Published in final edited form as:

J Pediatr. 2007 July ; 151(1): 67–72.e1. doi:10.1016/j.jpeds.2007.02.015.

Headache in Children with Sickle Cell Disease:

Prevalence and Associated Factors

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Abstract

Objective—To compare the prevalence of frequent headache in children with sickle cell disease (SCD) to that of black control subjects and to assess factors associated with headache in SCD.

Study design—In this cross-sectional study, a headache questionnaire was administered to subjects with SCD and black control subjects. Subjects answered supplementary questions about SCD complications. Clinical and radiographic information were abstracted from medical charts for subjects with SCD.

Results—Children (n = 241) with SCD and 141 control subjects were studied; 32.4% (95% CI 26.5%-38.7%) of subjects with SCD reported having headaches at least weekly, similar to control subjects at 27% (95% CI 19.8%-35.1%, *P* = NS); however, in children <13 years, headache was more common in subjects with SCD than in control subjects (24% vs 9.7%, *P* = .013). The prevalence of headache was similar among the different SCD genotypes. Factors associated with frequent headaches in subjects with SCD included older age, frequent vaso-occlusive pain episodes, symptoms of obstructive sleep apnea, and cerebral vessel stenosis detected by magnetic resonance angiography.

Conclusion—The prevalence of headaches in children with SCD is similar to the general population; however, younger children with SCD report headaches more frequently than control subjects. The cause of headache is likely multifactorial, and SCD-specific factors may contribute.

Children with sickle cell disease (SCD) frequently complain of headaches, but there are limited data concerning the prevalence and causes of headache in these children. The prevalence of headache in healthy children has been reported to range from 8% to 60%, depending on the population studied and the definition used.¹ The most common causes of headache in childhood are tension and migraine headache.² Children with SCD may have headaches related to these common causes, but headaches also may be related to their underlying SCD such as bony infarction, severe anemia, or frequent opioid medication use. One particular concern is that headache may be a manifestation of cerebrovascular disease.³ A child with SCD who presents with frequent headache often undergoes an extensive evaluation, which may include brain computed tomography, magnetic resonance imaging (MRI) and angiography (MRA), and transcranial Doppler (TCD) ultrasonography, to determine the cause and to rule out cerebral vasculopathy and stroke. It is unclear, however, how often headache is the sole symptom of central nervous system disease, or whether frequent headache signifies the presence of cerebrovascular disease.

This cross-sectional study was performed to determine the prevalence of frequent headache in children with SCD compared with healthy black control subjects. Our secondary aim was to investigate whether specific SCD-related factors such as vasoocclusive pain episodes (VOE) and cerebrovascular disease are associated with frequent headache. These data could facilitate the evaluation of headache in the pediatric population with SCD and suggest areas for future study.

METHODS

Patients

This study was approved by the Institutional Review Boards at The Children's Hospital of Philadelphia (CHOP) and Duke University Medical Center. Subjects with SCD were consecutively recruited from the Sickle Cell Center at CHOP, and black control subjects were recruited from the General Pediatrics and Adolescent Medicine clinics at CHOP between February and October 2004. Inclusion criteria for subjects with SCD were ages 6 to 21 years and any SCD genotype (SS, SC, $S\beta^0$ -thalassemia, and $S\beta^+$ -thalassemia). Eligibility criteria for control subjects included black ethnicity, age 6 to 21 years, and without known sickle cell trait or a diagnosis of significant chronic medical illness that required hospitalization at least once a year. Informed consent was obtained from guardians, and assent was obtained from children 7 years and older.

Data Collection

During routine clinic visits, subjects with SCD and control subjects, with the help of their caretakers, completed an identical headache questionnaire. The study questionnaire was developed on the basis of the International Headache Society (IHS) classification system for headache in children⁴ and asked historical questions about headache, including frequency, characteristics, and associated symptoms, as well as questions about medication use and activity limitations related to headache (sample questions appear in the Appendix; available at www.jpeds.com).

