Autosomal Deletion Syndrome

46,XX,18p- : A new case report with absence of IgA in serum

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Twenty-one cases of presumptive deletion of the short arm of a No. 18 chromosome were recently reviewed by Reinwein *et al.* (1968) together with a new case from their own material. Five additional reports describing 6 cases have since been published (Grouchy, Rossier, and Joab, 1967; Gilgenkrantz, Marchal, and Neimann, 1968; Gorlin, Yunis, and Anderson, 1968; McDermott *et al.*, 1968; Jacobsen and Mikkelsen, 1968).

It is becoming increasingly evident that the clinical features attributable to this syndrome are confined very largely to errors of development involving the same systems. The phenotypic manifestations, however, range from severe holoprosencephalies incompatible with life, to cases with various mild abnormalities of the eyes, nose, mouth, ears, and teeth. All are mentally defective. In contrast to trisomy D, extracerebral malformations are absent or trivial.

In addition to these physical and mental stigmata, dysgammaglobulinaemia has recently been associated with deficiencies involving chromosome No. 18. To date, an absence of serum and salivary IgA has been reported in two cases of deletion of the short arm (D. Daentle and D. Smith, 1968, personal communication to Stewart *et al.*, 1968; Ruvalcaba and Thuline, 1969), two cases of deletion of the long arm (Stewart *et al.*, 1968; Feingold *et al.*, 1969), and in two persons with a ring chromosome 18 (Finley *et al.*, 1968; Feingold *et al.*, 1969). We wish to report a case investigated in our clinic in which a presumptive short arm deletion of chromosome 18 is associated with an absence of IgA in the serum.

Case Report

The patient, a girl aged 14 years, presented with a history of juvenile metrorrhagia. She was an only

child born after an uncomplicated pregnancy, to a 26-year-old mother and 31-year-old father. There was no history of abortion preceding or subsequent to her birth. Birthweight was 3000 g. and length 52 cm. She walked at 1 year and spoke at 3; however, after two years at a regular school she was transferred to a special school because of 'speech difficulties'. The menarche was at 13 with irregular periods at intervals of about 4 months.

Clinical features. On inspection the patient presented as a squat adipose girl 158 cm. tall, arm span 156 cm., circumference of head 539 mm., weight 78½ kg. The face was moon shaped, with a saddle nose and a mild prognathism (Fig. 1). Her neck was short, with a deep hairline but no definite pterygium colli. There was no abnormality of the ears. Her fingers were tapered with a shortening of the middle phalanx of the small fingers (Fig. 2). Her feet resembled those in the Rubenstein Taybi syndrome (Rubenstein and Taybi, 1963). The

FIG. 1. The patient.

Received 5 November 1969.

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FIG. 2. Hands illustrating tapering and shortened middle phalanx of fifth digit.

toes were wide and plump and there was an increased space between the first and the second member with zygodactyly of the second and third toes of both feet (Fig. 3). She had a high arched palate, a large tongue, and severe dental caries. Her left breast was larger than her right. Axillary and pubic hair distribution were normal; no gross abnormality was evident on clinical examination.

FIG. 3. Feet illustrating increased space between first and second member and zygodactyly of the second and third toes.

Gynaecological examination revealed a virgo intacta with conical portio, small uterus, and normal adnexa. A small perioral cervical erosion was present.

Ophthalmological examination. There was no ptosis, no epicanthus, or hypertelorism. A divergent strabismus was present, and myopia in combination with an astigmatism. Visual acuity on the right eye was 6/6P Jg. 1 on the left 6/9 Jg. 1. The fundi were normal.

Psychological examination. A severe degree of mental debility was present, with an IQ (Wechsler) of 74. The Rorschach test showed a primitive undifferentiated personality structure attributable to the low IQ. There were no signs of psychosis.

Laboratory investigations. ESR, erythrocyte, and white blood count, blood pressure, and urine analysis showed normal values. Fasting blood sugar, glucose tolerance tests, and ECG were normal. 17-ketosteroids in a 24-hour specimen of urine were 10.1 mg., and 17-hydroxycorticosteroids 17.6 mg. X-ray revealed a normal size and configuration of the pituitary fossa. The ECG was normal. Blood groups and serum factors of the patient and her parents (Table I) showed no deviation from the expected inheritance pattern.

