Trisomy D₁ (13-15) Associated with XO/XY Mosaicism

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Double aneuploidy in which an extra sex chromosome coexists with autosomal trisomy was first reported in a child with trisomy 21 and XXY sex chromosomes (Ford, Jones, Miller, Mittwoch, Penrose, Ridler, and Shapiro, 1959); since then XXX trisomy 21 (Day, Wright, Koons, and Quigley, 1963; Yunis, Hook, and Alter, 1964), XYY trisomy 21 (Verresen and van den Berghe, 1965), XXX trisomy 18 (Uchida and Bowman, 1961; Ricci and Borgatti, 1963), and XXY trisomy 13-15 in an embryo (Pergament and Kadotani, 1965) have been reported.

Sex chromosome mosaicism associated with autosomal trisomy is less common, being described in only three cases, all with trisomy 21: XO/XX (van Wijck, Blankenborg, and Stolte, 1964; Root, Bongiovanni, Breibart, and Mellman, 1964) and XO/XX/XXX (Zergollern and Hoefnagel, 1964). The infant to be described represents a hitherto unrecognized association of XO/XY mosaicism and trisomy 13-15. He showed many features characteristic of the trisomy 13-15 syndrome, together with Arnold-Chiari malformation, sacral meningocele, gonadal agenesis, and a minor degree of feminization of the pelvic organs.

Case Report

A Caucasian male, birthweight 2570 g., was the result of the tenth pregnancy of a 43-year-old mother who had been married for 18 years. By the age of 36 years she had had six normal babies but thereafter had two miscarriages and one normal infant. All the normal babies weighed over 3500 g. at birth. The father was 42 years old. A maternal aunt had four healthy female children but had had six miscarriages. There was no history of congenitally malformed children on either side of the family.

The present pregnancy was complicated only by persistent breech position of the foetus, though the mother

thought that foetal movements were more active than during her previous pregnancies. Labour occurred spontaneously at 40 weeks' gestation and the infant was delivered precipitately by the breech. He showed multiple congenital anomalies suggestive of the D trisomy syndrome, together with a pedunculated sacral meningocele measuring 6 × 4.5 cm., associated with reduced tonicity of the lower limbs which were held in extension and showed few spontaneous movements. The meningocele was repaired surgically at the age of 11 hours. A loud systolic murmur and an early mid-diastolic murmur were heard on auscultation at 2 days when electrocardiography showed right axis deviation of 110° and evidence of right ventricular hypertrophy. The infant had recurrent apnoeic attacks following operation and went into mild congestive cardiac failure five days later. He died suddenly following an apnoeic attack on the seventh day of life.

Necropsy Findings. Weight 2020 g., length crown-rump 35 cm., crown-heel 49 cm. The head was small (circumference 29 cm.), with a flat occiput and pointed frontal region. In the parieto-occipital region there was an irregular area of aplasia of the skin measuring 2.5 × 1.5 cm. The cranio-facial features are illustrated in Fig. 1a and b. The nose was bulbous at the tip and had a broad bridge. There were short horizontal palpebral fissures and redundant folds of skin of the eyelids. Both eyes were microphthalmic with oval corneae, bilateral colobomata of the iris and choroid, and lens opacities were present. The mouth was rather small with a high arched palate and the tongue was notched at its tip. The upper lip overhung an everted lower lip and there was a mild degree of micrognathia. The ears were slightly low set with primitive helices, and the skin was reflected from the edge of each pinna directly onto the scalp, fixing both ears flat against the head. Minimal webbing of the neck was present. There were no external thoracic or abdominal abnormalities. A hypoplastic scrotum extended almost to the tip of a small penis (Fig. 2), and gonads could not be palpated in scrotum or inguinal canals. The hands were spade-like with flexion deformities of the fingers and retroflexible thumbs. A horizontal palmar crease was present

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FIG. 1a and b. Cranio-facial features.

on the right palm only and all nails showed transverse hyperconvexity. There was severe talipes calcaneovalgus and the soles were oblong and fleshy with a vertical crease between the first and second toes. Surgical repair of the meningocele had left an operation wound 4 cm. long over the sacrum.

Cardiovascular system. The heart (21 g.) showed dilatation and hypertrophy of the right side with a hypoplastic ventricle. The great vessels were completely transposed with atresia of the pulmonary valve and hypoplasia of the pulmonary trunk, though the pulmonary arteries were of normal size. The foramen ovale was fenestrated, and there was a high ventricular septal defect (0.4 × 0.3 cm.) and a widely patent ductus arteriosus. The right umbilical artery was absent and the left artery lay in the edge of a peritoneal fold attached along the left side of the brim of the pelvis.

