

Specific Polysaccharide Antibody Deficiency in Chromosome 18p Deletion Syndrome and Immunoglobulin A Deficiency

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■ Abstract

Immunoglobulin (Ig) A deficiency has long been recognized in patients with chromosome 18 abnormalities. We present the case of a young girl in whom a chromosome 18p deletion syndrome (46,XX,del[18][p11.1]) was associated not only with IgA deficiency, but also with an inability to make antibody to the unconjugated pneumococcal polysaccharide vaccine, Pneumovax II, indicating a concomitant specific polysaccharide antibody deficiency. The patient suffered from recurrent upper respiratory tract and genitourinary infections, which were controlled by the use of prophylactic antibiotics. The association of specific polysaccharide antibody deficiency, IgA deficiency, and chromosome 18p deletion syndrome has not been described previously, and extends the immunological phenotype of antibody deficiencies associated with defects of chromosome 18. The presence of specific polysaccharide antibody deficiency should be investigated in patients with chromosome 18 abnormalities, as these patients may have a more severe spectrum of infections than patients with chromosome 18 abnormalities and selective IgA deficiency alone.

Key words: Chromosome 18. 18p deletion syndrome. IgA deficiency. Specific polysaccharide antibody deficiency. Antibody deficiency.

■ Resumen

Hace tiempo que se ha identificado una deficiencia de inmunoglobulina (Ig) A en pacientes con anomalías del cromosoma 18. Aquí se presenta el caso de una chica joven cuyo síndrome de deleción del cromosoma 18p (46,XX,del[18][p11.1]) se asoció no solo a una deficiencia de IgA, sino también a una incapacidad de producir anticuerpos frente a una vacuna antineumocócica polisacárida no conjugada, Pneumovax II, hecho indicativo de una deficiencia simultánea de anticuerpos específicos anti-polisacáridos. La paciente padecía infecciones recurrentes de las vías respiratorias altas y del aparato genitourinario, que se controlaban con antibióticos profilácticos. La asociación de deficiencia de anticuerpos específicos anti-polisacáridos, deficiencia de IgA y síndrome del cromosoma 18p no se ha descrito con anterioridad, y amplía el fenotipo inmunológico de las deficiencias de anticuerpos asociadas a defectos del cromosoma 18. Debe estudiarse la presencia de una deficiencia de anticuerpos específicos anti-polisacáridos en pacientes con anomalías del cromosoma 18, ya que estos pacientes pueden presentar un espectro más grave de infecciones que los pacientes con anomalías del cromosoma 18 y solo una deficiencia selectiva de IgA.

Palabras clave: Cromosoma 18. Síndrome de deleción 18p. Deficiencia de IgA. Deficiencia de anticuerpos específicos anti-polisacáridos. Deficiencia de anticuerpos.

Introduction

The association between immunoglobulin (Ig) A deficiency and aberrations of chromosome 18 was first described in the 1960s. Deletions of both the short and long arms, and ring chromosome 18, have all been associated with IgA deficiency (reviewed by Hammarstrom and Smith [1]).

As only 1 chromosome 18 is affected in these patients, the clinical phenotype results from haploinsufficiency of an as yet unidentified gene or genes encoded by chromosome 18.

Chromosome 18 deletion syndromes are among the commonest autosomal deletion syndromes. The clinical spectrum includes dysmorphic features (often not striking at birth, but becoming evident by around 3 years of age), mental

impairment of variable severity, and a tendency towards autoimmune disorders, including autoimmune thyroiditis, diabetes mellitus, pernicious anemia, and rheumatoid arthritis. Growth delay is common, and growth hormone deficiency has been described in a number of cases. IgA deficiency is present in approximately half of reported cases [1].

Case Description

The patient was born at term (birth weight, 3.6 kg). There were no perinatal problems, but at 5 days she was referred to a pediatrician for possible dysmorphic features, which were considered to be within normal limits at that time. At 10 months she was referred to a geneticist for assessment of dysmorphism and developmental delay. She was noted to have a large head (circumference on the 90th percentile, compared with height and weight between the 3rd and 10th percentiles), with a broad brow, small nose, thin upper lip, micrognathia, prominent ears, and bilateral ptosis. She was noted to be

