

COMPARISON BETWEEN DIGITAL SUBTRACTION ANGIOGRAPHY AND MAGNETIC RESONANCE ANGIOGRAPHY IN INVESTIGATION OF NONLACUNAR ISCHEMIC STROKE IN YOUNG PATIENTS

Preliminary results

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ABSTRACT - *Purpose:* We preliminarily investigated the relevance of performing digital subtraction angiography (DSA) in addition to magnetic resonance angiography (MRA) in definition of ischemic stroke etiology in young patients. *Method:* DSAs and MRAs from 17 young patients with nonlacunar ischemic stroke were blindly analyzed and their impact on stroke management was evaluated. *Results:* Etiologies were the same considering results of either DSA or MRA in 12/17 cases. In 15/17 patients no changes would have been made in treatment, regardless of the modality of angiography considered. *Conclusion:* These preliminary results suggest that DSA may be redundant in two thirds of ischemic strokes in young patients. Further larger prospective studies are necessary to determine indications of DSA in this age group.

KEY WORDS: TOAST, stroke etiology, embolism, arterial lesions, cryptogenic stroke.

Comparação entre arteriografia digital e angioressonância na investigação de acidente vascular cerebral isquêmico não-lacunar em pacientes jovens: resultados preliminares

RESUMO - *Propósito do estudo:* Investigar de forma preliminar a relevância da realização de angiografia digital (AD) adicionalmente a angioressonância (AR) na definição de etiologias de acidente vascular cerebral isquêmico (AVCI) em pacientes jovens. *Método:* ADs e ARs de 17 pacientes jovens com AVCI não-lacunares foram analisadas. Avaliamos o impacto destes exames no manejo clínico dos casos. *Resultados:* Em 12/17 casos, as etiologias dos AVCI de acordo com os resultados de AD ou de AR foram idênticas. Em 15/17 pacientes, nenhuma mudança de conduta terapêutica seria realizada, independentemente da modalidade de exame considerada. *Conclusão:* Estes resultados preliminares sugerem que os resultados da AD podem ser redundantes em relação à AR em até dois terços dos pacientes jovens com AVCI. Estudos prospectivos maiores são necessários para otimizar o estabelecimento de indicações de AD nesta faixa etária.

PALAVRAS-CHAVE: TOAST, etiologia de acidente vascular cerebral, embolia, lesões arteriais, criptogênico.

High incidences of stroke in young individuals have been reported in developing countries¹⁻³. In Brazil, it has been estimated that 10.6% of ischemic strokes affect patients aged 15-40 years². In young patients, cryptogenic strokes account for 8.3-55% of ischemic strokes worldwide, reflecting the challenge of determining stroke mechanisms in this age group¹⁻¹¹. While ethnical and regional lifestyle differences are likely to influence incidence and etiological mechanisms of

stroke in the young in different populations, other factors such as use of strict criteria and extent of neurovascular investigation are equally important for diagnosis^{4,7-9}. Given that therapeutic decisions depend on stroke etiology, accurate diagnosis is crucial for proper management of these patients.

It is known that characteristics of vascular lesions and etiologies of infarcts are influenced by age^{4,11}. Abnormal digital subtraction angiography (DSA) re-

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Received 13 September 2005, received in final form 29 December 2005. Accepted 15 February 2006.

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sults have been reported in 39.6-76% of young stroke patients^{4,9,10,12-14}. However, because of concerns about complications of the procedure¹⁵, DSA has been progressively substituted by magnetic resonance angiography (MRA) for evaluation of cervicocranial arteries in clinical practice. Indeed, good correlations between MRA and DSA have been reported for extracranial and intracranial arterial lesions but studies have focused predominantly on patients older than 45 years¹⁶⁻²⁰ or in lacunar strokes in younger patients²¹. Therefore, it remains to be determined whether limitations in MRA accuracy and underperformance of DSA have implications in definition of etiology of nonlacunar stroke in the young and in therapeutic decisions.

We have preliminarily investigated the clinical relevance of performing DSA in addition to MRA in definition of stroke etiology and treatment in a Brazilian sample of patients with ischemic cerebrovascular disease aged less than 45 years.

