



Retrospective Evaluation of 214 Cases of Down Syndrome

Fatih Akın, Abdullah Yazar, Esra Türe

Department of Pediatrics, Necmettin Erbakan University, Meram Faculty of Medicine, Konya, Turkey

Abstract

Introduction: This study was a retrospective evaluation of the clinical and demographic features, as well as the congenital and acquired diseases of patients with Down syndrome (DS) followed up at the clinic.

Methods: The hospital admission records and files of patients diagnosed with DS before the age of 18 were reviewed retrospectively. The age, gender, drugs used, and clinical diagnoses of the patients were recorded and statistical analysis was performed.

Results: The data of a total of 214 DS patients who were admitted to the pediatric clinic between January 2014 and January 2017 were analyzed. In all, 96 (44.9%) patients were female and 118 (55.1%) were male. The mean age of the total group was 6.01 ± 3.97 years. The mean age of the boys was 6.15 ± 3.96 years, and it was 5.83 ± 4.01 years for the girls. There was a significant difference in immunodeficiency between genders: 73.3% (n=33) of the 45 patients who were found to be immunodeficient were male ($p=0.006$). When the distribution of cases was analyzed according to concomitant diagnoses and age group, it was observed that 42.1% (n=24) of the 57 patients who were diagnosed with hypothyroidism were between 6 and 10 years of age ($p=0.00$), 52.1% (n=25) of the 48 patients who were diagnosed with epilepsy were between 6 and 10 years of age ($p=0.00$), all of the 13 patients who were diagnosed with anemia were between 0 and 5 years of age ($p=0.009$), 68.9% (n=31) of the 45 patients who were diagnosed as immunodeficient were between 0 and 5 years of age ($p=0.019$), and 90.6% (n=29) of the 32 patients who were diagnosed with hearing loss were between 0 and 5 years of age ($p=0.00$). There was a statistically significant difference in the age group of 0 to 5 years of age.

Discussion and Conclusion: Periodic follow-up of children with DS should be performed in terms of additional diseases. With appropriate and timely treatment approaches, the quality of life of these patients can be improved.

Keywords: Congenital anomaly; congenital heart disease; Down syndrome.

Down syndrome (DS) is the most frequently seen chromosomal anomaly among live births (1/733). It is characterized by various dysmorphic features, congenital malformations, and other health problems and medical conditions. The syndrome occurs as the result of the formation of an extra chromosome on the chromosome 21 pair due to an error occurring during cell division [1,2].

Diagnosis of DS is generally made during prenatal screening. If no prenatal diagnosis is made, generally, the phe-

notypic features of the newborn establish the diagnosis. Diagnosis should be confirmed with cytogenetic analysis. The results of cytogenetic analyses have indicated that of the different types of DS, 95% were free trisomy, 4% were Robertsonian-type translocation, and 1% were mosaicism [1,3].

The aim of this study was to analyze congenital and acquired additional diseases as well as the clinical and demographic features of patients with the diagnosis of DS followed up at the clinic.

Correspondence (İletişim): Fatih Akın, M.D. Department of Pediatrics, Necmettin Erbakan University, Meram Faculty of Medicine, Konya, Turkey

Phone (Telefon): +90 505 403 82 78 **E-mail (E-posta):** drfatihakin@gmail.com

Submitted Date (Başvuru Tarihi): 02.10.2017 **Accepted Date (Kabul Tarihi):** 30.11.2017

Copyright 2018 Haydarpaşa Numune Medical Journal

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc/4.0/>).



Materials and Methods

After receiving approval for the study from the Necmettin Erbakan University Meram Medical Faculty Ethics Committee, hospital admission records and files of patients who admitted to pediatrics clinic of Necmettin Erbakan University Meram Medical Faculty between January 2014 and January 2017 and who were diagnosed with DS were retrospectively reviewed. Data of age, gender, drugs used, and diagnoses were recorded in standard data entry forms. Additional diagnoses of congenital heart disease (CHD), hypothyroidism, epilepsy, diabetes mellitus (DM), hypertension, asthma, immune deficiency, undescended testis, diaphragmatic hernia, umbilical hernia, anal/duodenal atresia, Hirschsprung's disease, anemia, thrombocytopenia, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), hearing loss, cataract, talipes equinovarus, and congenital hip dislocation were also recorded. The patients were divided into 4 groups based on age. Patients with missing data were excluded from the study.