hypotonic, and had short, tapering fingers, with normal palmar creases. Karyotypic analysis confirmed a chromosome 18p deletion (46,XX,del[18][p11.1]). No cardiac or renal malformations were found, but a magnetic resonance image of the brain showed reduced or delayed myelination. At 18 months, she was referred to the growth clinic for assessment of her short stature, with height and weight both below the 3rd percentile. At this stage, her medical records show that she was prone to respiratory tract infections. IGF1 and IGFBP3 levels were 2.6 nmol/L (reference range, 4-20) and 1.3 mg/L (reference range, 0.5-2.9), respectively, and a growth hormone provocation test showed a maximum stimulation level of 18 (reference range, >20). She was started on growth hormone (Norditropin SimpleXx, 0.3 mg/d by subcutaneous injection; Novo Nordisk, Crawley, UK), with some improvement in her growth.

In the following years, she developed recurrent upper and lower respiratory tract infections, which responded to treatment with courses of antibiotics. Over a period of 1 year, she also developed a series of vulval infections, which were

Table. Immunologic Parameters in the Patient Over Time^a

	3 Years 9 Months	6 Years 2 Months	6 Years 6 Months ^b	7 Years 5 Months ^c
IgG, g/L	8.4 (4.9-16.1)	10.8		8.9 (5.4-16.1)
IgA, g/L	<0.25 (0.4-2.0)	<0.06		<0.25 (0.5-2.0)
IgM, g/L	0.79 (0.5-2.0)	0.90		0.82 (0.5-2.0)
IgG1, g/L		7.48 (3.6-7.3)		
IgG2, g/L		1.36 (1.4-4.5)		
IgG3, g/L		0.74 (0.3-1.1)		
IgG4, g/L		<0.04 (0-1.0)		
Tetanus Ab, IU/mL		0.21 (>0.1)	1.53	
Hib Ab, mg/L		0.20 (>1.0)	>9.0	
Pneumococcal Ab				
Serotype 4, mg/L		0.05	0.11	>2.8
6B, mg/L		0.02	0.13	>10.4
9, mg/L		0.05	0.08	>2.9
14, mg/L		0.16	0.07	>6.5
18C, mg/L		0.10	0.38	8.95
19F, mg/L		0.24	0.99	>9.5
23F, mg/L		0.26	5.73	>6.3
1, mg/L		0.05	0.04	0.01
3, mg/L		0.22	0.57	0.13
5, mg/L		0.09	0.13	0.12
7F, mg/L		0.09	0.08	0.04
8, mg/L		–	0.64	0.10
19A, mg/L		0.23	0.06	0.05

Abbreviations: Ab, antibody; Hib, Haemophilus influenzae B.

^aAge-related normal ranges for serum immunoglobulins and IgG subclasses are given in parenthesis.

^bAfter vaccination with Menitorix and Pneumovax II.

^cAfter vaccination with Prevenar; all 13 pneumococcal serotypes tested are contained in 23-valent Pneumovax II; serotypes 4, 6B, 9V, 14, 18C, 19F and 23F are contained in 7-valent Prevenar.

treated with antiseptic bath washes and antibiotics as required. At the age of 6 years she was referred for an immunology workup. She had received all her routine childhood immunizations (which did not include pneumococcal immunization). Physical examination was unremarkable, except for the features noted above. Baseline immunological investigations (Table) showed normal serum levels of IgG and IgM, but serum IgA level was below the limit of detection. IgG subclasses showed borderline high IgG1 and borderline low IgG2 levels, with normal IgG3 and IgG4 levels for age. She had low but protective levels of antitetanus toxoid antibody, suboptimal anti-*Haemophilus influenzae* type B (Hib) antibody (to both of which she had been immunized), and essentially absent antibody to pneumococcus (to which she had not been immunized). Lymphocyte markers showed mild polyclonal B cell lymphocytosis, with normal numbers of T cells and NK cells. Other immunological parameters were normal. She was immunized with the conjugated Hib/MenC vaccine, Menitorix (GSK, Uxbridge, UK), and the 23-valent unconjugated pneumococcal vaccine, Pneumovax II (Sanofi Pasteur, Maidenhead, UK). Four weeks after vaccination, she had made a good antibody response to tetanus toxoid and Hib, but no antibody response to 12 of 13 pneumococcal serotypes tested (Table). She subsequently received 2 doses of the 7-valent conjugated anti-pneumococcal vaccine, Prevenar (Wyeth, Maidenhead, UK), to which she made a good antibody response. She continues to be treated with courses of antibiotics for respiratory and vulval infections as required, with regular antiseptic bath washes to reduce the incidence of vulval infections.

