Increased Risk of Cerebrovascular Disease Among Patients With Neurofibromatosis Type 1
Population-Based Approach

Anna R. Terry, MD, MPH; Justin T. Jordan, MD; Lee Schwamm, MD; Scott R. Plotkin, MD, PhD

Background and Purpose—Although neurofibromatosis type 1 (NF1) may be associated with an incompletely understood vasculopathy, relative odds of stroke in this population is not known.

Methods—Using the 1998 to 2009 US Nationwide Inpatient Sample, we performed a case–control study matching cases of NF1 to controls without such a diagnosis. We then compared the odds of stroke between the 2 groups. We used multivariable logistic regression to adjust for known or suspected confounders.

Results—NF1 was associated with younger mean age at the time of stroke (41 versus 48) and a lower prevalence of stroke risk factors among adult patients. Pediatric patients with NF1, however, were more likely to have hypertension. Patients with NF1 were significantly more likely to be diagnosed with any stroke (odds ratio, 1.2; \( P < 0.0001 \)) than the general population. The odds of intracerebral hemorrhage were greatest among hemorrhagic stroke types analyzed (odds ratio, 1.9; \( P < 0.0001 \)). In the pediatric NF1 population, the odds of intracerebral hemorrhage were more dramatically elevated (odds ratio, 8.1; \( P < 0.0001 \)). The odds of ischemic stroke were also increased with NF1 in the pediatric (odds ratio, 3.4; \( P < 0.0001 \)) but not in the adult population.

Conclusions—When compared with the general population, the odds of any type of stroke are significantly increased for patients with NF1, both adult and pediatric. This risk is most notable for hemorrhagic strokes although it is also increased for ischemic strokes in children. Physicians should be aware of the increased risk of stroke in this population, and consider stroke as a potential cause of new neurological symptoms. (Stroke. 2016;47:60-65. DOI: 10.1161/STROKEAHA.115.011406.)

Key Words: case-control studies ■ cerebral hemorrhage ■ genetics ■ neurofibromatosis ■ stroke

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumor suppressor syndrome characterized by histologically benign tumors of the peripheral and central nervous system, as well as the skin. In addition, NF1 carries an 8% to 13% lifetime risk of developing malignant peripheral nerve sheath tumors. With a birth incidence of ≈ 1 in 3000, NF1 is the most common neurocutaneous disorder, and among the most common neurogenetic disorders. Recent population-based studies combining cancer surveillance and genetic registries have demonstrated a 42% rate of de novo mutations among patients with NF1. The median life expectancy in NF1 is several years less than the general population.

Along with a predisposition to certain types of neoplasms, NF1 is additionally associated with an incompletely understood vasculopathy. An association with vascular abnormalities including moyamoya arteriopathy,16 cerebral aneurysms,14 and stenotic or ectatic cerebral vessels15 increases the risk of ischemic and hemorrhagic stroke in affected individuals. Conversely, an autopsy study of 25 subjects did not demonstrate a significant increase in intracranial aneurysm in NF1 patients.16 NF1 predisposes to pheochromocytoma and renal artery stenosis, both of which cause secondary hypertension, a major risk factor for stroke and cardiac disease. In the pediatric NF1 population, there is an increased prevalence of both peripheral and cerebral vasculopathy. Finally, our recent work on pregnancy outcomes suggests that phenomena such as preeclampsia and cerebrovascular disease are more common in NF1.

Given the prevalence of vasculopathy and cerebrovascular anomalies with NF1, an elevated risk of stroke has been postulated in previous research. Several case reports describe the link between stroke in NF1 patients with moyamoya syndrome20-22 and other cerebral arteriopathies. Also, at least 1 case report describes a hypertensive stroke in a child with NF1. However, to the best of our knowledge, there have been no population-based studies that address the risk of cerebrovascular events requiring hospitalization among patients with NF1. To better understand this risk, we used a nationally representative sample of hospitalized US patients to determine...
whether a clinical diagnosis of NF1 is an independent risk factor for stroke.

Methods

The Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality (AHRQ, Rockville, MD), collects deidentified administrative and clinical data on US hospital discharges. The 2009 NIS, used here, contains discharge data on 7.7 million discharges from 1050 hospitals in 44 states, a 20% stratified sample of all nonfederal hospitals. Reporting of cell sizes <10 is prohibited, to minimize the possibility of privacy violation. Information available from the NIS includes ≤15 International Classification of Diseases-Ninth Revision- Clinical Modification (ICD-9-CM) diagnosis and procedure codes for each hospitalization, geographic region, hospital characteristics, and payer information. We used the NIS data sets from 1998 to 2009, a timeframe chosen to capture patients after the widespread introduction of magnetic resonance imaging for diagnosis of ischemic stroke.

