Aging and Disease
www.aginganddisease.org
Volume 2, Number 6; 538-545, December 2011

Review

Down Syndrome: Is It Really Characterized by Precocious Immunosenescence?

Maaike AA. Kusters[1,2], Ruud HJ. Verstegen[1,3], Esther de Vries[1*]

[1]Department of Pediatrics, Jeroen Bosch Hospital,'s-Hertogenbosch, the Netherlands
[2]Department of Pediatrics, Maastricht University Medical Centre, Maastricht, the Netherlands
[3]Department of Pediatrics, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

[Received June 8, 2011; Revised August 12, 2011; Accepted August 15, 2011]

ABSTRACT: The immune system declines with aging, leading to an increased susceptibility to infections and higher incidence and progression of autoimmune phenomena and neoplasia. Down syndrome prematurely shows clinical manifestations that are normally seen with aging. This review provides a concise overview of abnormalities in the adaptive immune system of Down syndrome in comparison to normal and precocious (Progeria syndromes) aging. Clinical signs and immunological changes are reviewed. We challenge the hypothesis that the immunological abnormalities in Down syndrome should be interpreted as precocious immunosenescence.

Key words: Immunosenescence; Down syndrome; Progeria syndromes; Adaptive immune system

In humans, as in all species, a progressive functional decline occurs with aging in all organ systems due to loss and instability of genetic material. To protect the genome, chromosomes are capped by so-called telomeres which prevent degradation of genes near the ends of the chromosome. But with each cell division a small part of the telomere is lost. This proces is limited, but not prevented, by the enzyme telomerase which increases the length of the telomeres. Therefore, cumulative cell divisions ultimately result in genome instability and apoptosis of cells [1].

The immune system is essential for detection and elimination of pathogens and thereby for prevention of damage and degeneration of the organism. Lymphocytes continuously undergo proliferation [2]. So, especially lymphocytes are highly susceptible to telomeric shortening, leading to aging of the adaptive immune system, which is often referred to as 'immunosenescence'. As a result, elderly people are more susceptible to infections. Also, malignancies and autoimmune phenomena are more common with aging due to failing immune surveillance secondary to immunosenescence [3, 4].

Down syndrome is the most frequent genetic cause of mental retardation in man; it is caused by an extra chromosome 21. People with Down syndrome (DS) prematurely show signs that are normally seen with aging; for example, adults with DS show early signs of Alzheimer's disease [5]. Also, clinical features reminiscent of immunosenescence are seen, with higher rates of infections, malignancies, and autoimmune phenomena. It is therefore not unlogical to hypothesize that the immune system in DS shows accelerated aging as well [6].

This review provides a concise overview of the abnormalities found in the DS immune system in comparison to normal immunosenescence and the immunological findings in the precocious aging or Progeria syndromes (PS) [7]. The scope of this article is not exhaustive with respect to this complex topic, but

***Correspondence should be addressed to:** Dr. Esther de Vries, MD, PhD, Department of Pediatrics, Jeroen Bosch Hospital, the Netherlands. Email : e.d.vries@jbz.nl

ISSN: 2152-5250

Table 1 The adaptive immune system in normal aging, Progeria syndromes and Down syndrome

