

Neurofibromatosis Type 1 in Children: A Single-Center Experience

Ayşe Gonca Kaçar¹ ID, Burcu Kılınç Oktay¹ ID, Simge Çınar Özeli¹ ID, Süheyla Ocak¹ ID, Nilay Güneş² ID, Dilek Uludağ Alkaya² ID, Beyhan Tüysüz² ID, Hilmi Apak¹ ID, Tülin Tiraje Celkan¹ ID

¹Department of Pediatric Hematology and Oncology, İstanbul University-Cerrahpaşa School of Medicine, İstanbul, Turkey

²Department of Genetics, İstanbul University-Cerrahpaşa School of Medicine, İstanbul, Turkey

What is already known on this topic?

- Neurofibromatosis type 1 (NF-1) is a genetic disease that can cause tumor development in many parts of the body, especially the central nervous system.
- It is the most common form of neurocutaneous diseases and has an autosomal dominant pattern of inheritance.
- The most common clinical features are café au lait (CAL) spots, axillary freckling, neurofibromas, and Lisch nodules.

What this study adds on this topic?

- In NF-1 patients, sometimes the genotype-phenotype relationship cannot be established. It is thought that other mutations that have not yet been detected may also cause the disease.
- Vitamin D treatment is very important in NF-1 patients. It can prevent tumor development as well as protect patients from osteoporosis.
- Early diagnosis becomes important in patients with neurofibromatosis, as it will prevent the development of sequelae. Regular and multidisciplinary follow-up for neurologic and malignant features should be planned carefully in this patient group.

Corresponding author:

Ayşe Gonca Kaçar
goncakacar@gmail.com
Received: August 4, 2020
Accepted: October 22, 2020

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



ABSTRACT

Objective: Neurofibromatosis (NF) is the most common autosomal dominantly inherited neurocutaneous syndrome. The characteristic features of NF type 1 (NF-1) are café au lait spots, axillary and inguinal freckling, peripheral neurofibromas, optic pathway glioma, and Lisch nodules. The present study aimed to analyze the clinical features of children with NF-1.

Materials and Methods: In this study, the children with NF-1 diagnosed and followed-up in our center between 2000 and 2020 were retrospectively evaluated. Demographic and clinical features of patients were defined.

Results: The study group consisted of 52 patients. Of those, 25 were boys and 27 were girls. The children's median age at diagnosis was 5.9 years (1-15.8). Café au lait (CAL) spots and axillary/inguinal freckling were observed in 50 and 24 patients, respectively. Neurofibroma was present in 22 cases. Ten of the cohort had optic gliomas, and 39 of them had cranial hamartomas. Orthopedic complications such as scoliosis, tibial pseudoarthrosis, and osteoporosis were observed in 13 patients. Eleven children had neurocognitive disorders.

Conclusions: Early diagnosis is important in neurofibromatosis to prevent the complications of the disease. Also, neurological development and secondary malignancy follow-up should be done carefully in this group of patients.

Keywords: Child, inherited neurocutaneous syndrome, neurofibromatosis, optic glioma

INTRODUCTION

Neurofibromatosis type 1 (NF-1) is a genetic disease that predisposes to malignancies in many parts of the body, especially the central nervous system.^{1,2} It is the most common form of neurocutaneous diseases and has an autosomal dominant pattern of inheritance with a reported incidence of 1/3000 to 1/4000.² NF-1 has a wide clinical spectrum and can affect almost any organ. The disease might present with different clinical pictures in affected family members, and some of the findings might appear with increasing age. Therefore, it is a challenge to diagnose and follow-up for both patients and clinicians.^{2,3} The most common clinical features are café au lait (CAL) spots, axillary/inguinal freckling, neurofibromas, and Lisch nodules.

The children with NF-1 could admit to different departments with a wide range of symptoms like skin lesions, visual problems, seizures, learning difficulties, growth retardation, endocrine disorders, and unexplained hypertension. Although it has familial characteristics, the course and severity of the disease can be quite different within the same family. The diagnosis and follow-up of these children should be pursued with a multidisciplinary approach. This study aims to define the clinical characteristics and outcomes of NF-1 in children.

