Antenatal Diagnosis of Patau's Syndrome (Trisomy 13) including a Detailed Pathological Study of the Fetus

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Summary. The first ever antenatal diagnosis of Patau's syndrome (trisomy 13) during the 19th week of the pregnancy of a 42-year-old woman is reported. Karyotypes were obtained from amniotic fluid cell cultures established at 17 weeks and the results were confirmed by chromosome banding studies and fetal skin cultures. The pregnancy was terminated by hysterotomy and sterilization was performed at the same operation. A detailed description of the fetus is included and the pathogenesis of arrhinencephaly is discussed. The current status of antenatal screening for chromosome anomalies is presented.

Following a feasibility study for antenatal chromosome screening (Butler and Reiss, 1970), we have examined a number of pregnancies where the recurrence risk of fetal abnormality was high because of a familial translocation, including both Down's syndrome and non-Down's syndrome problems. We have also instituted a small-scale survey of pregnancies judged to be at low risk principally where the mother is aged over 40 or where a random chromosome anomaly, particularly trisomy 21, has occurred previously. This is an on-going study and will be reported in detail in due course. This paper records the first ever prenatal detection of a fetus with Patau's syndrome (trisomy 13).

Case Report

This woman was referred to us at the age of 42 years for investigation of her fourth pregnancy which was unplanned and which she obviously did not wish to continue if the chromosome pattern proved to be abnormal. She was concerned about the possibility of Down's syndrome occurring because of her age and she had been the first to mention antenatal screening tests having seen a television programme about them.

Her previous obstetric history was uneventful and she had given birth to three normal children aged 19, 16, and 15 years at the time of this investigation. She had had no miscarriages.

The gestation of the present pregnancy had already reached 17 weeks when she received her obstetric examination before amniocentesis and the specimen was therefore collected immediately via the abdominal route as previously described (Butler and Reiss, 1970). A total of 10 ml of noticeably blood-stained liquor was collected and divided equally between two sterile plastic containers.

Cell Culture and Cytogenetics

Despite rapid transportation, in ice, to the cytogenetics laboratory, small clots were already apparent in the tubes. Two 8-cm Carrell cultures were established by our standard method using 80% medium 199 and 20% calf serum. The calf serum used is now marketed as Bovine Serum by Flow Laboratories and is collected when the animals are six months old.

Despite the contamination of the specimen with maternal blood, the cultures were highly active and the first culture containing eight colonies was harvested after 14 days. The second culture, with 13 colonies was processed following a subculture five days later. Ample material was obtained on both occasions and the chromosome count in 25 cells was consistently 47 with an XY male sex chromosome constitution and an extra chromosome in group D(13–15) (Fig. 1).

Some unstained preparations were treated with a Trypsin solution to produce banding before staining with Leishmann stain. This banding method differs in detail from the one described by Seabright (1971) and is the subject of a separate publication.
which is in preparation. The banding patterns observed were consistent with a diagnosis of trisomy 13 (Fig. 2).

These results were subsequently confirmed using cultures of fetal skin.

Management of Pregnancy

The patient was informed immediately of the findings and she elected to have a termination by abdominal hysterotomy so that she could be sterilized by tubal ligation at the same time. This was performed at 20 weeks and the fetus in the intact gestation sac was removed with minimum damage for detailed pathological examination. The patient’s postoperative progress was uneventful.

Necropsy of Fetus

The fetus was male and moderately hydropic (Fig. 3). The weight (442 g), and crown-rump length (16.5 cm) corresponded to a gestational age of about 20 weeks. Over the vertex there was an area of apparent aplasia of the scalp measuring 1.9 x 1.2 cm. Microscopically it was sharply differentiated from the surrounding normal immature skin and consisted of a thin layer of avascular myxomatous tissue the surface of which was covered by a single layer of cuboidal epithelium. No accessory skin organs were present. The ears were lowset but not otherwise abnormal and the upper lip was long with a clearly marked filtrum. The posterior half of the hard and soft palate was cleft. There was a
large cystic hygroma of the right side of the neck extending into the right cheek composed of cysts up to 1 cm in diameter lined by endothelium and containing yellowish watery fluid. The thorax was wide and the sternum relatively short. A small extra digit was present on the ulnar aspect of each hand but there were no obvious flexion deformities. Both feet showed talipes equino-varus.

Cardiovascular System. There was an ostium secundum defect of the atrial septum with a high ventricular septal defect and severe stenosis of the pulmonary valve. The aorta arose completely from the right ventricle with the aortic valve situated behind the pulmonary valve. The ductus arteriosus was atretic. Both umbilical arteries were present.

