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Underlying factors of recurrent infections in patients with down syndrome

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ABSTRACT

Down syndrome is the most common chromosomal aberration. Patientswith Down syndrome suffer more infections than those without the disease. Underlying immunological disorders are consideredto be the reason for the increasing frequency of infections in patients with Down syndrome. In addition, some anatomical abnormalities in the respiratory tractaccompanying Down syndrome can disturb the innate immunity and contribute to the increase in infection rate. Respiratory tract infections are one of the most common causes of mortality in patients with Down syndrome. Awareness of the underlying reason for frequent respiratory tract infections should result in a decrease in mortality among these patients and contribute to an improvementin their quality of life.

Keywords: Down syndrome; infections; innate immunity; immune deficiency.

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Down syndrome (DS) is the most common chromosomal aberration. Its frequency varies between 1/6000 and 1/8000 in the Turkish population [1]. It is also the most common genetic reason of mental retardation. DS is also associated with various congenital anomalies such as congenital heart disease (CHD), gastrointestinal anomalies, orthopedic problems alongwith characteristic dysmorphic features. Endocrine and neurologic disorders besides visual and hearing problems can be seen in patients with DS. In addition,hematologic disorders, particularly leukemia; autoimmune diseases such as celiac disease; and type 1 diabetes mellitusis seen in patients with DS. The rise inthe prevalence of both infections and autoimmune disorders are thought to be related to immune disorders [2].

Respiratory tract infectionsare the most commonly observed infection in patients with DS. Furthermore, CHD and respiratory tract infections are important reasons of mortality. Even though many immunologic disorders have been defined in patients with DS, there are still undefined topics in underlying immune deficiency in patients with DS [3]. Immune deficiency may be the reason for frequent respiratory tract infection. In this study, we aimed to review the underlying factors of recurrentinfections inpatients with DS.

The frequency of upper and lower respiratory tract infections is higherin patients with DS than in those without the disease. Pharyngitis and otitis media with effusion are the most commonly diagnosed upper respiratory tract infections and pneumonia as the most commonly diagnosed lower respiratory tract infection. Moreover, pneumonia is the most important cause of hospitalization and mortality inpatients with DS [3]. Secondary respiratory distress syndromedue to pneumonia is higher and severe in children with DS [4].

Respiratory syncytial virus (RSV) is the most commonly observed cause of lower respiratory tract infections and bronchiolitis in infancy and early childhood

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[5]. Some studies have shownthat the rate of hospitalization because of RSV infection is higher in patients with D Seven if they do nothavea Congenital Heart Diesase (CHD) [6]. However, there is no explanation about the increased risk of RSVinfection in patients with DS. Staglianao et al. [5] found that length of hospital stay is longer and requirement of respiratory support is much higherin patients with DS during RSV infection. RSV has no specific treatment, but in infants at a risk of RSV (e.g., prematurity, bronchopulmonary dysplasia, CHD, etc.) palivizumab (monoclonal antibody against RSV) is used prophylactically for reducing hospitalization and/or its duration and need for respiratory support. Recently, prophylactic use of palivizumab has been recommended for patients with DS [7]. Hao Yi et al. [7] used palivizumab prophylaxis to prevent RSV infections in patients with DS and demonstrated that palivizumab prophylaxis shortens hospitalization duration in patients with DS.

The risk of serious infections occurring in patients with DShas been found to beincreased compared with the normal population [8]. Studies show that the risk of mortalitydue to sepsis is higher in children with DS [8].

1) Non-Immunologic Causes of Increased Infections in Patients with DS: It is assumed that some dysmorphic features in affected individuals andanatomicalabnormalities contribute to the frequency of infections in patients with DS (Table 1) [2].