SUBJECTS WITH SCD—Subjects with SCD also answered additional questions pertaining to SCD, including current medication use, history of transfusion therapy, number of VOE in the preceding 12 months, history of acute chest syndrome, symptoms of obstructive sleep apnea (OSA), and history of silent or overt infarction. Clinical information was abstracted from the medical charts of subjects with SCD and included SCD genotype, history of overt stroke, history of dactylitis before age 1 year (a marker of severe disease⁵), and most recent pulse oximetry value. Complete blood count results were recorded, and the average hemoglobin level, white blood cell count, platelet count, and reticulocyte count from the last 3 well clinic visits were calculated. In addition, the fetal hemoglobin level within 6 months of the study date was recorded. Records were reviewed for all acute visits to the emergency department or other hospital-based sites and for all inpatient hospitalizations for the year before the study visit, and the final discharge diagnosis(es) were recorded.

Magnetic Resonance Imaging and Angiography

All brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) study results obtained for clinical reasons within 6 months of the study visit date were analyzed. In addition, for MRI analyses, study results obtained more than 6 months before the study visit date were included if the earlier study showed infarction because infarctions are unlikely to regress.⁶ Earlier abnormal MRA results were not included because vascular stenosis may change over time.^{7,8} Indications for the MRI/MRA were abstracted from the radiology report and chart review. Our institutional screening protocol to assess for central nervous system abnormalities includes screening brain MRI/MRA for children with SCD-SS and SCD- $S\beta^0$ -

thalassemia, as well as follow-up studies for those with elevated TCD velocities, prior silent infarcts, or other risk factors for stroke. All MRI/MRA scanning was performed on a 1.5 T Siemens Magnetom Vision (Siemens Medical Systems, Iselin, NJ) with our standard SCD imaging protocol.⁹

At least 2 neuroradiologists reviewed each study. All images were read, and a clinical report was dictated by one of several neuroradiologists. All images were reviewed by the study neuroradiologist (A.P.), who was blinded to the clinical report, the subject's clinical history, and questionnaire responses. The study neuroradiologist's findings were then compared with the clinical report to assess for agreement. A second neuroradiologist (R.Z.) reviewed all studies where there was a discrepancy between the initial clinical report and the study neuroradiologist's (A.P.) review, and consensus was reached.

Cerebral infarction was defined as an area of abnormally increased signal on T₂-weighted and fluid-attenuated inversion recovery imaging. The number, size, and location of lesions were recorded. Lesions were classified as punctate (<5 mm), medium (5-15 mm), or large (>15 mm). Limited abnormality was defined as a single, punctate lesion, whereas more extensive abnormality was defined as multiple or moderate-to-large lesions. Silent infarction was defined as the presence of lesions without a clinical history of stroke. Stenosis was defined as an area of narrowing or focal signal dropout in an artery of the circle of Willis and graded as mild, moderate, severe, or occlusion. Significant stenosis was defined as at least 1 vessel with a stenosis grade of moderate or higher. The presence or absence of moyamoya disease, significant bone marrow hyperplasia (graded moderate or severe), and sinusitis also were recorded. TCD results also were reviewed, and the highest time-averaged mean velocities on both the most recent study and on any study to date were recorded.

Data Analysis

The study was powered to detect a 15% difference in the prevalence of frequent headache between subjects and control subjects with $\beta = 0.8$ and $\alpha = 0.05$. Frequent headache was defined as headache reported to occur at least once a week.¹⁰ The prevalence of frequent headache with 95% confidence interval (CI) was calculated for subjects and control subjects and compared by use of χ^2 analysis. Headaches that met the following characteristics were classified as migraine headache on the basis of IHS criteria⁴: duration of longer than 2 hours; at least 2 of the following: unilaterality, pulsating quality, moderate to severe intensity (applied in this study as resulting in missed school), or aggravation by routine physical activity; and at least 1 of the following: nausea and vomiting or photophobia and phonophobia.

Clinical factors associated with headache were evaluated only for subjects with SCD. Frequent VOE was defined as 3 or more pain episodes per year for which medical attention was sought. Evidence of OSA was recorded as positive if the subject reported at least 1 of the following on questionnaire: snoring "most of the time" or witnessed pauses in breathing. Only subjects with SCD-SS or SCD-S β^0 -thalassemia were included in the analysis of cerebrovascular disease and headache association, because stroke is most common in SCD-SS,¹¹ SCD-S β^0 -thalassemia has clinical severity similar to that of SCD-SS, and current recommendations for screening for stroke risk include only these 2 genotypes.¹² Laboratory results were analyzed separately for those with SCD-SS or SCD-S β^0 -thalassemia and for those with SCD-SC or SCD-S β^+ -thalassemia. Subjects receiving chronic transfusions were excluded from laboratory analyses.

