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Evaluation of the Clinical Profile and Malignancies in Children With Neurofibromatosis Type 1

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Abstract

Purpose:

Neurofibromatosis type 1 (NF 1) is a significant disease as it is one of the most common autosomal dominant disorders in childhood. Several systems are affected due to significant progression. This study aimed to analyze the clinical findings in children with NF 1 and investigate the characteristics of those with malignancy.

Methods:

Medical records of 55 children with NF 1 that were followed up for ten years (2004-2015) in our center were analyzed. We assessed clinical and demographical characteristics of patients, presence NF 1 diagnostic criteria, NF 1 related complications, and malignancies. The patients without malignancy are classified in group 1 while patients with malignancy are in group 2.

Results:

The mean age was 7.68 ± 4.65 years. Female gender was dominant in both groups. Café au lait spots were present in all patients. Axillary-inguinal freckling was observed in 76.4% of patients, followed by neurofibromas in 30.9%, Lisch nodules in 29.1%, bone dysplasia in 14.5%, optic gliomas (OG) in 23.6%, and a history of first degree relative with NF 1 in 63.6%. Central nervous system (CNS) tumors were present in 40%. Tumors beyond CNS were acute myeloid leukemia and schwannoma. None of the diagnostic criteria was a risk factor for malignancy. Having >3 criteria was the risk factor for malignancy in NF-1 (OR:5.891, CI 95%: 1.676-20.705, p=0.006).

Conclusions:

The major problem is malignancies in NF -1 patients. There are no clearly defined risk factors predicting malignancies in NF-1 at present. However, we found the risk of malignancy higher in patients with more diagnostic criteria.

Introduction

Neurofibromatosis type 1 (NF-1) is one of the common neurocutaneous diseases. Recent studies report a birth incidence of 1/2000 and prevalence of 1/4000 [1–3]. It has a broad spectrum of clinical effects on several organ systems [4]. NF-1 has an autosomal dominant pattern of inheritance, while half of the patients have a de novo mutation. It is caused by mutations of the NF-1 gene located in 17q11.2. NF-1 gene encodes neurofibromin which is one of the tumor suppressor proteins [5]. This mutation provokes proliferation and tumorigenesis in various tissues, especially in neurocutaneous tissue. The most common features in NF-1 are hyperpigmented macules called café-au-lait macules (CALMs), Lisch nodules, and neurofibromas. The malignancy rate is high in patients with NF-1. Central nervous system (CNS) tumors, malignant peripheral nerve sheath tumor (MPNST), leukemias and rhabdomyosarcoma

(RMS) are the mostly reported malignancies in NF-1 [4]. The life expectancy is 10-15 years lower in NF-1 patients compared to healthy population [6]. Clinical findings vary among affected individuals due to highly variable clinical expressivity. Manifestations of NF-1 increase with age making clinical picture worse at older ages [7–9].

In this study, we aimed to determine the clinical features of NF-1 patients and the remarkable characteristics of NF 1 patients with malignancy and evaluate the treatment and follow-up outcomes.

Methods

Patients data

We scanned electronic medical records of NF-1 patients followed at Kocaeli University Pediatric Oncology Department in years 2004-2015 We reached files of 88 patients that were diagnosed with NF-1. Fifty-five patients who fulfilled the inclusion criteria were enrolled. Inclusion criteria were age under 18 years, a minimum follow-up time of three months in our center, meeting the National Institutes of Health (NIH) NF-1 diagnostic criteria [10], and having full access to medical records regarding diagnosis and treatment.

Demographic findings, diagnostic criteria, clinical findings other than diagnostic criteria, malignancy, and family history were evaluated. We grouped the patients considering presence of malignancy. The patients without malignancy were in group 1; patients with malignancy were in group 2. We evaluated treatment modalities, treatment response, and prognosis of the disease in group 2.

Ethics and consent to participate declarations

All patients/parents signed the consent form and accepted use of their medical records for scientific research. The Ethics Committee of Kocaeli University had approved this study (KOU KAEK 14/98).