Anatomical Abnormalities in Children with DS

Laryngomalacia, narrowed trachea, tracheomalacia, tracheal stenosis, and subglottic stenosis are the most frequently encountered congenital anomalies in patients with DS. Airway narrowingis caused by various reasons in patients with DS. Bertrand et al. [9] foundanatomical abnormalities in the airways in 75% of patients with DSwho underwent bronchoscopy because of lowerrespiratory tract infections. The mostly common seen abnormality among these is laryngomalacia [10]. Subglottic stenosis is another frequently seen abnormality, which occurs post-intubation [11].

Table 1. Abnormalities (nonimmunological) known to increase the incidence of infections in patients with Down syndrome

Anatomical abnormalities of the airways
Obstructive sleep apnea
Congenital anomalies of the lower respiratory tract
Congenital heart disease
Congenital ear anomalies
Gastroesophageal refluxand deglutition disorders

Another important cause of airway narrowing seen in patients with DS is phenotypic findings specific to the syndrome. When the nasopharynx is narrowerthan usual, sinusitis formation and nasal congestion occurs. Hypoplasia of the nose and sinus contributes to nasal obstruction, and repetitive nasal congestion occurs. Adenotonsillar hypertrophy, macroglossia, and choanal stenosis also contribute to narrowing of the airways [2].

Tracheal bronchus, which originates from the trachea, is described as an accessory bronchus. It has been shown that tracheal bronchus is associated with repetitive right lower lobe pneumonia [12]. The frequency of tracheal bronchus abnormality with repetitive right lower lobe pneumonia caused by it is high in patients with DS. Congenital anomalies of the airways cause both repetitive wheezing and coughing, increased risk of respiratory tract infection, and pulmonary hypertension [13]. Creating awareness in patients with congenital airway malformations will contribute to the treatment of patients.

Sleep-related respiratory disorders are one of the most commonly seen respiratory disorders in patients with DS. The rate of obstructive sleep apnea is 30%–80% [14]. Hypoplasia of the nose and sinus, narrowness of the upper respiratory tract, macroglossia, mandibular hypoplasia, adenotonsillar hypertrophy, and obesity are factors that contribute to the development of obstructive sleep apnea in patients with DS. Although adenotonsillectomy provides improvement in symptoms, obstructive sleep apnea may continue in patients with structural airway abnormalities [14]. Even though these patients are asymptomatic, they should be assessed using polysomnography for obstructive sleep apnea. Above all, obstructive sleep apnea may lead to pulmonary hypertension and cor pulmonale by causing intermittent hypoxia and respiratory acidosis.

An autopsy study performed in patients with DS showed that there was a smaller number of alveoli with largened alveoli in the lungs [15]. Because subpleural cyst is another finding, which is a lung parenchymal abnormality, its frequency is highin patients with DS [15].

CHD is one of the main problems causing morbidity in patients with DS (approximately 40% of patients)

[16]. The most frequently observed types of CHD are atrioventricular septal defect, atrial septal defect,and ventricular septal defect. Faria et al. [17] found that the risk of serious infections such as pneumonia and sepsis in patients with DS with CHD is considerably higher than in those without CHD.

Chronic otitis and hearing loss are more frequently seen in patients with DS [18]. These may be caused by a variety of anatomical defects. A study showeda stenosis of the external auditory canal in approximately 50% of patients with DS [19]. Small width of the Eustachian tube and its increased cylindricity leads to collection of more fluid in the middle ear . This contributes to chronic otitis formation [18, 20]. Barr et al. [21] showed that the frequency of middle ear infections in patients with DS aged >1 year rises up to 93%. Moreover, repetitive middle ear infections lead to hearing loss [20].

Gastroesophageal reflux may lead to chronic lung inflammation and bronchospasm. It has also been known that recurrent silent aspiration of gastric fluid causes recurrent respiratory tract infections [22]. It is thought that hypotony, which is seen in patients with DS,reduces pharyngeal muscle tonus and increases the risk of aspiration [22]. The frequency of gastroesophageal reflux disease in patients with DS is higher than that in those with out the disease [22]. There is an increased frequency of esophageal atresia in patients with DS, and disturbed physiological mechanisms after surgery lead to respiratory complications, such as pneumonia, asthma, and high rates of hospitalization due to respiratory tract infections [23].