Discussion

Our patient had an immunological defect that consisted of IgA deficiency and specific polysaccharide antibody deficiency. The association between IgA deficiency and chromosome 18 abnormalities has been widely reported. However, there have been no reports of chromosome 18p deletion syndrome with IgA deficiency and a specific polysaccharide antibody deficiency. Whilst most reports of immune deficiency associated with chromosome 18 abnormalities have focused on selective IgA deficiency, several patients have shown a more extensive or progressive antibody deficiency. Michaels et al [2] reported a girl with ring chromosome 18, intestinal nodular hyperplasia, and hypogammaglobulinemia affecting IgG, IgA, and IgM titers. Slyper and Pietryga [3] described a case of progression from IgA deficiency to common variable immunodeficiency (CVID) in an adolescent female with an 18q deletion. More recently, Litzman et al [4] described a 14-year-old girl with markedly decreased IgG and IgA and progressively falling IgM titers. The patient described in this report was unable to mount a serotype-specific antibody response to the unconjugated pneumococcal polysaccharide vaccine, Pneumovax II, but was able to make antibodies to bacterial polysaccharides when these were presented in conjugate vaccines (Menitorix and Prevenar). This profile is consistent with specific polysaccharide antibody deficiency [5], and

extends the spectrum of immune deficiencies seen in patients with chromosome 18 abnormalities. The association of IgA deficiency and specific polysaccharide antibody deficiency is recognized in patients without defined chromosomal abnormalities, and may have significant implications, as those patients with isolated IgA deficiency had fewer lower respiratory tract infections and a lower incidence of bronchiectasis than patients with IgA deficiency associated with other immune defects, such as specific polysaccharide antibody deficiency [6].

The prevalence of chromosome 18 abnormalities in patients with IgA deficiency is unclear. Burgio et al [7] identified a single case of ring chromosome 18 in 50 children with IgA deficiency, whilst Taalman et al [8] found a single case among 17 children with IgA deficiency. The genetic relationship between IgA deficiency and chromosome 18 abnormalities is obscured by the fact that IgA deficiency has been reported in patients with deletions in both the long and short arms [9], indicating that a single gene on chromosome 18 is unlikely to be the culprit. In a recent study, Dostal et al [10] identified a potential susceptibility gene locus for IgA deficiency in patients with 18q deletion syndrome at a distal region of 18q22.3-q23. This is broadly in keeping with the finding of Lewkonia et al [11] of an association between IgA deficiency and chromosome breakage at 18q23. Li et al [12] suggested that the NFATc gene, located at the q-terminus of chromosome 18, might be responsible for the association between 18q deletion and IgA deficiency, a finding supported by NFATc gene expression studies in patients with 18q deletion syndrome with and without IgA deficiency [13]. However, Vorechovsky et al [14] failed to identify allele sharing at 17 chromosome 18 marker loci in a study of 449 patients with familial IgA deficiency/CVID. No candidate genes have been identified to date on 18p.

Similar to IgA deficiency, growth hormone deficiency (as found in our patient) has been reported in patients with 18p or 18q deletion syndromes and ring chromosome 18 [15-19]. As with IgA deficiency, there is no clear association with an individual gene on either 18p or 18q, although the distal regions of 18p [20] and 18q22.3-q23 [18] have been implicated.

This case illustrates that patients with chromosome 18 abnormalities should be investigated not only for the presence of IgA deficiency, but also for specific antibody deficiency to polysaccharide antigens, particularly where there is a history of upper or lower respiratory tract infections. In addition, the antibody deficiency associated with chromosome 18 abnormalities may be progressive, and serial measurement of serum immunoglobulins may be indicated in selected patients.