METHOD

We reviewed cases of ischemic stroke or transient ischemic attack (TIA) consecutively referred to our neurology ward. The study was part of a larger stroke database protocol approved by the Ethics Committee of Hospital das Clínicas/São Paulo University. The study was retrospective and informed consent was considered unnecessary as long as patients were not identified. Inclusion criteria were: age less than 45 years; performance of intracranial MRA (iMRA), cervical MRA (cMRA) and DSA. Images that did not fulfill quality criteria were excluded. MRAs and DSAs were reviewed independently by two senior neuroradiologists (PP and CCL). Both were blind to clinical data and lesional topographies in cranial magnetic resonance imaging (MRI).

Standard imaging protocols for our institution were used. iMRAs were performed with a 1.5 T system with unenhanced 3D time-of-flight (TOF) multiple overlapping thin-slab acquisition (MOTSA) sequences, three-dimensional maximal intensity projection (MIP) images (TR/TE 33.3/3 ms, flip angle 20°, thickness=0.8 mm, matrix 256x192, field of view from 13x13 to 22x22 cm, 0 mm interval). cMRAs were performed with contrast-enhanced 3D TOF MOTSA sequences with MIP images (TR/TE 7-23/4.4 ms, flip angle 45-50°, thickness=2.6 mm, matrix 256x160, field of view 26x26 cm, 0 mm interval) and a smart preparation technique. Intra-arterial 4-vessel selective DSA was performed via the femoral artery, starting with imaging of the aortic arch followed by selective injections of contrast material into both carotid and vertebral arteries. DSA (GE Medical Systems) was performed in the anteroposterior, lateral and oblique projections. Non-ionic contrast of low osmolarity (Iopamiron®, Schering) was administered with a power injector at a rate of 6 mL/s in the common carotid and subclavian arteries (volume: 8 mL) and a rate of 4 mL/s in the internal carotid and vertebral arteries (6 mL). Hydrophilic coated guide wi-

res and 4 or 5-F sheaths were used. Sheaths were intermittently flushed with heparinized saline (5000 IU of heparin in 1000 mL of normal saline). Manual compression at the puncture site was usually performed for 10 minutes after the end of the procedure. No DSA complications were reported.

A standard protocol was systematically used for analysis of DSAs and MRAs blindly to clinical features, MRI findings and laboratory results. Arterial segments were classified as: normal/stenosis $\leq 50\%$; stenosis $>50\%$; occlusion. Final diagnoses were defined based on characteristics of lesions and overall findings. Signs considered suggestive of embolism were: carotid "T" or basilar tip occlusion; abrupt and isolated occlusion of an intracranial arterial branch in the absence of signs of progressive disease in other arteries. Sources of emboli in proximal vessels were evaluated.

All of the patients underwent clinical and neurological evaluation, electrocardiogram, hemogram, blood biochemistry lipid profile, erythrocyte sedimentation rate, immunologic and coagulation testing, cranial computed tomography and MRI. Other investigations included transesophageal echocardiogram (TEE) (16), duplex ultrasonography of extracranial vessels (15), transthoracic echocardiogram (TTE) (7), serology for syphilis and Chagas' disease (15), cerebrospinal fluid analysis (16), transcranial Doppler (8), Holter monitoring (7). The only patient who underwent TTE but not TEE had a positive serology for Chagas' disease and evidence of cardiomyopathy on TTE. Chagas' disease is caused by *Trypanosoma cruzi* infection, endemic in some South American regions²². Two experienced neurologists (MS and FY) defined by consensus the most likely etiological diagnosis according to TOAST criteria²³: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology. In addition, when serology for Chagas' disease was positive and there was evidence of cardiomyopathy, the diagnosis was cardioembolism. Results of DSA and MRA were given for each case; neurologists were blind to the modality of angiography and the order of DSA and MRA results was randomized. Treatment of each patient (antiplatelet drugs/ anticoagulants/ other) was defined, considering clinical and laboratorial investigation as well as results of MRA or DSA. We evaluated agreement between etiology of stroke and agreement between treatment, considering results of either exam.

