Lack of Evidence for an Association Between Neurofibromatosis Type I and Intracranial Aneurysms

Autopsy Study and Review of the Literature

James E. Conway, MD, PhD; Grover M. Hutchins, MD; Rafael J. Tamargo, MD

Background and Purpose—Neurofibromatosis type I (NF1) is an autosomal dominant, hereditary, neurocutaneous syndrome purported to be associated with intracranial aneurysms. To study the relationship between NF1 and intracranial aneurysms, we have analyzed all intracranial autopsies of NF1 patients performed at our institution from 1889 to 1999 and analyzed all intracranial aneurysm cases at our institution from 1990 to 1999 in an attempt to identify patients with NF1. In addition, we have reviewed published clinical series of NF1 patients.

Methods—The autopsy database at our institution, which contains 50,000 cases from 1889 to 1999, was searched to identify NF1 patients, and the results of these autopsies were reviewed. The prevalence of intracranial aneurysms in these NF1 patients was compared with the prevalence of intracranial aneurysms in our hospital’s autopsy population and with the published prevalence of intracranial aneurysms in the general population. To identify patients with intracranial aneurysms and NF1, our institution’s intracranial aneurysm database was searched for patients with clinical manifestations of NF1. Published clinical series of NF1 patients were identified through searches of the literature.

Results—None of the 25 autopsy patients with NF1 had an intracranial aneurysm. None of the 925 patients treated for intracranial aneurysms were affected by NF1. A review of the literature identified 8 comprehensive clinical studies, all of which failed to document any relationship between NF1 and intracranial aneurysms.

Conclusions—The autopsy prevalence of no NF1 patients with intracranial aneurysms out of 25 is not different from the prevalence of intracranial aneurysms in the general autopsy population. In addition, no patients treated for intracranial aneurysms at this institution had NF1. These findings are supported by the observation that an association between NF1 and intracranial aneurysms has never been identified in 8 large clinical studies of NF1 patients. We conclude that there is a lack of evidence for any association between NF1 and intracranial aneurysms. (Stroke. 2001;32:2481-2485.)

Key Words: aneurysm □ autopsy □ neurofibromatosis

Neurofibromatosis type I (NF1) is a hereditary neurocutaneous syndrome resulting from mutations in the NF1 gene (chromosome 17q11.2).1-3 NF1 encodes the tumor suppressor neurofibromin, a GTPase-activating protein thought to negatively regulate the ras signal transduction pathway.4-8 Neurofibromin is expressed in a variety of tissues, including the brain, blood vessels, muscle, and skin.6,9-11 Aberrant neurofibromin function in affected tissues results in the clinical features of NF1.12-18

Clinical features of NF1 include neurofibromas, café-au-lait spots, Lisch nodules, malignancies (central nervous system tumors and pheochromocytoma), vascular occlusive disease, and skeletal deformities (thinning of the cortex of long bones, pseudoarthrosis, and scoliosis).12,15,17,19-24 In the literature, it has also been suggested that there exists an association between intracranial aneurysms and NF1. The basis for this purported association is a series of 23 case reports describing intracranial aneurysms in NF1 patients.19,25-41 The alleged increased prevalence of intracranial aneurysms in NF1 patients has led to the recommendation that NF1 patients should be screened for these lesions.33

The purpose of the present study was to analyze our institution’s clinical experience with NF1 patients and to review the literature for assessment of the perceived association between NF1 and intracranial aneurysms. Specifically, we determined the prevalence of intracranial aneurysms in an autopsy series between 1889 and 1999 of NF1 patients and compared it with that of the general autopsy population. In addition, we report the prevalence of NF1 in patients requiring neurosurgical treatment of intracranial aneurysms at our institution between 1990 and 2000. Eight comprehensive clinical studies are also reviewed to assess the association between NF1 and aneurysms.
TABLE 1. Diagnostic Criteria for NF1

