Original Contribution

Workup for Perinatal Stroke Does Not Predict Recurrence

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Background and Purpose—Perinatal stroke, including neonatal and presumed perinatal presentation, represents the age in childhood in which stroke occurs most frequently. The roles of thrombophilia, arteriopathy, and cardiac anomalies in perinatal ischemic stroke are currently unclear. We took a uniform approach to perinatal ischemic stroke evaluation to study these risk factors and their association with recurrent stroke.

Methods—We reviewed records of perinatal stroke patients evaluated from August 2008 to February 2016 at a single referral center. Demographics, echocardiography, arterial imaging, and thrombophilia testing were collected. Statistical analysis was performed using Fisher exact test.

Results—Across 215 cases, the median follow-up was 3.17 years (1.49, 6.46). Females comprised 42.8% of cases. Age of presentation was neonatal (110, 51.2%) or presumed perinatal (105, 48.8%). The median age at diagnosis was 2.9 days (interquartile range, 2.0–9.9) for neonatal stroke and 12.9 months (interquartile range, 8.7–32.8) for presumed perinatal stroke. Strokes were classified as arterial (149, 69.3%), venous (60, 27.9%), both (4, 1.9%), or uncertain (2, 0.9%) by consensus imaging review. Of the 215 cases, there were 6 (2.8%) recurrent ischemic cerebrovascular events. Abnormal thrombophilia testing was not associated with recurrent stroke, except for a single patient with combined antithrombin deficiency and protein C deficiency. After excluding venous events, 155 patients were evaluated for arteriopathy and cardioembolic risk factors; neither was associated with recurrent stroke. Positive family history of thrombosis was not predictive of abnormal thrombophilia testing.

Conclusions—Thrombophilia, arteriopathy, or cardioembolic risk factors were not predictive of recurrent events after perinatal stroke. Thrombophilia evaluation in perinatal stroke should only rarely be considered. **(*Stroke*. 2017;48: 00-00. DOI: 10.1161/STROKEAHA.117.017356.)**

Key Words: echocardiography ■ pregnancy ■ perinatal ■ stroke ■ thrombophilia

Perinatal ischemic stroke is the most common presentation of pediatric stroke.[1] Perinatal ischemic stroke is defined as a focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life through 28th postnatal day, confirmed by neuroimaging.[2] Thus, perinatal ischemic stroke occurs in the prenatal, birth, or postnatal time periods. Clinical presentation from birth to 28 days of life is termed neonatal stroke, while presentation later in life is called presumed perinatal stroke.

Risk factors that have been associated with cases of ischemic perinatal stroke can be divided into maternal, placental, and fetal. Maternal risk factors include thrombophilia, infertility, prolonged rupture of membranes, preeclampsia, smoking, intrauterine growth restriction, and infection.[1,3–6] The placental risk factors include chorioamnionitis, placental infarcts, and placental weight less than the 10th percentile.[7] Fetal risk factors include thrombophilia, congenital heart disease, and arteriopathy.[6,8–10] The roles of fetal risk factors, including thrombophilia, arteriopathy, and cardioembolic risk factors, in the pathogenesis of perinatal ischemic stroke or recurrence risk are unclear.

Thrombophilia has been associated with perinatal ischemic stroke, including deficiencies in antithrombin, protein C, protein S, factor V Leiden, and prothrombin gene mutation *G20210A*, as well as with elevations in homocysteine and lipoprotein (a) and positive antiphospholipid antibodies.[11–14] Limited by their retrospective, multicenter approach, these studies compile data from varied laboratory panels with inconsistent definitions of abnormal thrombophilia testing. Recent evaluation of 135 patients and 77 controls found no increase in thrombophilia in children after perinatal stroke.[15] However, this study did not assess risk factors for recurrent stroke after perinatal stroke.

Arteriopathy is rarely reported in perinatal arterial ischemic stroke, except for 1 case report of an arterial dissection.[8] Congenital heart disease is associated with perinatal arterial

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ischemic stroke, including recurrent stroke.[16,17] The utility of echocardiogram for the use of prediction of recurrent stroke after neonatal stroke in the absence of known concern for congenital heart disease is unknown.

