

Gliomas presenting after age 10 in individuals with neurofibromatosis type 1 (NF1)

Abstract—Children with neurofibromatosis 1 (NF1) often develop low-grade gliomas, but brain tumors are infrequently encountered in adults with NF1. The authors present evidence from two clinical series, one including patients known to have NF1 and another focusing on adults with new onset brain tumors, that suggests an association between NF1 and symptomatic gliomas in older individuals. They also summarize the clinical data on 17 adolescents or adults with NF1 and symptomatic gliomas. The findings suggest that individuals with NF1 are at increased risk of developing gliomas throughout their lives.

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D.H. Gutmann, MD, PhD; S.A. Rasmussen, MD; P. Wolkenstein, MD, PhD; M.M. MacCollin, MD; A. Guha, MD; P.D. Inskip, ScD; K.N. North, MD; M. Poyhonen, MD; P.H. Birch, MSc; and J.M. Friedman, MD, PhD

Neurofibromatosis 1 (NF1) is a common autosomal dominant disorder in which affected individuals develop both benign and malignant tumors. Children with NF1 typically present with café-au-lait macules, skinfold freckling, and iris hamartomas (Lisch nodules). Nearly all adults with NF1 develop benign tumors, termed neurofibromas, that arise from the peripheral nerve sheath. The second most common tumor in individuals with NF1 is the astrocytoma (glioma), seen in 15 to 20% of patients.¹ Astrocytomas usually affect patients with NF1 in early childhood, with a mean age at diagnosis of 4.5 years.² Most of these low-grade pilocytic astrocytomas are located in the optic nerve, optic chiasm, and hypothalamus and, less frequently, in the brainstem and cerebellum. In contrast to optic pathway gliomas in children without NF1, NF1-associated optic pathway gliomas are frequently asymptomatic, and some have been reported to spontaneously regress.³ Brainstem gliomas in children with NF1 are commonly found in the medulla and frequently present with headache or evidence of neurologic dysfunction. Similar to NF1-associated optic pathway gliomas, radiographic or clinical progression occurs in only one-third of patients with NF1 with brainstem gliomas.⁴ Cerebellar gliomas are less common than optic pathway gliomas

in patients with NF1 and the majority represent pilocytic astrocytomas. In one series of children with cerebellar gliomas, only one of six with NF1 was symptomatic at the time of diagnosis, compared with 64 of 65 who did not have NF1.⁵

Although brain tumors are believed to be a complication of NF1 that is restricted to childhood, a recent study found reports of such tumors much more frequently on death certificates of adults with NF1 than among the general population.⁶ Brain tumors were reported 11 times more often than expected on death certificates of patients with NF1 who died between 10 and 19 years of age, nine times more often than expected between 20 and 29 years of age, and eight times more often than expected between 30 and 39 years of age. In addition, scattered published reports have described adults with NF1 and brain tumors.^{7,8} These findings collectively suggest that the increased risk of developing brain tumors in NF1 extends beyond the first decade of life.

To extend these observations, we determined the number of adult patients with NF1 in a National Cancer Institute (NCI)-sponsored study of newly diagnosed gliomas organized by one of us (P.I.). Three of 489 adults (>18 years of age) with newly diagnosed gliomas were reported as having NF1 (Patients 3, 13, and 15 in the table). This number may under-represent the true frequency, because not all NF1 patients in this study may have been identified; however, the observed rate of NF1 (0.6%) is at least 20 times greater than what would be expected in the general population.⁹

Based on this initial finding, we used the National Neurofibromatosis Foundation International Database (NNFFID), a multicenter collaboration designed to collect information about clinical manifestations and natural history of NF1, to determine the frequency with which adolescents or adults known to have NF1 were reported with symptomatic nonoptic pathway brain tumors. Such tumors were reported in 17 (0.8%) of 2,108 patients with NF1 over 10 years of age. The observed prevalence by age among these patients was compared to that in the general population using Surveillance, Epidemiology, and End Re-

