Oral-facial-digital Syndrome, with Polycystic Kidneys and Liver: Pathological and Cytogenetic Studies

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In 1954 Papillon-Léage and Psaume (1954a, b) described 8 patients with a syndrome characterized by congenital anomalies of the face, oral cavity, and digits. Since then, several groups of patients have been reported (Gorlin, Anderson, and Scott, 1961; Ruess, Pruzansky, Lis, and Patau, 1962; Gorlin and Psaume, 1962; Kaplan, Vaharu, Voorhess, and Gardner, 1962; Kushnick, Massa, and Baukema, 1963; Doege, Thuline, Priest, Norby, and Bryant, 1964) with this disorder, and the name 'oral-facial-digital syndrome' (OFD) has been suggested (Ruess *et al.*, 1962).

Chromosome studies have been carried out on a number of patients with OFD. Patau, Therman, Inhorn, Smith, and Ruess (1961) described a mother and child who presumably had a 'partial trisomy' resulting from an insertion into a No. 1 chromosome (Denver classification). Gorlin (1961) also reported one of his six patients to have an abnormal No. 1, though no karyotype was published. However, the majority of patients studied have had normal karyotypes (Ruess *et al.*, 1962; Gorlin and Psaume, 1962; Kaplan *et al.*, 1962; Doege *et al.*, 1964).

Kushnick *et al.* (1963) described another chromosomal aberration in association with OFD. Their patient had 47 chromosomes, the extra chromosome matching best with group A, and the authors believed this probably was a trisomy for the No. 1 chromosomes. To our knowledge, this patient is the only male reported with OFD.

In a recent article Doege *et al.* (1964) described a family of 89 persons in which 15 females from 4 generations had OFD. The pedigree was compatible with a dominant mode of inheritance, and the male-female ratio (12:21) was noted to fit with the expected ratio (1:2), if this syndrome is lethal to males. In this series of patients, necropsies were done on 3 affected members. One of these had

polycystic kidney disease, and one had polycystic liver and kidney disease. These patients had normal karyotypes in cells derived by culture of their peripheral leucocytes. It is of interest, however, that the patient with polycystic liver disease had an extra chromosome similar to group G in hepatic cells. The authors were unable to assess the significance of this finding.

Case Report

Clinical Findings. The patient was a newborn Caucasian female, dead at the time of examination. The mother, a 13-year-old unmarried girl, was physically normal and was thought by her teachers to have low-normal intelligence. Her expected date of confinement was estimated as April 14, 1965, but the infant was born on January 13. Pregnancy and delivery were otherwise normal as far as could be determined. The infant was severely malformed at birth and expired about 2 hours after delivery.

The mother was one of 16 children, 10 males and 6 females. Two male sibs died in infancy from unknown causes. Several of the sibs had children who were in good health. There was no history of malformations in any of the family members. The grandmother died at the age of 51 of cancer. The grandfather was 53 and was probably the father of the patient.

The female infant, who was 41 cm. in length, weighed 2440 g. She had hypertelorism, marked micrognathia, and webbed neck. The gums appeared thickened, and there were numerous thick frenula extending from the buccal to the gingival mucosa. The tongue was bifid. An encephalocele was present posteriorly. There was a large omphalocele, and a portion of colon was prolapsed through the anus. The abdomen was protuberant, and the genitalia appeared normal for a female infant. The right hand was everted to the ulnar side; there was a simian line and an extra digit, and only one flexion line on the little finger. The left hand similarly had a simian line and one interphalangeal joint on the 5th finger. The fingers were tightly flexed but could be straightened with effort. Both wrists were flexed. There was bilateral talipes valgus, and the toes were short.

FIG. 1a. Both polycystic kidneys.

FIG. 1b. External and cut surfaces of liver, showing the multiple cysts.

Necropsy. Inspection of the body confirmed the numerous developmental abnormalities previously noted in the physical findings. Examination of the liver and kidneys (Fig. 1a and b) revealed multiple variable-sized, multilocular thin-walled cysts containing serous fluid. The brain showed a pattern of microgyria throughout both cerebral hemispheres, hypoplasia of the medial portion of the right parietal lobe, a communicating channel between the subarachnoid space and the right lateral ventricle, and an encephalocele arising from the posterior mid-line of the cerebellum and communicating

directly with the fourth ventricle. Aside from focal pulmonary atelectasis, the other organs showed a normal gross appearance.

The microscopical examination showed focal atelectasis and haemorrhage in the lungs, and mild pulmonary vascular hyperplasia. Cystic dilatation of intrahepatic bile-ducts throughout the portal areas accounted for the gross cystic changes of the liver. Multiple cysts lined by low cuboidal epithelium were seen in sections from both kidneys. There were no demonstrable glomerular or blastogenic zones, which gave the kidneys a microscopical

appearance similar to that described in failure of development of the metanephrogenic renal anlage (Morris and Johnson, 1961).

Cytogenetic Observations. All chromosome preparations were made from cell cultures which were derived from a pectoral muscle biopsy done at necropsy. A previously described technique (Gustavson, Hagberg, Finley, and Finley, 1962) was used for preparing the material. A post-mortem blood specimen was also obtained, but cultures were unsuccessful.

Twenty-three metaphase plates were counted and photographed, and 23 karyotypes were prepared. The majority (19) of the cells had 46 chromosomes. Four had less than 46 and were presumed to be damaged, but an analysis was carried out, because all the chromosomes in group 1-3 (A) were present in these cells, and the abnormality which has been described in OFD is in a No. 1 chromosome. Both members of the No. 1 pair were subjected to careful comparison, and in each of the 23 karyotypes there was no significant difference detected between the pair members. The karyotypes were interpreted as normal for a female.

Discussion

A number of patients with oral-facial-digital syndrome have been reported, and the clinical features of the disorder are fairly well established. The aetiology remains less clear. Patau *et al.* (1961) found in 2 patients a karyotype abnormality which he interpreted as a partial trisomy resulting from the insertion of a part of another chromosome into a No. 1 chromosome. However, the published results of chromosomal studies in patients with OFD reveal the majority to be normal. Our patient did not have a demonstrable chromosomal aberration in cells derived by culture of pectoral muscle.

Only 3 of the previously reported cases of OFD included a necropsy. Since 2 of these 3 had polycystic disease, it is suggested by Doege *et al.* (1964) that there may be a relation between OFD and polycystic disease. The pathological findings in our case substantiate this possibility.

The presence of polycystic disease in these 3 patients with OFD may have been coincidental or these patients may have represented a more severe form of the disease. The pathological study of other patients with OFD will help clarify the

relationship. If polycystic disease proves to be a consistent finding, the term 'oral-facial-digital' does not adequately describe the clinical and pathological features of this syndrome.

Summary

A newborn Caucasian female with oral-facial-digital syndrome is reported. Chromosomal analysis revealed a normal number and configuration of her chromosomes. A significant finding on necropsy was the presence of polycystic liver and kidneys.

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