

Thus, it seems likely that the association between atretic lesions of the gastrointestinal tract and the Waardenburg syndrome may be significant, but because of its rarity it has been overlooked.

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## Multifocal meningiomas in a patient with a constitutional ring chromosome 22

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**SUMMARY** We report a patient with a constitutional ring chromosome 22, in whom multifocal meningiomas were confirmed at necropsy, and discuss the relationship between the constitutional chromosome change and tumourigenesis of meningiomas in this patient.

There have been many reports of patients with partial monosomy of chromosome 22, but the clinical features of a chromosome 22 monosomy syndrome have not been established.<sup>1,2</sup> However, monosomy 22 and deletion of the distal end of the long arm of chromosome 22 (22q-) are the commonly observed cytogenetic changes in cultured meningioma cells.<sup>3</sup> There has been no report so far of meningiomas arising in patients with constitutional chromosome 22 anomalies.

#### Case report

The proband, an institutionalised mentally retarded

male, was found to have a ring chromosome 22 during a cytogenetic survey, which has been reported previously.<sup>4</sup> He was the second child of unrelated healthy parents and was born to a 32 year old father and 29 year old mother. A brother and a sister were healthy and of normal intelligence. He was delivered at term after an uneventful pregnancy, birth weight 2715 g and length 49 cm. Chest and head circumferences were 28 cm and 30 cm, respectively. Early development was slightly delayed and he began walking alone at 18 months. He suffered infantile tuberculosis at 2 years which was cured after treatment. His mental development was very retarded.

At the age of 20, the proband was admitted to an institution because of an IQ of 21. On examination, he was 158 cm tall (-1.6 SD) and weighed 50 kg (-2.5 SD). His occipitofrontal circumference was 52 cm (-2.5 SD). His skull was microcephalic and dolichocephalic (cephalic index 0.85), with a flat occiput and cutis verticis gyrata. Secondary sexual development was normal. Cutaneous nodules and café-au-lait patches were not present. Other abnormalities noted were unusual facial appearance with

full eyebrows, long eyelashes, hypertelorism (inner canthal distance 4.5 cm, outer 9.5 cm), high nasal bridge, large nose, and large ears. He also had definite kyphosis, increased reflexes, and hearing loss (fig 1a-c).

At 25 years of age, he had episodes of apathy, insomnia, anorexia, vomiting, mask-like facial expression, tremor of the upper extremities, instability of gait, and convulsions. These symptoms worsened and he died at 27 years.

#### CYTOGENETIC STUDIES

Chromosome analysis was performed on peripheral blood lymphocytes. A total of 30 cells was analysed. In all cells examined there were 46 chromosomes, but one of the G group chromosomes was replaced by a small ring chromosome. Using the Giemsa staining method of Seabright,<sup>5</sup> the ring chromosome was identified as originating from chromosome 22. The size and banding pattern showed that the breaks were at p12 and q13.3 (fig 2a, b). Other tissues were not available for chromosome analysis.

#### NECROPSY FINDINGS

The brain was microcephalic (brain weight 1090 g). Macroscopic examination revealed a subarachnoid multilocular cyst, approximately 6×4×3.5 cm in size, filled with slightly turbid fluid at the medullocerebellar angle, which had compressed the medulla oblongata and other surrounding brain tissues. This was the apparent cause of death. On

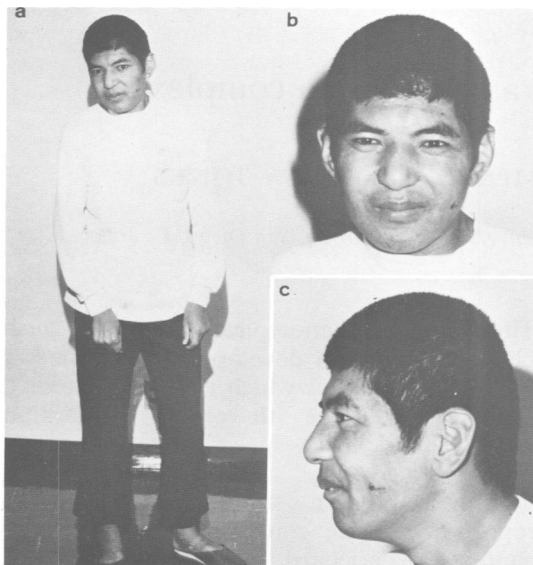


FIG 1(a-c) The proband aged 23 years.