Cite this article as: Kaçar AG, Kılınç Oktay B, Çınar Özeli S, et al. Neurofibromatosis type 1 in children: A single-center experience. *Turk Arch Pediatr.* 2021; 56(4): 339-343.

METHODS

In this study, children who were followed up with the diagnosis of NF-1 between 2000 and 2020 at Istanbul University Cerrahpasa, Cerrahpasa Medical Faculty, Division of Pediatric Hematology and Oncology, were evaluated retrospectively.

Diagnostic criteria for NF-1 were defined by the National Institute of Health in 1987. The diagnosis was made in the presence of at least 2 of these criteria (Table 1).^{1,4,5} Files of 54 patients in total were examined; 2 patients were not included in our study because they did not fulfill the NF criteria, although NF-1 was considered clinically.

Ethics committee approval for this study was obtained from Istanbul University Cerrahpasa Medical Faculty Ethical Committee (Approval number: 83045809-6040102). This study has been carried out in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistical methods (mean, median) as well as qualitative data were compared using the chi-square test. $P < .05$ was considered as a significance level.

RESULTS

Demographic Characteristics

Fifty two patients were included in the study. Twenty four of these patients were referred with a diagnosis of NF-1, and twenty eight were patients who were evaluated in our outpatient clinic and diagnosed with NF-1. Twenty seven (52%) of the patients were female, and 25 (48%) were male. The median age of the patients at the time of the evaluation was 6.5 (1-17 years). The median age at diagnosis was 5.9 years (1-15.8 years). Stigmata of NF-1 was stated to be present in first-degree relatives of 75% of the patients. Genetic mutations were studied in 10 of these patients. About 30% of the patients had a family history of cancer among their first-degree relatives and 62% among their second-degree relatives.

Demographic and Clinical Findings

Six or more CAL spots were present in 96% of the patients. The number of spots in 2 patients under age 2 was less than 6. Lesion sizes were evaluated in 20 children, and an average

1. Six or more CAL spots larger than 5 mm before puberty and 15 mm after puberty
2. Freckling in the armpit or groin area
3. Two neurofibromas or one plexiform neurofibroma
4. Optic pathway glioma
5. Bone lesion
6. At least 2 iris hamartomas (Lisch nodules)
7. A first-degree relative diagnosed with NF-1
*At least 2 of these criteria should be used for diagnosis. CAL, Café au lait; NF-1, neurofibromatosis type 1.

Characteristics of Patients	Number of Patients, n	%
F/M	27/25	
Six or more CAL spots	50	96
Hamartomatous or hyperintense lesion in cranial MRI	39	84
CAL spots in first-degree relatives	39	75
Axillary/inguinal freckling	24	46
Lisch nodule	15	29
Cancer in the family	14	27
Skeletal findings	14	27
Dermal neurofibroma	13	25
Developmental and behavioral problems	11	21
Plexiform neurofibroma	9	17
Optic nerve glioma	10	17
Epilepsy	9	17
Skeletal findings	14	27

of 3.5 (± 0.7) cm was measured. One patient had a hyperpigmented lesion that measured approximately 20 cm, and this patient had an associated lumbosacral plexiform neurofibroma, mental retardation, and scoliosis. Sirolimus (mTOR inhibitor) was given to the patient, but the size of neurofibroma remained stable.

The clinical findings of the patients are shown in Table 2. Plexiform neurofibroma was detected in 9 patients: 3 in the orbital cavity and 6 in the medulla spinalis. Patients with neurofibroma in the eye had also simultaneous proptosis. One of these patients received chemotherapy, but no regression was achieved. Lisch nodules were present unilaterally and bilaterally in 10 and 5 children, respectively. Five of the patients had bilateral optic nerve gliomas; 5 of them were diagnosed with unilateral optic glioma. Systemic chemotherapy was given to 4 children since the visual acuity was affected (2 with bilateral and 2 with unilateral optic gliomas).

