Selective IgA deficiency with 18q+ and 18q—
karyotypic anomalies

R M LEWKONIA, C C LIN, AND R H A HASLAM

From the Divisions of Internal Medicine, Medical Biochemistry, and Pediatrics, Faculty of Medicine,
University of Calgary, Calgary, Alberta, Canada T2N 1N4.

SUMMARY A case is described of selective immunoglobulin A deficiency in association with an
18q+ anomaly, apparently the result of a break at 18q23 and a de novo translocation. The pre-
sentation is compared with the phenotypic and immunological features in an IgA deficient 18q—
patient. The findings in these two patients suggest that gene(s) concerned with regulation of IgA
synthesis are located on the distal long arm of chromosome 18 between 18q23 and qter.

Selective IgA deficiency occurs with a population
frequency of approximately 1 in 500. Both sporadic
incidence and familial cases with variable patterns
of inheritance have been reported. In addition,
deficiency or absence of serum IgA has been
reported as a rare occurrence in association with
anomalies of chromosome 18, the majority of those
reports having described deletions of the long arm
of chromosome 18. The relationship between
selective IgA deficiency and 18q anomalies is
complex, since most reports of 18q— describe
normal immunoglobulin levels. This may indicate
that an allele on the homologous non-deleted
chromosome can maintain normal IgA levels, but it might also represent variation in deletional
breakpoint sites. We report two IgA deficient
patients with anomalies of the long arm of chro-
mosome 18 and discuss the localisation of gene(s)
concerned with regulation of IgA synthesis.

Case reports

Case 1
This male child was born at 40 weeks' gestation
after an uneventful pregnancy to a 29-year-old
mother and 33-year-old father. Within 2 weeks of
birth he developed his first upper respiratory tract
infection and was noted to have a poor sucking
reflex. Because of recurrent upper respiratory tract
infections, tonsillectomy and adenoidectomy was
performed at 2 years. In early childhood surgery
was performed for correction of a congenital squint
and orchidopexy. Bouts of recurrent diarrhoea and
respiratory tract infections occurred throughout
early childhood and his failure to thrive and small
stature were attributed to these episodes. At 5 years
his weight and height were both on the 15th centile.
Educational development was markedly retarded
and special school facilities were required. Selective
IgA deficiency was first documented at 11 years
with a level of 3 IU/ml (normal for age, 46 to 268
IU/ml).

On referral for investigation at 14 years, height
and weight were below the 3rd centile and his head
circumference was at the 50th centile. The facies was
unusual with abnormal outer helical ear formation,
a somewhat flattened nasal bridge, and a high
arched palate. The upper limbs showed bilateral
cubitus valgus, tapering fingers, and clinodactyly.
Early secondary sexual characteristics were present.
Formal neurological examination was normal but
intellectual development was noted to be retarded
and he was generally hyperactive.

On investigation, karyotype analysis of cultured
leucocytes showed him to be 46,XY,18q+ (figure)
and repeat analysis confirmed these findings.
The source of the extra material on the long arm
of chromosome 18 was not demonstrated by Q
banding studies. The breakpoint was at q23 where
the extra segment was attached.

The karyotypes of both parents were examined
and both were normal. Serum protein electropho-
resis showed a normal pattern and quantitative
immunoglobulin assay showed selective IgA defi-
ciency (table). Both IgA and IgA secretory piece
were shown in saliva by immunodiffusion in gel.
Lymphocyte transformation by phytohaemagglu-
tinin in various concentrations gave normal
results.

Received for publication 18 February 1980

453
TABLE Immunological findings in case 1 (18q+) and case 2 (18q−)

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral total white cell count (μl)</td>
<td>5700</td>
<td>7500</td>
</tr>
<tr>
<td>Lymphocytes (μl)</td>
<td>3100</td>
<td>4125</td>
</tr>
<tr>
<td>(Normal for age)</td>
<td>(67 ± 9%)</td>
<td>(60 ± 12%)</td>
</tr>
<tr>
<td>T cells (E rosette)</td>
<td>68%</td>
<td>51%</td>
</tr>
<tr>
<td>(Normal for age)</td>
<td>(67.9%)</td>
<td>(60.12%)</td>
</tr>
<tr>
<td>B cells (direct surface staining for immunoglobulin) Total</td>
<td>18%</td>
<td>21%</td>
</tr>
<tr>
<td>(Normal for age)</td>
<td>(13 ± 6)</td>
<td>(13 ± 6)</td>
</tr>
<tr>
<td>IgA staining</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>(Normal for age)</td>
<td>(3–9)</td>
<td>(3–9)</td>
</tr>
<tr>
<td>Serum immunoglobulins (g/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>10.68</td>
<td>19.75</td>
</tr>
<tr>
<td>(6.7–14.5)</td>
<td>(7.1–10.75)</td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>1.64</td>
<td>0.95</td>
</tr>
<tr>
<td>(0.45–1.5)</td>
<td>(0.4–0.8)</td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>0.32</td>
<td>0.25</td>
</tr>
<tr>
<td>(0.85–2.11)</td>
<td>(0.35–1.10)</td>
<td></td>
</tr>
</tbody>
</table>

