1997). On the other hand, Rice *et al.* (1997), in an experimental study, using mice treated and untreated with human GH, reported the existence of catch-up growth of skull after the time when normal and dwarf mice, do not usually show any substantial growth. These authors also reported that catch-up growth is an example of both re-stimulated and prolonged growth beyond the time when normal growth has stopped. In this case, the treatment was particularly effective on nasal, maxillary, and mandibular lengths, elements due largely to endochondral ossification. However, the effect of the GH on the size of skull bones and how this action affects their relationships have not been studied.

Because human studies can be limited by small sample sizes, cross-sectional designs, uncontrolled variables, and often retrospective nature, animal models have been used to obtain more rigorous analyses (Nathanielsz, 2006; Singleton *et al.*, 2006). In this sense, during the last decades, IUGR has been studied through experimental models. Many of these models used ligation of uterine vessels in gestating rats as a means to produce the retarded state and are relevant for questions related to human gestation (Wigglesworth, 1964; Ogata *et al.*, 1985; Oyhenart *et al.*, 1998; Huizinga *et al.*, 2004, Vuguin, 2007).

This study presents a longitudinal analysis of morphological changes occurred in the skull of pups from mother rats with reduced blood flow during gestation, utilizing a functional craniofacial model. The skull is a highly complex integrated region of the skeleton that contains diverse organs and carries out numerous dynamic functions, some of which involve mechanical forces that affect multiple regions. It comprises different components that perform specific functions—vision, audition, olfaction, breathing, mastication, and neural integration (Moss and Young, 1960; Moss, 1973). Such functions are maintained through the shape and size changes brought about during ontogenetic development (Moss and Young, 1960; Moss, 1997; Hallgrímsson *et al.*, 2007).

Particularly, we evaluated the following hypotheses: 1. if a reduction of blood flow determines growth retardation, it will have effects on the two major functional components and 2. if the growth retardation continues during the post lactation period, the GH treatment will promote catch-up growth.

Materials and methods

Wistar rats (*Rattus norvegicus albinus*), raised at the Instituto de Genética Veterinaria (IGEVET, Facultad de Ciencias Veterinarias, CCT La Plata-CONICET), were maintained as an outbred colony. The animals were kept free of pathogens and treated in compliance with standardized institutional guidelines. They were housed in solid stainless steel cages at a room temperature ranging from 21 to 25°C and a 12:12 hour photoperiod (lights on at 06:00 a.m.). The animals were fed on a pelleted and sterilized commercial stock diet containing proteins (23 per cent), carbohydrates (44 per cent), lipids (11 per cent), water (8 per cent), fibre (5 per cent), ash (5 per cent), minerals (3 per cent), and a vitamin mix (1 per cent). When the rats reached adulthood (70 days), they were mated overnight. Beginning of pregnancy was determined by presence of spermatozoa in vaginal smears. Pregnant rats were housed in individual steel cages, fed on a stock diet *ad libitum*, and assigned to one of three experimental groups: control (C), intrauterine growth retarded (IUGR), and sham-operated (SH). Control dams did not receive any treatment. A lower midline laparotomy under ether anaesthesia was done on the pregnant females of the IUGR group at day 14 of gestation. The arteries near the lower end of each uterine horn were partially ligated with a 3-0–silk suture (Oyhenart *et al.*, 1998). Pregnancy was allowed to proceed until delivery. The SH dams were subjected to laparotomy, but without vessel bending, in order to isolate the effects of surgery from those of vessel ligation.

After delivery, IUGR (37 males and 31 females) and SH (15 males and 15 females) pups were cross-fostered to well nourished control dams. Control pups (16 males and 15 females) continued lactation with their own mothers. A standard diet was available *ad libitum* to the mothers. The IUGR group was divided into two subgroups: non-treated IUGR (14 males and 14 females) and IUGR + GH (23 males and 17 females), which were injected subcutaneously with GH (3.0 mg/kg/day of Genotropin®) between 21 and 60 days old. SH pups were injected with only the hormonal vehicle with the same doses and periodicity as those for the IUGR + GH group.

