Growth failure and pituitary function in CHARGE and VATER associations

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Abstract
Growth failure and anterior pituitary dysfunction are clinical features of the CHARGE and VATER associations. This study investigated pituitary dysfunction as a potential cause of poor growth in a series of four and three patients with the CHARGE and VATER associations, respectively, who had height standard deviation scores (SDS) less than –2. Five of the seven patients had associated subnormal growth velocity SDS. Patients were investigated with a combination of dynamic and basal endocrine tests. All patients were found to be normonatraemic and to have normal basal thyrotroph and stimulated corticotroph function. The one peripubertal patient had evidence of biochemical gonadotroph dysfunction. Although two patients had marginally low stimulated serum growth hormone responses to glucagon stimulation testing, this was associated with either normal growth velocity or normal serum insulin-like growth factor binding protein 3 (IGFBP-3) concentrations. Thus, somatotroph dysfunction could not be demonstrated unequivocally in any patient. Poor childhood linear growth in the CHARGE and VATER associations does not appear to be associated with pituitary dysfunction.

Keywords: CHARGE; VATER; growth; pituitary function

The CHARGE and VATER associations are characterised by growth failure and pleotropic congenital malformation.1–5 The acronym, CHARGE, describes the diagnostic features: colobomata of the eyes, heart defects, choanal atresia, retardation of growth, genital hypoplasia, and ear abnormalities.6–7 While the acronym, VATER, stands for the diagnostic features: vertebral defect, anal atresia, tracheo-oesophageal fistulae, oesophageal atresia and radial/renal dysplasia.8 Clinically there appears to be some phenotypic overlap between the two associations,9–11 especially with regard to associations of midline malformation and poor growth. Affected children may have endocrine dysfunction, with hypogonadotropic hypogonadism being reported frequently in patients with the CHARGE association,12 and occasionally in patients with the VATER association.13 There have also been single case reports of hypopituitarism and athyrosis being associated with the CHARGE association.14–15 To date, there has been no documented systematic inquiry as to possible endocrine causes of growth failure in children with either the CHARGE or VATER associations. We have had the opportunity to study this issue in a series of patients with the CHARGE or VATER associations.

Patients
We analysed endocrine function in four patients (three boys and one girl) with the CHARGE association, aged 1.6–5.2 years, and three patients (one boy and two girls) with the VATER association, aged 2.1–13.5 years (table 1). All patients had been referred to the endocrine clinic at Great Ormond Street Hospital for Sick Children NHS Trust for investigation of short stature (height standard deviation score (SDS) less than –2), with or without genital hypoplasia. The diagnoses of CHARGE and VATER associations had been made by clinical geneticists. The diagnosis of CHARGE association was made when four or more of the diagnostic features indicated above were present. Additional phenotypic features included: tracheo-oesophageal atresia in two patients, hearing loss in all four patients, microphthalmia in two patients, and cleft palate in one patient (table 1). The diagnosis of VATER association was made when three or more of the diagnostic features indicated above were present. Additional features in the VATER group included: cardiac defects in one patient, malrotation in one patient, and cleft palate in one patient (table 1). All respiratory, cardiac, and gastrointestinal anomalies in both CHARGE and VATER patient groups were surgically corrected within the 1st year of life.

Methods
Patients were examined in an outpatient endocrine clinic at Great Ormond Street Hospital. Auxiological data were assessed using the techniques described by Tanner et al.16–17 Growth velocities were calculated over a six month period immediately before endocrine testing. Dynamic pituitary tests were performed according to the protocols outlined by Hughes.18 Somatotroph and corticotroph function were assessed using glucagon (0.1 mg/kg intravenous) stimulation testing and measuring peak concentrations of serum growth hormone (GH) and serum cortisol. Somatotroph function was assessed further with simultaneous measures of serum insulin-like growth factor 1 (IGF-I) and IGF binding factor 3 (IGFBP-3). Basal thyroid function (serum thyroxine and thyroid stimulating hormone (TSH) concentrations) were measured in all patients. One patient, who was of appropriate age (13.5 years), had gonado-
troph function assessed according to peak serum luteinising hormone (LH) concentrations after luteinising hormone releasing hormone (LHRH) stimulation (2.5 µg/kg).