Neurological Findings

On neurological evaluation, 17% of the patients had epilepsy, and all these patients had hamartomas or hyperintense lesions in the cranial MRI. Most commonly, partial seizure (in 6 patients) was diagnosed in epileptic children. Response to antiepileptic treatment was good, but uncontrolled epilepsy was present in 1 child. About two-thirds (66%) of the patients had a developmental and/or behavioral problem, and mental/motor development retardation was the most common neurological deficit compared to their peers. In particular, fine motor and mathematical skills were under average (16 cases). School-age children received guidance for mood disorders (18 cases).

Orthopedic Problems

Skeletal problems were seen in 14 patients. Although scoliosis was the most common, 2 patients had osteoporosis, 2 patients had spinal cord anomalies, and 1 patient had pseudoarthrosis of the tibia. 25-OH Vitamin D level was examined in 7 of the patients, and the mean value was low (14.5 ng/mL).

Imaging

Forty-five patients were evaluated with cranial MRI. Hamartomatous or hyperintense lesions were observed in 39 (86%). These lesions were in the form of hyperintense foci in deep white matter, most commonly in the cerebellum, pons, and medulla oblongata. Hydrocephalus developed in 2 patients due to multiple lesions causing an obstruction on the fourth ventricle. Hamartomatous lesions were usually unilocular and mostly located in the thalamus and deep white matter of the temporal lobe.

Secondary Malignancy

Malignancy was diagnosed in 3 patients: in 2 cases, it was acute lymphoblastic leukemia (ALL), and in 1, it was genitourinary rhabdomyosarcoma (RMS). The first patient with leukemia had only CAL spots on admission, but additional diagnostic criteria for NF-1 developed during the long-term follow-up. The genetic analysis reported no known mutation for NF-1, but the patient was diagnosed as NF-1 on a clinical basis. The second patient with leukemia was later diagnosed with a peripheral nerve sheath tumor located in the parotid region, and then spindle cell carcinoma, and died of secondary malignancies. The patient with RMS had accompanying liver hemangioma and renal artery aneurysm and did not benefit from mTOR treatment (Table 3).

Treatment

One patient with bilateral optic nerve glioma received chemotherapy and surgery (enucleation of the right eye), and the other 3 received only chemotherapy. There was no progression in the patient who underwent surgery after treatment. Regression was observed in 2 of 3 patients who received chemotherapy and no objective response was noted in the third. Three patients had increased thickness and hyperintensity in the optic chiasm and were followed up without treatment, as their vision was not affected (Table 3).

DISCUSSION

Neurofibromatosis (NF) is the most common autosomal dominant inherited neurocutaneous syndrome with well-known clinical findings by physicians, and in fact, diagnosis is easy in the presence of clinical stigmata.¹ Our study group includes 52 patients with NF-1 diagnosis. Genetic studies were performed in 10 of our cases. The NF1 gene is a tumor suppressor gene that is located in the 11p12 region of chromosome 17, encoding a protein called neurofibromin. In 5% of individuals meeting the diagnostic criteria, a mutation in the NF1 gene may not be detected by molecular analysis because the NF1 gene is a large gene consisting of 58 exons and 12 425 base pairs, and more than 1500 different mutations have been identified in NF-1 cases to date.⁶⁻⁸ Therefore, the genotype-phenotype

relationship cannot be established in most cases. It is thought that other mutations that have not yet been detected may also cause the disease.⁹ Although one of our patients fulfilled the diagnostic criteria, no mutation was detected in the genetic test. In 2 patients who did not meet the criteria, there were 6 CAL spots, one had a grandfather diagnosed with NF-1, and the other had a hamartomatous lesion of 11 × 13 mm in the posterior of the right thalamus. These 2 patients were not included in the study group. Due to the different phenotypes that have emerged in recent years, the molecular genetics of the less common types of neurofibromatosis have been described.^{7,9} Therefore, only cases with CAL spots and/or neurofibromas are now considered neurofibromatosis, even if there is no family history.¹⁰⁻¹² We suggest that the patients with skin findings should be followed up carefully for the appearance of new features of the disease. Especially, the number and size of skin lesions may change significantly over time. In studies, the presence of family history is reported to be 39-54%.¹⁶ This rate was 56% in our patients, consistent with the literature. We had parents who were diagnosed after their children were diagnosed.

