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Neurofibromatosis: Evaluation of Clinical Features of 39 Cases

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ABSTRACT

Objective: Our study aims to evaluate the clinical findings of childhood neurofibromatosis type 1 cases.

Material and Methods: The clinical features of childhood patients who were followed up and treated by Pamukkale University Faculty of Medicine, Department of Pediatric Neurology between 2015 and 2023 were evaluated retrospectively.

Results: 39 children were included in the study. Twenty-one of the cases were male and 18 were female. The mean age was 11.71±4.05 years. 11 (28.2%) patients had a family history of neurofibromatosis. Lisch nodule was seen in 14 patients, and axillary freckling was seen in 21 patients. Six of the cases had neurofibroma. Plexiform neurofibroma was not present in any of the cases. Four children had scoliosis. Nine of the cases had learning disabilities.

Conclusion: The symptoms, signs, and complications of the cases in our study are consistent with the literature. It was thought that the low number of complications was due to the young age of the cases. In this study, we emphasized the importance of early recognition of NF-1 in terms of informing families about the disease and preventing treatable complications with regular clinical follow-up of these children.

Keywords: Child; neurofibromatosis type 1, neurofibroma, Cafe au lait

INTRODUCTION

Nofibromatoses are a group of diseases in which nerve sheath tumors are seen. Neurofibromatosis consists of 3 groups of diseases: Neurofibromatosis Type 1 (NF-1), Neurofibromatosis Type 2 (NF-2), and schwannomatosis. NF-1 type, which is the most common neurocutaneous disease, is autosomal dominant, and its incidence is reported as 1/3000-1/4000 (1). The NF-1 gene has been cloned in the 11p12 region of the 17th chromosome, this gene encodes a tumor suppressor protein called Neurofibromin. Today, more than 1500 mutations specific to the NF-1 gene have been reported (2). One of the reasons for tumor formation in NF1 is explained by the '2 hit hypothesis'. With 'first hit', one of the alleles is structurally inactivated. With the 'second hit', loss of heterozygosity develops as a result of a somatic germline mutation in the other allele (3). Since NF-1 is a disease that can affect many systems, its findings vary. Cafe au late, Lisch nodules, neurofibromas, axillary and inguinal freckles, and hamartomatous of the brain are quite common. NF-1 patients may have learning difficulties, endocrine disorders, bone defects, nutritional problems, and additional problems such as hypertension. Disease symptoms may differ between patients as well as among affected individuals within the same family (4).

MATERIAL AND METHODS

In this study; File information of patients with NF1 who applied to Pamukkale University Pediatric Neurology Outpatient Clinic between January 2015 and January 2023 were retrospectively analysed. Demographic information (age, gender), physical examination findings, brain Magnetic Resonance Imaging (MRI), abdominal ultrasound (USG), electrocardiography (ECHO) results, and laboratory data were recorded for each patient. The files of the other polyclinics where the patients followed up with the diagnosis of NF-1 were referred in terms of endocrinological, cardiological, orthopedic, and psychiatric pathologies that may accompany their routine controls were reviewed. National Health Organizations (NIH) NF-1 diagnostic criteria were used in the diagnosis of NF1. With the presence of two or more of these criteria, the patient was diagnosed with NF-1 (5). Cases that came to regular controls were included in the study.

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Statistic

The collected data were analyzed using SPSS Statistics 18.0 (Predictive Analytics Software Statistics for Windows, Version 18.0, SPSS Inc., Chicago, IL, US, 2009) software package. Continuous variables were expressed as median (interquartile range) values, and categorical variables were expressed as numbers and percentage values. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to analyze the normal distribution characteristics of the continuous variables. Mann-Whitney U and Kruskal-Wallis analysis of variance (post hoc) tests were used in the comparisons of non-parametric independent data. The probability (p) statistics of < 0.05 indicated statistical significance.

RESULTS

Twenty-one (53.8%) of the patients included in the study were male and 18 (46.1%) were female. Patient ages ranged from 3 to 17 years. While 11 patients (28.2%) had a family history, 28 patients (71.7%) had no family history (Table I). It was determined that there was a history of consanguinity between the parents in four of the cases. Cafe au lait spots were present in all patients, and axillary and/or inguinal freckles were present in 21 patients (53.8%). Lisch nodules were detected in 14 patients (35.8%), and optic glioma was not found in any patient. Neurofibroma was detected in 6 patients. When the patients were evaluated neurologically; There were learning difficulties and cognitive disorders in 12 patients (34.4%), epilepsy in 5 patients (12.8%), and macrocephaly in 2 patients (5.1%). Abnormal MRI imaging was detected in 21 patients (Table II). T2 hyperintense lesions were detected in 16 (76.1%) of them, ventricular enlargement in 2 patients (9.5%), CSF spacing in the optic nerve sheath in 2 patients (9.5%), cavernous hemangioma in 1 patient (4.7%), and brain stem glioma was detected. MRI was normal in 15 patients (38.4%). When the patients were evaluated in terms of malignancies in NF1, peripheral neurofibroma was found in 2 patients (5.1%). Abdominal USG was performed in 30 (76.9%) of the patients in terms of the possible gastrointestinal stromal tumor, and no pathology was detected in any of the patients. In the endocrinological evaluation, 3 patients (7.6%) had short stature, and 2 patient (5.1%) had precocious puberty. Mitral valve prolapse (MVP) was detected in 2 (5.1%) of 11 patients who underwent cardiac examination, and no pathology was found in 9 patients (23%). When orthopedic comorbidities were screened, 4 patients (10.2%) had orthopedic pathology (scoliosis, pes planus), while no pathology was found in 25 patients (64.1%). The genetic examination was not performed in 27 (69.2%) of 39 patients. While mutations in the NF1 gene were detected in 12 (30.7%) of 39 patients who underwent genetic analysis.

