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

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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 presentation 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 500.¹ Both sporadic incidence and familial cases with variable patterns of inheritance have been reported.² 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.³ This may indicate that an allele on the homologous non-deleted chromosome can maintain normal IgA levels,⁴ but it might also represent variation in deletional breakpoint sites. We report two IgA deficient patients with anomalies of the long arm of chromosome 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 electrophoresis showed a normal pattern and 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 in various concentrations gave normal results.

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FIGURE Partial Q banded karyotypes from cultured peripheral leucocytes of case 1 (A) and case 2 (B) showing 18q+ in case 1 and 18q- in case 2.

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

	Case 1	Case 2
Peripheral total white cell count (μ l)	5700	7500
Lymphocytes (μ l)	3100	4125
T cells (E rosette)	68%	51%
(Normal for age)	(67 $\pm$ 9%)	(60 $\pm$ 12%)
B cells (direct surface staining for immunoglobulin) Total	18%	21%
	(13 $\pm$ 6)	(13 $\pm$ 6)
IgA staining	6%	7%
	(3-9)	(3-9)
Serum immunoglobulins (g/l)		
IgG	10.68	19.75
	(6.7-14.5)	(7.1-10.75)
IgM	1.64	0.95
	(0.45-1.5)	(0.4-0.8)
IgA	0.32	0.25
	(0.85-2.11)	(0.35-1.10)

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-.³⁻⁵ Two previous reports described mild deficiency of serum IgA in association with non-deletional anomalies of chromosome 18. Yanagisawa⁶ 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*⁷ reported a

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.⁵ 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.*,⁸ Schinzel and Schmid,⁹ and Knorr-Gartner *et al.*¹⁰ 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,⁵ perhaps because of variation in patterns of deletion,³ 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.*¹¹ 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.⁴ Further, the occurrence of selective IgA deficiency in one of identical twins¹² 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.*¹³

Waldmann *et al.*¹⁴ 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 Schwartz¹⁵ 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.*³ 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,¹⁶ 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.

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