Determination of immunoglobulins in serum and saliva. The concentration of IgA and IgM was determined by means of immunodiffusion. Immunochemical quantitation was performed with Partigen R plates (Behringwerke, Marburg) (Becker *et al.*, 1968).

Electrophoretic serum protein fractions were determined by means of cellulose acetate electrophoresis.

Sedimentation analysis was performed on the analytical ultra-centrifuge (Spinco model E) at 52,640 r.p.m. (220,000 g). The results of the serum analyses are summarized in Table II. While the IgG and IgM proteins

TABLE I

BLOOD GROUPS AND SERUM FACTORS OF PATIENT WITH 46,XX,18p- AND HER PARENTS

Father	Mother	Patient
A ₁	O	O
MNSs	MsMs	MSMs, Mg-, Vw-, U+, CCDec/Cw- = R ₁ R ₁
CCDec/Cw-	CCDec/Cw-	
P+	P+	P-
K-	K-	kk
Fy(a-b+)	Fy(a+b+)	Fy(a+b+)
Jk(a+b+)	Jk(a+b+)	Jk(a+b+)
Lu(a-)	Lu(a-)	Lu(a-b+)
Le(a-b+)	Le(a-b+)	Le(a-b+)
Xg(a+)	Xg(a+)	Be(a-)
pBPB	pAPa	Xg(a+)
Hp 2-2	Hp 1-1	Vel(+)
Gc 1-1	Gc 2-1	pAPB
Gm(a-x-b+f+)	Gm(a+x-b+f+)	Hp 2-1
Inv(1-)	Inv(1-)	Gc 1-1
		Gm(a+x-b+f+)
		Inv(1-)

TABLE II

QUANTITATIVE DISTRIBUTION OF IMMUNOGLOBULINS, ELECTROPHORETIC SERUM PROTEIN FRACTIONS, AND PROTEIN FRACTIONS OBTAINED BY SEDIMENTATION ANALYSIS IN A CASE OF 46,XX,18p-

Immunoglobulins* (mg./100 ml.)	Patient	Mother	Father
IgG	1960	1750	1225
IgA	0	203	155
IgM	154	247	160
Electrophoretic Fractions	mg./100 ml.		
Albumin	3540		
Alpha ₁ -globulin	670		
Alpha ₂ -globulin	1050		
Beta-globulin	1240		
Gamma-globulin	1550		
Fractions by Ultracentrifugation			
4.5 S	6430		
7.0 S	1390		
19.0 S	230		

* For comparison, the immunoglobulin patterns of the patient's parents are shown.

were in the normal range in the patient's serum as well as in the parental sera, the IgA protein was deficient in the patient's serum.

The patient's saliva contained a concentration of IgG of 10 mg./100 ml., other immunoglobulins could not be seen. The sedimentation analysis and electrophoresis of the patient's serum showed no deviation from normal expected values for the same age-group.

Dermatoglyphic findings.* The dermatoglyphic findings are set out in Tables III and IV.

There were no abnormalities of the palmar crease of the left hand. On the right hand the third finger crease was split, the ulnar portion which reached to the base of the fourth finger was transverse, the other curved and ended in the second interdigital space.

The richness of patterns on the soles was striking (Table IV). Of special interest was the presence of a whorl on the left distal hypothenar and of a fibular loop in the right distal hypothenar. Whorls and fibular loops are rare in the local population. However, as no imprints of the parents were available it was not possible to ascertain whether these were the result of a familial peculiarity or related to the chromosome aberration. A similar finding has not as yet been reported in other cases with this syndrome.

Cytogenetic analysis. Peripheral blood cultures were set up according to the method of Moorhead *et al.* (1960). Karyotype analysis (Fig. 4) revealed a deletion of the short arm of a chromosome in the E group, morphologically a 17 or 18 in all metaphases examined. Autoradiographic studies were performed by the addition of ³H thymidine† six hours before culture fixation. Slides were then exposed for 10 days to AR 10 stripping film and metaphases showing an end of S pattern were studied by the duplicate photography formvar technique (German, 1966). This identified the abnormal chromosome as late replicating, consistent with the expected patterns for chromosome 18. Both parents had normal karyotypes.

