Phenotype of partial trisomy 8 (q21 → qter) in two unrelated patients with de novo translocation

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SUMMARY Two unrelated patients with a de novo partial trisomy 8 (q21 → qter) are presented. They had strikingly similar phenotypes, characterised by a wide face with hypertelorism, a broad based nose, malformed ears, micrognathia, and a very short neck. A cleft palate, cardiac defects, and hydronephrosis were present in both patients. The relation between the 8qter syndrome and trisomy 8 (Warkany syndrome) is discussed.

Two newborns with very similar abnormal phenotypes caused by trisomy 8 (q21 → qter) are presented. They both had a wide face with hypertelorism, a broad based nose, abnormal ears, and micrognathia. The neck was very short, and internal anomalies consisted of a cleft palate and cardiac and renal anomalies. They presented some specific symptoms of trisomy 8 (Warkany syndrome), but the most striking fact was their resemblance to each other, which made the diagnosis of an 8qter syndrome in the second patient very likely on clinical evidence.

Case reports

CASE 1

This girl, born 6.4.78, was the second child of non-

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consanguineous parents. At the time of birth her mother was 23 and her father 29 years old. Delivery took place at 37 weeks' gestation. The patient was admitted to hospital on the day of birth because of a strange face and cleft palate. The birthweight was 2700 g and the height 46 cm, both at the 3rd centile. Head circumference was 34.7 cm (50th centile). The forehead was short and wide, hypertelorism was present, and the broad flat nose had a short septum (fig 1). The ears showed a thick helix superiorly which flattened in the mid-portion, while the lobules were large. The tongue was short and broad with a short frenulum, and a cleft of the posterior third part of the palate was present. Micrognathia and a very short neck resulted in a typical profile with the skin of the face resting directly on the body. Several telangiectatic naevi were present on the head and

FIG 1 Patient 1 showing broad nose, retrognathia, and malformed ears.

neck. The thorax was symmetrical and short with widely spaced nipples. The cardiac sounds were regular and clear. The liver was palpable at 1 cm and the spleen could not be felt. The external genitalia showed no abnormalities. The vertebral column was straight. The limbs were normal, with normal and symmetrical reflexes.

Radiological examination showed a wide skull of normal size with a steep base. In the thorax a bilateral enlargement of the heart with a relatively small truncus arteriosus was seen. The lungs appeared emphysematous with overfilled blood vessels. Hydronephrosis of the right kidney with great extension of the pyelum and some calices was seen on intravenous pyelogram. The pelvis was wide with steep iliac wings, but no anomalies were observed in the vertebral column.

Dermatoglyphs consisted of three arches, one ulnar loop on digit 1, and a whorl on digit 5 on the left hand, while on the right hand there were four arches on the fingers and an ulnar loop on digit 1, adding up to a total of seven digital arches. Simian creases and a raised palmar triradius (r'') were observed in both hands.

CYTOGENETIC FINDINGS

The karyotype showed a trisomy for part of the long arm of chromosome 8 resulting from a translocation of the segment $8(q21 \rightarrow qter)$ onto chromosome 9(p24) (figs 2,3). Chromosome studies of both

parents showed normal results and there was no cause to doubt paternity.

FOLLOW-UP

In view of the more or less severe mental retardation found in all previously described patients with partial trisomy 8, the cardiac defect of our patient was not explored further. She was referred to an institution for mentally retarded patients where she died of heart failure at the age of 4.5 months. Necropsy showed a double outlet of the right ventricle and hypoplasia of the left heart. The right ventricle carried out the circulation of the lungs and body. The ductus Botalli and foramen ovale were open. The right kidney had a great distension of the pyelum and some calices. An bicornate uterus was present.

CASE 2

This patient, a boy, born 23.3.79, was the second child of non-consanguineous parents. The first pregnancy resulted in the delivery of a calcified fetus of 4 months. At the time of birth of the proband the mother was 22 and the father 26 years old. The pregnancy was uncomplicated and delivery took place at 42 weeks' gestation. The patient was admitted to hospital at the age of 3 days on account of cleft palate and loss of weight. The birthweight was 3300 g, the height 51 cm (both at the 10th centile), and the head circumference was 37 cm (10th centile). The fontanelle was tense. The forehead was wide, hypertelorism

FIG 2 Karyotype of patient 1:
 $46,XX,-9,+der(9)(8qter \rightarrow q21::9p24 \rightarrow qter)$.

