Case reports

Endocrine abnormalities in a patient with partial trisomy 4q

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SUMMARY Partial trisomy of the long arm of chromosome 4, usually resulting from a familial segregation of a balanced translocation, has been described in a number of patients. This report describes the genetic and endocrine findings in a 16 year old 46,XY,12q+ mentally retarded male. The banding pattern of the extra chromatin material from this de novo unbalanced translocation shows that the distal segment of the long arm of chromosome 4 is involved. Comparison of the clinical features in this patient with cases of partial trisomy 4q previously reported support the cytogenetic evidence for this translocation involving the distal portion of 4q. Endocrine data suggested an end-organ resistance, characterised by extreme hyperinsulinaemia, primary hypothyroidism, and hypergonadotrophic hypogonadism associated with no signs of autoimmunity. To our knowledge, no endocrine evaluation has been previously reported in patients with partial trisomy 4q.

Partial trisomy is usually the result of segregation of a familial balanced translocation. The trisomic segment common to all clinically similar patients with partial trisomy 4q corresponds to the distal third of the long arm of chromosome 4. Partial trisomy 4q is manifested by growth retardation, microcephaly, brachycephaly, receding forehead, narrow palpebral fissures with downward slant, epicanthic folds, long nose with prominent bridge, low set ears, downturned fish-like mouth, pointed chin, short neck, widely spaced nipples, cryptorchidism, inguinal hernias, hypotonia, and mental retardation.

To our knowledge no endocrine evaluation has been previously reported in patients with partial trisomy 4q. This report describes the endocrine abnormalities of a 16 year old, white, mentally retarded male with a 46,XY,12q+ chromosome complement. The extra segment of chromosome in this patient has a G banding pattern similar to that of the distal quarter of the long arm of chromosome 4. Our patient has in addition the clinical features of partial trisomy 4q.

Case report

This 16 year old white male came to the Pediatric Growth Clinic at the Nassau County Medical Center for evaluation of short stature, obesity, mental retardation, and aggressive behaviour.

He was born at 40 weeks’ gestation by normal delivery to a 40 year old mother and had a birth-weight of 2200 g. He was the only child of the mother’s second marriage. His father was 51 years old and there was no history of similarly affected members on either side of the family. His two brothers and two sisters of the mother’s first marriage were healthy and phenotypically normal.

He was found to have psychomotor retardation during the first 2 years of life. During that period he had an inguinal hernia repaired. He developed periods of unprovoked and uncontrollable aggressive behaviour at home and at school at the age of 15, which worsened over the following year. Psychological evaluation at the age of 16 revealed a moderate range of mental retardation with a mental age of 6 to 8 years corresponding to an IQ of 45. He was admitted to an institution for mentally retarded children where he was found to have glycosuria (3+) and 2 hour postprandial glucose of 253 mg/100 ml.

Physical examination revealed an adolescent Caucasian male with poor verbal articulation and a high-pitched, nasal voice. He had normal vital signs and increased subcutaneous fat, and was 86 kg in weight (−2 SD) and 160 cm tall (−2 SD). His head circumference was 56·5 cm (average).

He had a protruding forehead, narrowing of the
palpebral fissures, epicanthic folds, large ears, prominent nasal bridge, short philtrum, carp mouth, high arched palate, small and slightly receding chin, short neck, barrel shaped chest with widely spaced nipples, stage I axillary hair, stage III pubic hair (Tanner), a testicular volume of 12 ml, and stretched penile length of 10 cm (fig 1).

CYTOGENETIC FINDINGS
Chromosome preparations were made from peripheral blood cultures by standard methods. Giemsa staining after trypsin treatment was used to identify the rearrangements.2

The proband showed in all metaphases analysed a modal number of 46 chromosomes and one atypical chromosome 12 with strikingly elongated long arms. Since his parents had apparently normal chromosomes, the identity of the piece translocated to chromosome 12 could not be ascertained with absolute certainty. The banding pattern of the additional chromatin material, however, was most consistent with that of the distal segment of the long arm of chromosome 4 (fig 2). If this is the case, this translocation most likely arose in a germ cell from one of the parents, when breaks occurred at band 4q31 in the long arm of chromosome 4 and at

FIG 1 General and facial characteristics of the proband.