* Performed by Dr. Dora M. Kahlich, Department of Forensic Medicine, University of Vienna.

† 1 μCi/ml. culture specific activity 22,400 mCi/mM, The Radiochemical Centre, Amersham.

TABLE III
FINGERTIP PATTERNS, FINGER RIDGE COUNTS, AND PALMER FORMULA

	Left					Right				
	I	II	III	IV	V	I	II	III	IV	V
Fingertip patterns	U	U	U	W	U	U	U	W	W	U
Finger ridge count	20/0	11/0	13/0	15/9	16/0	16/0	11/0	15/9	16/12	11/0

Total ridge count: 14.4

Occasional white lines on IV left and right

Intermediate lines on II left; I, IV, and V right

Palmar formula

Left: 11.9.7.5'-t'-V.O.O.L.V

Right: 11.9.7.4-t^u-B⁺.O.O.L.O

TABLE IV
TOE PATTERNS, RIDGE COUNTS, AND PLANTAR FORMULA

	Left					Right				
	I	II	III	IV	V	I	II	III	IV	V
Toe patterns	F	F	D	F	F	F	D	W	F	F
Toe ridge count	6/0	9/0	25/17	18/0	6/0	5/0	13/6	22/19	26/0	6/0

Total ridge count: 13·6
No white lines present
Intermediate lines on I-V left; II, IV, and V right

Plantar formula	Thenar	I Area	II Area	III Area	Hypothenar	Thenar prox.	Calor
Left	W	L ²	W	O	W	V	O
Right	W	W	W	O	F	V	O

Discussion

To date, 28 cases of short arm deletion of chromosome 18 have been described. Five of these manifested various grades of holoprosencephaly incompatible with life (Faint and Lewis, 1964; Uchida *et al.*, 1965; Nitowsky *et al.*, 1966; Gorlin *et al.*, 1968; McDermott *et al.*, 1968). Of the 23 viable cases, 22 had mild signs of craniofacial dysplasia, and in one, severe bilateral clefts of the lips and palate were present (Pfeiffer, 1966). Most cases occurred spontaneously, but in three families the disease was transmitted, once through maternal mosaicism (Uchida *et al.*, 1965) and twice through unbalanced transmission in a translocation heterozygote (Lejeune *et al.*, 1966; McDermott *et al.*, 1968). As in other autosomal abnormalities, both the average maternal (35·6 years) and paternal (33 years) age was advanced in those cases arising spontaneously; 17 were female and 7 were male. In its mild form the cardinal signs of this syndrome are mental deficiency, a variety of eye defects, and a facies characterized by a flat or saddle nose, malformed ears, and dental caries. Short stature, a short neck with or without webbing, and mild deformities of fingers and toes with partial fusion are sometimes present. Endocrine disorders are described in three cases, two having a mild hypothyroidism (Bühler, Bühler, and Stalder, 1964; D. B. Hickox, 1964, personal communication to Uchida *et al.*, 1965) and one a diabetes mellitus (Van Dyke, Valdmanis, and Mann, 1964).

Mental retardation, craniofacial dysplasia, and eye defects are present in most cases of chromosomal aberration, indicating that a large number of loci, widely distributed over the genome, are responsible for the development of the cranial area. However,