	Normal aging	Progerias	Down syndrome
References	**[1,3,4,22-24,29]**	**[7,37-43]**	**[5,6,8,10-13,19-21,25-28,30-36]**
T-lymphocytes			
$CD3^+$ T-lymphocytes	Decreased (abs)	HGPS: decr/normal (abs) CS, Werner, XP: normal (abs/rel)	Decr/normal (abs)
$CD3^+CD4^+$ Th	Decreased (abs)	HGPS: decr/normal (abs) CS, XP: normal (abs)	Decreased (abs)
$CD3^+CD8^+$ Tc	Decreased (abs)	Normal (abs)	Decr/normal (abs)
$CD4^+CD45RA^+$ (Naive Th)	Decreased (abs)		Decreased (abs)
$CD4^+CD45RO^+$ (Memory Th)	Increased (abs)		Normal (abs)
$CD8^+CD45RA^+CD27^+$ (Naive Tc)	Decreased (abs)		Incr/normal (abs)
$CD8^+CD45RA^+CD27^-$ (Term Diff Tc)	Increased (abs)		Normal (abs)
T-lymphocyte proliferation	Decreased	CS:normal HGPS:decr/normal Werner:decr/normal XP:decr/normal	Decr/normal
Thymus	Abnormal structure		Smaller, abnormal structure
TREC count	Decreased		Decreased
Th1/Th2 ratio	Normal		Increased
CD4/CD8 ratio	Normal	Decreased	Decreased
B-lymphocytes			
$CD19^+$ B-lymphocytes	Normal (abs)	HGPS: incr/normal (abs) Werner: normal (rel)	Decreased (abs)
$CD19^+CD27^+$ (Naive B)	Decreased (abs)		Decreased (abs)
$CD19^+CD27^-$ (Memory B)	Increased (abs)		Normal (abs)
B-lymphocyte proliferation (PWM)	Decreased	HGPS: incr/normal Werner: decr/normal	Decreased
Immunoglobulins			
IgG	Decr/normal	HGPS: decr/normal Werner: normal	Increased >2yr
IgM	Normal	Normal	Decreased
IgA	Decr/normal	HGPS: decr/normal Werner: normal	Normal
IgG_1	Normal		Increased > 3yr
IgG_2	Normal		Decreased
IgG_3	Normal		Incr/normal
IgG_4	Normal		Decreased
Auto-antibodies	Increased	HGPS: no increase	Increased

Oligo/monoclonal antibodies	Increased		No increase
Escherichia coli antigen	Decreased response		Decreased response
Response to vaccines			
Tetanus	Decreased		Decreased avidity
Pneumococcal polysaccharide vaccine	Decreased		Decr/normal
Meningococcal conjugate vaccine	Decreased		Decreased
Pertussis vaccine (acellular)	Decreased		Decreased
Hepatitis B vaccine	Decreased		Decr/normal
Hepatitis A vaccine	Decreased		Normal
Influenza vaccine	Decr/normal		Decr/normal
Polio vaccine (oral)	Normal		Decreased
Response to viruses			
CMV	Increased specific T-subsets, increased reactivation		Normal
RSV	Increased risk		Increased risk and severity
Response to bacteria			
Bacterial sepsis	Increased rate	HGPS, Werner: increased rate	Increased rate
Mortality/morbidity	Increased rate	Increased rate	Increased rate
Auto-immune diseases			
Thyroid	No increase	No increase	Increased
Diabetes Mellitus	Increased type 2	Incr/normal type 2	Increased type 1
Celiac disease	No increase		Increased
Malignancies			
Hematological	Increased	XP: possible increase	Increased
Non-hematological	Increased	Werner: increased XP: increased skin cancer	No increase
Age-related disease			
Osteoporosis	Increased	Increased	No increase
Atherosclerosis	Increased	Increased	No increase
Alzheimer disease	Increased	Increased	Increased
Periodontal disease	Increased		Increased

Abs = absolute counts; CD = cluster of differentiation; CMV= cytomegalovirus; CS= Cockayne syndrome; decr= decreased; HGPS = Hutchinson-Gilford progeria syndrome; Ig = immunoglobulin; Incr=increased; PWM = pokeweed mitogen; rel= relative counts; RSV = respiratory syncytial virus; TCR = T-cell-receptor; Tc= cytotoxic-T-lymphocyte; Term Diff = terminally differentiated; Th = helper-T-lymphocyte; TREC = T-cell receptor rearrangement excision circles; XP= xeroderma pigmentosum; yr = years. Empty column = not described in current literature.

attempts to show that the immune alterations in DS should – in spite of previous publications on the subject – *not* be interpreted as precocious immunosenescence [8].

