Facial morphometry of Ecuadorian patients with growth hormone receptor deficiency/Laron syndrome

G B Schaefer, A L Rosenbloom, J Guevara-Aguirre, E A Campbell, F Ullrich, K Patil, J L Frias

Abstract

Facial morphometry using computerised image analysis was performed on patients with growth hormone receptor deficiency (Laron syndrome) from an inbred population of southern Ecuador. Morphometrics were compared for 49 patients, 70 unaffected relatives, and 14 unrelated persons. Patients with growth hormone receptor deficiency showed significant decreases in measures of vertical facial growth as compared to unaffected relatives and unrelated persons with short stature from other causes. This report validates and quantifies the clinical impression of foreshortened facies in growth hormone receptor deficiency.

(J Med Genet 1994;31:635-639)

A syndrome of severe growth failure with facial features that resembled growth hormone (GH) deficiency, but with high levels of GH in the serum, was described initially in 1966 by Laron *et al.*¹ Affected subjects were Oriental Jews from largely consanguineous unions.² Administration of exogenous GH failed to stimulate somatomedin (IGF-I) production,³ indicating a defect in cellular response to GH which was eventually proven to be the result of failure of the GH receptor.^{4,5} Some 180 patients have been described with growth hormone receptor deficiency (GHRD)/Laron syndrome, of whom all but a few are of Mediterranean or Middle Eastern origin, and nearly 70% are semitic. These numbers include 65 patients from a small region (120 km diameter) of southern Ecuador who are inbred white Spaniards with names that indicate that they are conversos, Jews who became Catholics during the Inquisition.⁶

Affected persons have been described as having "acromicria", defined as small hands, feet, and faces. Craniofacial disproportion was described and quantified as an abnormal difference between the biparietal and bicondylar diameter compared to normal.⁷ We questioned whether the face might appear small because it is proportionate to body size while the more normal head appears macrocephalic (fig 1).⁸ This craniofacial disproportion is particularly striking in young children, who often also have the "setting sun sign", the appearance of sclera above the iris. These findings may be so striking that hydrocephalus is suspected.

There has been recent interest in the application of quantitative facial morphometrics techniques in clinical genetics, resulting primarily

from two factors: (1) dramatic improvement in microcomputer technology producing affordable, readily available processing of extremely complex algorithms, (2) refinement, adaptation, and simplification of previous morphometric techniques with a great reduction in systematic errors,⁹⁻¹³ and (3) the availability of large age and sex matched normative data.^{14,15} Such techniques have been applied to a variety of specific clinical entities to answer questions about craniofacial characteristics in conditions such as Crouzon syndrome,¹⁶ fetal alcohol syndrome,¹⁷ X linked hypohidrotic ectodermal dysplasia,¹⁸ Angelman syndrome,¹⁹ in utero exposure to marijuana, ethanol, and cocaine,²⁰ cleft lip and palate,²¹ Down's syndrome,²² hemifacial microsomia,²³ Prader-Willi syndrome,²⁴ fragile X syndrome,²⁵ Treacher Collins syndrome,²⁶ and Apert syndrome.²⁷ We report the results of facial morphometric analysis of 49 Ecuadorian patients with GHRD.

Examination of photographs of patients with GHRD suggested that their abnormality was not in overall facial size, but in the vertical dimension and that this was the principal feature giving the appearance of craniofacial disproportion (fig 1). This study was designed to quantify facial dimensions and analyse head size data in these patients.

Materials and methods

SUBJECTS

Probands with GHRD included 15 males and 34 females proven to be homozygous for the codon 180 mutation of the GHR gene.²⁸ Their mean age was 22.3 years. Sixty-nine of the first and second degree relatives (24 male, 45 female, mean age 23.2 years) and 16 unrelated Ecuadorian patients with other causes of short stature (eight male, eight female, mean age 14.2 years) served as controls. Most of the latter group had GH deficiency which had been under treatment with GH injections.

CRANIAL MEASUREMENT

Head circumference measurements of probands were compared to standards for chronological age, osseous maturation (in those under 18 years of age),²⁹ height, and age, and were expressed as standard deviation scores (SDS).³⁰ For this portion of the study, all head circumference data were analysed, comprising measurements from 60 probands. Statistical comparisons were made using single tailed tests.

