Hypopituitarism is the clinical syndrome that results from failure of the anterior pituitary gland to produce one, more than one, or all of its hormones. Hypopituitarism can result from: (1) intrinsic or primary pituitary disease; (2) intrinsic hypothalamic or secondary pituitary disease; or (3) extrinsic extramellar or parasellar disease. The etiologies of primary hypopituitarism are miscellaneous. The dominant clinical picture of hypopituitarism in the adult is that of hypogonadism. Reports have associated hypopituitarism with antipituitary antibodies, hereditary syndrome and chromosome defects, but hypopituitarism has rarely been associated with balanced chromosome translocation (11;22)(q24;q13). Here, we describe a case of anterior pituitary failure with a balanced chromosome translocation. A 19-year-old Chinese teenager presented with failure of puberty and sexual infantilism. On examination, the patient had the classic appearance of hypogonadism. Endocrine studies and three combined pituitary function tests revealed panhypopituitarism. A chromosomal study revealed 46, XY, t(11;22)(q24;q13), a balanced translocation between 11q24 and 22q13. Chest films showed delayed fusion of bilateral humeral head epiphyses and bilateral acromions. Scrotal sonography revealed testes were small bilaterally. Magnetic resonance imaging (MRI) of the sella revealed pituitary dwarfism. The patient received 19 months replacement therapy, including steroids (prednisolone 5 mg each day), L-thyroxine (Eltroxin 100 ug each day), and testosterone enanthate 250 mg every two weeks. His height increased 4 cm with secondary sexual characteristics developed, and muscle power increased. [Chin Med J (Taipei) 2001;64:247-252]

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As the manifestations of hypopituitarism are usually of gradual onset and related to particular hormone deficiencies such as gonadotropin (complete failure of puberty development with sexual infantilism), GH (growth failure), TSH (loss of energy, slowing of mental and physical functions), and ACTH (weakness, lethargy, fatigue, neonatal jaundice, electrolyte imbalance).

The diagnosis of hypopituitarism includes neuroradiologic, neuroophthalmologic, and functional tests. Therapy for hypopituitarism is based on recognition and removal or reversal of the cause, and on substitution of the deficient hormone.

Hypopituitarism has in various reports been associated with antipituitary-antibodies, 18p- syn drome, mutation of the POU (Pit-1;Oct-1;Oct-2;Unc-86)-specific do main of Pit-1, paracentric inversion of the short arm of chromosome 1, hemochromatosis, septo-optic dysplasia, chorioretinopathy, Pallister-Hall syndrome, X-chromosome recessive (regional duplication in Xq25-q26) or autosomal recessive trans mission, and mutation of the PROP1 gene. Hypopituitarism has never before been reported as associated with such a translocation (11;22)(q24;q13). Here, we describe a case of anterior pituitary failure as associated with such a translocation.

### Case Report

A 19-year-old Chinese teenager presented with failure of puberty development and sexual undergrowth. His family history was unremarkable. He had one sister who was otherwise well. He had experienced normal growth except for development of secondary sexual characteristics. In March 1999, the patient visited our outpatient department (OPD) and his presenting symptoms led to his admission to our institution.

On examination, the patient's height, weight, and mental development were within normal limits for his age (height 167 cm, weight 65 kg, BMI 23.3). He had the classic appearance of hypogonadism. He was noted to have a small penis, scrotum, and small testes. His secondary sexual characteristics were absent with no axillary hair, pubic hair, or beard. His voice was childlike and had a high-pitched quality and the Adam's apple was absent.

Hematological investigations revealed a normocytic anemia. Biochemistry profiles all showed within normal limits. Endocrine studies revealed panhypopituitarism (growth hormone [GH], 0.04 ng/mL.

<table>
<thead>
<tr>
<th>Time</th>
<th>-15 min</th>
<th>0 min</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
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<tbody>
<tr>
<td>PS (mg/dL)</td>
<td>104</td>
<td>78</td>
<td>37</td>
<td>153</td>
<td>108</td>
<td>110</td>
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<tr>
<td>Cortisol (ug/dL)</td>
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<td>1.9</td>
<td>1.6</td>
<td>1.2</td>
<td>0.7</td>
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<tr>
<td>HGH (ng/mL)</td>
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<td>0.05</td>
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<td>0.04</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>0.13</td>
<td>0.23</td>
<td>0.42</td>
<td>0.73</td>
<td>0.88</td>
<td>1.04</td>
<td>0.81</td>
<td>1.02</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
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<td>&lt; 0.07</td>
<td>&lt; 0.07</td>
<td>0.08</td>
<td>0.12</td>
<td>0.13</td>
<td>0.11</td>
<td>0.08</td>
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<td>12.540</td>
<td>14.197</td>
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</tr>
</tbody>
</table>

