HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2023.44342
Haydarpasa Numune Med J 2024;64(3):279–285

ORIGINAL ARTICLE

The Role of Genetic Factors in Specific Language Impairment

Bertuğ Sakın[1], Hakan Beyaztaş[2], Selman Aktaş[3], Eray Metin Güler[2,4], Hayati Sencer Polat[5]

[1]Department of Speech and Language Therapy, University of Health Sciences Türkiye, Hamidiye Faculty of Health Sciences, Istanbul, Türkiye
[2]Department of Medical Biochemistry, University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Istanbul, Türkiye
[3]Department of Biostatistics, University of Health Sciences Türkiye, Hamidiye Faculty of Medicine, Istanbul, Türkiye
[4]Department of Medical Biochemistry, University of Health Sciences Türkiye, Haydarpaşa Numune Health Practice and Research Center, İstanbul, Türkiye
[5]Istanbul Private Çengelköy Final Anatolian High School, İstanbul, Türkiye

Abstract

Introduction: The objective of this investigation was to determine the impact of genetic factors on SLI and to assess the role of oxidative stress and inflammation in SLI.

Methods: A sample of 40 children, aged five, diagnosed with SLI by a licensed speech and language therapist, were selected for the study. The levels of oxidative stress (TAS, TOS, TT, and NT) and inflammation (TNF-α, IL-1β, and IL-6) were measured using photometric methods and commercially available kits. DNA damage analysis was performed using the Comet Assay technique.

Results: The results showed that the levels of oxidative stress, inflammation, and DNA damage were significantly higher in the group that did not receive SLT, as compared to the control group. The levels of oxidative stress, inflammation, and DNA damage decreased significantly in the group receiving SLT compared to the group not receiving SLT.

Discussion and Conclusion: This study sheds light on the role of DNA damage in the presence of SLI in children and highlights the significance of oxidative stress and inflammation in Specific Language Impairment. Furthermore, it demonstrates that the levels of DNA damage, oxidative stress, and inflammation change positively with speech and language therapy support in children with Specific Language Impairments.

Keywords: DNA damage; Inflammation; Oxidative stress; Specific language impairment.

Specific Language Impairment (SLI) is a disorder that can be observed in some children's language skills, although they do not have any neurological disease, have no problems with their auditory system, have no emotional disorders, have no inadequacy in oral-motor skills, and despite having average intelligence and a normal social environment in which they can acquire language[1,2]. Children with specific language disorders show delays in their linguistic development processes compared to their peers with typical development[3-5]. While some children with SLIs only have difficulty in expressing themselves, others may have problems with both expressive and receptive language[6]. Although some different results have been obtained in the studies conducted, in general, SLI can be observed in at least 1.5% of children and at most 7% of them. The highest rate of 7% is observed in children in the age group of five years. The incidence rate in girls is stated as 6%, while it is 8% in boys[7,8].

Correspondence: Bertuğ Sakın, M.D. Department of Speech and Language Therapy, University of Health Sciences Türkiye, Hamidiye Faculty of Health Sciences, Istanbul, Türkiye
Phone: +90 544 545 79 97 **E-mail:** bertugsakin@gmail.com
Submitted Date: 13.04.2023 **Revised Date:** 22.05.2023 **Accepted Date:** 25.05.2023
Haydarpaşa Numune Medical Journal

Children with SLIs have a weak vocabulary and a language system in which they experience difficulty in terms of form, content, and usage[9-11]. The existing problems, primarily arising from grammatical and syntactical components of the language, manifest themselves as phonological, semantic, and pragmatic difficulties and difficulties in acquiring new words[12]. In particular, they face problems with verb structures, such as learning new verbs, using verbs and auxiliary verbs correctly in the natural flow of the language, and forming verb tenses correctly. When compared to the other components of the language, it is seen that pragmatic language is the best one[13,14].

Unlike other language disorders that can be seen in childhood, the cause of SLI has still not been fully determined. When other relevant studies in the field are examined, it is seen that the reasons for the emergence of SLI are tried to be explained based on lack of environmental input, neurobiological factors, cognitive effects, and genetics[15]. The environmental input theory argues that some children do not encounter the necessary linguistic input during their language development period and that they have SLI due to this deficiency[16]. In the neurobiological approach, the opinion that these disorders occur as a result of the differences in the size, number, and myelination of the neurons in the language regions of the brain is dominant[17]. In the approach that deals with the problem in terms of cognitive effects, it is suggested that children with SLIs have language disorders due to working memory problems[18].

