



Evidence for increased risk of stroke in neurofibromatosis type 1: a population-based approach

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Background and Significance

- There are currently no population-based studies that investigate whether neurofibromatosis type 1 (NF1) is an independent risk factor for stroke.
- NF1 has been associated with both cerebrovascular anomalies (moyamoya, aneurysms, stenotic/ectatic vessels) and secondary hypertension (pheochromocytoma, renal artery stenosis).
- Several population-based studies have demonstrated excess cardiovascular mortality in NF1.
- For these reasons, we hypothesized that there would be a positive association between NF1 and stroke.

Methods

- Case-control design using the Nationwide Inpatient Sample (NIS), 1998-2009
- Outcomes: ischemic stroke, hemorrhagic stroke (ICH or SAH), venous sinus thrombosis (VST)
- Multivariable logistic regression models adjusted for diabetes, hypertension, atherosclerosis, and other potential confounders.

Results

- 21,378 admissions were associated with a diagnosis of NF1 (0.02% of all admissions).
- Overall, NF1 was associated with younger mean age (41 vs. 48) and a lower prevalence of common stroke risk factors such as hypertension and diabetes.
- However, pediatric NF1 was more likely to be associated with hypertension.
- Hospitalized patients with NF1 were significantly more likely to be diagnosed with stroke (OR 1.2, p<0.0001) compared to the general population, primarily due to non-traumatic intracranial hemorrhage (ICH) (OR 1.9, p<0.0001).
- For the pediatric population, the odds of ICH (OR 8.1, p<0.0001) and ischemic stroke (OR 3.4, p<0.0001) were dramatically elevated.

Table 1

Characteristic	Pediatric (0-18 years)		Adult (>18 years)	
	NF1 (N=4460)	Non-NF1 (%)	NF1 (N=16,918)	Non-NF1 (%)
Age, mean (SD)	9.3 (5.6)	3.0 (5.7)	49.5 (17.7)	57.1 (20.9)
Race, N (%)				
White	1995 (44.7)	39.4	9198 (54.4)	53.8
Black	669 (15.0)	11.2	2084 (12.3)	10.1
Hispanic	547 (12.3)	17.0	940 (5.6)	7.8
Other	223 (5.0)	7.1	530 (3.1)	4.1
Missing	1026 (23.0)	25.3	4166 (24.6)	24.2
Income quartile, N (%)				
1 (least wealthy)	20.0	20	3979 (23.5)	19.5
2	24.9	25.2	4687 (27.7)	26.1
3	24.9	24.5	4232 (25.0)	24.7
4 (most wealthy)	27.2	28.4	3603 (21.3)	27.2
Missing	3.0	2	417 (2.5)	2.5
Insurance payor, N (%)				
Medicare	<10	0.23	6821 (40.3)	44.7
Medicaid	1917 (43.0)	41.4	3429 (20.3)	13.4
Private	2255 (50.6)	50.6	5382 (31.8)	33.4
Self-pay/Other	280 (6.3)	7.8	1286 (7.6)	8.5

Characteristics of NF1 vs. non-NF1 inpatients, 1998-2009. p<0.001 for all comparisons

Conclusions

- Stroke is more common in hospitalized patients with NF1, possibly due to a higher risk of cerebrovascular pathology and an inherent vasculopathy.
- The excess risk appears to arise mostly from hemorrhagic etiologies, although the prevalence of ischemic stroke is also higher in the pediatric NF1 population.

Table 2

Stroke type, N (%)	Pediatric (0-18 years)		Adult (>18 years)	
	NF1 (N=4460)	Non-NF1 (%)	NF1 (N=16,918)	Non-NF1 (%)
All	54 (1.2)	0.10	547 (3.2)	4.0
Ischemic	22 (0.49)	0.05	431 (2.6)	3.5
Hemorrhagic (SAH and ICH)	31 (0.70)	0.05	116 (0.69)	0.49
ICH	30 (0.67)	0.04	91 (0.54)	0.40
SAH	<10*	0.01	28 (0.17)	0.10
VST	<10	0.01	<10*	0.01
Stroke risk factor, N (%)				
Diabetes	23 (0.52)*	0.66	1085 (6.4)	19.5
Hypertension	234 (5.3)	0.39	5278 (31.2)	39.7
Atrial fibrillation/flutter	<10*	0.03	978 (5.8)	9.9
Atherosclerosis	47 (1.1)	0.01	1753 (10.4)	19.0
Unruptured aneurysm	<10	0.00	36 (0.21)	0.08
Moyamoya	50 (1.1)	0.01	15 (0.09)	0.00

Stroke subtypes and risk factors for NF1 vs. non-NF1 inpatients. *NS

Table 3

Stroke type	Pediatric (0-18 years)	P	Adult (>18 years)	P
All	4.3 (2.9-6.5)	<0.001	1.2 (1.1-1.3)	<0.001
Ischemic	3.5 (1.7-7.2)	<0.001	1.1 (1.0-1.2)	0.05
Hemorrhagic (ICH + SAH)	4.7 (2.8-7.8)	<0.001	1.7 (1.3-2.0)	<0.001
ICH	5.7 (3.3-9.9)	<0.001	1.7 (1.3-2.1)	<0.001
SAH	0.7 (0.09-5.8)*	0.75	1.4 (0.9-2.1)	0.14
VST	4.0 (1.1-14.9)*	0.04	1.7 (0.3-8.3)	0.53

Multivariable OR and 95% CI for stroke subtypes in pediatric and adult inpatients.

*Univariate only (not enough events)

Learning Objectives

- To demonstrate that adults and children with NF1 may be at a higher risk of stroke.
- To demonstrate how administrative databases can be used to address challenging clinical questions.

References

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