All biochemical assays were performed by the department of chemical pathology at Great Ormond Street Hospital. Growth hormone concentrations were assessed using an immunoradiometric assay (NIETRA) and serum cortisol measured using fluorescence polarisation immunoassay (TDx/TDxFLx cortisol assay; Abbott Laboratories, Abbott Park, Illinois, USA). IGF-I and IGFBP-3 concentrations were measured using the active extraction method (Diagnostic Systems Laboratories, Webster, Texas, USA). LH and TSH were measured using a microparticle enzyme immunoassay (IMx ultrasensitive hTSH assay, IMx Instruments, Webster, Texas, USA). LH and TSH were measured using the active extraction method (Diagnostic Systems Laboratories, Webber, Texas, USA). IGF-I and IGFBP-3 concentrations were measured using a microparticle enzyme immunoassay (IMx ultrasensitive hTSH assay, IMx Instruments, Webster, Texas, USA). LH and TSH were measured using a microparticle enzyme immunoassay (IMx ultrasensitive hTSH assay, IMx Instruments, Webster, Texas, USA). IGF-I and IGFBP-3 concentrations were measured using a microparticle enzyme immunoassay (IMx ultrasensitive hTSH assay, IMx Instruments, Webster, Texas, USA).

**Results**

**CLINICAL DETAILS**

Despite feeding difficulties and assisted enteral feeding in all patients (either by nasogastric or percutaneous feeding tubes) all patients were well nourished with normal body mass indices for age (data not shown) at the time of initial assessment. The two patients with renal anomalies were normotensive and had normal serum creatinine concentrations. The patient with congenital heart disease (patient 7) showed no signs of heart failure.

All patients had height SDS less than −2 at the time of assessment (table 1). Five patients were exceptionally short with height SDS less than or equal to −3. All children studied were normally proportioned with respect to subischial leg length and sitting height ratios. The growth velocity SDS over the period before testing were less then −2 in three of four of the patients with the CHARGE association and two of three of the patients with the VATER association (table 1). Two patients (patients 1 and 5) had normal growth velocities.

All of the boys in both groups had micropenis with two of three in the CHARGE group and one of one in the VATER group having bilateral undescended testes. All patients were clinically euthyroid and none had symptoms suggestive of adrenal insufficiency. No patients had symptoms of diabetes insipidus and all were normonatraemic.

**ENDOCRINE RESULTS (TABLE 1)**

Three of four of the CHARGE group (patients 2, 3, and 4) and two of three of the VATER group (patients 5 and 6) had normal stimulated GH concentrations. The remaining two patients (patients 1 and 7) had stimualted GH concentrations that were marginally low. Patient 1 had a normal growth velocity. Both patients 1 and 7 had normal IGF-I concentrations, and patient 7 had a normal serum IGFBP-3 concentration. Patient 5 had a subnormal serum IGF-I concentration (less than −3 SD for age), although his serum GH and IGFBP-3 concentrations were normal. Thus, GH deficiency could not be demonstrated convincingly in any patient in either the CHARGE or the VATER groups.

All patients had normal stimulated serum cortisol concentrations. Similarly, basal thyroxine and TSH concentrations (data not shown) were normal in all patients. In the one patient of a pubertal age (patient 5) subjected to LHRH testing, a deficient LH response was found.

**Discussion**

Normal growth in childhood depends upon skeletal integrity, adequate nutritional intake, absence of chronic disease, and normal anterior pituitary function. Suboptimal postnatal linear growth occurs in up to 90% of children with the CHARGE association1 and 45% of children with the VATER association.2 Growth retardation in these two conditions appears to occur mainly within the first 3 years of life with some long term, catch up growth occasionally seen.2,3 The pattern of growth failure seen in patients with CHARGE and VATER, associated with midline malformation and clinical evidence of hypogonadotropic hypogonadism, indicates the possibility of more generalised anterior pituitary dysfunction.