Statistical Method

Statistical analysis of the study was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for the analysis of distribution and frequency of data, and for the comparison of frequency in 2 independent groups, a chi-square test was used. A multicell chi-square test was applied for 3 or more groups. In all statistical analyses, the level of significance was accepted as $p < 0.05$.

Results

In all, 96 female (44.9%) and 118 male (55.1%) children (total $n = 214$) diagnosed with DS presented at the clinic of children's health and diseases between January 2014 and January 2017. The mean age of the entire patient group was 6.01 ± 3.97 years; the

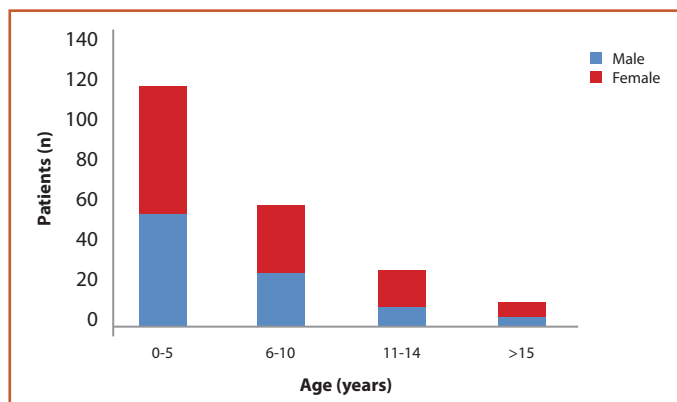


Figure 1. Distribution of the patients according to age and gender.

mean age of the males was 6.15 ± 3.96 years, and the mean age of the female children was 5.83 ± 4.01 years. When evaluated according to age group, children under 5 years of age were referred to the hospital most frequently ($n = 117$, 54.7%). No statistically significant difference was detected when age groups were compared with respect to gender (Fig. 1).

Analysis revealed that 73.3% ($n = 33$) of 45 patients diagnosed as having immunodeficiency syndrome were male, and that was statistically significant ($p = 0.006$). The distribution of the following diagnoses, however, did not differ statistically significantly between male and female children: CHD, hypothyroidism, epilepsy, DM, hypertension, asthma, diaphragmatic hernia, umbilical hernia, anal/duodenal atresia, Hirschsprung's disease, anemia, thrombocytopenia, ALL, AML, hearing loss, cataract, talipes equinovarus, and congenital hip dislocation ($p > 0.05$) (Table 1).

Distribution of the cases according to age group indicated that 42.1% ($n = 24$) of the patients with the diagnosis of hypothyroidism were in the age group of 6 to 10 years, which was statistically significant ($p = 0.00$). In addition, 52.1% ($n = 25$) of 48 patients who received the diagnosis of epilepsy were in the age group of 6 to 10 years, which was also statistically significant ($p = 0.00$). Furthermore, it was statistically significant that all of the 13 patients who were diagnosed with anemia were in the age group of 0 to 5 years. Most ($n = 31$, 68.9%) of the 45 patients diagnosed as having immunodeficiency were in the age group of 0 to 5 years, which was, again, statistically