From the Department of Neurology (Dr. Gutmann), Washington University School of Medicine, St. Louis, MO; National Center on Birth Defects and Developmental Disabilities (Dr. Rasmussen), Centers for Disease Control and Prevention, Atlanta, GA; Department of Dermatology (Dr. Wolkenstein), Henri-Mondor Hospital (AP-HP), Paris XII University, Créteil, France; Neuroscience Center MGH East (Dr. MacCollin), Charlestown, MA; Department of Neurosurgery (Dr. Guha), University of Toronto, Ontario, Canada; Radiation Epidemiology Branch (Dr. Inskip), Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; Department of Paediatrics and Child Health (Dr. North), University of Sydney, Australia; Department of Medical Genetics (Dr. Poyhonen), Family Federation of Finland, Helsinki; and Department of Medical Genetics (P.H. Birch and Dr. Friedman), University of British Columbia, Vancouver, Canada.

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Address correspondence and reprint requests to Dr. David H. Gutmann, Department of Neurology, Washington University School of Medicine, Box 8111, 660 S. Euclid Avenue, St. Louis, MO 63110; e-mail: gutmann@neuro.wustl.edu

Table Brain tumors presenting after age 10 in individuals with neurofibromatosis type 1 (NF1)

Patient no.	Age at diagnosis, y/sex	Pathology	Location	Presenting symptoms	Source
1	14/F	WHO II	Parietal lobe	Headache	NNFF
2	15/M	WHO II	Cerebellum	Headache, ataxia, dizziness	NNFF
3	18/F	WHO II	Third ventricle	Headache, hydrocephalus	PI
4	19/M	WHO II	Tectum	Weakness, headache, seizures	NNFF
5	23/F	WHO III	Frontal lobe	Headache, vomiting, balance problems	Other
6	26/F	NA	Frontal lobe	Headache	NNFF
7	26/M	WHO I	Frontal lobe	Headache	Other
8	27/M	WHO III	Brainstem	Headache, nystagmus	NNFF
9	28/M	WHO I	Frontal lobe	Headache, dizziness	Other
10	29.5/M	NA	Brainstem	Headache, paralysis	NNFF
11	36/F	WHO IV	Thalamus	Headache, seizures	NNFF
12	45/F	WHO II	Corpus callosum	Headache	NNFF
13	48/F	WHO III	Parietal-occipital lobe	Headache, paralysis	PI
14	49/F	WHO II	Tectum	Headache, drowsiness, ataxia	Other
15	52/F	WHO IV	Frontal lobe	Seizures	PI
16	52.5/F	WHO I	Frontal lobe	Paralysis	NNFF
17	53/M	WHO III	Cerebellum	Headache	NNFF

The 17 individuals with NF1 are arranged in order of age at presentation. The source of the patient is denoted as NNFF (National NF Foundation International Database), PI (National Cancer Institute–sponsored newly diagnosed adult glioma study), or Other (other clinical centers). The pathologic grade of the tumor was known for all tumors except two (NA = not available).

sults (SEER) estimates of the prevalence of brain tumors in these age groups. As shown in the figure, the observed prevalence of brain tumors in patients with NF1 up to 50 years of age is more than 100 times greater than expected, and the prevalence remains significantly elevated at all ages.

Adequate clinical information was available on 10 of the original patients from the NNFFID study to determine whether the tumor became symptomatic after the first decade of life, and similar information

was available on seven additional patients provided through the NCI newly diagnosed adult glioma study or our own clinical practices (see the table). Of these 17 patients with NF1, brain tumors were diagnosed in four individuals between 10 and 20 years of age, seven individuals between 21 and 40 years of age, and six individuals 41 years of age or older. The tumors were located in the brainstem (n = 2), cerebellum (n = 2), and cortical (n = 8) and subcortical regions (n = 5). None of these patients is known to