CAL spots are 0.5-50 cm flat, contoured, irregularly shaped macules. This is the most common finding in NF-1. However, these lesions can also be seen between 11 and 25% in the healthy population. Therefore, their number and size are important. They may be present at birth or develop within the first 2 years, and their color may fade as age progresses. They are not found on the scalp, eyebrows, palms, and soles. They lead to cosmetic problems and do not have malignant potential. Freckles are spots with a diameter of 1-3 mm, similar to CAL spots, generally unrelated to sun exposure on the axilla, groin, and base of the neck. Although axillary freckling is specific to NF-1, it usually appears after CAL and before dermal neurofibroma.¹⁵ In our study, 96% of the patients had 6 or more CAL spots, and 44% had axillary freckles.

Cutaneous and subcutaneous neurofibromas are benign soft-tissue tumors with gelatinous skin color. In advanced ages, they may increase in size and turn into papillomatosis form. They are mainly located on the trunk and could be painful or itchy in some cases. Rarely, malignant (sarcomatous) changes were reported in dermal neurofibromas. Therefore, fast-growing and painful lesions should be evaluated and removed surgically.^{13,14} In their study, Mc Gaughan et al.¹⁵ reported that 217 (66.3%) out of 365 patients with NF-1 had cutaneous and subcutaneous fibroma, and 32 (15%) had plexiform neurofibroma. In the present study, 13 patients (25%) had dermal neurofibroma and 9 (17%) had plexiform neurofibroma. We think that the low number of children with neurofibromas was associated with the younger median age of the study populations.

Table 3. Neurofibromatosis Patients with Malignancy

Disease	N	Bilateral	CT	CT Response	Surgery	RT	Follow-up without Treatment	Having Outcome
Optic nerve glioma	15	5	4	2	1	-	11	15
ALL	2	-	2	2	-	1200 cGy cranial	-	1
RMS	1	-	1	1	1	-	-	1

ALL, acute lymphoblastic leukemia; RMS, rhabdomyosarcoma; CT, chemotherapy.

Lisch nodules are harmless, asymptomatic iris hamartomas. They are seen as a dome-shaped light brown lesion on slit-lamp examination. They usually appear after CAL, but before neurofibromas, they are specific to NF-1, and are important in confirming the diagnosis.¹⁶ In the study by Abdolrahimzadeh et al.,¹⁷ Lisch nodules were observed with a rate of 22% up to the age of 5 and 96% for those aged 20 and over. Therefore, they are the most common finding of NF-1 in adults. Consistent with that study, they were seen in 15 patients (29%) in our study.

The most common pathology observed in cranial MRI in neurofibromatosis is hyperintense lesions seen in different locations in the T2A series. The characteristics of these lesions, which are called hamartomas, are that they are benign and there are no accompanying neurological problems.¹⁸ However, strict monitoring of the lesions is important considering the tendency for malignancies. The change in the character and shape of the lesions or the emergence of new neurological symptoms requires further investigation. In cases with uncontrolled epilepsy due to hamartomatous lesions, surgical intervention might be considered. The probability of a seizure in patients with neurofibromatosis is 3.8-6%, while epilepsy was diagnosed in 7% of children with NF-1.¹⁹ Mostly partial seizures (85%) are experienced depending on the localization of the hamartomatous lesion.

Macrocephaly can also be seen approximately in 40% of the NF-1 patients.¹⁹ Therefore, NF should be considered in the differential diagnosis of macrocephaly and hydrocephalus. In our study population, 5 patients (9.6%) had macrocephaly.

