Immunological Profile in a Chromosome 18 Deletion Syndrome with IgA Deficiency

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Autosomal deletion syndromes are of great interest since measurable loss of genetic material could lead to the mapping of the human autosomes. Short arm deletions and long arm deletions of chromosome 18 have been described in association with phenotypic changes (Grouchy et al., 1963, 1964) and reviewed recently by Wolf et al. (1967) and Reinwein, Ritter, and Wolf (1967). Since a ring chromosome presumably has double deficiencies resulting from the loss of the distal part of both arms, it was considered significant that a 15-year-old female with a ring-18 chromosome was deficient in the immunoglobulin IgA in serum and saliva (Finley et al., 1968). In this report, we present detailed analysis of this patient and discuss some of the genetic implications of the association of chromosome 18 deletions and IgA deficiency.

Case Report

The propositus, a 15-year-old Caucasian female, was the product of an uncomplicated term pregnancy and delivery and had a birthweight of 3.5 kg. There was no history of parental radiation or maternal drug ingestion. The mother was 21 and the father 27 years of age at the time of delivery. Three sibs, one older and two younger, are living and well. There was no history of abortion. The infant was well at birth but was noted to have abnormalities of the feet. Her speech and motor development were slow. She did not begin walking alone until almost 2 years of age. At 7 years of age she was found to have a hearing defect associated with small ear canals. She had several upper respiratory infections during the first two years of life, has had several episodes of otitis media, had pneumonia at age 13, and has had a chronic productive cough for several years. There was no history of gastro-intestinal disease. Examination at age 14 revealed a well-developed, well-nourished co-operative female with eyebrows that met in the midline, bilateral epicanthic folds more pronounced on the left, minimal antimongoloid slant to the eyes, slight hypertelorism, narrow external auditory canals, high arched palate, normal breast development, and abnormalities of the feet with dorsi flexion of all except the two great toes. Her height was 157 cm. and weight was 43 kg. There were scattered nevi over the body. Pelvic examination was within normal limits. Neurological examination revealed no abnormalities except horizontal nystagmus occurring bilaterally on lateral gaze. There were no dental anomalies but she had much caries. Skull films were interpreted as showing microcephaly. Her bone age was normal. The electroencephalogram was interpreted as borderline, with fairly numerous sharp waves scattered through most leads; localized sharp waves were more prominent in the right temporal region (Fig. 1).

The psychologist who evaluated the patient concluded that she had a verbal scale IQ of approximately 61. Dermatoglyphic studies revealed that all digits had whorls except for the right fifth finger which had an ulnar loop. The total digital ridge count was 222 which is an

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Fig. 1. Photograph of propositus at age 14 years.
well 2

Laboratory findings included normal serum electrolytes, cholesterol, creatinine, alkaline phosphatase, iron, total iron-binding capacity, and total protein. Protein-bound iodine and radioactive iodine uptake were also normal. Urinalysis including paper chromatographic analysis revealed no abnormality. Blood grouping and serum haptoglobin studies on the patient and other family members revealed no unusual findings. Haemoglobin electrophoretic pattern was A.

Deficiency of serum IgA was detected first by agar gel immunoelectrophoresis using polyvalent goat antiserum from Hyland Laboratories (Los Angeles, California, U.S.A.). This finding was confirmed on several occasions by radial immunodiffusion in agar gel using specific anti-IgA antiserum (Mancini et al., 1964). Using this method, IgA was not detectable in the serum of this child. Trace amounts of IgA were found using the more sensitive method of Preer (1956); however, this was confirmed by studies of the patient’s serum at the N.C.I. Immunoglobulin Reference Center, Springfield, Virginia. The striking deficiency of serum IgA is illustrated by use of the double diffusion in agar technique in Fig. 2, which was obtained through the courtesy of Dr. Arthur Steinberg. Serum immunoglobulin levels for the propositus, parents, and sibs are shown in Table I. Serum samples from the propositus, her parents, and three sibs were tested for Gm antigens 1, 2, 3, 5, 6, 13, and 14, and for Inv (1) by Dr. A. Steinberg who found that all samples had the phenotype Gm 3, 5, 13, 14, and were negative for all other antigens. A thorough evaluation of the patient’s immunological capabilities revealed no deficits other than the inability to synthesize in normal amounts the heavy chains of IgA (Table II).

