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Clinical implications of immune mediated diseases in children with Down syndrome

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Running title

Immune-mediated diseases in Down syndrome

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Abstract

Children with Down syndrome have changes in their innate and adaptive immunity, which contribute to increased rates of infections, auto-immune diseases, and haematological malignancies. While improved care for congenital heart disease has decreased mortality and morbidity, complications related to immune mediated diseases continue to limit the life expectancy in Down syndrome.

Infectious diseases are common and have a significant effect on development, behaviour and quality of life. Infection frequency and severity is influenced by various anatomical and physiological alterations in addition to immunological changes in Down syndrome. Thus, prevention of respiratory tract infections requires a multifactorial approach. This could include additional active and/or passive immunizations, prophylactic antibiotics, immunoglobulin replacement and ear, nose and throat surgical interventions. Auto-immune conditions like celiac disease, type I diabetes mellitus and thyroid disease are classically mentioned in the context of Down syndrome. However, auto-inflammatory conditions are more prevalent as well. Screening for auto-immune diseases is required and immunosuppression has to be used with caution.

Future studies should address optimal screening programs for immune mediated diseases in individuals with Down syndrome, as well as the effect of immune modulation, to further decrease morbidity and mortality, and improve the quality of life of individuals with Down syndrome.

Keywords: Down syndrome, infectious diseases, leukaemia, auto-immune disease, auto-inflammatory disease, allergy

Introduction

Down syndrome (trisomy 21; OMIM 190685) is a multi-system condition associated with mental and motor developmental impairment, congenital abnormalities, and facial and general dysmorphia. In addition, individuals with Down syndrome are more likely to develop haematological malignancies, infections, and autoimmune diseases, leading to the hypothesis of syndromic immunodeficiency. Indeed, the immune system in Down syndrome shows many alterations, affecting both innate and adaptive immunity, which have been reviewed by us in the past.¹ In this review we outline the current understanding of immune mediated diseases in Down syndrome, their effect on mortality and quality of life, as well as the implications for clinical care.

Immune mediated diseases

Malignancies

Haematological malignancies are more common in individuals with Down syndrome. The risk to develop acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) is 20-24 times higher in Down syndrome.²⁻⁴ With regards to ALL, children with Down syndrome used to have poorer outcomes as a result of higher treatment associated toxicity.^{5, 6} Fortunately, toxic-related mortality has decreased due to improved awareness, adjusted treatment protocols and better supportive care.⁷ Nevertheless, a higher risk of relapse persists due to different cytogenetic profiles (i.e., higher frequency of IKZF1 mutations).⁶

AML in Down syndrome is recognized as a unique leukaemia subtype,⁸ which is mainly found in young children (<3 years old). The prognosis of this subtype is better compared to the other AML subtypes in children without Down syndrome.⁹ Also, the quality of life in AML survivors with Down syndrome appears similar to that of survivors of AML without Down syndrome.¹⁰

Transient myeloproliferative disorder (TMD) is another megakaryoblastic proliferative disease that has been found uniquely in Down syndrome and affects fetuses as well as newborns up to the age of 3 months (~10%).^{8, 11} TMD regresses in most children within the first months of life, but chemotherapy may be required. Approximately 20% of children with a history of TMD regression in peripheral blood, develop AML later in life.¹²

Whereas haematological malignancies are more common in Down syndrome, the overall risk to develop lymphomas seems to be comparable to the general population. Solid tumours are less frequent in Down syndrome with the exception of testicular cancer which is more frequently found.²⁻⁴

Because of the known alterations in the immune system, often the assumption is made that the increased incidence of haematological malignancies in individuals with Down syndrome is due to impaired

tumour immune surveillance. However, patients with other immunodeficiencies or on immunosuppressive therapy have a different pattern of malignancies, with for instance higher incidence rates of lymphoma, melanoma, renal cell carcinoma, and non-small cell lung cancer.^{4, 13, 14} While impaired tumor immune surveillance may play a role in the increased frequency of haematological malignancies, it cannot fully explain the observations in Down syndrome. Since the gene expression profile is altered for many genes – not only those located on chromosome 21 – oncogenes may be increasingly expressed and protective genes may have decreased expressions.¹⁵

