A Patient with a Short Arm Deletion of Chromosome 18 (46,XY,18p-)

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Recent advances in human cytogenetics have provided impetus for the mapping of autosomal genes. Inherited variations in the morphology of the chromosomes, such as translocations and deletions, can be used as markers in identifying chromosomes and possibly in localizing the genes within such chromosomes. Penrose and Delhanty (1961) and Shaw (1962) described two different pedigrees in which a 15/21 translocation chromosome was segregating. Though the MN and Rh loci were eliminated as being located in the translocation chromosomes, the evidence for the ABO locus being located in these chromosomes was not conclusive.

The deletion of various segments of a chromosome has been used by geneticists to localize a given gene in many experimental organisms. In the case of man, a valuable 'experiment of nature' is to be found in subjects in whom there is a deletion of a portion of an autosomal chromosome. There are well-defined syndromes, such as the *cri du chat*, a deletion of a short arm of chromosome No. 5 (Lejeune *et al.*, 1963), and deletions of a segment of the long arm of No. 18 (Destine *et al.*, 1967), that can be suspected or diagnosed clinically. There have been a number of other reports of patients with deleted chromosomes that do not fit into easily diagnosed syndromes (Weleber, Hecht, and Giblett, 1968). An example of the latter category is a ring chromosome that has, in effect, a terminal deletion at both ends of the chromosome (Wolf *et al.*, 1967).

This report deals with one of the more poorly defined chromosome deletion syndromes, deletion of the short arm of the chromosome 18. By describing these cases in detail, including the genetic information obtained from family studies, the spectrum of anomalies associated with this chromosome deletion may eventually be clarified.

Case Report

The patient was first seen at the age of 37 months. He was referred to the Henry Ford Hospital for the evaluation of short stature and mental retardation. A provisional diagnosis of 'male Turner's syndrome' had been made. The child weighed 3288 g. (7 lb. 4 oz.) and was the product of a term pregnancy, born to a 27-year-old mother and a 32-year-old father. His length at birth was 48 cm. (19 in.). Neither his mother nor his father had any known infectious disease in the six months before conception or during pregnancy. There is no history of maternal or paternal exposure to radiation or mutagenic drugs. His weight has varied between the 3rd and 10th centile, and his height paralleled but has been consistently below the 3rd centile on the Stuart Anthropometric chart. The child was slow in passing the developmental milestones. His first tooth erupted at 15 months. He crawled and sat alone at 11 months. He walked at 20 months, but was not toilet trained at 37 months of age. He could understand simple commands, but could not speak.

There was an 8-year-old female sib and a 7-month-old male sib. Both children appeared to be normal. His mother had a spontaneous abortion six months before conceiving the patient. The other family members had no history of miscarriages, retarded children, congenital anomalies, or sterility problems.

Physical examination revealed an active, alert, child who was functioning at about the level of 28 months (his chronological age was 37 months). He weighed 13.4 kg. (29 lb. 8 oz.). His height was 86 cm. (34 in.) and his head circumference was 48 cm. (19 in.). He did not resemble either of his parents (Fig. 1). His ears were prominent and low set. His palate was high and arched, a left lower central incisor had not erupted. Bilateral pterygium colli was present. The nipples were small and laterally positioned. The heart and lungs were normal. Examination of the abdomen revealed no abnormalities except for diastasis recti. His genitalia and femoral pulses were normal. His musculature was hypotonic and his joints hyperextensible. There were no localizing neurological signs. He had bilateral clinodactyly. The second toe bilaterally was shorter than the great toe and was raised above the adjacent toes.

FIG. 1. Patient.

Laboratory Studies. Complete blood count, urinalysis, fasting blood sugar, blood urea nitrogen, serum electrolytes, serum calcium and phosphorus, and protein-bound iodine were all normal. His urine was negative when tested for phenylketonuria and histidinuria. X-ray examination revealed a normal skull. He had bilateral clinodactyly, and his bone age, according to hand standards, showed considerable variation between carpals and phalanges. The phalangeal age was about 2 years, while the carpal and radial maturation was approximately 6 months. A similar disproportion existed between the tarsals and phalanges of the foot, the tarsals being at about 9 months while the phalanges were at 21 months. There were no other radiological abnormalities. Electroencephalogram was normal. Formal psychological testing with the Stanford Binet Test and Denver Developmental Screening Test revealed performance scores almost up to chronological age, but there was difficulty in expressive scores. There was no hearing deficit and the child did not appear to be autistic.

