Oncologic manifestations in children with neurofibromatosis type 1 in Turkey

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Children with neurofibromatosis type 1 (NF1) are predisposed to malignancies such as brain tumors, leukemia, and pheochromocytomas. The aim of this study was to evaluate malignancy in patients with NF1. We studied 120 patients with NF1 in this study. Demographic data from these patients were retrospectively reviewed. We found 20 malignancies in 19 patients in our study. Ten children with NF1 had optic glioma. Four children had solid central nervous system tumors (3 pilocytic astrocytomas, 1 glioblastoma multiforme). Three patients had myeloid malignancies (1 juvenile myelomonocytic leukemia, 1 acute myeloid leukemia, 1 acute lymphocytic leukemia). Hodgkin lymphoma, T-cell lymphoblastic lymphoma, and malignant triton tumor were found in one patient each. Patients with NF1 are predisposed to both benign and malignant tumors of neurogenic and non-neurogenic origin. Therefore, systematic medical follow-up in patients with NF1 is important.

Key words: Neurofibromatosis type 1, malignancy, children.

Neurofibromatosis type 1 (NF1) is a multisystem disease affecting 1 in 3,500 people worldwide[1]. The clinical course is generally progressive but highly variable. Diagnostic features of this fully penetrant, autosomal dominant disease include café-au-lait spots, skin fold freckles, Lisch nodules, cutaneous, subcutaneous, and plexiform neurofibromas, optic gliomas (OGs), and bony lesions.

Neurofibromatosis type 1 (NF1) is one of the malignancy-predisposing syndromes, and malignant tumors developed four times as often in the NF1 patient group as in the general population. The spectrum of NF1-related tumors shows selective patterns. Malignant peripheral nerve sheath tumors and central nervous system (CNS) tumors, such as OG or astrocytoma, are the most common NF1-associated tumors[2,3]. Rhabdomyosarcoma, leukemia, lymphoma, and pheochromocytoma are also known as common tumors in NF1 patients[2,4-6]. To our knowledge, a study of the incidence and spectrum of malignancy in children with NF1 was not reported previously in Turkey.

Herein, we report the incidence and spectrum of malignancy among NF1 children in Turkey.

Material and Methods

The medical records of children with NF1 who were treated and followed up from 2006 to 2011 in tertiary centers were analyzed. One hundred and twenty children met the diagnostic criteria for NF1. We used the criteria for NF1 established by the National Institutes of Health (NIH) Consensus Development Conference Criteria[7].

The diagnosis of NF1 was made on the basis of clinical features requiring the presence of at least two of the following criteria: (1) six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals; (2) axillary or inguinal freckling; (3) two or more neurofibromas of any type or one plexiform neurofibroma; (4) two or more Lisch nodules; (5) optic pathway glioma; (6)

bony dysplasia; or (7) a first-degree relative with NF1.

Medical records of patients were retrospectively analyzed for age, sex, family history, clinical features of NF1, abdominal ultrasonography, histopathologic findings, orbital and cerebral magnetic resonance imaging (MRI), and benign and malignant tumors. Abdominal ultrasonography, MRI, and ophthalmologic examination were performed at diagnosis in all patients.

Results

One hundred and twenty children were included in the study (boy/girl, 67/53). Sixty-seven patients had sporadic NF1, and 53 patients had familial form. The median age of the patients was 7.0 years (range: 2-16 years), and the median follow-up was 3.13 years (range: 1-9 years).

Twenty malignant tumors developed in 19 patients (15.8%) among the 120 NF1 patients. Sixteen patients had malignant tumors at the time of diagnosis of NF1. Four malignant tumors developed during the follow-up, as follows: 2 OG, 1 glioblastoma multiforme (GBM), and 1 acute myeloid leukemia (AML). Fourteen tumors were of nervous system origin and six were non-nervous system tumors. Ten children with NF1 had OG (Fig. 1). Seven patients with OG were asymptomatic and were diagnosed on systematic imaging. Three patients were symptomatic, and had decreased vision. Two of the OGs developed during follow-up, and one was detected at diagnosis of NF1. Six of the children were ≤6 years old at the time of the diagnosis of OG. Four children had solid CNS tumors, including three patients with pilocytic astrocytomas and one patient with GBM (Fig. 2). Three patients had myeloid malignancies (1 juvenile myelomonocytic leukemia (JMML), 1 AML, and 1 acute lymphocytic leukemia (ALL)). Hodgkin lymphoma, T-cell lymphoblastic lymphoma, and malignant triton tumor (MTT) were found in one patient each. One patient had both OG and brain tumor (GBM). In this patient, OG was detected at diagnosis of NF1, and GBM developed during the follow-up. Three patients died with progressive GBM, complication of ALL, and progressive MTT. Histological study of the tumor was performed in seven patients in our study. The characteristics of the patients are shown in Table I.