After weaning, all the animals were fed a stock diet *ad libitum*. This experimental protocol was approved by the UNLP ethics committee for animal research.

Measurements

Males and females of each group were X-rayed under light ether anaesthesia at 1, 21, 42, 63, and 84 days of age in order to obtain the longitudinal data for each animal. After sedation, the rats were oriented in a cephalostat and radiographed in dorsoventral and lateral planes with a Siemens Heliophos 4 at 240 mA/125 kV. Shoots were regulated at 100 mA, 0.02 seg, 40–50 kW (according to the age of the animal). AGFA Mamoray MR5-II, 18 × 24 cm film was used for the radiographs. A 110 cm focus–film distance was used to reduce the magnification effect, calculated as MgC = Bx/Ax, where MgC is the magnification coefficient, Ax a variable measured on the 84th day radiograph, and Bx the same variable measured on the skull (Pucciarelli *et al.*, 2001). The length, width, and height of major neurocranial (NL, NW, and NH) and facial (FL, FW, and FH) components were measured on each radiograph with a Fowler Max-Cal Digitrix caliper (0.01 mm accuracy; Figure 1). All measurements were made by one author (F.A.Q.), which precluded interobserver differences. Intraobserver repeatability was assessed by remeasuring 20 randomly selected cases per age (15 per cent of the total sample). Intraobserver error was calculated using the Dahlberg statistic: $\sqrt{(\sum d^2/2n)}$, where d^2 is the quadratic difference between pairs of repeated measurements and n the number of pairs of measurements. This statistic is expressed in millimetres and can be interpreted as the average disparity between measurement sessions. Intraobserver error was less than 0.1 mm for all variables.

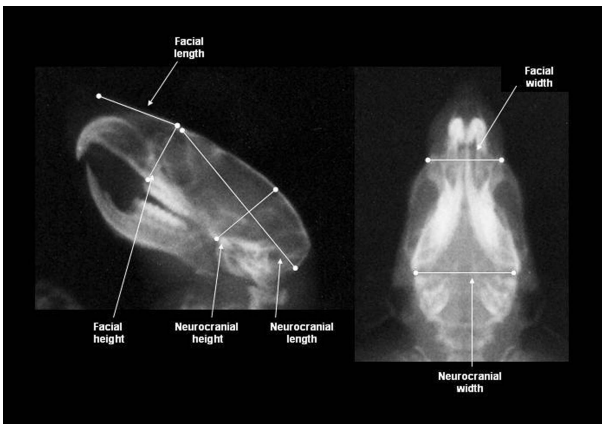

Figure 1 Radiography of rat skull showing measurements used in this study.

To estimate the size variations of the major components with respect to age and gender, volumetric indices were calculated as follows: neurocranial index (VNI) = $\sqrt[3]{}$NL × NW × NH; facial index (VFI)= $\sqrt[3]{}$FL × FW × FH (Cesani *et al.*, 2006).

Statistical analysis

The data corresponding to neurocranial and facial lengths, widths, and heights were processed statistically by analysis of variance (ANOVA) and the values for final age (day 84) by principal components analysis (PCA). In order to avoid the full-size differences between males and females and according to the patterns of sexual dimorphism exhibited by this species (Hughes and Tanner, 1970; Jansson *et al.*, 1983; Rol De Lama *et al.*, 2001), data for each gender were analysed through separate PCAs.

Table 1 Analysis of variance (ANOVA) test for neurocranial and facial variables on postnatal day 1.

	Neurocranial						Facial					
	Neurocranial length		Neurocranial weight		Neurocranial height		Facial length		Facial weight		Facial height	
	F-value	*P*	*F*-value	*P*	*F*-value	*P*	*F*-value	*P*	*F*-value	*P*	F-value	*P*
Intercept	43265.74	**	32445.61	**	26269.45	**	3245.87	**	8973.94	**	4618.79	**
Gender	0.41	ns	0.01	ns	0.45	ns	0.18	ns	1.01	ns	0.01	ns
Treatment	37.93	**	6.94	**	24.17	**	1.87	ns	32.29	**	0.20	ns
Gender × treatment	5.28	**	0.26	ns	0.12	ns	0.02	ns	4.25	**	0.87	ns

Control, sham, and intrauterine growth retardation (IUGR) animals. ns, not significant.
*$P < 0.05$, **$P < 0.01$.