2) Immune Disorders in Children with DS: Immunity is defined as the body's defense against infectious diseases. It consistsof natural/innate immunity (first protectivebarrier against infectious diseases) and acquired immunity (provides specific and more effective defenses against infections) [24].

Innate immunity provides the first defense when a foreign microorganism appears in the body. It exists in every person from birth and is fast. Becauseit cannot form memory cells, it gives the same response in each case and is not specific to any microorganism [24]. Normal anatomical development and normalphysiological process of organs arean essential part of innate immunity. Several innate and acquired immune disordershave been reported in children with DS (Table 2) [24].

To date, a reduction in neutrophil chemotaxis in patients with DS has been shown in many studies [25]. In addition, the cause of chemotaxis reduction has not yet been fully clarified. On the other hand, studies on neutrophil functions (especially in patients with DS who have recurrent periodontitis) indicate that there are no significant problems in neutrophil oxidative burst reaction or in phagocytosis capacity [25]. Another problem in natural immunity is the decrease in absolute number of monocytes [26]. A study by Bloemers et al. showed that even though the number of absolute monocyte is low, the number of CD14+CD16+ monocytes (a subset of monocytes) is higher in patients with DS. It is well known that monocytes belonging to this subgroup are very effective in the event of proinflammation. This situation may be responsible for the chronic inflammatory events observed in patients with DS [26].

NK anddendritic cells are another important part of innate immunity, and dendritic cells are also responsible for the delivery of antigens to T helper cells. It has been

TABLE 2. Major immune system disorders in patients with Down syndrome

Natural/innate immunity	Acquired immunity
Decreased neutrophil chemotaxis	Decrease in the number of T cells (particularly naive T cells)
Decreased number of NK cells	Low number of B cells
Decrease in the absolute number of monocytes	Lack of memory cell formation
Decrease in the number of dendritic cells	Lack of T cell proliferation
Reduction in mannose-binding lectin level	Size of the thymus is smaller than normal
	Inadequate antibody response to vaccination
	Decrease in the levelof humoral IgA
	Low levelof IgM, IgG2, and IgG4-type antibody

shown that the numbers of these two cells are significantly lower in patients with DS than in those without the disease [26]. Another disorder in innate immunity in patients with DS is the lackof mannose-bindinglectin (MBL). MBL starts the lectin-dependent pathway of the complement system and acts as opsonin for phagocytosis. MBL deficiency is one of the most common immune deficiencies. There is an increased frequency of infections especially with extracellular pathogensdue to MBL deficiency. Nisiharaet al. [27] showed that the MBL level was lower in children with DS. In particular, regarding repetitive respiratory tract infections in patients with DS, MBL deficiency is much more common than in those who do not have recurrent infections [27].

Acquired immunity isalso known as acquired and specific immunity. Response is specifically formed against unique microorganisms. Its effect is slower but more powerful. It can create a stronger response when faced with the same microorganism again by its ability to create memory cells. Although all types of lymphocytes are produced in the bone marrow, T-lymphocytes mature in the thymus and B cells mature in the bone marrow [24].

Various studies have shown that total lymphocyte and T-lymphocyte counts arelow in patients with DS. A low level of T-lymphocytes is also reflected in the T-lymphocyte subsets.The levels of both CD4+ T-lymphocytes and CD8+ T-lymphocytes are low in patients with DScompared with those without the disease. Thissituation wasespeciallyseen in the naive T cells and becomes apparent in the first 2 years of life. The number of T-lymphocytes increases with age and eventually reaches normal levels [28]. The primary expansion of T- and B-lymphocytes was severely defectivein children with DS [29]. In addition, it has been reportedthat the T-cell receptorexcision circle, which reflects the number of naive T cells secreted from the thymus was low in patients with DS [28, 29].