References

1. Hammarstrom L, Smith CIE. Genetic approach to common variable immunodeficiency and IgA deficiency. In: Ochs HD, Smith CIE, Puck JM, editors. Primary immunodeficiency diseases. Oxford: Oxford University Press: 1999. p250-62.
2. Michaels DL, Go S, Humbert JR, Dubois RS, Stewart

- JM, Ellis EF. Intestinal nodular lymphoid hyperplasia, hypogammaglobulinaemia, and haemolytic abnormalities in a child with a ring 18 chromosome. *J Pediatr.* 1971;79:80-8.
3. Slyper AH, Pietryga D. Conversion of selective IgA deficiency to common variable immunodeficiency in an adolescent female with 18q deletion syndrome. *Eur J Pediatr.* 1997;156:155-6.
 4. Litzman J, Brysova V, Gaillyova R, Thon V, Pijacjova A, Michalova K, Zemanova Z, Lokaj J. Agammaglobulinaemia in a girl with a mosaic ring 18 chromosome. *J Paediatr Child Health.* 1998;34:92-4.
 5. Paris K, Sorensen RU. Assessment and clinical interpretation of polysaccharide antibody responses. *Ann Allergy Asthma Immunol.* 2007;99:462-4.
 6. Aghamohammadi A, Cheraghi T, Gharagozlou M, Movahedi M, Rezaei N, Yeganeh M, Parvaneh N, Abolhassani H, Pourpak Z, Moin M. IgA deficiency: correlation between clinical and immunological phenotypes. *J Clin Immunol.* 2009;29:130-6.
 7. Burgio GR, Duse M, Monafò V, Ascione A, Nespoli L. Selective IgA deficiency: clinical and immunological evaluation of 50 patients. *Eur J Pediatr.* 1980;133:101-6.
 8. Taalman RD, Weemaes CM, Hustinx TW, Scheres JM, Clement JM, Stoelinga GB. Chromosome studies in IgA deficient patients. *Clin Genet.* 1987;32:81-7.
 9. Cunningham-Rundles C. Genetic aspects of immunoglobulin A deficiency. *Adv Hum Genet.* 1990;19:235-66.
 10. Dostal A, Linnankivi T, Somer M, Kahkonen M, Litzman J, Tienari P. Mapping susceptibility gene locus for IgA deficiency at del(18)(q22.3-q23); report of familial cryptic chromosome t(18q;10p) translocations. *Int J Immunogenet.* 2007;34:143-7.
 11. Lewkonia RM, Lin CC, Haslam RH. Selective IgA deficiency with 18q+ and 18q—karyotypic anomalies. *J Med Genet.* 1980;17:453-6.
 12. Li X, Ho SN, Luna J, Giacalone J, Thomas DJ, Timmerman LA, Crabtree GR, Francke U. Cloning and chromosomal localization of the human and murine genes for the T-cell transcription factors NFATc and NFATp. *Cytogenet Cell Genet.* 1995;68:185-91.
 13. Wang Z, Cody JD, Leach RJ, O'Connell P. Gene expression patterns in cell lines from patients with 18q- syndromes. *Hum Genet.* 1999;104:467-75.
 14. Vorechovsky I, Blennow E, Nordenskjold M, Webster AD, Hammarstrom L. A putative susceptibility locus on chromosome 18 is not a major contributor to human selective IgA deficiency: evidence from meiotic mapping of 83 multiple-case families. *J Immunol.* 1999;163:2236-42.
 15. Leisti J, Leisti S, Perheentupa J, Savilahti E, Aula P. Absence of IgA and growth hormone deficiency associated with short arm deletion of chromosome 18. *Arch Dis Child.* 1973;48:320-2.
 16. Gul D, Sayli BS, Gok F, Gokcay E. IgA deficiency associated with growth hormone deficiency in a boy with short arm deletion of chromosome 18 (46,XY,18p-). *Ann Genet.* 1994;37:82-5.
 17. Cody JD, Hale DE, Brkanac Z, Kaye CI, Leach RJ. Growth hormone insufficiency associated with haploinsufficiency at 18q23. *Am J Med Genet.* 1997;71:420-5.
 18. Feenstra I, Vissers LE, Orsel M, van Kessel AG, Brunner HG, Veltman JA, van Revenswaaij-Arts CM. Genotype-phenotype mapping of chromosome 18q deletions by high-resolution array CGH: an update of the phenotypic map. *Am J Med Genet A.* 2007;143A:1858-67.
 19. Meloni A, Boccone L, Angius L, Loche S, Falchi AM, Cao A. Hypothalamic growth hormone deficiency in a patient with ring chromosome 18. *Eur J Pediatr.* 1994;153:110-2.
 20. Portnoi MF, Gruchy N, Marlin S, Finkel L, Denoyelle F, Dubourg C, Odent S, Siffroi JP, Le Bouc Y, Houang M. Midline defects in deletion 18p syndrome: clinical and molecular characterization of three patients. *Clin Dysmorphol.* 2007;16:247-52.
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