The most common brain tumor in patients with NF-1 is an optic pathway glioma.²⁰⁻²³ Optic pathway gliomas (OPG) are pilocytic astrocytomas that cause expansion of the optic nerve. It may involve optic chiasm, the opposite optic nerve, the thalamus, and the internal capsule. These lesions may cause the accumulation of cerebrospinal fluid and hydrocephalus by causing a ventricular outflow obstruction. The mean age of OPG occurrence in NF-1 is 4.9 years. While OPG is seen in MRI in an average of 20% of patients with NF-1, symptoms occur only in 1-5%. Rarely, spontaneous shrinkage can be seen.²¹ The most common symptoms are decreased visual acuity and peripheral vision loss. On ophthalmological examination, retinal vascular tortuosity, optic atrophy, strabismus, and pupillary abnormalities can be detected. Proptosis and precocious puberty may develop with the rapid growth of the tumor. In the current guidelines, annual visual examination is recommended until the age of 10 and every 2 years thereafter till 25 years of age.^{1,5} Routine cranial imaging is not recommended in asymptomatic children. Cranial MRI should only be considered for unexplained ophthalmological and neurological findings and in cases with precocious puberty. Early initiation of treatment is not recommended as it does not affect the clinical course. In the presence of clinical symptoms, chemotherapy (vincristine, carboplatin) is preferred as it has fewer side effects than radiotherapy, but it does not affect the long-term prognosis. Surgery can also be performed in patients with symptomatic unilateral lesions.²⁰⁻²³ Duffner et al.¹⁸ detected hamartoma in 62% of NF cases and non-hamartoma abnormal findings at a rate of 12%. Similarly, in our study, 84% had hamartomatous or hyperintense lesions, and 17% had optic nerve gliomas. Overall,

10 patients in our study had OPG with loss of visual acuity and adjuvant treatment in 4 cases. Regression was observed in 2 of 3 patients who received chemotherapy, the other patient's lesion did not regress. Three other patients had increased thickness and hyperintensity in the optic chiasm. Since their vision was not affected, these patients were followed up without treatment.

Malignant tumors are seen 4 times more frequently in NF-1 patients than in the healthy population.^{1,4,24} The frequency of low-grade gliomas, neurofibrosarcoma, pheochromocytoma, and childhood lymphocytic leukemia has increased.^{3,5,11,24} In our patients, ALL was found in 2 and vaginal RMS in one child. The prognosis of malignancies seen in patients with NF-1 is not different from the group without this genetic disease, therefore treatment modification is not required. All 3 cases had uneventful courses of chemotherapy. However, the child with RMS experienced a pathological fracture of the femur after the cessation of treatment in the presence of low serum 25-OH cholecalciferol.

In NF-1 patients, mental retardation, learning difficulties, language problems, attention and organization deficit, and psychosocial problems are more common than in the normal population.^{25,26} It has been proposed that the change in the expression of neurofibromin in the brain contributes to cognitive impairment. In the study of Gresham et al.,²⁷ learning disability was reported in 75% of 152 NF-1 cases. Neurodevelopmental disorders were also detected in 11 of our patients (21%) and the patients were followed up by pediatric neurology and psychiatry. Although it is stated that autism is observed 100-190 times more than normal in this patient group, no autistic child was found among our patients.²⁵

Bone anomalies are common in NF-1.^{1,5,28} Although dystrophic and idiopathic scoliosis is seen in 10% of patients, pseudoarthrosis can also be seen in the long bones.²⁷ Findings related to the skeletal system were found in 14 (27%) of our patients. Although scoliosis was the most common diagnosis, 2 patients had osteoporosis, 2 patients had spinal cord anomalies, and 1 patient had pseudoarthrosis of the tibia. Osteoporosis may be secondary to vitamin D deficiency in these patients and the mean serum level of 25-OH was found to be low (14.5 ng/mL) in our study. In the study by Lammert et al.,²⁹ vitamin D level was found to be low in patients with multiple dermal neurofibromas. The neurofibroma protein formed by the NF1 gene is a negative regulator of the RAS signaling pathway that ensures normal bone development. Vitamin D is thought to interact with neurofibromin at the cellular proliferation level. Vitamin D deficiency may decrease antiproliferative and proapoptotic effects and increase the tendency to tumor formation. Therefore, vitamin D treatment is very important in this group of patients. It can prevent tumor development as well as protect patients from developing osteoporosis.³⁰

