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Intrinsic defect of the immune system in children with Down syndrome: a review

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Summary

Down syndrome (DS) is the most frequent cause of mental retardation in man. Immunological changes in DS have been observed since the 1970s. The neurological system appears to be ageing precociously, with early occurrence of Alzheimer disease; until now, the observed immunological differences have been interpreted in the same context. Looking back at past and present results of immunological studies in DS children in relation to the clinical consequences they suffer, we conclude that it is more likely that the DS immune system is intrinsically deficient from the very beginning.

Keywords: children, Down syndrome, immune system, primary immunodeficiency

Introduction

Down syndrome (DS), or trisomy 21, is the most frequent genetic cause of mental retardation in man; the incidence is approximately one in 750 live births [1]. Consequently, doctors frequently see patients with DS and encounter their complex medical problems. Individuals with DS are invariably cognitively impaired, although the severity is highly variable. Characteristic facial features and hypotonia are present in almost all patients; approximately 50% suffer from congenital cardiac anomalies. Congenital cataract, abnormalities of the gastrointestinal tract and orthopaedic, eye and ear problems occur with increased frequency compared with non-DS individuals. Histopathological studies show a small and hypocellular brain and, by the fourth decade, characteristic features of Alzheimer disease [2,3].

Autoimmune phenomena such as acquired hypothyroidism, coeliac disease and diabetes mellitus occur at higher frequency compared with non-DS subjects. Leukaemia is estimated to be 15–20 times more frequent in DS [4–7]. Despite advances in treatment, infections – especially pneumonia – and leukaemia are still major causes of morbidity and mortality in DS [7–12]. The increased frequency of haematological malignancies, autoimmune diseases and infections in DS, and the observed high frequency of hepatitis B surface antigen carriers, had already led in the 1970s to the hypothesis that DS is associated with abnormalities of the immune system [4,13–16]. Indeed, many differences between the immune system of DS and non-DS individuals have been found throughout the years, and several hypotheses have been formulated which, if true, could have consequences for everyday clinical care in DS (findings relevant for everyday clinical care are summarized in Table 1).

Higher rates of infections, malignancies and autoimmune phenomena are seen normally in elderly individuals [17–20], and DS was therefore hypothesized to be a form of abnormal precocious ageing in various papers published in the late 1980s and early 1990s (e.g. [21–22]), which are still being cited (e.g. [23]).

Natural killer cells and innate immunity

The supposedly higher percentages of natural killer (NK) cells found in DS seems to support this theory of precocious ageing [21,24], as high percentages of NK cells are seen normally with ageing. However, these studies were performed in small groups of DS individuals with single- and double-colour flow cytometric staining techniques that could not differentiate between NK cells ($CD3^-$) and NK marker-bearing T lymphocytes ($CD3^+$). Our recent study on lymphocyte subpopulations in DS shows lower absolute numbers of $CD3^-CD16$ and/or 56^+ NK cells in all age groups [25]. Populations with different NK activity, capable of low, intermediate and high cytotoxicity against the NK-sensitive tumour cell line K562, respectively, were described in the 1980s [26,27]. Several authors describe a significant increase of cells possessing the low NK activity phenotype in DS, associated with a significant decrease of cells with the intermediate and high NK activity phenotype [21,28]. With longevity, however, NK cells with well-preserved cytotoxic function increase [29].

Table 1. Overview of differences relevant to everyday clinical care found between the immune systems of Down syndrome (DS) and non-DS individuals since the 1970s.

