Prenatal diagnosis of a de novo Y/22 translocation

The wife became pregnant again in 1976. At that time the ages of the parents were 39 (mother) and 41 (father). Again, amniocentesis for prenatal diagnosis was performed at 17 weeks. The a-fetoprotein estimation was within normal limits: 10-4 µg/ml. Cyto-
genetic analysis (Q-banding) revealed 46 chromosomes, 2 of which were abnormal. The karyotype was interpreted as a balanced (?) Y/22 translocation. Because of this finding the parents were karyotyped immediately. Both of them had a normal chromosome constitution.

With the help of an interpreter we discussed these findings with the parents. We explained the impossibility of determining whether the translocation found in the amniotic fluid cells was balanced or unbalanced, and consequently that we were unable to reassure them about the normality of the fetus. The parents decided to continue the pregnancy as it was not certain that the translocation would give rise to phenotypic abnormalities.

The second half of the pregnancy passed without complications. After a normal delivery, an apparently healthy boy was born at 39 weeks’ gestation (Apgar score: 1 min, 9; 10 min, 10). His birthweight was 2950 g (± 10th centile; Kloosterman, 1970), his length 50 cm. Physical examination up to 4 weeks after birth revealed no abnormalities; notably the testes were descended and of normal size.

Methods and results

Amniotic fluid cells were cultured in an atmosphere of 5% CO₂ on 3 coverslips, each placed in a small petri dish. The culture medium was 10% Ham’s F10 (75%) and fetal calf serum (25%), supplemented with 100 units penicillin G and 100 µg streptomycin sulphate per ml. After 10 days in culture, chromosome preparations were made directly on the coverslips without trypsinisation. Thirty Q-banded metaphases were analysed from various clones of different cultures. A translocation was found between chromosome 22 and the Y chromosome (Fig. 1). The long arm of one of these chromosomes was translocated to the short arm of the other and a centromeric fragment was left. It was not clear whether this fragment was the centromeric region of chromosome 22 or the Y chromosome. It was not found in association with a D or G group chromosome. The most probable karyotype, therefore, was 46,X,t(Y;22)(q11;p11). The karyotype
46,X,t(Y;22)(p11;q11), however, could not be excluded. Lymphocyte cultures were established from peripheral blood in the usual manner. The parental chromosomes were studied with Q, R, and G banding. The karyotypes of both were normal (Fig. 2). Chromosomal analysis of the baby was performed soon after birth from peripheral blood. Karyograms of Q, G, and NOR stained chromosomes confirmed the prenatal diagnosis and established the karyotype as 46,X,t(Y;22)(q11;p11).

Blood grouping to check paternity was not carried out, as the birth of a healthy baby was a tremendous relief to the parents and we did not wish to raise doubts about the healthiness of their son by further investigations.

The H-Y antigen expression was determined on PHA-stimulated T lymphocytes of this patient by a series of 2 absorption tests using mouse H-Y antibody raised in C57BLACK/6 females by 5 weekly injections of male B6 spleen cells (Nagai and Ohno, 1977). On arrival in Duarte, dead cells and cellular debris were removed from the lymphocyte preparation by double Ficoll-gradient centrifugation. 50 μl of 1/4 diluted H-Y antibody was then absorbed with purified lymphocytes from the patient at two levels: 4 x 10⁶ and 8 x 10⁶ cells. Absorption was carried out for 45 minutes on ice. The residual cytotoxicity of absorbed H-Y antibody was then titrated on male BALB/c tail epidermal cells using agarose-absorbed guinea pig complements (Scheid et al., 1972; Nagai and Ohno, 1977). Dead cell percentages are shown in Fig. 3 as absolute values, taking the complement control value as zero. At the level of 8 x 10⁶ cells, lymphocytes from this patient caused roughly 50% absorption of H-Y antibody. Thus, the H-Y antigen expression of this patient appears to have been unequivocally proved. However, since our experience with newborn human males is quite limited, we cannot say with...
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confidence whether or not the H-Y antigen level of this patient represents the normal male level at this developmental stage.

Discussion

The frequency of de novo reciprocal translocations in newborn infants is low. Jacobs et al. (1974) described the results of cytogenetic examination of 11680 newborn infants and also reviewed data from 5 similar studies. The combined data include 43558 chromosomal studies. Of this total series, 8 children were shown to be carriers of a balanced de novo translocation, which gives an incidence of about 1:5000 in postnatal studies.

Prenatal chromosome investigations have also revealed de novo translocations. A Canadian survey of 1020 prenatal studies found one established de novo, apparently balanced, translocation (Medical Research Council, Canada, 1977). The fetus was aborted and showed no abnormalities on examination. Review studies of 1040 American (National Institute of Child Health and Human Development, 1976), and 6121 European (Galjaard, 1976), prenatal chromosomal investigations only mentioned the occurrence of fetal translocations. But as no information is given about the parental karyotypes, it is not possible to evaluate the incidence of de novo balanced translocations in these prenatal series.

