Journal of Pediatric Academy

Original Article

Year: 2022 Volume: 3 Issue: 2
Doi: 10.51271/jpea-2022-170

The Association of Malignancies with the Clinical Profile of Children with Neurofibromatosis Type 1

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Article Information

Article Type: Original Articles
Article Group: Pediatric Oncology

Received: 20.03.2022
Accepted: 04.04.2022
Available Online: 30.08.2022

Cite this article as: *Şahin N, Demirsoy U, Çorapcıoğlu F. The Association of Malignancies with the Clinical Profile of Children with Neurofibromatosis Type 1. J Pediatr Acad 2022; 2: 47-53.*

Abstract

Neurofibromatosis type 1 (NF-1) is a significant autosomal dominant disorder with a wide spectrum of clinical findings. These signs (Café au lait spots, bone dysplasia, Lisch nodules) usually start to emerge after the first months of life and most are benign in nature. On the other hand, neoplasms (optic glioma, neurofibroma, malignant peripheral nerve sheath tumor, soft tissue sarcoma, leukemia, breast cancer) are a major cause of morbidity and mortality in NF-1 patients. Cancer risk during lifetime of a NF-1 patient is almost 10 times more than a person without NF-1, but what drives these patients into cancer is still unknown. This study aims to analyze the possible association of clinical findings with malignancies in children with NF-1. Medical records of 55 children with NF-1 who were followed up in a tertiary care pediatric oncology clinic between January 2005 and December 2014 were analyzed. We assessed clinical and demographic characteristics of patients, as well as the NF-1 diagnostic criteria, NF-1 related complications, and malignancies. The NF-1 patients without malignancy were classified in Group 1 while patients with malignancy were in Group 2. Logistic regression analysis was used to determine the risk factors of malignancy in NF-1. The mean age was 7.68±4.65 years. Female sex 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 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 other than CNS tumors were acute myeloid leukemia and schwannoma. None of the diagnostic criteria was a risk factor for predisposing to malignancy by itself. Having >3 criteria was found to be the risk factor for malignancy in NF-1 (OR:5.891, CI 95%: 1.676-20.705, p=0.006). There are no clearly defined risk factors predicting occurance of malignancies in NF-1 at present. However, we found a higher risk of malignancy association in patients who meet more than 3 diagnostic criteria of NF-1.

Keywords: Children, low grade glial tumors, neurocutaneous syndromes, neurofibromatosis

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Introduction

Neurofibromatosis type 1 (NF-1) is one of the most common (NF1 prevalence: 1/2600-4000) genetic disorders and it is placed among the neurocutaneous syndromes.[1–3] It has a broad spectrum of clinical findings which affects several organ systems.[4] NF-1 has an autosomal dominant pattern of inheritance and half of the patients have a de novo mutation. Mutations in the NF-1 gene lead to neurofibromin accumulation which is one of the tumor suppressor proteins.[5] This mutation also provokes proliferation and tumorigenesis in tissues, especially of the neuroectodermal origin. Clinical findings vary among affected individuals due to highly variable clinical expressivity.[6–8] Café-au-lait macules (CALMs), Lisch nodules, and neurofibromas are the most common features of NF-1, and can cause significant morbidity.[4] Manifestations of NF-1 increase with growing age making clinical picture worse at older ages.[6–8]

Highlights

- The clinical manifestations of NF-1 are very heterogeneous.
- The risk of malignancy is markedly increased in patients with NF-1.
- The most frequently detected malignancy is optic glioma in patients with NF-1.

The major cause of mortality in NF-1 are malignant neoplasms.[4] The standardized incidence ratio of the malignancy risk was found 35.6 for children with NF-1 in the Finnish Cancer Registry. Central nervous system (CNS) tumors, malignant peripheral nerve sheath tumor (MPNST), and rhabdomyosarcoma (RMS) are reported malignancies in these studies.[9] Studies of adult NF-1 patients have shown that cutaneous neurofibromas did not differentiate into malignancy, but, MPNSTs are known to develop from pre-existing plexiform neurofibroma.[10,11]

Briefly, life expectancy is 10-15 years lower in NF-1 patients compared to healthy population.[12] Malignancies play a critical role regarding this statement. It is not clear which NF-1 patients develop cancer. In this study, we aimed to identify the clinical features of NF-1 patients that are possibly associated with increased malignancy risk.