Statistical analysis

We used IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. Normality tests were performed for continuous variables. Data were presented as mean ± standard deviation for normally distributed continuous variables, median (25-75 percent) for abnormally distributed continuous variables, and proportions for categorical variables. Continuous variables showing normal distribution were compared between groups using Student's t-test, and abnormally distributed variables were compared using the Mann–Whitney U test. Categorical variables were compared using the Chi-square test. Univariate binary logistic regression analysis was performed to identify the risk factors for malignancy in NF 1. Odds ratios were calculated with 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant.

Results

Thirty-two patients (58.2%) were female. The mean age at diagnosis was 7.68±4.65 years; the median follow-up duration was 2 (0.08-11.50) years. The mean age at diagnosis of malignancy was 8.90±4.22 years. The demographic and clinical characteristics of both groups were summarized in table 1.

The diagnostic criteria of patients

All patients had CALMs. Axillary/groin freckling followed CALMs in 42 (76.4%) patients. Seventeen patients (30.9%) had neurofibromas. Cutaneous neurofibromas and plexiform neurofibroma were observed in 11 (20%) and 10 (18.2%) patients, respectively. Eight (14.5%) patients had bone dysplasia. Congenital tibial pseudoarthrosis was observed in 3 (5.4%) patients; while congenital tibial dysplasia in 2 (3.6%) patients; sphenoid wing dysplasia in 1 (1.8%) patient; ulnar dysplasia was in 1 (1.8%) patient and humerus dysplasia in 1 (1.8%) patient. The other diagnostic criteria were showed in table 1.

The frequency of diagnostic criteria was not different between 0-1 age-year, 2-6 age-year and ≥7 age-year groups. No patients had Lisch nodules or bone dysplasia in the 0-1 age-year group. The number of criteria did not correlate with the age at diagnosis NF-1 ($r(55)=0.34$; $p=0.80$).

The clinical findings out of the diagnostic criteria

Weight and height percentiles were below the 3rd percentile in 19 (34.5%) and 11 (20%) patients, respectively. Head circumference percentile was above the 90th in 18 (32.7%) patients and was below the 3rd in 1 (1.8%) patient.

Three (5.5%) patients had delayed puberty, and 2 (3.6%) patients had precocious puberty. All patients with delayed puberty had malignancy. These tumors were cerebellar astrocytoma in one patient, cerebral hemispheric glioma in one, and brainstem and cerebral hemispheric glioma in one.

Cranial magnetic resonance imaging (MRI) was performed in 51 (92.7%) patients, and 43 (78.2%) of these patients had abnormalities on MRI . The cranial MRI abnormality was unidentified bright objects (UBO) in 40 (72.2%) patients. Other cranial MRI abnormalities except for UBO and malignancy were present in 12 (21.8%) patients. Ten (18.2%) patients had an abdominal abnormality, 4 (7.3%) patients had a urinary abnormality on ultrasonography; 2 (3.6%) patients had an echocardiographic abnormality and, 7 (12.7%) patients had endocrinologic disorders (Table 2).

We compared patients with and without UBO regarding seizures, mental retardation, and cranial malignancies, and we did not find a significant difference (Table 3). Eleven (20%) patients had seizures. The cause of seizures was febrile convulsion and epilepsy in 5 (9.1%) and 6 (10.9%) patients, respectively. Mental retardation was mild in 19 (34.5%) patients, moderate in 6 (10.9%) patients and severe in 2 (3.6%) patients. Other neurological problems were headache due to CNS tumor in 2 (3.6%) patients, urinary and bowel incontinence in 1 (1.8%), and hemiplegia in 1 (1.8%) patient due to plexiform neurofibroma.