To identify stroke-related hospitalizations, we searched for relevant ICD-9-CM codes for nontraumatic cerebrovascular disease (430.xx-436.xx, 325.xx), which includes subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), occlusion and stenosis of precerebral arteries (ie, embolism from or thrombosis of extracranial carotid and vertebral arteries), occlusion of cerebral arteries (ie, embolism from or thrombosis of intracranial arteries), transient ischemic attack, and acute but ill-defined cerebrovascular disease. These cases were included with (x1) or without (x0) documented imaging evidence of infarction, as designated by the suffix codes. With respect to hemorrhagic stroke subtypes, the ICD-9-CM distinguishes between ICH (431-432) and SAH (430), and we maintain this distinction in reporting our data. Cases with both SAH and ICH diagnosis codes were coded in both categories although additional clinical information as not captured because of small cell sizes. Cerebral venous sinus thrombosis was considered, but ultimately omitted from this analysis because of its rarity and the restrictions on reporting small cell sizes, as mentioned above.

To identify NF1-related hospitalizations, we began by searching diagnosis codes for NF1 (237.71), neurofibromatosis type 2 (NF2, 237.72), and unspecified neurofibromatosis (NF NOS, 237.70). Because the fifth digit ICD-9-CM modifier was not consistently used before 1990, we assumed that many patients previously coded as 237.7 were subsequently labeled as NF NOS (237.70). Because NF1 is much more common than NF2, we assumed that NF NOS would nearly always be classified as NF1 if appropriate clinical criteria were applied. To test these assumptions, we estimated the specificity of the NF2 code by comparing the frequency of hospitalizations involving surgery for vestibular schwannoma resection in the various groups (as bilateral vestibular schwannoma is pathognomonic for NF2). Approximately 1 in 6 discharges coded as 237.72 were associated with a vestibular schwannoma resection when compared with 0.1% in discharges coded as 237.70, 237.71, 237.7, or in the non-NF population. Thus, codes 237.70, 237.71, and 237.7 were all imputed as NF1.

We sought to reduce bias toward NF1 prevalence in our population by eliminating all hospitalizations that occurred specifically because of NF1, such as for resection of a malignant peripheral nerve sheath tumor. However, the ICD-9 system does not contain any diagnosis or procedure that could be considered specific for NF1, so we elected to use the entire data set.

We used ICD-9-CM diagnosis codes to identify all hospitalizations associated with the following stroke risk factors: atrial fibrillation, atherosclerosis, family history of stroke, hypertension, diabetes mellitus, unruptured aneurysm, moyamoya disease or syndrome, and sickle cell anemia. We also identified demographic and hospital characteristics as potential confounders. Race or ethnicity was defined as non-Hispanic white, non-Hispanic black, Hispanic, or other. Elderly age was defined as ≥65 years old, and pediatric was defined as ≤18 years old. Socioeconomic status was defined as income quartile based on median total family income within the zip code of the patient’s primary residence. Information on primary insurance payor (Medicare, Medicaid, privately insured, or self-pay/uninsured) was directly available from the NIS.

Given the large total number of hospitalizations and challenges of generating interpretable results for a rare condition, we narrowed our study population with a specific methodologic strategy. Using the retrospective cohort of hospitalizations associated with NF1, we designed a case-control algorithm to limit analyses to a representative sample. We defined cases as hospitalizations with an associated diagnosis of NF1 and controls without such a diagnosis. Controls were matched to cases in a 5:1 ratio by age and sex. To account for clustering of cases within hospitals or regions, matching was also performed on the following factors: geographic region (Northeast, Midwest, South, or West), hospital size based on number of beds (small, medium, or large), and hospital type (rural, urban nonteaching, or urban teaching). Before the matching procedure, we eliminated observations with missing data for any of the variables of interest (<0.1% for all categories except race and income quartile, to which we assigned separate missing categories).