SLI may develop due to one reason, or it may arise due to the relationship between more than one different cause. One of the most emphasized possibilities in this regard, especially in recent years, is the genetic effect. Studies show that a quarter of children with this disorder have a family history of speech and language disorders[3,19,20]. Some research has focused on language genes. Although it has been suggested that FOXP1, FOXP2, CNTNAP2, ATP2C2, and CMIP gene structures may be effective on SLI, it has not been proven with definite findings[21]. In this study, it is aimed to determine the genetic effect in SLI, the cause of which cannot be fully revealed, to reveal the role of the presence of oxidative stress and inflammation in SLI, and to determine the differences between the typical developmental healthy control group and the groups with SLI who received SLT and those who did not.

Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki.

Ethics Committee Approval

Ethics committee approval of the study was obtained from University of Health Sciences, Hamidiye Scientific Research Ethics Committee (Approval number: 22/513).

Consent Form

For this research, informed consent was secured from the guardians of the participants through the execution of a consent form. The guardians were thoroughly apprised of their right to withdraw from the study at any juncture.

Research Pattern

This study employed a comparative descriptive research design, with the objective of comparing the levels of DNA damage, oxidative stress, and inflammation in children with SLIs to those of a healthy control group, which was comprised of individuals who received SLT and individuals who did not receive such therapy[22].

Participants

The participant group of the study consisted of 40 children aged five years, who did not have any neurological, auditory, or psychological disorders, had no oral-motor problems, had average intelligence, and were diagnosed with an SLI by a speech and language therapist. Sharing the same demographic characteristics with this group, 20 healthy children with typical development in the age group of five, who have no chronic disease, no recent disease or drug use, and no existing language and speech disorders, were included. A demographic summary of the study participants is presented in Table 1.

Collection of Samples

In this study, approximately 3 milliliters of blood were collected from participants diagnosed with SLI, utilizing routine procedures and sterile gel biochemistry tubes. The samples were then subjected to centrifugation at a speed of 3000xg for 10 minutes. The resulting serum samples were stored in the Medical Biochemistry Research and Development Laboratory of the Health Sciences University, at a temperature of -80°C, until analysis.

Measurement of Oxidative Stress Levels

The levels of Total Oxidant Status (TOS), Total Antioxidant Status (TAS), Total Thiol (TT), and Native Thiol (NT) in the samples were determined through a photometric method utilizing commercially available kits. The quantity of dynamic disulfide (DIS) bonds was computed by determining half the difference between the TT and NT values. The Oxidative

Table 1. Demographic characteristics of the participants

Variables	Statistics	
	n	%
Gender (male/female)		
Not receiving SLT		
Female	5	25
Male	15	75
Receiving SLT		
Female	5	25
Male	15	75
Healthy control group		
Female	5	25
Male	15	75
SLT		
Not receiving SLT	0	0
Receiving SLT	20	100
Healthy Control Group	0	0
Duration of SLT (month) (mean±SD)		
Not receiving SLT	0±0	
Receiving SLT	14.55±4.39	
Healthy control group	0±0	
Age (year) (mean±SD)		
Not receiving SLT	5±0	
Receiving SLT	5±0	
Healthy Control Group	5±0	

SLT: Speech and language therapy; SD: Standard deviation.

Stress Index (OSI) was calculated through the application of mathematical formulas (TOS/TAS).

Measurement of Inflammation Levels

The quantification of IL-1β (BT Lab, E0143Hu), IL-6 (BT Lab, E0090Hu), and TNF-α (BT Lab, E0082Hu) was performed using a photometric approach and commercially obtained ELISA kits. The kits used are: Total Antioksidan Status Assay (RL0017; Rel Assay Diagnostics, Mega Tıp), Total Oksidan Status Assay (RL0024; Rel Assay Diagnostics, Mega Tıp), Native Thiol Assay (RL0185; Rel Assay Diagnostics, Mega Tıp), Total Thiol Assay (RL0192; Rel Assay Diagnostics, Mega Tıp).