<table>
<thead>
<tr>
<th>Presence of ≥2 of the Following Conditions in Patients for Diagnosis of NF1</th>
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<tr>
<td>≥6 café-au-lait macules &gt;5 mm in greatest diameter in prepubertal individuals and &gt;15 mm in greatest diameter in postpubertal individuals</td>
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<tr>
<td>≥2 neurofibromas of any type or 1 plexiform neurofibroma</td>
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<tr>
<td>Freckling in axillary or inguinal region</td>
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<tr>
<td>Optic pathway tumor</td>
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<tr>
<td>≥2 Lisch nodules</td>
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<tr>
<td>Distinctive osseous lesion (such as sphenoid wing dysplasia or thinning of cortex of long bones)</td>
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<tr>
<td>First-degree relative (parent, sibling, or offspring) with NF1 diagnosed with these criteria</td>
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Criteria were established by the National Neurofibromatosis Foundation Clinical Care Advisory Board42,43 (Table 1). According to these criteria, a diagnosis of NF1 requires that patients exhibit ≥2 of the conditions described in Table 1.

Methods

NF1 Diagnosis

Patients with NF1 were identified by using the criteria established by the National Neurofibromatosis Foundation Clinical Care Advisory Board42,43 (Table 1). According to these criteria, a diagnosis of NF1 requires that patients exhibit ≥2 of the conditions described in Table 1.

Autopsy Cases

The Department of Pathology at the Johns Hopkins Medical Institutions maintains a database of >50,000 autopsies performed at this institution from 1889 to 1999. A query of this database using the search words “neurofibromatosis,” “café-au-lait,” “optic glioma,” “neurofibroma,” and “Recklinghausen” was performed to identify NF1 patients. The medical records and autopsy results of all patients identified in this search were analyzed. Pertinent information for each patient was then recorded and included the patients’ sex, race, cause of death, age at death, and a family history of NF1. Possible manifestations of NF1 that were recorded included the following: (1) type, number, size, and location of neurofibromas; (2) number, size, and location of café-au-lait spots; (3) presence of axillary or inguinal freckling; (4) presence of an optic pathway tumor; (5) presence and number of Lisch nodules; and (6) presence of distinctive osseous defect. The diagnostic criteria for NF1 described above were used to identify patients with NF1, and those NF1 patients with intracranial autopsies were included in the present study.

Intracranial Aneurysm Series

The Division of Cerebrovascular Neurosurgery at the Johns Hopkins Medical Institutions maintains a database of all patients treated for intracranial aneurysms at this institution from 1990 to 2000. All patients in this database have had an angiographic or autopsy-proven diagnosis of an intracranial aneurysm. This database was searched for any patient with a clinical manifestation of NF1 or a diagnosis of the disease.

Statistical Analysis

The prevalence of intracranial aneurysms observed in NF1 autopsy patients was compared with the prevalence of intracranial aneurysms in the autopsy population at our institution44 and with the prevalence of intracranial aneurysms in the general population.45 Statistical comparisons were made by using the binomial probability test (Stata Statistical Software, version 6.0, Stata Corp).

Results

NF1 Autopsy Series

Sixty-three possible cases were discovered during the autopsy database search for NF1 patients. Of these 63 cases, 61 had intracranial autopsies. Analysis of these 61 cases revealed that 25 met the criteria for a diagnosis of NF1. These 25 cases represented 25 different families and were autopsied between the years 1905 and 1990.

Epidemiological characteristics of 25 confirmed NF1 patients are listed in Table 2. Of the 25 NF1 patients, 15 were male (60%), and 10 were female (40%). The mean age of death was 30 years, and the range of age at the time of death was 3 to 69 years. Twenty-two of the 25 patients were in at least their second decade of life. Seven patients (28%) died from complications of surgery for NF1-associated malignancies, including plexiform neurofibromas (3 patients), central nervous system (CNS) astrocytomas (2 patients), neurogenic sarcoma (1 patient), and optic glioma (1 patient). Six patients (24%) died from medical complications of NF1-associated malignancies, including plexiform neurofibromas (2 patients), CNS astrocytomas (2 patients), rhabdomyosarcoma (1 patient), and ganglioneuroma (1 patient). Two patients (8%) died from the medical complications of gastric carcinoma and bladder carcinoma. Ten patients (40%) died from additional causes, including pneumonia, meningitis, cardiac arrest, and AIDS.

