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Is neurofibromatosis type 1 diagnosed in every patient who presents with café au lait macules? A single-center experience

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ABSTRACT

Objective: Neurofibromatosis type 1 (NF1) is the most common hereditary neurocutaneous syndrome. The most crucial morbidity of NF1 is tumors that may develop. Cases with café-au-lait macules (CALMs) which is the first clinical finding of NF1, due to the anxiety of its associated morbidity, are referred to the pediatric oncology clinic. In this study, we aimed to examine the characteristics of the patients who applied to our outpatient clinic with CALMs.

Patients and Methods: The data of 157 pediatric patients who applied to our institution with the diagnosis of CALMs between June 2010 and November 2020 were analyzed retrospectively.

Results: There were 157 pediatric cases referred to us for CALMs. According to the National Institutes of Health (NIH) diagnostic criteria, 109 (69.4%) cases were diagnosed with NF1. The diagnosis of 22 cases with NF1 were supported by genetic examination. Optic glioma was detected in 39 (24.8%) cases. In 15 (38.4%) of cases with optic glioma, visual functions were also affected. Second diagnostic criterion did not develop during the follow-up period, except for macules, in 48 cases (30.5%).

Conclusion: In cases with multiple CALMs, the probability of NF1 diagnosis is high, and close and regular follow-up is of great importance in catching the development of the second clinical criterion and minimizing its morbidity.

Keywords: Café-au-lait macule, Neurofibromatosis, Children, Tumor

1. INTRODUCTION

Café-au-lait macules (CALMs), are used to name the milky brown skin macules with different sizes on the skin, which are congenital or acquired. While its incidence is 2.7% in the neonatal period, more than three CALMs can be seen in 1% of children [1,2]. These macules can be the first sign of various genetic syndromes and neurocutaneous diseases. The most well-known syndrome is neurofibromatosis type 1 (NF1).

Neurofibromatosis type 1 is the most common hereditary neurocutaneous syndrome. The incidence is reported as 1 in 2500 births [3]. Clinical findings occur due to mutations in the NF1 gene, which is a tumor suppressor gene. Although, it usually occurs due to germline mutations showing autosomal dominant inheritance, it can also rarely be encountered with de novo mutations and can be the first case in the family. The NF1 gene is located on the 17q11.2 chromosome and encodes a protein called neurofibromin [4]. This protein acts as a negative regulator of the Ras proto-oncogene. Therefore, as a result of mutations in the NF1 gene, the frequency of mostly benign and malignant tumors of the central and peripheral nervous system, gastrointestinal stromal tumors, breast cancer, pheochromocytoma, leukemia, lymphoma, and rhabdomyosarcoma are also higher in these cases compared to the normal population [4]. The most crucial morbidity of NF1 is tumor that may develop and gliomas in the optic tract, which can cause vision impairment. Neurofibromas are the most frequently detected tumors, and more rarely, plexiform neurofibromas, which have the risk of malignant transformation, can be seen [5]. Although, not among the diagnostic criteria, hamartomatous lesions in the central

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nervous system (CNS) are typical radiologically and usually not symptomatic. However, these patients may also experience regression in neurocognitive functions. Apart from neurological findings, skeletal deformities, cardiovascular pathologies, and endocrine disorders are among the other findings. Diagnosis is made by meeting two or more criteria from the National Institutes of Health (NIH) criteria (Table I) [6].

Table I. *NIH consensus criteria for diagnosis of NF1 (Two or more criteria are required for diagnosis) [6]*

Six or more café-au-lait macules over >5 mm diameter in prepubertal individuals and >15 mm diameter in post pubertal individuals
Two or more neurofibromas or 1 plexiform neurofibroma
Freckling in the axillary or inguinal regions
Optic glioma
Two or more Lisch nodules
A distinctive osseous lesion
A first degree relative with NF-1

NIH:National Institutes of Health, NF-1: Neurofibromatosis type 1

Cases with CALMs, which is the first clinical finding of NF1 due to the anxiety of NF1 and its associated morbidity, are referred to the pediatric oncology outpatient clinic, and NF1 scans are performed. In this study, we aimed to examine the characteristics of the patients who applied to our outpatient clinic with CALMs, the degree of compliance with the NF1 diagnostic criteria, the frequency of developing benign or malignant tumors, and the follow-up results in treatment retrospectively.