We took a uniform approach to perinatal ischemic stroke evaluation to better understand thrombophilic risk factors. Since 2008, our evaluation of children with perinatal ischemic stroke has consistently included a standard thrombophilia evaluation and a magnetic resonance angiography (MRA) or computed tomography angiography of head and neck and echocardiogram in children with perinatal arterial ischemic stroke. We have reviewed these data to determine the frequency of abnormal findings and whether these predict stroke recurrence after perinatal stroke in this retrospective study.

Materials and Methods

Following Boston Children's Hospital Institutional Review Board approval, we reviewed records of all patients evaluated in our Cerebrovascular Disorders and Stroke Program from August 2008 to February 2016. Inclusion criteria for this study included any patient with a diagnosis of perinatal stroke, including arterial and venous infarcts, as well as neonatal and presumed perinatal presentation. We retrospectively collected demographics, thrombophilia, arterial imaging, and echocardiography data into a Research Electronic Data Capture database.[18]

All data were extracted by a study team member and verified by a stroke physician. Demographic data included sex, race, ethnicity, birth date, age at stroke diagnosis, and age at last follow-up. Data reviewed included family history of thrombosis, specific thrombophilia testing, MRA and computed tomography angiography and echocardiogram findings. If a child did not have thrombophilia laboratory testing done, the patient was not included, which was <5% of our cohort. Details around recurrent cerebrovascular events were also collected, and all recurrent events underwent multidisciplinary review for confirmation. Infarcts were defined as arterial, venous, or indeterminate through consensus discussion in an unblinded multidisciplinary conference review including neuroradiologist, neurologists, and a hematologist.

Thrombophilia was assessed as a risk factor for recurrence for all types of perinatal strokes with acute laboratory assessment in neonatal stroke patients and deferred to older than 6 months in presumed perinatal stroke patients. Because arteriopathy and cardioembolic sources do not explain venous infarcts, assessment of these risk factors was restricted to the subset of arterial ischemic or indeterminate strokes. Factor V Leiden was diagnosed by activated protein C resistance and confirmed with genetic testing. Prothrombin gene mutation (FII G20210A) was diagnosed with genetic testing. Thresholds for protein C, protein S, and antithrombin deficiencies used published age-normalized reference ranges on modern instruments.[19] Patients were diagnosed with antithrombin, protein C, or protein S deficiency when functional testing was low for age after 6 months of age for protein S and antithrombin and after 1 year of age for protein C. If the child only had testing at diagnosis but not repeat testing, these patients were not diagnosed with thrombophilia, and testing was considered unconfirmed. Unconfirmed testing in the analysis was considered not done. Elevated lipoprotein(a) and homocysteine levels were defined as a single test greater than reference range. For lipoprotein(a), age-appropriate reference ranges are not available, and we used a conservative normal range of 0 to 29 mg/dL. Antiphospholipid antibodies, including lupus anticoagulant, anti-cardiolipin IgG and IgM, and anti-β2 glycoprotein-1 IgG and IgM, were tested and considered positive if >40 U/mL tested at least twice >12 weeks apart. Lupus anticoagulant was considered positive if a screening lupus anticoagulant-sensitive activated partial thromboplastin time (Stago; Parsippany, NJ) is prolonged and then neutralized with addition of hexagonal phospholipids. Positive family history was defined as first degree family member with myocardial infarction or stroke before age 50 years, deep vein thrombosis, pulmonary embolus, or recurrent miscarriages.

We defined arteriopathy as abnormal arteries found on initial computed tomography angiography or MRA interpreted as likely causing the perinatal arterial ischemic stroke. Embryonic variants and diminished flow to large infarcts were not considered arteriopathies. All cases of possible arteriopathy underwent multidisciplinary review for consensus. Cardioembolic risk factors included patent foramen ovale (PFO), congenital heart disease, extracorporeal membrane oxygenation, cardiac surgery, cardiac catheterization, and intracardiac thrombus.

Statistical Analysis

We used Fisher exact test to examine whether family history of thrombosis predicted abnormal thrombophilia testing and whether thrombophilia, arteriopathy, or cardioembolic risk factors predicted recurrent event. Statistical significance was defined as a P value <0.05.