CONCLUSION

Neurofibromatosis type 1 is a genetic disease with multisystemic involvement and an increased risk of malignancy. The management of the disease requires a careful multidisciplinary approach due to the high number of complications. Genetic counseling is an important component of management

for affected individuals and their families. The new drugs that will emerge when the pathogenesis of the disease is fully elucidated will be promising for both the disease itself and its complications.

Early diagnosis becomes important in patients with neurofibromatosis as it will prevent the development of sequelae. Regular and multidisciplinary follow-up for neurologic and malignant features should be planned carefully in this patient group.

Ethical Committee Approval: Ethics committee approval for this study was obtained from Istanbul University Cerrahpasa Medical Faculty Ethical Committee (Approval number: 83045809-6040102).

Informed Consent: Inform consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – T.T.C., A.G.K.; Design – T.T.C., A.G.K.; Supervision – T.T.C., A.G.K.; Funding – A.G.K.; Materials – A.G.K.; Data Collection and/or Processing – A.G.K., B.K.O., S.Ç.Ö., S.O., B.T., H.A., T.T.C., N.G., D.U.A.; Analysis and/or Interpretation – T.T.C., A.G.K.; Literature Review – T.T.C., A.G.K.; Writing – T.T.C., A.G.K.; Critical Review – T.T.C., A.G.K.

Acknowledgment: I would like to thank all my patients who helped me to accomplish this study.

