Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2019;44(4):1208-1214
DOI: 10.17826/cumj.538984

ARAŞTIRMA / RESEARCH

Nörofibromatozis tip 1 tanılı hastalarda nöroradyolojik bulguların kognitif fonksiyonlara etkisi

Effect of neuroradiological findings on cognitive functions in patients with neurofibromatosis type 1

Gülen Gül Mert[1], Habibe Koç Uçar[2]

[1]Cukurova University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Neurology, Adana, Turkey
[2]Gazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Neurology, Ankara, Turkey

Cukurova Medical Journal 2019;44(4):1208-1214.

Abstract

Purpose: The aim of this study was to evaluate the clinical and radiological findings of children with Neurofibromatosis Type 1 (NF1), and to investigate the factors affecting cognitive functions.

Materials and Methods: Fifty-one patients who were diagnosed as NF1 in the Pediatric Neurology Clinic of Çukurova University Medical School were included in this study. Age, sex distribution, presence of family history, presence of parental consanguinity, intelligence tests, learning disabilities, presence of motor retardation, presence of autism, presence of attention deficit and hyperactivity disorder presence of behavior disorder, neuroimaging findings, seizure histories, and number of antiepileptic drugs used were evaluated retrospectively.

Results: Of the patients, 27 (50.9%) were female and 26 (49.1%) were male. Twenty-seven (50.9%) were hereditary, 26 (49.1%) were sporadic, while 8 (29.6%) of the hereditary patients were from the mother and 19 (70.4%) were from the father. A statistically significant relationship was found between the presence of T2 hyperintensity in cerebral magnetic resonance imaging (MRI) and female gender, presence of macrocephaly and mental retardation. Additionally, an important relationship was established between the presence of autism, and attention deficit hyperactivity disorder and mental retardation.

Conclusion: Although a relationship between clinical and radiological findings have been found, there are associations waiting to be clarified in patients with NF1 who are not included in the diagnostic criteria, such as macrocephaly.

Keywords: Neurofibromatosis Type 1, mental retardation, cognitive function, macrocephaly, autism

Öz

Amaç: Bu çalışmada, Nörofibromatozis Tip 1 (NF1) tanısıyla takip edilen çocukların klinik ve radyolojik bulgularının değerlendirilmesi, kognitif fonksiyonlara etki eden faktörlerin araştırılması amaçlandı.

Gereç ve Yöntem: Bu çalışmaya 2 Çukurova Üniversitesi Tıp Fakültesi Çocuk Nöroloji Polikliniğinde NF1 tanısı alan, en az 1 yıllık izlemi olan 53 hasta alındı. Hastaların yaşı, cinsiyet dağılımı, aile öyküsü varlığı, anne-baba arasında akrabalık varlığı, zeka testleri, öğrenme güçlüğü, motor gerilik varlığı, otizm varlığı, dikkat eksikliği ve hiperaktivite bozukluğu varlığı, davranış bozukluğu varlığı, nörogörüntüleme bulguları, nöbet öyküleri, kullandığı antiepileptik ilaç sayıları açısından retrospektif olarak değerlendirildi.

Bulgular: Hastaların 27'si (%50.9) kız, 26'sı (%49.1) erkekti. Yirmiyedisi (%50.9) herediter, 26'sı (%49.1) sporadik geçişliyken, herediter olanların 8'i (%29.6) anneden, 19'u (%70.4) babadan geçişli idi. Serebral manyetik rezonans görüntülemede (MRG) T2 hiperintensitesi varlığı ile hastaların kız cinsiyette olması, makrosefali varlığı ve mental retardasyon varlığı arasında istatistiksel olarak anlamlı bir ilişki saptandı. Ayrıca otizm varlığı ve dikkat eksikliği hiperaktivite bozukluğu ile mental retardasyon arasında önemli bir ilişki saptandı.