Department of
Pediatrics, University
of Nebraska Medical
Center, Omaha,
Nebraska, USA
G B Schaefer
E A Campbell
J L Frias

Department of
Pediatrics, University
of Florida, Gainesville,
Florida, USA
A L Rosenbloom

Institute for
Endocrinology,
Metabolism, and
Reproduction, Quito,
Ecuador
J Guevara-Aguirre

Department of
Biostatistics,
University of
Nebraska Medical
Center, Omaha,
Nebraska, USA
F Ullrich
K Patil

Correspondence to
Dr Schaefer, Department of
Pediatrics, Meyer
Rehabilitation Institute,
University of Nebraska
Medical Center,
600 S 42nd Street, Omaha,
NE 68198-5430, USA.

Received 8 October 1993
Revised version accepted for
publication 24 March 1994

Figure 1 Photographs taken at the same distance of a 52 year old patient (upper right), her 76 year old unaffected mother (upper left), a 9 year old patient (lower right), and his unaffected 11 year old brother (lower left).

Figure 2 Clinical landmarks used in facial morphometrics in this study (after Claren et al¹⁷).

PHOTOGRAPHY

All subjects were photographed with a single lens reflex 35 mm camera using a 135 mm lens at a distance of exactly 2.4 m. Frontal and lateral pictures with no detectable rotation were printed to scale as standard 5 × 7 glossy prints.

COMPUTERISED FACIAL MORPHOMETRICS

Photographic images were input into the computer via a high resolution black and white video camera. Images were captured and digitised using a DT 2851 Frame Grabber and DT 2858 auxiliary math coprocessor board (Data Translation, Wellesly, MA) and Image ProII (Media Cybernetics, Silver Spring, MD) software. Morphometrics were accomplished with Image Measure IP/2500 add in morphometry module (MicroScience, Federal Way, WA).

Analysis of facial features was carried out using the triangulation methods developed by Bookstein.^{31 32} We used the 23 landmark points defined by Claren et al^{17 20} and an additional five points that we chose based upon our suspicion of areas of the face that might have altered development in our particular patients (fig 2).

In brief, the triangulation method uses an internal relative scale. Two strategic reference points are chosen (for example, points 1 and 4, fig 2) and digitised. The first point is assigned the value of the origin (X = 0, Y = 0), the second point is given the value X = 0, Y = 1. Thereafter, the digitised X and Y coordinates of any other point represent a relative distance and direction from the established axis. These methods are detailed elsewhere.^{17 20 31 32} Because the triangulation method uses a relative scale, most potential sources of non-random measurement variability (for example, slight differences in distance and angle of the photographic line) are trivialised. In fact, in our replicate studies the inter- and intra-investigator variability was consistently less than 0.5%.

STATISTICAL ANALYSIS

Morphometry of each landmark (triangle) was compared between the three groups by use of multivariate analysis of variance. When this analysis showed significant differences, a contrast method was used to assess which of the coordinates, X or Y or both, differed pairwise between the groups. These results were also examined with Scheffe's test. The statistical significance was noted at p < 0.01.

Results

CRANIAL SIZE (FIG 3)

The head circumference SDS means for chronological age and height age were separately determined for children (under 18 years, n = 30) and adults (n = 30). There were similar means for chronological age in these two groups (−3.1 (SD 1.2), −3.3 (SD 1.7)). Their means can be compared to the statural SDS mean of −8.4 (SD 1.5), suggesting greater

Figure 3 Mean head circumference standard deviation score (SDS) for chronological age, bone age, and height age in 30 children (<18 years of age) (open bars) and for chronological and height age in 30 adults (shaded bars) with growth hormone receptor deficiency. Extensions from the bars represent standard error. Child and adult means for chronological age are not different, but SDS means for height age differed significantly ($p<0.01$).

Facial morphometric comparisons between patients with GHRD (group 3, $n=49$), unaffected relatives (group 2, $n=69$), and unrelated persons (group 1, $n=16$)