Malignancies of the patients

Malignancy was detected in 23 (41.8%) patients. Fourteen (60.9%) of these patients were diagnosed with NF-1 during workup for malignancy. The longest duration between diagnosis of NF-1 and malignancy was three years. Three (60%) patients in the 0-1 age group, 4 (25%) patients in the 2-6 age group, 16 (47.1%) patients in the ≥ 7 age group had malignancy (p=0.257). We evaluated the diagnostic criteria as possible risk factors for malignancy with univariate logistic regression analysis. None of the diagnostic criteria was a risk factor for malignancy in NF-1 (Table 4). We compared the number of diagnostic criteria (optic glioma criteria was excluded) between patients with and without malignancy. The patients were grouped in three groups; patients with less than 3 criteria, with 3 criteria and more than 3 criteria. Eleven (20.6%) of patients with less than or with 3 criteria and 12 (76.2%) of patients with more than 3 criteria had malignancy (p=0.004). In univariate regression analysis, having more than 3 criteria was the risk factor for malignancy in NF-1 (OR:5.891, CI 95%: 1.676-20.705, p=0.006).

There was at least one CNS tumor in 22 (40%) patients. Two (3.5%) patients had malignancies other than CNS tumors. Optic glioma in 13 (23.6%) patients was the most prevalent tumor (Table 5). Seven (30.4%) patients with tumors were followed without treatment. Sixteen (69.6%) patients were treated for progressive disease and received chemotherapy (CTX). In 2 patients who received CTX, the tumor was excised before CTX. One of these patients had glioma in the hypothalamus, and the other had glioma in the right temporal lobe. Glioblastoma multiforme (GBM) was detected on the biopsy of the patient with temporal lobe glioma. Two patients with GBM and brainstem glioma received radiotherapy (XRT).

Eight (50%) of patients who received CTX were given carboplatin-vincristine (CV) combination. Carboplatin-vincristine combination was switched to temozolomide in two of these patients (12.5%) due to progressive disease. Five (31.2%) patients with low-grade glial tumors received temozolomide as a primary CTX protocol. In one patient with acute myeloid leukemia, CTX induction was applied before bone marrow transplantation. Only one patient showed an allergic reaction to carboplatin at the last cycle, and the treatment was stopped. Thirteen (81.3%) patients finished the treatment. Three (18.7%) patients left the treatment.

In the patients group with malignancy, 9 (39.1%) had stable disease, 4 (17.4%) had a partial response, and 3 (13%) had progressive disease. Seven patients did not follow up. One of the patients with progressive disease had GBM, and received temozolomide and XRT after tumor excision. However, the patient died due to progression of the tumor. The characteristics of patients with malignancy were shown in supplemental Table 1.

Discussion

Our study showed that the clinical heterogeneity of NF-1 in children is as broad as in adults, and the risk of malignancy increases in patients with more than three NIH criteria (excluding optic glioma).

Neurofibromatosis type 1 occurs in childhood and is one of the most common autosomal dominant diseases [11–13]. Since the disease penetrance is 100%, the number and severity of clinical symptoms increase with age. Our results, that, more than half of patients were seven years old and had three diagnostic criteria, were consistent with this fact. However, we did not find a linear correlation between the age of diagnosis and the number of criteria. Café-au-lait macules were one of the primary diagnostic criteria. Café-au-lait macules start to occur after birth, and both, the diameter and the number of CALMs increase with age [14, 15]. All of our patients had greater than/equal to 6 CALMs. Previously studies detected cutaneous neurofibroma in more than 80% of patients and plexiform neurofibroma in 30-50% of patients [15, 16]. Neurofibromas occur in adolescence and after [15, 16]. Some patients in our study were in adolescence or older. Therefore, the frequency of neurofibroma was low in our study. Another classical feature of NF-1 is the dysplasia of long bones in infants [9]. The frequency of bone dysplasia in our patients was similar to literature.

In NF-1, several features other than malignancies vary by age and interest to organ systems [16]. Although our study was held in a pediatric group, we detected several manifestations in almost all organ systems. Unidentified bright object, mental retardation, and scoliosis were common manifestations of our patients which are not classified in diagnostic criteria.