IHST = insulin hypoglycemic stimulation test; RI = regular insulin; TRH = thyrotropin releasing hormone; LH-RH = luteinizing hormone releasing hormone; PS = plasma sugar; hGH = human growth hormone; FSH = follicle stimulating hormone; LH = luteinizing hormone; TSH = thyroid-stimulatory hormone.
[adult < 7] was measured by commercial RIA kit (Diiichi, Japan); corticotropin [ACTH], 1.0 pg/mL [9-52] was measured by commercial RIA kit (Nicros, USA); prolactin, 36.3 ng/mL [male 2.1-17.7]; leute-
eining hormone [LH], < 0.07 mIU/mL [male 1.5-9.3]; follicle stimulating hormone [FSH], 0.2 mIU/mL [male 1.4-18.1]; progesterone, < 0.11 ng/mL [0.28-1.22]; tes tos ter one, 5 ng/dL [male 241-827]; cortisol 8 AM, 0.6 ug/dL [6-28]; high sensitivity thyroid-stimulatory hormone [HS-TSH]: 2.366 uU/mL [normal, 0.45 to 6.2]; thy rox ine [T4], 2.1 ug/dL [nor mal, 4.5 to 12] were mea 
sured by chemoluminescence using a kit from Chiron Di ag nos tics (East Wal pole, MA 02032 USA)). Three com bined pi tu itary func tion tests (in clud ing the in su lin hypoglycemic test, TRH [thy roto 
triphin re leas ing hor mone] test, and LHRR [leute-
eining hor mone re leas ing hor mone] test) in di cated panhypopituitarism (Table 1). A chro mo somal study re vealed 46, XY, t(11;22)(q24;q13), a bal anced trans-
location be tween 11q24 and 22q13 (Fig. 1).

Pulmonary functional tests showed mildly ob 
struc tive and re strictive ventilatory im pairment. Chest films re vealed de layed fu sion bi lat er ally of the hu 
mer al head epiphyses and of the acromions. Scrotal sonography showed that the tes tes were small bi lat er 
ally, sized 1.2 cm each and with no focal nodules. Mag netic re so nance im age ing of the sella re vealed pi tu itary dwarf ism (Fig. 2).

Panhypopituitarism with a balanced chro mosome translocation (11;22)(q24;q13) was di ag nosed. The pa 
tient re ceived re place ment ther apy, com pris ing ste 
roids: prednisolone 5 mg each day, L-thyrox in e (Eltrox in 100 ug each day), and tes tos ter one enanthate 250 mg ev ery two weeks. Af ter 19 months of treat ment, the pa 
tient’s hor mone data showed: GH, 0.1 ng/mL; prolactin, 45.9 ng/mL; cortisol 8 AM, 0.2 ug/dL; E2, 31 pg/mL; FSH, 0.6 mIU/mL; LH, < 0.07 mIU/mL; tes tos ter one ter, 892 ng/dL; T4, 7.2 ug/dL; HS-TSH, < 0.002 mU/mL. His height had in creased 4 cm, his sec 
ond ary sexual char ac ter is tics were de vel oped, and 
mus cle power was in creased.

Discussion

Many of the ge netic reg u la tory pro cesses in the hu 
man or gan ism are me di ated by hor mones. Qual i ta 
tive and quan ti ta tive ge netic de fects may also af fect hor mone se cre tion, well be ing and be hav ior. The mo 
lec u lar ba sis of hypopituitarism has been pos tu lated as in vol ving Pit-1, a pi tu itary-specific tran scrip tion fac 
tor re spon si ble for pi tu itary de vel op ment and hor mone ex pres sion in mam mals, and PROP1. The phe no 
types pro duced by point mu ta tions in the Pit-1 gene in 
volve de fi cien cies of growth hor mone (GH), pro 
lactin (PRL), and thyroto 
propin (TSH), and are un re lated to corticotropin (ACTH), go 
ad o tro pin (FSH, LH), and some TSH cells (which are also known as non-Pit-1-
dependent cells). The point mu ta tions in clude Pit-1 gene (POU-homeo 
coden 271) and other nu clear fac tors, such as Zn-15, Prl gene, enhancer ele ments (RAREs) (re tinoid acid re sponse ele ments). The Pit-1 lo cus is
on chromosome 16. The PROP1 gene encodes a transcription factor with a single paired-like-DNA-binding domain. Persons with inactivating mutations in PROP1 have deficiencies of LH and FSH, as well as GH, PRL, and TSH. At least seven human mutations have been recognized. The gene responsible is located on chromosome 11. Given that our patient’s hormone deficiency involved the TSH, LH, FSH and ACTH axes, it is unlikely to be associated with Pit-1 mutations. No other causes of hypopituitarism could be traced. So, it is likely that patient’s disease may be associated with chromosomal defect.

