Research Article / Araştırma Makalesi

The Effects of Medical Comorbidities on Neurodevelopmental Features in Children with Down Syndrome

Down Sendromlu Çocuklarda Tıbbi Komorbiditelerin Nörogelişimsel Özellikler Üzerine Etkisi

Yaşar TANIR [1], Selçuk ÖZKAN [2]

[1]İstanbul University, İstanbul Medical Faculty, Child and Adolescent Psychiatry Department, İstanbul, TÜRKİYE
[2]Kütahya Health Sciences University Training and Research Hospital, Child and Adolescent Psychiatry Department, Kütahya, TÜRKİYE

Abstract

Background: Down Syndrome (DS) is one of the most common genetic anomalies observed in approximately one out of 700 live births, which occurs as a result of an excess of chromosome 21 (trisomy 21). Cognitive development in DS children is generally in the range of moderate to severe retardation, and mental age is rarely above eight years. The aim of this study is to investigate the neurodevelopmental characteristics of children with DS between the ages of 1-6 years and their relationship with comorbid medical pathologies.
Materials and Methods: A total of 83 DS children who applied to the child and adolescent mental health outpatient unit, were included in the study, and the relationships between sociodemographic and medical histories and neurodevelopmental characteristics were analyzed. Denver II Developmental Screening Test was used to evaluate their development. Four areas were evaluated: gross motor development, fine motor development, language-cognitive development and personal-social development.
Results: The rates of medical comorbidities in children with DS was 75.9% (38 had heart problems, 17 had thyroid dysfunction, and 8 had epilepsy). There was no statistically significant difference between genders in terms of Denver II Developmental Screening Test scores. Children with hypothyroidism have significantly lower Denver II Developmental Screening Test scores in all domains. Other medical comorbidities did not have a significant effect on Denver II Developmental Screening Test scores.
Conclusions: Concomitant medical diseases in children with DS may affect the development of the child. Therefore, early diagnosis and treatment of these conditions is essential. Due to the negative effects of hypothyroidism on the development of children, care should be taken in the treatment and close follow-up of these children.

Key Words: Down Syndrome, Neurodevelopment, Medical comorbidity

Öz

Amaç: Down Sendromu (DS), 21. kromozomun fazlalığı (trizomi 21) sonucu ortaya çıkan, yaklaşık 700 canlı doğumdan birinde görülen en yaygın genetik anomalilerden biridir. DS'lu çocuklarda bilişsel gelişim genellikle orta ila şiddetli gerilik aralığındadır ve zihinsel yaş nadiren sekiz yaşın üzerindedir. Bu çalışmanın amacı, 1-6 yaş arası DS'lu çocukların nörogelişimsel özelliklerini ve eşlik eden tıbbi patolojiler ile ilişkisini araştırmaktır.
Materyal ve Metod: Çocuk ve ergen ruh sağlığı polikliniğine başvuran toplam 83 DS'lu çocuk çalışmaya dahil edilerek sosyodemografik ve tıbbi öykü ile nörogelişimsel özellikler arasındaki ilişkiler incelenmiştir. Gelişimlerini değerlendirmek için Denver II Gelişimsel Tarama Testi kullanıldı. Dört alan değerlendirildi: kaba motor gelişim, ince motor gelişim, dil-bilişsel gelişim ve kişisel-sosyal gelişim.
Bulgular: DS'li çocuklarda tıbbi ek hastalık oranları %75.9'du (38'inde kalp sorunu, 17'sinde tiroid disfonksiyonu ve 8'inde epilepsi vardı). Denver II Gelişimsel Tarama Testi puanları açısından cinsiyetler arasında istatistiksel olarak anlamlı fark yoktu. Hipotiroidili çocuklar, tüm alanlarda önemli ölçüde daha düşük Denver II Gelişimsel Tarama Testi puanlarına sahiptir. Diğer tıbbi komorbiditelerin Denver II Gelişimsel Tarama Testi puanları üzerinde anlamlı bir etkisi olmamıştır.
Sonuç: DS'lu çocuklarda eşlik eden tıbbi hastalıklar çocuğun gelişimini etkileyebilir. Bu nedenle, bu durumların erken teşhisi ve tedavisi önemlidir. Hipotiroidinin çocukların gelişimine olumsuz etkileri nedeniyle bu çocukların tedavi ve yakın takibinde dikkatli olunmalıdır.