Sonuç: Klinik ve radyolojik olarak bazı bulgular arasında ilişki varlığı saptansa da oluş mekanizmaları bilinmemekle birlikte, makrosefali gibi tanı kriterleri içinde yer almayan ancak NF1'li hastalarda aydınlatılmayı bekleyen birliktelikler mevcuttur.

Anahtar kelimeler: Nörofibromatozis Tip 1, mental retardasyon, kognitif fonksiyon, makrosefali, otizm

Yazışma Adresi/Address for Correspondence: Dr. Gülen Gül Mert, Cukurova University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Neurology, Adana, Turkey. E-mail: dr_gulen@hotmail.com
Geliş tarihi/Received: 07.01.2019 Kabul tarihi/Accepted: 12.03.2019 Çevrimiçi yayın/Published online: 10.09.2019

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a common autosomal dominant neurodevelopmental disorder affecting approximately 1 in 3500 individuals[1]. Approximately one-half of the cases are familial (inherited). The remainder are the result of de novo (sporadic) mutations. NF1 is due to mutations in the NF1 gene, located at chromosome 17q11.2. Neurofibromin, the protein product encoded by the gene, is expressed in many tissues, including brain, kidney, spleen, and thymus. Neurofibromin plays an important role in the regulation of synaptic plasticity and signal transformation, memory and learning[2]. Clinical features of NF1 include café au-lait spots, skin fold freckling, Lisch nodules, neurofibromas, optic pathway gliomas and bone lesions[3,4]. Several brain abnormalities have been observed in NF1, including neoplasms, T2 hyperintensities (T2H), macrocephaly, and abnormalities in white matter (WM) integrity[5]. Focal areas of increased signal intensity were first identified on T2-weighted magnetic resonance imaging (MRI) of the brain in children with NF1. The term "unidentified bright objects" (UBOs) is discouraged because it can be upsetting to parents[6].

Cognitive deficits are reported in up to 80% of school-aged children with NF1. However, the intelligence quotient (IQ) scores of these patients are within the normal range or only slightly lower compared with unaffected sibling controls[7]. More recently, there has been increased interest in social outcomes in children with NF1 and there is a growing body of literature reporting a range of social and behavioural difficulties. Data are conflicting on the relationship between NF-associated bright spots and cognitive function. In one report, 25 of 40 children (62%) with NF1 had bright spots present on MRI. These patients had significantly lower IQ and language scores and impaired visuomotor integration and coordination compared with children without them[8]. In another study, these lesions were not associated with intellectual impairment[9]. In our study, we investigated the factors affecting cognitive functions in NF1 patients.

MATERIALS AND METHODS

Fifty-three patients with NF1 who were followed-up regularly between January 2012 and December 2018 at the Pediatric Neurology Clinic of Çukurova University Faculty of Medicine were included in the study. At the 78th meeting of Çukurova University Faculty of Medicine Non-Interventional Clinical Researches Ethics Committee on March 8, 2019, approval was given by the ethics committee with the decision No. 86 and consent was given by the families of the patients to participate in the study.

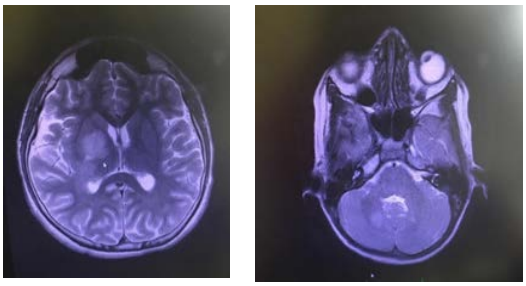

Figure 1. Axial T2 sequence. Hyperintensities in globus pallidus, thalamic, cerebellum.

In the Pediatric Neurology Outpatient Clinic, NF1 is diagnosed according to the criteria of American National Institutes of Health (1988) by taking clinical and radiological findings into account[10]. Seven patients with inadequate file information and inadequate follow-up were excluded from the study. The cases were evaluated by a pediatric neurologist in terms of the findings of NF1.