The adaptive immune system

The immune system defends the human body against invading micro-organisms. It consists of two parts: the innate and the adaptive immune system. The innate immune system provides a primary immune response. Although a fast reaction takes place within minutes to hours, no memory is generated. The innate immune system therefore provides only short-term solutions. The adaptive immune system plays a pivotal role for long-term survival [9]. An essential difference between innate and adaptive immune cells is that the latter react specifically to a myriad of antigens while providing long-term memory as well. Since immunosenescence primarily affects the adaptive immune system, that system will be the focus of this review.

Key players in the adaptive immune response are B- and T-lymphocytes. B-lymphocytes are responsible for humoral immunity by producing specific antibodies. T-lymphocytes are accountable for cellular immune responses by helping other immunological cells through cytokine production and stimulation, and by direct cytotoxicity. Both T- and B-lymphocyte precursors are generated from hematopoietic stem cells in the bone marrow. While B-lymphocytes fully develop in the bone marrow, T-cell-precursors migrate to the thymus for further proliferation and development. In the secondary lymphoid organs (spleen, tonsils, lymph nodes) antigens are collected and presented. Also, T- and B-lymphocytes migrate there, and proliferate and differentiate into different effector and memory subsets after stimulation.

Within the thymus, T-cell-precursors can only survive if their T-cell receptors can interact with self major histocompatibility complexes (MHC) expressed on cell membranes, so-called positive selection. Too strong binding to self-antigens leads to cell death by negative selection, no binding at all results in cell death by neglect. Thymocytes binding to MHC-type II differentiate into helper-T-lymphocytes (Th), thymocytes binding to MHC-type I differentiate into cytotoxic-T-lymphocytes (Tc). As only antigen-presenting cells such as B-lymphocytes, dendritic cells and phagocytes express MHC-type II molecules, Th can only interact with these types of cells. Th are responsible for coordination and communication with both innate and adaptive immune cells; they serve as immunoregulators. Tc interact with MHC-type I expressing cells, which almost all human cells are, and can act directly as "killing machines" after activation and proliferation. Tc are especially suitable for strong cellular immune responses against tumour cells and intracellular pathogens such as viruses, whereas Th can help both humoral and cellular immune responses. The continuous generation of new Th and Tc from the thymus is crucial to maintain a functional immune system. Recent thymic emigrants all carry T-cell receptor rearrangement excision circles (TREC) as a by-product of DNA recombination processes. TRECs are not replicated and therefore diluted in the progeny that is formed after cell division. The TREC content can therefore be used to estimate the thymic output and also – indirectly – the thymic involution with aging.

Primary B-cell development takes place in the bone marrow. A unique B-cell antigen receptor is created on each B-lymphocyte membrane through gene rearrangements without previous antigen-exposure. B-lymphocytes do not need MHC for antigen recognition and can respond not only to peptides, but also to polysaccharides. Naive B-lymphocytes react to antigen exposure by producing immunoglobulins (Igs), primarily IgM. Extracellular pathogens such as bacteria are the main focus for these Igs. T-lymphocytes and T-lymphocyte-derived factors are necessary for further B-lymphocyte development. With the help of Th, B-lymphocytes can class-switch to the production of IgG, IgA and IgE, with altered effector function while maintaining antigen specificity. Repeated exposure to T-lymphocyte dependent antigens activates selected clones of memory B-lymphocytes to undergo somatic hypermutation (SHM) leading to higher affinity Igs.

The net result of all these processes is a broad diversity of B- and T-lymphocytes, which can survive for many years and provide resistance against the pathogens attacking the human body.

Down syndrome compared to normal aging

A comparison between the adaptive immune systems of DS, normal aging and PS is summarized in Table 1.