FIG 3 Diagram of chromosomes 8, der(8), der(9), and 9 of both patients resulting in trisomy 8 (q21→qter).

was present, and the wide nose had a broad base (fig 4). The ears had thick helices in the upper part, large flattened lobules, and small fistules. There was a cleft of the soft palate, micrognathia, and a very short neck, which made the double chin rest on the breast. The symmetrical thorax had widely spaced nipples. A protosystolic murmur of the heart was shown on catheterisation to originate from a ventricular septal defect; an insufficient tricuspid valve caused secondary pulmonary hypertension. In the abdomen the liver was palpable at 1 to 2 cm and the spleen could not be felt. The penis was small and the testes had not descended. The hands showed clinodactyly of the 5th finger and the 3rd toe was abnormally implanted.

Radiological examination demonstrated bilateral enlargement of the heart and symmetrical excretion of the kidneys which had normal calices. The vertebral column showed no anomalies.

Dermatoglyphs showed simian creases and raised palmar triradii (r'') in both hands. Fingertip patterns consisted of eight ulnar loops, one whorl on the right 4th digit, and an arch on the left 2nd digit.

CYTOGENETIC FINDINGS

The karyotype showed a translocation of the segment 8(q21→qter) to chromosome 8(p23). The other chromosome 8 being normal, this rearrangement resulted in trisomy of the translocated part (figs 3,5). Karyotypes of both parents were normal. There was no reason to doubt paternity.

FOLLOW-UP

The patient was readmitted to hospital at the age of 5 months on account of vomiting and a tense fontanelle. His height and weight were both far below the 10th centile. The head circumference was 37 cm (10th centile). Severe mental and motor retardation

FIG 4 Patient 2, closely resembling patient 1.

FIG 5 Karyotype of patient 2:
46,XY,-8,+der(8)(8qter→q21::8p23→qter).

had become obvious and there was occasional cardiac decompensation. The third and final admission took place at the age of 6 months because of convulsions. Hydrocephalus had developed and the head circumference was 45.5 cm (90th centile). The CT scan demonstrated a large hydrocephalus and the posterior fossa appeared to be filled with fluid. The patient developed a fever and died within a few days. At necropsy a hydrocephalus internus of the Dandy Walker type was seen. An atrial septal defect, a ventricular septal defect, and malformed pulmonary and tricuspidal valves were seen. The lungs showed oedema and diffuse bleeding. There was agenesis of the gall bladder. The small left kidney had hydronephrosis and a hydroureter was present bilaterally.

Discussion

The first patient with trisomy 8qter was reported by Lejeune *et al* in 1972.¹ Riccardi² compared the clinical features of nine patients with partial trisomy 8 with those of trisomy 8 aneuploidy, the Warkany syndrome, in an international study of 70 patients in 1977. Since then two more patients have been reported by Schinzel³ and two by Fineman *et al*.⁴ Riccardi² selected five features which distinguished the Warkany syndrome. These features were a characteristic facies, abnormal patellae, joint contractures, palmar/plantar furrows, and distinctive toe posture. Three other features were abnormal number or morphology of vertebrae, narrow pelvis, and ureteral or renal anomalies or both. Of these features only the palmar/plantar furrows were not common to the 8q2 translocation patients. Riccardi² and Riccardi

and Crandall⁵ concluded that 8q2 partial trisomy is sufficient to cause the Warkany syndrome. Rethoré *et al*,⁶ Townes and White,⁷ Fujimoto *et al*,⁸ and Fineman *et al*⁴ were also of the opinion that trisomy 8q2 is at least partially responsible for the Warkany syndrome. The only author to disagree was Schinzel.³ The phenotypical similarity of patients with trisomy 8q and trisomy 8q2 can of course be diminished by concurrent deletions caused by the 8q2 translocation. This may have been the case in Schinzel's patients.³ Our patients were both trisomic for the same segment of the long arm of chromosome 8 (q21→qter). Their similarity, and their resemblance to patients with the Warkany syndrome, could only be caused by this specific trisomy and not by a deletion, since the trisomic part of chromosome 8 was translocated to different chromosomes causing different (if any) deletions. They had several symptoms of the Warkany syndrome, consisting of mental and motor retardation, a broad based nose, abnormal ears, cleft palate, congenital heart disease, renal anomalies, slender pelvis (case 1), and abnormal toe posture (case 2). Hydrocephalus of the Dandy Walker type (case 2) has also been described in one patient with trisomy 8 (q23→qter) by Fineman *et al*.⁴ The extensive bone malformations, which have been detected in patients with trisomy 8 and trisomy 8qter,⁹ were not present in our patients, nor did they have joint contractures or abnormal patellae.

We can therefore support the opinion that trisomy 8q2 is partially responsible for the Warkany syndrome. The very striking mutual resemblance of our patients made an early diagnosis of trisomy 8q21→qter possible.

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