Published in final edited form as:

J Pediatr Endocrinol Metab. 2009 January ; 22(1): 47–53.

Facial Metrics in Children with Corticotrophin-Producing Pituitary Adenomas Suggest Abnormalities in Midface Development

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Abstract

Background—Tumors of the hypothalamic-pituitary unit have been linked to genetic syndromes that are associated with midfacial abnormalities.

Aim—We hypothesized that mutations of genes that affect the development of the face (and consequently of the anterior pituitary) may be present in children with ACTH-producing pituitary adenomas, and if this is true then facial measurements would be different from those predicted by parental features.

Methods—We studied 20 children with cortico-tropinomas and a control group and their parents. All facial measurements were expressed according to standard deviation scores.

Results—Significant differences were seen between the children with pituitary adenomas and their parents for vertical facial height measures: nasal length ($p < 0.001$), lower facial height ($p < 0.03$) and overall facial height ($p < 0.01$).

Conclusion—We conclude that some of the indices of midline craniofacial development, in particular those affecting the vertical axis, are different in children with corticotroph adenomas producing ACTH.

Keywords

Cushing's disease; anthropometrics; middle face; pituitary gland; development

INTRODUCTION

Studies of craniofacial (CF) malformations have shown that they frequently arise from subtle alterations in the coordinated program of cell division in the cranium-forming cells^{1,2}. Tumors and anatomical defects of the hypothalamic-pituitary unit have been linked to genetic syndromes with CF abnormalities, from pituitary adenomas in Opitz syndrome to hamartomas, dermoid cysts and teratomas in Pallister-Hall, oro-facio-digital type VI (Varadi type) and related syndromes^{3,4}. Likewise, pituitary developmental defects, including ectopic

or hypoplastic anterior lobe, stalk formation abnormalities and septo-optic defects, are often associated with CF defects, such as midfacial hypoplasia manifested by hypertelorism, flat nasal bridge and malformed philtrum and small mouth^{5,6}. Perhaps the best example of a pituitary developmental transcription factor defect associated with tumor development is the recent identification of masses of the hypothalamic-pituitary unit developing in patients with *PROP 1* mutations^{7,8}. Children with *PROP 1* defects have a variety of minor midline abnormalities associated with pituitary hypoplasia and/or ectopia⁹.

Among functional pituitary tumors in early childhood, corticotropin (ACTH)-producing adenomas are the most common albeit they are still considerably rare: the cumulative incidence of such tumors in children does not exceed a tenth of the annual incidence of 2–5 new cases of Cushing's syndrome per million people per year¹⁰. To date, no genetic defects have been consistently associated with childhood corticotropinomas, which only rarely occur in the familial setting, and then most commonly in the context of multiple endocrine neoplasia type 1 (MEN1)^{11,12}. Growth hormone (GH) and/or prolactin (PRL)-producing tumors are the second in frequency of functional pituitary tumors in early childhood; these tumors in children almost always occur in the familial setting or in the context of known genetic defects: *GNAS*, *menin*, *PRKARIA*, *AIP* and perhaps p27 (*CDKNJB*) mutations^{13–15}. Somato- and/or mammotropinomas become significantly more frequent than corticotropinomas in late childhood, adolescence and adulthood¹⁶. Thus the evidence supports the notion that pituitary tumors in children are associated with genetic defects of factors involved in hypophyseal development and/or function.

Although *menin*, *PRKARIA*, *AIP* and p27 (*CDKNJB*) are not known to be involved in CF development, the earlier pituitary tumors form, the likelier it appears to be that they are related to a genetic defect or a factor that is also involved in the development of the gland, because anterior pituitary lobe development is part of an early process that results in the normal formation of the face¹⁷. This process is very sensitive to minor perturbations induced by genetics or the environment^{18,19}.

We hypothesized that mutations of genes that affect CF development may be present in young children with corticotropinomas. If our hypothesis is true, and corticotropinoma genes affect CF development, then facial measurements in these patients would be different from those predicted by parental features. Indeed, in an earlier pilot investigation, we presented results of CF measurements of ten children with various pituitary adenomas that showed a significant difference in vertical axis measurements of the face compared to mid-parental measurements²⁰. Ultimately, the identification of the factors responsible for CF changes in our patients may lead to important clues about associated genetic factors.

PATIENTS AND METHODS

Clinical protocol and patient description

The patients were studied at the National Institutes of Health Warren Magnuson Clinical Center under National Institute of Child Health & Human Development (NICHD) protocols 97-CH-0076, 00-CH-0160 and 00-CH-0180 between the years 1997 and 2006. The NICHD institutional review board approved these studies and informed consent from the patients' parents (and assent from older children) was obtained in all cases. We have described elsewhere the criteria that were used for the confirmation of Cushing's syndrome in these patients and the diagnostic testing that was performed^{21–23}.