Table 1. Distribution of concomitant diseases among patients with Down syndrome

Diseases	Female		Male		Total	
	n	%	n	%	n	%
Hypothyroidism	29	30.2	28	23.7	57	26.6
Epilepsy	16	16.7	32	27.1	48	22.4
Diabetes mellitus	3	3.1	5	4.2	8	3.7
Asthma	4	4.2	7	5.9	11	5.1
Hypertension	0	0	1	0.8	1	0.5
Diaphragmatic hernia	0	0	1	0.8	1	0.5
Anal/duodenal atresia	1	1	2	1.7	3	1.4
Acute lymphoblastic leukemia	2	2.1	0	0	2	0.9
Anemia	7	7.3	6	5.1	13	6.1
Immune deficiency	12	12.5	33	28	45	21
Thrombocytopenia	0	0	2	1.7	2	0.9
Acute myeloid leukemia	1	1	1	0.8	2	0.9
Hirschsprung's disease	0	0	2	1.7	2	0.9
Hearing loss	15	15.6	17	14.4	32	15
Umbilical hernia	5	5.2	1	0.8	6	2.8
Congenital hip dislocation	3	3.1	5	4.2	8	3.7
Cataract	3	3.1	2	1.7	5	2.3
Talipes equinovarus	4	4.2	7	5.9	11	5.1

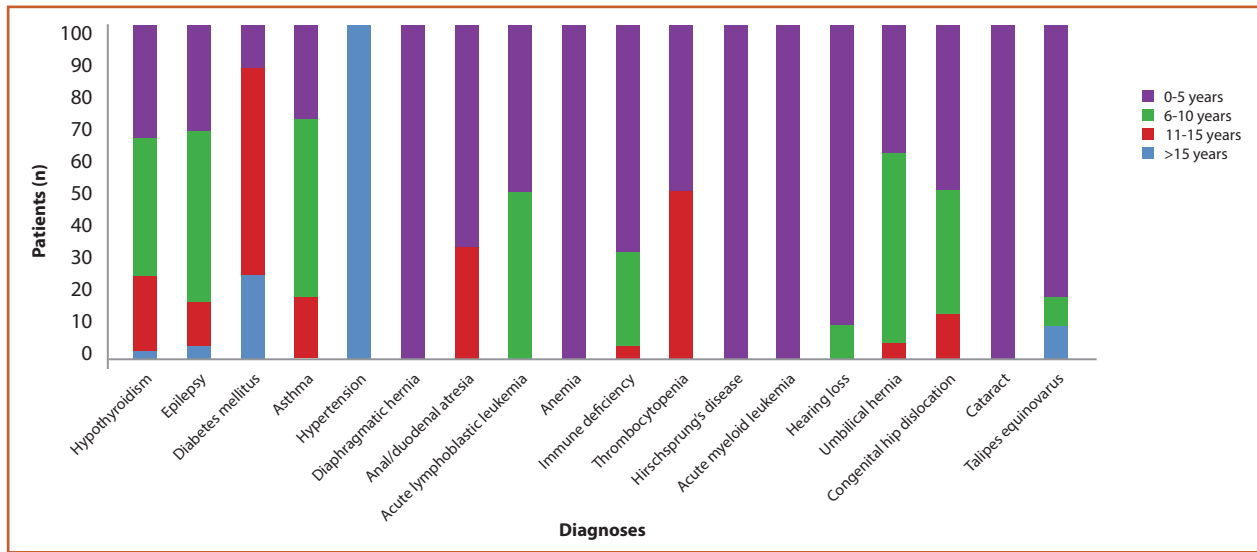


Figure 2. Distribution of the diagnoses of the patients according to age group.

significant ($p=0.019$). Of 32 patients diagnosed with hearing loss, 90.6% ($n=29$) were in the age group of 0 to 5 years, which was also statistically significant ($p=0.00$). The distribution of other additional diagnoses of the patients according to age group did not demonstrate a statistically significant difference ($p>0.05$) (Fig. 2).

In 29.9% ($n=64$) of the 214 patients, no evidence of cardiac pathology was detected. In 54% ($n=81$) of the 150 patients with a cardiac anomaly, most frequently atrial septal defect (ASD) was detected, followed by atrioventricular septal defect (AVSD) (17.3%, $n=26$), and ventricular septal defect (VSD) (12%, $n=18$). In 8.6% ($n=13$) of the patients, more than 1 cardiac anomaly was found (Fig. 3). A

statistically significant 52.6% ($n=30$) of 57 patients with CHD also had hypothyroidism ($p=0.002$), and 54.5% ($n=6$) of 11 asthmatic patients had ASD ($p=0.005$), which was also statistically significant. CHD was not statistically significantly associated with other diagnoses ($p>0.05$).