Results

We evaluated 215 cases of perinatal ischemic stroke with a median follow-up of 3.17 years (interquartile range [IQR], 1.49–6.46) counted since birth. The median age at diagnosis was 2.9 days (IQR, 1.9–9.9) for neonatal stroke and 12.9 months (IQR, 8.7–32.8) for presumed perinatal stroke. Out of the 215 children, 14 (6.5%) were preterm infants. Characteristics of this patient cohort are described in Table 1. Of the 215 cases, 6 (2.8%) had recurrent ischemic

Table 1. Demographics of Children With Perinatal Stroke

Characteristic	N=215 (%)
Sex	
Females	92 (42.8%)
Race	
White	148 (68.8%)
Black	16 (7.4%)
Asian	4 (1.9%)
Other	18 (8.4%)
Unknown	29 (13.5%)
Type of stroke	
Arterial	149 (69.3%)
Venous	60 (27.9%)
Both	4 (1.9%)
Indeterminate	2 (0.9%)
Presentation	
Neonatal	110 (51.2%)
Arterial	68 (61.2%)
Venous	39 (35.5%)
Both	3 (2.7%)
Indeterminate	0 (0%)
Presumed perinatal	105 (48.8%)
Arterial	81 (77.1%)
Venous	21 (20.0%)
Both	1 (0.9%)
Indeterminate	2 (1.9%)

cerebrovascular events: 3 venous, 2 arterial, and 1 arterial and venous. Of the recurrences, there was 1% recurrence rate in the presumed perinatal stroke group (1/105) compared with 4.5% rate in the neonatal stroke group (5/110). The anatomic distribution and associated risk factors in all 6 cases of recurrent stroke are reviewed in Table 2.

Brief case vignettes are provided below for each case of recurrent stroke. Patient 1 is a male born at 32 weeks gestation. Both his brother and mother had known antithrombin deficiency. Initial head ultrasound was concerning for left hemispheric hemorrhage. Subsequent magnetic resonance imaging (MRI) at 6 days of life identified a left middle cerebral artery stroke with hemorrhagic transformation and a normal MRA of the head. Repeat MRI at 15 days of life identified new cerebral sinovenous thrombosis involving the sagittal sinus, right transverse sinus, straight sinus, and vein of Galen with bilateral ischemic and hemorrhagic venous infarct. Patient 2 is a male born at 30 weeks gestation who presented with apneic episode. Head ultrasound found hemorrhage, confirmed by MRI at 2 days old, showing left temporal lobe hemorrhage with medullary venous thrombosis and right middle cerebral artery stroke with normal MRA of the head. Subsequent MRI at 2 weeks old was found to have a new large superior sagittal sinus thrombosis. Case 3 is a male born at 41 weeks, diagnosed postnatally with Pierre–Robin Sequence who presented soon after birth with seizures. MRI at 7 days old identified hemorrhagic venous infarction and a superior sagittal venous thrombosis. He later developed a right middle cerebral artery territory stroke at 11 years of age after spinal fusion surgery. Patient 4 was born full term. He had an MRI when he was 11 weeks old because of concern of bilateral extremity weakness. His MRI was significant for bilateral encephalomalacia in the bilateral middle cerebral artery territories and left anterior cerebral artery territory. He presented again at 6 months of age with seizure and had bilateral watershed injury with again a normal MRA. At 8 months of age, MRI for recurrent seizure showed watershed ischemia again, and his MRA was read as normal but retrospectively showed evidence of early moyamoya. At 3 years of age, he was diagnosed with bilateral moyamoya when he presented with an acute right middle cerebral artery stroke. Patient 5 is a female born at 39 weeks with abnormal placental pathology consistent with fetal thrombotic vasculopathy. She had an MRI at 10 days old because of multiple congenital anomalies, revealing an acute left posterior cerebral artery stroke. Genetic testing demonstrated trisomy 12p. She had a follow-up MRI and MRA at 4 years of age for transient ischemia attack when she presented with left-sided weakness that resolved completely; this MRI showed no acute injury, and MRA was normal. She presented at 9 years of age with a right hemiparesis and had a left hemispheric stroke involving anterior cerebral artery, posterior cerebral artery, and middle cerebral artery and was diagnosed with bilateral large vessel vasculitis. She was treated with steroids, and her vasculature improved. Patient 6 is a male born at 39 weeks gestation with significant perinatal distress and was treated with therapeutic hypothermia. His postcooling MRI at 5 days