Anahtar Kelimeler: Down Sendromu, Nörogelişim, Tıbbi komorbidite

Corresponding Author/Sorumlu Yazar

Dr. Yaşar TANIR
Istanbul University,
Istanbul Medical Faculty,
Child and Adolescent Psychiatry Department,
İstanbul, TÜRKİYE

E-mail: yasar.tanir@istanbul.edu.tr

Received / Geliş tarihi: 20.06.2023

Accepted / Kabul tarihi: 12.07.2023

DOI: 10.35440/hutfd.1317423

Introduction

Down syndrome (DS) is one of the most common genetic anomalies, which affects individuals from different races, ethnic groups and socioeconomic classes, occurs as a result of an excess of the 21st chromosome (trisomy 21), causing intellectual disability, immunodeficiency, congenital heart diseases, and is observed in approximately one in 700 live births (1,2).

Although the clinical picture varies, structural changes in the central nervous system, congenital heart disease, immunodeficiency, metabolic disorders, gastrointestinal problems and also characteristic physical phenotype can be defined (3). Developmental problems including motor development, language development, cognitive domain and personal-social dimensions in DS children are remarkable. Problems found in different areas of development are not always proportional, but each area affects and is affected by the other (4).

The cognitive development of DS children varies from person to person, and often children have moderate or severe intellectual disability (the mental age is rarely above 8 years) (5). However, very few children with DS have been reported to have cognitive capacities in the normal range (5). One study from a sample of 56 Italian children with DS reported that the average IQ was 44.7 and reported that it ranged from 28 to 71 (6,7). It should be noted that, unlike neurotypically children, IQ of children with DS gradually decreases with age (8).

Children with DS generally do not acquire motor skills at the same rate as their typically developing (TD) peers. However, DS children begin to roll between 5 and 6.4 months, while they sit independently between 8.5 and 11.7 months, meaning they develop with only a slight delay in the first year. However, the developmental delay is more pronounced in motor skills that develop later. It has been reported that children with DS crawl at 12.2-17.3 months and walk independently at 15-74 months (5,9).

Language development is also impaired in children with DS. However, infants with DS use communicative gestures more extensively than neurotypical infants who are at the same stage of communicative-linguistic development (10). Children with DS generally very poor language capacities (11). In addition to hearing loss, which can be seen in 40-80% of cases, a significant proportion of cases have language disorders (5). The hearing loss seen in cases is usually mild to moderate hearing loss due to otitis media and less frequently accompanied by sensorineural loss (12). Studies have not shown an association between hearing loss and language disorders (13,14). Vicari et al. reported a lower performance in language skills of children with DS compared to TD controls (15).

Characteristics and associated systemic and functional malformations are common in individuals with DS, although there is wide interindividual variation in clinical manifestations, particularly in neonates. The phenotype of DS consists of intellectual impairment, short stature, heart diseases, digestive disorders, thyroid disease, especially subclinical hypothyroidism, and orthopedic anomalies accompanying abnormal physical and neurological findings (16). The frequency of congenital heart diseases, which is the most common malformation in children with DS, varies between 16% and 62%, and the incidence of congenital heart diseases in the normal population is reported to be 8-9 per 1000 live births (17).

Although developmental areas interact with each other, it is known that the development of DS children is not homogeneous. There are not enough studies in the literature on the interaction between the factors that affect the development of DS children. Anatomical and physiological conditions of the central nervous system, congenital hypothyroidism, hearing and vision losses, presence of obsessive behavior patterns, prematurity and low birth weight are among the factors affecting the development of children with DS (16,18).