Urogenital system. The kidneys (R. 22 g., L. 26 g.—normal 11 g.) were large and hyperlobated, and on microscopy showed a number of cortical cysts lined by cuboidal epithelium and occasionally surrounded by strata of connective tissue. A structure composed of smooth muscle, measuring 1.8 cm. long and 0.5 cm. diameter, lay in front of the rectum below the rectovesical pouch. It possessed a tiny lumen which communicated with the posterior urethra immediately below the verumontanum and was lined by infantile endometrium. Superiorly it terminated in a rather pointed extremity, with no evidence of division into Fallopian tubes. No gonads or epididymis could be found in the scrotum, inguinal canals, or pelvic tissues, and neither the vasa deferentia, seminal vesicles, nor prostate gland could be identified. An accessory adrenal gland 0.4 cm. diameter was present in the pelvic tissues.

Head. Microscopy of the aplastic area of scalp showed complete absence of hair follicles; the epidermis was thin in places and absent elsewhere. There was an accessory bone measuring 2.5 × 0.8 cm. between the anterior parts of the frontal bones, and the pituitary fossa was unusually shallow. The tentorium was poorly developed and situated rather higher than normal, producing a deep groove of the uncus, temporal, and occipital lobes on the right side of the brain, and a shallow

FIG. 2. Hypoplastic scrotum and small penis.

indentation of the left uncus and medial aspect of the parietal lobe.

Central nervous system. The brain (302 g.) showed absence of olfactory bulbs, tracts, and trigones, and the olfactory sulci and gyri recti were not demarcated. The portion of the right occipital lobe lying below the tentorium indented the upper surface of the cerebellum and was soft and gelatinous on section. The third to the twelfth cranial nerves had a pronounced upward course and were slightly adherent to thickened leptomeninges over the base of the brain. The midbrain was elongated with a slit-like, patent aqueduct. The cerebellum and brain-stem (together 21 g.) showed a well-marked Arnold-Chiari malformation with the vermis of the cerebellum and much of the medulla descending below the foramen magnum. Coronal section showed normal lateral ventricles and a rather narrow third ventricle. The fimbriae, fornices, and basal ganglia were normal but the corpus callosum did not entirely roof over the posterior parts of the thalami.

Microscopically, groups of ectopic nerve cells were found in the area occupied by the dentate nucleus in the cerebellar white matter and the middle pontine peduncles. There was a possible excess of such cells in the angles of the lateral ventricles and their inferior horns, and the anterior surface of the pons was covered by a layer of ectopic glial tissue replacing the soft meninges.

Ocular system. The right eye was microphthalmic and showed a coloboma of the infero-medial part of the iris and a large choroidal coloboma involving the optic disc. Two white folds arising in the area of the coloboma passed forwards to become adherent to the lens (Fig. 3). Microscopically, the cornea was normal, but the lens was cataractous with a small portion of retinal tissue adherent to it. Section through the coloboma showed

elongated ciliary muscle which was lined by folds of pigmented ciliary epithelium adherent to some more posteriorly placed retinal tissue. A tongue of sclera extended through the coloboma into the eye. Although the trabecular meshwork and Schlemm's canal were present on both sides, the filtration angle was not formed. Near the equator both choroid and retina were absent in one area, posterior to which the retina was dysplastic and showed rosette formation. Within the sclera at the site of the optic nerve there was a cystic space lined by aberrant retinal tissue.

TABLE
CHROMOSOME COUNTS AND KARYOTYPE DIAGNOSES

Tissue	Broken Cells		Trisomy D (13-15)		> 47
	< 46	46	46/XO	47/XY	
Skin	3	2	16	42	—
Blood	2	1	8	22	—
Totals	5	3	24	64	—

The left eye was similar to the right eye with a large coloboma of iris and choroid involving the optic disc. Anteriorly there was a similar fold of white tissue adherent to the ciliary body near the lens.

Other organs. Apart from a universal mesentery, no other congenital anomalies were noted. Death was due to extensive right alveolar pneumonia.