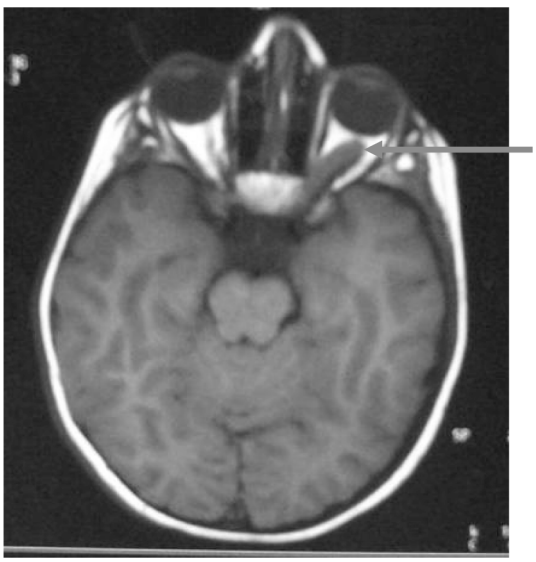

Fig. 1. Magnetic resonance imaging of the brain demonstrated left optic glioma.

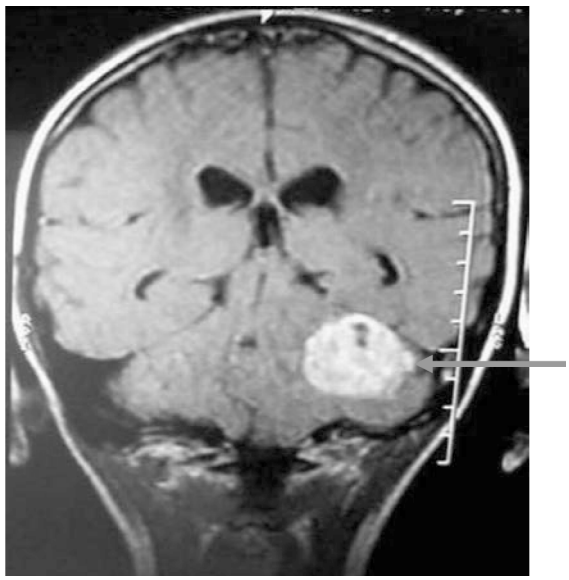

Fig. 2. T2-weighted axial image shows a mass lesion in the left cerebellum (GBM).

Discussion

Neurofibromatosis type 1 (NF1) is the most common neurocutaneous disease with multisystem involvement. Fifty percent of cases are transmitted by autosomic dominant inheritance and the other 50% are caused by de novo mutations8. In both types of presentation,

Table I. The Characteristics of Patients with Neurofibromatosis Type 1

Patient no	Diagnosis	Age	Sex	Family history	Symptoms
1	Optic glioma	8	F	+	Loss of vision
2	Optic glioma	5	M	-	Asymptomatic
3	Optic glioma	5	M	-	Asymptomatic
4	Optic glioma	6	M	-	Asymptomatic
5	Optic glioma	12	F	+	Loss of vision
6	Optic glioma	5	M	-	Asymptomatic
7	Optic glioma	4	F	-	Asymptomatic
8	Optic glioma	7	F	-	Loss of vision
9	Optic glioma	10	M	-	Asymptomatic
10	Pilocytic astrocytomas	14	M	+	Increased intracranial Pressure
11	Pilocytic astrocytomas	11	F	+	Increased intracranial Pressure
12	Pilocytic astrocytomas	9	M	+	Increased intracranial Pressure
13	Optic glioma + Glioblastoma multiforme	6	F	-	Increased intracranial Pressure
14	Acute myeloid leukemia	11	F	-	Fever, weight loss, purpuric skin rash
15	Acute lymphocytic leukemia	7	M	+	Fever, loss of appetite, weight loss
16	Juvenile myelomonocytic leukemia	2	M	-	Fever, hepatomegaly, splenomegaly
17	Hodgkin Lymphoma	8	M	-	Cervical lymphadenopathy, weight loss
18	Malignant triton tumor	11	M	+	Constipation, abdominal pain
19	T-Cell lymphoblastic lymphoma	7	F	+	Respiratory problems, weight loss

