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Abnormal serum IgG subclass pattern in children with Down's syndrome

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Abstract

Susceptibility to infections is a well known feature of Down's syndrome. The possible relation between this predisposition and the serum concentrations of the IgG subclasses was studied in 38 children with Down's syndrome aged 1–12 years. An age matched group of 50 healthy children served as controls. The serum concentrations of IgG_1 and IgG_3 were significantly raised among children with Down's syndrome in all three age groups studied (that is 1–2·5, 4–8, and 9–12 years). The serum concentrations of IgG_2 were normal in the first two groups but significantly reduced in the third age group. In contrast, the concentrations of IgG_4 among children with Down's syndrome were significantly reduced in all three age groups. Moreover, among the children with Down's syndrome aged 4–12 years 68% (15/22) had IgG_4 concentrations below 2 SDs of the geometrical mean of the controls. The results may partially explain the proneness of children with Down's syndrome to infections with encapsulated bacteria. Although the underlying cause of these abnormalities is unknown, IgG subclass determination seems relevant in the clinical evaluation of children with Down's syndrome.

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Susceptibility to infections is a feature of Down's syndrome, and is likely to be due to abnormalities of host defence, that is, of the immune response. Reported defects include components of cell mediated[1] and humoral immunity,[2] the inflammatory response,[3 4] and interferon production.[5 6] The results of studies of serum immunoglobulin concentrations in subjects with Down's syndrome have been conflicting. Both normal and raised serum concentrations of IgG, IgA, and IgE have been found and raised, normal, and decreased concentrations of IgD.[1 7] In adults with Down's syndrome the serum concentrations of IgG_2 and IgG_4 have been found to be significantly reduced and those of IgG_1 and IgG_3 to be normal or raised.[8] Recently it has been claimed that about half of the children with Down's syndrome are deficient in IgG_4.[9] The aim of the present study was to investigate the serum concentrations of all IgG subclasses in children with Down's syndrome and to compare them with those in healthy children of the same ages.

Patients and methods

The study comprised 38 non-institutionalised children with chromosomally verified Down's syndrome, 16 girls and 22 boys, who were aged 1 to 12 years. Nine of these patients had congenital cardiovascular malformations, none of which was of major clinical significance. Three of the patients had been operated upon in the neonatal period for treatment of congenital gastrointestinal malformations, and none of them suffered subsequently from any complications of these conditions. In the 38 children with Down's syndrome blood samples were taken for serum IgG subclass determination. A brief interview with the parents concerning the dietary habits of the children confirmed that they had a normal diet. The proneness to infectious diseases was evaluated and the children underwent physical investigation at the time of blood sampling. None of them showed signs of current infection at that time.

Fifty age matched healthy children served as controls and because of the age dependency of IgG subclass concentrations, particularly IgG_2 and IgG_4 in early childhood,[10] the children were split into three age groups: 1–2·5, 4–8, and 9–12 years. There were 16, 12, and 10 children with Down's syndrome and 20, 15, and 15 control children in the three age groups respectively.

The serum samples were stored at −20°C before analysis. The concentrations of the subclasses of IgG were determined by a competitive two step microtitre enzyme linked immunosorbent assay (ELISA) based on subclass specific monoclonal antibodies. The assay conditions regarding the buffers used, incubation times, and sample dilutions, and the specificity, sensitivity, linearity, precision, and accuracy will be described in detail elsewhere (C G M Magnusson, to be published). All serum samples were assayed in duplicate and a commercial standard serum (H00–03, Janssen, Belgium), calibrated against the WHO 67/97 standard,[11] was used to produce standard curves. The interassay imprecision, which was evaluated by including two dilutions of a control serum on each plate, gave coefficients of variation on seven different plates not exceeding 9% for all four subclasses.

The Mann-Whitney U test with correction for ties was used in the statistical analyses of the results and a two tailed $p<0·05$ was considered significant.