the presence of these signs in association with mild deformities of the hands and feet and no other major extracranial abnormality should allow a clinical diagnosis of a possible deletion of the short arm of chromosome 18 to be made. Alopecia has now been described in two cases (Uchida *et al.*, 1965; Jacobsen and Mikkelsen, 1968) and a uni or bilateral ptosis in nine (F. J. W. Lewis, R. H. Poulding, and G. Woods, 1963, personal communication to Uchida *et al.*, 1965; Uchida *et al.*, 1965; Grouchy, Bonnette, and Salmon, 1966; Lejeune *et al.*, 1966; Coetsier and Orye, 1967; Reinwein *et al.*, 1968; Gilgenkrantz *et al.*, 1968; Jacobsen and Mikkelsen, 2 cases, 1968). The presence of either of these signs in association with the aforementioned stigmata of mild cranio-facial dysplasia should strongly support a diagnosis of this autosomal deletion. Points of differential diagnosis between 18p- and the two other well-documented autosomal deletion syndromes are the presence of cardiac signs in cases of deletion of the long arm of chromosome 18 (Reinwein *et al.*, 1968) and severe hypertelorism and micrognathia combined with cardiac signs and the characteristic cry in the cri du chat syndrome (James *et al.*, 1969a). Multiple systems are usually involved in both the trisomy D and E syndromes (James *et al.*, 1969b; James, Belcourt, and Janower, 1969c).

The case described by Pfeiffer (1966) of a female infant with microcephaly, absent nasal bones, and a severe median cleft of the lips and palate could be considered a link between the mild and severe manifestations of this syndrome. Though no mention is made of the absence of a philtrum in this infant, the description given and the accompanying picture would suggest this to be the case. Landau, Barry,

FIG. 4. Karyotype from peripheral blood culture of the patient showing deletion of the short arm of a chromosome 18.

and Koch (1963), describing a case of arrhinencephaly with a normal chromosome complement, state that even in extensive bilateral clefts of the lips the philtrum is present. Absence of the philtrum is extremely rare and when present should suggest arrhinencephaly. The five cases so far reported, of short arm deletion of chromosome 18 with craniofacial abnormalities incompatible with life, represent various grades of holoprosencephaly, two having cyclopia, two cebocephaly, and one arrhinencephaly

with bilateral clefts of lips and palate. Significant extracranial abnormalities were absent.

Holoprosencephaly is a term used to describe a group of teratological entities exhibiting anomalous development of the nose, mouth, ears, defective development of olfactory and optic structures, and impaired midline cleavage of the embryonic forebrain (Gorlin, *et al.*, 1968). The term arrhinencephaly is used to designate the neurological portion of this teratism, and is a constant feature of the

trisomy D syndrome, usually in association with severe extracranial malformations (Miller *et al.*, 1963). Recently, however, two cases of cyclopia with trisomy D and no major extracranial malformations have been described (Arakaki and Waxman, 1969; Toews and Jones, 1968). Both were females with normal external genitalia. In the first, post-mortem examination was not allowed, but beyond an abnormal situation of the anal opening no external defects were noted. In the second case, rudimentary tubular structures were identified histologically in the region of the absent ovaries. No other abnormalities were present.

A normal karyotype has been reported in at least six cases of arrhinencephaly without extracranial manifestations (J. Lejeune, 1966, personal communication cited by Cohen, 1966; R. C. Juberg, 1966, personal communication to Cohen, 1966; Demyer and Zeman, 1963; Landau *et al.*, 1963; Marshall *et al.*, 1964; Schleiermacher and Schroeder, 1966). The cyclops with mosaic chromosomal constitutions have also been described. The first had a monosomy for a group G chromosome in 22 of 104 cells analysed (Cohen, 1966), and in the second a fragment was present in 30% of cells from a fibroblast culture (Pfitzer and Müntefering, 1968). A hypothesis to explain the occurrence of the wide variation in phenotype in cases of 18p— was suggested by Uchida *et al.* (1965). She postulated that genes on the remaining short arm of chromosome 18 would determine the phenotype, and that a hemizygous recessive gene in a deficient heterozygote could account for cases of arrhinencephaly. Her two transmitted cases were the progeny of different fathers, one mildly affected child and one infant with cebocephaly being produced. Gorlin *et al.* (1968) supported her hypothesis, and proposed a homozygous recessive condition to explain those cases of arrhinencephaly with normal karyotype. Another mechanism would however be required to explain the association of arrhinencephaly with trisomy D. Such a mechanism could be the presence of genes on the short arm of chromosome 18 controlling loci on chromosome 13. Under these conditions a homozygous recessive state of genes on the short arms of chromosome 18 in persons with a normal karyotype, deletion of a short arm of chromosome 18, or a trisomy 13, would produce in each case a functional excess of genetic activity in chromosome 13. Phenotypic variation in the 18p— syndrome would depend on the relative preponderance of dominant and recessive alleles on the remaining short arm of chromosome 18. Additional loci on chromosome 13, not associated with chromosome 18, would cause