2. PATIENTS and METHODS

The data of 157 pediatric patients who applied to our institution with the diagnosis of CALMs between June 2010 and November 2020 were analyzed retrospectively. Demographic characteristics of the patients, NF1 family history, NF1 diagnostic criteria, benign/malignant tumors if advanced, visual function evaluation results with central nervous system and orbital MRI, and endocrine, neurocognitive function, skeletal system, and genetic evaluation results were analyzed. This study is a retrospectively designed descriptive type of study. Mean, median, minimum and maximum values and numbers (n) and percentages (%) were used for data description. Patients whose parents refused to give consent were excluded from the study. Study was approved by the institute's ethic committee (09.2022.119).

3. RESULTS

One hundred and fifty-seven pediatric patients referred to our clinic for CALMs. The median age of the cases was 96 months (range, 1-210 months). Ninety-three (59.2%) cases were male, and 64 (40.7%) were female. Characteristic findings of the patients are listed in Table II. Median follow-up period of all cases was 33.5 months. While, there was a family history of NF1 in 39 (24.8%) cases, 6 (3.8%) patients had an undiagnosed family member with widespread CALMs. Presenting complaint of all cases was widespread CALMs on the body. At the time of admission, apart from the macules, the headache was present in 5 (3.1%), visual problems in 7 (4.4%), and swelling in the body in 6 (3.8%) cases. Regarding the distribution of the macules, data of 4 cases could not be reached. In one hundred and fifty-one (96.1%) cases, widespread macules were present, and in 3 (1.9%) of them, sizes of the spots were 0.5 cm-1 cm, in 18 (11.4%) cases 1-1.5 cm, in 136 (%86,6) cases larger than 1.5 cm. There was only one macule in two cases, and their sizes were 2x2 cm and 3x5 cm, respectively. In addition to spots, 30 (19.1%) cases had axillary/inguinal freckles. Lisch nodules were detected in 35 (22.2%) cases in eye examinations. When patients were evaluated according to the other NF1 diagnostic criteria; neurofibroma developed in 27 (17.1%) cases, one of which was spinal, and the others were cutaneous. The mean age of the patients who developed neurofibroma was 10.1 years. Ten (6.3%) cases had plexiform neurofibroma, and the mean age was 7.68 years. Malignant transformation was not observed in any patients with plexiform neurofibroma during their follow-up. When evaluated in terms of a skeletal anomaly; Skeletal system anomaly was present in 19 (12.1%) cases, and scoliosis was the most common skeletal system pathology with 9 (47.3%) cases. Neurological findings were present in 19 (12.1%) cases. Of these, 15 (78.9%) had neurocognitive dysfunction, 4 (21%) epilepsy, and 1 (5.2%) autism spectrum. When evaluated in terms of endocrine pathologies; precocious puberty was found in 5 (3.1%) cases, short stature in 3 (1.9%), hypothyroidism in 1 (0.6%), and diabetes insipidus in 1 (0.6%) cases. In the cardiac evaluation results; aortic coarctation in 2 (1.27%) cases, 4 (2.5%) mitral valve prolapse and 1 (0.6%) atrial septal defect were followed up in the cardiology outpatient clinic. According to the NIH diagnostic criteria, 109 (69.4%) cases were diagnosed with NF1. There were only 22 (14%) cases whose diagnosis was supported by genetic examination.

According to the NIH, a second criterion did not develop during the follow-up period, except for stains, in 48 cases (30.5%). There were hamartomas in 19 (39.5%) cases on brain imaging of these cases. When the stain characteristics were examined, only 2 cases had one stain, while 46 cases had widespread stains over 1 cm. Twenty-seven (56.25%) of these cases did not come to regular follow-up. The mean age of 21 patients who followed up regularly was 5.74 years.

When evaluated in terms of non-neurofibroma tumoral formations; Optic glioma was detected in 39 (24.8%) cases. In 15 (38.4%) of these cases, visual functions were also affected. Three cases had received chemotherapy due to progressive visual impairment and were being followed up for stable disease. Visual functions of 12 patients who did not receive treatment continued to be stable. One patient was followed up for pilocytic astrocytoma outside the optic tract, and another was followed up for a cardiac mass.