Given the small sample size of this study (17 patients), this study was underpowered for performance of statistical tests. Therefore, the two methods of neuroimaging were compared in a descriptive way.

RESULTS

A total of 35 patients younger than 45 years were admitted between January and October, 2002; 20/35 patients underwent iMRA, cMRA and DSA. Films from 19 patients were available and were photographed. Two cases did not meet quality criteria and were excluded; in one case, only the posterior cerebral arteries did not fulfill quality criteria and were therefore

Table. Clinical features, affected territories, MRA diagnosis, DSA diagnosis, TOAST diagnosis considering MRA findings, TOAST diagnosis considering DSA findings.

Clinical features	Affected territory	MRA	DSA	TOAST (MRA)	TOAST (DSA)
1. M, 26 y. Headache and right hemiparesis after sexual intercourse.	L MCA	L cICA dissection, L iICA occlusion	L cICA dissection, L iICA occlusion	4 (D)	4 (D)
2. F, 19y. Headache after handball game. One day later, left hemiplegia.	R MCA	R cICA dissection	R cICA dissection, R iICA and LS occlusion	4 (D)	4 (D)
3. M, 44y. Dizziness and vomiting after sexual intercourse; Wallenberg's syndrome. History of smoking.	R PICA	Normal	R PICA occlusion#	4 (D)	4 (D)
4. F, 42y. Sudden loss of consciousness followed by ataxia, anacusia, tinnitus. Right hemiparesis and hemihypesthesia, nystagmus.	BA	R/L VA and BA occlusions	R/L VA dissection and BA occlusion	4 (D)	4 (D)
5. F, 36y. Right hemiparesis and aphasia.	L MCA	R/L ACA, L MCA stenoses	L ACA, L MCA stenoses	5	5
6. F, 41y. Headache, left hemianopsia. History of smoking, oral contraception.	R PCA	Normal	R calcarine artery occlusion#	5	5
7. F, 22y. Loss of consciousness followed by diplopia, right hemiparesis, dysphagia, left oculomotor palsy.	BA	Normal	L MCA parietal branch occlusion#	5	5
8. M, 24y. Aphasia, right hemiparesis and hemihypesthesia.	L MCA	L MCA stenosis	L MCA branch occlusions#	5	5
9. F, 41y. Left hemiparesis. History of smoking.	R MCA	L MCA branch stenoses	L VA dissection	5	5
10. F, 17y. Right hemiparesis, partial motor seizure, aphasia.	L MCA	L MCA stenosis	L iICA, L AC stenoses; L MCA, L LS occlusions#	5	5
11. M, 28y. Left hemiparesis, left hemihypesthesia. History of smoking. Positive serology for Chagas' disease, sickle cell trait.	R MCA	R MCA branch stenoses	R MCA branch occlusions#	2	2
12. M, 38y. Spells of left hemiparesis. Right hemianopsia, left hemiparesis. History of smoking and migraine with aura. TEE: mitral stenosis, left atrial enlargement.	R MCA, L MCA, L PCA	Normal	R MCA posterior parietal branch occlusion#	2	2
13. F, 43y. Spells of right hemiparesis for two weeks. Right hemiparesis and hemihypesthesia, aphasia. History of smoking, hypercholesterolemia.	L MCA	L MCA stenosis	L MCA angular branch occlusion#	1	5
14. M, 30y. Right hemiparesis. History of smoking.	L ICA	L cICA occlusion	L cICA FMD, L iICA, LS occlusions	1	4(FMD)
15. F, 29y. Seizures, dysarthria, left crural monoparesis. Hands and feet swelling. History of smoking, TIAs, arthralgias, alopecia, Raynaud phenomenon. Diffuse white matter lesions, positive lupus anticoagulant and anticardiolipin, positive antinuclear factor, proteinuria. TEE: Inteartrial septum aneurysm.	R ICA, L PCA	Normal	Diffuse lesions in cortical arteries	5	4 (V)
16. M, 44y. Paresthesias on right arm and leg, dizziness, diplopia, dysphagia, disarthria. History of arterial hypertension, hypercholesterolemia, smoking.	BA	L MCA branch stenoses	L VA dissection	5	4 (D)
17. M, 43y. Woke up with right hemiparesis, aphasia. History of smoking. Positive serology for Chagas' disease, normal ECG and TEE.	LMCA	R MCA stenoses	L cICA dissection and L MCA branch occlusions	5	4 (D)