The volumetric indices were analysed by non-linear regression curves, adjusted to: $y = e^{a+b/x}$. The parameter *a* estimated in this model was the value for maximum growth, while the reciprocal of age represented the growth rate; with e^a being the size of the final neurocranial component, *b* the growth rate, and *e* the base in Napierian logarithms. Differences in the neurocranial and facial volumetric indices among the groups studied, with the control group as reference, were calculated based on the estimations made in this model.

Results

The ANOVA on postnatal day 1 showed highly significant differences in neurocranial length, width, and height and facial width between treatments (Table 1). The *post hoc* analysis revealed significant differences in neurocranial length between C and SH of both genders (Table 2). Consequently, the SH animals were chosen as the reference group. Moreover, IUGR males and females evinced significant growth retardation in both neurocranial (length and height) and facial (length and width) components; in addition, females exhibited significant differences in neurocranial width (Table 2).

Table 3 presents the mean and standard deviation of neurocranial and facial volume from day 1 through 84.

Table 4 summarizes the results from non-linear regression analysis of neurocranial and facial volumes. In both genders, final neurocranial volume did not exhibit significant differences between the animals of the SH and IUGR + GH groups, with the IUGR group having a lower value. On the other hand, there was no difference in the growth rates of the neurocranium between SH and IUGR animals. In contrast, IUGR + GH showed significant slower growth than the SH group. Final facial volume did not exhibit significant differences among the three groups; however, growth rates were different because the SH group presented higher values than the IUGR and IUGR + GH rats. Figure 2 shows the differences between the means of neurocranial and facial volumetric indices, estimated by the regression model, for the pairs SH–IUGR and SH–IUGR + GH.

In males, the first PCA axis accounted for 50.0 per cent of the total variance with an eigenvalue of 1.19, and all variables correlated positively with this axis (with the exception of facial length), thus reflecting a strong effect of size on separating the different treatment groups (SH = IUGR + GH > IUGR). The second axis summarized 24.8 per cent of the remaining variance with an eigenvalue of 0.59, thus indicating shape variation (Table 5, Figure 3).

In females, the first PCA axis accumulated 47.8 per cent of the total variance with an eigenvalue of 1.03, separating the treatment groups (SH = IUGR + GH > IUGR) and showing positive correlation with all the variables, i.e. effect of size. The second axis captured 30.6 per cent of the remaining variance with an eigenvalue of 0.66, expressing shape variation (Table 5, Figure 4).

Table 2 Multiple range test (least significant difference) for cranial variables on postnatal day 1.

Comparison	Neurocranium						Splanchnocranium					
	Neurocranial length		Neurocranial weight		Neurocranial height		Splanchnocranium length		Splanchnocranium weight		Splanchnocranium height	
	Mean difference	Significance	Mean difference	Significance	Mean difference	Significance	Mean difference	Significance	Mean difference	Significance	Mean difference	Significance
Males												
Control/sham	−0.56	*	−0.04	ns	−0.20	ns	0.36	ns	−0.20	ns	−0.28	ns
Sham/intrauterine growth retardation (IUGR)	0.50	*	0.23	ns	0.46	**	0.55	**	0.53	**	0.16	ns
Females												
Control/sham	−0.57	*	0.07	ns	0.00	ns	0.45	ns	−0.45	ns	0.21	ns
Sham/IUGR	1.09	**	0.34	*	0.40	**	0.54	**	1.13	**	−0.06	ns

ns, not significant.
*$P < 0.05$, **$P < 0.01$.

Table 3 Mean and standard deviation (SD) of neurocranial and facial volume from the day 1 at 84 day. IUGR, Intrauterine growth retardation.