Table I. Demographic features of NF1 patients

Demographic	n(%)
Gender	
Male	*21(53.8)*
Famele	*18(46.1)*
Years	7.65 ± 4.25
Consanguinity	4(10.2)
Family history	11(28.2)

Table II. Clinical features of NF1 patients

Special feature	n(%)
Lish Nodule	14 (35,9)
Axillary freckling	21 (53.8)
Neurofibroma	6 (15.2)
Cafe aut lait	39 (100)
Epilepsy	5 (12.8
Learning disability	9 (23)
Short stature	3 (7.7)
Optic Glioma	0(0)
Precocious puberty	2 (5.1)
Macrocephaly	2 (5.1)

DISCUSSION

In our study, the clinical features of 39 NF-1 cases were evaluated. Parents or siblings of 11 of these cases had NF-1 diagnosis. In studies, positive family history has been found at different rates ranging from 39% to 54% (6,7). The data in our study were compatible with the literature data. Cafe au late are one of the major diagnostic criteria of NF-1. It is typical for their number and size to increase with age (8). In our study, there were many cases in all cases. These spots, which cause cosmetic problems, cannot potentially cause a malignant lesion. Axillary or inguinal freckling, which is one of the diagnostic criteria for NF-1, usually occurs in late childhood, and school age (4). Axillary freckling was observed in 12 children. Lisch nodules are melanocytic hamartomas of the iris and are specific for NF1 (6). These lesions begin to appear on the iris surface from the age of 2.5 years and are seen in more than 90% of affected adults (10).In a study conducted in 162 pediatric patients with NF1, the presence of Lisch nodules was found to be 5% in patients younger than 3 years of age, 42% between 3-4 years of age, and 55% between 4-5 years of age (11). Lisch nodules are often asymptomatic, do not cause any visual impairment and do not require treatment (12). This study detected Lisch nodules in 14 patients (34.4%) in line with the literature. We detected Lisch node at the earliest in a case of 5 years old. Macrocephaly is a common finding in patients with NF-1 (4). The incidence of macrocephaly was reported as 40% in cases with NF-1, but in our study, macrocephaly was found to be 2.1%. Regular measurement of head circumference records is very important in terms of detecting macrocephaly. It should also be kept in mind in hydrocephalus. The most common pathology observed in neurofibromatosis in brain MRI examinations is hyperintense lesions seen in different localizations in T2W series. The characteristics of these lesions, called hamartomas, are that they are benign and have no accompanying neurological problems (1). The most common brain tumor in patients with NF-1 is optic gliomas. Most are asymptomatic (13). Duffner et al.(14) found hamartoma in 62% and abnormal findings other than hamartoma in 12% in NF patients. In our study, 16 of the cases had findings consistent with NF. Optic glioma was not detected in any of the cases. The frequency of seizures in neurofibromatosis patients is reported more frequently than in the normal population. Five cases in our study group had epileptic seizures and used drug therapy. Of these patients, 3 use valproic acid and 2 use levetiracetam. In a study, it was reported that the prevalence of epilepsy was 7% (15). Mental retardation, learning difficulties, language problems, lack of

attention and organization, and psychosocial problems are more common in neurofibromatosis type 1 patients than in the normal population. A study reported that the prevalence of learning disabilities in 152 cases of NF-1 was 75% (16). Ten of our cases exhibited learning difficulties and were monitored by the child psychiatry department. Additionally, our two patients with epilepsy also experienced learning difficulties. Thirteen percent of NF patients had a height below -2 standard deviations (17). Within this study, three patients (13.7%) exhibited short stature, while two patients (3.45%) experienced precocious puberty.

The patient with precocious puberty did not have optic glioma or pituitary adenoma. The frequency of diseases such as congenital heart diseases (especially pulmonary stenosis), hypertension, and renal artery stenosis has increased in NF1 patients (18).

In the study, MVP was detected in 2 (3.45%) of 11 patients who underwent cardiac examination, and no pathology was found in 8 patients (27.5%). Another comorbidity with increasing frequency in NF1 is orthopaedic comorbidities, and pathologies such as scoliosis, kyphosis, bone dysplasia, and non-ossifying fibroma are more common in NF1.

CONCLUSION

NF-1 is a clinically complex and heterogeneous disease. It has been concluded that close follow-up of NF1 patients is necessary and important because of the involvement of many systems, the risk of malignancy in patients, the comorbidities that may accompany it, and their effects on quality of life.

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Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions.

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