The chromosomes are ordered and numbered according to their length. Patou proposed subdivision of the 23 pairs of chromosomes into groups A-G (group A [Nos. 1-3], group B [Nos. 4 and 5], group C [Nos. 6-12], group D [Nos. 13-15], group E [Nos. 16-18], group F [Nos. 19 and 20], and group G [Nos. 21 and 22]) and the sex chromosomes (X, Y). Human chromosomal pathology can be classified as:

1. syndromes due to numeric anomalies of autosomes, such as triploidy or mosaics;
2. syndromes due to structural anomalies of autosomes, such as gaps, breaks, rearrangements, deletions, and translocations; and
3. sex chromosome defects.12

Autosomal chromosome aberration syndrome was described as having many signs, including low birth weight, failure to thrive, mental retardation, short stature, head and face defects, various anomalies of the hands and feet, and internal or abdominal defects. Our patient’s chromosome defect belongs to the group comprising structural anomalies of the autosome, and was without signs of an autosomal chromosome aberration syndrome.

Chromosome 11 belongs to group C and is relatively submetacentric, with a centromeric index of 27-35. Chromosome 11 defects had been associated with endocrine disease (such as MEN II), Beckwith-Wiedemann syndrome (BWS),12 long QT syndrome, and RAS (rat sarcoma)-related tumors. Chromosome 22 belongs to group G and is a small acrocentric chromosome with centromeric index of 13 and 33. Chromosome 22 had been associated with DiGeorge syndrome, Type II neurofibromatosis, chronic myelogenous leukemia, Ewing’s sarcoma, and Cat-cry syndrome. Translocations are relatively rare. Most chromosome some translocations in volve groups D and G. The short arms of D and G chromosomal segments contain the nucleolus or gene ron re gions that are stained specifically by the silver method. Our patient’s chromosome translocation involved groups C and G, which is rarer than translocations between groups D and G, but has been reported as being associated with tumors.

Fig. 2. Magnetic resonance image (MRI) of the sella turcica (A) coronal view (B) sagittal view: showing scanty intermediate T1 tissue in a small sellar turcica. The pituitary stalk is absent. There is an enhanced nodule adjacent to the tuberculum. The cavernous sinuses and Meckel’s caves are unremarkable. The suprasellar cistern is clear. Pituitary dwarfism is likely.
Translocation can be classified into unbalanced (reciprocal) and balanced (Robertsonian) translocations. Unbalanced translocation carriers have lost some genetic material and have an increased incidence of malformations; about half of all translocations give rise to malformations and the others invariably lead to fetal death. Balanced translocation carriers have a complete set of genetic material and should therefore be phenotypically normal. However, there have been multiple reports describing incidences of malformations, mental retardation, and minor birth defects with balanced translocations. Our patient only demonstrated hypogonadism with sexual infantilism and had no apparent mental retardation or other malformations.

There are many chromosomal translocations associated with tumor formation, such as t(11;22) (p13;q12) as so ciated with Ewing’s sarcoma, Wilm’s tumor, cerebellar primitive neuroectodermal tumor, and desmoplastic small round cell tumor, t(2;13) found in alveolar rhabdomyosarcoma, and trisomy 21 associated with MALT lymphoma. Other chromosomal defects are associated with other syndromes, such as t(Y;15)(q12;q11.2) in Prader-Willi syndrome, 15q(del)(15)(q11.2q130) in Angelman syndrome, and 11q13, 15q22.3 in Bardet-Biedl syndrome. Our patient was a 19-year-old with no apparent tumors, but he has an increased risk of developing tumors in the future. For this reason, and for monitoring progress, long-term observation will be necessary.

Acknowledgements

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References