Presence of Turner stigmata in a case of dysgenetic male pseudohermaphroditism with 45,X/46,X+mar karyotype

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Abstract

A case is reported of dysgenetic male pseudohermaphroditism (DMPH) having Turner stigmata and 45,X/46,X+mar karyotype. The marker chromosome of this patient consisted of most if not all of the short arm, including the sex determining region of the Y chromosome. Although this karyotype is relatively common in Turner's syndrome and occasionally observed in mixed gonadal dysgenesis, DMPH is usually exemplified by a 46,XY karyotype except for one patient reported with 45,X/46,XY mosaicism. Turner stigmata have not previously been reported in DMPH. The present patient is an intermediate case between mixed gonadal dysgenesis and typical DMPH, and this indicates that 45,X/46,X+mar karyotype abnormality can result in a wide range of phenotype such as DMPH, mixed gonadal dysgenesis and Turner's syndrome.

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In 1967, Federman first described dysgenetic male pseudohermaphroditism (DMPH) as a rare disorder of sexual differentiation caused by embryogenic failure in the normal processes of testicular differentiation.¹ This syndrome is characterised by bilateral dysgenetic testes, persistent internal müllerian duct structures, cryptorchidism, and inadequate virilisation, and is classified at present as a form of male pseudohermaphroditism.¹⁻³ Patients with mixed gonadal dysgenesis (MGD), which is a more common disease than DMPH and characterised by a unilateral dysgenetic testis and a contralateral streak gonad, also show defective virilisation and persistence of the müllerian ducts.^{3,4} The risk of gonadal tumours, such as gonadoblastoma, has been estimated to be high in both patients with DMPH and MGD.^{2,3} From these findings, DMPH is thought to be closely related to MGD.^{2,3,5} Furthermore, it is thought that a close relationship also exists between MGD and Turner's syndrome because a 45X/46XY karyotype, which is typical of MGD,^{4,6} is seen in Turner's syndrome,^{6,7} and features of Turner's syndrome are seen in patients with MGD.^{4,6} Although patients with DMPH reported on to date had a 46,XY

karyotype,^{1,2} except for one with 45,X/46,XY mosaicism,⁶ and Turner stigmata have not previously been reported in classical DMPH, we here report a case of DMPH with Turner stigmata and 45,X/46,X+mar karyotype, which is a relatively common karyotype in patients with Turner's syndrome.^{7,8} We investigated the loci of the Y chromosome, including the sex-determining region (SRY) on the marker chromosome, by using the polymerase chain reaction (PCR) method. The aetiological backgrounds of sexual differentiation disorders related to testicular development are also discussed.

Case report

This phenotypic male infant was a 2332 g (appropriate for gestational age) product of a 37 week 4 day gestation with normal delivery in a 23 year old woman. His height at birth was 45.5 cm (1.5 SD below the mean for gestational age). He had ambiguous genitalia such as a small phallus with chordee, perineal hypospadias, bifid scrotum, and palpable gonad in the left scrotum. There was no lymphoedema over the dorsum of the fingers and toes. Chromosome analysis was performed on 40 peripheral blood lymphocytes of the patient using G banding, C banding, and Q banding. His karyotype was 45,X/46,X+mar mosaicism (26 lymphocytes had 46,X+mar karyotype and the karyotype of the other 14 lymphocytes was 45,X). The non-consanguineous parents were clinically normal and the karyotype of the father was 46,XY. DNA analysis of a marker chromosome in peripheral blood lymphocytes using the PCR method was performed by Dr Yutaka Nakahori (Department of Human Genetics, School of International Health, University of Tokyo, Tokyo, Japan). A schematic map of the Y chromosome and loci investigated in this case is shown in fig 1. The marker chromosome of this patient consisted of most if not all of the short arm, including the SRY locus and the centromere of the Y chromosome, while the bulk of the long arm of the Y chromosome was missing.

On radiography, computed tomography, and magnetic resonance imaging, a vagina between the rectum and bladder, and a gonad-like mass in the right inguinal region were detected but no uterus was observed (fig 2). This infant was reared as a male according to the parents' wishes after the risk of gonadal tumours had been explained to them.