The clinical features found in the patients used to establish a definite diagnosis of NF1 are listed in Table 3. Neurofibromas (cutaneous, dermal, and plexiform) were the most common clinical trait associated with NF1 documented at autopsy. Café-au-lait macules, osseous defects, axillary or inguinal freckling, optic gliomas, and Lisch nodules were also observed at autopsy in these patients.

These 25 NF1 patients had detailed intracranial examinations at autopsy, and none were found to have an intracranial

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Patients, n (%)</th>
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<tr>
<td>Neurofibroma</td>
<td>24 (96)</td>
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<tr>
<td>Café-au-lait macules</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Osseous defect</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Axillary or inguinal freckling</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Optic glioma</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Lisch nodules</td>
<td>3 (12)</td>
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aneurysm. During autopsy, 4 patients were found to have had intracranial hemorrhages, but none were caused by ruptured aneurysms. One of these patients was a 5-year-old female who experienced a subdural and subarachnoid hemorrhage as a complication of surgery for an optic glioma. The second patient was a 29-year-old female who suffered an intraventricular hemorrhage that was a complication of surgery for a CNS ganglieneuroma. The third patient was a 46-year-old female who died from a spontaneous intraparenchymal brain stem hemorrhage. At autopsy, this intraparenchymal hemorrhage was found to have extended into the perimesencephalic cisterns. The fourth patient was a 12-year-old female who died of cardiac arrest during a seizure. She had previously experienced disseminated intravascular coagulation for several days and, concurrent with this disorder, experienced a right occipital hemorrhage.

Statistical Analysis
We have previously established that the prevalence of intracranial aneurysms in the autopsy population at this institution is 1.3% in a study of 13,042 consecutive autopsy subjects. This figure is in accordance with the widely accepted statistic for the prevalence of intracranial aneurysms in the general population of 2%, which is derived from a review of 8 autopsy series. In our NF1 autopsy series, the prevalence of intracranial aneurysms was 0 of 25 patients. The prevalence of 0 of 25 patients is not statistically different from the 1.3% prevalence of intracranial aneurysms in the autopsy population at this institution \(P = 0.72\) or from the 2.0% prevalence of intracranial aneurysms in the general population \(P = 0.60\).

Intracranial Aneurysm Series
At our institution, 925 patients have been treated for intracranial aneurysms over the last decade. A search of the intracranial aneurysm database identified no patients with NF1.

Discussion
Clinical manifestations of NF1 include neurofibromas, café-au-lait spots, Lisch nodules, malignancy, skeletal manifestations, and cognitive deficits. \(^{12,15,17,20,21,23,24}\) Vascular manifestations associated with NF1 include renal artery stenosis and cerebral artery occlusive disease. \(^{15,19,46,47}\) An association between NF1 and intracranial aneurysms has also been suggested on the basis of a series of 23 case reports describing intracranial aneurysms in NF1 patients. \(^{19,25–41}\) As a result of this proposed association, it has been suggested that patients with NF1 be screened for intracranial aneurysms. \(^{33}\)

In addition to NF1, other hereditary diseases have historically been associated with intracranial aneurysms. These diseases include autosomal dominant polycystic kidney disease, Ehlers-Danlos syndrome type IV, pseudoxanthoma elasticum, and Marfan’s syndrome. \(^{48,49}\) Except for autosomal dominant polycystic kidney disease, however, the evidence supporting an association between the diseases and intracranial aneurysms is suspect and is based only on case reports. \(^{48,49}\) For example, we have recently reported that there exists no evidence that Marfan’s syndrome is actually associated with an increased prevalence of intracranial aneurysms, and we have concluded that there is no need to screen Marfan patients for these lesions. \(^{50}\) In the present study, the purported association between NF1 and intracranial aneurysms was similarly analyzed.