Triangle	Group 3			v	group 2			v	Group 3			v	group 1		
	Coordinate	I/D	p		Coordinate	I/D	p		Coordinate	I/D	p		Coordinate	I/D	p
1- 4-12	Y	D	0.0001						Y	D	0.0001				
1- 4-24	Y	D	0.0001						Y	D	0.0001				
1- 4-25	Y	D	0.0001						Y	D	0.0001				
1- 4-26	Y		NS						Y	D	0.0057				
9-10-26	Y	D	0.0064											NS	
27-28-12	Y	D	0.0002											NS	
27-28-24	Y	D	0.0001						Y	D	0.001				
27-28-25	Y	D	0.0019								NS				
6- 7-24			NS						Y	D	0.0093				
6- 7-25	Y	D	0.0001						Y	D	0.0001				
5- 8-24	Y	D	0.00019								NS				
5- 8-25	Y	D	0.0001								NS				
14-18-23			NS						Y	I	0.0019				
14-19-18	X	D	0.002						X	D	0.002				
22-19-18	X	D	0.00059						X	D	0.00059				
22-17-14	Y	D	0.0001						Y	D	0.0001				
22-17-14	X	D	0.0008						X	D	0.0008				

I = increased, D = decreased.

deviation from normal in stature than for head circumference. Head circumference SDS for height age, however, was normal for both children (+0.5 (SD 1.3)) and adults (-0.4 (SD 1.4)), not reflecting the statural versus head circumference SDS that would have dictated a substantially large head circumference for height age. Children’s mean head circumference SDS for height age was significantly greater than that of the adults. In the children, the mean head circumference SDS for bone age (-1.8 (SD 1.2)) was intermediate between the means for chronological age and height age, reflecting the relative advance of bone age compared to height age in these patients.^{6,33}

FACIAL MORPHOMETRICS
We initially compared morphometric data

between affected subjects with GHRD (group 3) and unaffected first or second degree relatives (group 2). It was particularly attractive initially to compare these two groups as they had nearly identical age distributions, the same 2:1 female predominance (as previously reported), and the ability to use relatives to correct for any familial facial differences. When the two groups were compared, numerous strongly significant differences were noted (table). All of these differences have in common a decrease in the absolute vertical dimension of the entire face, most impressively in the midface region. When patients in group 3 were compared to those in group 1 (unrelated subjects with short stature from other causes) the findings were similar to comparisons with group 2 (table). Again, the findings were suggestive of a decreased vertical dimension of the entire face in patients with GHRD.

Comparison of unaffected relatives (group 2) to unrelated controls with other causes of short stature (group 1) showed only two significant differences. Group 1 as compared to group 2 had an increase in the Y coordinate of triangle 14-16-17 ($p=0.0001$) and a decrease in the Y of triangle 14-19-18 ($p=0.001$). Neither of these findings relates to the changes noted in the patients with GHRD, which supports the notion that the findings above are clinically significant.

Discussion

These data (table) show a striking decrease in vertical facial growth in patients with GHRD. When patients with GHRD (group 3) are compared to their unaffected relatives (group 2), all measures of vertical facial dimensions, with the exception of triangle 6-7-24 (fig 2) were significantly reduced. The measurements for this triangle bordered on statistical significance ($p=0.07$) but there was a relatively large variance in their parameters which negated significance. It is not certain why the dimensions of this particular triangle should show such a large degree of variance. One possible explanation could be that the reference line (6-7), a measure of inner canthal distance, simply has a naturally occurring large degree of variance within this kinship. Regardless, the clear pattern from these data is that vertical facial growth is markedly foreshortened in patients with GHRD.

When we compared patients with GHRD to unrelated persons (group 1) with short stature on the basis of other problems (mainly GH deficiency) we found similar results (table). It is interesting that triangle 6-7-24 was significantly different in this comparison, again suggesting some inherent degree of variability in the kinship studied. Five measures (triangles 9-10-26, 27-28-25, 27-28-12, 5-8-25, and 5-8-24), which were significantly different when group 3 (patients with GHRD) was compared to group 2 (unaffected relatives), were not different when groups 3 and 1 were compared. This may be in part because of the fact that groups 2 and 3 have similar mean ages and a 2:1 female to male ratio, while group 1 had a smaller mean age and a 1:2

male to female ratio. Comparison of group 2 to group 1 showed no differences in vertical facial dimensions, however. As mentioned previously, group 1 consisted largely of patients with GH deficiency; all patients in this group had a height of less than 2 SDS from the age appropriate mean, whereas group 2 all had normal stature. Thus, the difference seen in our patients with GHRD cannot be explained on the basis that they simply had a shorter total body height.