Material and Method

Patients Data

We scanned electronic medical records of NF-1 patients followed at Kocaeli University Pediatric Oncology Department between January 2005 and December 2014. Patients registered as neurofibromatosis with the International Classification of Diseases 10 code Q85.0 were listed. Eighty eight patients were tagged with ICD 10 code Q85.0. 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[13] that are detailed in the next sentence, and full access to patients' medical records regarding diagnosis and treatment. NIH diagnostic criteria for NF-1 are six or more CALMs >5 mm in diameter in prepubertal individuals or >15 mm in diameter in postpubertal individuals, two or more neurofibromas of any type or 1 plexiform neurofibroma, axillary or inguinal freckling, optic glioma, two or more Lisch nodules, a distinctive osseous lesion such as sphenoid wing dysplasia or thinning of long bone cortex, and a first-degree relative with NF-1. All patients met the NIH diagnostic criteria. In our center, genetic analysis was not performed on patients who met the diagnostic criteria. Since the study was retrospective, genetic analyzes of the patients were not performed. Fifty-five patients who fulfilled the inclusion criteria were enrolled. Thirty-three patients were not included in the study as they did not fulfill the diagnostic criteria for NF-1 or their medical data were missing.

Demographic findings, diagnostic criteria, clinical findings other than diagnostic criteria, malignancy, and family history were evaluated. Patients were grouped regarding their history of malignancy in two groups, NF-1 patients without cancer (Group 1) and NF-1 patients with cancer (Group 2). All tumors were diagnosed after biopsy except optic glioma which was identified by magnetic resonance imaging. Bone marrow examination was performed in the diagnosis of hematological malignancies. We also evaluated treatment modalities, treatment response, and prognosis of malignancy.

Ethics and Consent to Participate Declarations

All patients/parents signed the consent form and accepted use of their medical records for scientific research.The study was carried out with the permission of Kocaeli University Clinical Researches Ethics Committee (Date: 18.03.2014, Decision No: 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. The presence of malignancy with NF-1 categories were coded as 0=absent and 1=present. Because there was one significant variable at $p<0.05$ in univariate analysis, we could not analyze the multivariate logistic regression model to identify the independent risk factors. Optic glioma, one of the NF-1 NIH diagnostic criteria, was considered a confounder factor since it is also a malignancy. It was not included in the number of diagnostic criteria in the logistic regression analysis.

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 (0.25-11.50) years. The mean age at diagnosis of malignancy (n=23) was 8.90±4.22 years. The demographic and clinical characteristics of both groups are 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 neurofibroma and plexiform neurofibroma were observed in 11 (20%) and 10 (18.2%) patients, respectively (Four patients had both cutaneous neurofibroma and plexiform neurofibroma.). 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 in 1 (1.8%) patient and humerus dysplasia in another (1.8%) patient. The other diagnostic criteria are shown in **Table 1**.

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]	2.46 (0.25-11.50)	2.00 (0.25-9.90)	0.87
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), Group 1; the NF-1 patients without malignancy, group 2; the NF-1 patients with malignancy

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 of 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 and 2 of them received chemotherapy (CTX). These tumors were cerebellar astrocytoma in the first patient, cerebral hemispheric glioma in the second, and brainstem and cerebral hemispheric glioma in the third.

Cranial MRI was performed in 51 (92.7%) patients, and 43 (78.2%) of these patients had radiologic abnormalities on MRI. The most common cranial MRI abnormality was unidentified bright objects (UBO) in 40 (72.2%) patients. Excluding UBO and malignancies, other cranial MRI abnormalities were observed in 12 (21.8%) patients (Table 2). Ten (18.2%) patients had an abdominal abnormality and 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**).

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
Clinodactyly	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, UBO; unidentified bright objects

We compared patients with and without UBO regarding seizures, intellectual developmental disorders (IDD), and cranial malignancies, and no significant difference was found (**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. Intellectual developmental disorders were mild in 19 (34.5%) patients, moderate in 5 (10.6%) patients and severe in one (2.1%) patient. Eight patients could not be evaluated in regard to IDD as they were under 6 years of age. Other neurological problems were headache due to CNS tumor in 2 (3.6%) patients, urinary and bowel incontinence in one (1.8%), and hemiplegia in another (1.8%) patient due to plexiform neurofibroma.