the extracranial malformations common to the trisomy D1 syndrome. That such a close functional relation could exist between these two portions of the genome is suggested by the observations of Ferguson-Smith and Handmaker (1963) on the association of satellited chromosomes with specific chromosomal regions in cultured human somatic cells. These associations take place near secondary constrictions, the nucleolar organizer region which probably contains the cistrons for ribosomal RNA. They showed a significant increase in association between the end of the short arm of chromosome 18 and the satellited chromosomes. A secondary constriction is present on the long arm of chromosome 13, the acrocentric chromosome implicated in the trisomy D syndrome. Ferguson-Smith suggests that there may be an increased probability for translocation to occur between two non-homologous chromosomes if they are attached to a common nucleolus. In nine instances of reciprocal translocation between a satellited and a non-satellited chromosome, three involved the 17-18/13-15 groups. Should these two chromosomes be shown to have a common nucleolus, a functional association at the genetic level would seem quite possible, and could account for the presence of similar malformations in individuals with different genotypes.

The association of an isolated deficiency of IgA with a deletion involving chromosome 18 was first shown by Feingold *et al.* (1969), and since then reports on IgA levels of 8 additional cases have been published (Table V). Absence of serum and salivary IgA in our patient strengthens the case for

TABLE V
ESTIMATION OF SERUM AND SALIVARY IgA IN
PERSONS WITH DELETIONS INVOLVING
CHROMOSOME NO. 18

Author	Cases		Type of Deletion	IgA
	Sex	Age (yr.)		
Feingold <i>et al.</i> (1969)	M	3	Ring 18	Absent*
	F	9	Long arm	Very low*
Finley <i>et al.</i> (1968)	F	14	Ring 18	Absent
Richard and Hobbs (1968)	M	11	Ring 18	Normal
Stewart <i>et al.</i> (1968)	F	31/2	Long arm	Absent
	M	18/12	Mosaic ring 18	Normal
D. Daentle and D. Smith (1968, personal communication to Stewart <i>et al.</i>)		?	Short arm	Absent
Borgaonkar <i>et al.</i> (1969)	F	31	Ring 18	Normal*
	M	20/12	Long arm	Normal*
Ruvalcaba and Thuline (1969)	F	18	Short arm	Absent
Present case	F	16	Short arm	Absent

* No report on salivary levels.

the location of genes controlling this immunoglobulin on chromosome 18. More than one locus would have to be present, however, as the deficiency can involve either the long or short arm. Conflicting results in cases of a ring chromosome 18 could be caused by variations in the amount of material deleted from each arm in different patients. Jacobsen and Mikkelsen (1968) report that electrophoresis of serum proteins was normal in their two cases of 18p-, but no details of quantitative immunoglobulin estimations are given. Such data on more cases of deletion syndromes, especially those involving chromosome 18, are needed in order to establish a causal relationship between loss of chromosome material and dysgammaglobulinaemia.

Summary

A case of short arm deletion of chromosome 18 of spontaneous origin in a female subject is described. She was mentally retarded and had mild defects of the eyes, nose, teeth, fingers, and toes, and an absence of IgA in the serum. The syndromes associated with this autosomal deletion are discussed, and a possible functional association between chromosomes 13 and 18 is suggested.

We are grateful to Prof. Dr. H. Husslein, Director of the Second Gynaecological Clinic for his advice and encouragement; to Dr. R. Quatember of the Psychiatric-Neurological Clinic who furnished the psychological report, and to Doz. Dr. W. Auinger of the Second Gynaecological Clinic for the medical examination. Erika Moser and Ulrike Ruthner performed the blood cultures and Lilian Dörsek gave secretarial assistance. We acknowledge receipt of grant No. R 00151 from the World Health Organisation, Geneva.

The investigations recorded in Table I were carried out at the Serological Institute, University of Vienna, by Professor Dr. P. Speiser.

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