Data analysis was performed with STATA 9 software (StataCorp, College Station, Texas). Statistical assessment was carried out with Student's *t* test for continuous variables and χ^2 tests and Fisher's exact tests for binomial variables, with $P < .05$ considered to be statistically significant. Logistic regression was performed using variables with $P < .1$ in the univariate

analysis. Spearman correlation coefficients were used to assess correlations between patient report and chart review results for clinical events.

RESULTS

Characteristics of Subjects with SCD and Control Subjects

A total of 241 children with SCD and 141 black control subjects were enrolled. Clinical characteristics of subjects and controls are shown in Table I.

Prevalence of Frequent Headache

The prevalence of frequent headache in children with SCD and control subjects is shown in Table I. In both groups, headache was more common with increasing age ($P < .001$). There were no significant differences in the prevalence of headache between SCD genotypes (SCD-SS: 30.5%; SCD-SC: 32.0%; SCD- $S\beta^+$ -thalassemia: 46.7%; SCD- $S\beta^0$ -thalassemia: 41.7%). In those with frequent headache, 22.1% of subjects with SCD and 21.1% of control subjects reported headache characteristics that met IHS criteria for migraines ($P = \text{NS}$).

Analysis of Factors Associated with Headaches in Subjects with SCD

Clinical and laboratory features—Factors associated with frequent headache in subjects with SCD are shown in Table II. These associations remained when the group with SCD-SS or SCD- $S\beta^0$ -thalassemia and the group with SCD-SC or SCD- $S\beta^+$ -thalassemia were analyzed separately, as well as when those receiving chronic transfusions were excluded from analyses (data not shown). In addition, within the group with SCD-SC or SCD- $S\beta^+$ -thalassemia, frequent headache was associated with both higher hemoglobin level (11.3 ± 0.8 g/dL v. 10.8 ± 0.8 g/dL, $P = 0.03$) and higher platelet count ($336 \pm 140 \times 10^9/\text{L}$ vs $273 \pm 86 \times 10^9/\text{L}$; $P = .03$). Those receiving chronic transfusion therapy or long-term hydroxyurea therapy were not more or less likely to have headache (data not shown). There was a good correlation of the subject's report of VOE with the results of the chart review ($r = 0.71$). The results of the multivariate analysis are shown in Table III.

Brain imaging studies—Brain MRI studies were available for 114 (64.8%) and MRA for 97 (55.1%) of 176 children with SCD-SS or SCD- $S\beta^0$ -thalassemia. Thirty-two of 55 (58.2%) children with frequent headache had MRI studies compared with 82 of 121 (67.8%) without frequent headache ($P = \text{NS}$). The indications for brain MRI were elevated TCD velocities (29.8%), routine screening (14%), headaches (12.3%), hypoxia or nocturnal hypoxemia (11.4%), history of stroke (9.6%), history of silent infarct (7%), worsening academic performance (7.9%), acute neurologic symptoms (6.1%), and other (1.8%).

The proportion of subjects with TCD and brain MRI/MRA abnormalities is shown in Table I. Most silent infarcts were located in the frontal or parietal deep white matter or periventricular regions. In those with silent infarcts, 58% had only punctate-sized lesions, 78% had more than 1 lesion, and 50% had bilateral infarcts. Cerebral vessel stenosis was graded as mild (33.3%), moderate (28.6%), severe (28.6%), and occluded (9.5%). The internal carotid artery was involved in all but 1 case. Stenosis of the anterior cerebral artery also was seen in 4 (19%) and of the middle cerebral artery in 6 children (28.6%).

Results of the univariate analysis of the association of neuroimaging abnormalities with frequent headache are shown in Table IV. Stenosis detected by brain MRA was significantly associated with both elevated TCD velocity ($P = .005$) and history of overt stroke ($P < .001$). All but 4 children with vessel stenosis (3 mild, 1 moderate) had either abnormal TCD or a history of overt stroke. Only 4 children with available brain MRA had moyamoya disease; 3

reported frequent headache ($P = .066$). There was no association of frequent headache with MRI evidence of sinus disease (data not shown).