Edad	Neurocranial volume								Facial volume							
	Sham		IUGR		IUGR + growth hormone (GH)		IUGR + Ca		Sham		IUGR		IUGR + GH		IUGR + Ca	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Males																
1	30.94	0.73	29.75	1.05	—	—	—	—	16.21	0.77	15.31	1.44	—	—	—	—
21	48.53	0.98	46.85	1.06	47.42	1.43	46.94	1.18	27.25	0.73	26.20	0.98	26.24	0.98	26.14	1.37
42	54.41	0.91	52.90	1.06	53.19	1.34	53.19	0.86	34.99	1.25	34.24	1.03	34.07	1.38	33.34	0.92
63	57.89	0.75	56.40	1.38	57.01	1.18	56.74	0.66	39.86	1.16	39.08	0.80	39.30	1.01	38.24	1.28
84	60.29	0.81	58.06	1.52	59.32	1.31	58.40	0.88	42.51	1.10	42.05	1.41	41.47	0.97	40.83	1.18
Females																
1	31.11	0.65	29.28	1.12	—	—	—	—	16.21	0.85	14.89	1.52	—	—	—	—
21	48.46	0.87	45.88	1.59	46.38	1.20	46.87	1.02	27.09	1.08	26.01	1.33	25.33	0.88	24.45	1.41
42	53.53	0.78	51.96	0.75	52.76	0.61	53.03	1.12	34.78	0.99	33.79	0.90	33.99	0.80	33.83	1.12
63	55.90	1.16	54.06	0.69	55.35	0.49	55.87	1.15	38.42	1.19	37.83	1.15	38.19	0.82	38.43	0.88
84	57.39	1.20	55.59	0.92	57.48	0.89	57.72	0.89	40.51	1.43	40.21	0.78	40.27	0.83	40.87	1.00

Table 4 Non-linear regression analysis of neurocranial and facial volumes on postnatal day 84.

	Neurocranial volume				Facial volume			
	Residual standard error: 0.02995 − multiple R^2: 0.9826, adjusted R^2: 0.9822 − F.: 2455 (P value: < 2.2×10^{-16})				Residual error standard: 0.05171 − multiple R^2: 0.9807, adjusted R^2: 0.9803 − F.: 2209 (P value: < 2.2×10^{-16})			
	Estimate	Standard error	T value	Pr (>|t|)	Estimate	Standard error	T value	Pr (>|t|)
Intercept (volume)	3043	0.006	471 978	$<2 \times 10^{-16}$***	2823	0.011	253 580	$<2 \times 10^{-16}$***
Gender	0.041	0.009	4551	6.78×10^{-6}***	0.040	0.015	2559	0.010*
Growth rate	−0.721	0.011	−60 493	$<2 \times 10^{-16}$***	−1186	0.020	−57 660	$<2 \times 10^{-16}$***
Maximum volume								
Intrauterine growth retardation (IUGR)	−0.024	0.009	−2641	0.008**	0.001	0.016	0.069	0.945
IUGR + growth hormone (GH)	−0.009	0.008	−1065	0.287	0.003	0.015	0.259	0.795
Gender								
Growth rate	−0.051	0.016	−3030	0.002**	−0.043	0.029	−1490	0.136
IUGR	−0.003	0.013	−0.283	0.777	−0.008	0.022	−0.359	0.719
IUGR + GH	−0.003	0.012	−0.279	0.780	−0.015	0.020	−0.738	0.460
Growth rate								
IUGR	−0.024	0.016	−1517	0.130	−0.078	0.029	−2650	0.008**
IUGR + GH	−0.034	0.017	−2000	0.046*	−0.083	0.028	−2950	0.003**
Interaction								
Gender + IUGR + growth rate	0.022	0.024	0.917	0.359	0.026	0.041	0.645	0.519
Gender + IUGR + GH + growth rate	0.005	0.022	0.242	0.809	0.039	0.038	1016	0.310

R^2 (R squared) = coefficient of determination; F = F-statistic - goodness of fit.
*$P > 0.01$, **$P > 0.001$, ***$P > 0.000$.