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Figure 1 Schematic map of the Y chromosome with loci investigated in this case. (+) indicates the presence of locus and (-) indicates the absence of locus on the marker chromosome. PABY, proximal border of the pseudoautosomal region of Y; AMGL, amelogenin-like sequence; DYZ and DYS, D = DNA, Y = Y chromosome, Z = Z-repetitive copy DNA, S = segment, and the number indicates published order of specific cloned DNA sequence.

Figure 2 Magnetic resonance imaging at 2 years of age showing the presence of the vagina (V) between the bladder (B) and the rectum (R) but the absence of a uterus. P indicates phallus.

At 6 months of age, endocrinological examination showed that the serum luteinising hormone (LH) concentration was 0.3 U/l (normal 0.02–0.3 U/l) and follicle stimulating hormone (FSH) was 2.7 U/l (normal 0.26–3.0 U/l). The serum level of testosterone increased from <0.17 nmol/l (normal 0.10–0.35 nmol/l) to 14.04 nmol/l (normal above twofold in-

crease of basal value) by human chorionic gonadotrophin (hCG) administration. However, there was no response of serum oestradiol to human menopausal gonadotrophin stimulation.

At 28 months of age, the gonad-like mass and its appendixes in the right inguinal canal were resected. Histological examination revealed that this gonad-like tissue was testicular but its architecture was abnormal. Although a tunica albuginea was present, ectopic seminiferous tubules were observed. The seminiferous tubules were disorganised and separated by oedematous stroma. There was no ovarian-like stroma or gonadoblastoma. In the appendixes, epididymis and fallopian tube were observed adjacent to the dysgenetic testis. A uterus was also detected by microscopic examination on the contralateral side to the dysgenetic testis (fig 3).

At 3.4 years of age, we diagnosed him as having DMPH because his scrotal gonad significantly responded to hCG stimulation (testosterone increased from 0.17 to 4.44 nmol/l).⁶ The response to LH releasing hormone was within the normal range (LH increased from <0.1 to 5.8 U/l, FSH increased from 1.7 to 16.1 U/l) found in children of corresponding age. His height was 86.2 cm (2.7 SD below the mean for his age). Serum concentration of insulin-like growth factor I was 17.9 nmol/l (normal 5.88–30.07 nmol/l) and urinary growth hormone concentration during sleep was 575.8 pg/μmol creatinine (normal above 79.2 pg/μmol creatinine). Serum growth hormone concentration was increased from 6.7 to 20.8 μg/l by intravenous administration of growth hormone releasing factor (normal peak value, above 15 μg/l) and from 5.0 to 19.9 μg/l by arginine administration (normal peak value, above 10 μg/l). These findings indicate that his short stature was not due to growth hormone deficiency.

At 3.8 years, urethroplasty was performed. At 4 years of age, his penis was very short (2 cm) and left testicular volume was very much below the lower limit normal for his age (<0.5 ml). Turner stigmata, such as short neck, mild webbed neck, broad chest, low set and posteriorly rotated ear, micrognathia, and low posterior hairline, were observed as shown in fig 4. The short metacarpal of the fourth finger (fig 5A), cubitus valgus (fig 5B), and hyperconvex nails became apparent with growth. However, he had no cardiovascular abnormalities.

Discussion

This case report shows the variability of sexual differentiation in individuals with 45,X/46,X+mar karyotype. This karyotype is the most common in Turner's syndrome. About 50% of patients with Turner stigmata show mosaicism, and a marker chromosome is present in 3% of such patients.⁸ Nagafuchi *et al*⁷ reported that marker chromosomes of 23 of 41 Japanese patients with Turner's syndrome with a 45,X/46,X+mar (37 patients) or 46,X+mar karyotype (four patients) consisted of the short arm and centromere of the Y chromosome. As shown in our case, their break points were dis-

Figure 3 Histological sections of the right gonad (A) and its appendixes (B, C, D). (A) dysgenetic testis showing separation of disorganised seminiferous tubules (S) by oedematous stroma and presence of the tunica albuginea (T) with ectopic seminiferous tubules (arrow); (B) epididymis; (C) fallopian tube; (D) uterus.

Figure 4 Photographs of whole body and face at 4 years of age. Short neck, mild webbed neck, broad chest, low set and posteriorly rotated ear, micrognathia, and low posterior hairline were observed.

tributed evenly over the long arm of the Y chromosome.⁷ A 45,X/46,X+mar karyotype was also seen in one of 48 Japanese patients with MGD.⁴ Of particular interest is our first observation that the present patient with DMPH, which is the most masculinised of these three diseases, had a 45,X/46,X+mar karyotype. Furthermore, the coexistence of mosaicism and Turner stigmata in this case suggests that it is intermediate between MGD and typical DMPH.