DISCUSSION

We report the prevalence of frequent headache in children with SCD compared with a control group and we investigate the association of headache with SCD-related factors. Interestingly, the overall prevalence of frequent headache of 32.4% in subjects with SCD was not significantly different than that of black control subjects. Our study group was representative of our clinic population, except there was a slightly higher proportion of children receiving long-term transfusions (25% compared with 20% in our population with SCD-SS and SCD- $S\beta^0$ -thalassemia), probably because these children are seen in clinic more frequently and subjects were recruited consecutively. Our control subjects were drawn from primary health care clinics at an urban tertiary health care center, and it is possible that this represented a sicker population than that of a community physician's office. Nonetheless, the prevalence of frequent headache in our study is comparable to the prevalence reported in healthy Canadian children of 26.3% in 12- to 13-year-olds and 31.2% in 14- to 15-year-olds.¹⁰ The prevalence is also strikingly similar to the 32.1% prevalence of frequent headache in a prior report of 42 children with SCD.¹³ The frequency of migraine headache also was comparable between subjects with SCD (22.1%) and control subjects (21.1%) and is similar to rates quoted in the literature of 10.6% for children ages 5 to 15 and 28% for adolescents ages 15 to 19.¹⁴ Thus frequent headache appears to be a common complaint in black children with and without SCD. Causes of headache in the general population, such as migraine and tension headache, should be considered in the evaluation of headache in children with SCD.

In younger children, frequent headache was significantly more common in children with SCD compared with control subjects. In addition, the average age of children with SCD who reported frequent headache was younger than that of control subjects. Clinical factors associated with headache in the young children were similar to those found in the entire cohort, although not all associations reached statistical significance. This suggests that SCD may contribute to the cause of headache.

The overall prevalence of headache was similar among the different SCD genotypes, although smaller numbers of patients with SCD- $S\beta$ -thalassemia genotypes limited these analyses. Clinical factors associated with headache (excluding neuroimaging findings) also were comparable across genotypes. Thus clinicians should address symptoms of headache in patients with all SCD genotypes. The laboratory findings of higher hemoglobin levels and higher platelet counts in those with SCD-SC or SCD- $S\beta^+$ -thalassemia and frequent headache are intriguing and may reflect increased viscosity and inflammation, respectively.

In our study, children with frequent headache were more likely both to report frequent VOE and to experience headache and VOE concurrently. Vaso-occlusive pain and headache may have a common underlying pathophysiology related to vascular damage and increased blood viscosity. Vaso-occlusion with infarction of facial bones¹⁵ or of the skull^{16, 17} also may directly cause headache. In addition, headache is a known side effect of opioid pain medications frequently used for treatment of VOE.¹⁸ Interestingly, bone marrow hyperplasia, perhaps because of pain from bony expansion or reflecting a marker of more severe disease, also was associated with frequent headache.

Overall, children with SCD and frequent headache also were more likely to have symptoms suggestive of OSA, specifically snoring and witnessed periods of apnea, but this finding was not significant in multivariate analysis in the younger children. OSA may cause headache in healthy children¹⁹ and may also cause headache in children with SCD. Given that most

children in our study did not have formal polysomnography, which is the gold standard for diagnosis of OSA, further prospective study with more specific testing is warranted.

Neither silent cerebral infarction nor history of overt stroke was associated with headache in our study, which suggests that chronic brain parenchymal disease is not a significant cause of frequent headache in SCD. However, headache may be a symptom of cerebral vasculopathy in SCD given the observed association of both cerebral vessel stenosis and moyamoya disease with frequent headache. Furthermore, in the general population headache is a known symptom of moyamoya disease, a severe vasculopathy.^{20,21} In our study, although higher TCD velocities, suggestive of large-vessel stenosis, were not associated with headache, the combination of abnormal TCD and abnormal MRA was associated with frequent headache. This combination appears to signify a more specific vasculopathy since in the Stroke Prevention Trial in Sickle Cell Anemia, among children with abnormal TCD, stroke risk was higher in those with abnormal MRA than in those with normal MRA.²² Given that almost all children with abnormal MRA in our study had either a history of stroke or an abnormal TCD result, screening with TCD may be beneficial in the evaluation of frequent headache. In those with frequent headache and abnormal TCD or known stroke, MRA may aid in assessing for the presence or progression of vessel stenosis. Our study is limited because not all of our subjects with SCD-SS and SCD- $S\beta^0$ -thalassemia had brain MRI/MRA, and these studies were obtained for a variety of clinical reasons. Thus the relationship between cerebrovascular abnormalities and headache in SCD deserves further investigation.