Over a period of one year repeated samples of blood were obtained for leucocyte culture using both macro- and micro-techniques. A total of 238 metaphase spreads was counted; 37 had 45 chromosomes while 201 had the normal diploid number. Among 115 cells analysed in some detail, the complete chromosomal complement was analysed in 62 cells, but in the rest detailed analysis was confined to the E group: 90 had 46 chromosomes including a ring-18, while of the rest with 45 chromosomes, 7 had random chromosome loss and 17 were monosomic for chromosome 18 (Table III). Three of the cells had dicentrics and one cell was interpreted as having normal karyotype. In fibroblasts derived by culture of a skin biopsy 30 cells were suitable for study. The majority of these likewise had a karyotype of 46,XX,18 ring, with a few of them having a monosomy for 18 and two of the 30 having a normal karyotype. The structurally abnormal chromosome 18 showed up clearly as a ring in cells where the

### Table I

<table>
<thead>
<tr>
<th></th>
<th>IgA (mg./100 ml.)</th>
<th>IgM (mg./100 ml.)</th>
<th>IgG (mg./100 ml.)</th>
</tr>
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<tbody>
<tr>
<td>Father</td>
<td>240</td>
<td>61</td>
<td>1210</td>
</tr>
<tr>
<td>Mother</td>
<td>137</td>
<td>&gt;300</td>
<td>1100</td>
</tr>
<tr>
<td>Sib 1</td>
<td>Not detectable</td>
<td>51</td>
<td>1150</td>
</tr>
<tr>
<td>Sib 2</td>
<td>175</td>
<td>81</td>
<td>Not done</td>
</tr>
<tr>
<td>Sib 3</td>
<td>137</td>
<td>160</td>
<td>Not done</td>
</tr>
<tr>
<td>Normal</td>
<td>118-360</td>
<td>47-300</td>
<td>137-360</td>
</tr>
</tbody>
</table>

* Measured by the radial diffusion method of Mancini et al. (1964).
† Though IgA was not detectable by this method, trace amounts of IgA were detectable by the Preer method (1965); presence of IgA in small amounts was confirmed by Dr. William Terry at the N.C.I. Immunoglobulin Reference Center.

Fig. 2. Photograph of double diffusion in agar showing presence of serum IgG in propositus (X), mother (A), father (B), and three sibs (C, D, and E) on the left, and the striking deficiency of serum IgA in propositus (X) on the right. Centre well 1 contains antiserum to IgG and well 2 contains antiserum to IgA.
chromosomes were elongated (Fig. 3). Cells in late anaphase and early telophase were scored for mitotic irregularities. Among a total of 69 plates examined, 8 showed bridge formation, 2 had lagging rod chromosomes, and the rest resulted in clean division.

Both parents and the three sibs had normal karyotypes in cells derived by leucocyte culture.

### TABLE II

**IMMUNOLOGICAL EVALUATION OF PATIENT**

**I. EVALUATION OF THYMUS SYSTEM**

A: No clinical difficulty with childhood viral diseases or smallpox vaccination.

B: Normal number (1,482/cu. mm.) and morphology of circulating lymphocytes.

C: Existing delayed allergy:
   1. Mumps-positive
   2. Candida-negative
   3. Trichophyton-negative
   4. Streptokinase-streptodornase-negative
   5. Histoplasmin-negative

D: Active induction of delayed allergy:
   1. Keyhole limpet haemocyanin-positive

E: In vitro lymphocyte responsiveness to phytohaemagglutinin (Uptake of 14C thymidine): | Cell Source | Stimulant | CPM |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>None</td>
<td>306</td>
</tr>
<tr>
<td>Patient</td>
<td>PHA</td>
<td>4280</td>
</tr>
<tr>
<td>Control</td>
<td>None</td>
<td>306</td>
</tr>
<tr>
<td>Control</td>
<td>PHA</td>
<td>4520</td>
</tr>
</tbody>
</table>

**II. EVALUATION OF IMMUNOGLOBULIN-PRODUCING SYSTEM**

A: Repeated URI's, recurrent otitis media, chronic bronchitis and pneumonia on one occasion.