Discussion

Functional cranial components can be differentially altered by environmental factors. As a result, the facial component appears to be more susceptible than the neurocranial one (Pucciarelli, 1981; Fields, 1991). Accordingly, previous reports have indicated that IUGR rats, whose mothers had their uterine vessels ligated at the beginning of gestation, showed more significant facial than neurocranial growth retardation (Oyhenart *et al.*, 1998). In this case, the ligation was made during the last third of gestation, and growth retardation affected both these major components. Thus, this discrepancy might have arisen as a consequence of differences in timing of the prenatal stress period.

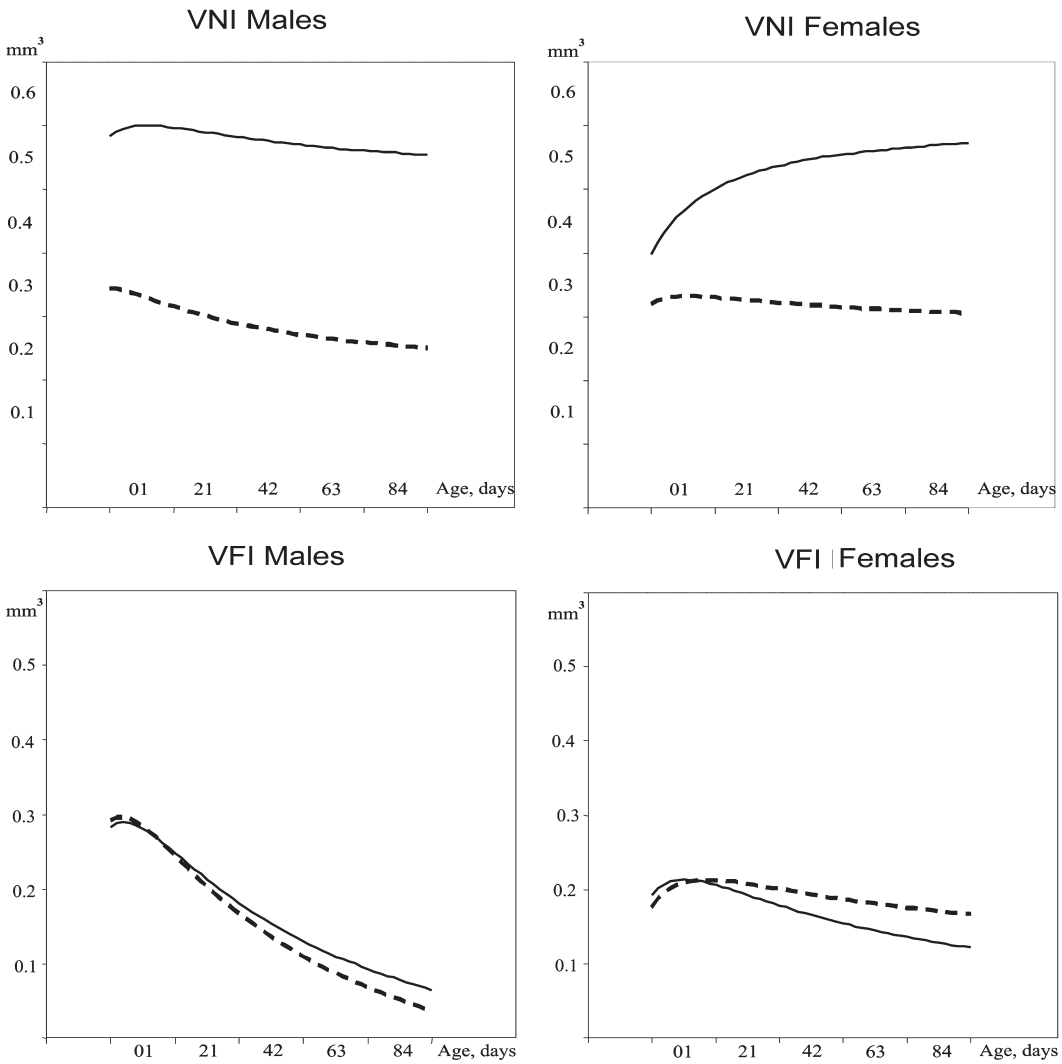

Figure 2 Plots of estimated differences in the neurocranial and facial volumetric indices between sham-operated (SH)–intrauterine growth retardation (IUGR) and SH–IUGR + growth hormone (GH) groups. Continuous line: SH group compared with IUGR group; dashed line: SH group compared with IUGR + GH group; VNI, volumetric neurocranial index; VFI, volumetric facial index.