Table 2. Recurrent Ischemic Cerebrovascular Events

Patient No.	Presenting Event	Timing of Presentation	Recurrent Event	Age at Recurrence	Risk Factors Identified
1	Arterial: left MCA AIS with hemorrhagic transformation	Neonatal; 6 days old	Venous: dural venous sinus and medullary vein thrombosis	16 days old	Deficiencies of antithrombin (36%) and protein C (63%)*
2	Arterial and venous: right MCA multifocal AIS and temporal lobe hemorrhage with medullary vein thrombosis and infarction	Neonatal; 2 days old	Venous: superior sagittal sinus thrombosis	17 days old	None
3	Venous: venous infarction with hemorrhage and superior sagittal venous thrombosis	Neonatal; 7 days old	Arterial: right MCA AIS	11 y old	Perioperative (spinal fusion); elevated lipoprotein(a)
4	Arterial: multifocal encephalomalacia bilateral MCA and left ACA	Presumed perinatal; 11 weeks old	Arterial: multiple AIS	6 mo old (seizure with watershed white matter infarction); 8 mo (watershed acute injury in setting of seizure); 3 y (seizure, R MCA stroke and Moyamoya)	Moyamoya identified at 3 y of age
5	Arterial: left PCA AIS	Neonatal; 10 days old	Arterial: left hemispheric AIS involving ACA, MCA, and PCA	7 y old	CNS vasculitis identified at recurrence, elevated lipoprotein(a)
6	Venous: left periventricular venous infarction	Neonatal; 5 days old	New hemorrhagic venous infarct and new right PCA AIS	12 days old	None

ACA indicates anterior cerebral artery; AIS, arterial ischemic stroke; CNS, central nervous system; DOL, day of life; GA, gestational age; MCA, middle cerebral artery; MRA, magnetic resonance angiography; and PCA, posterior cerebral artery.

*In parentheses are the functional levels.

old showed small left acute ischemic periventricular venous infarction. He had his follow-up MRI and MRA at 12 days of life showing acute right posterior cerebral artery stroke and a large temporal lobe hemorrhagic venous infarct.

All of the recurrent events were documented as a separate event not an extension of the initial event. Analysis of laboratory testing for thrombophilia and association with recurrent stroke was performed (Table 3). Approximately one third of patients had at least 1 abnormal test, most commonly elevation of lipoprotein(a). The only single test associated with stroke recurrence was antithrombin deficiency, found in 1 patient with recurrent stroke who also had protein C deficiency. However, when we used the Bonferroni correction for multiple comparisons, the *P* value was not significant (*P*=0.255). Family history of thrombosis was analyzed as a predictor of abnormal thrombophilia testing. Of 18 patients with a positive family history, 10 patients had no thrombophilia abnormalities (*P*=0.2970).

Analysis of arteriopathy and cardioembolic risk factors was restricted to the 155 cases of perinatal arterial ischemic stroke because arteriopathy and cardioembolic risk factors are irrelevant to venous strokes. Arterial imaging (MRA or computed tomography angiography) was performed in 114 patients, and echocardiogram was performed in 97 patients. Of 155 perinatal arterial ischemic stroke cases, there were no cases of arteriopathy on initial imaging. There were 4 recurrences, and none had arteriopathy on initial imaging (*P*=1.000). Subsequently, 3 children had arteriopathy at time of recurrence.

Of 97 patients with echocardiogram data, 50 (51.5%) patients had PFOs. Out of the 85 children with presumed perinatal strokes, 10 (11.8%) had PFOs compared with 40 (54.8%) of the 85 infants with neonatal stroke. Out of the 4 (4.1%) with recurrent strokes, 2 (50.0%) of these had PFOs. Of the 93 patients without recurrent stroke, 48 (51.6%) had PFOs. In our current sample, PFO was not predictive of recurrent stroke (*P*=1.000). None of the recurrent cases had other (non-PFO) cardioembolic risk factors compared with 13 (14.0%) of the cases without recurrence. Other cardioembolic risk factors identified included 1 with valve vegetations, 3 with atrial septal defect, 3 with ventricular septal defect, 1 with cardiomyopathy, and 5 with complex congenital heart disease; none of these were associated with stroke recurrence (*P*=1.000).