DNA Damage Analysis

The alkaline single-cell gel electrophoresis (Comet Assay) method developed by Singh et al.[23] was used to analyze leukocyte DNA damage with minor modifications, as previously mentioned. Briefly, a 6 µL aliquot of whole blood that had been dissolved was combined with low melting temperature agarose (0.7%) and embedded on microscope slides that had been coated with agarose gel (1%) of a normal melting temperature. The agarose gel was solidified in a cold environment by placing a coverslip over it. The cells embedded in agarose gel on slides were subjected to lysis by exposure to a buffer for a minimum of 4 hours. Subsequently, the cells underwent electrophoresis in an alkaline buffer of pH 13 at 300 mA for 20 minutes. Following electrophoresis, the cells were treated with 5 mg/mL of Ethidium Bromide and subjected to examination under fluorescence microscopy. The excitation wavelength was adjusted to 546 nm and the emission wavelength to 20 nm. The tail density (% tail) in DNA was evaluated as a marker of DNA damage. The Comet Assay Analysis Program IV (Perceptive Instruments, Suffolk, UK) was used to obtain comet analyses by counting an average of 50 cells[24].

Statistical Analysis

The data collected were analyzed using descriptive statistical methods with the aid of Statistical Packages for the Social Sciences (SPSS) version 25. Quantitative variables were represented by mean±standard deviation, while qualitative variables were presented in terms of frequency (%). One-Way Analysis of Variance was employed to compare the three groups with normal distribution, whereas the Kruskal-Wallis test was utilized to compare the three groups that did not have normal distribution.

Results

The levels of oxidative stress biomarkers were measured in the serum samples of the participants who received SLT and those who did not receive SLT, as well as a healthy control group. The results are depicted in Figures 1 and 2. The individuals in the speech and language therapy cohort were dubbed the "SLT group," whereas those who did not undergo such therapy were called the "non-SLT group." According to the results, the levels of TOS and OSI were found to be significantly elevated in the group that did not receive SLT, in comparison to the healthy control group, with a p-value of less than 0.001. Conversely, the levels of TT ($p<0.01$), NT, and TAS were found to be significantly lower in the group that did not receive SLT in comparison to the healthy control group, with a p-value of less than 0.001.

The study's findings showed that the SLT group displayed significantly lower levels of TOS and OSI compared to the non-therapy group ($p<0.001$). On the contrary, the SLT group had significantly higher TT levels compared to their counterparts ($p<0.01$). The therapy group also demonstrated statistically significant and elevated levels of NT and TAS compared to the non-therapy group ($p<0.001$). While both the therapy and non-therapy