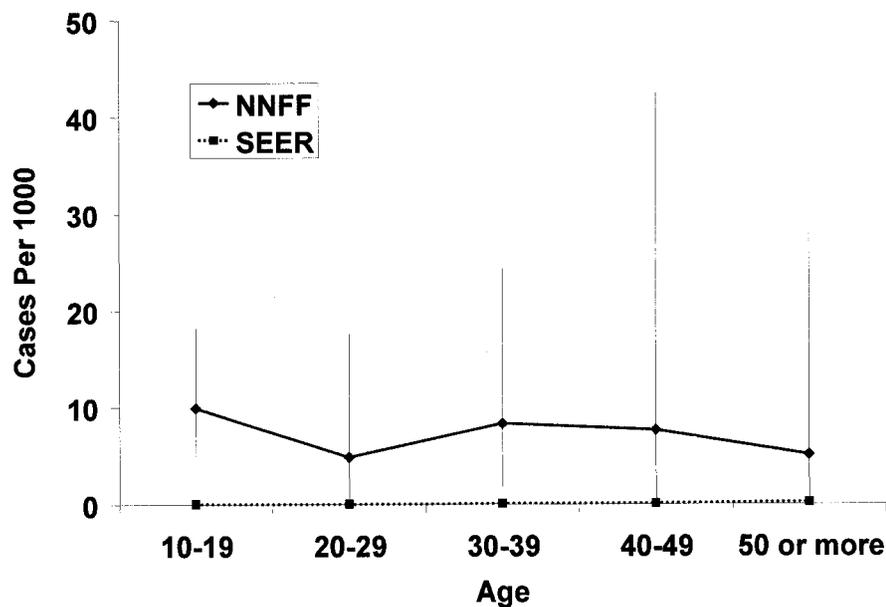


Figure. Prevalence of symptomatic nonoptic pathway brain tumors among patients with neurofibromatosis 1 reported to the National Neurofibromatosis Foundation (NNFF) International Database by age group. Surveillance, Epidemiology, and End Results (SEER) estimates of the prevalence of brain tumors in these age groups in the US general population (<http://seer.cancer.gov/>) are provided for comparison. Rates are given as cases per 1,000 with Poisson exact 95% CIs indicated by vertical bars.

have been treated previously with chemotherapy or radiation.

In 15 of the 17 patients, the pathologic grade of the tumor was known. All tumors were classified using conventional WHO criteria for astrocytomas.¹⁰ Three tumors were pilocytic astrocytomas; six were grade II, four were grade III, and two were grade IV (glioblastoma multiforme) neoplasms. The most frequent presenting symptom was headache (15 patients), whereas paralysis or seizures were among the initial clinical symptoms in three patients each. It should be noted that the higher grade gliomas (grades III and IV) in our series were found in the patients older than 20 years. The small number of patients in this study does not permit comparisons between patients with NF1 and those in the general population with regard to the age at onset of these high-grade brain tumors.

Although we do not know whether all of these tumors arose de novo after the age of 10, none of the teenagers in our study had a pilocytic astrocytoma, characteristic of childhood NF1 brain tumors. Because pathologic transformation of pilocytic astrocytomas is exceedingly rare and is usually a sequelae of cranial irradiation,¹⁰ it is unlikely that these grade II astrocytic tumors arose from pre-existing pilocytic tumors that had been asymptomatic since early childhood. Moreover, these grade II gliomas did not have histopathologic features of anaplastic "pilocytic" astrocytomas. Studies are underway to characterize NF1-associated astrocytomas in adolescents and adults more fully with respect to histopathologic features and genetic alterations.

Our findings suggest that individuals with NF1 remain at substantially increased risk for the development of astrocytomas beyond the first decade of life, and that such tumors are not always "benign" pilocytic astrocytomas. We cannot accurately quantify the risk of astrocytomas in older patients with

NF1 from this study because our data are not population-based. Population-based epidemiologic studies will be required to estimate the risk of brain tumors in teenagers and adults with NF1 accurately. The findings described here reinforce the need to perform brain imaging studies and provide careful clinical follow-up in patients with NF1 of any age who present with persistent headache or neurologic abnormalities.

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