Cytogenetic Studies. The buccal smear was chromatin negative. Chromosome analysis was performed using modifications of peripheral blood technique of Moorehead *et al.* (1960). Twenty-five suitable metaphases were counted and analysed. The chromosome number was 46. The karyotype was normal, except that one member of the E group was missing, and there was an abnormal telocentric chromosome which was the same size as the long arm of chromosome No. 18 (Fig. 2). Short arms could not be seen on this chromosome. The abnormal chromosome was present in all 25 cells.

The karyotype was therefore interpreted as representing a short arm deletion of chromosome 18, (46,XY,18p-). The parents and the female sib had normal karyotypes.

Blood Groups. The proband, his female sib, and both parents were analysed for various blood group antigens. The results are presented in the Table.

TABLE
BLOOD GROUPS OF FAMILY

	ABO	Rh	MNSs	Fy ^a	K	P
Father	A ₁	DCe/e	MsNs	a+	kk	P-
Mother	B	DCE/E	MSNs	a+	kk	P-
Proband	A ₁ B	DCE/e	MSNs	a+	kk	P-
Female sib	A ₁ B	DCE/e	MSNs	a+	kk	P-

Discussion

Since de Grouchy *et al.* (1963) reported the first patient with a deletion of chromosome No. 18, there have been a number of others reported (Van Dyke, Valdmanis, and Mann, 1964; Bühler, Bühler, and Stalder, 1964; Summit, 1964; Uchida *et al.*, 1965; Migeon, 1966; Gorlin, Yunis, and Anderson, 1968; McDermott *et al.*, 1968). All the patients except the one reported by de Grouchy were short in stature, and all patients were mentally retarded, primarily in their verbal scores. Van Dyke *et al.* (1964) mentions the similarities between his patients and individuals with Turner's syndrome; and Migeon (1966) stated that her patient had puffy hands and feet similar to that seen in the Bonnevie-Ullrich syndrome.

Several patients including ours have had webbed necks (Van Dyke *et al.*, 1964; Summit, 1964). Both hypo- and hypertelorism have been reported (de Grouchy *et al.*, 1963; Uchida *et al.*, 1965). Uchida *et al.* (1965) described a patient with cebocephaly who had deleted short arms of chromosome 18; and Faint and Lewis (cited by Migeon, 1966) studied a patient with a cyclops malformation who had the same chromosome anomaly. There have also been abnormalities of the extremities ranging from clinodactyly to micromelia. We can speculate that, while the growth disturbance and intellectual impairment are non-specific findings common to patients with many different chromosome abnormalities, the disproportion between the performance IQ and the verbal IQ, as well as the variations in the defects of the extremities and the variations in the defects of the holoprosencephalic variety (ranging from hypotelorism to anencephaly, cebocephaly, and cyclops), might be due to the uncovering of deleterious recessive genes as first suggested by Uchida *et al.* (1965). Uchida also suggested that because telocentric autosomes

FIG. 2. Karyotype of patient (46,XY,18p-).

are unstable these deleted chromosomes were probably acrocentric. We were unable to demonstrate short arms on any of the deleted chromosomes, and therefore believe that they are stable telocentric chromosomes.

Of the 1487 genes in man catalogued by McKusick (1966), 119 are described as being located on the X chromosome. The location of the remaining 1368 genes has not been identified with certainty. There are two autosomal loci tentatively identified. Crawford, Punnett, and Carpenter (1967) described a patient with a long arm deletion of chromosome 16 in whom there was anomalous inheritance of the Duffy blood group. Gerald *et al.* (1967) reported a possible haptoglobin linkage with the deleted portion of a ring D chromosome. Attempts have been made to localize the ABO blood group genes in the 21st chromosome by studying the gene frequencies in the trisomic and disomic populations Shaw and Gershowitz, 1962; Kaplan *et al.*, 1964; Goodman and Thomas, 1966; Mayeda, Luthardt, and Woolley, 1968). These investigators concluded that the ABO locus did not reside in the 21st chromosome.

In the case of our propositus, the ABO locus does not reside in the short arm of the deleted chromosome 18 because he is heterozygous for the A and B genes. Similarly, the Rh and MN loci do not reside in the short arm of chromosome 18. These observations confirm the findings of the earlier case reports.

Summary

In order to clarify the syndromes associated with a deletion of the short arm of chromosome 18, a detailed description of the patient is presented. It is hoped that the spectrum of anomalies associated with this chromosome deletion will eventually be clarified. Genetic analysis of the blood group genes indicates that the ABO, Rh, and MN loci are not located in the short arm of chromosome 18.

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