Results

The individual values and the geometrical mean concentrations and ±1 SD of the four IgG subclasses in the controls and children with Down's syndrome are presented in figs 1 and 2 and the table. There were no significant age

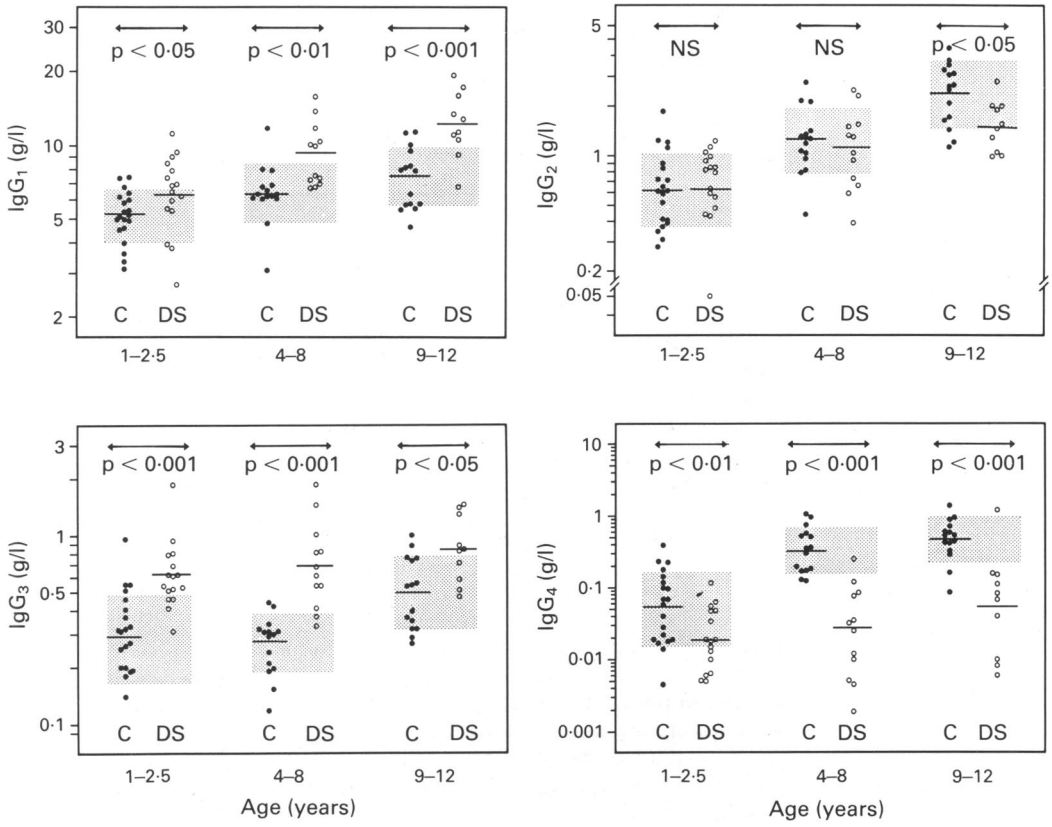

Figure 1 Individual and geometrical mean concentrations of the four IgG subclasses in children with Down's syndrome (DS) and control children (C). The children are split into three age groups (1–2·5, 4–8, and 9–12 years). The ±1 of the geometrical mean concentrations of healthy children are indicated (shaded area). The levels of significance are given in the figure.