B: Circulating immunoglobulins:
   1. IgM-51 mg./100 ml.
   2. IgA-trace
   3. IgG-1150 mg./100 ml.
   4. IgD-2.6 mg./100 ml.
   5. IgE-present
   6. Kappa light chains predominant light chain
   7. Lambda light chains present

C: Salivary immunoglobulins and 'transport piece' (concentrated X20).
   1. IgM-7 mg./100 ml.
   2. IgA-not detected
   3. IgG-not detected
   4. Kappa light chains predominant light chain
   5. Lambda light chains present

D: Immunoglobulin allotyping:
   1. Gm 3, 5, 13, 14-positive Gm 1, 2, 6-negative
   2. Inv 1-negative

E: 'Natural' antibodies in circulation.
   1. α isoagglutinins-1/128
   2. β isoagglutinins-1/64
   3. Sheep erythrocyte agglutinins-1/64

F: Active induction of antibody response:
   1. Salmonella O antigen-1/1,024
   2. Salmonella H antigen-1/2,048

**III. 'NON-SPECIFIC' DEFENCE FACTORS**

A: Normal whole complement level-38C'H50 units.

B: Normal neutrophil morphology and numbers (5,226/cu. mm.).

C: Normal monocyte morphology and numbers (312/cu. mm.).

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**Fig. 3.** Karyotype from cultured peripheral leucocytes showing ring chromosome 18.
TABLE III
SUMMARY OF CYTOGENETIC DATA

<table>
<thead>
<tr>
<th>Metaphase Plates Counted</th>
<th>Blood</th>
<th>Skin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>37</td>
<td>12</td>
<td>49</td>
</tr>
<tr>
<td>46</td>
<td>201</td>
<td>25</td>
<td>226</td>
</tr>
<tr>
<td>Total</td>
<td>238</td>
<td>30</td>
<td>268</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metaphase Plates Analyzed</th>
<th>45, haplo 18</th>
<th>45, random loss</th>
<th>46, with ring</th>
<th>46, normal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17</td>
<td>7</td>
<td>90</td>
<td>1</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>7</td>
<td>94</td>
<td>3</td>
<td>124</td>
</tr>
</tbody>
</table>

Discussion
In the majority of cases derived by culture of peripheral leucocytes and skin biopsy, the karyotype interpretation was 46,XX,18r. This aberration is associated with far less severe malformations than is trisomy 18 and is compatible with survival through childhood and in this patient with the onset of puberty.

Somatic rings in general are unstable because of the complexities that arise during separation of the chromatids after replication. The instability of the ring-18 in the present case is born out by its absence in some cells and the presence of a large dicentric in others. Aside from the dicentric itself, it was not possible to identify other changes in size resulting from broken dicentric rings. Such changes may not occur when small rings are involved (McClintock, 1941). Bridge formation during anaphase appears to restrict movement of the centromeres towards opposite poles, with consequent lagging of dicentric or interlocked rings. Dicentric rings may be incorporated into one telophase nucleus but probably are more often lost from both nuclei. We were unable to identify with certainty bridging of interlocked rings or the consequences of such interlocking.

The observation of three cells with an apparently normal karyotype suggests that the ring formation probably occurred after fertilization. Lucas et al. (1963) also observed a line of normal cells in their patient who had a ring-18 chromosome in the majority of cells.

Since the ring chromosome presumably is formed as a result of breakage and loss of material on both ends of a chromosome with reunion of the broken ends, it is not surprising that features of both long arm and short arm deletion syndromes of chromosome 18 are present in a patient with a ring. The features in our case which are consistent with partial deletion of the long arm of chromosome 18 (18q−) include mental retardation, microcephaly, hypertelorism, atriect ear canals, nystagmus, and wholes on more than five fingers. The mental retardation, conspicuous epicanthic folds, hypertelorism, dental caries, and high total digital ridge count in our patient may be related to deletion of the short arm (18p−). Wertelecki, Schindler, and Gerald (1966), in reviewing long arm deletions of chromosome 18, and Migeon (1966), in reviewing short arm deletions of chromosome 18, both record cases with anomalies of the feet.

At least 11 subjects having a ring chromosome (Lucas et al., 1963; Wang et al., 1962; Genest, Leclerc, and Auger, 1963; Gropp, Jussen, and Ofteringer, 1964; Grouchy, 1965; Bernard et al., 1966; Lejeune et al., 1966; Palmer, Fareed, and Merritt, 1967; Gripenberg, 1967; Petit and Poncelet, 1967; Mikelsaar, Talvik, and Sitska, 1967) were reported before the present one, but this child and one investigated by Feingold et al. (1968) appear to be the first whose immunoglobulin levels were determined and in both of these IgA was deficient. Feingold et al. (1968) also reported the absence of IgA in a partial long arm deletion of an 18 chromosome, which they suggest may indicate that the locus of a gene controlling synthesis of IgA is on the long arm. In early 1968 when this association was first reported (Finley et al., 1968; Feingold et al., 1968), it was suggested that other investigators should examine the immunoglobulin levels in patients with 18 deletion syndromes. To our knowledge 12 such patients have now had immunoglobulin levels reported (Table IV). Of 6 patients having karyotype interpretation of ring-18, 2 had IgA deficiency (Finley et al., 1968; Feingold et al., 1968), while 4 patients with ring-18 chromosome had serum IgA (I. A. Uchida, 1968, personal communication; Richards and Hobbs, 1968; Stewart et al., 1968; Borgaonkar et al.,

