Increase in serum concentrations of IgG_2 and IgG_4 by selenium supplementation in children with Down's syndrome

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Abstract

In a previous study on children with Down's syndrome a reduced rate of infections was reported by their parents after the children had received six months' treatment with selenium supplements. In the present study the concentrations of the four IgG subclasses were measured in 29 of these children in samples of serum obtained before and immediately after the period of supplementation and one year after it had finished. Selenium had a significant augmentative effect on the serum concentrations of IgG_2 and IgG_4, but not of IgG_1 and IgG_3. This effect was not related to age, as among children over the age of 6 years the serum concentrations of IgG_2 and IgG_4 had decreased significantly one year after the treatment had been stopped. This study suggests that selenium has an immunoregulatory effect, which might be of importance in both basic research and clinical practice.

Susceptibility to infections is a feature of Down's syndrome and is likely to be caused by abnormalities in host defence—for example, in the immune response.[1] In patients with Down's syndrome the serum concentration of IgG is either normal or slightly raised.[1] The serum concentrations of the IgG_2 and IgG_4 subclasses are significantly reduced, and those of IgG_1 and IgG_3 are normal or increased in both adults[2] and children with Down's syndrome (G Annerén *et al*, unpublished observations). In a study of six months' selenium supplementation in children with Down's syndrome that was designed to investigate the effect on the activity of glutathione peroxidase in erythrocytes and on the concentrations of selenium in the plasma and erythrocytes, many of the parents spontaneously reported a reduced rate of infections among their children after treatment with selenium.[3]

Older patients with Down's syndrome tend to develop a presenile dementia that has striking similarities to Alzheimer's disease. It has been suggested that this might be due to increased lipid peroxidation as a secondary gene dosage effect of the 50% increase in the activity of superoxide dismutase in trisomy 21 cells. The rationale for selenium supplementation was to find out whether the activity of the selenium dependent enzyme glutathione peroxidase would increase and improve the protection against oxygen radicals.[3]

The aim of the present study was to investigate whether the reported decrease in infections could be related to a change in the serum pattern of IgG subclasses among children with Down's syndrome.

Patients and methods

In the previous study 48 children with Down's syndrome, verified by chromosomal analysis, who were living at home were enrolled.[3] Selenium was given as selenium rich yeast tablets (Novamed Selen, Huhtamäki OY) in a dose of 10 μg/kg body weight/day for six months. The children were examined clinically before and immediately after the six month supplementation period, and again one year later. On each of these three occasions a sample of serum was collected and stored at −20°C until it was analysed. The plasma and erythrocyte selenium concentrations increased roughly fourfold during the period of supplementation and had almost regained the pretreatment concentrations one year after withdrawal.[3] Sufficient volumes of serum for the present study were available from 29 of the 48 children: 19 boys and 10 girls, aged 1·5 to 15 years.

The serum concentrations of the four subclasses of IgG were determined by a competitive two step microtitre enzyme linked immunosorbent assay (ELISA) based on subclass specific monoclonal antibodies and rabbit antimouse immunoglobulin antibodies conjugated to alkaline phosphatase. The assay conditions regarding the buffers used, incubation times, sample dilutions and the evaluation of specificity, sensitivity, linearity, precision and accuracy will be described in detail elsewhere (CG M Magnusson, unpublished observations). All three serum samples from each patient were assayed in duplicate on the same plate to minimise intrasubject variations. A commercial standard serum (H00–03, Janssen, Belgium), calibrated against the World Health Organisation 67/97 standard,[4] was used to produce standard curves. Interassay imprecision, which was evaluated by including two dilutions of a control serum on each plate, gave coefficients of variation on seven different plates of 4·9% for IgG_1, 5·8% for IgG_2, 5·1% for IgG_3, and 8·9% for IgG_4. Undetectable IgG_4 (<5 mg/l) was assigned a value of 2·5 mg/l.

Statistical analysis was by Wilcoxon's signed rank test. Because of the age dependence of IgG subclass concentrations, the children were split into two age groups, ≤6 (n=13) and >6 years (n=16), for the statistical analyses.