Seventy-five (35%) of the 214 patients did not use any drug. Among those who did, the most frequently used (14%, $n=30$) was levothyroxine sodium, followed by drugs used by the immunodeficient patients (13.6%, $n=29$) (Fig. 4). A statistically significant difference was not found between drugs used, age group, and gender ($p>0.05$).

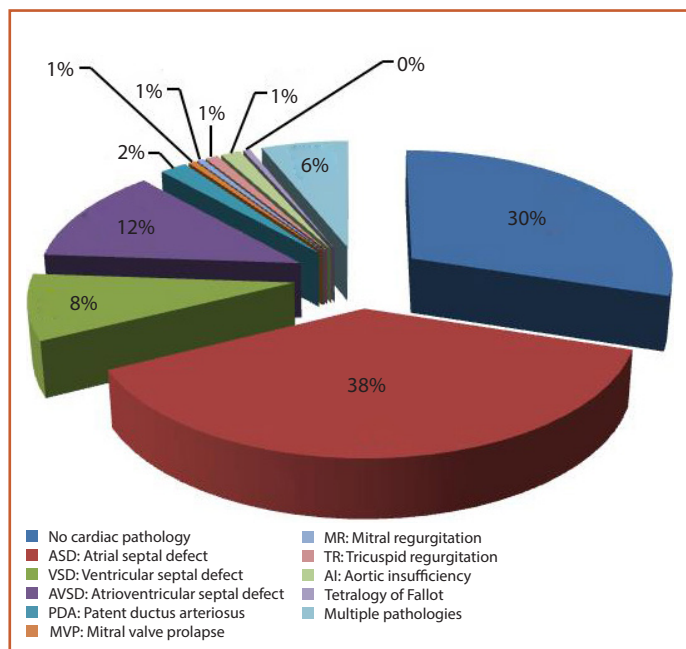


Figure 3. Distribution of congenital heart diseases among patients with Down syndrome.

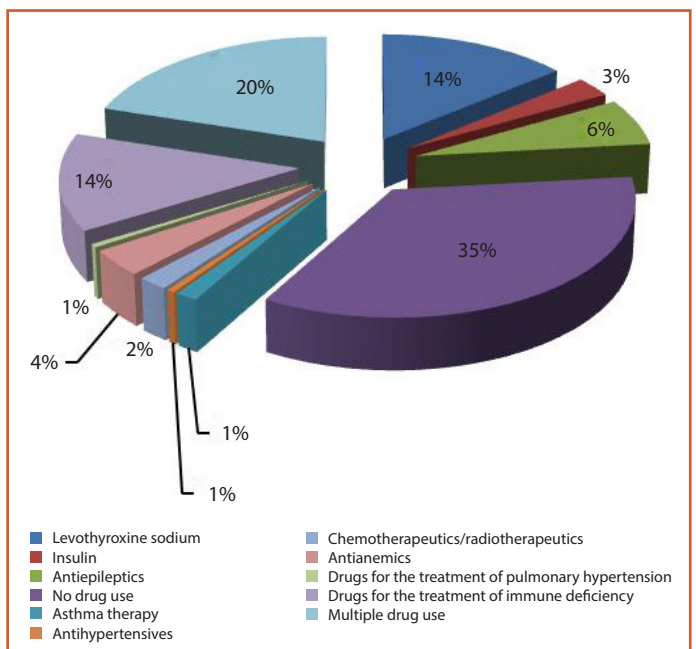


Figure 4. Distribution of the drugs used by patients with Down syndrome.

When the correlation between concomitant clinical diagnoses was investigated, 4 out of 5 (80%) cases with a cataract were statistically significantly ($p=0.00$) associated with hearing loss. In addition, 22 (38.6%) of 57 cases with hypothyroidism were also statistically significantly ($p=0.00$) associated with hearing loss.