The first aim of this study was to examine the development of children with DS with the Denver II Developmental Screening Test and to compare scores in different developmental domains. The second aim is to evaluate the relationships between congenital hypothyroidism, cardiac anomalies, epilepsy, hearing and vision problems and language, personal-social, fine motor and gross motor development areas in DS children aged 1-6 years. The first hypothesis of the study is that the Language Development of children with DS will be more impaired than in other neurodevelopmental areas. The second hypothesis is that DS children diagnosed with hypothyroidism will be more impaired in all developmental areas than those without.

Materials and Methods

Study Population and Data Collection

The participants were recruited from the Kütahya Health Sciences University Training and Research Hospital, Child and Adolescent Psychiatry Clinic. A total of 83 children with DS, aged 1-6 years, who applied to the Child and Adolescent Mental Health outpatient unit, were included in the study. In addition, all cases are cases followed in the pediatrics department of Kütahya Health Sciences University Training and Research Hospital.

The comorbid medical diagnoses of the cases were made after evaluation by the pediatrician. Cases with Mosaic and translocation type were excluded from the study because it is a rare genetic type in DS children and would be a confounding factor in the results (five case excluded). Verbal assent and written consent were taken from all subjects and their families. The study was approved by the Kütahya University of Health Sciences Clinical Research Ethics Committee (date: 15.04.2021, no: 2021/07-17). Sociodemographic features and medical histories and neurodevelopmental features were recorded through sociodemographic

forms developed by the author of the study. The form included questions about parental age, parental education, socioeconomic status and children's past medical histories (hypothyroidism, cardiac anomalies such as atrial septal defect and ventricular septal defect, previous surgery, epilepsy). Previous surgery is eight cases underwent congenital heart surgery (for ventricular septal defect) and two cases underwent ear surgery (for chronic middle ear effusion). Subsequently, the development of the children was evaluated by an experienced psychologist with the Denver II Developmental Screening Test. Four areas were examined: gross motor development, fine motor development, language development and personal-social development. The Denver II Developmental Test is a practical observational screening test which has been standardized in many countries including Turkey. Previous experience in children with various disorders support Denver II's sensitivity in detecting adverse neurodevelopmental outcome (19).

Statistical analyses

All analyses were conducted with SPSS version 21.0 (Statistical Package for the Social Sciences, IBM Inc., Armonk, NY). Descriptive data were presented as percentage, mean and standard deviation. Normality of continuous variables was assessed using the Kolmogorov-Smirnov Test. The chi-square test was employed to examine the differences between categorical variables in the sample. For normally distributed variables, Student's t-test was used to compare the differences between the two groups. Non-normally distributed continuous data were analyzed using the Mann-Whitney U test and expressed as the median (25-75 IQR). Probability (p) values <0.05 were regarded as statistically significant.

Results

The sample consisted of 50 males (60.2%) and 33 females (39.8%). The mean age of the cases was 2.5 ± 0.72 years. The mean age of the mother and father was 36±6.1 and 40±6.4, respectively. Frequency of concomitant medical problems were as follows: 38 of the children had cardiac problems, 17 had thyroid dysfunction and 8 had epilepsy.

The mean age at which children with DS acquire important motor skills: 12.3±7.9 months for holding their head upright, 17.4±9.1 months for sitting without support, 23.5±11.2 months for crawling, 31.2±10.4 months for independent walking. There was no statistically significant difference between the genders in terms of developmental domains according to the Denver II Developmental Screening Test scores (Table 1).

There was no statistically significant difference between the Denver II Developmental Screening Test scores of children who had heart problems, epilepsy and surgery, and those who did not. Children with hypothyroidism have significantly lower Denver II Developmental Screening Test scores in all domains. Language-Development area was 8 (7-9) month in cases with hypothyroidism, while it was 9 (9-9) month in cases without hypothyroidism (p=.024). Gross Motor Development area was 7 (6-15) month in cases with hypothyroidism, while it was 11 (8-20.5) month in cases without hypothyroidism (p=.046). Fine Motor Development area was 8 (7-11.5) month in cases with hypothyroidism, while it was 11 (8.5-22) month in cases without hypothyroidism (p=.022). Personal-Social Development area was 8 (8-10) month in cases with hypothyroidism, while it was 11 (8-14) month in cases without hypothyroidism (p=.005) (Table 2).