FIG 2 Karyotype from blood cultures of the patient showing the abnormal chromosome 12.
band 12q24 in the long arm of chromosome 12, and the
distal portions of these chromosomes were
exchanged. This patient’s chromosome constitution
is the result of having received the rearranged
chromosome 12 and the normal chromosome 4 at
fertilisation.

ENDOCRINE STUDIES
All hormone assays were performed by standard
RIAs, as described previously.3-7 Serum LH and
FSH were measured in samples drawn before and
at 15 minute intervals after an intravenous bolus of
synthetic LRH (100 µg) over 90 minutes. Basal FSH
and LH were 35 mIU/ml and 25 mIU/ml respectiv-
ely (normal FSH 2 to 10; normal LH 4·3 to 11·5).
LRH administration induced an excessive response
of both gonadotrophins, with a peak at 40 minutes
(FSH 120 mIU/ml, LH 100 mIU/ml). Basal testo-
sterone level was 210 ng/100 ml and its response
to the administration of HCG 2500 IU intramuscularly
daily for 5 consecutive days was impaired (220
ng/100 ml before and 310 ng/100 ml after). Basal
serum T4 (3·8 µg/100 ml) and free T4 (0·4 ng/100 ml)
were found to be low. His basal TSH levels were
increased (50 µU/ml). Antimicrosomal and antithy-
roglobulin antibodies were not detected. The intravenous
administration of 250 µg TRH pro-
voked an exaggerated response of TSH and pro-
lactin (TSH peak 130 µU/ml, PRL peak 135 ng/ml).
The normal TSH response to TRH administration
was achieved after 3 months’ treatment with L-
thyroxine (200 µg orally daily). Normal growth hor-
mones (GH) response (14·5 ng/ml) was seen at 60
minutes after an intravenous infusion of arginine
HCl 10 % (0·5 g/kg). Insulin induced hypoglycaemia
could not be obtained at doses of 0·1, 0·2, 0·3, and
0·4 U/kg, and no significant changes were seen in
GH and cortisol levels. A moderate rise of ACTH,
however, was seen after a 41·6 % drop in blood
glucose concentration induced by the maximum
insulin dose (fig 3).

Fasting serum glucose (173 mg/100 ml), insulin
levels (400 µU/ml), and haemoglobin A1c (11 %)
were found to be raised. A 5 hour glucose tolerance
test with simultaneous measurements of serum insulin
levels was found to be greatly impaired (table 1)
indicating glucose intolerance associated with hyper-
insulinism. Anti-insulin antibodies and islet cell
antibodies were not detectable.

Additional laboratory studies, which included
total blood cell count, erythrocyte sedimentation
rate, antinuclear antibodies, serum electrolytes,
liver enzymes, PTH (654 pg/ml), somatomedin C
(0·93 U/ml), immunoglobulins, and serum and
urine amino acids, were all normal. His bone age
estimated by the method of Greulich and Pyle8 was
16 years. An IVP was normal and a CT scan of the
head showed a mild to moderate degree of atrophy
of the grey matter.

Discussion

Most reported cases of partial trisomy 4q result from
a balanced parental rearrangement. Trisomy of the

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**TABLE 1** Oral glucose tolerance test (100 g glucose).