M, male; F, female; y, years; ECG, electrocardiogram; TEE, transesophageal echocardiogram; R, right; L, left; PICA, posterior inferior cerebellar artery; BA, basilar artery; PCA, posterior cerebral artery; ICA, internal carotid artery; cICA, cervical ICA; iICA, intracranial ICA; ACA, anterior cerebral artery; VA, vertebral artery; LS, lenticulostriate arteries; LVA, vertebral artery; D, dissection; FMD, fibromuscular dysplasia; V, vasculitis; 1, Large-artery atherosclerosis; 2, cardioembolism; 3, small-vessel occlusion; 4, stroke of other determined etiology; 5, stroke of undetermined etiology; #lesion suggestive of embolism.

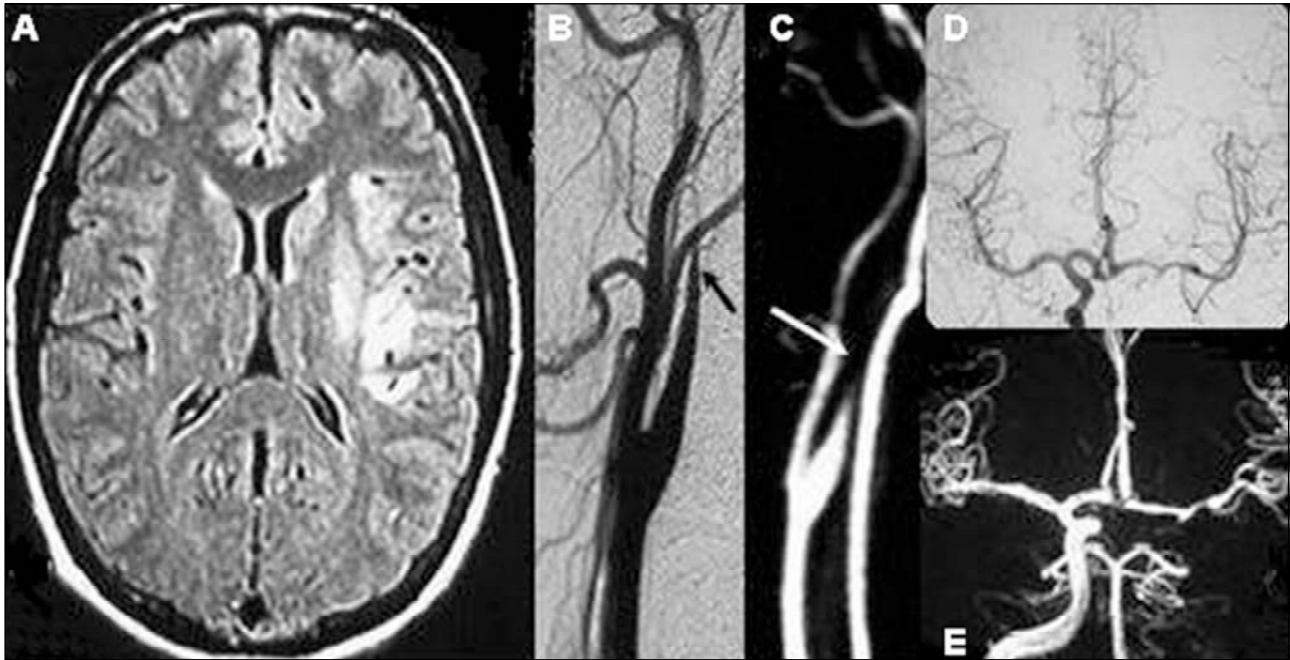


Fig 1. Patient 1, a 26-year-old male, had sudden onset of headache, nausea, right hemiparesis and dysarthria after sexual intercourse. (A) Fluid attenuated inversion-recovery (FLAIR) sequence in cranial MRI showed an infarction involving the territory of left lenticulostriate and insular MCA branches. (B) DSA demonstrated left cervical ICA segmental stenosis (arrow) suggestive of arterial dissection and left intracavernous ICA occlusion. (D) left ACA and MCA were filled by the Willis circle. (C, E) MRA disclosed similar findings.