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
Patients with seizures	8 (20%)	3 (20%)	1.00
Patients without seizures	32 (80%)	12 (80%)	
Intellectual developmental disorders*			0.85
No	15 (42.9%)	7 (58.3%)	
Mild	15 (42.9%)	4 (33.3%)	
Moderate	4 (11.4%)	1 (8,3%)	
Severe	1 (2.1%)	0 (0%)	
Patients with CNS tumor	18 (45%)	4 (26.7%)	0.35
Patients without CNS tumor	22 (55%)	11 (73.3%)	

CNS: Central nervous tumor, UBO: Unidentified bright object, *Wechsler Intelligence Scale for Children-R was perfomed. Intellectual Developmental Disorders was classified 50-69 intelligence quotient (IQ) as mild, 35-49 IQ as moderate, and 20-34 IQ as severe.

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 and 16 (47.1%) patients in the ≥ 7 age group had malignancy (p=0.257).

The malignancy types in the family were brain tumor in 4 patients, breast cancer in one patient, lymphoma in one patient, soft tissue sarcoma in one patient, gastric cancer in one patient, and gastric cancer and renal cell carcinoma in one patient. Two patients had a similar malignancy type as in their families. In these patients, the malignancy type in the family was a brain tumor. One of the patients had optic glioma and the other one had optic glioma, brain stem glioma, cerebral hemispheric glioma, and meningioma.

We evaluated the "NF-1 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 analyzed the number of diagnostic criteria (other than optic glioma) as a predictor of malignancy comparing patients with and without malignancy. To achieve this, patients were stratified 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 was the most prevalent tumor, in 13 (23.6%) patients (**Table 5**). Seven (30.4%) patients with tumors were followed without treatment. Sixteen (69.6%) patients were treated for progressive disease and received CTX. Two of them had primary surgery of the tumor (glioma in the hypothalamus of the first patient, and the other had high-grade glioma in the right temporal lobe) and had adjuvant CTX. Two patients with GBM and brainstem glioma received radiotherapy (XRT).

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

Variables	p	OR	95% CI
Follow-up duration (year)	0.79	0.97	0.80-1.19
Male sex	0.832	1.12	0.38-3.33
The presence of neurofibroma	0.266	1.93	0.61-6.14
The presence of freckling	0.127	3.03	0.73-12.60
The presence of bone dysplasia	0.789	0.81	0.17-3.79
The presence of an individual with neurofibromatosis 1 in the family	0.836	0.89	0.29-2.72
The presence of malignancy in the family	0.366	1.94	0.460-8.223
The number of diagnostic criteria >3	0.006	5.89	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 leukemia	1 (1.8%)

*Five patients had more than one tumor

Eight patients (50%) 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, bone marrow transplantation was performed after CTX induction. Only one patient showed an allergic reaction to carboplatin at the last cycle, and the treatment was stopped. Thirteen (81.3%) patients finished treatment while three (18.7%) patients left it with their own will.

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 gave up follow up. One of the patients, who received temozolomide and XRT after surgery, died with progressive GBM. The characteristics of patients with malignancy are shown in **Supplemental Table 1**.

Discussion

Our patients had abnormalities of almost all organ systems which showed that clinical heterogeneity of NF-1 is broad in children. The risk of malignancy increases in patients with more than three NIH criteria.

Neurofibromatosis type 1 occurs in childhood and is one of the most common autosomal dominant diseases.[14–16] Since penetrance of NF-1 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