Table 1. Neurodevelopmental characteristics by gender

	F (n=33)	M (n=50)	p
	(median (25-75 IQR))		
Language-Development	9 (8.75-9)	9 (9-9)	.576
Gross Motor Development	11 (7-23)	10 (7-15)	.637
Fine Motor Development	11 (7.75-24)	10 (8-13)	.805
Personal-Social Development	11 (8-13.25)	10 (8-13)	.649

Abbreviations: F: female, M: male, IQR: interquartile range, Mann-Whitney U test

Table 2. Medical Comorbidity and Developmental Features in Children with Down Syndrome

	Hypothyroidism			Congenital heart disease			Epilepsy			History of surgery		
	Yes (n=17)	No (n=66)	p	Yes (n=38)	No (n=45)	p	Yes (n=8)	No (n=75)	p	Yes (n=10)	No (n=73)	p
Language-Development	8 (7-9)	9 (9-9)	.024	9 (8-9)	9 (9-9)	.189	9 (7.5-11)	9 (9-9)	.642	9 (9-12)	9 (8.75-9)	.266
Gross Motor Development	7 (6-15)	11 (8-20.5)	.046	10 (6-19)	10 (8-19)	.386	12.5 (7-22)	10 (7-19)	.860	15 (7-26.5)	10 (7-16.75)	.309
Fine Motor Development	8 (7-11.5)	11 (8.5-22)	.022	10 (8-15)	11 (8-16)	.412	8 (7.5-15)	11 (8-16)	.329	12 (9.5-27)	10 (8-12.75)	.170
Personal-Social Development	8 (8-10)	11 (8-14)	.005	10 (8-13)	10 (8-13)	.389	10 (6.5-13)	10 (8-13.5)	.454	10 (9-17)	10 (8-13)	.478

Abbreviations: IQR: interquartile range, Mann-Whitney U test

Discussion

In this study, we investigated the neurodevelopmental characteristics of children with DS between the ages of 1-6 years and their relationship with comorbid medical pathologies. We have shown that the children with DS showed more impairment in language development than in other neurodevelopmental domains (gross motor, fine motor and personal-social development). In addition, children with hypothyroidism have significantly lower Denver II Developmental Screening Test scores in all domains. On the other hand, other medical comorbidities did not have a significant effect on Denver II Developmental Screening Test scores.

In the present study, children with DS showed more impairment in language development than in other neurodevelopmental domains (gross motor, fine motor and personal-social development). Although the average age of the children in our study was 30 months, their language development characteristics were 10 months and were considerably lower than other developmental areas. Iversen et al. reported that they used the Bayley test for language and cognitive assessment in their studies and found the average total language score to be 18 months and the average total intelligence score to 22 months (10). It has been reported in the literature that there is no difference between the genders in terms of cognitive and language skills. Our findings are compatible with the literature.

Kim et al. reported the average speed of reaching the motor development stages of children with DS as head control at 6.1±2.6 months, sitting without support at 11.9±3.3 months, crawling at 18.1±5.0 months, and independent walking at 28.0±8.3 months (20). In a study examining the development of gross motor skills in DS children, it was found that they started to sit at a mean of 10.3±3.1 months and to walk at 26.0±8.4 months (21). It

was determined that the average speed of reaching the motor development milestones of the children in our study was similar to the studies in the literature, but there was a slight difference. The difference in the speed of reaching motor developmental stages between this study and previous studies may be due to factors such as socioeconomic, cultural and early education.

Developmental disability in different areas may be caused by the basic mechanism of DS rather than concomitant medical conditions such as heart disease and epilepsy. However, hypothyroidism, unlike other medical conditions, can cause additional developmental problems. In the present study, DS children with hypothyroidism were significantly lower in all neurodevelopmental domains than those without. Thyroid dysfunction may also be present congenitally in children with DS, and it may appear later (22). The frequency of thyroid dysfunctions in DS patients is reported as 10-15% (18). We obtained a higher rate (20%) in our study. Evaluation of the time of occurrence and severity of thyroid dysfunction could have provided a clearer understanding of its effects on development. Compliance with treatment and inclusion of laboratory tests in future studies may provide more meaningful results in this regard.