Age, sex distribution, presence of family history, presence of parental consanguinity, neurocutaneous findings, intelligence tests, learning disabilities, presence of motor retardation, presence of autism, presence of attention deficit and hyperactivity disorder, presence of behavior disorder, neuroimaging findings, seizure histories, and number of antiepileptic drugs used were evaluated retrospectively.

While measuring the head circumference, the measuring tape was placed on the most protruding point of the head at the back, parietal regions on the sides and a line passing over the glabella. The obtained data was evaluated by using percentile curves for Turkish children developed by Neyzi et al. and the main percentile curves proposed by the WHO for international use, since the head percentile curves for Turkish children were only available up to 2 years of age. Macrocephaly was accepted as 95th percentile (or mean ± 2 SS)[11].

Intelligence tests were performed by expert psychologists using appropriate test measures. Stanford-Binet was used for children aged 2 to 6

years, and WISC-R scale was used for children 6 years and older. IQ value between 70-79 was considered as border level intelligence, 80-89 as dull normal, 90-109 as normal; below 70 as mental retardation (MR), 50-69 as mild MR, 35-49 as moderate MR, 20-34 as severe MR; and dull normal and border intelligence, i.e. between 70-90, were categorized as learning disabilities.

Seizure history, seizure types and the number of antiepileptic drugs the patients used were recorded. History of epilepsy and epileptic seizures were determined according to 1981 ILAE classification[12]. Motor retardation of the cases was determined by history from the family and examination.

Table 1. Demographic findings of patients with neurofibromatosis type 1

Parameters		Number (n)	Percentage (%)
Sex	Male	26	49.1
	Female	27	50.9
Age range	<10	19	35.8
	>10	34	64.2
Hereditary family history	Hereditary	27	50.9
	Sporadic	26	49.1
Genetic transmission	Maternal	8	29.6
	Paternal	19	70.4
Parental consanguinity	Yes	15	28.3
	No	38	71.7
Cafe-au-lait	Yes	53	100
	No	0	0
Solitary neurofibroma	Yes	8	15.1
	No	45	84.9
Plexiform neurofibroma	Yes	3	5.7
	No	50	94.3
Lisch nodule	Yes	24	45.3
	No	29	54.7
Optic pathway glioma	Yes	11	20.8
	No	42	79.2
Axillary freckling	Yes	37	69.8
	No	16	30.2
Inguinal freckling	Yes	15	28.3
	No	38	71.7
Bone dysplasia	Yes	5	9.4
	No	48	90.6
Pathological fracture	Yes	1	1.9
	No	52	98.1
Pseudoarthrosis	Yes	2	3.8
	No	51	96.2
Kyphoscoliosis	Yes	6	11.3
	No	47	88.7
Cerebral MRI lesion	Yes	35	66.0
	No	18	34.0
Spinal MRI abnormality	Yes	0	0
	No	53	100
Abdominal USG	Abnormal	0	0
	Normal	53	100
Hypertension	Yes	1	1.9
	No	52	98.1

Table 2. The relationship between T2 hyperintensity and cognitive functions in cerebral MRI in patients with neurofibromatosis type 1

		Signal Changes on MRI				
		Yes		No		
		(n)	(%)	(n)	(%)	p
Sex	Female	22	61.1	5	29.4	**0.031**
	Male	14	38.9	12	70.6	
Hereditary trait	Hereditary	17	47.2	10	58.8	0.430
	Sporadic	19	52.8	7	41.2	
Macrocephaly	Yes	15	41.7	2	11.8	**0.029**
	No	21	58.3	15	88.2	
Mental retardation	Yes	16	44.4	1	5.9	**0.005**
	No	20	55.6	16	94.1	
Autism	Yes	5	13.9	0	0.00	0.163
	No	31	86.1	17	100.0	
Attention Deficit and Hyperactivity Disorder	Yes	9	25.0	3	17.6	0.730
	No	27	75.0	14	81.4	
Motor development retardation	Yes	4	11.1	2	11.8	1.00
	No	32	88.9	15	88.2	
Epilepsy	Yes	6	16.7	1	5.9	0.408
	No	30	83.3	16	94.1	

Statistical analysis

All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation, and as median and minimum-maximum, where appropriate. Chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Shapiro Wilk test. For comparison of continuous variables between two groups, the Student's t-test or Mann-Whitney U test were used depending on whether the statistical hypotheses were fulfilled or not. (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.)