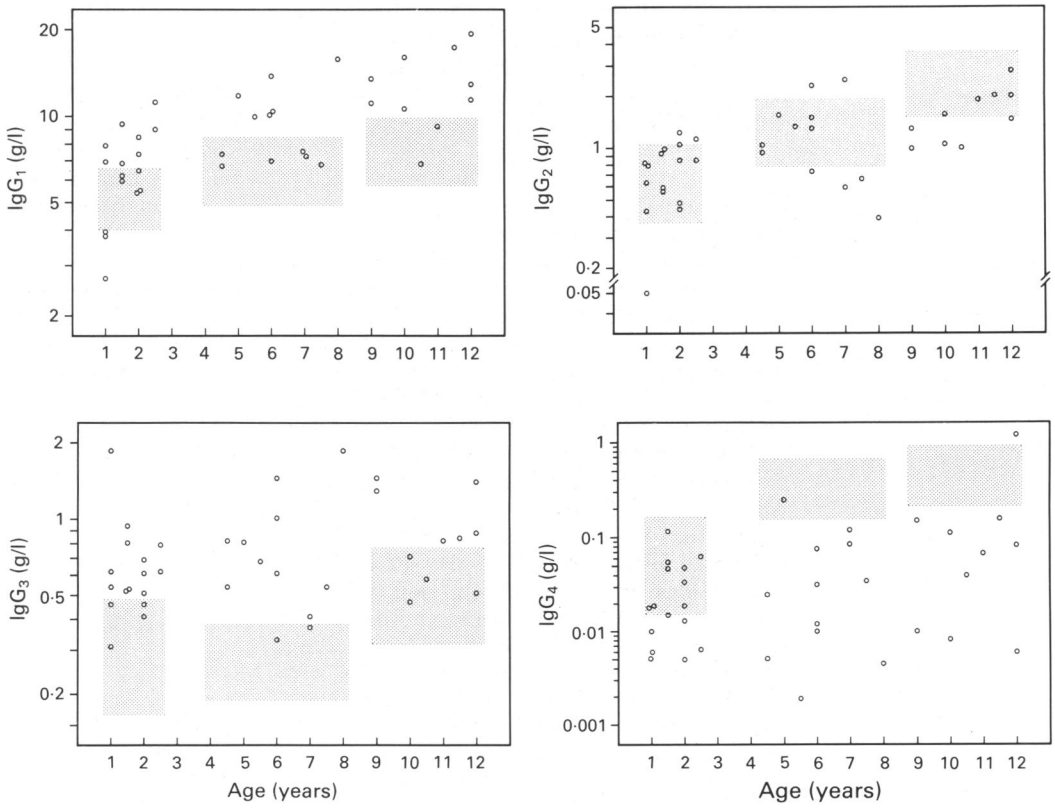

Figure 2 Individual concentrations of the four IgG subclasses in children with Down's syndrome in relation to age. The geometrical mean ±1 SD of healthy children are indicated (shaded area).

IgG subclass concentrations (g/l) in serum of children with Down's syndrome compared with healthy age matched control children in three age groups. Geometrical means (GM) ± 1 SD are presented

	Age groups (years)					
	1–2·5		*4–8*		*9–12*	
	Controls (n=20)	*Down's syndrome (n=16)*	*Controls (n=15)*	*Down's syndrome (n=12)*	*Controls (n=15)*	*Down's syndrome (n=10)*
Age (GM)	1·5	1·6	6·0	6·1	10·0*	10·7*
IgG_1 (GM)						
+1SD	5·1*	6·3*	6·4**	9·1**	7·3***	12***
−1SD	6·5	9·1	8·5	12	9·8	17
	4·0	4·5	4·8	6·8	5·5	9·0
IgG_2 (GM)						
+1SD	0·62	0·63	1·2	1·1	2·4*	1·5*
−1SD	1·0	1·3	1·9	1·9	3·6	2·2
	0·37	0·30	0·78	0·62	1·5	1·1
IgG_3 (GM)						
+1SD	0·29***	0·61***	0·26***	0·69***	0·49*	0·83*
−1SD	0·49	0·91	0·38	1·2	0·76	1·3
	0·17	0·41	0·18	0·41	0·32	0·55
IgG_4 (GM)						
+1SD	0·053**	0·019**	0·34***	0·024***	0·46***	0·057***
−1SD	0·17	0·52	0·69	0·10	0·92	0·29
	0·016	0·0072	0·16	0·0053	0·23	0·011

Calculated significance levels in Mann-Whitney U test: *p<0·05, p<0·01, ***p<0·01.

differences between controls and children with Down's syndrome in the two youngest groups, but the children with Down's syndrome were slightly older than the controls in the oldest age group (p=0·04) (table). The children with Down's syndrome had significantly higher concentrations of IgG_1 (figs 1 and 2, upper left) and IgG_3 (figs 1 and 2, lower left) than the controls in all three age groups. In contrast, the serum concentrations of IgG_2 were normal in the children with Down's syndrome in the two youngest age groups but significantly reduced among the oldest children with Down's syndrome (figs 1 and 2, upper right). The IgG_4 concentrations were significantly reduced in all three age groups of children with Down's syndrome (figs 1 and 2, lower right). In fact, in the two age groups with the oldest children, 68% (15/22) had IgG_4 concentrations below 2SD from the geometrical mean.