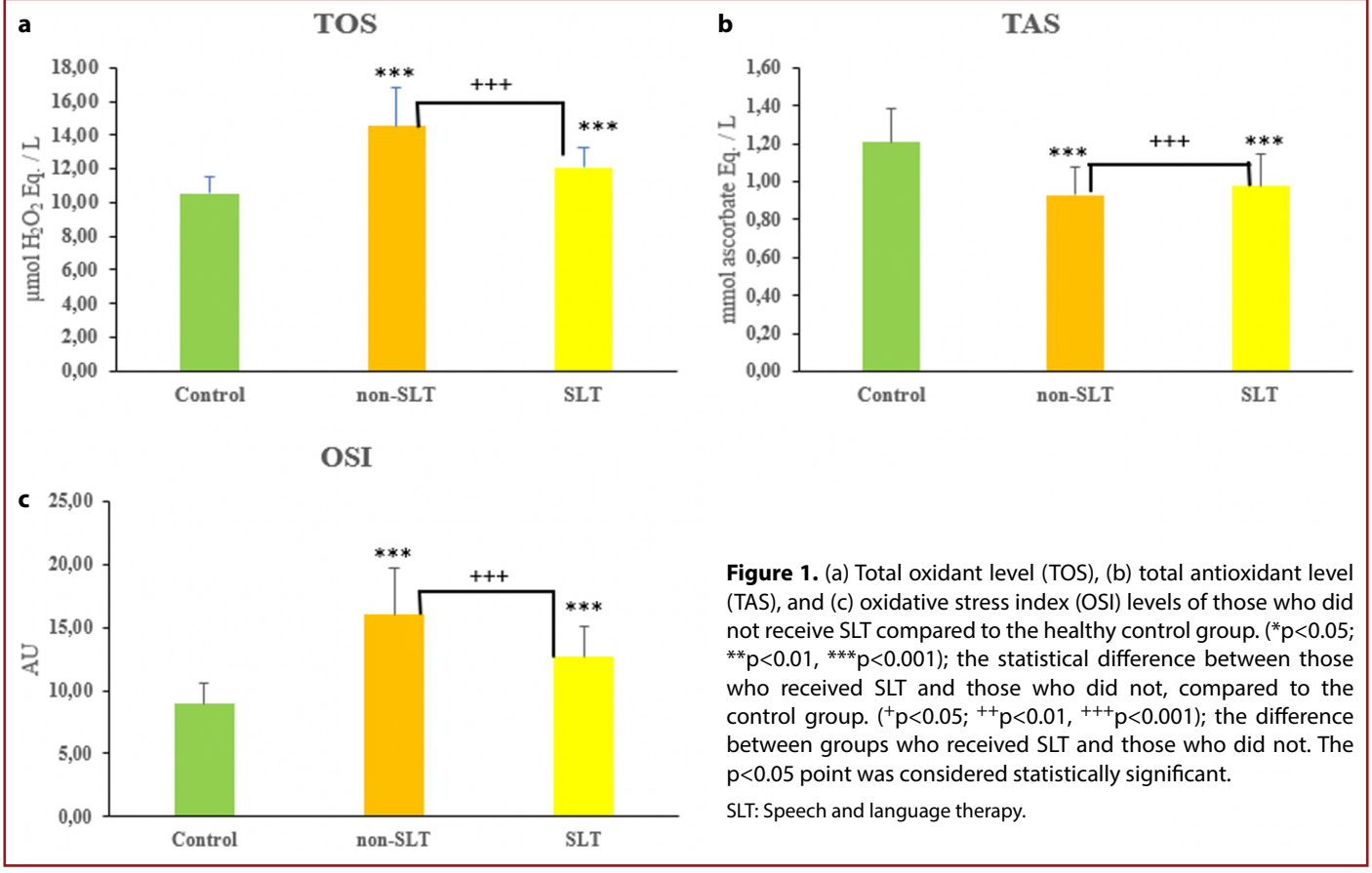

Figure 1. (a) Total oxidant level (TOS), (b) total antioxidant level (TAS), and (c) oxidative stress index (OSI) levels of those who did not receive SLT compared to the healthy control group. (*p<0.05; **p<0.01, ***p<0.001); the statistical difference between those who received SLT and those who did not, compared to the control group. ($^{+}$p<0.05; $^{++}$p<0.01, $^{+++}$p<0.001); the difference between groups who received SLT and those who did not. The p<0.05 point was considered statistically significant.

SLT: Speech and language therapy.