Patients with other karyotypes also exhibit great clinical variability. Kofman *et al* reported that five patients with 45,X/46,XY included two with Turner's syndrome, two with MGD, and one with DMPH.⁶ Berkovitz *et al* also reported that the clinical and pathological spectrum of 15 patients with 46,XY gonadal dysgenesis consisted of seven patients with 46,XY pure gonadal dysgenesis, five with MGD, and three with DMPH.³ Two patients with 46,XY pure gonadal dysgenesis had evidence of ovarian differentiation of streak

gonads such as clusters of granulosa-like cells. Their streak gonads were not histologically distinguishable from those found in patients with Turner's syndrome. Interestingly, one patient with MGD had primordial follicles within the ovarian portion of the dysgenetic testis. In addition, another patient with MGD had a single primordial follicle in the streak gonad. Of additional interest, two patients with DMPH had a cortex composed of ovarian-like stroma in their dysgenetic testes. These histological findings suggest that their dysgenetic gonads were ovotestes resulting from inadequate or delayed testicular determination during fetal life and, in the absence of two X chromosomes, the ovarian tissue would be expected to regress, leading to the subsequent appearance of a dysgenetic testis. On the other hand, absent testicular determination, resulting from the abolished function of SRY and other related genes, would permit ovarian differentiation of the gonads and finally lead to the streak gonads as seen in MGD, Turner's syndrome, and 46,XY pure gonadal dysgenesis. In addition, it is well known that the biological effect of antimüllerian hormone secreted by Sertoli cells leads to the regression of müllerian ducts, and the differentiation of both wolffian ducts and external genitalia is due to the effect of testosterone secreted by Leydig cells. Differentiation of these two cell types and the amount and timing of the secretion of these two hormones are important for sexual differentiation, as Kofman *et al* have established a correlation between endocrine findings with gonadal morphology and phenotype in patients with mosaicism.⁶

It has recently been recognised that the genes for Turner stigmata are present on the short arm of the Y and X chromosomes, and that haploinsufficiency of these genes results in the development of Turner stigmata.¹⁰ Even if the loci for Turner stigmata exist, a structurally abnormal sex chromosome may result in inactivation of them.¹¹ Somatic growth is also thought to be controlled by the pseudoautosomal growth gene on Yp.¹² On the other hand, the gene responsible for initiating testicular development in the fetal gonad is considered to be identical with SRY.^{13,14} These findings indicate that Turner stigmata have no relation to sexual differentiation and are the result of the deletion or inactivation of these genes. The presence of Turner stigmata in DMPH has not previously been demonstrated and the typical karyotype for DMPH is 46,XY, so we consider that the Turner stigmata seen in our patient may have resulted from his 45,X/46,X+mar karyotype, which is normally seen in Turner's syndrome.

In addition, we consider that Turner's syndrome patients with a chromosome derived from Y, particularly SRY, should be regarded as having male gonadal dysgenesis, as the present case indicates that the streak gonads seen in Turner's syndrome patients with a Y chromosome may result from faulty testicular differentiation. At least, they should be distinguished from Y chromosome negative Turner's syndrome patients, as the gonadoblastoma locus is

Figure 5 Radiographs taken at 4 years of age demonstrating a short fourth metacarpus (A) and an increased carrying angle (cubitus valgus) (B). In many patients with Turner's syndrome, the angle is between 15 and 30°.⁹

now thought to exist on Yq⁷ and, as seen in MGD and DMPH, a high incidence of gonadoblastoma has also been observed in patients with Turner's syndrome having a part of the Y chromosome.^{6,7} These results indicate that evaluation of the Y chromosome by molecular methods should be carried out in patients with a marker chromosome.

We consider that a single karyotype abnormality can result in a wide range of phenotypes, and that DMPH, MGD, and SRY positive Turner's syndrome may be alternative responses to almost the same abnormal genetic complement. The most important factors for gonadal and phenotypic differentiation may

not be the karyotype or the ratio of mosaic cells including the Y chromosome⁶ but the expression of SRY and other related genes, the degree of testicular differentiation, and the amount and timing of antimüllerian hormone and testosterone secretion.

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