RESULTS

Of the 53 patients included in the study with a neurofibromatosis type 1 diagnosis, 27 (50.9%) were female and 26 (49.1%) were male. The mean age was 11.32 ± 3.6 years and the mean follow-up period was 3.65 ± 2.1 years. 28.3% of the patients had consanguinity and 50.9% had family history of NF1. Clinical findings were determined as the following: cafe-au-lait spots (100%), axillary freckles (69.8%), inguinal freckling (28.3%), solitary neurofibroma (15.1%), plexiform neurofibroma (5.7%), pseudoarthrosis (3.8%), bone dysplasia (9.4%), Lisch nodule (45.3%) and optic pathway glioma (20.8%), presence of T2H in cerebral MRI (66.0%), learning disability (32.1%), and epilepsy (13.2%) (Table 1) (Figure 1). Seventeen patients (32.1%) had IQ <70, 16 patients (30.2%) had between 70 and 90, and 20 patients (37.7%) had >90. A statistically significant relationship was found between the presence of T2 hyperintensity in cerebral MRI and female gender, presence of macrocephaly and mental retardation ($p<0.05$). The relationship between cerebral MRI findings and motor development retardation, presence of epilepsy, attention deficit hyperactivity disorder and autism were not statistically significant ($p>0.05$). An important relationship was established between the presence of autism, and attention deficit hyperactivity disorder and mental retardation ($p<0.05$) (Table 2).

DISCUSSION

Neurofibromatosis type 1 is a disorder caused by mutations in the neurofibromin gene, which affects the synthesis of a protein widely expressed and involved in many vital pathways. Neurofibromin is involved in Ras GTPase activation. Ras GTPase downregulates Ras, a family of proteins involved in

cell proliferation and differentiation. Thus, lack of neurofibromin due

to NF1 gene defects may lead to a lack of inhibitory control over Ras, resulting in increased cell formation, migration and differentiation[2,6]. Its presentation is characterized by multiple *cafĕ-au-lait* spots, skin-fold freckling, cognitive and behavioral deficits, and benign or malignant tumors[13]. In a study by Ferner RE et al. in 2006, the initial presentation age and frequency of major clinical symptoms for NF1 were defined and reported as follows: cafe-au-lait 99% and 0-12 years of age, freckling 85% 3 years-adolescent, lisch nodule 90-98%, >3 years old, cutaneous neurofibroma >99% and >7 years of age, plexiform neurofibromas 30-50% and 0-18 years, pseudoarthrosis 2% and 0-3 years, mental retardation, IQ <70, 4-8% and at birth, difficulty understanding 30-60% and at birth, epilepsy 6-7% and throughout life, optic pathway gliom (OPG) as 15% and 0-7 years of age[3]. In our study, these rates were determined as follows: cafe-au-lait spots (100%), axillary freckling (69.8%), inguinal freckling (28.3%), solitary neurofibroma (15.1%), plexiform neurofibroma (5.7%), pseudoarthrosis (3.8%), bone dysplasia (9.4%), Lisch nodule (45.3%) and optic pathway glioma (20.8%), presence of T2H in cerebral MRI (66.0%), learning disability (32.1%),and epilepsy (13.2%) (Tables 1-2). Differences in the prevalence of some clinical findings may be due to differences in the size of patient populations, increase in phenotypic expression in NF with age, and as is well known, factors such as genetic heterogeneity.