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Table II. *Clinical Characteristics of Patients*

	n (%)
Total number of patients	157(100%)
Age (months)	96 (1-210)
Sex	
Male/Female	93(59.2%) /64(40.7%)
Family History	39 (24.8%)
Other NF1 Diagnostic Criteria	
Neurofibroma	
Plexiform Neurofibroma	10 (6.3%)
Cutaneous Neurofibroma	26 (16.5%)
Spinal Neurofibroma	1.0 (0.6%)
Skin-Fold Frecking	30 (19.1%)
Lisch Nodules	35 (22.2%)
Optic Glioma	39 (24.8%)
Visual Function Affected	15 (9.5%)
Chemotherapy	3.0 (1.9%)
Bone Lesions	19 (12.1%)
Hamartoma	87(55.4%)
Cardiac Malformation	7.0(4.4%)
Mitral valve prolapse	4.0 (2.5%)
Aortic coarctation	2.0 (1.27%)
Atrial Septal Defect	1.0 (0.6%)
Endocrine Disorders	10(6.3%)
Precocious puberty	5.0(3.1%)
Short stature	3.0(1.9%)
Hypothyroidism	1.0(0.6%)
Diabetes Insipidus	1.0(0.6%)
Neurological Problem	20(12.7%)
Neurocognitive Dysfunction	15 (9.5%)
Epilepsy	4.0(2.5%)
Autism spectrum	1.0(0.6%)
Genetic Diagnosis	22 (14%)

NF-1: Neurofibromatosis type 1

4. DISCUSSION

Out of 157 cases who applied to our outpatient clinic with the complaint of CALMs, 109 of them were diagnosed with NF1 as a result of median follow-up of 33.5 months. CALMs are usually the first sign of NF1 syndrome, and other diagnostic criteria other than family history emerge over the years. While, CALMs usually occur in the first two years of life, axillary and inguinal freckles develop in 5-8 years, Lisch nodules in 5-10 years, neurofibromas in late childhood, and plexiform neurofibromas in the first ten years [7]. Optic gliomas, which can be seen in the first seven years, and skeletal dysplasia, which can be seen in the first seven years, can be diagnosed early by suspecting the disease with these clinical findings, thus, minimizing the risk factors for morbidities that may occur due to the disease. In conclusion, CALMs have an important place in the early diagnosis of NF1 disease. In a study in which 110 individuals with CALMs were evaluated, it was determined that 23% of these cases with six or more CALMs did not develop NF1 diagnostic criteria. It was emphasized that the number of CALMs alone was not sufficient for the diagnosis of NF1 [8]. In this study, while the median age at presentation was 96 months and the median follow-up period was 33.5 months, a second criterion did not develop in 30.5% of the cases (n=48) during the follow-up period. Since, 56.2% of these cases did not come to regular follow-up, this rate of no follow-up made the possibility of developing diagnostic criteria with a higher rate controversial. The median age of 21 cases that were followed up regularly was 5.74 years, and they were being followed up in terms of the possibility of developing the second criterion. Another remarkable feature in these 48 cases was the presence of hamartomatous lesions in 39.5%, which were not included in the NIH diagnostic criteria, but were pathognomonic for NF1 on brain MRI imaging. 55.4% of 157 patients had hamartomas on brain MRI imaging. In a study from Korea, hamartomatous cranial lesions were found in 20% of the 42 NF1 cases on brain MRI [9]. In the literature, it was stated that in 43% of the cases with NF1 diagnosis, hamartomas could be seen on brain MRI, growth may occur in less than 10%, and it was emphasized that after the age of 10 years old, a biopsy may be considered to rule out tumor formation in cases with enlarged hamartomas [10]. In this study, the cases with hamartoma were stable, and none of them needed a biopsy.

In another study in which 19 cases were evaluated, it was emphasized that 9 of these cases admitted with CALMs were diagnosed with the NIH diagnostic criteria, and four were diagnosed with genetic analysis. It is recommended that the diagnosis of NF1 should be persistently considered in cases presenting with multiple CALMs [11]. In our study, the cases diagnosed according to the NIH diagnostic criteria were 64.9% (109 cases) of all cases and in addition to macules, the second most common criterion for diagnosis was family history, with 24.8% of the cases. Although, there was no definite diagnosis in the family, genetic analysis was performed in only one of the 6 cases with multiple CALMs, and a mutation was detected. Of the remaining five patients, two were diagnosed with plexiform neurofibroma, one with cutaneous neurofibroma, and another with Lisch nodule, which was later diagnosed as NF1. According to this result, we would like to remind that assessment of a family member with multiple CALMs other than the diagnosis of NF1 should be included in anamnesis of cases. Although, NF1 is stated to be an autosomal dominant disease in literature, 50% of NF1 cases originates from de novo mutations without presenting a family history [7]. Diagnosis was supported by genetic analysis only in 22 (14%) cases in our study. Since, genetic analysis was

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not performed on every patient, a correct assessment of the genetic transmission rate could not be made for this study.