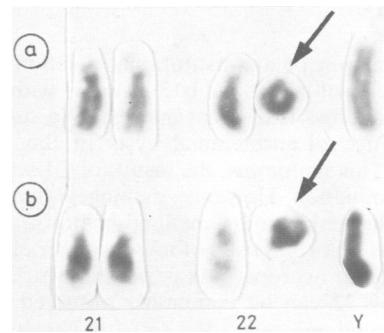


FIG 2 Partial karyotype of chromosomes 21, 22, and Y from the patient, using conventional Giemsa staining (a) and trypsin-Giemsa staining (b). The arrows indicate the ring chromosome 22.

microscopic examination, the cyst wall consisted of two layers; an outer fibrovascular layer and an inner meningotheial-like cell layer. The latter showed varying thickness and a peculiar tendency to protrude into the cavity, subdividing the cyst into irregularly anastomosing partitions (fig 3a). In addition, the meningotheial-like cells showed multiple varying nodules of hyperplasia in many areas, each of which had histological patterns similar to those of fibroblastic, transitional, or angioblastic meningiomas. Degenerative features were not prominent.

Several small meningeal nodules with diameters less than 0.6 cm were found attached to the dura mater and the falx cerebri. Their histological picture was that of transitional meningioma with psammoma bodies (fig 3b).

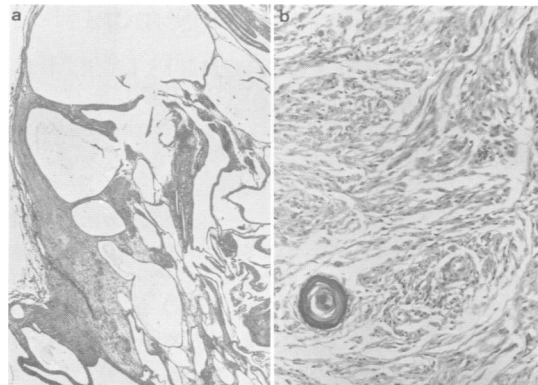


FIG 3 Microscopic morphology of multilocular portion of cyst with numerous nodules of hyperplastic fibroblastic cells (a) and typical transitional meningioma with a psammoma body (b).

## Discussion

The association of a constitutional deletion of the terminal end of q22 (band q13.3→qter) with multiple meningiomas is of great interest. We suspected the presence of intracranial cysts in the patient because of his symptoms, the results of CT scan, and EEG examination. However, meningeal hypoplasia and dysplasia, including meningiomatosis, and an anomalous cyst composed of meningocytic elements were found at necropsy. As is well known, 22q- or monosomy 22 can be commonly observed in cultured meningioma cells.<sup>3</sup> Recently, the relationship between constitutional and somatic chromosomal changes in patients with retinoblastoma<sup>6</sup> and Wilms' tumour<sup>7</sup> has been shown. These findings tend to support a close relationship between a partial deletion of chromosome 22 and meningeal malformations including tumours. The karyotype of the tumour cells was not investigated in our patient. However, the presence of a constitutional ring chromosome 22, which may lack the distal end of the long arm, supports the suggestion of Zankl and Zang<sup>3</sup> that genetic information involved in the control of cell proliferation is located in this segment. Recently, the human homologue of the simian sarcoma virus oncogene, c-sis, has been assigned to 22q.<sup>8</sup> The proto-oncogene c-sis might be related to the genesis of meningiomas. Furthermore, these chromosome changes may be tissue specific, in the sense that they may predispose specifically to meningiomas, because necropsy revealed no neoplasia in other organs of our patient.

In conclusion, the findings described in this paper suggest that constitutional deletions of chromosome 22 may predispose to tumourigenesis of meningiomas. To confirm this, further neuropathological studies of patients with 22q- or monosomy 22 are required. Clinical examination for congenital anomalies and chromosome analysis should be carried out in all patients with meningiomas.

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## Prenatal diagnosis and follow up of a child with a complex chromosome rearrangement

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**SUMMARY** A case of de novo, apparently balanced, three way exchange by translocation plus a pericentric inversion is described. The karyotype is 46,XX,t(6;11)(p21;q21),t(11;21)(q21;p13),inv(6)(p21q11) and was ascertained through second trimester amniocentesis. The structural rearrangements appear balanced.

The child was phenotypically normal at birth. Growth and motor development were normal until 30 months, at which time linear growth dropped below the 5th centile. In addition, there was delayed speech development at 2 years of age.

As far as we can determine, this is the first report of a three chromosome exchange including a pericentric inversion ascertained through genetic amniocentesis.