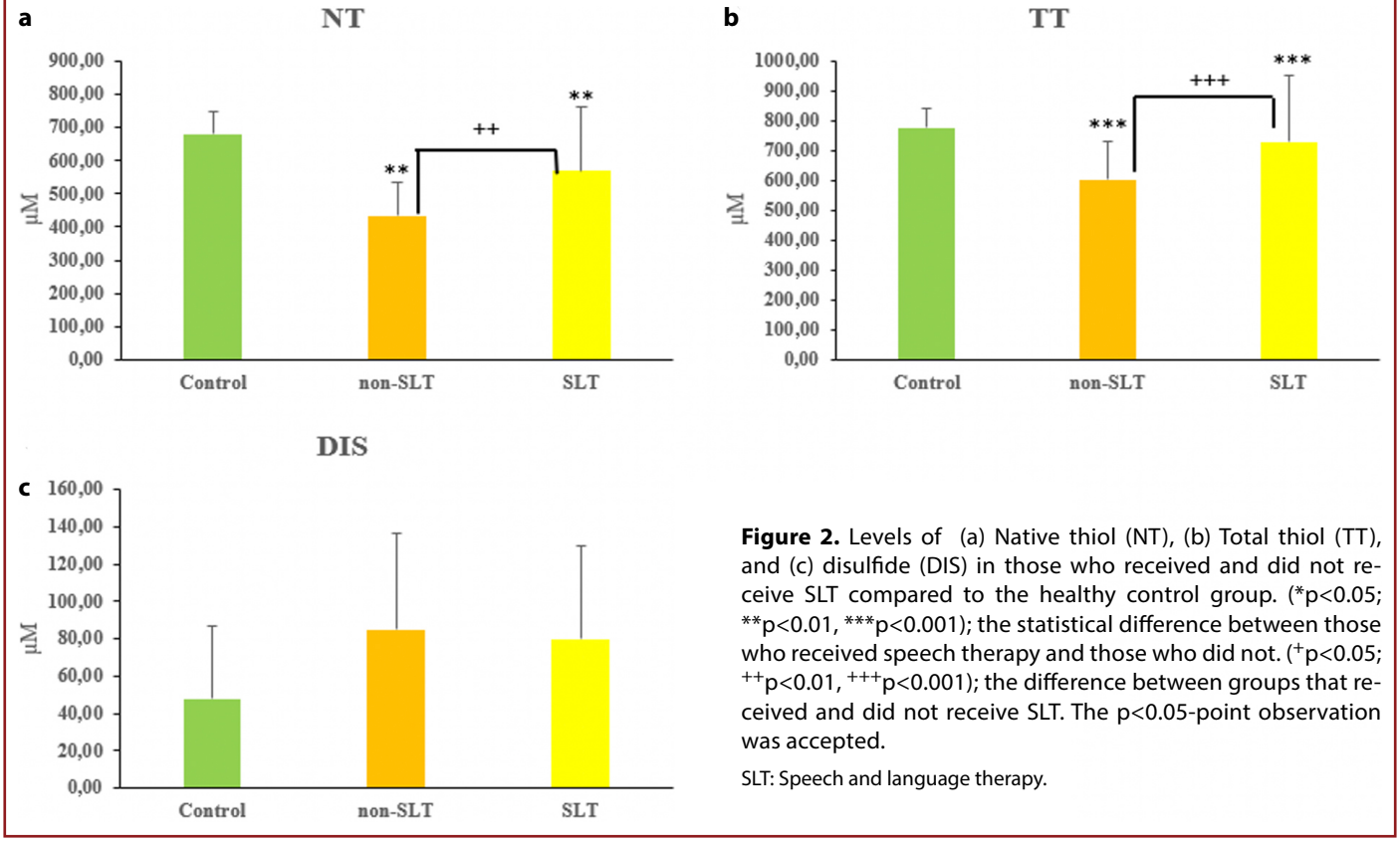

Figure 2. Levels of (a) Native thiol (NT), (b) Total thiol (TT), and (c) disulfide (DIS) in those who received and did not receive SLT compared to the healthy control group. (*p<0.05; **p<0.01, ***p<0.001); the statistical difference between those who received speech therapy and those who did not. ($^{+}$p<0.05; $^{++}$p<0.01, $^{+++}$p<0.001); the difference between groups that received and did not receive SLT. The p<0.05-point observation was accepted.

SLT: Speech and language therapy.