		Reference
Lymphocyte subpopulations		
$CD3^-CD16$ and/or 56^+ NK cells	Decreased (abs)	[25]
$CD19^+$ B lymphocytes	Decreased (abs; %)	[24,25]
$CD3^+$ T lymphocytes	Decreased/normal (abs)	[25]
$CD3^+CD4^+$ T helper lymphocytes	Decreased (abs; %)	[25]
$CD3^+CD8^+$ cytotoxic T lymphocytes	Decreased/normal (abs)	[25]
$CD4^+CD45RA^+$ cells	Decreased (%)	[37,38]
Th1/Th2 ratio	Increased	[69]
CD4/CD8 ratio	Inverted ratio	[22]
TCR-$\alpha\beta^+$ T lymphocytes	Decreased (%)	[37]
$CD8^+CD57^+$ cells	Increased (%)	[21]
Immunoglobulins		
IgG	Increased > 6 years	[15,28,30]
IgM	Decreased > 6 years	[15,28]
IgA	Increased > 6 years/normal	[15,30]
IgG_1	Increased/normal	[30,70]
IgG_2	Decreased/normal	[30,70]
IgG_3	Increased/normal	[30,70]
IgG_4	Decreased/normal	[30,70]
Response to vaccination		
Pneumococcal polysaccharide vaccine	Decreased/normal	[28,54]
Tetanus vaccine	Decreased	[74]
Pertussis vaccine (acellular)	Decreased	[58]
Hepatitis B vaccine	Decreased/normal	[52,57,60]
Hepatitis A vaccine	Normal	[56]
Influenza vaccine	Decreased	[74]
Polio vaccine (oral)	Decreased	[59]

Abs, absolute counts; CD, cluster of differentiation; Ig, immunoglobulin; NK, natural killer; TCR, T cell receptor; Th, T helper lymphocyte; %, relative counts.

Thymus and T lymphocytes

The thymus is smaller in DS subjects, even in newborns, and has an abnormal structure [16,26,28,30–32]. This suggests that T lymphocytes are the core of the problem in DS; however, children with congenital heart disease who require cardiac surgery with (partial) thymectomy show rapid and permanent changes in T lymphocyte numbers [33,34] but, unlike in DS, their frequency of infections and autoimmune diseases is not increased [35]. The DS thymus shows a decreased proportion of phenotypically mature thymocytes expressing high levels of the $\alpha\beta$ form of the T cell receptor (TCR-$\alpha\beta$) and associated CD3-molecule [36], and overexpression of tumour necrosis factor (TNF)-α and interferon (IFN)-γ cytokines [27]. Overexpression of these cytokines suggests a dysregulation in cytokine production in DS and may provide an explanation for the abnormal thymic anatomy and thymocyte maturation [27]. An increased percentage of peripheral T lymphocytes expressing the alternative $\gamma\delta$ form of the TCR-$\gamma\delta$ has been reported [26,37], as well as a lower percentage of $CD4^+CD45RA^+$ naive cells – then considered to represent cells that have recently emigrated from the thymus – and a higher percentage of $CD29^+$ memory [26,38]. TCR excision circle (T_{REC}) counts are used to estimate recent thymic emigrants (VDJ recombination events excise intervening stretches of DNA) [39]. A significantly lower number of T_{REC}^+ peripheral blood cells is found in DS children in comparison with healthy control children [23,40]. These findings could be interpreted as early senescence of the immune system [26,38], because naive helper and cytotoxic T lymphocytes [29,41] as well as T_{REC}^+ peripheral blood cells [42] decrease with ageing, while central and effector memory T helper lymphocytes and effector memory and terminally differentiated cytotoxic T lymphocytes increase [43]. We have recently demonstrated a T lymphocytopenia in all age groups, however, not only in older DS children, that concerns $CD4^+$ helper as well as $CD8^+$ cytotoxic T lymphocytes with absence of the tremendous expansion that is seen normally in the first year of life, suggesting a deficient reaction to antigenic stimulation [25,41,44]. Absolute numbers of T lymphocyte populations gradually approach those of normal children over time [25], but it is doubtful whether these cells have normal phenotype and function, having shown a lack of the antigen-driven expansion in earlier years. Functional abnormalities of T lymphocytes that have been described support this: the *in vitro*

proliferative response to phytohaemagglutinin (PHA) is markedly below normal in DS infants as well as adults [15,16,45–47]. In addition, bacterial and viral antigen-induced *in vitro* interleukin (IL)-2 production is reduced markedly, although PHA-stimulated IL-2 production is not impaired [13,42,43]. An interesting hypothesis is that overexpression of the cell adhesion molecules lymphocyte function-associated antigen-1 and DS cell adhesion molecule – located on chromosome 21 – causes higher affinity between cells leading to abnormal maturation and function [48,49], but in most genetic studies in trisomy 21 an overall 150% increase of gene expression is not seen; the genetic overexpression is often specific for a particular organ [50]. Enhanced cell death by apoptosis could also play a role, as transgenic copper–zinc superoxide dismutase mice (in humans located on chromosome 21) show enhanced apoptosis [51].