Infectious diseases

Respiratory tract infections are more frequent in individuals with Down syndrome, but thorough epidemiologic data is lacking.¹⁶ The impact of these infections on children with Down syndrome is significant. Children with Down syndrome with recurrent respiratory tract infections have more developmental delay and behavioural problems, and health related quality of life was poorer in parent reported studies.^{17, 18} Besides the higher frequency of respiratory infections, their disease course can be more severe as well. Children with Down syndrome have more hospital admissions compared to the general population, in particular related to infections.¹⁹ The length of stay is approximately twice as long compared to hospitalized children without Down syndrome.²⁰ And despite advances in clinical care, these infections contribute significantly to mortality in Down syndrome.²¹⁻²⁴ The latter is in part the result of higher incidences of acute lung injury, including acute respiratory distress syndrome (ARDS).^{25, 26}

Little is known about the pathogens that cause infections in Down syndrome. Only for Respiratory Syncytial (RS) virus and the H1N1 2009 pandemic there are cohort studies available that show their correlation with higher incidences of hospitalization, increased requirement for respiratory support (i.e., oxygen, mechanical ventilation), and higher mortality.²⁷⁻²⁹

There is limited data concerning other types of infections. One study showed that children with Down syndrome have a higher mortality rate for bacterial sepsis.²¹ However, there is no general incidence rate known, and within the context of gastrointestinal surgery there appears to be less sepsis in Down syndrome.³⁰ Appendicitis seems to be less common in Down syndrome.³¹ Individuals with Down syndrome who are institutionalized are more likely to be hepatitis B carriers, however this has not been studied since the 1980s nor in the context of non-institutionalized individuals with Down syndrome.³² *Helicobacter Pylori* carrier status in Down syndrome is increased, irrespective of whether individuals are institutionalized, but it is unknown if

this relates to clinical symptoms.^{33, 34} Recently, a large cohort study identified that 22% of individuals with Down syndrome had intestinal parasite infections.³⁵

It is unclear why certain infections are more common in Down syndrome. For respiratory infections it is clear that contributing anatomical and physiological alterations will play a role (Table 2). However, the changes found in the immune system of individuals with Down syndrome have not been consistently linked to the clinical presentation of specific infections.¹

Auto-immune and auto-inflammatory diseases

Individuals with Down syndrome are more likely to develop auto-immune diseases. The risk to develop celiac disease is increased 6 to 10 fold compared to the general population and affects up to 7% of patients.³⁶⁻⁴⁰ Therefore, routine screening seems reasonable and could include HLA-DQ2 and HLA-DQ8 typing.^{39, 41} Nevertheless guidelines differ per country, for instance in the United States screening is only advised in the context of clinical symptoms.⁴² Individuals with Down syndrome have a 3 to 4 fold increased risk to develop type I diabetes mellitus,^{3, 43, 44} which occurs more often at a younger age.⁴⁵ Hypothyroidism is common and related to auto-antibody formation (i.e., thyroid peroxidase (TPO) antibodies), and structural changes in the thyroid.^{42, 46} In adults, up to 50% of individuals with Down syndrome have a decreased thyroid function,^{3, 47-49} and continued screening of thyroid stimulating hormone (TSH) and free T4 is advised at all ages. Alopecia areata is more common in Down syndrome (up to 8.9% of individuals), and is related to the presence of thyroid disease.⁵⁰⁻⁵² Auto-antibodies against hair follicles in Down syndrome have not been studied.⁵³

Musculoskeletal symptoms are common in Down syndrome and include a higher incidence of arthritis.⁵⁴⁻⁵⁶ It appears that the diagnosis is often delayed, and that the disease course is more severe compared to children with juvenile idiopathic arthritis.⁵⁶ There is ongoing debate whether to classify arthritis in Down syndrome as a unique entity (i.e., Down's arthropathy, Down syndrome associated arthritis).⁵⁶ However, it is important to realize that patients historically have been classified under existing umbrella terms (i.e., juvenile idiopathic arthritis, rheumatoid arthritis, etc.), and removing patients with Down syndrome from existing cohort studies might actually limit future research efforts on this condition.