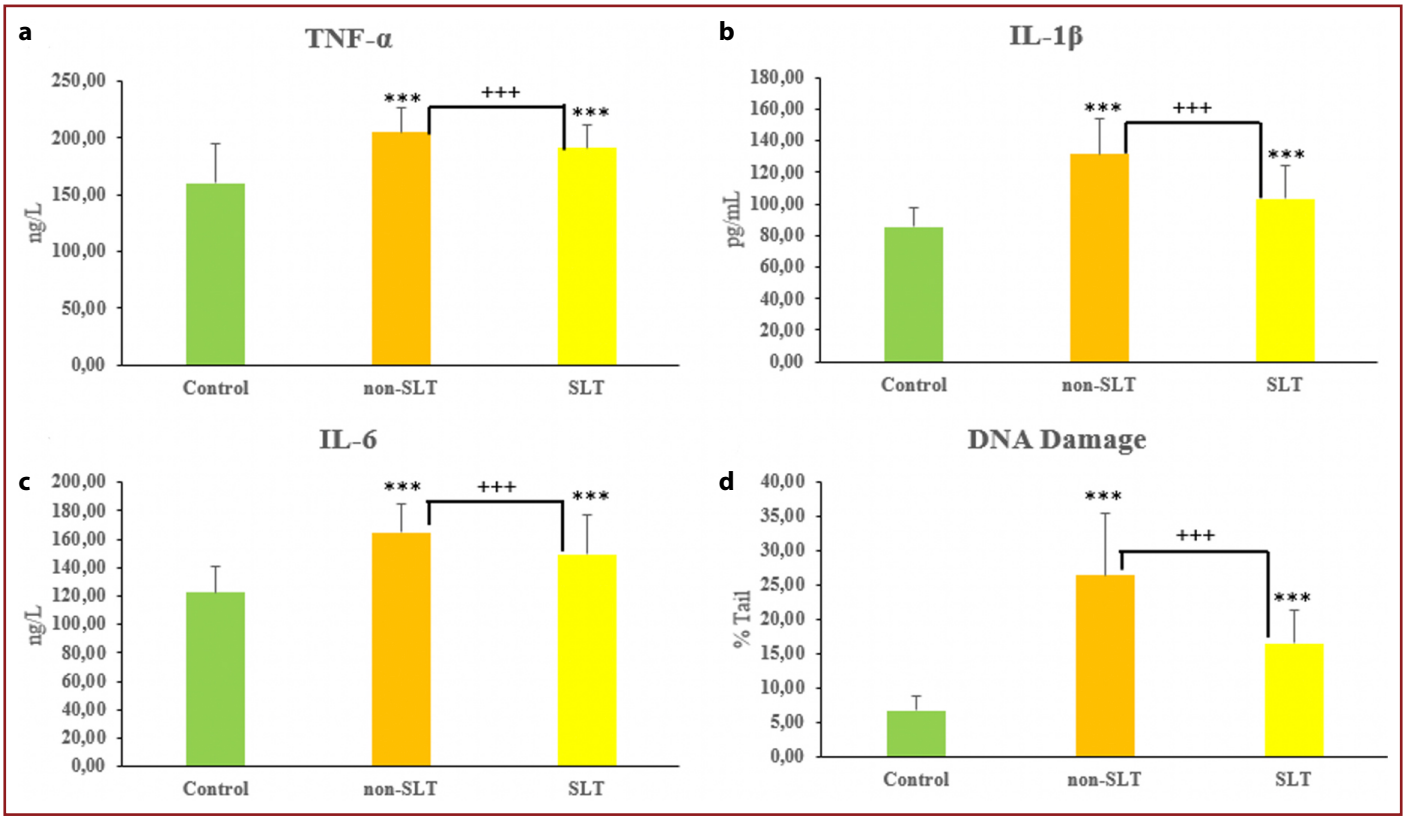

Figure 3. Those who did not receive SLT compared to healthy controls, (a) Tumor necrosis factor alpha (TNF-α), (b) interleukin-1 beta (IL-1β), (c) interleukin-6 (IL-6), and (d) DNA damage levels. (*p<0.05; **p<0.01, ***p<0.001); statistical difference between those who received SLT and those who did not. ($^{+}$p<0.05; $^{++}$p<0.01, $^{+++}$p<0.001); the difference between groups who received SLT and those who did not. The p<0.05 point was considered statistically significant.

SLT: Speech and language therapy.

groups had higher levels of dynamic DIS bonds compared to the healthy control group, no significant differences were observed between these groups.

Serum inflammatory cytokine levels and leukocyte DNA damage levels of those who received SLT, those who did not, and the healthy control group are shown in Figure 3. When compared to the healthy control group, TNF-α, IL-1β, IL-6, and DNA damage levels were found to be higher and statistically significant in the group that did not receive SLT. TNF-α, IL-1β, IL-6, and DNA damage levels were significantly decreased in the group that received SLT compared to the group that did not receive SLT (p<0.001).

Discussion

Language disorders refer to the difficulties that individuals have in spoken, written, or other types of communication skills, and delays or impairments in the acquisition and use of language. These impairments or delays can be seen in multiple components of the language at the same time, or they can be observed in a single component. Language disorders, which are more common in men, especially among children, can be seen in the preschool period with a rate of 5% and at school age with a rate of 3%[25,26].

Language disorders are classified according to the cause, symptom, and severity of the disorder. Language disorders, according to the cause, are divided into two categories: primary and secondary disorders. Language disorders according to their symptoms are given under the headings of comprehension and expression, form, content, and usage. Language disorders are classified according to their severity as mild, moderate, severe, and advanced[6].

