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

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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 faces in growth hormone receptor deficiency.

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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. Affected subjects were Oriental Jews from largely consanguineous unions. Administration of exogenous GH failed to stimulate somatotropin (IGF-I) production, indicating a defect in cellular response to GH which was eventually proven to be the result of failure of the GH receptor. 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 they are conversos, Jews who became Catholics during the Inquisition. 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. We questioned whether the face might appear small because it is proportionate to body size while the more normal head appears macrocephalic (fig 1). 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, and (3) the availability of large age and sex matched normative data. Such techniques have been applied to a variety of specific clinical entities to answer questions about craniofacial characteristics in conditions such as Crouzon syndrome, fetal alcohol syndrome, X linked hypohidrotic ectodermal dysplasia, Angelman syndrome, in utero exposure to marijuana, ethanol, and cocaine, cleft lip and palate, Down’s syndrome, hemifacial microsomia, Prader-Willi syndrome, fragile X syndrome, Treacher Collins syndrome, and Apert syndrome. 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. 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), height, and age, and were expressed as standard deviation scores (SDS). 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.
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 ProI (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. We used the 23 landmark points defined by Claren et al 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 \( X = 0, Y = 1 \). Therefore, 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. 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 \([-3.1 \text{ (SD 1.2)}, -3.3 \text{ (SD 1.7)}]\). Their means can be compared to the statural SDS mean of \(-8.4 \text{ (SD 1.5)}\), suggesting greater

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

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

<table>
<thead>
<tr>
<th>Triangle</th>
<th>Group 3 v</th>
<th>Group 2</th>
<th>Group 3 v</th>
<th>Group 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coordinate</td>
<td>l/D</td>
<td>p</td>
<td>Coordinate</td>
</tr>
<tr>
<td>1-4-12</td>
<td>Y D 0.0001</td>
<td>NS</td>
<td>NS</td>
<td>Y D 0.0001</td>
</tr>
<tr>
<td>1-4-24</td>
<td>Y D 0.0001</td>
<td>NS</td>
<td>NS</td>
<td>Y D 0.0001</td>
</tr>
<tr>
<td>1-4-25</td>
<td>Y D 0.0001</td>
<td>NS</td>
<td>NS</td>
<td>Y D 0.0001</td>
</tr>
<tr>
<td>1-4-26</td>
<td>Y D 0.0001</td>
<td>NS</td>
<td>NS</td>
<td>Y D 0.0001</td>
</tr>
<tr>
<td>9-10-26</td>
<td>Y D 0.0064</td>
<td>NS</td>
<td>NS</td>
<td>Y D 0.0001</td>
</tr>
<tr>
<td>27-28-12</td>
<td>Y D 0.0002</td>
<td>NS</td>
<td>NS</td>
<td>Y D 0.001</td>
</tr>
<tr>
<td>27-28-24</td>
<td>Y D 0.001</td>
<td>NS</td>
<td>NS</td>
<td>Y D 0.001</td>
</tr>
<tr>
<td>27-28-25</td>
<td>Y D 0.0019</td>
<td>NS</td>
<td>NS</td>
<td>Y D 0.0019</td>
</tr>
<tr>
<td>6-7-24</td>
<td>Y D 0.0001</td>
<td>NS</td>
<td>NS</td>
<td>Y D 0.0001</td>
</tr>
<tr>
<td>6-7-25</td>
<td>Y D 0.0001</td>
<td>NS</td>
<td>NS</td>
<td>Y D 0.0001</td>
</tr>
<tr>
<td>5-8-24</td>
<td>Y D 0.0001</td>
<td>NS</td>
<td>NS</td>
<td>Y D 0.0001</td>
</tr>
<tr>
<td>5-8-25</td>
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<td>NS</td>
<td>NS</td>
<td>Y D 0.0001</td>
</tr>
<tr>
<td>14-18-23</td>
<td>X D 0.002</td>
<td>NS</td>
<td>NS</td>
<td>X D 0.002</td>
</tr>
<tr>
<td>14-19-18</td>
<td>X D 0.0009</td>
<td>X D 0.0009</td>
<td>X D 0.0009</td>
<td>X D 0.0009</td>
</tr>
<tr>
<td>22-19-18</td>
<td>X D 0.0001</td>
<td>X D 0.0001</td>
<td>X D 0.0001</td>
<td>X D 0.0001</td>
</tr>
<tr>
<td>22-17-14</td>
<td>X D 0.0008</td>
<td>X D 0.0008</td>
<td>X D 0.0008</td>
<td>X D 0.0008</td>
</tr>
</tbody>
</table>

I = increased, D = decreased.

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

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.

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. 633

FACIAL MORPHOMETRICS

We initially compared morphometric data
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 circum-
ference 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 circum-
ference 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 magni-
tudes 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 hypoplas-
tic nasal bridge, and the normal width and
height of the forehead. We found that the
diabetes did have relatively larger heads for
height age compared to affected adults, consist-
tent with clinical impressions of head size seem-
ing greater in the children, relative to stature.

We have previously noted that arm span and
lower segment are reduced in adults with
GHRD.3,8,13 Children had normal arm spans and
ratios of upper to lower body segments.
The development of the facial bones may reflect
cumulative delay in the children and the dis-
proportion 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 growth. This does not, however, appear to
be an influence of sufficient magnitude to affect
intelligence.3,4

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

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