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Requests for reprints to Dr A Tabor, Section of Clinical Genetics, Department of Gynecology and Obstetrics YA, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark.

Tetraploidy in a liveborn infant with spina bifida and other anomalies

SUMMARY Although tetraploidy of human chromosomes (92,XXYY) has been described frequently in abortuses, only one example in a liveborn infant has previously been described.¹ A second malformed infant with a complete tetraploid chromosome complement, who lived for 15 days, is reported. In addition to many of the malformations described in the first case, this infant also had a sacral myelomeningocele and skeletal anomalies. The probable origin of the tetraploidy was a failure of cytoplasmic cleavage at the first mitotic division of the fertilised ovum.

Although tetraploidy of human chromosomes (92,XXYY) has been described frequently in abortuses, only one example in a liveborn infant has previously been described.¹ We report here a second example, with some similar phenotypic effects, which are listed in the table.

*She has since this report had a second pregnancy monitored by amniocentesis, which showed a 46,XX fetus; α -fetoprotein levels were normal.

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TABLE Features of liveborn human tetraploids

Features	Golbus et al ¹	Present case
Length	<10th centile	90th centile
Head circumference	<3rd centile	10th centile
<i>Face</i>		
Hypertelorism	-	+
L anophthalmia	+	-
R microphthalmia	+	-
Beaked nose	+	+
Short philtrum	+	+
Low set ears	+	-
Preauricular tags	+	-
Unravalled helices	+	+
Absent ear cartilage	+	+
Prominent narrow forehead	+	+
Bifid uvula	+	-
<i>Brain</i>		
	'encephalopathy'	hydrocephalus microgyria Arnold-Chiari malformation aqueduct forking ectopic grey matter
<i>Spine</i>		
	kyphosis, scoliosis (mid-thoracic)	sacral meningo- myelocele
<i>Musculoskeletal</i>		
Hyperconvex finger nails	+	-
Low set thumbs	+	-
Left simian line	+	partial
Bilateral hallux 2nd toe gaps	+	+
Flexed wrists	+	+
Flexed fingers	+	±
Flexed ankles	+	talipes, inversion and flexion of feet
Flexed knees	+	+
Arachnodactyly	-	+ hands and feet
Hypotonia	+	-
<i>Urogenital</i>		
Kidneys	normal	{ hypoplastic (6·9 g together) dysplastic
Rest of GU tract	bilateral megaureter, bilateral ureteral reflux, urethral stenosis	normal
	-	undescended testes
<i>Respiratory</i>		
	-	lung hypoplasia (29·3 g together)

Case report

This child, born 17.3.79, was the first baby of healthy unrelated parents; the mother was 26 and the father 27 years old. There was no family history of any relevant birth defects except for a paternal second cousin with spina bifida (male). During the pregnancy the mother was well except for late toxemia, for which she was admitted to hospital one week before labour was induced. During pregnancy there were no infections and no exposure to known toxic agents such as drugs, cigarettes, and x-rays. The mother's previous menstrual cycle had been normal (28 days) and the contraceptive pill had been stopped 6 months before conception.*

The baby was thought to be at term on dates, but

subsequent examination indicated a gestation of 36 to 38 weeks. Following a Syntocin drip induction of labour (because of maternal pre-eclamptic toxæmia), delivery was achieved after a pudendal block with a forceps delivery for the second stage. There was no neonatal distress. Birthweight was

2650 g and head circumference was 31.5 cm. Spina bifida and other abnormalities were noted and the child was transferred to the Royal Children's Hospital. Death occurred on the 15th day.

At necropsy there was flexion deformities of elbow and knees, and talipes calcaneovalgus of both feet