SLI, which is not generally caused by a medical condition, is defined as a communication disorder that occurs in children. Although they have no neurological, hearing loss, mood, oral-motor, and intelligence-related problems or there is no lack of any social input that may affect their language acquisition, communication disorders are observed in children with SLI. The severity and symptoms of these disorders may not be similar for all children. Some children may have problems with expressive language, some with receptive language, and some children with both. Contrary to the communication

problems seen in other developmental disorders, the reason for the language deficiencies in children with SLIs has not been fully revealed[1,6].

The primary objectives of this study were to investigate the relationship between genetic factors and the etiology of SLI in children, to shed light on the impact of oxidative stress and inflammation on SLI, and to discern any differences between the healthy control group and the groups receiving or not receiving SLT.

SLI is most common in 5-year-old children. For this reason, the participant group of the study consists of 40 children aged 5 years who were diagnosed with an SLI by a speech and language therapist, and the control group comprises 20 children with typical development with no health problems, having similar demographic characteristics to those with SLI.

When the findings obtained in the study were interpreted, it was determined that there was DNA damage in children with SLIs. This result is consistent with previous studies in the field. Studies show that SLI can be seen in children with a family history of language disorders. The SLI seen in monozygotic and dizygotic twins also supports the data obtained. In addition, studies in the field show that the view that the FOXP1, FOXP2, CNTNAP2, ATP2C2, and CMIP gene structures may be related to linguistic problems in children is in line with the findings[21,27,28].

Oxidative stress and inflammation levels were significantly higher in children with SLIs. In the comparison of the data obtained between the groups, a significant difference was determined between the children with SLI who had never received SLT before and the healthy control group. Significant differences were also found between children with a diagnosis of SLI who had previously received SLT, and children with SLI who had never received SLT. Accordingly, it was determined that the oxidative stress, inflammation, and DNA damage levels of children with SLI who received SLT support were found to be significantly lower than the group with SLI who did not receive SLT.

Limitations of the Study

Being conducted with participants aged five, which is the age group where SLI is most prevalent, and therefore not revealing the differences in other age groups are the study's shortcomings.

Conclusions

This study proves that genetic factors play a significant role in understanding the cause of SLI in children. It also reveals that oxidative stress and inflammation play an important role in SLI. It has also been determined that DNA damage, oxidative stress, and inflammation levels change positively when children with SLIs receive SLT support.

In future studies on the subject, it is recommended that researchers expand the age group and the number of participants, examine DNA damage, oxidative stress, and inflammation, investigate the dominant language genes, and provide detail on the individual differences of the participants along with the linguistic problems they experience.

Ethics Committee Approval: The study was approved the University of Health Sciences Hamidiye Scientific Research Ethics Committee (no: 22/513, date: 04/11/2022).

Peer-review: Externally peer-reviewed.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept: B.S., H.B., S.A., E.M.G., H.S.P.; Design: B.S., H.B., S.A., E.M.G., H.S.P.; Supervision: B.S., H.B., S.A., E.M.G., H.S.P.; Fundings: B.S., H.B., E.M.G.; Materials: B.S., H.B., E.M.G.; Data Collection or Processing: B.S., H.B., S.A., E.M.G., H.S.P.; Analysis or Interpretation: B.S., S.A., E.M.G.; Literature Search: B.S., H.B., S.A., E.M.G., H.S.P.; Writing: B.S., H.B., S.A., E.M.G., H.S.P.; Critical Review: B.S., H.B., S.A., E.M.G., H.S.P.

Conflict of Interest: None declared.