We used multivariable logistic regression to determine odds ratios and 95% confidence intervals for the risk of ischemic or hemorrhagic stroke among hospitalized individuals with NF1. Final adjusted models included subsets of the covariates described above. We used an automated score selection algorithm to determine the set of covariates that provided the best explanation of the variation in the data, allowing ≤1 covariate for every 10 events. For all statistical analyses, we used SAS software (version 9.0; SAS Institute Inc., Cary, NC). Statistical significance is defined as P<0.05; all P values are 2-tailed. Because obtaining accurate national estimates was not a focus of this study, the unweighted NIS data set was used, without accounting for its sampling design. No institutional review board approval was required for the use of the NIS, as it is a deidentified, publically available database.

Results

We identified >90 million admissions that occurred between 1998 and 2009. Of these, 21,378 (0.02%) admissions carried a diagnosis of NF1. Furthermore, 2998,370 admissions (3%) carried a coded diagnosis of any type of stroke (as defined in the methods section). Cumulatively, 601 admissions carried diagnosis codes for both NF1 and any type of stroke.

We first evaluated all cases of NF1, regardless of stroke diagnosis, to identify demographic trends. Patients admitted with NF1 had a younger mean age than all patients without NF1. Furthermore, hospitalized patients with NF1 were less likely to be elderly and slightly more likely to be children (Table 1). Racial, ethnic, and regional differences between NF1 and the general inpatient population were small. However, hospitalized patients with NF1 were more likely to be from lower income quartiles and to be covered by Medicaid. Finally, patients with NF1 were more likely to be cared for in urban-teaching hospitals than the general population. All observed associations were significant to a level of P<0.0001.

In the adult population, ischemic stroke was the most common for both NF1 and non-NF1, followed by hemorrhagic stroke (predominantly ICH; Table 2). In the pediatric population, hemorrhagic stroke was the most common stroke subtype regardless of NF1 status. Adult hospitalized patients with NF1 were less likely to have common stroke risk factors including diabetes mellitus, atrial fibrillation, and atherosclerosis, but were about as likely to have hypertension and more likely to have other cerebrovascular abnormalities such as an unruptured aneurysm or moyamoya syndrome than those without NF1. Although there was no significant difference
in the baseline prevalence of diabetes mellitus in the pediatric NF1 and non-NF1 population, pediatric patients with NF1 were far more likely to have hypertension and associated vascular abnormalities such as atherosclerosis, unruptured aneurysms, and moyamoya syndrome.

We present both univariate and multivariable analyses in Table 3. In the combined adult and pediatric population, hospitalized patients with NF1 were significantly more likely to be diagnosed with stroke, and this enhanced risk was primarily because of hemorrhagic stroke subtypes. In adults with NF1, there was similarly a significantly increased odds of stroke although the odds of ischemic stroke and SAH were not elevated. Finally, in children with NF1, the odds of any stroke type were elevated when compared with all pediatric hospitalized patients, including specifically elevated odds of both ischemic and hemorrhagic strokes. The odds of SAH were not specifically elevated in this group. Notably, the number of events for cerebral venous sinus thrombosis in adults and children, as well as SAH in children, were too small for individual multivariable analysis, so we elected not to include them in the article.

Discussion

In hospitalized patients with NF1, the odds of stroke diagnosis were elevated when compared with non-NF1 individuals, both in adults and children. This was primarily because of a significantly higher incidence of hemorrhagic stroke subtypes (ICH and SAH), whereas the odds of ischemic stroke were higher only among children with NF1. Importantly, the odds of all stroke subtypes, except SAH, were more dramatically elevated in the pediatric NF1 population. This likely reflects not only a stark contrast between the exceedingly low risk of stroke among non-NF1 pediatric patients versus those with NF1 but also possibly a more severe NF1 phenotype, including cerebrovascular abnormalities. Indeed, both adult and pediatric patients with NF1, regardless of stroke, were more likely to have concurrent cerebrovascular abnormalities such as moyamoya arteriopathy and unruptured aneurysms. The NF1 population with pediatric onset of vascular disease may thus reflect a cohort of patients at higher risk of occult cerebrovascular disease category that requires more aggressive screening. In contrast, an autopsy study from a single institution found no evidence for an association between NF1 and intracranial aneurysms, and thus the authors did not recommend screening.\textsuperscript{16} However, the number of NF1 cases was only 25, highlighting the difficulty of interpreting findings in a rare disease and underscoring the need for future prospective studies of vascular risk factors in NF1.