Optic glioma was the most common clinical diagnostic criterion after family history. Low-grade glial tumors occur with a frequency of 15-20% in cases with NF1, and 80% of them are seen in the optic tract [5]. These tumors can occur from birth, and only 5% of them can be symptomatic [7]. Early diagnosis is crucial in preserving visual functions in cases with optic glioma. Diagnosis is made by visual acuity, visual field, and orbital MRI examinations when the disease is suspected. MRI imaging in young children is not accessible due to the need for anesthesia, and visual function evaluations gain importance in this period. Visual functions should be evaluated regularly in cases with NF1 diagnosis. Children with NF1 had a better visual acuity outcome than sporadic optic glioma [12]. In our study, optic glioma was detected in 24.8% of the cases, consistent with the literature [5]. Visual functions were also affected in 38.4% of these cases. While patients with stable disease were followed, 5 patients with progression received chemotherapy treatment. After treatment, these cases continued to be followed up with stable disease. In our study, low-grade glial tumor formation outside the optic tract was detected in only one case and it was followed up as stable disease.

The third most common diagnostic criteria were neurofibromas (17.1%) and plexiform neurofibromas (6.3%), which are skin findings. Studies have shown that the incidence of cutaneous neurofibromas is 99% in cases with a diagnosis of NF1. While plexiform neurofibromas can occur from birth to 18 years of age, it generally occurs above 7 years of age [5]. In our study, mean age of the patients with neurofibroma was 10.1 years and it was found only in 17.1% of the patients. In literature, it is stated that 30% of plexiform neurofibromas are visible by naked eye and 50% of them are diagnosed by imaging studies [5]. In our study, the mean age of patients with plexiform neurofibroma was 7.69 years, while the incidence was 6.3%, and all of them were diagnosed with imaging studies. The lower rate can be explained by the fact that the mean age of the cases is still low. Since the incidence of scoliosis is 10-26% in patients with NF1 diagnosis, spinal examination gains importance in physical examination [13]. In a single center study, skeletal problems were seen in 14 of 52 patients with NF1 [14]. In our cases, skeletal system disorders were detected in 12.1% of cases, and 47.3% of them were scoliosis. We think that it should be kept in mind during the physical examination since it is a finding that can be missed if attention is not paid to the examination.

Although, there are few studies in the literature, the frequency of endocrine problems in cases diagnosed with NF1 is reported to be 1-3% [15-17]. In a multicentric study in which 116 cases were examined, endocrine problems were found in 27.6% of the cases, and 71.9% were central precocious puberty [18]. In our single-center study, 6.3% of 157 cases were found to have endocrine problems. Among them, the most common problem was precocious puberty followed by short stature. Due to the study's retrospective nature, the presence of cases whose hormone data could not be reached, limits the study in this respect. Previous literature reported frequency of cardiac pathologies to be 2.3% and 18.8% among NF1 cases [19, 20]. In the study of İncecik et al., it was reported that among 65 NF1 patients cardiac anomaly was observed in 15.3% of the cases, and mitral valve regurgitation was the most common anomaly which was observed in 5 cases [21]. In this study, the cardiac anomaly was detected in 7 patients, while mitral valve prolapse was found to be the most common anomaly in 4 (2.5%) cases. However, proper cardiac assessment record of some patients could not be accessed. Therefore, number of patients with cardiac anomaly was found to be limited in our study.

In conclusion, NF1 is a neurocutaneous syndrome that can cause severe morbidity by affecting many systems. Due to CALMs, which is its first finding, morbidity can be minimized with close follow-up, early diagnosis, and treatment. In cases with multiple CALMs, the probability of NF1 diagnosis is high, and close and regular follow-up is of great importance in catching the development of the second clinical criterion.

Compliance with Ethical Standards

Ethical Approval: The study was approved by the Marmara University, School of Medicine Ethics Committee (09.2022.119).

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