Discussion

Down syndrome (trisomy 21) is the most known and most often seen chromosomal disorder. It is typically characterized by the presence of an extra, third chromosome number 21. Hypotonia, short stature, dysmorphic facial characteristics (hypertelorism, depressed nasal root, mongoloid face), brachycephaly, occipital plagiocephaly, and a simian line are typical findings [4]. In this study, we retrospectively analyzed the demographic characteristics and the congenital and acquired additional pathologic findings of patients with DS seen in our region.

In DS, mental retardation; congenital heart defects; gastrointestinal, genitourinary, neuromuscular, immune, skeletal, and hematopoietic system anomalies; audiovisual disorders; and the characteristic facial and physical disorders, as well as other medical disorders are frequently seen. The risk of giving birth to a baby with DS is greater most frequently seen in pregnant women older than 35 years of age [1].

In studies, DS has been more frequently reported among male children. Kilic et al. [5] detected a female/male ratio in our country of 1/1.83, while in an international study, Kava et al. [6] reported a ratio of 1/1.37. In accordance with the literature, in our study, DS was more frequently detected among male patients (1/1.25).

Among congenital malformations seen in DS cases, CHD is the most frequent, and the frequency has been reported at 40% to 60% [7,8]. In studies where echocardiographic examinations were routinely performed, a higher incidence of CHD has been reported [8,9].

Abbag et al. [8] and Freeman et al. [9] reported incidence rates of CHD of 61.3%, and 44%, respectively. In our study, the incidence of CHD was higher than that of other studies (70.09%). We think that the reason for the high frequency of CHD detected in our study group when compared with the literature is the referral of cases from the neighboring provinces to our pediatric cardiology clinic.

The most frequently seen cardiac anomalies in DS are endocardial cushion defects. ASD is the most frequently seen endocardial cushion defect [10]. In the largest population-based study cited in the literature, between 1985 and 2006, 821 infants with DS were analyzed, and cardiovascular abnormalities were detected in 42% ($n=342$). In 23% of the patients, more than 1 anomaly was detected, and as a second anomaly, ASD and patent ductus arteriosus were mostly identified. Among those with CHD, most frequent-

ly, AVSD was diagnosed (37%), followed by VSD (31%), and ASD (15%) [10]. In our study, multiple cardiac anomalies were found in 8.6% of our patients, and consistent with the literature, ASD was the second most frequently seen anomaly; ASD was observed in 54% of the patients with CHD.

Children with DS are at increased risk for congenital or acquired gastrointestinal system anomalies, such as duodenal atresia, annular pancreas, imperforate anus, Hirschsprung disease, celiac disease, and neonatal cholestasis [1,8]. Abbag [8] performed a study with 98 patients with DS, and reported 8% duodenal atresia, 7% imperforate anus, and 4% Hirschsprung disease. In the present study, anal/duodenal atresia was detected in 1.4% ($n=3$) of the patients, but annular pancreas was not observed in any patient. The small number of cases with anal/duodenal atresia found in our study when compared with the literature data may be related to the smaller size of our patient population. Although Hirschsprung's disease is more prevalent among patients with DS relative to the overall population, its incidence is less than 1%. DS is seen in 2% to 15% of children with Hirschsprung's disease [11]. In accordance with the literature data, Hirschsprung's disease was detected in 0.9% ($n=2$) of our patients with DS. Umbilical hernia is frequently seen in association with DS; however, diaphragmatic hernia is rarely encountered [12]. Umbilical hernia was detected in 2.8% ($n=6$) of our cases, and 1 (0.5%) patient had diaphragmatic hernia. Especially in DS patients with recurrent pulmonary infection, diaphragmatic hernia should come to mind, and the patient should be examined accordingly.

Hearing loss is seen in 38% to 78% of individuals with DS. Otitis media affects 50% to 70% of those with DS, and generally leads to hearing loss [13,14]. Therefore, monitoring of patients with DS for the presence of otitis media is important in order to preserve hearing. In our study, hearing loss was detected in 15% of the patients. The lower rate of hearing loss found is thought to be related to hearing tests conducted at various centers.

