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Quantitative assessment of craniofacial morphology in Johanson-Blizzard syndrome

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Abstract

BACKGROUND—Here we apply objective, reliable methods of dysmorphology diagnosis to a patient with Johanson-Blizzard syndrome (MIM #243800). Using an extensive normative database, we computed standardized scores on a graded continuum for operational definitions of nasal alar hypoplasia, a commonly observed feature of this condition.

CASE—Most of these measurements in this case were greater than 2 standard deviations below the mean, adjusted for age, gender, and ethnicity.

CONCLUSION—This report provides a worked example of quantitative anthropometric assessment in the context of a case report, using tools that may find general application in clinical genetics.

Keywords

Johanson-Blizzard syndrome; autosomal recessive; UBR1 mutations; anthropometry; craniofacial dysmorphology

INTRODUCTION

Single physical features may have high predictive value in identifying specific craniofacial syndromes. We describe an infant with Johanson-Blizzard syndrome (MIM #243800) whose diagnosis was prompted by identification of the nasal hypoplasia that is distinctive to this condition and its validation through objective anthropometric methods.

This rare syndrome, first reported by Johanson and Blizzard (Johanson and Blizzard, 1971), is characterized by a wide array of symptoms, including congenital exocrine pancreatic insufficiency (achylia), hypothyroidism, malabsorption, growth retardation, deafness, scalp defects, and anorectal and genitourinary anomalies (Baraitser and Hodgson, 1982; Gershoni-Baruch et al, 1990; Moeschler et al, 1987; Nagashima et al, 1993). It is often associated with failure to thrive.

Its phenotypic expression is variable with intelligence ranging from mental retardation to normal IQ (Alkhouri et al, 2008; Elting et al, 2008; Moeschler and Lubinsky, 1985; Vanlieferinghen et al, 2003; Vieira et al, 2002). Neuropsychiatric manifestations have not yet been well characterized, though there is a single report of obsessive-compulsive disorder and aggression in a 29 year-old patient with Johanson-Blizzard syndrome (Prater and D'Addio, 2002).

Zenker et al. (2005) mapped the Johanson-Blizzard syndrome-associated locus to chromosome 15q14-21.1. Positional cloning identified loss-of-function mutations in the Ubiquitin-Protein Ligase E3 Component N-reconin 1 (UBR1) gene (MIM #605981) on 15q to be associated with the syndrome in more than a dozen unrelated families (Zenker et al, 2006). This gene encodes one of at least four functionally overlapping E3 ubiquitin ligases of a conserved proteolytic system (the *N-end rule pathway*) whose substrates include proteins with destabilizing N-terminal residues (Zenker et al, 2005).

Perhaps the most pathognomonic craniofacial feature of this condition is the alar hypoplasia with an overhang of the nasal tip. The “beak-like” nose (psittichorhina) in Johanson-Blizzard syndrome is distinctive, and is so conspicuous that it has been identified at 21 weeks of gestation using ultrasonography (Auslander et al, 1999).

What characterizes alar hypoplasia in Johanson-Blizzard syndrome? In this study we have characterized its morphology using direct anthropometry as a worked example of this quantitative approach. Using objective measures and a normative dataset that includes measurements in early infancy, we describe this distinctive morphology of the nose.

CASE REPORT

M.B., a male, was born at 36 weeks of gestation, the last eight weeks of which were complicated by polyhydramnios. At birth he had respiratory distress for which he was intubated and transferred to Massachusetts General Hospital for further evaluation.

At initial evaluation, he was hypotonic. Ultrasound examination at 48 hours of age showed calcification of the inferior vena cava and papillary nephrocalcinosis. At four weeks of age he developed chronic seborrheic dermatitis that was refractory to treatment with hydrocortisone cream therapy. Thereafter, he developed chronic diarrhea. A small bowel biopsy showed villous atrophy and superficial epithelial necrosis; no granulomas, parasites, or viral inclusions were observed. The large bowel biopsy showed mild acute colitis. The auditory brainstem response at 7 weeks of age appeared normal, but MRI and CT scans of the head showed progressive cortical atrophy consistent with an hypoxic encephalopathy. Routine chromosome analysis and amino and organic acid screenings in blood and urine identified no abnormalities. His muscle tone improved with time; no abnormalities were identified in a muscle biopsy or EMG.

At birth, his head circumference was 365 mm (90th percentile), but by 18 weeks of age it had grown to only 385 mm (< 3rd percentile). He showed no weight gain, despite intravenous alimentation, and remained ventilator-dependent until his death at 23 weeks of age. No autopsy was performed.

The thyroid testing included these findings: slightly lower-than-normal total T4 Thyroxine 4.2 µg/dL (normal 4.5-12.5 µg/dL), indicative of mild hypothyroidism; normal total T3 92 ng/cl (normal 75-195 ng/cl); and normal TSH 1.5 micro µIU/L.

During the course of treatment, the patient had endotracheal intubation intermittently until he had a tracheostomy (at 14 weeks). There was no nasal intubation that might account for nasolabial anomalies. Re-examination four weeks later (once the tape covering his nose was removed) led to the initial recognition that he had bilateral, symmetrical hypoplasia of the alae nasi (see Figure 1). The diagnosis of Johanson-Blizzard syndrome was consistent with this craniofacial phenotype.

An anthropometric examination of the patient at 22 weeks of age was performed at bedside.