Results

After a six month period of selenium supple-

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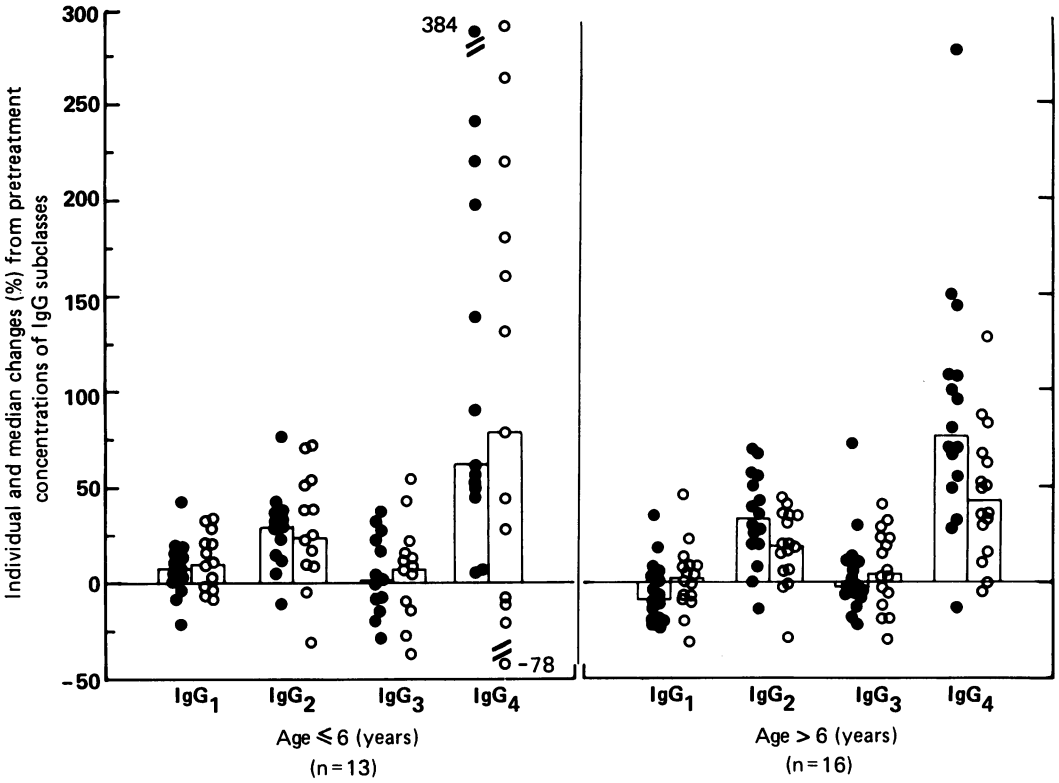

Individual and median percentage changes from pretreatment serum concentrations of the four IgG subclasses in 29 children with Down's syndrome, after a six month course of selenium supplementation (●) and one year after withdrawal of the supplementation (○). The histograms indicate the median percentage changes.

Mean IgG subclass serum concentrations (g/l) in 29 children with Down's syndrome before (0) and after a six month course of selenium supplementation (6), and 12 months after withdrawal of the selenium supplementation (18).

Group	Sample time (months)	Immunoglobulin subclass			
		IgG_1	IgG_2	IgG_3	IgG_4
Age ≤6 years (n=13)	0	7·55	0·76	0·56	0·016
	6	8·11	0·97	0·57	0·031
	18	8·36	0·96	0·58	0·025
Age >6 years (n=16)	0	10·7	1·21	0·72	0·048
	6	10·1	1·59	0·74	0·087
	18	10·8	1·41	0·75	0·069

mentation the serum concentrations of IgG_2 and IgG_4 were significantly increased in both the younger and the older children (figure). The median increase in IgG_2 was 30% ($p<0·005$) in the younger age group and 33% ($p<0·001$) in the older group. The corresponding median increases in IgG_4 were 61% ($p<0·005$) and 75% ($p<0·0005$). The IgG_2 ($p<0·05$) and IgG_4 ($p<0·005$) concentrations had declined significantly in the older age group (>6 years of age) one year after the stopping of selenium, but were essentially unchanged in the younger age group. In contrast, the serum concentrations of IgG_1 and IgG_3 were not significantly affected by selenium supplementation in either age group.

Discussion

In this study selenium supplementation was found to have an augmentative effect on the serum concentrations of IgG_2 and IgG_4 in children with Down's syndrome, which is of particular interest because concentrations of these two subclasses are low in patients with Down's syndrome (G Annerén *et al*, unpublished observations).[2] Although no control group was included the data seem convincing because both the IgG_2 and IgG_4 concentrations declined significantly during the year after withdrawal of supplementation among children >6 years. A corresponding decrease in the younger age group was probably masked by an expected rise in these subclasses with age.[5] To our knowledge this is the first study showing a linkage between selenium treatment and immunological host defence in man.

Children with Down's syndrome are especially prone to respiratory bacterial infections.[1] This may be partly explained by a deficiency in IgG_4,[6] and IgG_2 antibodies, of which the latter are known to be directed against bacterial polysaccharide antigens of encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.[7] The effect of selenium serum IgG_2 and IgG_4 concentrations may therefore be of clinical importance and in some way related to the spontaneously reported reduced rate of infections among the children with Down's syndrome. We are unable to present trustworthy clinical correlates to our laboratory data, however, as the original study was not designed for this purpose. It also remains to be investigated whether the observed effects upon IgG_2 and IgG_4 are confined to patients with Down's syndrome alone.

Our limited knowledge about the biological role of selenium is partly because selenium defi-

ciency is uncommon. In Keshan disease, an endemic cardiomyopathy afflicting Chinese children, there is a protein deficiency that coexists with selenium deficiency, making it difficult to decide which symptoms are the result of the selenium deficiency.[8] From animal experiments and veterinary medicine, however, selenium supplementation is known to be beneficial for host defence.[9] Although in a few studies in man selenium has been found to have no or only slight effects on granulocyte and lymphocyte function,[10] low selenium concentrations have been found among patients with severe bacterial infections, but not in those suffering from viral infections.[11] Our results confirm these data, in view of the fact that it is mainly IgG_2 that plays a part in the immune response to bacterial antigens,[7] while viral infections trigger mainly IgG_1 and IgG_3 responses.[12] Thus with a low dietary intake of selenium there seem to be grounds for suspecting that there is a vicious circle comprising selenium deficiency, reduced serum IgG_2, and repeated infections.

The results of the present study were unexpected and no explanation of the mechanisms of action can be offered. Further studies are under way to elucidate the immunoregulatory effect of selenium and to find out if it can be of any clinical value in the management of infection prone children, with or without Down's syndrome.

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