TABLE IV
SERUM IgA IN CHROMOSOME 18 DELETION SYNDROMES

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient's Age (yr.) and Sex</th>
<th>Karyotype</th>
<th>Serum IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finley et al. (1968)</td>
<td>14 F</td>
<td>Ring-18</td>
<td>*</td>
</tr>
<tr>
<td>Feingold et al. (1968)</td>
<td>3 M</td>
<td>Ring-18</td>
<td></td>
</tr>
<tr>
<td>I. A. Uchida et al., 1968, personal communication</td>
<td>9 F</td>
<td>18q−</td>
<td></td>
</tr>
<tr>
<td>Richards and Hobbs (1968)</td>
<td>10 F</td>
<td>Ring-18</td>
<td>+</td>
</tr>
<tr>
<td>Stewart et al. (1968)</td>
<td>3 F</td>
<td>Ring-18</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>18/12 M</td>
<td>Ring-18/normal mosaicim</td>
<td>+</td>
</tr>
<tr>
<td>Borgaonkar et al. (1969)</td>
<td>31 F</td>
<td>Ring-18</td>
<td></td>
</tr>
<tr>
<td>Rudd et al. (1969)</td>
<td>20/12 M</td>
<td>18q−</td>
<td></td>
</tr>
<tr>
<td>Haddad et al. (1969)</td>
<td>7/12 M</td>
<td>Eq−</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 F</td>
<td>18q−</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 F</td>
<td>18q−</td>
<td></td>
</tr>
</tbody>
</table>

* Absent as measured by the radial diffusion method of Mancini et al. (1964) but subsequently found in trace amounts by Freer method (1956).
Feingold et al. (1968) and Stewart et al. (1968) reported the absence of IgA in 2 patients with deletion of the long arm of chromosome 18, while Rudd, May, and LaMarche (1969) and Haddad et al. (1969) reported raised levels of serum IgA in 2 patients. Borgaonkar et al. (1969) reported normal levels of serum IgA in a child with long arm deletion of 18. Since patients with 18q- have been reported to have normal serum IgA, decreased IgA, and even raised IgA, the relation if any between the chromosomal aberration and the serum IgA is not clear at the present time. However, deficiency of IgA in 4 of 12 patients having either a ring-18 or a long arm deletion of chromosome 18 strongly suggests a relation between these two findings. Initially, we considered the possibility that the 18 deletion syndrome in our family might represent a hemizygous state for a locus involved in production of IgA and that the active allele was lost through the deletion. Such an explanation, however, indicates that at least one parent was a heterozygote in each of the above cases who were deficient in IgA. Deficiency of IgA in 4 of the 12 patients indicates a high incidence of heterozygosity in the population and a higher incidence of the homozygous state with IgA deficiency than the reported incidence of approximately 1 out of 700 (Bachmann, 1965).

Since of the three major immunoglobulins IgA develops last ontogenetically as well as phylogenetically, another possible explanation is that the IgA deficiency represents a fetal arrest such as the persistence of foetal haemoglobin in the trisomy D syndrome (Huehns et al., 1964). The immunological deficit in our patient was limited to an inability to synthesize α chains of the IgA molecule in normal amounts, perhaps reflected by the occurrence of repeated infections of the respiratory tract. It should be emphasized that what first appeared to be a complete absence of IgA in our patient proved rather to be a severe deficiency on more discriminating analysis. It will be important to perform comprehensive immunoglobulin evaluation in other patients with abnormalities of chromosome 18. Grouchy (1965) has suggested a tentative mapping of chromosome 18 with regard to locating regions which when deleted may be responsible for certain phenotypic signs. This approach can be expanded by identification of biochemical anomalies in such patients. While the association of abnormalities in chromosome 18 and IgA antibody production may be coincidental, further data on more patients with 18 syndromes will be needed to clarify the relation. These data could contribute to future understanding of the genetics of the immunoglobulins.
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