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

References

1. Dollaghan CA. Taxometric analyses of specific language impairment in 6-year-old children. J Speech Lang Hear Res 2011;54:1361–71. [CrossRef]
2. Toğram B, Maviş İ. Aileler, öğretmenler ve dil ve konuşma terapistlerinin çocuklardaki dil ve konuşma bozukluklarına yönelik tutum ve bilgilerinin değerlendirilmesi. Ank Univ Egit Bilim [Article in Turkish] 2009;10:71–85. [CrossRef]
3. Lust BC. Child language. New York: Cambridge: Cambridge University Press; 2006.
4. McCauley RJ. Assessment of language disorders in children. 1st ed. New York: Psychology Press; 2000.
5. Watkins RV, Kelly DJ, Harbers HM, Hollis W. Measuring children's lexical diversity: Differentiating typical and impaired language learners. J Speech Hear Res 1995;38:1349–55. [CrossRef]
6. Turan F. İletişim dil ve konuşma bozukluğu olan çocuklar. In: Metin N, editor. Özel Gereksinimli Çocuklar. Ankara: Anı Yayıncılık; 2018. p.179–226.
7. Beitchman JH, Brownlie E. Language disorders in children and adolescents. Göttingen: Hogrefe Publishing; 2014.
8. Tomblin JB, Records NL, Buckwalter P, Zhang X, Smith E, O'Brien M. Prevalence of specific language impairment in kindergarten children. J Speech Lang Hear R 1997;40:1245–60. [CrossRef]
9. Fortunato-Tavares T, Andrade CRF, Befi-Lopes D, Limongi SO, Fernandes FDM, Schwartz RG. Syntactic comprehension

and working memory in children with specific language impairment, autism or Down syndrome. Clin Linguist Phon 2015;29:499–522. [CrossRef]
10. Owens R. Language disorders: A functional approach to assessment and intervention. 6th ed. London: Pearson Education; 2004.
11. Prelock PA, Hutchins TL. Children with specific language impairment. In: Volkmar FR, editor. Clinical guide to assessment and treatment of communication disorders. 1st ed. New York: Springer International Publishing; 2018. p.53–64. [CrossRef]
12. Marinis T. On the nature and cause of specific language impairment: A view from sentence processing and infant research. Lingua 2011;121:463–75. [CrossRef]
13. Hick RF, Joseph KL, Conti-Ramsden G, Serratrice L, Faragher B. Vocabulary profiles of children with specific language impairment. Child Lang Teach Ther 2002;18:165–80. [CrossRef]
14. Rescorla L, Lee E. Language impairement in young children. In: Layton TL, Crais ER, Watson LR, editors. Handbook of early language impairement in children. New York: Delmar Publishers; 2000.
15. Bishop DVM. What causes specific language impairment in children? Curr Dir Psychol Sci 2006;15:217–21. [CrossRef]
16. Watkins R, Rice ML. Specific language impairment in children. Baltimore: Brookes Publishing Company; 1994.
17. Korkmaz B. Dil ve beyin; Çocuklarda dil ve konuşma bozuklukları. İstanbul: Yüce Yayınları; 2005.
18. Owens RE. Language development: An introduction. 9th ed. London, England: Pearson; 2012.
19. Ervin M. SLI: What we know and why it matters. ASHA Lead 2001;6:4–31. [CrossRef]
20. Hegde MN, Maul CA. Language disorders in children : An evidence-based approach to assessment and treatment. London, England; Pearson; 2006.
21. Newbury DF, Fisher SE, Monaco AP. Recent advances in the genetics of language impairment. Genome Med 2010;2:6.
22. Karasar N. Bilimsel araştırma yöntemi: Kavramlar ilkeler teknikler. 38th edition. Ankara: Nobel Akademik Yayıncılık; 2021.
23. Singh NP, McCoy MT, Tice RR, Schneider EL. A simple technique for quantitation of low levels of DNA damage in individual cells. Exp Cell Res 1988;175:184–91. [CrossRef]
24. Beyaztas H, Aslanoglu CE, Yıldız A, Guler EM. Providing preclinical prediction of diabetic retinopathy via oxidative stress levels. Rom J Diabetes Nutr Metab Dis 2022: 29:236–44.
25. Beitchman JH, Cantwell DP, Forness SR, Kavale KA, Kauffman JM, Bernet W, et al. Practice parameters for the assessment and treatment of children and adolescents with language and learning disorders. J Am Acad Child Adolesc Psychiatry 1998;37:46–62. [CrossRef]
26. Sadock BJ, Sadock VA, Ruiz P. Kaplan and Sadock's synopsis of psychiatry: Behavioral sciences/clinical psychiatry. 11th ed. Philadelphia: Wolters Kluwer Health; 2015.
27. Leonard LB. Children with specific language impairment. 2nd ed. Cambridge: The MIT Press; 2017. [CrossRef]
28. Nation K. Developmental language disorders. Psychiatry 2005;4:114–7. [CrossRef]