Discussion

We evaluated 215 cases of perinatal ischemic stroke at a single hospital referral center. Similar to other studies of children with perinatal ischemic stroke, 49% were presumed perinatal stroke and 51% were neonatal in presentation.[20,21] We found a rate of recurrent cerebrovascular events of 2.8% similar to the previously reported rate of 3%.[16]

Using a strict definition of thrombophilia and Fisher exact test, only antithrombin deficiency was associated with recurrent stroke, based on a single patient who also had a protein C deficiency. We hesitate to conclude that antithrombin deficiency is specifically associated with stroke recurrence after perinatal stroke based on 1 case. Factor V Leiden, prothrombin gene mutation, protein C deficiency, protein S deficiency, elevated homocysteine, elevated lipoprotein (a), and persistent antiphospholipid antibodies were not associated with recurrent stroke. Existing literature is limited to case reports, case series, or meta-analyses associating variable thrombophilia evaluations to stroke in limited numbers of patients.[14] A small number

Table 3. Thrombophilia in Children With Perinatal Stroke

Thrombophilia	Recurrence (N=6)	No Recurrence (N=209)	Total=215	*P* Value
Any abnormal				
None	3 (50.0%)	139 (66.5%)	142 (66.0%)	0.4105
One or more	3 (50.0%)	70 (33.5%)	73 (34.0%)	0.4105
Factor V Leiden				
Heterozygote	0 (0.0%)	15 (7.6%)	15 (7.4%)	1.0000
Wild-type	6 (100.0%)	183 (92.4%)	189 (92.6%)	1.0000
Prothrombin				
Heterozygote	0 (0.0%)	8 (4.2%)	8 (4.0%)	1.0000
Wild-type	6 (100.0%)	184 (95.8%)	190 (96.0%)	1.0000
Antithrombin				
Deficient	1 (20.0%)	0 (0.0%)	1 (0.5%)	0.0255*
Normal	4 (80.0%)	191 (100.0%)	195 (99.5%)	0.0255*
Protein C				
Deficient	1 (16.7%)	11 (5.7%)	12 (6.0%)	0.3135
Normal	5 (83.3%)	183 (94.3%)	188 (94.0%)	0.3135
Protein S				
Deficient	0 (0.0%)	13 (6.8%)	13 (6.6%)	1.0000
Normal	5 (100.0%)	178 (93.2%)	183 (93.4%)	1.0000
Lipoprotein (a)				
Elevated	2 (50. %)	33 (17.6%)	35 (18.2%)	0.1525
Normal	2 (50.0%)	155 (82.4%)	157 (81.8%)	0.1525
Homocysteine				
Elevated	0 (0%)	0 (0%)	0 (0%)	1.0000
Normal	6 (100%)	197 (100%)	203 (100%)	1.0000
Anticardiolipin IgG				
Elevated	0 (0%)	0 (0%)	0 (0%)	1.0000
Normal	5 (100%)	102 (100%)	107 (100%)	1.0000
Anticardiolipin IgM				
Elevated	0 (0%)	0 (0%)	0 (0%)	1.0000
Normal	5 (100%)	102 (100%)	107 (100%)	1.0000
β2-glycoprotein IgG				
Elevated	0 (0%)	0 (0%)	0 (0%)	1.0000
Normal	3 (100%)	84 (100%)	87 (100%)	1.0000
β2-glycoprotein IgM				
Elevated	0 (0%)	0 (0%)	0 (0%)	1.0000
Normal	3 (100%)	83 (100%)	86 (100%)	1.0000
Lupus anticoagulant				
Positive	0(0%)	0 (0%)	0 (0%)	1.0000
Negative	4 (100%)	102 (100%)	106 (100%)	1.0000

*Using Bonferroni correction *P* value is not significant (*P*=0.255).

of studies exist that examine cohorts of children after perinatal stroke, with only a few of these studies reporting recurrent events and none having enough recurrent events to answer the question of whether thrombophilia is associated with recurrence.[16] Our rate of abnormal thrombophilia testing (33.5%) may be lower than other series because of our strict definition of thrombophilia and the use of elevated homocysteine rather than methylenetetrahydrofolate reductase polymorphisms as a thrombotic risk factor. Even though antiphospholipid antibody syndrome is associated with recurrent stroke in older children, we did not have a single case of persistently elevated antiphospholipid antibodies after perinatal stroke.[22] Our data raise questions about the role of thrombophilia testing in perinatal stroke.