NF1 patients may have various neurological complications. Seizures are approximately twice as common in patients with NF1 compared with the general population. Approximately 6-10% of patients have epileptic seizures. Seizures can be of any type and begin at any age. Focal seizures may be due to an intracranial neoplasm. Thus, new seizures should prompt a repeat neuroimaging, even if previous imaging was normal[14]. Creange et al. in a study conducted in 1999 of 158 NF1 patients aged between 11 and 77 years of age, prevalance of epilepsy was 4%; in 2008, Karl McKeever et al. reported the prevalance of epilepsy as 4%, in a study of 75 NF1 patients, of children under 16 years of age; in the prevalence study conducted by Ferner RE et al in 2006, prevalance of epilepsy was reported to be 6-8% and they commented that epileptic seizures may be associated with cortical dysgenesis and may occur at any time in life[3,15,16]. In our study, epilepsy was found in 6 patients (13.2%) similar to the literature. Four of these patients (66.7%) had generalized tonic-clonic seizure, while one (33.3%) had complex partial seizure. Three of our patients had seizure control with a single antiepileptic, and two had control with double antiepileptic drugs. Three of our epilepsy patients also had macrocephaly. In all five epilepsy patients, there was no significant correlation with the increase in MRI signal. Therefore, currently the possibility of cerebral dysgenesis in the etiology of epilepsy remains valid. However, three of the patients had mental retardation (IQ<70) and the relationship between them was significant. We could not find any information in the literature about this relationship in NF 1 patients (Table 1). In addition, three patients with epilepsy were being followed up with autism, one with attention deficit hyperactivity disorder. This relationship was not statistically significant.

In addition to these clinical findings, NF1 is becoming increasingly recognized as a neurodevelopmental disorder conferring increased risk for several specific neurodevelopmental problems, including lowering of intellectual abilities, deficits in executive functioning, impaired visuospatial processing, and motor delays[17,18]. The cause of the learning disability in NF1 is unknown. Data are conflicting on the relationship between NF-associated bright spots and cognitive function. In one report, 25 of 40 children (62 percent) with NF1 had bright spots present on MRI[19]. These patients had significantly lower IQ and language scores and impaired visuomotor integration and coordination compared with children without them. In another study, the number of locations containing spots accounted for much of the lowering of IQ scores in NF1 patients compared with unaffected siblings[20]. In the study by Bruce et al., and in some other studies, it has been suggested that these hyperintense images detected in MRI will depend on gliosis or increase in the water content of myelin. Localization of these images has been reported as basal ganglion, internal capsule, brain stem and cerebellum. They are believed to be prone to disappearing over time. Although not highly predictive, the number and/or location of lesions may be associated with learning disability[13]. However, in a third series, these lesions were not associated with intellectual impairment[9]. In a study by Ramanjam et al., the rate of learning difficulty was found to be 70% in African children with NF1 and this ratio, which is higher than others in the literature, was tried to be explained by reasons such as poor socioeconomic level, bad nutrition, maternal

education and education system[21]. In our study, 22 (61.1%) of the patients with T2H of cerebral MRI were girls and this relationship was statistically significant. Of the female patients, 10 (37.1%) and of the male patients, 7 (26.9%) had an IQ score of <70. There was no statistically significant relationship between gender and mental retardation. It is suggested that gender may be a prognostic factor in NF1 patients. According to the results of these studies, neuronal deficits are more common in female patients and learning difficulties are more common in male patients[22]. Fifteen of 17 patients with macrocephaly (88.2%) had hyperintensity on their cerebral MRI, in T2-weighted sections, especially on the basal ganglia, cerebellum and brainstem. In addition, 12 of these patients (70.6%) had IQ<70 and 5 (13.9%) had an IQ score of 70-90. There was a statistically significant relationship between the presence of T2H on the cerebral MRI of the patients, female gender, presence of macrocephaly and the presence of mental retardation.