T-lymphocytes

With aging the renewal capacity of stem cells declines, the hematopoietic tissue in the bone marrow decreases, and thymic involution with low peripheral blood TREC counts ensues [1]. T-lymphocytes can influence their own differentiation and proliferation process in the thymus and periphery by cross-talk and feedback-mechanisms. Decreased output of thymic emigrants can therefore normally be compensated in aging individuals by an increase in effector and memory Th and Tc

numbers. In this way, total T-lymphocyte counts remain relatively stable in aging adults despite decreasing naive counts, as effector and memory subsets fill up the T-lymphocyte pool [3, 4]. However, these T-lymphocytes are continuously antigen-driven and eventually accumulate in "dead end" T-lymphocyte subsets such as terminally differentiated (TD) Tc. In other words, the T-lymphocyte pool becomes more experienced but less flexible with aging, and the cells show a restricted repertoire and reduced proliferative response [3, 4].

People with DS show T-lymphocyte abnormalities from an early age onwards. Newborns and fetuses with DS already show an altered thymic anatomy with impaired thymic output and lower TREC counts [10]. Some interesting candidate genes influencing thymocyte production by altered cross-talk and feedback-mechanisms can be found on chromosome 21. For example, increased expression of DS-cell-adhesion molecules on thymic epithelia and thymocytes can cause abnormal T-lymphocyte maturation and inefficient T-lymphocyte release to the peripheral blood [11]. Naive Tc and Th are decreased from birth [18]. Apart from decreased production, proliferation is impaired in DS as well. Tc and Th lack the normal antigen-driven expansion in the first years of life. Memory Tc show a gradual increase over time, but in contrast to normal aging memory Th do not. The expansion of TD Tc with normal aging is not seen in DS either [12].

The continuous DNA rearrangement processes make the lymphocyte pool extremely vulnerable for DNA errors. Lymphocytes are capable of upregulating telomerase and thereby can prolong their lifespan [1, 2]. The constant microbial pressure throughout life leads to an ongoing proliferative demand, which ultimately results in genome instability, senescence and apoptosis of cells. Enhanced cell death by apoptosis could play an extra role in DS besides decreased T-lymphocyte production and proliferation. Increased telomere shortening is found in DS T-lymphocytes, which could lead to higher apoptosis rates [13-16]. Recent studies however did not find increased apoptosis in peripheral T-lymphocytes, despite increased apoptosis markers on T-lymphocytes in earlier reports [10,17,18] .

Functional impairment in DS T-lymphocytes is supported by decreased proliferative and antigen T-cell responses [10]. Functional T-lymphocyte impairment could explain the increased incidence of hematological malignancies.

B-lymphocytes

With aging, fewer B-lymphocytes are produced in the bone marrow. Total peripheral B-lymphocyte numbers do not decline with age, but the composition of the peripheral B-lymphocyte compartment changes: antigen-experienced memory B-lymphocytes increase and naive B-lymphocytes decrease in number. Memory B-lymphocytes with a decreased susceptibility to apoptosis accumulate in elderly persons, leading to clonal expansions of certain B-lymphocyte specificities, which may limit the diversity of the repertoire [3, 4].

Alterations of the B-lymphocyte compartment in DS are on the contrary present from birth onwards: newborns show decreased naive B-lymphocyte numbers, early expansion is absent, and memory B-lymphocytes do not increase with age. This results in extremely low total B-lymphocyte counts [19, 20].

Although serum immunoglobulin levels remain stable during normal aging, antibodies generated in old age are of lower affinity because of an age-associated decrease in somatic hypermutation due to decreasing help from Th, and restricted B-lymphocyte repertoire due to clonal expansions.

In DS, despite the low B-lymphocyte numbers, a profound hypergammaglobulinemia develops from around 3 years of age onwards, without evidence of mono- or oligoclonality [21]. This hypergamma-globulinemia with increased total IgG, IgG_1 and IgG_3, but decreased IgM, IgG_2 and IgG_4 serum levels [21] is more suggestive of dysregulation in class-switching and somatic hypermutation of B-lymphocytes within the germinal centers than of an impaired B-lymphocyte production in the bone marrow. An altered Ig-pattern can result from both an intrinsic defect in DS B-lymphocyte activation and proliferation or B-T-miscommunication in the periphery. Decreased numbers of Th type 2 – essential for the humoral immune response – have been reported in patients with DS [10] and could be associated with this altered Ig-pattern through impaired SHM and class-switching.