We have previously noted that head circumference SDS for chronological age was much less abnormal than height SDS in persons with GHRD in Ecuador. This discrepancy was thought to contribute to the appearance of a large cranium and small facies. Cranial circumference is, however, normal for height age in these patients, indicating that the comparison of head circumference SDS and height SDS is inappropriate because of the different magnitudes of growth in head size and body length. For example, there is a 12% increase in head circumference from 2 years to maturity in males while there is a greater than 100% increase in stature during this time. Thus, the head is not relatively large, but normal for body size. The impression of macrocephaly, particularly in young children, appears to reflect the reduction in vertical dimension of the face, the hypoplastic nasal bridge, and the normal width and height of the forehead. We found that the children did have relatively larger heads for height age compared to affected adults, consistent with clinical impressions of head size seeming greater in the children, relative to stature.

We have previously noted that arm span and lower segment are reduced in adults with GHRD.^{8,33,34} Children had normal arm spans and ratios of upper to lower body segments. The development of the facial bones may reflect maturational delay in the children and the disproportion in the long bones in adults. Growth of the skull would be expected to respond to brain growth with, however, delay in closure of the fontanelles which is a feature of GHRD. The fact that head size is proportionate to stature thus indicates an important influence of the GH-GH receptor-IGF-I axis on overall brain size. This does not, however, appear to be an influence of sufficient magnitude to affect intelligence.³⁴

The availability of recombinant human IGF-I has made it possible to initiate trials of therapy of children with GHRD. The effects of this therapy on craniofacial growth will be of great interest.