In our study, unidentified bright object was more common than axillary or inguinal freckling, even though UBO is not a diagnostic criterion. Some researchers suggested that UBO can be used as another diagnostic criteria [17–21]. Our result supports this attitude. Although, an association between cognitive disorders and UBO was detected in previous studies [22], we did not find a relationship between mental retardation and UBO. Also, malignancies of CNS and seizures were not significant in our patients with UBO.

The most common malignancies are intracranial tumors in NF1. Optic glioma is the primary intracranial tumor in NF-1. The frequency of optic glioma was reported as 15-20% in children with NF-1 [4]. Varan et al. [23] found intracranial tumors other than optic glioma in 2.3% of patients with NF-1. Almost half of our patients had a malignancy, and we detected optic glioma in 23.6% of them. Besides, the frequency of other intracranial tumors was ten times higher in our study. We think that these results were provided by the help of detailed evaluation of NF-1 patients referred to our pediatric oncology clinic with an intracranial tumor. Schwannoma, meningioma, and acute myeloid leukemia were malignancies other than gliomas in our patients.

A study which evaluated CV efficiency on progressive low-grade glioma showed that event-free survival and tumor response rates were superior in children with NF-1 compared to children without NF-1 [24]. Temozolomide did not have a superior effect than CV in regard to survival of patients with low-grade glioma in past studies. However, temozolomide is increasingly preferred due to its better tolerance and easy administration [25]. We used CV in 8 and temozolomide in 5 low-grade glioma patients as primer CTX protocol. Carboplatin-vincristine was switched to temozolomide in one patient due to progressive disease We added RTX to CTX in two patients. One of these had GBM, and the other had brainstem

glioma. The patient with GBM died due to progressive disease. High-grade CNS tumors were reported in a few patients with NF-1, and these patients had a poor prognosis, too [26].

In the recent years, several studies about risk factors of glioma formation and progression in NF-1 were reported. Various factors, such as the germline *NF1* gene mutation, patient age, patient gender, background genomics (ethnicity/race), co-existing atopic conditions (eczema, asthma), were investigated [27]. Risk factors related to vision loss were female gender, age less than two years, and posterior involvement in optic glioma with NF-1, as in optic glioma without NF-1 [28–30]. However, optic glioma incidence in NF1 is similar in male and female gender [31, 32]. Tabata et al. [16] did a cluster analysis in adults with NF 1 and found positive correlations between spinal neurofibromas and optic gliomas; between optic gliomas and sphenoid wing dysplasia. Also, they reported that increasing cutaneous neurofibromas was a risk factor for MPNST [16]. In our study, gender and age were unremarkable in patients with malignancy. We could not find any NIH diagnostic criteria as a risk factor in the univariate analysis of malignancy-risk factors. However, we found that having more than three diagnostic criteria except optic glioma increased the risk of malignancy six times.

In conclusion, children with NF-1 have clinical heterogeneity similar to adult patients. Malignancies are the most crucial factor in mortality and morbidity in NF-1. Risk factors for developing malignancy in NF-1 are still unclear. However, we suggest being vigilant about potential malignancy in patients with more diagnostic criteria.

Declarations

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Conflicts of interest: None of the authors have any conflicts of interest.

Authors' contributions: All authors contributed to the study conception and design and had an essential part in caring for the patients whose data was used in this manuscript. Data collection and analysis were performed by NS. The first draft of the manuscript was written by NS and the final draft edited and approved by UD and FC.

Ethics approval: The Ethics Committee of Kocaeli University had approved the study (KOU KAEK 14/98).

Consent to participate: Informed consent was obtained from legal guardians.

Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1: The comparison of clinical characteristics according to the presence of malignancy

Variables	Group 1 n=32 (100%)	Group 2 n= 23 (100%)	p
Age of diagnosis (year)[a]	7.38 ± 4.61	8.07 ± 4.77	0.61
Duration of follow-up (year)[b]	2.00 (0.08-11.50)	2.08 (0.08-9.90)	0.61
Female	19 (59.4%)	13 (56.5%)	0.83
Cafe au lait spots	32 (100%)	23 (100%)	-
Neurofibroma	8 (25%)	9 (39.1%)	0.26
Lisch nodules	7 (21.9%)	9 (39.1%)	0.17
Freckling	22 (68.8%)	20 (87%)	0.12
Optic glioma	-	13 (56.5%)	-
Bone dysplasia	5 (15.6%)	3 (13%)	1.00
Neurofibromatosis type 1 in family	20 (62.5%)	15 (65.2%)	0.84
Malignancy in family	4 (12.5%)	5 (21.7%)	0.36

[a] mean±SD, [b] median (minimum-maximum)

Table 2: Abnormalities detected in systemic examinations

Abnormalities	n
Skeletal abnormalities other than diagnostic criteria	20
Scoliosis	10
Pectus excavatum	6
Cubitus valgus	1
Genu valgum	1
Klindodactyly	1
Scoliosis, genu valgum, pectus excavatum, duplication of finger	1
Abnormalities in cranial imaging other than malignancy and UBO	12
Hydrocephalus	4
Asymmetric ventricular volume	3
Aquaduct stenosis	2
Arachnoid cyst	1
Putamen cyst	1
Wallerian degeneration	1
Abnormalities in abdominal ultrasonography *	10
Splenomegaly	6
Hepatomegaly	4
Accessory spleen	3
Endocrinologic abnormalities	7
Hypothyroidism	3
Growth hormone deficiency	2
Type 1 Diabetes mellitus	1
Panhypopituitarism †	1
Abnormalities in urinary ultrasonography	4
Increase in renal parenchyma echo	1
Decreased kidney size	1
Hydronephrosis	1
Nephrolithiasis	1

Abnormalities in echocardiography	2
Tricuspid regurgitation	1
Mitral valve prolapse, mitral regurgitation, tricuspid regurgitation	1

* Three patients had more than one abdominal ultrasonography pathology

†Secondary to hypothalamic glioma resection

Table 3: Evaluation of patients with unidentified bright object

Variables	UBO (+) n=40 (100%)	UBO (-) n=15 (100%)	p
Mean age (years)	7.20±4.03	8.96±5.97	0.30
Seizures	8 (20%)	3 (20%)	1.00
No seizures	32 (80%)	12 (80%)	
No mental retardation	18 (45%)	10 (66.7%)	0.08
Mild mental retardation	15 (37.5%)	4 (26.7%)	
Moderate mental retardation	5 (12.5%)	1 (6.7%)	
Severe mental retardation	2 (5%)	0 (0%)	
CNS tumor	18 (45%)	4 (26.7%)	0.35
No CNS tumor	22 (55%)	11 (73.3%)	

*CNS: Central nervous tumor, UBO: Unidentified bright object

Table 4: Evaluation of risk factors for malignancy development with univariate logistic regression analysis

Variables	p	OR	95% CI
Follow-up duration	0.78	0.973	0.800-1.182
Gender	0.83	1.124	0.380-3.327
Neurofibroma	0.26	1.929	0.606-6.142
Freckling	0.13	3.030	0.729-12.603
Bone dysplasia	0.79	0.810	0.173-3.792
Neurofibromatosis type 1 in family	0,.4	0.889	0.291-2.720
Malignancy in family	0.37	1.944	0.460-8.223
The number of diagnostic criteria >3	**0.006**	**5.891**	**1.676-20.705**

Table 5: Dispersion of malignancies in patients

Tumors	n (%)
Central nervous system tumors	22 (40%)
Glial tumors	22 (40%)
Optic glioma	13 (23.6%)
Cerebral hemispheric glioma	7 (12.7%)
Brainstem glioma	5 (9.1%)
Cerebellar astrocytoma	1 (1.8%)
Meningioma	3 (5.4%)
Non-Central nervous system tumors	2 (3.6%)
Schwannoma	1 (1.8%)
Acute myeloid leuchemia	1 (1.8%)

*Five patients had more than one tumor

Supplementary Files

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