Immunizations

An indirect way to look at B-T-lymphocyte communication and the functional capacity of B- and T-lymphocytes is by studying vaccination responses. The specific antibody response to T-cell dependent protein antigens requires combined T-lymphocyte function, T-B interaction and B-lymphocyte function, whereas the response to T-cell independent polysaccharide antigens is largely determined by B-lymphocyte function alone.

The age-related decreased output and functional deficiency of the T- and B-lymphocyte pool hampers the adaptive immune response to both T-cell dependent and independent booster- and neo-vaccinations in the elderly [4]. Quantitative antibody responses are lower, decline

faster and the affinity of the antibodies is diminished [4, 22-24].

Impaired specific antibody responses to both T-cell-dependent (e.g. Tetanus [25], influenza [26]) and T-cell-independent (e.g. Pneumococcal polysaccharide [27]) vaccines [28] are repeatedly reported in DS as well, which suggests both altered T- and B-lymphocyte function and communication.

Clinical relevance

The restricted B- and T-lymphocyte repertoire in the elderly, with antibodies of lower affinity, leads to immunodeficiency and immunodysregulation, resulting in a trias of higher infection and malignancy rates and more auto-immune phenomena such as rheumatoid arthritis (RA) [29]. This clinical trias is seen in DS as well. The increased susceptibility to respiratory tract infections in DS could – at least in part – be explained by a combination of anatomic and functional ear-nose-throat abnormalities, hypotonia, mental retardation and increased incidence of gastro-oesophageal reflux, but these cannot explain the increased auto-immune phenomena and hematological malignancies [30]. Although patients with DS have the same clinical trias of increased infections, malignancies and auto-immune diseases as elderly people, the actual pathogens and disease-burden are to some extent different [31]. In DS a higher frequency of mainly hypothyroidism [33], celiac disease [34] and diabetes mellitus type 1 [35] is seen. Malignancies in DS consist mostly of hematological ones in contrast to elderly with an increase in non-hematological malignancies as well [36].

Progeria syndromes

Progeria syndromes (PS) are very rare diseases, leading to precocious and/or accelerated aging [7]. PS form a clinically and genetically heterogenous group. Most PS are only segmental in nature; they do not cause early or accelerated aging in all human cell lines. Also, humans with PS can present with symptoms that are not common during normal aging [7].

PS can be further subdivided on the basis of the underlying genetic defect [7]. Hutchinson-Gilford progeria syndrome (HGPS) is the first described PS; LMNA gene mutation results in accumulation of lamin A protein in the cell nucleus. Werner syndrome – also called adult-onset progeria – is caused by a mutation in ATP dependent helicase leading to repair defects in DNA-double-strand breaks, but with slower onset than HGPS. Cockayne syndrome (CS) and xeroderma pigmentosum (XP) are examples of DNA-repair defect disorders causing progeria-like disease. Because of the segmental nature of most PS, it is not always clear whether and to what extent hematological cell lines are influenced [7]. The immune system in these progerias has only been studied in case reports and small cohort studies. In a case report of a child with HGPS [37] increased B-lymphocyte numbers with severely decreased IgG and IgA serum levels were seen. In 12 adults with HGPS however normal levels of Igs and normal B- and T-lymphocyte counts were found (including Th and Tc) [38]. Five adults with Werner syndrome showed normal immunoglobulin levels, normal relative B-lymphocyte and normal to decreased relative T-lymphocyte counts [39]. Neoplasms and infections were found to be more frequent in Werner syndrome, which could be interpreted as clinically suggestive of immunosenescence. However, these neoplasms (e.g. sarcomas and melanomas) do not always overlap with commonly occurring neoplasms in aging [40].