Vision anomalies, such as epicanthus, mongoloid eye axis, Brushfield spots on the iris, congenital cataract, glaucoma, strabismus, and refractive errors are also frequently encountered in cases of DS. Sharmini et al. [15] investigated ocular anomalies in 60 DS patients aged <17 years, and found that epicanthus was detected most frequently (96.7%), followed by nystagmus (33.3%), strabismus (26.7%), bilateral congenital cataracts (13.3%), blepharconjunctivitis (10%), glaucoma (6.7%), nasolacrimal duct obstruction (3.3%), bilateral retinoblastoma (1.7%), and chronic uveitis (1.7%). We detected bilateral congenital cataracts in 2.3% ($n=5$) of our cases. DS patients should undergo ophthalmological examinations within the first 6 months of life to determine if there is any functional loss, and this should be followed up with annual control exams.

Thyroid disorders are also common in patients with DS. Tuysuz et al. [16] performed a study with 320 DS patients, and reported the development of abnormal thyroid function in 28% of those aged between 5 days and 10 years. Similarly, we also detected hypothyroidism in 26.6% of our patients, and 42.1% of these patients were in the age group of 6 to 10 years. Hypothyroidism may aggravate the growth delay and mental retardation seen in these patients. Therefore, any diagnosis of hypothyroidism should be made as soon as possible, treated accordingly, and regular hypothyroidism screening tests should be performed.

In patients with DS, the risk of developing type 1 diabetes mellitus (DM) increases. DS has been reported to be the most prevalent genetic syndrome associated with DM [17]. Bergholdt et al. [18] demonstrated that the prevalence of type 1 DM in patients with DS was 4.2-fold higher relative to the population in general. Varied data about the age of onset of DM in patients with DS have been reported. In a study conducted by Rohrer et al., [19] the mean age of onset of diabetes was as 8.2 ± 5.3 years, while Bergholdt et al. [8] found a mean age of onset of DM of 6 years. In our study, 62.5% (n=5) of 8 patients with DM were aged between 11 and 15 years, and the mean age of all of the patients was 7.4 ± 2.7 years.

Especially in pediatric cases with DS, hematological abnormalities affecting the erythrocytes, leukocytes, and platelets are frequently seen, and the lifelong risk of developing leukemia ranges between 1% and 1.5% [20]. As in the literature data, leukemia was diagnosed in 1.8% of the current study patients. AML M7 is seen in 1/50-200 of patients with DS. The incidence is nearly 500-times higher in children with DS. AML M7 is most often detected within the first 4 years of life [21]. In our study, 2 patients were diagnosed with AML at <4 years, in compliance with the literature findings. The risk of development of ALL in children with DS is nearly 10- to 20-fold higher than in those without DS, and they represent 1% to 3% of all patients with ALL. The peak incidence is between the ages of 2-5 years, the same as those without DS [22]. In our study, the 2 patients diagnosed with AML were younger than 6 years of age, which was consistent with the literature.

Iron deficiency anemia (IDA) is a general public health problem, and patients with DS are at risk of developing IDA. Dixon et al. [23] detected IDA in 2.6% of 114 patients with DS. In a study of 149 patients with DS, Tenenbaum et al. [24] reported that the incidence of anemia in patients with DS increased with age, and indicated a prevalence of 8.1%. In our study group, 6.1% of the patients had anemia, and all of them were younger than 5 years of age.

Epilepsy is more frequently seen in patients with DS than in the general population, and the prevalence increases with age, while febrile convulsions are less often observed [25,26]. Shimakawa et al. [26] reported an incidence rate of 2.5% for febrile convulsions in patients with DS, and that the incidence of febrile convulsions

in patients with DS was significantly lower compared with their healthy siblings. The incidence of epilepsy in DS reportedly increases with age, and reaches 46% in patients older than 50 years of age [25]. Goldberg-Stern et al. [27] and Barcas et al. [28] found an incidence of 8% and 23%, respectively. In our study, we detected epilepsy in 22.4% (n=48) of our patients.