Table 5 Principal components analysis for neurocranial and facial variables on postnatal day 84.

	Males		Females	
	Axis 1	Axis 2	Axis 1	Axis 2
Eigenvalue	1.187	0.589	1.032	0.661
Percentage	50.002	24.817	47.76	30.607
Cumulative percentage	50.002	74.819	47.76	78.367
PCA variable loadings				
Neurocranial length	0.913	−0.115	0.902	−0.393
Neurocranial width	0.199	0.131	0.187	0.187
Neurocranial height	0.194	−0.014	0.137	0.135
Facial length	−0.013	0.921	0.329	0.861
Facial width	0.184	0.311	0.020	−0.176
Face height	0.234	0.156	0.155	0.140

According to Woodall *et al.* (1996) and Oyhenart *et al.* (2002), neurofacial proportions evidence a strong effect of IUGR. Our results agree with earlier findings reported by Quintero *et al.* (2005) in which intrauterine growth-retarded rats showed significant cranial allometric effects. Because the skull size of IUGR animals does not reach normal values, it is assumed that it does not recover by itself. The lack of growth recovery in IUGR has been associated with multiple causes, including growth rate during the very first months of life (Karlberg and Albertsson-Wikland, 1995), individual variability, nutritional circumstances (Stanley and Speidel, 1985), and endocrine dysfunctions such as insufficient secretion of GH or low somatomedin activity (Hokken-Koelega *et al.*, 1995).

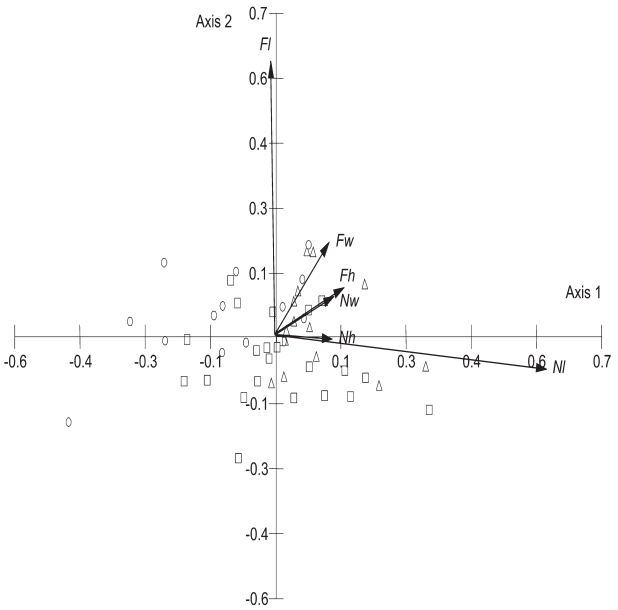

Figure 3 Plots of principal component scores for males. First and second components. Control animals (triangles), sham animals (squares), and intrauterine growth retardation (IUGR) animals (circles).