The symptom of headache in SCD is probably multifactorial and may be related to migraine, VOE, bone marrow hyperplasia, OSA, or cerebral vessel stenosis. These factors should be considered in the evaluation of headache in SCD; most can be assessed with a thorough history, and the addition of TCD and other ancillary studies, if indicated. Future prospective, multicenter studies are warranted to study these associations further and to evaluate therapeutic interventions.

Acknowledgements

We thank Dr. T. Haecker and Dr. J. Pletcher for allowing us to study patients under their care in the General Pediatrics and Adolescent Medicine Clinics at CHOP.

Supported in part by NIH grant 2 P60 HL38632 and a Doris Duke Clinical Research Fellowship.

Appendix. Selected items from questionnaire

Does your child ever experience headaches or migraines (yes, no)?
 How often does your child have headaches or migraines (almost every day, 2-3 times a week, once a week, 2 times a month, once a month)?
 How long does each headache typically last (less than 2 hours, more than 2 hours)?
 Does the headache get worse with bright lights (yes, no, don't know)?
 Does the headache get worse with loud noises (yes, no, don't know)?
 Does your child snore most of the time (yes, no, don't know)?
 How many pain episodes has your child had in the past 12 months that you saw a doctor for (for example: Hematology Acute Care Unit visit, emergency department visit, overnight stay in the hospital)?^{*}

^{*}SCD subject questionnaire only.

Glossary

CHOP, The Children's Hospital of Philadelphia; IHS, International Headache Society; MRA, Magnetic resonance angiography; MRI, Magnetic resonance imaging; OSA, Obstructive sleep apnea; SCD, Sickle cell disease; TCD, Transcranial Doppler ultrasonography; VOE, Vaso-occlusive pain episode.

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Table I
Characteristics of subjects with SCD and control subjects

	SCD (n = 241)	Control subjects (n = 141)	P value
Age, years (mean ± SD)	12.8 ± 4.0	12.7 ± 4.4	.93
Sex (% male)	53.5	48.9	.39
Genotype distribution			
SCD-SS	164 (68%)	—	—
SCD-SC	50 (20.8%)	—	—
SCD-Sβ ⁺ thalassemia	15 (6.2%)	—	—
SCD-Sβ ⁰ thalassemia	12 (5%)	—	—
SCD-SS or Sβ ⁰ thalassemia (n = 176)	13 (7.4%)	—	—
History of overt stroke	36 (35.6%)	—	—
Silent cerebral infarction (n = 101)	21 (21.6%)	—	—
Cerebral vessel stenosis (n = 97)	23 (14.9%)	—	—
History of confirmed abnormal TCD (n = 154)	16 (10.4%)	—	—
History of conditional TCD (n = 154)	44 (25%)	—	—
Receiving transfusion therapy	30 (17%)	—	—
Receiving hydroxyurea [†]	32.4 (26.5-38.7)	27.0 (19.8-35.1)	.27
Prevalence of frequent headache [‡] (%; 95% CI)	14.2 ± 4.3	15.9 ± 3.2	.03
Age of those with frequent headache [‡] , years (mean ± SD)	24.0 (16.9-32.3)	9.7 (4.0-19.0)	.013
Prevalence of frequent headache [‡] , children <13 years old (%; 95% CI)			

* Indications for chronic transfusion were abnormal TCD (n = 19), history of stroke (n = 13), recurrent acute chest syndrome (n = 9); other (n = 3).

[†] Indications for hydroxyurea therapy were recurrent pain and/or acute chest syndrome (n = 29) and abnormal TCD with refusal of transfusion (n = 1).

[‡] Frequent headache defined as headache occurring at least once a week; Includes all SCD genotypes.