For more than 30 years, researchers and clinicians have reported significant attention problems in children with NF1. However, the link between attention and social competence deficits in children with NF1 remains unclear[23-25]. Huijbregts et al. presented in their study that T2H were identified in 66.7% (n = 10 of 15) of the patients; of whom 33.3% showed T2H in the thalamus, 40.0% in the cerebellum, 26.7% in the globus pallidus, 20.0% in the brainstem and cortical gray matter, 6.7% in the putamen and amygdala and 33.3% in the cerebral white matter. They reported no association between autism and attentional problems and presence of T2H. In our study, 9 out of 12 patients (75%) who were followed up due to attention deficit hyperactivity disorder, and all 5 patients followed up with autism had T2H on cerebral MRI. This relationship was not statistically significant, in accordance with the literature. In addition, our patients who were followed with the diagnosis of autism were IQ<70. There was a significant relationship between the presence of autism and mental retardation. We think that the diagnosis of NF1 patients is overlooked due to the partial absence of the hyperactivity phenotype, and we recommend that these patients be evaluated in detail by a child psychiatrist.

NF1 is a monogenic tumor-predisposition syndrome with various effects on neural structure and function, creating a wide variety of cognitive and behavioral abnormalities. Despite our wide knowledge concerning NF1, there are still numerous issues to be addressed. In patients with NF1, the relationship between the presence of T2H in the cerebral MRI and the neurocognitive functions is not clear, but it has been reported that there is an improvement in cognitive functions with the loss of these lesions in adults. In our study, we found that there was a significant relationship between the presence of T2H in cerebral MRI and mental retardation and the patient's macrocephaly. Future studies should combine multiple neuro-imaging techniques in order to provide a more complete picture of the neural substrates underlying cognitive and social functioning in NF1.

Yazar Katkıları: Çalışma konsepti/Tasarımı: GGM, HKU; Veri toplama: GGM, HKU; Veri analizi ve yorumlama: GGM, HKU ; Yazı taslağı: GGM; İçeriğin eleştirel incelenmesi: HKU; Son onay ve sorumluluk: GGM, HKU; Teknik ve malzeme desteği: GGM, HKU; Süpervizyon: HKU; Fon sağlama (mevcut ise): yok.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.
Teşekkür: Makaleye katkılarından dolayı Dr. Şakir Altunbaşak, Dr. Özlem Hergüner ve Duygu Kuşçu'ya teşekkür ederim.

Author Contributions: Concept/Design : GGM, HKU; Data acquisition: GGM, HKU; Data analysis and interpretation: GGM, HKU; Drafting manuscript: GGM; Critical revision of manuscript: HKU; Final approval and accountability: GGM, HKU; Technical or material support: GGM, HKU; Supervision: HKU; Securing funding (if available): n/a.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support
Acknowledgments: I would also like to extend my deepest gratitude to Dr. Şakir Altunbaşak, Dr. Özlem Hergüner, and Duygu Kuşçu, for their help in the study.

REFERENCES

1. Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A. 2010;152:327-32.
2. Ledbetter DH, Rich DC, O'Connell P, Leppert M, Carey JC. Precise localization of NF1 to 17q11.2 by balanced translocation. Am J Hum Genet. 1989;44:20-2.
3. Ferner RE, Huson SM, Thomas N, Moss C, Willshaw H, Evans DG et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet. 2007;44:81–8.
4. Beauchamp GR. Neurofibromatosis type 1 in children. Trans Am Ophthalmol Soc. 1995;93:445-72.
5. Violante IR, Ribeiro MJ, Silva ED, Castelo-Branco M. Gyrification, cortical and subcortical morphometry in neurofibromatosis type 1: an uneven profile of developmental abnormalities. J Neurodev Disord. 2013;5:1-3.