XP patients have normal T-lymphocyte (including Tc and Th) counts, but decreased natural killer (NK) activity [41-43]. CS patients show normal T-lymphocyte counts; their NK-activity is normal [41]. XP patients have an increased risk for skin cancer, but apparently no increased risk for infections and auto-immune diseases. CS patients have no associated increased cancer risk, possibly due to normal NK-cell and T-lymphocyte related immune surveillance [41].

More research is needed, but it seems that the picture in progeria and progeria-like syndromes is not comparable to normal ‘immunosenescence’; it is not the same in the different subtypes of PS and moreover is very different from the picture in DS.

Conclusion

At first sight, the DS profile seems to fit in with precocious immunosenescence, as thymic involution with low thymic output and T-lymphocyte dysregulation - resulting in higher rates of infections, malignancies and auto-immune disease - occur both in DS and normal aging. Appearances however can be deceptive.

The decreased naive B- and T-lymphocyte production from birth onwards combined with the lack of compensatory memory cell expansion and proliferation do not support precocious immunosenescence in DS; these findings fit intrinsic immunodeficiency better. The hypergammaglobulinemia in combination with decreased specific antibody responses support the theory that patients with DS harbor a combined T- and B-lymphocyte immunodeficiency with different mechanisms involved than in normal aging. Progeria

syndromes are not comparable to DS either. PS show segmental aspects of accelerated/precocious aging at most reflected in minor lymphocyte changes. Also, the PS clinical profile differs from DS with respect to the occurrence of malignancies, infections and auto-immune diseases.

Therefore, we challenge the hypothesis that the immunological abnormalities in Down syndrome should be interpreted as precocious immunosenescence. More genetic and immunological research is needed to study the true nature of the effect of an extra chromosome 21 on the immune system in DS.

References

[1] Andrews NP, Fujii H, Goronzy JJ and Weyand CM (2010). Telomeres and immunological diseases of aging. Gerontology, 56: 390-403

[2] Shay JW and Wright WE (2005). Senescence and immortalization: role of telomeres and telomerase. Carcinogenesis, 26: 867-874

[3] Ponnappan S and Ponnappan U (2011). Aging and immune function: molecular mechanisms to interventions. Antioxid Redox Signal, 14: 1551-1585

[4] Weiskopf D, Weinberger B and Grubeck-Loebenstein B (2009). The aging of the immune system. Transpl Int, 22: 1041-1050

[5] Lott IT (1982). Down's syndrome, aging, and Alzheimer's disease: a clinical review. Ann N Y Acad Sci, 396: 15-27

[6] Cuadrado E and Barrena MJ (1996). Immune dysfunction in Down's syndrome: primary immune deficiency or early senescence of the immune system? Clin Immunol Immunopathol, 78: 209-214

[7] Burtner CR and Kennedy BK (2010). Progeria syndromes and ageing: what is the connection? Nat Rev Mol Cell Biol, 11: 567-578

[8] Kusters MA, Verstegen RH, Gemen EF and de Vries E (2009). Intrinsic defect of the immune system in children with Down syndrome: a review. Clin Exp Immunol, 156: 189-193

[9] Roitt IM, Brostoff J, Male D, editors. Immunology fifth edition. St Louis: CV Mosby, 1985

[10] Roat E, Prada N, Lugli E, Nasi M, Ferraresi R, Troiano L, Giovenzana C, Pinti M, Biagioni O, Mariotti M, Di Iorio A, Consolo U, Balli F and Cossarizza A (2008). Homeostatic cytokines and expansion of regulatory T cells accompany thymic impairment in children with Down syndrome. Rejuvenation Res, 11: 573-583

[11] Murphy M, Insoft RM, Pike-Nobile L, Derbin KS and Epstein LB (1993). Overexpression of LFA-1 and ICAM-1 in Down syndrome thymus. Implications for abnormal thymocyte maturation. J Immunol, 150: 5696-5703

[12] Kusters MA, Gemen EF, Verstegen RH, Wever PC and E DEV (2010). Both normal memory counts and decreased naive cells favor intrinsic defect over early senescence of Down syndrome T lymphocytes. Pediatr Res, 67: 557-562

[13] Trotta MB, Serro Azul JB, Wajngarten M, Fonseca SG, Goldberg AC, Kalil JE (2011). Inflammatory and immunological parameters in adults with Down syndrome. Immun Ageing, 8:4.