As a genetic syndrome, DS is most frequently associated with immune disorders [29]. Infectious diseases are frequently seen in cases with DS. This may be due to a greater susceptibility to infection as a result of some of the diseases associated with DS and the effects on immune response. Immune defects seen in DS include a smaller thymus compared with healthy children, fewer T and B cells, a lymphocyte count that does not increase as is usually seen in infancy, a naive T cell ratio that decreases slightly or moderately, a suboptimal antibody response to vaccines, low levels of total and specific immunoglobulin A, and weakened neutrophil chemotaxis [30]. According to our data, 21% (n=45) of our patients were followed up with a diagnosis of immune deficiency. In our study, talipes equinovarus was observed in 5.1% (n=11) of the patients, and 63.6% of them were male.

In conclusion, it should be highlighted that DS is a frequently encountered, easily recognized, and well-studied syndrome. Children with DS should be followed up for concomitant diseases to maximize quality of life.

Ethics Committee Approval: The approval of the local Ethics Committee was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: F.A., A.Y., E.T.; Design: F.A., A.Y.; Data Collection or Processing: E.T.; Analysis or Interpretation: E.T.; Literature Search: F.A.; Writing: F.A., E.T.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Lee B. Down Syndrome and Other Abnormalities of Chromosome Number. In: Kliegman RM, Stanton BF, St Geme III JW, Schor NF, editors. Nelson Textbook of Pediatrics. Philadelphia, Elsevier; 2016. p. 610–6.
2. Gardiner KJ. Molecular basis of pharmacotherapies for cognition in Down syndrome. Trends Pharmacol Sci 2010;31:66–73.
3. Morris JK, Mutton DE, Alberman E. Revised estimates of the maternal age specific live birth prevalence of Down's syndrome. J Med Screen 2002;9:2–6. [\[CrossRef\]](#)
4. Kazemi M, Salehi M, Kheirollahi M. Down Syndrome: Current Status, Challenges and Future Perspectives. Int J Mol Cell Med 2016;5:125–33.
5. Kılıç M, Taşkın E, Aygün AD, Özdiller Ş. The retrospective evalu-