Discussion

The higher serum concentrations of IgG subclasses 1 and 3 in the children with Down's syndrome compared with the controls may well be a consequence of polyclonal stimulation from repeated bacterial infections, which obviously does not include IgG_2 and IgG_4. This contrast strengthens the concept that children with Down's syndrome fail to respond properly with antibodies of the latter subclasses. The results are in accordance with recent data for adults with Down's syndrome[8] and for children concerning IgG_4[9] and are likely to be of pathogenetic significance for the susceptibility to infections. It is interesting to note that IgG_4 deficiency is found in Down's syndrome at all ages,[8 9] but an IgG_2 deficiency tends to develop later in life among children and adults with Down's syndrome.[8] Thus the IgG_4 deficiency is not accompanied by an IgG_2 deficiency in childhood in Down's syndrome.

Children with Down's syndrome are especially prone to respiratory bacterial infections.[4] This may be partially explained by a deficiency in IgG_2 and IgG_4 antibodies, of which the former are known to be directed primarily against bacterial polysaccharide antigens of encapsulated bacteria, such as *Diplococcus pneumoniae* and *Haemophilus influenzae*.[12] Even though the serum concentration of IgG_4 is low, it may play a part in mucosal defence because of its higher relative concentration in secretions.[13] Virus specific IgG antibodies are often of subclasses 1 and 3.[12]

The mechanism underlying the abnormal serum IgG subclass pattern is probably not a gene dosage effect as none of the chromosome 21 genes are known to regulate immunoglobulin production. Secondary effects of either a factor related to immunoglobulin production or a deficiency of a trace element such as selenium[14] are proposed as alternative explanations. We have recently reported that selenium supplementation in children with Down's syndrome has a significant augmentative effect on the serum concentrations of IgG_2 and IgG_4, but not on those of IgG_1 and IgG_3.[14]

Although the mechanism behind the abnormal subclass pattern in individuals with Down's syndrome is unknown, it seems relevant to assay the IgG subclass concentrations among patients with Down's syndrome who have repeated infections. If only the total serum IgG concentration is assayed a deficiency in the IgG_2 and IgG_4 subclasses will escape detection.

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The uses of laparoscopy*

If the October 1991 issue of the *Journal of Pediatric Surgery* is anything to go by, laparoscopy is something of a buzz word in paediatric surgical circles at the moment. It contains five articles about laparoscopic surgery: three about cholecystectomy,[1–3] one about pyloromyotomy,[4] and one about untwisting a torsion of the uterine adnexa.[5]

Gallbladder disease in children is not common (see Archivist 1991:940) but not rare and workers in Montreal,[1] Washington DC, and Nashville, Tennessee[3] report a total of 13 laparoscopic cholecystectomies in children between the ages of 7 and 16 years. There were no complications and the children were less distressed postoperatively and recovered quicker.

A report from Limoges, France describes the treatment of 10 babies with pyloric stenosis using laparoscopic pyloromyotomy.[4] The operation was successful and without complications in all 10. The final article in the series is one from Israel reporting the use of laparoscopic surgery in a girl of 11 years with torsion of the uterine adnexa.[5]

An accompanying editorial discusses the advent of laparoscopic surgery (laparoscopic cholecystectomy in adults was first described in 1989) and lays emphasis on the need to ensure adequate training in these techniques and the potential for disaster in inexperienced hands.[6] Clearly any surgeon new to the technique should at first operate only under supervision. According to the team in Nashville it takes some 15 to 20 operations to become competent.

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*A good title is worth imitating. Richard Hoggart's best known book, *The Uses of Literacy*, was published in 1957 and stays in the memory, I suspect, largely because of its title. In fact, it was to have been called 'the abuses of literacy', but was changed because of the objections of a libel lawyer. By the time I got round to reading it, it was way out of date and not very relevant. I enjoyed the first part of his autobiography[7] though and am settling into the second[8]; recommended reading for when you've finished the *Archives* and want a break from paediatrics.

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