FIG 1 *Tetraploid infant.*

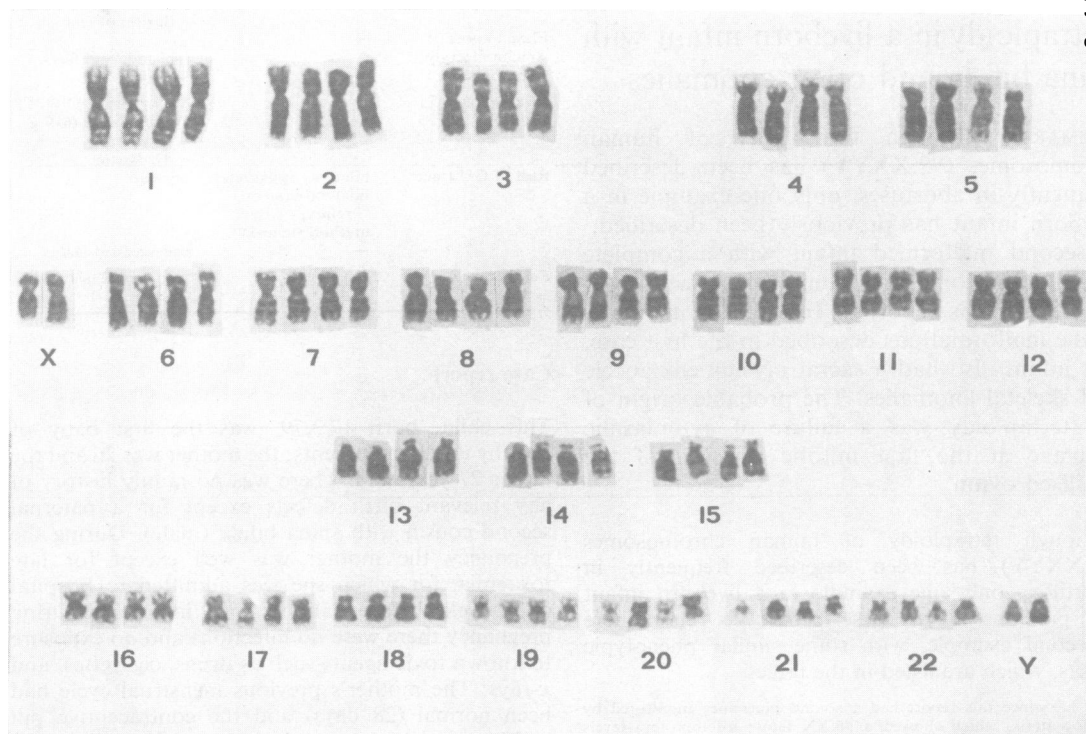


FIG 2 *Karyotype.*

especially the right, with arachnodactyly. Crown-heel length was 53 cm. The facies was peculiar, with turricephaly, a narrow forehead, micrognathia, and flat untravelling ears lacking cartilage (fig 1). A sacral meningocele was present (4.8×4 cm) with a patulous anus.

Internal examination showed hypoplastic kidneys and lungs with cystitis and pyelonephritis. The brain had hydrocephalus, microgyria, Arnold-Chiari malformation, a thin septum pellucidum, aqueduct forking, and ectopic grey matter in the ventricular wall. The eyes showed no abnormality (Dr C G Keith).

CYTOGENETICS

Chromosome analysis was performed on two samples of peripheral blood lymphocytes. All cells examined (1000) were tetraploid, 92,XXYY (fig 2). Sex chromatin was negative in fibroblast culture.

Fibroblast cultures derived from five other tissues were also scored and were found to be tetraploid in skin (1000 cells), lung (200 cells), pericardium (150 cells), spleen (100 cells), and testis (50 cells), a total of 2500 cells. No evidence of diploid mosaicism was detected in any culture. Both fibroblasts and transformed lymphocytes were stored in liquid nitrogen for future use.

Parental karyotypes were found to be normal. G and C banding techniques were employed in an attempt to determine the probable origin of the infant's tetraploidy.

When the 92 chromosomes are set out in a G banded karyogram (fig 2), there are only slight differences between pairs of the same chromosome (for example, see XX). The only informative normal variant in the karyotype was the size of the heterochromatin on chromosome 9, and the larger and smaller variants were consistently paired in G and C banded cells.

Discussion

Although human tetraploidy is rare enough to justify a case report, triploidy (69,XXX;69,XXY, etc) is estimated to occur in about 1% of conceptuses.² Although the vast majority are expelled early in pregnancy, a number have survived beyond 28 weeks of gestation, including eight term babies.¹ These eight babies had a variety of malformations involving many systems: growth deficiency, microphthalmia, coloboma of iris, hypertelorism, abnormal pinnae, skeletal defects, cardiac defects, genital defects, simian creases, cerebral defects, including hydrocephalus, and occasionally lumbosacral meningocele and other defects. Many of these widespread anomalies, presumably caused by a

gross distortion of the action of many genes, were seen also in these two tetraploid infants.

The origin of both triploidy and tetraploidy is discussed by Kajii and Niikawa,³ who used sequential Q and R fluorescence banding techniques on 16 triploid abortuses, one tetraploid 92,XXXX abortus, and their parents. Several mechanisms (errors in both maternal and paternal meiosis, dispermy) were demonstrated in the triploid cases, and in the XXXX tetraploid case duplication of several maternal and paternal chromosomes indicated normal division of chromosomes and suppression of cell division at the first cleavage division of the zygote.

As the sex chromosome complements of all reported human tetraploids have been either XXXX or XXYY, it is highly probable that tetraploidy is a post-conceptual event owing to failure of cell cytoplasm cleavage at a mitotic division, at which, nevertheless, the 46 chromosomes divide to create 92 chromosomes in the same undivided cell. The absence of mosaicism in the present case, in which 2500 cells from six tissues were all tetraploid, indicates that the mitotic division at fault was probably the first.

The occurrence of a neural tube defect in a tetraploid baby is a further example of the heterogeneity in this group of disorders and emphasises the importance of further investigation in patients with neural tube defects who show atypical features.⁴

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DAVID PITT, MARGARET LEVERSHA,
CHERYL SINFIELD, PETER CAMPBELL,
ROSS ANDERSON, DOUGLAS BRYAN,
AND JOHN ROGERS

*Departments of Genetics, Paediatrics, and Pathology,
Royal Children's Hospital, Melbourne, Australia*

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Requests for reprints to Dr David Pitt, Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Parkville, Victoria 3052, Australia.