the disease is caused by a mutation in chromosome 17q11.2, and the responsible gene is neurofibromin. Neurofibromin, the protein encoded by the NF1 gene, is a negative regulator of the Ras-MAPK pathway, which functions as a GTPase-activating protein for Ras by catalyzing the hydrolysis of active Ras-GTP to an inactive Ras-GDP, and the NF1 gene is thus considered as a tumor suppressor gene. Additional somatic inactivation of the wild type NF1 allele results in complete loss of functional neurofibromin activity, and cell proliferation and differentiation are activated[9]. Malignant tumors occur in 3-15% of NF1 patients, and the high incidence of neoplasms is related with mutation of the NF1 gene[10,11]. In a recent study, Kim et al.11 reported 18 malignant tumors developing in 16 patients (12.8%) among 125 Korean NF1 patients. We detected a rate of 15.8% among 120 patients with NF1.

These individuals are prone to develop nervous system tumors, and the most common is the OG. OG is thought to be a benign low-grade pilocytic astrocytoma, seen in approximately 5-20% of patients[12]. Although the OG themselves are benign, and many patients may be asymptomatic, some cases result in clinical symptoms, including decreased vision, precocious puberty, and other hypothalamic-pituitary-adrenal axis disorders[2]. The results of our review of 120 patients with NF1 show that the prevalence of OG was approximately 8.3% in our population. Our results are similar with previous studies. Only three of these patients were symptomatic secondary to the OG (defined as decreased vision).

Varan et al.[13] evaluated 101 patients with newly diagnosed OG. A total of 53 patients (52.5%) had NF1. They detected patients with NF1 and those older than 10 years, which is associated with a better prognosis. Recently, Segal et al.[14] reported that the prevalence of OG was 13% within the sample of patients with NF1 by using baseline routine neurological MRI, and the mean age at diagnosis for OG was 6 years. Children with NF1 aged ≤6 years are at greatest risk for the development of OG. In our patients, six of 10 children were ≤6 years old at the time of the diagnosis of OG.

There are a few reports of the association of high-grade tumors of the CNS, including glioblastoma and gliomatosis cerebri, with NF1 in childhood[15,16]. The prognosis of these tumors is poor. Recently, Huttner et al.[17] reported that patients with NF1 and GBM co-occurrence have an increased survival compared to children without NF1. GBM usually affects the cerebral hemispheres in older patients, while cerebellar GBM is a rare tumor seen especially in younger patients. In our study, one patient developed high-grade tumors in the cerebellar hemisphere. Three other patients had pilocytic astrocytomas. The patients with GBM died with progressive disease.

Children with NF1 are predisposed to myeloid malignancies, particularly JMML[2]. The NF1 gene encodes neurofibromin, which acts as a GTPase-activating protein for p21Ras[18,19]. Among leukemias, NF1 is predominantly associated with nonlymphocytic leukemia[20]. Consequently, childhood ALL has been reported rarely in association with NF1. Interestingly, as seen in a few elaborate studies reported in the literature, sporadic NF1 has shown a higher incidence in ALL cases than in nonlymphocytic leukemia cases[2]. We described three children with NF1 who developed leukemia. Patient 14 was diagnosed as AML-M2 with NF1 at age 11 years. Patient 15, a seven-year-old with NF1, was diagnosed with ALL. Patient 16 was seen at two years of age, and diagnosed with JMML.

Malignant triton tumor (MTT) is a relatively rare subtype of malignant peripheral nerve sheath tumors, histologically defined as a malignant peripheral nerve sheath tumor with additional rhabdomyoblastic differentiation. MTTs are usually located in the head, neck, extremities, and trunk. Less common sites include the buttock, mediastinum and retroperitoneum[21]. Tumors in the retroperitoneum are extremely rare[22]. In our study, MTT was found in one patient. Patient 18, a four-year-old boy, was admitted with constipation and abdominal pain, and was found to have an abdominal mass on abdominal ultrasound. A biopsy was performed, and the histological diagnosis of retroperitoneal fibrosarcoma (MTT) was made.

In conclusion, the NF1 phenotype is variable; some patients are mildly affected and others have severe manifestations of disease. Specific complications are associated with age and some are progressive. Patients with NF1 are predisposed to both benign and malignant tumors. Although only a minority of patients

with NF1 develops malignancy as a complication of their disorder, cancer remains an important cause of morbidity and mortality in the disorder. Therefore, systematic medical follow-up in patients with NF1 is important.

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