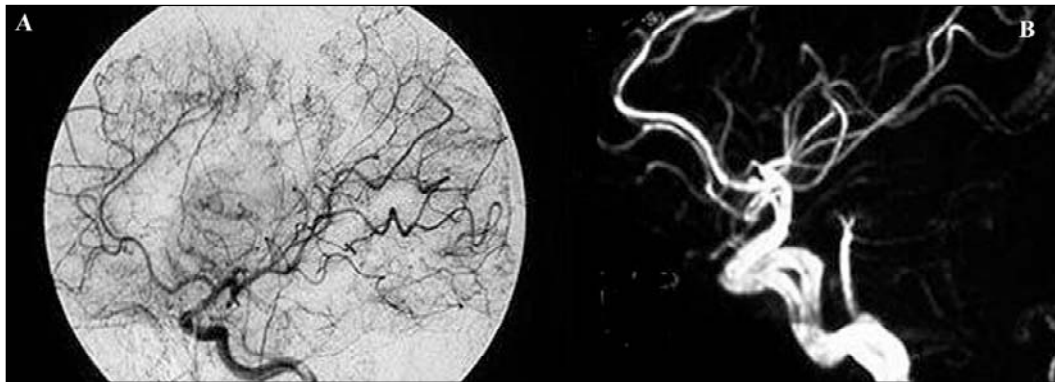


Fig 2. Patient 15, a 29 year-old female, had history of seizures, arthralgias, Raynaud phenomenon and alopecia. She had sudden onset of left monoparesis. DSA showed contrast retention in cortical vessels (A). MRA was normal (B).

not evaluated. Therefore, iMRAs, cMRAs and DSAs from 17 patients aged 17-44 years (mean±standard deviation, 33±9 years), 8 male, were analyzed.

All DSAs and 12/17 MRAs revealed abnormalities. Clinical features, affected arterial territories, DSA and MRA results as well as diagnosis according to TOAST criteria considering either DSA or MRA results are shown in the Table. None of the infarcts was lacunar. The most frequently affected artery was the middle cerebral artery (MCA) (8/17 in both MRA and DSA) (Table). MRA and DSA final diagnoses were complete-

ly concordant in only 4 patients (Table, patients 1, 2, 4, 5). Fig 1 (A-E) shows images from patient 1. Intervals between examinations were (mean±standard deviation): iMRA and DSA, 3.5±5.6 days, cMRA and DSA, 1.4±7.1 days.

MRA had lower resolution than DSA for detection of arterial branch lesions (Patients 6-8, 10-13, 15). Fig 2 shows images from case 15. Also, MRA did not reveal a posterior cerebellar inferior artery (PICA) lesion (patient 3), a lesion of fibromuscular dysplasia (patient 14) and 2 arterial dissections (patients 16

and 17) (Table). In case 9, DSA disclosed left VA dissection and MRA, left MCA lesions but the patient had a right striatocapsular infarction. Therefore, DSA probably showed a false positive result in this case.

In patients 3, 6-8 and 10-13, DSA revealed focal lesions suggestive of embolism in arteries supplying the infarcted area^{3,6,7,12}. Yet, emboligenic sources were only detected in patients 11 and 12.

Etiologies according to TOAST criteria were the same considering results of either DSA or MRA in 12/17 cases (Table, patients 1 to 12) and were different in 5/17 cases (Table, patients 13-17). In patient 14, diagnosis was large-artery atherosclerosis based on MRA findings but DSA revealed fibromuscular dysplasia. In patient 13, the diagnosis was large-artery atherosclerosis considering the MRA finding of MCA stenosis but was undetermined considering the absence of large-artery stenosis and the presence of a lesion suggestive of embolism in DSA. In 9/17 cases (patients 5-10, 15-17) etiological diagnosis was undetermined considering MRA results. In 3 out of these 9 cases, DSA contributed significantly to definition of stroke etiology: vasculitis (patient 15) and arterial dissection (patients 16 and 17). In the remaining cases, etiological diagnosis remained undetermined in spite of DSA results.