In many respects, hospitalized patients with NF1 were similar to the general population in our study, both in their baseline characteristics and in the distribution of stroke subtypes. However, they differed in several key ways. First, they were younger, implying earlier and potentially more sustained contact with the healthcare system. Second, they were from lower socioeconomic strata and more likely to be insured by Medicaid. Third, they were more likely to be cared for in urban-teaching hospitals, reflecting referral patterns of patients with genetic disorders to specialists and tertiary care centers. Finally, in the adult population with NF1, prevalence of common stroke risk factors including diabetes mellitus, atherosclerosis, and atrial fibrillation was lower, which was not entirely explained when controlling for younger age.

Although we attempted to address these differences by conducting a rigorous multivariate analysis and controlling for clinically important factors, these observations should be further explored in additional studies.

Although NF1 is among the most common neurogenetic disorders, it is nonetheless relatively rare in the general population. As such, the use of large databases, including the NIS or a dedicated NF1 clinical registry, may be the only feasible approach to address the clinical importance of the risk factors and outcomes in NF1.
way to achieve an adequate sample size for association studies. Because the NIS incorporates all payors (including the uninsured) and all types of hospitals, it enables sampling of a more nationally representative population than other US databases such as the Medicare or VA registries. Although stroke is more common in the elderly, NF1 affects people of all ages, and its manifestations occur as early as childhood. Our approach allowed us to collect the largest possible number of stroke cases in all age groups, an effort that could take years or decades if subjects were recruited prospectively. It is limited, however, in the fidelity of the diagnoses captured in administrative databases.

Additional limitations to the use of databases include the unavoidable lack of clinical detail. In the current study,

<table>
<thead>
<tr>
<th>Stroke subtype</th>
<th>Adult NF1 Cases (%)</th>
<th>Adult Controls, %</th>
<th>Pedi NF1 Cases (%)</th>
<th>Pedi Controls, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>547 (3.2)</td>
<td>4</td>
<td>54 (1.2)</td>
<td>0.1</td>
</tr>
<tr>
<td>Ischemic</td>
<td>431 (2.6)</td>
<td>3.5</td>
<td>22 (0.49)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hemorrhagic (SAH/ICH)</td>
<td>116 (0.69)</td>
<td>0.5</td>
<td>31 (0.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>ICH</td>
<td>91 (0.54)</td>
<td>0.4</td>
<td>30 (0.67)</td>
<td>0.04</td>
</tr>
<tr>
<td>SAH</td>
<td>28 (0.17)</td>
<td>0.1</td>
<td>&lt;10*</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke risk factor</th>
<th>Adult NF1 Cases (%)</th>
<th>Adult Controls, %</th>
<th>Pedi NF1 Cases (%)</th>
<th>Pedi Controls, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>1,085 (6.4)</td>
<td>19.5</td>
<td>23 (0.52)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5278 (31.2)</td>
<td>39.7</td>
<td>234 (5.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>Atrial fibrillation/flip</td>
<td>978 (5.8)</td>
<td>9.9</td>
<td>&lt;10*</td>
<td>0.03</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>1753 (10.4)</td>
<td>19.0</td>
<td>47 (1.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Unruptured aneurysm</td>
<td>36 (0.21)</td>
<td>0.1</td>
<td>&lt;10*</td>
<td>0</td>
</tr>
<tr>
<td>Moyamoya</td>
<td>15 (0.09)</td>
<td>0.0</td>
<td>50 (1.1)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage; NF1, neurofibromatosis type 1; Pedi, pediatric; and SAH, subarachnoid hemorrhage. *Healthcare Cost and Utilization Project guidelines prohibit reporting of cell sizes with <10 observations.

Table 3. Univariate and Multivariate OR and 95% Confidence Intervals for Stroke Subtypes in Combined, Adult, and Pediatric NF1 Population Compared With All US Hospital Admissions, 1998 to 2009