The Y chromosome is seldom involved in mutant translocations. To our knowledge, the present case is the first one detected prenatally. A study of published reports showed 13 patients carrying a de novo Y translocation diagnosed after birth. The karyotypes of 7 of these patients appear to have balanced translocations. Of these patients, 3 had azoospermia but were otherwise normal (Van den Berghe et al., 1973; Laurent and Dutrillaux, 1976; Turleau et al., 1976), 2 had moderate developmental anomalies (Develing et al., 1973; Van den Berghe et al., 1977), and 2 showed severe psychomotor retardation from birth (Krmpotic et al., 1972; Pfeiffer et al., 1973). The symptoms of the 6 patients with an unbalanced translocation were very diverse (Caspersson et al., 1971; Gilgenkrantz et al., 1973; Khudr et al., 1973; Hillman et al., 1974; Park et al., 1974; Van den Berghe et al., 1977) and included 3 patients who were chromosomal mosaics. A chromosome 22 was not involved in translocations in any of these 13 cases. However, familial Y/22 translocations, very similar to the one we found prenatally, have been reported by Lundsteen and Philip (1973), Mikkelsen (1973), Reitalu (1973), Chandley et al. (1975), and Nielsen and Rasmussen (1976). The patients described had normal sex chromosomes, while extra Y chromosome material, consisting of the distal part of the long arm, was present on the short arm of chromosome 22. This unbalanced translocation was always accompanied by a normal phenotype.

Aetiological, 2 points attracted particular attention in the present case history: the parental age (mother, 39 and father, 41), and the fact that healthy and chromosomally normal parents gave birth to 2
children, each with a different chromosomal aberration. The family histories of the 13 reported cases of a de novo Y chromosome translocation were also considered from these points of view. The parental age at the time of birth was reported 7 times, the average being 29.5 years. In 10 obstetrical histories, no abnormal sibs were mentioned. We must therefore conclude that these 2 facts in our case were probably coincidental. Other risk factors (for example, contact with mutagens) were not significant because, as far as we know, neither parent had received medical treatment, or been exposed to ionising radiation or dangerous chemicals. In addition, neither had suffered from any serious infectious disease. Serologically-detected H-Y antigen has been conserved in evolution to the extreme (Wachtel et al., 1975a). This is the reason that H-Y antibody, raised in the mouse, can readily be used for the detection of H-Y antigen in human male cells. So far, no cross-reacting materials have been found in human female cells. In a very strict sense, the primary (gonadal) sex of mammals is determined not so much by the presence or absence of the Y chromosome, but by the expression or non-expression of H-Y antigen. This is shown by the occurrence of H-Y antigen positive XO males and H-Y antigen negative XO females in one rodent species, Eliobius lutescens (Nagai and Ohno, 1977), as well as the occurrence of H-Y antigen negative XY females in another rodent species, Myopus schisticolor (Wachtel et al., 1976b). This is one of the reasons for assigning the testis-organising function to H-Y antigen (Wachtel et al., 1975b). Indeed, all human XX males, and even one true hermaphродite, have been found to express H-Y antigen (Wachtel et al., 1976a).

It is obvious that counselling the parents was difficult after finding a seemingly balanced fetal Y/22 translocation. As described earlier, a phenotypically normal boy was born at term. Data from physical examination up to 4 weeks after birth appear to justify the decision of the parents to continue the pregnancy.

Financial support from the municipality of Amsterdam and the Amsterdam 'Ziekenfonds' allowed for the prenatal investigation. We are grateful for the dedicated help of the technical staff in this case, and thank Mrs R. M. Slater-Sweeting for help in preparing this paper. Banding techniques on chromosomes from lymphocyte cultures were performed under the supervision of Dr H. F. De France.

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Partial trisomy 6p with karyotype 46,XY,der(22), t(6;22)(p22;q13)mat

SUMMARY A case of partial trisomy 6p is reported with a review of the various characteristics of this syndrome.

Case report

The propositus was the second child of unrelated healthy parents, born only 10 days before term after an uneventful pregnancy. The father was then 30, the mother 25, and the elder healthy brother 2. The mother had had a spontaneous abortion at 2½ months before having her two sons. At birth the propositus weighed 1800 g. He spent the first 3 months of his life in 2 different paediatric departments where he had feeding difficulties and failed to thrive. X-rays taken during that period showed normal bones in the skull, chest, and pelvis. Blood urea, glucose, and cholesterol, as well as serum immunoglobulin levels, phenylalanine, and sweat test, were normal. There were no reducing substances in the urine.

Feeding problems continued at home. He vomited frequently and could not swallow solid food; at 13 months he still only took milk. He was admitted to our unit with a persistent cough due to pertussis. Clinical examination showed severe psychomotor and growth retardation, with height, weight, and head circumference below the 3rd centile. The child had an odd facies (Fig. 1a) with slight micrognathia and low-set, large, simple ears with a very thin helix (scapha) without antitragus and posterior branch of the anthelix (Fig. 1b). He had extremely long eyelashes, eyes which were always closed, bilateral cataracts, a long philtrum, no definite border to the vermilion, no teeth, an enlarged abdomen, an omphalocele, a deep sacral dimple, normal genitals, and normal hands and feet without abnormal creases. No heart defect could be detected. His skin was dry and his hair thin and sparse. A day after admission he had convulsions without fever. Multiple cultures for bacteria in blood, urine, and spinal cord fluid were negative. The electrolytes showed low sodium, low chloride, and high potassium. Proteinuria was also significant. The child died within 10 days with symptoms of encephalitis due to pertussis. The parents did not allow necropsy.

Fig. 1 (a) The propositus at 13 months. (b) His ear is shown in inset.