A total of eight children had epilepsy. According to the literature, the frequency of epilepsy in patients with DS is 10.3% (23). Interestingly, it was determined that the developmental characteristics of DS children with epilepsy were the same as those without, and the presence of epilepsy did not increase developmental problems. The results of the present study are consistent with the literature.

In our study, approximately half of the children diagnosed with DS had congenital heart disease. In the literature, congenital heart disease has been reported in almost half of the children with DS (20). It has been reported in the literature that developmental features are not affected by the presence of heart disease, and the results of our study are also compatible with the literature.

The male to female ratio in our study was 1.7. In the literature, the male-female ratio is given as approximately 1.3, and it is reported that the male-to-female ratio increases as the age of the mother and father decreases (25,26). In our study, no difference was found between the gender of the children and the age of the mother and father. Although there are data in the literature that there may be differences between the sexes in terms of development (16,24), in our study, it was determined that the developmental characteristics of children did not differ according to gender.

One of the most important factors in the etiology for DS is advanced maternal age (25). In our study group, the mean maternal age was 36 and the mean paternal age was 40. 14 of the mothers are under 30 years old, 48 of them are between 30-40 years old and 21 of them are over 40 years old. It was determined that both maternal and paternal ages were not statistically different in children with DS with and without concomitant cardiac problems, thyroid dysfunctions and epilepsy.

This study has several limitations that should be noted. First, this was a cross-sectional study, and the results in the work may not be generalized to all DS diagnosed children. Second, it is performed in a single center and a relatively limited cohort of patients was included in the study. Therefore, a multicenter study with a large sample size is needed for further confirmation.

Conclusion

Neurodevelopmental retardation is an important feature of DS children. Medical comorbidities such as hypothyroidism can also affect cognitive development. Careful attention to early diagnosis and treatment of hypothyroidism can enable DS children to achieve optimal developmental outcomes. In addition, the most significantly affected developmental area of DS children is seen as the language-development area. DS children can be referred to speech-language therapy from an early age.

Ethical Approval: *The study was approved by the Kütahya University of Health Sciences Clinical Research Ethics Committee (date: 04.15.2021, no: 2021/07-17).*

Author Cotributions:
Concept: Y.T., S.Ö.
Literature eview: Y.T., S.Ö.
Design : Y.T., S.Ö.
Data acquisition: Y.T., S.Ö.
Analysis and interpretation: Y.T., S.Ö.
Writing manuscript: Y.T., S.Ö.
Critical revision of manuscript: Y.T.