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Glucose (mg/100 ml)</th>
<th>Insulin (µU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>116</td>
<td>180</td>
</tr>
<tr>
<td>1/2</td>
<td>210</td>
<td>400</td>
</tr>
<tr>
<td>1</td>
<td>320</td>
<td>640</td>
</tr>
<tr>
<td>2</td>
<td>300</td>
<td>820</td>
</tr>
<tr>
<td>3</td>
<td>215</td>
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<td>4</td>
<td>190</td>
<td>790</td>
</tr>
<tr>
<td>5</td>
<td>160</td>
<td>680</td>
</tr>
</tbody>
</table>

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**FIG 3** Insulin tolerance test demonstrating glucose, growth hormone (HGH), ACTH, and cortisol response at different insulin doses.
distal third of 4q appears to be necessary for development of most of the clinical features first cytologically demonstrated in 1972 and clinically delineated in 1975. Fewer than 30 cases have been reported, including two cases arising de novo associated with increased maternal age. The phenotypic features of our patient are summarised and compared with 22 previously reported cases of partial trisomy 4q in table 2. The clinical picture of such chromosome abnormality varies considerably. With the exception of microcephaly, hypertelorism, and congenital heart disease, our patient had most of the clinical features associated with partial trisomy 4q. This variation may be related to such variables as age, sex, and different lengths of the long arm of chromosome 4, as well as the terminal loss of genetic material of the second chromosome involved in such an unbalanced translocation.

Although the translocation of 4q can occur onto any other chromosome, the chromosome analysis of the 22 cases used for comparison and others more recently reported reveals a relative predilection of 4q for chromosome 18 (11 out of 28 cases).

The patient's basal gonadotrophin levels and their response to the administration of LRH are characteristic of hypergonadotrophic hypogonadism. This is further supported by the greatly impaired testosterone response to the administration of HCG. The primary gonadal failure and the impaired secretion of gonadal steroids lead to a decreased negative feedback and raised FSH and LH. It is interesting that the most common forms of primary gonadal failure are associated with chromosomal abnormalities and characteristic physical findings. Our patient may represent another chromosome abnormality associated with hypergonadotrophic hypogonadism. The TSH level, and its response to TRH administration, is also characteristic of primary hypothyroidism. In contrast to most common forms of acquired hypothyroidism, no autoimmune aetiology could be demonstrated in our case, since antithyroidal and antithyroglobulin antibodies were not detected. Evidence of an insulin resistant state in our patient derived first from the reduced effectiveness of exogenous insulin and secondly from the endogenous hyperinsulinism in the face of hyperglycaemia observed during the glucose tolerance test.

The association of glucose intolerance and hyperinsulinism are indicative of impaired insulin action. In our patient, the hyperinsulinaemia greatly exceeded that seen in obesity, and therefore his insulin resistance is probably not solely due to his obesity.

Insulin resistance has been found to be associated with insulin antibodies, antireceptor antibodies, receptor deficiency, and post-receptor defects. Unfortunately, insulin receptor studies were not carried out in our case and, therefore, the pathogenesis of his insulin resistance remains undetermined. Our patient had extreme insulin resistance without increased anti-insulin antibodies, associated with an inborn defect (an unbalanced chromosome translocation).

In summary, our case seems to represent a partial trisomy 4q associated with exaggerated insulin resistance, hypergonadotrophic hypogonadism, and primary hypothyroidism. In contrast to most common forms of primary endocrine gland failure, no autoimmune aetiology could be demonstrated in our case. Therefore, it is tempting to speculate that a multiple hormone resistance could explain the pathogenesis of the endocrine abnormalities seen in our patient. Further studies are necessary to determine whether these endocrine abnormalities are part of the constellation of features associated with partial trisomy 4q, or if they are related to the loss of the terminal portion of chromosome 12.

### References


Deletion of the short arm of chromosome 3: a case report with necropsy findings

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SUMMARY. A male infant with partial deletion of the short arm of chromosome 3 is described. The features this patient shares with six previously reported cases include microcephaly, dolichocephaly, micrognathia, epicanthic folds, ptosis, low set or malformed ears, postaxial polydactyly, and growth or mental retardation or both. In addition, visceral anomalies not previously reported in association with this chromosomal abnormality are described. These characteristics may constitute a recognisable clinical syndrome.

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