Early aging, decreased thymic production, intrinsic defects, and one or more mechanisms of apoptosis are responsible for the reduction in the number of T-lymphocytes. Kusters et al. [30] stated that naive T-lymphocytes have a low rate and memory T cells have a normal rate of reduction. Therefore, they claimed that the reason for the reduction in the number of T-lymphocytes isan intrinsic defect in patients with DS. Bloemers et al. [28] conducted a study to determine the reason for the decrease inthe number of naive T cells. They concluded that reduced thymic production is responsible for the decrease in the number of naive T cells [28, 29]. In severalstudies, it has also been shown that areduction in the number of naive T cells is not associated with frequent infection [28, 29]. Regulatory T cells are responsible for both the elimination of autoreactive T cells, which get rid of negative selection from the thymus, and suppression of inflammatory response. The effect of regulatory T cells on the increased frequency of autoimmune diseases in patients with DSwas studied; Pellegrini et al. [31] showed that the number of regulatory T cellswas higher but their functions weredefective.

A reduction in the number of T-lymphocytes (especially naive T-lymphocytes) was associated with pathology in the thymus where T-lymphocytesmature. Therefore, some studies focused on the development of the thymus. Studies have revealed that the thymus gland is very small inpatients with DS even in newborns [32]. Levin et al. [33] reported cortical atrophy in the thymus, corticomedullary border loss, defect of thymocyte development, and expansion of Hassall's corpuscles in patients with DS. Although there was a defect in thymocyte maturation, mature CD3+ and TCRαβ+ cells were present in the blood [28].

The number of B-lymphocytes in patients with DS is lower than that in those without DS. In contrast to T-lymphocytes, thissituationdoes not improve with age. Furthermore, the proliferation and maturation of lymphocytes are not observed in these patients, which were normally seen in the first years of life. Studies related to B-lymphocyte subsets showed that there is a decrease in CD27+ IgM+ memory B cells, natural effector B cells, CD27+ IgA+, and CD27+ IgG+ memory cells [34]. Despite the problems of memory B cells,plasma cells are present in normal numbers and lymph nodes are not defective in the germinal centers [35]. It is thought that one of the reasons for frequent infections is the reduction in class-switching and thedecreasing number of memory B cells, which are responsible for effective response to vaccination. Carsetti et al. [34] described an imperfection in B-lymphocytes based on a defect in the maturation of B-lymphocytes. Valentini et al. [36] evaluated antibody production and memory B cellsthat perform class-switching after polysaccharide vaccine. They stated that there is no problem in terms of antibody production after vaccination, but they showed that there was no success in terms of the production and maintenance ofclass-swiched B cells.

The immunoglobulin (Ig) levels and IgG subclasses of patients with DS were evaluated several times. Stud-

ies have revealed that the IgA and IgG levels were normal,butthe IgM level was decreased [35, 36]. Subgroups IgG1- and IgG3-type antibodies, which are effective in the fight against viruses, were at normal or high levels. IgG2 and IgG4, which are effective in response to bacterial polysaccharide antigen,were at low levels [37].

Summary

It is known that frequent infections, particularly respiratory tract infections, areincreasedin patients with DS. Both anatomical and immunological problems associated with DS are thought to be the reason for this. These anatomical problems can be classified as anatomical abnormalities of the airways, obstructive sleep apnea, congenital anomalies of the lower respiratory tract, CHD, congenital ear anomalies, gastroesophageal reflux, and deglutition disorders. The best known immunological problems aredecrease in T- and B-lymphocytes; small size of the thymus;reduction in the number of memory B cells;inadequate response to vaccine; decrease in the number of IgG2, IgG4, and IgM levels; and defects in neutrophil chemotaxis.

Conclusion

Even though many immunological problems have been defined in patients with DS, the underlying mechanism is not fully understood. Studies about memory cells, T- and B-lymphocytesubsets, and dendritic cells are promising. Nevertheless, further research is needed on this topic.

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