Twenty children with corticotroph adenomas (13 boys and 7 girls; mean age 12.5 ± 3 years) and 16 age- and body mass index (BMI)-matched normal children (10 boys and 6 girls; mean age 12.2 ± 3.7 years) were studied. Race and ethnicity of the two groups were similar

(pituitary patients: 19 Caucasian, non-Hispanic; 1 Caucasian Hispanic; controls: 14 Caucasian, non-Hispanic, 2 Caucasian Hispanic).

All children with corticotroph adenomas were referred for confirmation of the diagnosis of Cushing's disease and they all underwent trans-sphenoidal surgery (TSS). Patients who had undergone repeated surgeries or received irradiation, patients on long-term medications, known developmental defects and/or other syndromes (fragile X, MEN-1, tuberous sclerosis) were excluded from this analysis. All patients who were included in the present study had histological confirmation of their ACTH-producing tumors (histology was negative for GH) and were eventually cured of their disease (data not shown; one patient required radiation treatment, all others TSS only).

The 16 children of the control group were recruited to participate if they had no known history of pituitary disorder and both biological parents were available for measurement. This group consisted of children who were siblings of a child with a pituitary tumor (8 children), normal volunteers (2 children), adrenal tumor (3 children) or congenital adrenal hyperplasia due to known *CYP21B* molecular defects (3 children).

Methods

Measurements were obtained by one observer using standard anthropometric techniques as described by Hall *et al.*²⁴ using clear metric rulers for facial measurements and paper metric tape for head circumference. The measured variables included facial height (nasion-gnathion), lower facial height (subnasion-gnathion), nasal length (nasion-sub-nasion), philtrum (subnasion-labrale superius), inner canthal distance (endocantion-endocanthion), outer canthal distance (exocanthion-exocanthion), palpebral fissure (endocanthion-exocanthion), inter-pupillary distance (pupil center-pupil center), mouth (cheilion-cheilion), ear (superaurale-sub-aurale), and head circumference for all children (control and corticotroph adenoma patients) and both biological parents.

Statistical analysis

Z-scores (standard deviation scores) were computed using normative measurements (means and standard deviations) to control for age and sex²⁴. Data were standardized against ear (E) and head circumference (HC) measurements that are not affected by mid-line defects. Children's z-score measures were compared to the corresponding mid-parental z-scores. Analysis was performed by Wilcoxon matched pair test using SPSS statistical software (SPSS Inc., Chicago, IL). For all statistical comparisons, unadjusted p-values of <0.05 are reported. In addition, p-values that remained significant after adjustment for multiple comparisons with Bonferroni are also reported.

RESULTS

Mean z-scores have a normal distribution in the reference population^{24,25}. The median and ranges of z-scores for all measurements are shown in Table 1. The Wilcoxon matched pairs test showed significant differences between the children with corticotroph adenomas and their parents for the measurements of the vertical axis of the face, including: *nasal length* (children with corticotroph adenoma vs mid-parental z-score: -1.45 vs 0.42, $p < 0.001$), *lower facial height* (children with corticotroph adenoma vs mid-parental z-score: -1.5 vs -0.9; $p < 0.03$), *facial height* (children with corticotroph adenoma vs mid-parental z-score: -2.2 vs -1.1; $p < 0.01$). The age adjusted z-scores for facial vertical height measures of the children with corticotroph adenomas were significantly smaller than their mid-parental z-scores. After Bonferroni adjustment for multiple comparisons, *nasal length* ($p < 0.006$) and *mouth* ($p < 0.002$) z-scores of children with corticotroph adenomas remained significantly

different from mid-parental z-scores. This is in contrast with the control group of children who had facial vertical height z-score values similar to their corresponding mid-parental z-scores (Table 1).

No discrepancy was found for the mean z-scores for facial breadth measurements (inner canthal distance, interpupillary distance, and outer canthal distance) with either the children with corticotropinomas or the control group and their corresponding mid-parental z-scores. The mean philtrum and ear length measurements did not differ from mid-parental z-scores in either of the two groups.

DISCUSSION

About the middle of the fourth week of embryonic development the pituitary gland develops from the invagination of the oral ectoderm (stomodeum) to form the rudimentary primordium (Rathke's pouch). By the fifth week the pouch has elongated and constricts at the attachment to the oral epithelium. The adenohypophysis (pars anterior, pars intermedia, and pars tuberalis) develops from the ectoderm of the stomodeum. The neurohypophysis develops from the neuroectoderm (infundibulum)^{2,26}.