Anti-nuclear antibody (ANA) testing has not been performed in a systematic manner. In one cohort study of children with Down syndrome and arthritis (n=33) all patients were ANA negative.⁵⁶ Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) showed variable results in Down syndrome.⁵⁵⁻⁵⁹ Anti-dsDNA antibody production is increased in Down syndrome,⁶⁰ but the clinical relevance is uncertain as

there are only a few case reports on the association of Down syndrome with systemic lupus erythematosus (SLE).⁶¹

Individuals with Down syndrome have a specific pattern of auto-inflammatory conditions. Conditions such as Crohn's disease, ulcerative colitis and psoriasis have similar incidence rates in Down syndrome compared to the general population.³ However, there is a strong correlation between Alzheimer's-like dementia and Down syndrome, which affects at least three quarters of individuals and starts at much younger age.^{62, 63} Increasingly, it has become clear that neuro-inflammation is the hallmark of this condition.⁶⁴ Hidradenitis suppurativa has been reported more often in Down syndrome as well.⁶⁵⁻⁶⁸ Osteoarthritis of the hip requiring total hip arthroplasty is more common in Down syndrome, although hip dysplasia and slipped capital femoral epiphysis (SCFE) are often underlying this condition.^{69, 70} Although slightly higher C-reactive protein (CRP) levels were found,⁷¹ it appears that individuals with Down syndrome are relatively protected against atherosclerosis.⁷¹⁻⁷³ At last, based on a Japanese cohort study Kawasaki disease is less common in Down syndrome.⁷⁴

Thus, individuals with Down syndrome show a unique pattern of inflammatory conditions that are mainly characterized by specific auto-antibody production. The presence of Alzheimer's-like dementia and hidradenitis suppurativa is evidence of increased auto-inflammation as well. Although this pattern in Down syndrome might be caused by the combination of immunological changes, altered gene expression and specific infectious triggers, the exact pathways have not been elucidated yet.

Allergic diseases

Although children with Down syndrome are more likely to present with symptoms suggestive of asthma, such as recurrent wheeze, cough and/or shortness of breath,^{75, 76} it seems that 'true' asthma is found less frequently.^{3, 19, 20, 76-78} These respiratory symptoms often resolve in early childhood.⁷⁶ Also, in contrast to children with asthma, individuals with Down syndrome generally lack allergic sensitization: they have low levels of total IgE, no specific IgE sensitizations for common inhaled and food allergens, and fewer positive skin prick tests (Down syndrome: 18% vs non-Down syndrome: 54%).^{76, 79-81} It is likely that the anatomical and physiological alterations found in the respiratory tract of Down syndrome (Table 2) contribute to the development of respiratory symptoms such as wheezing and coughing.

Hay fever and eczema are found equally in individuals with and without Down syndrome.^{75, 76, 82-84} One study showed that parent-reported food allergies are more common in Down syndrome, but it is uncertain if these allergies were confirmed by a physician.⁷⁵

Modulation of the immune system in Down syndrome

Prevention of infectious diseases

Besides immunological defects, individuals with Down syndrome have many contributing factors to the development of (respiratory) infections (Table 2). As such, clinicians should assess which factors are most relevant to their patient and determine whether specific treatment options are available.

A limited number of studies have looked at the effect of immunomodulation, especially to reduce the burden of respiratory tract infections. While it is known that the quality of immunizations responses are overall lower in Down syndrome,¹ it is unclear whether additional or booster immunizations are helpful. To our knowledge, the use of intravenous immunoglobulin (IVIG) replacement therapy and prophylactic antibiotics to prevent – mainly respiratory – infections have never been studied in a systematic manner in Down syndrome.

In the 1980s/1990s, a few clinical trials took place that investigated the effect of oral zinc supplementation. This was based on the notion that children with Down syndrome have decreased serum zinc levels.⁸⁵ Two small open label trials report lower rates of infections after the intervention,^{86, 87} and improved immunologic studies have been observed (i.e., normalized lymphocyte proliferation and granulocyte chemiluminescence).^{87, 88} However, Lockitch et al. studied 64 children with Down syndrome and zinc supplementation in a double blind manner and did not find differences in infection rate or immunological markers, including immunoglobulin and complement levels, lymphocyte (subset) counts, and mitogen stimulation,⁸⁹ which led to the abandonment of zinc as a potential treatment.