ANTHROPOMETRIC METHODS

An abbreviated dysmorphology diagnostic protocol, based on the anthropometric methods of Deutsch and Farkas (1994), was administered. A large normative database permits computation of standard (z-) scores adjusted for age, sex, and ethnicity (Farkas, 1994). Since the publication of this atlas, the age-range in the database has been expanded to include infants. These norms permit assessment of dysmorphology on a continuous scale, ranging from minor to major physical anomalies (Deutsch and Farkas, 1994; Farkas et al, 1983a; Farkas et al, 1983b).

Measurements were chosen to assess the nasal hypoplasia described as a cardinal feature of Johanson-Blizzard syndrome. The following anthropometric landmarks were identified for the nasolabial region: alare (**al**), subnasale (**sn**), nasion (**n**), pronasale (**prn**), gnathion (**gn**), zygion (**zy**), and gonion (**go**) (defined by Farkas, 1994). The alare is the most lateral point on the alar contour, and the subnasale is the midpoint of the inflection point of the columella base, and the pronasale is the most protrusive point of the apex nasi. The nasion is the point at the midline of the nasal root and the underlying nasofrontal suture. The **al**, **sn**, and **prn** are shown for this patient in Figure 1. The zygion and the gonion are the most lateral points on the zygomatic arch and the mandible, respectively. Linear distances among landmarks were measured using calipers (GPM, Switzerland), and the nasolabial angle using an angle-meter (Mitsotomo, Japan). Anomalies were defined operationally as angles or as proportions of linear dimensions. For example, the proportion

$$[(\text{sn} - \text{prn}) \times 100] / [\text{al}(\text{rt}) - \text{al}(\text{lt})]$$

represents the protrusion of the nose (between the subnasale and the pronasale), expressed as a function of nose width (between the left and right alare), multiplied by a constant of 100, a common convention in medical anthropometry (Farkas, 1994; Farkas and Munro, 1987). The nasal height is expressed as a function of the facial height and the maxillary width, and the proportion of mandibular and maxillary widths was also computed. These proportions were expressed as z-scores, based on age- and gender-specific norms for Caucasian males (Farkas, 1994).

FINDINGS

These values and the two-tailed p-values associated with these z-scores are presented in Table 1. All of these z-scores exceeded the |1.5| cut-off point often used to operationally define anomalies, with most of them greater than 2 standard deviations below the mean.

We found that the nasal alae did not appear to be normally curved. There was pronounced alar curvature hypoplasia in this infant, contributing not only to a narrow alar width but also a beak-like appearance, with a pronounced overhang of the nasal tip over the philtrum. The nasal protrusion relative to nasal width was large, and the nasolabial angle was strikingly decreased, operationally defining the relative nasal protrusion and overhang, respectively.

It was also noteworthy that the nose height was markedly decreased relative to both facial height and maxillary width. Moreover, the mandibular width was very narrow, relative to maxillary width.

DISCUSSION

The patient's anthropometric measurements bore out the visual impression of markedly hypoplastic nasal alae. The lateral width of the alae nasi at their insertion points was

extremely small relative to both the protrusion of the columella and the philtrum. Narrowing of the mandible and shortening of the nasal bridge were pronounced, as well.

This anthropometric approach may provide a useful adjunct to clinical impression in the diagnosis of Johanson-Blizzard syndrome, as it has been in a variety of other craniofacial syndromes (Deutsch and Farkas, 1994; Farkas and Deutsch, 1996; Farkas et al, 2002; Farkas and Posnick, 1989; Kolar et al, 1988).

Hypoplasia of the alae nasi has been observed in individuals with abnormalities of chromosome 15, but who were not considered to have Johanson-Blizzard syndrome. These included microdeletion of 15q21 (Liehr et al, 2003) and interstitial deletion 15q derived from a paternal insertion (5;15)(q31.3;q21.1q22.1) (Yip et al, 1987). Forms of alar hypoplasia have also been seen in other syndromes as well, including Hutchinson-Gilford progeria (Wisuthsarewong and Viravan, 1999), Seckel (Rajamani et al, 2005), van den Ende-Gupta (Schweitzer et al, 2003), and Werner (Samantray et al, 1977). It would be of potential interest to determine the degree to which quantitative dysmorphology findings in Johnson-Blizzard syndrome are distinctive from this spectrum of disorders. The quantitative measures discussed here may find application in discriminating among these forms of hypoplastic nasal alae.

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Figure 1. This illustrates selected anthropometric landmarks used delineating the alar region. The measurements among landmarks and their standardized scores are summarized in Table 1.

Table 1

Anthropometric assessment of nasolabial morphology (Measurement and operational definition, patient z-score, p-value)

Measurement and operational definition	z-score	p
$[(\mathbf{sn} - \mathbf{prn}) \times 100] / [\mathbf{al}(\text{rt}) - \mathbf{al}(\text{lt})]$ nasal protrusion relative to nasal width	+1.70	.045
nasolabial angle angle between columella and philtrum	-2.38	.009
$[(\mathbf{go}(\text{rt}) - \mathbf{go}(\text{lt})) \times 100] / [\mathbf{zy}(\text{rt}) - \mathbf{zy}(\text{lt})]$ mandibular width relative to maxillary width	-2.18	.015
$[(\mathbf{n} - \mathbf{sn}) \times 100] / [(\mathbf{n} - \mathbf{gn})]$ nasal height relative to facial height	-2.08	.019
$[(\mathbf{n} - \mathbf{sn}) \times 100] / [\mathbf{zy}(\text{rt}) - \mathbf{zy}(\text{lt})]$ nasal height relative to maxillary width	-3.24	.001