- 1 Laron Z, Pertzalan A, Mannheimer S. Genetic pituitary dwarfism with high serum concentration of growth hormone – a new inborn error of metabolism? *Isr J Med Sci* 1966;2:152–5.
- 2 Pertzalan A, Adam A, Laron Z. Genetic aspects of pituitary dwarfism due to absence or biological inactivity of growth hormone. *Isr J Med Sci* 1968;4:895–900.
- 3 Laron Z, Pertzalan A, Karp M, Kowald-Silbergeld A, Doughaday WH. Administration of growth hormone to patients with familial dwarfism with high plasma immunoreactive growth hormone: measurement of sulfation factor, metabolic and linear growth responses. *J Clin Endocrinol Metab* 1971;33:332–42.
- 4 Eshet R, Laron Z, Pertzalan A, Arnon R, Dintzman M. Defect of human growth hormone receptors in the liver of two patients with Laron-type dwarfism. *Isr J Med Sci* 1984;20:8–11.
- 5 Godowski PJ, Leung DW, Meacham LR, et al. Characterization of the human growth hormone receptor gene and demonstration of a partial gene deletion in two patients with Laron-type dwarfism. *Proc Natl Acad Sci USA* 1989;86:8083–7.
- 6 Rosenbloom AL, Guevara-Aguirre J, Fielder PJ, et al. Growth hormone receptor deficiency/Laron syndrome in Ecuador: clinical and biochemical characteristics. In: Laron Z, Parks JS, eds. *Lessons from Laron syndrome (LS) 1966–1992*. Pediatric and Adolescent Endocrinology Vol 24. Basel: Karger, 1993:34–52.
- 7 Laron Z. Laron-type dwarfism (hereditary somatomedin deficiency): a review. In: Frick H, von Harnack GA, Kochsiek K, Martini GA, Prader A, eds. *Advances in internal medicine*. Heidelberg: Springer-Verlag, 1984:117–50.
- 8 Guevara-Aguirre J, Rosenbloom AL, Vaccarello MA, et al. Growth hormone receptor deficiency (Laron syndrome): clinical and genetic characteristics. *Acta Paediatr Scand (Suppl)* 1991;377:96–103.
- 9 DiLiberti JH, Olson DP. Photogrammetric evaluation in clinical genetics: theoretical considerations and experimental results. *Am J Med Genet* 1991;39:161–6.
- 10 DiLiberti JH. Application of D'Arcy Thompson's coordinate transformation approach to clinical genetics photographs using image processing techniques. *J Med Genet* 1991;28:472–6.
- 11 Ward RE. Facial morphology as determined by anthropometry: keeping it simple. *J Craniofac Genet* 1989;9:45–60.
- 12 Thomas IT, Hintz RJ, Frias JL. New methods for quantitative and qualitative facial studies: an overview. *J Craniofac Genet* 1989;9:107–11.
- 13 Matteson SR, Bechtold W, Phillips C, Staab EV. A method for three dimensional image reformation for quantitative cephalometric analysis. *J Oral Maxillofac Surg* 1989;47:1053–61.
- 14 Farkas LG, Cheung G. Facial asymmetry in healthy North American Caucasians. An anthropometrical study. *Angle Orthod* 1981;51:70–7.
- 15 Farkas LG, Kolar JC. Anthropometrics and art in the aesthetics of women's faces. *Clin Plast Surg* 1987;14:599–616.
- 16 Richtsmeier JT, Lele S. Analysis of craniofacial growth in Crouzon syndrome using landmark data. *J Craniofac Genet Dev Biol* 1990;10:39–62.
- 17 Claren SK, Sampson PD, Larsen J, et al. Facial effects of fetal alcohol exposure: assessment by photographs and morphometric analysis. *Am J Med Genet* 1987;26:651–66.
- 18 Saksena SS, Bixler D. Facial morphometrics in the identification of X-linked hypohidrotic ectodermal dysplasia. *Am J Med Genet* 1990;35:105–14.
- 19 Frias JL, Schaefer GB, Gray B, Williams CA. Morphometric analysis of facial features in patients with Angelman syndrome. *Proceedings and abstracts of the 12th annual David W Smith workshop on malformation and morphogenesis*. Lake Arrowhead, California, 1991.
- 20 Astley SJ, Claren SK, Little RE, Sampson PD, Daling JR. Analysis of facial shape in children gestationally exposed to marijuana, alcohol, and/or cocaine. *Pediatrics* 1992;89:67–77.
- 21 Farkas LG, Hajnis K, Posnick JC. Anthropometric and anthroposcopic findings of the nasal and facial region in cleft patients before and after primary lip and palate repair. *Cleft Palate Craniofac J* 1993;30:1–12.
- 22 Farkas LG, Posnick JC, Hreczko T. Anthropometry of the head and face in 95 Down syndrome patients. *Prog Clin Biol Res* 1991;373:53–97.
- 23 Farkas LG, Ros RB, James J. Anthropometry in lateral facial dysplasia: the bilateral form. *Cleft Palate J* 1977;14:41–51.
- 24 Meaney FJ, Butler MG. The developing role of anthropologists in medical genetics: anthropometric assessment of the Prader-Labhart-Willi syndrome as an illustration. *Med Anthropol* 1989;10:247–53.
- 25 Butler MG, Allen A, Haynes JL, Singh DN, Watson MS, Brog WR. Anthropometric comparison of mentally retarded males with and without the fragile-X syndrome. *Am J Med Genet* 1991;38:260–8.
- 26 Kolar JC, Munro IR, Farkas LG. Anthropometric evaluation of dysmorphology in craniofacial anomalies: Treacher-Collins syndrome. *Am J Phys Anthropol* 1987;74:441–51.
- 27 Farkas LG, Kolar JC, Munro IR. Craniofacial disproportions in Apert's syndrome: an anthropometric study. *Cleft Palate J* 1985;22:253–65.
- 28 Berg MA, Guevara-Aguirre J, Rosenbloom AL, Rosenfeld RG, Francke U. Mutation creating a new splice site in the growth hormone receptor genes of 37 Ecuadorian patients with Laron syndromes. *Hum Mutat* 1992;1:24–34.
- 29 Greulich WW, Pyle SI. *Radiographic atlas of skeletal development of the hand and wrist*. 2nd ed. Stanford: Stanford University Press, 1959.
- 30 Nellhaus G. Head circumferences from birth to eighteen years. Practical composite international and interracial graphs. *Pediatrics* 1968;41:106–14.
- 31 Bookstein FL. The geometry of craniofacial growth invariants. *Am J Orthod* 1983;83:221–34.
- 32 Bookstein FL. Describing a craniofacial anomaly: finite

- elements and the biometrics of landmark locations. *Am J Phys Anthropol* 1987;74:495–509.
- 33 Rosenbloom AL, Guevara-Aguirre JG, Rosenfeld RG, Fielder PJ. The little women of Loja – growth hormone-receptor deficiency in an inbred population of southern Ecuador. *N Engl J Med* 1990;323:1367–74.
- 34 Guevara-Aguirre J, Rosenbloom AL, Fiedler PJ, Diamond FB Jr, Rosenfeld RG. Growth hormone receptor deficiency in Ecuador: clinical and biochemical phenotype in two populations. *J Clin Endocrinol Metab* 1993;76:417–23.