NF1 is one of the most common genetic disorders and occurs with a prevalence of 1:3000 people. \(^{12,51}\) As a result of this high prevalence, our hospital, as a tertiary referral center, has acquired an extensive clinical experience with NF1 patients. \(^{32–59}\) To investigate the perceived association between NF1 and intracranial aneurysms, we have analyzed our institution’s pathological and neurosurgical experience with NF1 patients. A search of our institution’s autopsy database identified 25 confirmed NF1 patients. These 25 NF1 patients all underwent detailed intracranial examinations at autopsy, but none was found to have an intracranial aneurysm. In addition, none of the 925 patients requiring treatment for an intracranial aneurysm at our institution during the last decade was affected by NF1.

The assertion that NF1 patients have an increase prevalence of intracranial aneurysms is similarly not supported by 8 comprehensive clinical studies. In a hospital-based study byCrowe et al, \(^{12}\) the clinical manifestations of 223 neurofibromatosis subjects were documented. A symptomatic intracranial aneurysm was never observed in these patients, nor was the rupture of an intracranial aneurysm ever the cause of death in 15 of the patients who died. In a hospital-based study of NF1 patients conducted by Brasfield and Das Gupta, \(^{20}\) NF1 manifestations were recorded for 110 patients, of which 41 died. In that study, a symptomatic intracranial aneurysm was never documented. Sorensen et al, \(^{21}\) conducted a 40-year prospective study of 212 neurofibromatosis subjects, during which 113 deaths occurred. At the end of that study, the authors concluded that except for malignancies, their patients did not suffer an increased frequency of any other disease when they were compared with the general population. Huson et al \(^{17}\) have published the results of a population-based study of 135 NF1 patients and did not document a symptomatic intracranial aneurysm. In that study, the cause of death was known for 25 deceased affected relatives as well. One of these 25 deaths was caused by a subarachnoid hemorrhage in a patient who suffered from hypertension, but an aneurysmal source of the hemorrhage was never proven. Ricardi \(^{15}\) has studied and treated 947 NF1 patients referred to his institute and has compiled 1577 patient-years of direct observation and 6064 patient years of total clinical follow-up. In his study, Ricardi did not document any symptomatic intracranial aneurysm. Ricardi also determined the cause of death in 37 of 39 of his NF1 patients who died, and a ruptured intracranial aneurysm was never observed. Zoller et al \(^{22}\) have published the results of a 12-year follow-up of 70 NF1 patients. In their population-based study, only 1 patient was observed to have an intracranial aneurysm. An aneurysmal rupture was not the cause of death in 22 NF1 patients. Two recent studies have reported the neurological complications of 138 NF1 patients and the clinical features observed in 523 NF1 patients. \(^{23,24}\) In neither of these studies was a symptomatic intracranial aneurysm reported.

The mean age of aneurysmal rupture in the general population is 56 years. \(^{60}\) However, the prevalence of intracranial aneurysms detected at autopsy is high even during the
second and third decades of life. We have documented that the prevalence of intracranial aneurysms detected at autopsy during the second decade of life is \( \approx 1\% \) in the general population.\(^{44}\) In the third decade of life, the prevalence of intracranial aneurysms at autopsy is \( \approx 2\%.\)\(^{44}\) Thus, intracranial aneurysms are not infrequently found at autopsy even at a young age, suggesting that they begin to develop in the second or third decade of life and become clinically apparent later. In our NF1 autopsy series, the mean age of the subjects was 30 years, and 22 of the 25 subjects (88\%) were in at least their second decade of life. Therefore, the majority of patients in this series were not too young to have developed detectable intracranial aneurysms.

In summary, on the basis of a review of 8 clinical reports of NF1 patients, our autopsy series of 25 confirmed NF1 subjects, and a recent neurosurgical series of intracranial aneurysms, we find that there exists no evidence to associate NF1 with an increased prevalence of intracranial aneurysms. Therefore, we conclude that screening NF1 patients for intracranial aneurysms is not warranted.

References


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