Cytogenetic Findings. Using techniques described by Butler (1965) chromosome preparations were obtained from cultures of peripheral blood during life and of skin taken 24 hours after death. The results of chromosome counts are shown in the Table. All intact cells had counts of 46 or 47 and contained seven large acrocentric chromosomes consistent with a diagnosis of trisomy D₁ (13-15). On morphological grounds the additional chromosome was considered to be either No. 13 or No. 14. Although satellites were present, they were not unduly prominent or enlarged as they were in six of seven cases of trisomy D reported by Snodgrass, Butler, France, Crome, and Russell (1966).

Unbroken cells with 46 chromosomes showed absence of a member of Group G (Y-21-22). The Y chromosome was morphologically characteristic (Fig. 4) and a detailed microscopical examination of the 27 cells with 46 chromosomes revealed normal 21-22 pairs and an XO constitution in 24 of them (Fig. 5).

Discussion

Physical examination showed many congenital malformations commonly associated with the trisomy D₁ (13-15) syndrome. Typical craniofacial defects included microcephaly, marked trigonocephaly, a bulbous nose with a broad bridge, ocular defects, a long upper lip, low-set ears with primitive helices, and slight webbing of the neck

Fig. 3. Right eye showing retinal folds adherent to the lens.

FIG. 4. Karyotype showing trisomy D₁ (13-15) and XY sex chromosomes. FIG. 5. Karyotype showing trisomy D₁ (13-15) and XO sex chromosomes.

(facial category 2—Snodgrass *et al.*, 1966). The hands were spade-like with flexion deformities of fingers, retroflexible thumbs, and hyperconvex nails. There was marked talipes calcaneo-varus and prehensile halluci, but the heels were not protuberant. The presence of a sacral meningocele has not been recorded previously. Necropsy showed transposition of the great vessels with a ventricular septal defect and patent ductus arteriosus; the kidneys were hyperlobated and contained

microcysts. An accessory spleen, reported as common by Smith, Patau, Therman, Inhorn, and DeMars (1963), was embedded in the tail of the pancreas. The brain showed arrhinencephaly, an abnormality present in more than 50% of all patients with trisomy D₁ (13-15), together with an Arnold-Chiari malformation which has not been described before.

The range of ocular abnormalities in trisomy D₁ has been described by Keith (1966), and this infant's

eyes resembled those in the group of patients with moderately severe deformities. They usually have a coloboma of the iris and choroid, cataract, retinal septa, and dysplastic retina lining the back of the lens, and may have an ingrowth of sclera and a nodule of mesenchymal tissue at one pole of the lens. Ocular anomalies have not been described in XO/XY mosaicism and are uncommon in Turner's syndrome, though cases of oculomotor nerve palsies have been described (Duke Elder, 1964), and one case of posterior embryotoxon (Royer and Géhin, 1963) and one case of congenital glaucoma (Laurent, Royer, and Noel, 1961) have been described. No ocular anomalies have been found in 10 cases of Turner's syndrome examined at this hospital.

The external genitalia were similar to those described by Smith *et al.* (1963) in males with trisomy D₁ (13-15) but, in addition, complete gonadal agenesis and a rudimentary uterus were found at necropsy. Absence of gonads may be expected to result in feminization of both external and internal genitalia, as shown experimentally by Jost (1947) in castrated male rabbit foetuses. Thus, factors other than gonadal agenesis are probably involved in the sexual development of our patient. Ferguson-Smith (1965) has shown that differentiation of the genitalia may proceed in either a male or female direction in individuals with XO/XY mosaicism, though none of his cases had complete gonadal agenesis. A similar range of genital differentiation has been found in five examples of XO/XY mosaicism studied by the authors.

Studies of spontaneous abortions have shown a high frequency of the XO karyotype, indicating that only about 1 in 30 of such conceptions survive to become viable infants (Geneva Conference, 1966). Double aneuploidy involving XO cells and autosomal trisomy possibly has an even lower survival rate: indeed, in such cases, XO cell lines have been demonstrated only in mosaic form (van Wijck *et al.*, 1964; Root *et al.*, 1964; Zergollern and Hoefnagel, 1964).

Summary

A male child is described with congenital malformations which are commonly associated with the trisomy D₁ (13-15) syndrome. In addition a sacral meningomyelocele and an Arnold-Chiari malformation were present. The external genitalia

were hypoplastic, there was a rudimentary uterus, and the gonads were absent.

Cytogenetic studies revealed seven chromosomes in group D (13-15) representing probable trisomy 13. In addition, sex chromosome mosaicism of the type XO/XY was demonstrated. The major anomalies, including ocular defects and intersexuality, are discussed in relation to the chromosomal findings.

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