Table II
Univariate analysis of factors associated with frequent headache in SCD

	SCD, all ages*			SCD <13 years [†]		
	(+) Headache (n = 78)	(-) Headache (n = 163)	P value	(+) Headache (n = 31)	(-) Headache (n = 98)	P value
Demographics						
Age (y)	14.1 ± 4.2	12.1 ± 3.8	<.001	9.9 ± 2.3	9.6 ± 2.2	.40
Sex (% male)	43.6	58.3	.032	48.4	58.2	.34
Clinical factors						
Frequent VOE	37.7%	20.0%	.006	36.0%	18.8%	.07
VOE concurrent with headache	23.1%	8.6%	.002	16.1%	7.1%	.13
Dactylitis at age <1 yr [‡]	12.7%	11.6%	.83	10.0%	8.3%	1.0
Pulse oximetry <95%	20.0%	29.2%	.14	17.2%	32.3%	.12
Symptoms of OSA [§]	66.7%	45.0%	.002	72.4%	53.7%	.07
Witnessed apnea	29.0%	16.3%	.03	28.6%	20.7%	.38
History of ACS	59.7%	50.3%	.18	43.3%	42.1%	.91
Laboratory [¶]						
Hemoglobin (g/dL)	8.5 ± 0.9	8.2 ± 1.0	.21	8.2 ± 0.8	8.0 ± 1.0	.46
Fetal hemoglobin (%)	10.0 ± 6.6	10.3 ± 7.1	.88	10.3 ± 7.1	9.4 ± 6.6	.74
White blood cell count (10 ⁹ /L)	12.3 ± 3.4	12.0 ± 3.2	.67	13.1 ± 3.7	12.8 ± 3.2	.74
Platelet count (10 ⁹ /L)	436 ± 130	464 ± 121	.24	454 ± 143	462 ± 138	.84
Reticulocyte count (%)	9.0 ± 3.2	9.1 ± 3.9	.84	9.4 ± 3.4	9.7 ± 4.0	.84

* Includes all SCD genotypes, children of all ages.

[†] Includes all SCD genotypes, children younger than 13 years old.

[‡] SCD-SS and SCD-S/β0-thalassemia only.

[§] Snoring or witnessed apnea.

[¶] SCD-SS and SCD-S/β0-thalassemia only, excluding those receiving long-term transfusions.

Table III
Multivariate analysis of factors associated with frequent headache in SCD*

	SCD subjects, all ages			SCD Subjects < 13 years		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
OSA	2.4	1.2-4.7	.012	1.3	0.5-3.5	.62
Frequent VOE	2.4	1.2-4.8	.013	2.9	1.0-8.2	.043
Age (per year increase)	1.2	1.1-1.3	<.001	1.2	1.0-1.5	.054
Female sex	1.1	0.6-2.2	.68	1.1	0.4-2.7	.92

* Includes subjects with all SCD genotypes.

Table IV

Association of neuroimaging abnormalities with frequent headache in subjects with SCD-SS or SCD-S β^0 -thalassemia

	SCD-SS/S β^0 -thalassemia, all ages			SCD-SS or S β^0 -thalassemia <13 years*		
	(+) Headache	(-) Headache	P value	(+) Headache	(-) Headache	P value
Highest TCD velocity [†] (cm/s)	152 $\pm$ 38	157 $\pm$ 36	.39	177 $\pm$ 34	162 $\pm$ 37	.13
History of overt stroke	9.1%	6.6%	.56	10.0%	6.9%	.65
Silent infarct	25.9%	39.2%	.22	50.0%	41.3%	.59
Extensive silent infarct	14.8%	23.0%	.42	25.0%	26.1%	1.0
Any cerebral infarction (overt or silent)	37.5%	45.1%	.46	57.1%	47.1%	.50
Cerebral vessel stenosis	44.4%	12.9%	.001	50.0%	15.6%	.012
Moderate to severe cerebral vessel stenosis	33.3%	7.1%	.001	25.0%	8.9%	.15
Confirmed abnormal TCD	17.0%	14.0%	.63	29.4%	17.7%	.29
Abnormal TCD with cerebral vessel stenosis by MRA	26.1%	4.6%	.003	30.0%	7.1%	.08
Bone marrow hyperplasia	31.3%	14.8%	.047	21.4%	14.0%	.68

* Includes only children younger than 13 years old; number with brain MRI = 65 and number with brain MRA = 57.

[†] Highest TCD velocity to date; subjects with history of stroke excluded.