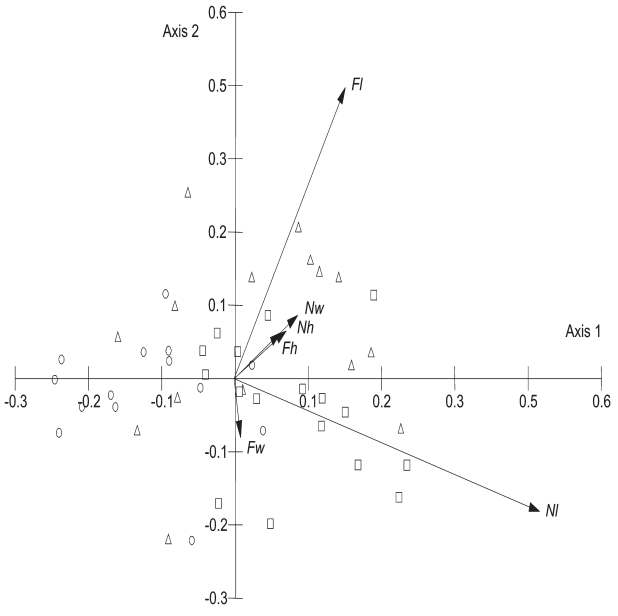

Figure 4 Plots of principal component scores for females. First and second components. Control animals (triangles), sham animals (squares), and intrauterine growth retardation (IUGR) animals (circles).

Analysis of the pattern of cranial dimensions in this experiment revealed the occurrence of differential catch-up in the volumes of the two functional components. The volume of the facial component was recovered in both IUGR and IUGR + GH groups. However, they both showed a decrease in the growth rate and a change in the timing of growth. The volume of the neurocranial component, however, was only regained after GH supplementation, but like the facial component, showed a decrease in growth rate. These findings indicated that both the neurocranial and the facial functional components displayed different potential for growth recovery, probably linked to GH therapy. It has been suggested that depending on the timing of GH supplementation, there is potential for change in proportions or shape of the craniofacial complex (Singleton *et al.*, 2006). In this sense, Vandeberg *et al.* (2004) reported that the relative maturity of different segments was able to limit skull growth. Consequently, different craniofacial morphologies may result depending on the timing of GH supplementation therapy. Also, Glen *et al*. (2008), in an experimental model of early GH supplementation on growth of the craniofacial complex, demonstrated that GH normal animals respond differently to GH supplementation than animals with a GH deficiency.

Although the prenatal development of vertebrates consists of a highly ordered process, it can become fragmented into relatively dissociated processes. This fragmentation, know as modularity, allows independent adaptation of different functions in the absence of interference with each other (Bonner, 1988; Raff, 1996; Polly *et al.*, 2001). In this way, each functional module can be modified differentially by environmental influences and exhibits an individual potential for recovery.

Several authors have proposed that the neurocranium, the facial skull, and the cranial base behave as separate modules, showing variation with a certain degree of independence (Lieberman *et al.*, 2000; Hallgrímsson *et al.*, 2004). Both the allometric effect observed in the skull of IUGR rats and the differing responses of the two major components in relation to the application of GH could be regarded as the result of a complex adaptive process. Each module shows a different developmental phenotypic reaction to early intrauterine injury and GH treatment. The effect of GH is also known to be different in different regions of the skull (Ramirez Yañez *et al.*, 2005).

Accordingly, it is proposed that the phenotypic plasticity of prenatal development allows mammals to delay or accelerate development depending on environmental conditions (Amiel Tison *et al.*, 2004). Postnatal development exhibits greater capacity than *in utero* development for varying over time. Nevertheless, changes *in utero* are very important since the adverse intrauterine environment results in prenatal reprogramming due to epigenetic mechanisms (Krause *et al.*, 2009; Vehaskari, 2010). This capacity to modulate development in response to the environment is considered an early acquisition in evolutionary terms (Amiel Tison *et al.*, 2004).

We conclude that a reduction of placental blood flow in rats modifies the cranial growth and its functional neurocranial and facial components. The skull of IUGR animals exhibits modular behaviour with different recovery strategies. Neurocranial growth exhibits a catch-up response only through the action of GH, changing the timing of growth.

Facial growth, in contrast, displays a catch-up development in IUGR animals, treated and untreated with GH, changing the growth rate. Furthermore, these results are relevant for pediatrics, orthodontics, and biological anthropology among other areas, in relation to the regulatory mechanisms of craniofacial growth and growth-retarded children treated with GH.

Funding

Consejo Nacional de Investigaciones Científicas y Técnicas (PIP 5384); Universidad Nacional de La Plata (11/V175).

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