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

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

REFERENCES

- Kresak JL, Walsh M. Neurofibromatosis: a review of NF1, NF2, and schwannomatosis. *J Pediatr Genet.* 2016;5:98-104. [CrossRef]
- Cimino PJ, Gutmann DH. Neurofibromatosis type 1. *Handb Clin Neurol.* 2018;148:799-811. [CrossRef]
- Ly KI, Blakeley JO. The diagnosis and management of neurofibromatosis type 1. *Med Clin North Am.* 2019;103:1035-1054. [CrossRef]
- Hirbe AC, Gutmann DH. Neurofibromatosis type 1: a multidisciplinary approach to care. *Lancet Neurol.* 2014;13:834-843. [CrossRef]
- Anderson JL, Gutmann DH. Neurofibromatosis type 1. *Handb Clin Neurol.* 2015;132:75-86. [CrossRef]
- Gutmann DH. Exploring the genetic basis for clinical variation in neurofibromatosis type 1. *Expert Rev Neurother.* 2016;16:999-1001. [CrossRef]
- Ferner RE, Gutmann DH. Neurofibromatosis type 1 (NF1): diagnosis and management. *Handb Clin Neurol.* 2013;115:939-955. [CrossRef]
- McKeever K, Shepherd CW, Crawford H, Morrison PJ. An epidemiological, clinical, and genetic survey of neurofibromatosis type 1 in children under sixteen years of age. *Ulster Med J.* 2008;77:160-163.
- Atik T, Çoğulu Ö, Özkinay F. Nörofibromatozis tip 1'de genetik danışmanlık. *J Pediatr Res.* 2014;1:152-154.
- Valero MC, Martín Y, Hernández-Imaz E, et al. A highly sensitive genetic protocol to detect NF1 mutations. *J Mol Diagn.* 2011;13:113-122. [CrossRef]
- Upadhyaya M, Cooper DN. *Neurofibromatosis type 1. From Genotype to Phenotype.* Oxford: Bios Scientific; 1998:21-38.
- Abeliovich D, Gelman-Kohan Z, Silverstein S, et al. Familial café-Au-lait spots: a variant of neurofibromatosis type 1. *J Med Genet.* 1995;32:985-986. [CrossRef]
- Miettinen MM, Antonescu CR, Fletcher CDM, et al. Histopathologic evaluation of atypical neurofibromatous tumors and their transformation into malignant peripheral nerve sheath tumor in neurofibromatosis 1 patients—a consensus overview. *Hum Pathol.* 2017;67:1-10. [CrossRef]
- Rad E, Tee AR. Neurofibromatosis type 1: fundamental insights into cell signaling and cancer. *Semin Cell Dev Biol.* 2016;52:39-46. [CrossRef]
- McGaughan JM, Harris DI, Donnai D, et al. A clinical study of type 1 neurofibromatosis in northwest England. *J Med Genet.* 1999;36:197-203.
- Kinori M, Hodgson N, Zeid JL. Ophthalmic manifestations in neurofibromatosis type 1. *Surv Ophthalmol.* 2018;63:518-533. [CrossRef]
- Abdolrahimzadeh S, Plateroti AM, Recupero SM, Lambiase A. An update on the ophthalmologic features in the phakomatoses. *J Ophthalmol.* 2016;2016:3043026. [CrossRef]
- Duffner PK, Cohen ME, Seidel FG, Shucard DW. The significance of MRI abnormalities in children with neurofibromatosis. *Neurology.* 1989;39:373-378. [CrossRef]
- Çarman KB, Coşkun Yazar C, Ekici A, et al. Nörofibromatozis tip 1: 49 olgunun değerlendirilmesi. *Haydarpasa Numune Med J.* 2017;57:157-160.
- Listernick R, Louis DN, Packer RJ, Gutmann DH. Optic pathway glioma in children with neurofibromatosis type 1: a consensus statement from the Optic Pathway Glioma Task Force. *Ann Neurol.* 1997;41:143-149. [CrossRef]
- Parazzini C, Triulzi F, Bianchini E, et al. Spontaneous involution of optic pathway lesions in neurofibromatosis type 1: serial contrast evaluation. *Am J Neuroradiol.* 1995;16:1711-1718.
- Freret ME, Gutmann DH. Understanding vision loss from optic pathway glioma in neurofibromatosis type 1. *J Neurosci Res.* 2019;97:45-56. [CrossRef]
- Campan CJ, Gutmann DH. Optic pathway gliomas in neurofibromatosis type 1. *J Child Neurol.* 2018;33:73-81. [CrossRef]
- Peltonen S, Kallionpää RA, Rantanen M, et al. Pediatric malignancies in neurofibromatosis type 1: a population-based cohort study. *Int J Cancer.* 2019;145:2926-2932. [CrossRef]
- Torres Nupan MM, Velez Van Meerbeke A, López Cabra CA, Herrera Gomez PM. Cognitive and behavioral disorders in children with neurofibromatosis type 1. *Front Pediatr.* 2017;5:227. [CrossRef]
- Acosta MT, Bearden CE, Xavier F, et al. The learning disabilities network (LeaDNet): using neurofibromatosis type 1 (NF1) as a paradigm for translational research. *Am J Med Genet A.* 2012;158A:2225-2232.
- Gresham FM, MacMillan DL, Bocian KM. Learning disabilities, low achievement, and mild mental retardation: more alike than different? *J Learn Disabil.* 1996;29:570-581. [CrossRef]
- Leppävirta J, Kallionpää RA, Uusitalo E, et al. Congenital anomalies in neurofibromatosis 1: a retrospective register-based total population study. *Orphanet J Rare Dis.* 2018;13:5. [CrossRef]
- Lammert M, Friedman JM, Roth HJ, et al. Vitamin D deficiency associated with number of neurofibromas in neurofibromatosis 1. *J Med Genet.* 2006;43:810-813. [CrossRef]
- Schnabel C, Jan KJ, Friedman M, et al. Effect of vitamin D₃ treatment on bone density in neurofibromatosis 1 patients: a retrospective clinical study. *Joint Bone Spine.* 2013;3:315-319.