[14] de Arruda Cardoso Smith M, Borsatto-Galera B, Feller RI, Goncalves A, Oyama RS, Segato R (2004). Telomeres on chromosome 21 and aging in lymphocytes and gingival fibroblasts from individuals with Down syndrome. J Oral Sci, 46:171-7.

[15] Jenkins EC, Velinov MT, Ye L, Gu H, Li S, Jenkins EC, Jr., Brooks SS, Pang D, Devenny DA, Zigman WB, Schupf N and Silverman WP (2006). Telomere shortening in T lymphocytes of older individuals with Down syndrome and dementia. Neurobiol Aging, 27: 941-945

[16] Vaziri H, Schachter F, Uchida I, Wei L, Zhu X, Effros R, Cohen D and Harley CB (1993). Loss of telomeric DNA during aging of normal and trisomy 21 human lymphocytes. Am J Hum Genet, 52: 661-667

[17] Abu Faddan N, Sayed D and Ghaleb F (2011). T lymphocytes apoptosis and mitochondrial membrane potential in Down's syndrome. Fetal Pediatr Pathol, 30: 45-52

[18] Roat E, Prada N, Ferraresi R, Giovenzana C, Nasi M, Troiano L, Pinti M, Nemes E, Lugli E, Biagioni O, Mariotti M, Ciacci L, Consolo U, Balli F and Cossarizza A (2007). Mitochondrial alterations and tendency to apoptosis in peripheral blood cells from children with Down syndrome. FEBS Lett, 581: 521-525

[19] de Hingh YC, van der Vossen PW, Gemen EF, Mulder AB, Hop WC, Brus F and de Vries E (2005). Intrinsic abnormalities of lymphocyte counts in children with down syndrome. J Pediatr, 147: 744-747

[20] Cetiner S, Demirhan O, Inal TC, Tastemir D, Sertdemir Y (2010). Analysis of peripheral blood T-cell subsets, natural killer cells and serum levels of cytokines in children with Down syndrome. Int J Immunogenet, 37:233-237.

[21] Verstegen RH, Kusters MA, Gemen EF and E DEV (2010). Down syndrome B-lymphocyte subpopulations, intrinsic defect or decreased T-lymphocyte help. Pediatr Res, 67: 563-569

[22] Gross PA, Hermogenes AW, Sacks HS, Lau J and Levandowski RA (1995). The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Intern Med, 123: 518-527

[23] Hainz U, Jenewein B, Asch E, Pfeiffer KP, Berger P and Grubeck-Loebenstein B (2005). Insufficient protection for healthy elderly adults by tetanus and TBE vaccines. Vaccine, 23: 3232-3235

[24] Lee H, Nahm MH and Kim KH (2010). The effect of age on the response to the pneumococcal polysaccharide vaccine. BMC Infect Dis, 10: 60

[25] Kusters MA, Jol-van der Zijde CM, van Tol MJ, Bolz WE, Bok LA, Visser M and de Vries E (2011).

Impaired avidity maturation after tetanus toxoid booster in children with Down syndrome. Pediatr Infect Dis J, 30: 357-359

[26] Philip R, Berger AC, McManus NH, Warner NH, Peacock MA and Epstein LB (1986). Abnormalities of the in vitro cellular and humoral responses to tetanus and influenza antigens with concomitant numerical alterations in lymphocyte subsets in Down syndrome (trisomy 21). J Immunol, 136: 1661-1667

[27] Costa-Carvalho BT, Martinez RM, Dias AT, Kubo CA, Barros-Nunes P, Leiva L, Sole D, Carneiro-Sampaio MM, Naspitz CK and Sorensen RU (2006). Antibody response to pneumococcal capsular polysaccharide vaccine in Down syndrome patients. Braz J Med Biol Res, 39: 1587-1592