In this study, positive family history of thrombosis was not predictive of abnormal thrombophilia testing. This finding may be limited by sample size because larger studies of pediatric venous thrombosis suggest that positive family history is predictive of thrombophilia and recurrence.[23]

Unlike stroke in older patients, the workup for arteriopathy and cardioembolic risk factors does not predict recurrent stroke.[24,25] Compared with a 5-year recurrence rate of 66% in pediatric stroke patients with arteriopathy, our study identified no patients with arteriopathy at diagnosis and recurrence after perinatal arterial ischemic stroke.[24] Arterial occlusion in neonatal arterial ischemic stroke is isolated and may result from thromboembolism rather than primary arterial pathology.[26,27] The presence of arteriopathy in perinatal arterial ischemic stroke is rare. When identified, especially if arteriopathy exists in the same vascular territory as the infarct, this may warrant additional investigation and follow-up. The role of arterial imaging to evaluate causation of perinatal stroke is unclear, and arteriopathy is not predictive of recurrent stroke in our study.

In older children, complex congenital heart disease is an established risk factor for recurrent stroke.[17,25] In our cohort of perinatal arterial ischemic stroke, none of the cases of recurrent stroke had congenital heart disease. In our cohort, the percentage of infants with PFOs at time of neonatal stroke (54.8%) and in older children with presumed perinatal stroke (11.8%) is similar to previously reported rates in the general population of infants, with 58% having a PFO on day of life one and 27% having a PFO at 6 weeks of life.[28,29] The presence of PFO and other cardiac anomalies on echocardiogram were also not predictive of recurrent stroke. As few of our patients had symptomatic congenital heart disease, our data provide contrast to literature on patients with symptomatic congenital heart disease in whom 14% had recurrent stroke after initial neonatal stroke.[17] In our cohort, only 5 patients had complex congenital heart disease, and all of these had known cardiac conditions prior to echocardiography. The role of echocardiography to detect occult cardioembolic causes of perinatal stroke is unclear.

Our study is limited by the sample size available to us at a single institution but strengthened by a uniform approach to risk factor assessment after perinatal stroke. We were also limited by having only a median of 3.17 years of follow up. The low recurrence rate after perinatal stroke is encouraging but limits our power to detect associations between various risk factors and recurrence. Although the majority of patients were seen in our multidisciplinary clinic, there was still some variation in practice, as well as clinician preference, leading to some patients not having MRA of head, echocardiogram, or complete thrombophilia evaluation. Further, our study does not include a control group of infants to determine whether rates of thrombophilia are greater in the perinatal stroke population; recent case–control study from a Canadian registry found no association with thrombophilia and perinatal stroke.[15] Our study included mostly white patients, which may limit applicability to other ethnic groups.

Because thrombophilia, arteriopathy, and cardioembolic risk factors are not predictive of recurrence, our data support other hypotheses about the pathogenesis of perinatal stroke, including those that address placental and maternal risk factors. Abnormal placental pathology has been associated with perinatal ischemic stroke.[7,30] The low recurrence rate after perinatal stroke supports placental or maternal risk factors as causative rather than thrombophilia, cardiac, or arterial risk factors because these risk factors persist in the patient and would be expected, theoretically, to carry increased risk of recurrent stroke if causative. Our data also suggest that the mechanisms of recurrent strokes are distinct from the mechanisms of perinatal events as, in this cohort, rare recurrent strokes occurred either acutely or years later because of acquired arteriopathy or periprocedural events.

Conclusions

Thrombophilia testing may not be indicated in the assessment of perinatal stroke in the absence of positive family history or additional thrombotic complications. Cervicocephalic arterial imaging and echocardiogram do not predict recurrent stroke, and their role in identifying causative arteriopathy or occult cardiac disease is unclear. In the absence of other clinical concerns, use of arterial or cardiac imaging after perinatal arterial ischemic stroke should be carefully considered. Clinicians should consider the cost and, for older children, the risk of sedation for these imaging studies. Future research should focus on placental and other risk factors as the pathogenesis of perinatal stroke.

Disclosure

None.

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