The patients in our series presented to an endocrine clinic with poor growth, and micropenis in males. The likelihood of detecting endocrine insufficiency in these patients could be expected to be greater than in other patients with the CHARGE and VATER associations who otherwise have normal growth and normal genital appearance. Auxological data and stimulated GH, IGF-I, and IGFBP-3 responses were studied in an attempt to increase the sensitivity and specificity in detecting somatotroph dys-

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**Table 1  Patient data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Reason for presentation</th>
<th>Features in addition to diagnostic features</th>
<th>Age at testing (years)</th>
<th>Height SDS</th>
<th>Growth velocity SDS</th>
<th>Serum GH (ng/ml)*</th>
<th>Serum IGFB-I (ng/ml)*</th>
<th>Serum IGFBP-3 (ng/ml)*</th>
<th>Peak serum cortisol (nmol/l) NR &gt; 500</th>
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<tr>
<td>CHARGE</td>
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<td></td>
<td></td>
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<tr>
<td>1</td>
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<td>1860</td>
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<td>−3.1</td>
<td>−3.8</td>
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<td>3720</td>
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<td>3</td>
<td>F</td>
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<td>5.2</td>
<td>−2.7</td>
<td>−2.5</td>
<td>60</td>
<td>899</td>
<td>1089</td>
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<td>4</td>
<td>M</td>
<td>Poor growth, micropenis, undescended testes</td>
<td>Deafness, microphthalmia, cleft palate</td>
<td>3.2</td>
<td>−4.3</td>
<td>−2.6</td>
<td>52</td>
<td>−</td>
<td>580</td>
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</tr>
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<td>VATER</td>
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<td>3500</td>
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<td>−3.6</td>
<td>29</td>
<td>4730</td>
<td>588</td>
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</tr>
</tbody>
</table>

*Normal range (provided by Diagnostic Systems Laboratories) varies with age.
†LHRH stimulated LH concentrations, 0.5 to > 0.5 IU/l; follicle stimulating hormone (FSH) concentrations, 1.2 to > 5.1 IU/l.
NR, normal range; TOF, tracheo-oesophageal fistula.
function. Serum IGF-I and IGFBP-3 concentrations are thought to increase the specificity and sensitivity of detecting GH deficiency. Subnormal IGF-I and IGFBP-3 concentrations are highly predictive of a subnormal GH response to stimulation testing, whereas normal IGF-I or IGFBP-3 concentrations do not necessarily exclude GH deficiency. Combining the auxological and biochemical data, the possibility of GH deficiency was entertained in only one patient (patient 7). This patient, however, was only 2.1 years of age at testing, had vertebral anomalies, and had undergone cardiac and facial surgery. Furthermore, her stimulated GH response was only marginally low. She has not been treated with replacement recombinant human GH (rhGH) after her biochemical assessment because we wish first to ascertain her growth velocity over a period in which no major surgery occurs. Dynamic and basal tests were also performed to assess the pituitary–thryoid and pituitary–adrenal axes. Using this comprehensive approach, no evidence of thyrotroph or corticotroph dysfunction could be detected convincingly in any patient. It is likely that some anterior pituitary dysfunction was present in our patients, with clinical evidence of gonadotroph dysfunction in all the boys and biochemical evidence of LH deficiency in the one peripubertal patient studied. This patient, who was the only patient old enough for his hypogonadal status to have had any potential impact upon his growth, had a normal growth rate despite subnormal stature. Thus, we were unable to invoke anterior pituitary dysfunction unequivocally as a cause of growth failure in any of the patients with CHARGE or VATER associations in our series.