[28] Joshi AY, Abraham RS, Snyder MR, Boyce TG (2011) Immune evaluation and vaccine responses in Down syndrome: evidence of immunodeficiency? Vaccine, 29:5040-6

[29] Goronzy JJ and Weyand CM (2003). Aging, autoimmunity and arthritis: T-cell senescence and contraction of T-cell repertoire diversity - catalysts of autoimmunity and chronic inflammation. Arthritis Res Ther, 5: 225-234

[30] Bloemers BLP, Broers CJM, Bont L, Weijerman ME, Gemke RJBJ, van Furth AM (2010). Increased risk of respiratory tract infections in children with Down syndrome: the consequence of an altered immune system. Microbes Infect, 12:799-808.

[31] Lang D. Susceptibility to infectious disease in Down syndrome. In: Lott IT, McCoy EE, editors. Down syndrome: advances in medical care. New York: Wiley-Liss; 1992. p. 83-92.

[32] Day SM, Strauss DJ, Shavelle RM and Reynolds RJ (2005). Mortality and causes of death in persons with Down syndrome in California. Dev Med Child Neurol, 47: 171-176

[33] Karlsson B, Gustafsson J, Hedov G, Ivarsson SA and Anneren G (1998). Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity. Arch Dis Child, 79: 242-245

[34] Sanchez-Albisua I, Storm W, Wascher I and Stern M (2002). How frequent is coeliac disease in Down syndrome? Eur J Pediatr, 161: 683-684

[35] Anwar AJ, Walker JD and Frier BM (1998). Type 1 diabetes mellitus and Down's syndrome: prevalence, management and diabetic complications. Diabet Med, 15: 160-163

[36] Goldacre MJ, Wotton CJ, Seagroatt V and Yeates D (2004). Cancers and immune related diseases associated with Down's syndrome: a record linkage study. Arch Dis Child, 89: 1014-1017

[31] Ozgenc A and Loeb LA (2006). Werner Syndrome, aging and cancer. Genome Dyn, 1: 206-217

[37] Harjacek M, Batinic D, Sarnavka V, Uzarevic B, Mardesic D, Marusic M. Immunological aspects of progeria (Hutchinson-Gilford syndrome) in a 15-month-old child. Eur J Pediatr. 1990;150:40-2.

[38] Merideth MA, Gordon LB, Clauss S, Sachdev V, Smith AC, Perry MB, Brewer CC, Zalewski C, Kim HJ, Solomon B, Brooks BP, Gerber LH, Turner ML, Domingo DL, Hart TC, Graf J, Reynolds JC, Gropman A, Yanovski JA, Gerhard-Herman M, Collins FS, Nabel EG, Cannon RO 3rd, Gahl WA, Introne WJ (2008). Phenotype and course of Hutchinson-Gilford progeria syndrome. N Engl J Med, 358:592-606.

[39] Nakao Y, Hattori T, Takatsuki K, Kuroda Y, Nakaji T, Fujiwara Y, Kishihara M, Baba Y, Fujita T (1980). Immunologic studies on Werner's syndrome. Clin Exp Immunol, 42:10-9.

[40] Ozgenc A, Loeb LA (2006). Werner Syndrome, aging and cancer. Genome Dyn, 1:206-17.

[41] Norris PG, Limb GA, Hamblin AS, Lehmann AR, Arlett CF, Cole J, Waugh AP, Hawk JL (1990). Immune function, mutant frequency, and cancer risk in the DNA repair defective genodermatoses xeroderma pigmentosum, Cockayne's syndrome, and trichothiodystrophy. J Invest Dermatol, 94:94-100.

[42] Wysenbeek AJ, Weiss H, Duczyminer-Kahana M, Grunwald MH, Pick AI (1986). Immunologic alterations in xeroderma pigmentosum patients. Cancer, 58:219-221.

[43] Berkel AI, Kiran O (1974). Immunological studies in children with xeroderma pigmentosum. Turk J Paed, 16:43-52.