Facial development occurs mainly between the fourth and eighth week after conception, from the first branchial arch, which also supports the lateral wall of the cranial part of the foregut (stomodeum). The facial prominences are produced by the proliferation of neural crest cells that migrated into the arches during the fourth week of embryonic development. The frontal portion of the frontal nasal prominence forms the forehead while the nasal part forms the rostral boundary of the stomodeum and forms the nose.

Facial proportions develop during the fetal period. Around the seventh week there is a shift in the blood supply from the internal to external carotid artery and during the same time period mesenchymal cell condensation occurs as a precursor to intramembranous and endochondral bone formation. The basic shape and size of bones are genetically determined. Although the growth rates of specific bones vary, there is a constant proportionality between growth rates^{27,28}.

The differentiation and growth of the chondro-cranium (midface area) appear to have a strong genetic determination and are subject to minimal environmental influence²⁸. The middle part of the face is a single growing unit rather than a mosaic of individual components. Byard *et al.* reported a path analysis to analyze familial resemblance for eight principal components of the craniofacial unit and found that the three orthogonal components of facial height along with the cranial size (head circumference) have higher transmissibilities than the three components of facial breadth and ear length²⁹. These findings of Byard *et al.* are in accordance with reports from other studies that also note a higher heritability for height versus breadth components of the craniofacial complex³⁰⁻³².

The evidence of higher transmissibility of vertical height measurements of the craniofacial unit is supported by the data for the control group of children in this study. The craniofacial measurements of children with corticotroph adenomas showed a significant difference from mid-parental measurements for vertical height, whereas no difference was noted for facial breadth components. This finding lends support to the hypothesis tested in this study, that children with corticotroph adenomas would have differences in craniofacial measures from the expected mid-parental z-scores. The control children in this study consisted of a large number of siblings (8 were siblings of a patient with pituitary adenoma) in which a high degree of congruence of measurements would be expected (Fig. 1).

Transcription factors that regulate anterior pituitary development have been implicated in corticotropinomas, in particular those that demonstrate a certain level of resistance to glucocorticoid-mediated negative feedback on ACTH secretion³³. However, to date no germline or somatic mutations in any of these factors have been shown in children or adults with ACTH-secreting tumors³⁴.

We conclude that some indices of midline craniofacial development, in particular those affecting the vertical axis, are different in children with corticotropinomas, perhaps indicating early somatic mutational event(s) affecting both craniofacial formation and pituitary tumorigenesis. Candidate genes include transcription factors that affect both processes.

Acknowledgments

This study was supported by the National Institute of Child Health & Human Development (NICHD), NIH intramural project ZO1-HD-000642-04 to Dr. C.A. Stratakis. We would like to thank Cara Olsen, Uniformed, Services University of the Health Sciences, for her assistance with statistical review.

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Fig 1. Child with pituitary Cushing's disease and family members. Z-scores for craniofacial measurements are shown in parentheses.

Craniofacial measurement z-scores - medians and ranges for children with pituitary tumors, control group, and mid-parental measurements

TABLE 1

	Nasal length		Facial height		Lower facial height	
	median	range	median	range	median	range
Pituitary patients	-1.45	-4 to 0.7	-2.2	-4.8 to -0.2	-1.5	-3.5 to 1
Mid-parental	0.42	-0.7 to 1.2	-1.1	-3.3 to 0.8	-0.9	-2.3 to 0.2
Controls	-0.33	-1.7 to 3.3	-1.8	-3.4 to 1.3	-1.7	-3.1 So -0.5
Mid-parental	0.33	-1.3 to -1.8	-1.3	-2.9 to -0.3	-1.1	-2.9 to 0

	Inner canthal distance		Outer canthal distance		Interpupillary distance	
	median	range	median	range	median	range
Pituitary patients	-0.16	-1.7 to 1.7	-2.4	-4 to -1	0.6	-1 to 1.5
Mid-parental	-0.23	-1.2 to 1.3	-2.2	-3.9 to 0.3	0.9	-0.3 to 1.6
Controls	-0.03	-1.4 to 2.2	-2.4	-4 to 1.6	0.7	-1 to 3
Mid-parental	0.27	-0.9 to 1.3	-2.1	-4 to -0.5	0.9	-0.1 to 2.5

	Mouth		Palpebral fissure		Ear	
	median	range	median	range	median	range
Pituitary patients	0.2	-2 to 3	1.53	-2 to 5.7	1.9	-0.3 to 4.5
Mid-parental	2.1	0 to 3.3	1.3	-3 to 3.5	2	-0.3 to 3.2
Controls	1.5	-0.3.1 to 3	-0.32	-1.7 to 2	0.27	-2 to 4
Mid-parental	1.9	0.9 to 3	0.8	-3 to 3.7	1.8	0.6 to 4