<table>
<thead>
<tr>
<th>Stroke type</th>
<th>Unadjusted OR</th>
<th>Adjusted OR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.9</td>
<td>1.2 (1.1–1.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischemic</td>
<td>0.7</td>
<td>1.1 (0.99–1.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hemorrhagic (ICH+SAH)</td>
<td>1.7</td>
<td>1.7 (1.4–2.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICH</td>
<td>1.6</td>
<td>1.9 (1.6–2.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAH</td>
<td>1.6</td>
<td>1.2 (0.8–1.9)*</td>
<td>0.3</td>
</tr>
<tr>
<td>Adult only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.81</td>
<td>1.1 (1.0–1.2)</td>
<td>0.013</td>
</tr>
<tr>
<td>Ischemic</td>
<td>0.72</td>
<td>1.0 (0.9–1.2)</td>
<td>0.47</td>
</tr>
<tr>
<td>Hemorrhagic (ICH+SAH)</td>
<td>1.39</td>
<td>1.4 (1.2–1.8)</td>
<td>0.0007</td>
</tr>
<tr>
<td>ICH</td>
<td>1.33</td>
<td>1.5 (1.2–1.9)</td>
<td>0.0005</td>
</tr>
<tr>
<td>SAH</td>
<td>1.63</td>
<td>1.3 (0.8–1.9)*</td>
<td>0.25</td>
</tr>
<tr>
<td>Pediatric only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>12.6</td>
<td>4.5 (3.0–6.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischemic</td>
<td>10.51</td>
<td>3.4 (1.8–6.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hemorrhagic (ICH+SAH)</td>
<td>15.37</td>
<td>6.3 (3.6–10.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICH</td>
<td>17.58</td>
<td>8.1 (4.4–14.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SAH</td>
<td>2.8 (0.39–19.8)*</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

Multivariate analyses are adjusted for age, sex, diabetes mellitus, hypertension, atrial fibrillation/flutter, atherosclerosis, race, socioeconomic status, and insurance payor. ICH indicates intracerebral hemorrhage; NF1, neurofibromatosis type 1; OR, odds ratio; and SAH, subarachnoid hemorrhage.

*Adjusted for age and sex.
†Univariate only (too few events to perform multivariate analysis).
the observed prevalence of NF1 in US hospitalizations was \(0.02\%\), which correlates with published estimates of 1 in 3000 for the condition’s prevalence in the general population. Although NF1 may have a wide variety of clinical presentations, it stands to reason that patients with a more severe phenotype, or those with more NF1-associated comorbidities, may be more likely to receive accurate diagnosis coding. Therefore, if biased toward more severe or classical NF1 phenotype, these associations may underestimate the true risk of stroke with NF1. Furthermore, the overall rate of hospitalization among NF1 patients may be under-reported. Also, as discussed in the Methods section of this article, our technique for NF1 case identification included an imputation of incomplete ICD-9-CM codes. Therefore, a small number of NF2 cases may have unknowingly been included in our data set, although to the best of our knowledge, there is no evidence of an increased risk of stroke related to NF2. As such, this technique would likely reduce the observed association between NF1 and stroke if affecting it at all.

Because the unit of analysis in the NIS is a hospitalization rather than an individual patient, we could not account for multiple admissions of a single patient during a calendar year. In addition, because there is no way to follow a single individual over time using the NIS, we were unable to furnishes estimates for cumulative and lifetime stroke risk, which should be a goal of future studies. Hospital-based mortality data would be an interesting topic of a future study because the NIS does include information on whether death occurred in the hospital. However, because most patients survive their hospital admission, meaningful statistical analysis and reporting of patient-specific data would not have been possible with this study design because of NIS limitations on reporting a small cell size. This clinical question might be more appropriately addressed with a large multi-institutional study with the opportunity for collecting a higher level of clinical detail.

Finally, we chose to adjust for race/ethnicity and socioeconomic status in our statistical analysis given that people of black race and lower socioeconomic status have repeatedly been shown to have worse health outcomes including an increased risk of stroke, hypertension, and cardiovascular disease. However, not every state reports data on race, ethnicity, and socioeconomic status, and consistency of reporting varies over time, with \(\approx30\%\) of race/ethnicity data missing here. To address this, we created separate missing categories and adjusted for them in the statistical analysis.

In summary, we found an increased odds of stroke in hospitalized patients with NF1. In particular, hemorrhagic stroke subtypes were increased in both adults and children, and ischemic subtypes were increased in children. Physicians who care for these patients should be aware of the potential for enhanced stroke risk and should triage these patients for primary prevention, potentially screening more frequently for cerebrovascular abnormalities. Given the challenges of studying outcomes in a rare disease, and the difficulty of generalizing our conclusions outside the inpatient population, well-designed prospective studies are needed to address the limitations described above, provide detailed patient-level information, and investigate pathophysiologic mechanisms. Finally, our work illuminates another facet of the vasculopathy associated with NF1, which at this time is incompletely understood. Our hope is that by examining areas of enhanced vascular risk, we can contribute to the understanding and management of neurological and neurovascular diseases in patients with genetic syndromes.

Disclosures

None.

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