When attempting to establish the aetiology of growth failure in patients with the CHARGE and VATER associations, the potential contributory effects of feeding difficulties, repeated episodes of surgery, and renal, gastrointestinal, and cardiovascular anomalies also have to be considered. In our series, all patients appeared to be well nourished and those with a renal or cardiovascular anomaly had stable disease. Whether patients with the CHARGE and VATER associations have skeletal dysplasia or not is a moot point. Patients with the CHARGE association are known to have midfacial and temporal bone dysplasia, and those with the VATER association are found frequently to have vertebral anomalies (including sacrococcygeal dysgenesis and hypersegmentation) and radial bone malformation. All of the patients in our series had normal upper segment:lower segment ratios, and vertebral anomalies were seen in only one of the patients with the VATER association (patient 7). This patient was relatively young, and with increasing age some degree of disproportion might become evident. Nevertheless, in most of our series of patients with the CHARGE and VATER associations, the cause of their growth failure remains uncertain.

One patient (patient 1) in our series has been treated with rhGH for approximately two years subsequent to these investigations. At a dosage of 20 U/m²/week of rhGH, this patient’s pretreatment growth velocity SDS of −0.4 increased to +1.6 after the first year. In the subsequent year of treatment the growth velocity SDS decreased to +0.5. Throughout treatment the patient’s somatic proportions have remained normal. Given the lack of catch up growth and the patient’s normal pretreatment growth velocity, it is unclear whether rhGH treatment will be of benefit with respect to his final adult height.

This is the first report to document anterior pituitary function in a series of patients with the CHARGE or VATER associations and growth failure. Despite the clinical suggestion that the growth failure of these two conditions might have an endocrine basis, no evidence of this was established. Whether rhGH treatment has a role in the management of these children, as in other non-GH deficient states, remains to be elucidated.
The writing on the wall

The heyday of unfettered alternative medicine is coming to an end. All right I can hear you saying: “What a ridiculous claim. Doesn’t he know that many, if not most, general practices have taken it on board and the public will brook no gainsaying of it?” I say it again, the end is in sight. Just you wait, ’ery ’iggins; just you wait and see.

I said unfettered—unrestrained, uninhibited, unregulated—that will stop. The good bits (of course there must be good bits) will become separated from the mire of therapeutic magic that has threatened to drag us back to an age of unreason. Why? The answer is obvious. Money—the American marketplace; the real thing for my dollar, and for the government’s dollar. The practitioners of unconventional medicine can be no more immune to these demands than are those of the medicine we call conventional. Evidence-based alternative medicine; why not? But then, of course it will be conventional medicine.

Quite recently, there has been a discernible change in attitude to alternative medicine, especially in the American medical journals, and it’s getting tougher. Over the years the pendulum has swung from “what a load of rubbish”, to “well, perhaps there’s something in it”, and now “prove it”. The often stated claim that alternative medicine cannot be subjected to scientific scrutiny no longer washes.

Listen to some of the opinion formers in US medicine in the second half of 1998: “It is time for the scientific community to stop giving alternative medicine a free ride.” “There cannot be two kinds of medicine—conventional and alternative. There is only medicine that has been adequately tested and medicine that has not” (New England Journal of Medicine September 17), “...there appears to be little evidence to support the value of spinal manipulation for nonmusculoskeletal conditions” (Ibid October 8), “To adopt alternative medicine without developing quality standards for its practices, products, and research is to return to a time in medicine when quackery and therapeutic confusion prevailed. ...The challenge is to move forward carefully ...as we attempt to separate the pearls from the mud,” (Journal of the American Medical Association November 11), “...until solid evidence is available ...uncritical acceptance of untested and unproven alternative medicine therapies must stop,” (Ibid November 11), “...insurers in the United States are only now beginning gingerly to tread the alternative waters. Some are already beating a hasty retreat,” (Ibid November 11). And a professor of complementary medicine at a British university, “...it seems uncertain whether chiropractic does more good than harm” (British Medical Journal July 18).

The US National Center for Complementary and Alternative Medicine at the National Institutes of Health has a US$50 million budget and funds a core of 13 research centres, the one for paediatrics being at the University of Arizona in Tucson. Things are moving on the alternative medicine front and the demand for evidence can no longer be ignored.