Supplemental Table 1
The characteristics of NF-1 patients with malignancy

Patient no	Tumor	Gender	Age at diagnosis of NF-1 (years)	Age at diagnosis of malignancy (years)	Duration of NF-1 (years)	Duration of tumor (years)	Treatment	Outcome
1	Optic glioma	M	0.33	1.83	3.37	1.87	CTX	Stable disease
2	Optic glioma	M	9.12	10.25	1.71	1.75	Follow-up	Stable disease
3	Optic glioma	F	10.25	10.25	0.58	0.58	CTX	Unfollowed
4	Optic glioma	F	6.75	9.75	6.25	3.25	CTX	Stable disease
5	Optic glioma	M	5.50	5.58	1.66	1.58	CTX	Stable disease
6	Optic glioma	M	8.41	8.50	1.34	1.25	CTX	Partial response
7	Optic glioma	M	0.83	1.41	2.33	1.75	CTX	Partial response
8	Optic glioma	F	3.58	3.58	7.50	7.50	CTX	Progressive disease
9	Optic glioma	F	0.25	3.25	5.41	2.41	CTX	Partial response
10	Optic glioma	F	16.5	16.5	0.58	0.58	Excision+ CTX	Unfollowed
11	Brainstem glioma	F	14.0	14.0	2.00	2.00	CTX	Unfollowed
12	Brainstem glioma	M	11.25	11.25	0.50	0.50	Follow-up	Stable disease
13	Cerebral hemispheric glioma	F	9.75	9.75	0.25	0.25	Follow-up	Unfollowed
14	Cerebral hemispheric glioma	F	7.16	7.24	0.8	0.72	Follow-up	Unfollowed
15	Cerebral hemispheric glioma	F	14.33	14.33	0.50	0.50	Excision+ CTX +RTX	Died
16	Cerebral hemispheric glioma	M	13.91	13.91	1.58	1.58	Follow-up	Progressive disease
17	Cerebellar astrocytoma	F	7.91	9.08	5.92	4.75	CTX	Stable disease
18	Acute myeloid leuchemia	F	7.50	7.50	9.90	9.90	CTX	Stable disease
19	Optic glioma + Brainstem glioma	M	8.08	8.08	2.17	2.17	CTX	Stable disease
20	Optic glioma + menengioma	M	4.00	4.00	2.16	2.16	CTX	Progressive disease
21	Brainstem glioma+ cerebral hemispheric glioma	F	14.50	14.50	0.50	0.50	Follow-up	Unfollowed
22	Cerebral hemispheric glioma + menengioma + schwannoma	M	11.6	11.6	0.58	0.58	Follow-up	Unfollowed
23	Optic glioma + brainstem glioma+ cerebral hemispheric glioma + menegioma	F	7.91	8.91	4.49	3.49	CTX +RTX	Stable disease

CTX: Chemotherapy, NF-1: Neurofibromatosis type 1, XRT: Radiotherapy

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.[17,18] All of our patients had greater than/equal to 6 CALMs. Previous studies detected cutaneous neurofibroma in more than 80% of patients and plexiform neurofibroma in 30-50% of patients.[18,19] Neurofibromas occur in adolescence and after.[18,19] Few patients (30.9%) 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.[8] The frequency of bone dysplasia in our patients was similar (14.5%) to literature.[19]

In NF-1, several features other than malignancies vary by age and interest to organ systems.[19] Although our study was held in a pediatric group, we detected several manifestations in almost all organ systems. Unidentified bright object, IDD, and scoliosis were common manifestations of our patients which are not classified in diagnostic criteria.

In our study, UBO 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.[20–24] Our result supports this attitude. Although, an association between cognitive disorders and UBO was detected in previous studies,[25] we did not find a relationship between IDD and UBO. Also, CNS malignancies and seizures were not significant in our patients with UBO. Therefore, we do not have an additional recommendation for follow-up in NF-1 patients with UBO. However, patients who were shown to have UBO may be evaluated for NF-1.

The most common malignancies are intracranial tumors in NF-1. Optic glioma is the primary intracranial tumor in NF-1. The frequency of optic glioma was reported as 15-20% in children with NF-14. Varan et al.[26] found intracranial tumors other than optic glioma in 2.3% of NF-1 patients. 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-127. Temozolomide did not have a superior effect than CV in regard to survival of patients with low-grade glioma in

the past studies. However, temozolomide has a better tolerance and it is easily administrated.[28] We used CV in 8 and temozolomide in 5 low-grade glioma patients as a primary CTX drug. 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 a 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.[29]

In the recent years, several studies investigating risk factors of glioma formation and progression in NF-1 were carried out. Various factors, such as the germline NF1 gene mutation, patient age, patient sex, background genomics (ethnicity/race) and co-existing atopic conditions (eczema, asthma) were investigated.[30–34] Risk factors related to vision loss were defined as female sex, age less than two years, and posterior involvement in optic glioma with NF-1, as well as in optic glioma without NF-1.[35–37] However, optic glioma incidence in NF1 is similar in male and female sex.[38,39] The parental age and the presence of tumors was not correlated in the NF-1 patients.[40] Tabata et al.[19] did a cluster analysis in adults with NF 1 and found positive correlations between spinal neurofibromas and optic gliomas, and also, between optic gliomas and sphenoid wing dysplasia. Furthermore, they reported increasing cutaneous neurofibromas as a risk factor for MPNST.[19] 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 risk of malignancy six times.

Retrospective design and limited number of patients in the cohort were the limitations of the study. Also, the study group consisted of patients referred in the pediatric oncology clinic, so patients may not have a homogeneous distribution.

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.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Kocaeli University Clinical Researches Ethics Committee (Date: 18.03.2014, Decision No: 14/98).

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: Informed consent was obtained from the parents of the patients.

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