- ation of fifty-one cases of down's syndrome. *Turkiye Klinikleri J Pediatr* 2003;12:222.
6. Kava MP, Tullu MS, Muranjan MN, Girisha KM. Down syndrome: clinical profile from India. *Arch Med Res* 2004;35:31–5. [\[CrossRef\]](#)
 7. Ko JM. Genetic Syndromes associated with Congenital Heart Disease. *Korean Circ J* 2015;45:357–61. [\[CrossRef\]](#)
 8. Abbag FI. Congenital heart diseases and other major anomalies in patients with Down syndrome. *Saudi Med J* 2006;27:219–22.
 9. Freeman SB, Taft LF, Dooley KJ, Allran K, Sherman SL, Hassold TJ, et al. Population-based study of congenital heart defects in Down syndrome. *Am J Med Genet* 1998;80:213–7. [\[CrossRef\]](#)
 10. Irving CA, Chaudhari MP. Cardiovascular abnormalities in Down's syndrome: spectrum, management and survival over 22 years. *Arch Dis Child* 2012;97:326–30. [\[CrossRef\]](#)
 11. Moore SW, Johnson AG. Hirschsprung's disease: genetic and functional associations of Down's and Waardenburg syndromes. *Semin Pediatr Surg* 1998;7:156–61. [\[CrossRef\]](#)
 12. Elawad ME. Diaphragmatic hernia in Down's syndrome. *Ann Trop Paediatr* 1989;9:43–4. [\[CrossRef\]](#)
 13. Shott SR, Joseph A, Heithaus D. Hearing loss in children with Down syndrome. *Int J Pediatr Otorhinolaryngol* 2001;61:199–205. [\[CrossRef\]](#)
 14. Roizen NJ, Wolters C, Nicol T, Blondis TA. Hearing loss in children with Down syndrome. *J Pediatr* 1993;123:S9–12. [\[CrossRef\]](#)
 15. Liza-Sharmini AT, Azlan ZN, Zilfalil BA. Ocular findings in Malaysian children with Down syndrome. *Singapore Med J* 2006;47:14–9.
 16. Tüysüz B, Beker DB. Thyroid dysfunction in children with Down's syndrome. *Acta Paediatr* 2001;90:1389–93. [\[CrossRef\]](#)
 17. Schmidt F, Kapellen TM, Wiegand S, Herbst A, Wolf J, Fröhlich-Reiterer EE, et al.; BMBF Competence Network Diabetes. Diabetes mellitus in children and adolescents with genetic syndromes. *Exp Clin Endocrinol Diabetes* 2012;120:579–85.
 18. Bergholdt R, Eising S, Nerup J, Pociot F. Increased prevalence of Down's syndrome in individuals with type 1 diabetes in Denmark: A nationwide population-based study. *Diabetologia* 2006;49:1179–82. [\[CrossRef\]](#)
 19. Rohrer TR, Hennes P, Thon A, Dost A, Grabert M, Rami B, et al. Down's syndrome in diabetic patients aged <20 years: an analysis of metabolic status, glycaemic control and autoimmunity in comparison with type 1 diabetes. *Diabetologia* 2010;53:1070–5. [\[CrossRef\]](#)
 20. Lange B. The management of neoplastic disorders of haematopoiesis in children with Down's syndrome. *Br J Haematol* 2000;110:512–24. [\[CrossRef\]](#)
 21. Zipursky A. Transient leukaemia—a benign form of leukaemia in newborn infants with trisomy 21. *Br J Haematol* 2003;120:930–8. [\[CrossRef\]](#)
 22. Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. *Lancet* 2000;355:165–9. [\[CrossRef\]](#)
 23. Dixon NE, Crissman BG, Smith PB, Zimmerman SA, Worley G, Kishnani PS. Prevalence of iron deficiency in children with Down syndrome. *J Pediatr* 2010;157:967–971.e1. [\[CrossRef\]](#)
 24. Tenenbaum A, Malkiel S, Wexler ID, Levy-Khademi F, Revel-Vilk S, Stepensky P. Anemia in children with down syndrome. *Int J Pediatr* 2011;2011:813541. [\[CrossRef\]](#)
 25. Aller-Alvarez JS, Menéndez-González M, Ribacoba-Montero R, Salvado M, Vega V, Suárez-Moro R, et al. Myoclonic epilepsy in Down syndrome and Alzheimer disease. *Neurologia* 2017;32:69–73. [\[CrossRef\]](#)
 26. Shimakawa S, Tanabe T, Ono M, Nonaka M, Nambu M, Shinohara T, et al. Incidence of febrile seizure in patients with Down syndrome. *Pediatr Int* 2015;57:670–2. [\[CrossRef\]](#)
 27. Goldberg-Stern H, Strawsburg RH, Patterson B, Hickey F, Bare M, Gadoth N, et al. Seizure frequency and characteristics in children with Down syndrome. *Brain Dev* 2001;23:375–8.
 28. Barca D, Tarta-Arsene O, Dica A, Iliescu C, Budisteanu M, Moatescu C, et al. Intellectual disability and epilepsy in down syndrome. *Maedica (Buchar)* 2014;9:344–50.
 29. Cruz NV, Mahmoud SA, Chen H, Lowery-Nordberg M, Berlin K, Bahna SL. Follow-up study of immune defects in patients with dysmorphic disorders. *Ann Allergy Asthma Immunol* 2009;102:426–31. [\[CrossRef\]](#)
 30. Ram G, Chinen J. Infections and immunodeficiency in Down syndrome. *Clin Exp Immunol* 2011;164:9–16. [\[CrossRef\]](#)
 31. Cleves MA, Hobbs CA, Cleves PA, Tilford JM, Bird TM, Robbins JM. Congenital defects among liveborn infants with Down syndrome. *Birth Defects Res A Clin Mol Teratol* 2007;79:657–63.
 32. Torfs CP, Christianson RE. Anomalies in Down syndrome individuals in a large population-based registry. *Am J Med Genet* 1998;77:431–8. [\[CrossRef\]](#)
 33. Stoll C, Dott B, Alembik Y, Roth MP. Associated congenital anomalies among cases with Down syndrome. *Eur J Med Genet* 2015;58:674–80. [\[CrossRef\]](#)