CASE 2
This male child was noted to have a cleft palate and hypospadias soon after birth. His first episode of pneumonia occurred at 10 weeks and was followed by very frequent respiratory tract infections. At 2 years he began to have recurrent ear infections and intermittent bouts of diarrhoea. An eczematous rash was noted around the lips. When investigated at 30 months there was evidence of both mental and physical growth retardation. He had been walking for only 6 months and both height and weight were below the 3rd centile. In addition to the developmental abnormalities previously noted, he was found to have stenotic auditory canals. Karyotype analysis showed 46,XY,18q− with deletion of the distal region from qter to q22 (figure). Both parents had normal karyotypes. Quantitative immunoglobulin assay showed selective IgA deficiency (table). Both IgA and IgA secretory piece were shown in saliva by immunodiffusion in gel. Lymphocyte transformation by phytohaemagglutinin produced a normal dose response curve.

Discussion
The mental retardation, short stature, and several developmental abnormalities described in our two patients have been previously reported in a distinctive phenotypic syndrome associated with 18q−. Two previous reports described mild deficiency of serum IgA in association with non-deletional anomalies of chromosome 18. Yanagisawa reported a 13-year-old female with an enlarged long arm of chromosome 18 who had a serum IgA concentration of 0.35 g/l. Ogato et al reported a
Selective IgA deficiency with 18q- and 18q- karyotypic anomalies

male child with a presumptive +i(18p) karyotype with a low serum IgA level of 0.15 g/l. In our case 1 with 18q-, the phenotypic abnormalities were those reported in other male cases of the 18q- syndrome. This is probably indicative that the 18q- karyotype in our patient was the result of deletion of the distal portion of the long arm and a de novo translocation. Three cases of inherited 18q- karyotype with t(4q-:18q+) translocations in the father have been reported by Fonatsch et al, Schinzl and Schmid, and Knorr-Gartner et al. In our case 1 both parents had normal karyotypes and the origin of the 18q- addition was not evident.

The particular interest of our two cases lies in the associated selective IgA deficiency and its genesis. This association is a variable feature of the 18q- syndrome, perhaps because of variation in patterns of deletion, but other factors should be considered. It should be noted that both of our patients had selective quantitative deficiency of IgA with normal levels or compensatory increases of other immunoglobulin classes. Lawton et al reported normal numbers of IgA staining peripheral B lymphocytes in subjects with selective IgA deficiency and this was the finding in both of our cases, who also had associated chromosome 18 anomalies. Thus, in patients who have deficiency rather than absence of IgA, the defect must be the result of a defective synthetic rate regulatory mechanism and not an IgA structural gene defect. The reported variability of the extent of IgA deficiency in 18q- subjects from normal levels to apparent absence may indicate that an allele on the homologous non-deleted chromosome determines synthesis or release of IgA. Further, the occurrence of selective IgA deficiency in one of identical twins suggested that environmental influence may also be important in determining the extent of deficiency, even when the genotype is capable of IgA synthesis, perhaps by induction of the regulatory genes postulated by Natvig et al.

Waldmann et al proposed two distinct mechanisms of IgA deficiency, namely overactivity of IgA specific suppressor T lymphocytes to inhibit B lymphocytes or defective terminal differentiation of B lymphocytes into plasma cells which synthesise and secrete IgA. The first of these mechanisms would imply a very complex derivation of selective IgA deficiency in 18q- subjects if there is, in eukaryotypic circumstances, a cumulative contribution of the homologous chromosomes to regulation of total IgA levels. Increased suppressor cell activity in the 18q- syndrome would require that the products of deleted genes normally serve to inhibit IgA specific suppressor T lymphocyte activity, also in a cumulative manner.

Variable class specific suppressor lymphocyte activity was reported by Schwartz in a group of patients with selective IgA deficiency, none of whom was stated to have had chromosomal anomalies. This report confirms the heterogeneity of immunological mechanisms of IgA deficiency, including the possibility that some patients have defective helper lymphocyte function, and illustrates the need for more detailed immunological investigation of patients with chromosome 18 anomalies and selective IgA deficiency.

Wilson et al reported eight patients with various patterns of deletion of the long arm of chromosome 18, of whom only one had selective IgA deficiency and this occurred in association with an interstitial deletion producing absence of the q22 band. These authors suggested that the locus for IgA may be in the area of q22 and adjacent chromatin. Our 18q- deficient case showed deletion from q22 to qter which is consistent with this suggestion, but the probable breakpoint at q23 in our 18q+ case, who had similar immunological findings, suggests that the postulated locus or loci concerned with regulation of IgA synthesis localise to a more distal region of chromosome 18, between 18q23 and qter. Since the locus for peptidase A has been mapped to this region, studies would be appropriate to investigate the activity of this enzyme in different categories of subjects with selective IgA deficiency, both with and without deletions of the long arm of chromosome 18.

We thank Dr R B Lowry for referring case 2 for investigation.

References


Requests for reprints to Dr R M Lewkonia, Department of Medicine, Calgary General Hospital, Calgary, Alberta, Canada T2E 0A1.