Palivizumab is a monoclonal antibody targeting the F protein expressed by the RS virus, which has been found to decrease disease severity when used prophylactic in children born prematurely, as well as those suffering from chronic lung disease or congenital heart disease.⁹⁰ Due to the increased burden of RS virus in children with Down syndrome it was hypothesized to be beneficial. Indeed, in a prospective cohort study, the hospitalization rate was significantly lower in children with Down syndrome who had received palivizumab.⁹¹ It is currently unknown whether children with Down syndrome but without concomitant congenital heart disease would benefit from palivizumab, as up to 50% of children in Down syndrome cohort would be eligible for palivizumab based on their cardiac history. Nevertheless, there is a growing support for its use in all children with Down syndrome given the high rate of RS virus related morbidity, as well as reports on the benefits of palivizumab.⁹²⁻⁹⁴

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Pidotimod has immunostimulatory effects, partly by inducing NFκB expression and enhancing dendritic cell maturation.^{95, 96} It was found to be effective in the treatment of children with recurrent respiratory tract infections.⁹⁷ Similar effects were found in a small open-label trial that included 14 children with Down syndrome and showed a reduction in frequency, severity and duration of infections.⁹⁸ However, further studies are lacking to support pidotimod as a treatment modality for recurrent respiratory tract infections in Down syndrome.

Treatment of inflammatory conditions

There are limited reports on the use of IVIG for inflammatory conditions. In a Japanese cohort of patients with Kawasaki disease and Down syndrome (n=16), 50% had a high risk of IVIG resistance at disease presentation.⁷⁴ It was therefore an unexpected finding that all children with Down syndrome responded to this first line treatment and none developed coronary abnormalities.⁷⁴

The safety and efficacy of immunosuppressive medications for inflammatory conditions in Down syndrome has not been studied systematically. Oncologic data shows that methotrexate toxicity in Down syndrome is higher,⁹⁹ however this has not been investigated in other settings where low-dose methotrexate is used.⁵⁵ There are no studies available that report on immunotherapy for allergic disease in Down syndrome.

Conclusion

Individuals with Down syndrome suffer from a variety of immune-mediated conditions that significantly impact on their quality of life. While virtually all components of their immune system show abnormalities, finding correlations between these alterations and clinical features remains challenging. In clinical care for individuals with Down syndrome, one should understand the complexity of this condition and the many immunological and non-immunological factors that contribute to a higher risk for (severe) infections. Also, because malignancies, auto-immune and inflammatory conditions are more common, one should look out for these in regular follow-up as well. Further research is needed to understand the complex interactions of the immune system in Down syndrome and the correlation with clinical features, as well as studies to further investigate potential treatment and prophylactic therapy options to support the immune system in these individuals.

Table 1. Immune-mediated conditions in Down syndrome

Condition	Incidence compared to the general population	Reference(s)
Malignancies		
Acute lymphoid leukaemia	Increased	2-4
Acute myeloid leukaemia	Increased	2-4
Transient myeloproliferative disorder	Increased	8, 11
Lymphoma	Unchanged	2-4
Solid tumours, general (specific: testicular cancer)	Decreased (Increased)	2-4
Infectious diseases		
Respiratory infections (H1N1 influenza virus, respiratory syncytial [RS] virus)	Increased	27-29
Appendicitis	Decreased	31
Helicobacter pylori carrier status	Increased	33, 34
Hepatitis B carrier status	Increased	32
Inflammatory diseases		
Celiac disease	Increased	36-40
Thyroid disease	Increased	42, 46
Type I diabetes mellitus	Increased	3, 43, 44
Alopecia areata	Increased	50-52
Arthritis (rheumatoid arthritis, juvenile idiopathic arthritis, Down's arthropathy)	Increased	54, 55
Psoriasis	Unchanged	3
IBD (Crohn's disease, ulcerative colitis)	Unchanged	3
Hidradenitis suppurativa	Increased	65-68
Kawasaki disease	Decreased	74
Osteoarthritis	Increased	69, 70
Atherosclerosis	Decreased	71-73
Alzheimer's-like dementia	Increased	62, 63
Allergic disease		

Asthma	Decreased	3, 19, 20, 76-78
Eczema	Unchanged	75, 76, 82-84
Hay fever	Unchanged	75, 76, 82-84
Food allergy	Increased	75

Table 2: Alterations in anatomy and physiology that contribute to frequency and severity of respiratory tract infections in Down syndrome

Anatomy	Physiology
Facial phenotype	Eustachian tube dysfunction
Macroglossia	Generalized hypotonia
Enlargement of tonsils and adenoid	Dysphagia
Small hypopharynx	Acid reflux
Laryngomalacia	Mucociliary defects
Tracheal bronchus	Pulmonary hypertension
Subglottic stenosis	
Tracheobronchomalacia	Natural barriers
Lung hypoplasia	Skin conditions
Subpleural cysts	Decreased salivary flow
Congenital heart defect	Decreased salivary IgA

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