There were several subcapsular foci of calcification of the liver particularly of the left lobe. Microscopically each focus was surrounded by connective tissue usually including several bile ducts and blood vessels. It is probable that calcification followed necrosis of unknown aetiology.

There was a deficiency of the anterior part of the left kidney exposing the renal pelvis but otherwise both kidneys were normal.

The brain weighed 39 g. Although its general appearance was consistent with the gestational age, neither olfactory tract was visible to the naked eye contrasting with the relative prominence in a normal brain of similar maturity where they have a diameter in the region of 0.3 cm. At the proximal end of each cribriform plate there was a small pale nodule about 0.1 cm diameter which was shown microscopically to represent the olfactory bulb. The ethmoid and the anterior part of the sphenoid including both nasal cavities were sectioned serially in the coronal plane. All sections showed a very thin olfactory tract on each side of the midline; these were closely applied to the periosteum of the ethmoid bone and received nerves directly from the epithelium lining the nasal cavities. On the medial aspect of each olfactory tract there was a small mass composed of nerve cells and fibres. Numerous axons were demonstrated by Holme’s stain in the region of these mitral cells but only occasional axons were stained in the olfactory nerves and olfactory tracts.

All other organs including the eyes were normal.

Discussion

Since 1967, when the first practical antenatal chromosome study was made, there has been a steady improvement in the relative success rate of cell culture for fetal karyotyping so that the leading centres throughout the world are now able to offer a 90% certainty of obtaining a result (Butler, 1972). Despite this improvement, the number of pregnancies screened during this four- to five-year period is still relatively small and the series of Nadler and Gerbie (1971) remains the largest on record. The experience of Ferguson-Smith et al (1971) and ourselves (Butler, 1972) is probably representative of the majority. From published sources and personal communications it would appear that by mid 1972 approximately 1000 antenatal chromosome investigations had been made throughout the world, the bulk of these being related to the risk of Down’s syndrome. The total includes studies of 50 pregnancies of high risk in families where a translocation between a G or D chromosome and a chromosome 21 was present, 13 of the fetuses being affected, and 385 pregnancies where there was a previous primary or regular Down’s patient (+21) in the family, five further Down’s patients being dis-
covered. Finally, in the group where the age of the mother was the important factor, the vast majority being over 40 years, 368 pregnancies were screened and 10 affected fetuses were detected, made up of nine Down's syndrome (+21) and the present case of Patau's syndrome (+13).

In the high maternal age group the frequency of anomaly of 2.7% is close to the figure predictable from the known frequencies of chromosome abnormalities, with Down's syndrome predominating as expected. Our experience, based on a 10-year survey in the North East Metropolitan Area of London (population approximately 3.4 million), indicates that the frequency at birth of trisomy 13 is not greater than 1 in 15,000 after making allowances for those cases not studied because of lack of clinical recognition. Our discovery antenatally of a fetus with this condition is therefore somewhat fortuitous although, as in Down's syndrome, over half of all the cases are born to women in the 'over 35' age group.

The social implications of the present case are worthy of emphasis. We were dealing with an unplanned pregnancy and therefore, presumably initially unwanted, though the mother was prepared to go to term if the chromosome pattern was normal. However, the result was adverse and she was spared the traumatic experience of giving birth to such a grossly abnormal child by having the pregnancy terminated at mid-term following our predictions. Tubal ligation was performed at the same time.

The spectrum of anatomical features of the fetus was similar to that found in most examples of trisomy 13 (Snodgrass et al., 1966). Examination of an affected fetus of this maturity was of interest in that it threw some light on the development of arrhinencephaly, a condition where the olfactory bulbs, tracts, and striae are absent. This is sometimes associated with developmental failure of the more central parts of the rhinencephalon such as the hippocampus, fimbria, indusium griseum, and fornices whilst the more severe forms involve agensis of the corpus callosum or prosencephaly (Crome and Stern, 1972). All grades of arrhinencephaly have been found in cases of trisomy 13. Microscopic examination of this fetus showed that migration of cells from the developing nervous system to the olfactory epithelium had occurred to form olfactory nerves of about normal size. In addition the mitral cells of the olfactory bulbs had developed, although in considerably reduced numbers, and their axons had formed olfactory tracts too small to be seen by the naked eye. It appears likely that in some cases of so-called arrhinencephaly, detailed examination would reveal hypoplasia of the olfactory bulbs and tracts as in this example.

The histological features of the scalp were similar to those of the only three other cases which we have examined where the lesion was not infected. In all, the dermis showed poor development of collagen and the surface epithelium consisted of one to three layers of cells with complete absence of hair follicles and sweat glands. It is evident that this condition is a localized dysplasia of skin.

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REFERENCES