Conflict of Interest: *The authors have no conflicts of interest to declare.*

Financial Disclosure: *Authors declared no financial support.*

References

1. Greber-Platzer S, Schatzmann-Turhani D, Wollenek G, Lubec G. Evidence against the current hypothesis of gene dosage effects of Trisomy 21: ets-2, encoded on chromosome 21 is not overexpressed in hearts of patients with Down syndrome. Biochem. Biophys. Res. Commun 254, 395–399, 1999.
2. Antonarakis SE, Lyle R, Chrast R, Scott HS: Differential gene expression studies to explore the molecular pathophysiology of Down syndrome. Brain Res. Rev. 36, 265–274, 2001.
3. Roizen NJ, Patterson D. Down's syndrome. *Lancet.* 2003;361(9365):1281–1289.
4. Ferreira-Vasques AT, Lamônica DA. Motor, linguistic, personal and social aspects of children with Down syndrome. *J Appl Oral Sci*. 2015;23(4):424-430.
5. Vicari S. Motor development and neuropsychological patterns in persons with Down syndrome. *Behav Genet*. 2006;36(3):355-364.
6. Vicari S, Bates E, Caselli MC, Pasqualetti P, Gagliardi C, Tonucci F, et al. Neuropsychological profile of Italians with Williams syndrome: an example of a dissociation between language and cognition?. *J Int Neuropsychol Soc*. 2004;10(6):862-876.
7. Vicari S, Marotta L, Carlesimo GA. Verbal short-term memory in Down's syndrome: an articulatory loop deficit?. *J Intellect Disabil Res*. 2004;48(Pt 2):80-92.
8. Pennington BF, Moon J, Edgin J, Stedron J, Nadel L. The neuropsychology of Down syndrome: evidence for hippocampal dysfunction. *Child Dev*. 2003;74(1):75-93.
9. Palisano RJ, Walter SD, Russell DJ, Rosenbaum PL, Gémus M, Galuppi BE, et al. Gross motor function of children with down syndrome: creation of motor growth curves. *Arch Phys Med Rehabil*. 2001;82(4):494-500.
10. Iverson JM, Longobardi E, Caselli MC. Relationship between gestures and words in children with Down's syndrome and typically developing children in the early stages of communicative development. *Int J Lang Commun Disord*. 2003;38(2):179-197.
11. Papagno C, Vallar G. Understanding metaphors and idioms: a single-case neuropsychological study in a person with Down syndrome. *J Int Neuropsychol Soc*. 2001;7(4):516-527.
12. Roizen NJ, Wolters C, Nicol T, Blondis TA. Hearing loss in children with Down syndrome. *J Pediatr*. 1993;123(1):S9-S12.
13. Jarrold C, Baddeley AD, Phillips C. Long-term memory for verbal and visual information in Down syndrome and Williams syndrome: performance on the Doors and People test. *Cortex*. 2007;43(2):233-247.
14. Chapman RS, Seung HK, Schwartz SE, Bird EK. Predicting language production in children and adolescents with Down syndrome: the role of comprehension. *J Speech Lang Hear Res*. 2000;43(2):340-350.
15. Vicari S, Caselli MC, Tonucci F. Early language development in Italian children with Down syndrome: asynchrony of lexical and morphosyntactic abilities. Neuropsychology. 2000a; 38:634–644.
16. Kava PM, Tullu MS, Muranjan MN, Girisha KM. Down syndrome: clinical profile from India. Arc Med Res 2004; 35:31-5.
17. Reller MD, Morris CD. Is Down syndrome a risk factor for poor outcome after repair of congenital heart disease? J Pediatr 1998; 132: 738-41.
18. Shaw CK, Thapalial A, Nanda S, Shaw P. Thyroid dysfunction in Down syndrome. Kathmandu Univ Med J (KUMJ) 2006;4:182-6.
19. Eratay E, Bayoglu B, Anlar B. Preschool Developmental Screening with Denver II Test in Semi-Urban Areas. *Online Submission*, 2015 *1*(2).
20. Kim MA, Lee YS, Yee NH, Choi JS, Choi JY, Seo K. Prevalence of congenital heart defects associated with Down syndrome in Korea. *J Korean Med Sci*. 2014;29(11):1544-1549.
21. Kim HI, Kim SW, Kim J, Jeon HR, Jung DW. Motor and Cognitive Developmental Profiles in Children With Down Syndrome. *Ann Rehabil Med*. 2017;41(1):97-103.
22. Pierce MJ, LaFranchi SH, Pinter JD. Characterization of Thyroid Abnormalities in a Large Cohort of Children with Down Syndrome. *Horm Res Paediatr*. 2017;87(3):170-178.
23. Robertson J, Hatton C, Emerson E, Baines S. Prevalence of epilepsy among people with intellectual disabilities: A systematic review. *Seizure*. 2015;29:46-62.
24. Kovaleva NV. Sex ratio in Down syndrome. TSitologiia i genetika. 2002; 36.6 2002: 54-69.
25. 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(1):2–6.
26. O'Nualláin S, Flanagan O, Raffat I, Avalos G, Dineen B. The prevalence of Down syndrome in County Galway. *Ir Med J*. 2007;100(1):329-331.