B lymphocytes and antibody production

A considerable hypergammaglobulinaemia of immunoglobulin (Ig)G and IgA after the age of 5 years, with high levels of IgG_1 and IgG_3 and low levels of IgG_2 and IgG_4, is described in DS [15,30,52], with IgM levels decreasing in adolescence. IgD levels are high [53]. Antibody responses to rabbit erythrocytes and *Escherichia coli* antigens are low [28], as are the responses to vaccine antigens such as influenza A, oral polio, acellular pertussis, tetanus and polysaccharide pneumococcal vaccine [54–59]. The frequency of hepatitis B virus carriers is much higher among DS children compared with age-matched controls; however, normal responses to hepatitis A and B vaccinations are seen, although specific IgG-subclasses can vary [56,60]. Autoantibodies against human thyroglobulin and gliadin are observed more often in DS children [15,30,61], as are high titres against casein and beta-lactoglobulin [15,61].

Somewhat paradoxically, we have found recently a profound B lymphocytopenia in DS, with absence of the normal enormous expansion in the first year of life [25]. This has been described previously [24,28,62,63], but so far has attracted little attention. Recent observations even show a significant decrease of B lymphocytes ($CD19^+$) in fetuses with DS [64]. These abnormalities can be due either to an intrinsic B lymphocyte defect or to the consequence of deficient T helper lymphocyte function causing inadequate control of B lymphocyte activation and proliferation. The combination of profound B lymphocytopenia and hypergammaglobulinaemia suggests the latter, with the possibility that antibody responses may be oligoclonal and/or inadequate in DS. However, we have found no mono- or oligoclonal M-proteins in 88 DS children, (unpublished data). Also, in comparison, patients with DiGeorge syndrome (DGS; 22q11-deletion) show a congenital thymic hypoplasia with a variable degree of T lymphocyte deficiency in 80% of cases [65,66]. As in DS, T_{REC}^+ cell counts are decreased in the periphery, and T lymphocytes gradually approach normal numbers over time [39] but – unlike in DS – B lymphocytopenia is not seen in DGS [67,68].

T helper lymphocyte type 1 cells (Th1) produce cytokines such as IFN-γ, IL-2 and TNF-β which stimulate cytotoxic T lymphocyte responses and IgG_1 and IgG_3 production, whereas T helper lymphocyte type 2 cells (Th2) produce cytokines such as IL-4, IL-5, IL-6 and IL-10, which stimulate antibody responses by B lymphocytes and the formation of IgG_2 and IgG_4. In comparison with individuals with mental retardation (no DS) and healthy controls, DS adults have significantly higher percentages of IFN-γ-producing $CD4^+$ and $CD8^+$ cells and a higher Th1/Th2 ratio [69]. This fits the increased levels of IgG_1 and IgG_3 and decreased levels of IgG_2 and IgG_4 in DS, and supports disturbed T helper lymphocyte function [30,70].

Clinical presentation in relation to immunodeficiency

The clinical presentation of DS children, seen in relation to possible immunodeficiency [71], is dominated by recurrent ear–nose–throat (ENT) and airway infections in their early years, followed by an increasing frequency of autoimmune diseases and lymphoproliferation thereafter. The recurrent ENT and airway infections could fit antibody deficiency, although the macroglossia, hypotonia and altered anatomy of the upper airways will also play an important role in these infants. The tendency towards autoimmune diseases and lymphoproliferation, on the other hand, points primarily to immunodysregulation. Partial reduction in the number and function of T lymphocytes can disturb the tolerogenic balance, generating a combination of immunodeficiency and immune dysregulation [72,73]. DS children as a group could fit the picture of primary immunodeficiency, but with apparent individual differences. The relation between the abnormality of immunological values in individual DS children and the clinical complications has, so far, unfortunately not been studied extensively.

Conclusion

In summary, it is much more likely that the immune system in DS is intrinsically deficient from the very beginning, and not simply another victim of a generalized process of precocious ageing. It is not yet clear but at least possible that, besides the apparent thymus and T lymphocyte abnormalities in DS, B lymphocytes are also intrinsically different.

Further studies are needed to resolve the underlying mechanisms of this immunodeficiency, and to assess the implications thereof for everyday clinical care.

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