6. Shen MH, Harper PS, Upadhyaya M. Molecular genetics of neurofibromatosis type 1 (NF1). J Med Genet. 1996;33:2-17.
7. Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology. 2005;65:1037-44.
8. North K, Joy P, Yuille D, Cocks N, Hutchins P. Specific learning disability in children with neurofibromatosis type 1: significance of MRI abnormalities. Neurology. 1994;44:878-83.
9. Rosenbaum T, Engelbrecht V, Krölls W, van Dorsten FA, Hoehn-Berlage M, Lenard HG. MRI abnormalities in neurofibromatosis type 1 (NF1): a study of men and mice. Brain Dev. 1999;21:268-73.
10. Savar A, Cestari MD. Neurofibromatosis Type 1: Genetics and clinical manifestations. Seminars in Ophthamology. 2008;23:45-51.
11. Neyzi O, Günöz H, Furman A, Bundak R, Gökçay G, Darendeliler F, Baş F. Türk çocuklarında vücut ağırlığı, boy uzunluğu, baş çevresi ve vücut kitle indeksi referans değerleri. Çocuk Sağlığı ve Hastalıkları Dergisi. 2008;51:1-14.
12. Engel J, Jr Chair. Report of the ILAE classification core group. Epilepsia. 2006;47:1558-68.
13. Korf BR. Clinical features and pathobiology of neurofibromatosis 1. J Child Neurol. 2002;17:573-7.
14. Ostendorf AP, Gutmann DH, Weisenberg JL. Epilepsy in individuals with neurofibromatosis type 1. Epilepsia. 2013;54:1810.
15. Creange A, Zeller J, Rostaing-Rigattieri S, Brugieres P, Wolkenstein P. Neurological complications of neurofibromatosis type 1 in adulthood. Brain. 1999;122:473-81.
16. Karl McKeever, Charles W Shepherd, Hilda Crawford, Patrick J Morrison. An epidemiological, clinical and genetic survey of Neurofibromatosis Type 1 in children under sixteen years of age. J Med 2008;77:160-3.
17. Adviento B, Corbin IL, Widjaja F, Desachy G, Enrique N, Rosser T et al. Autism traits in the RASopathies. Journal of Medical Genetics. 2014;51:10–2.
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th edn. Washington DC: American Psychiatric Association. 2013.
19. North K, Joy P, Yuille D, Cocks N, Mobbs E, Hutchins P et al. Specific learning disability in children with neurofibromatosis type 1: significance of MRI abnormalities. Neurology. 1994;44:878-83.
20. Denckla MB, Hofman K, Mazzocco MM, Melhem E, Reiss AL, Bryan RN et al. Relationship between T2-weighted hyperintensities (unidentified bright objects) and lower IQs in children with neurofibromatosis 1. Am J Med Genet. 1996;67:98-102.
21. Ramanjam V, Adnams C, Ndondo A, Fieggen G, Fieggen K, Wilmshurst J. Clinical phenotype of South African Children with neurofibromatosis 1. J Child Neurol. 2006;21:63-70.
22. Diggs-Andrews KA, Brown JA, Gianino SM, Rubin JB, Wozniak DF, Gutmann DH. Sex is a major determinant of neuronal dysfunction in neurofibromatosis type 1. Ann Neurol. 2014;75:309–16..
23. North K, Hyman S, Barton B. Cognitive deficits in neurofibromatosis 1. J Child Neurol 2002;17:605–12.
24. Garg S, Plasschaert E, Descheemaeker MJ, Huson S, Borghgraef M, Vogels A et al. Autism spectrum disorder profile in neurofibromatosis type I. J Autism Dev Disord. 2015;45:1649–57.
25. Hyman SL, Gill DS, Shores EA, Steinberg A, Joy P, Gibikote SV et al. Natural history of cognitive deficits and their relationship to MRI T2-hyperintensities in NF1. Neurology. 2003;60:1139–45.
26. Huijbregts SC, Loitfelder M, Rombouts SA, Swaab H, Verbist BM, Arkink EB et al. Cerebral volumetric abnormalities in Neurofibromatosis type 1: associations with parent ratings of social and attention problems, executive dysfunction, and autistic mannerisms. J Neurodev Disord. 2015;7:32-40.