Neurologists chose different treatments in patients 16 and 17 only (anticoagulation based on DSA results, antiplatelet drugs based on MRA results). In all other 15 cases, no changes would have been made in treatment, regardless of the modality of angiography evaluated.

DISCUSSION

To our knowledge, this is the first study to directly compare MRA and DSA findings in nonlacunar ischemic stroke in young adults. Concordance between final angiographic diagnoses obtained by different imaging modalities was low. On the other hand, concordance between stroke etiologies according to clinical and imaging criteria was high, as well as concordance between therapeutic decisions based on results of either MRA or DSA.

DSA identified abnormalities in at least one artery in all patients and MRA, in more than two thirds of the patients. It has been reported that lacunar strokes are highly predictive of normal DSAs in young patients with ischemic stroke²¹. None of the strokes in our series was lacunar (Table) and this is a likely reason to explain the high rate of abnormal DSAs in the present series.

Occlusion suggestive of embolism has been described as the most frequent DSA abnormality in young stroke patients^{12,14}. In this series, embolism to intracranial arteries may have been an important etiology of stroke. First, the most commonly affected artery was the MCA, an usual target for emboli. Second, DSA revealed lesions suggestive of embolism^{3,6,7,12} in arterial branches in 8 cases (Patients 3, 6-8 and 10-13). In 4 of these cases the lesions were not detected in MRA. In addition, in patient 15 lesions in cortical areas were demonstrated by DSA only. These findings may be explained by lower MRA resolution for visualization of terminal carotid branches and intracranial vessels²⁴.

The detection of intracranial branch arterial lesions in DSA in the absence of identifiable sources of embolism in the present series supports the view that underdiagnosed embolism may be partially responsible for a higher rate of cryptogenic strokes in younger individuals. Other authors have described angiographic findings suggestive of embolism in the absence of identifiable sources in stroke of undetermined cause^{6,25}. Some thrombi may lyse from their sources or may be too small to be detected by current tools of investigation^{26,27}. Therefore, quoting L.R. Caplan, it is possible that DSA may have revealed the "birds" while their "nests" remained unknown in some of the presented cases²⁸.

However, in order to consider embolism as the etiology of an infarction, it is crucial to identify an emboligenic source. In patients 11 and 12, emboligenic sources were determined and stroke etiology would be cardiac embolism regardless of the modality of angiography considered. In 5 of 8 patients (Table, cases 6-8, 10 and 13), DSA revealed lesions suggestive of embolism but no emboligenic sources were found and causes of stroke remained undetermined. These results indicate that differences in MRA and DSA sensitivity for detection of lesions suggestive of embolism did not substantially influence the final etiological diagnosis in these patients.

A critical finding was the concordance between diagnoses of stroke etiology according to TOAST criteria in two thirds of the cases, given the results of either MRA or DSA. Treatment would have been different in only two cases, both arterial dissections demonstrated by DSA. False negative results in MRA have been previously reported in arterial dissection²⁹. Cervical MRI with axial T1 or T2-weighted images with fat suppression increases sensitivity to dissection by identification of the hematoma in the arte-

rial wall³⁰ and was not performed in the two patients because of lack of clinical suspicion at the time they were evaluated. If MRI had shown intramural hematomas in the dissected arteries, no differences in diagnosis would have occurred considering MRA/MRI or DSA findings and therefore, no differences in treatment would have been made for any of the patients.

Technical improvements contributed to decrease the risk of neurologic complications reported in the literature^{31,32}: Wilinsky and colleagues reported 1.3% neurologic complications in 2,899 cerebral angiographies¹⁵. Complications were transient in 0.2%, reversible in 0.7% and permanent in 0.5% of the cases. Age greater than 55 years, presence of cardiovascular disease and fluoroscopic times of 10 minutes significantly increased risk associated with DSA. It is still a matter of controversy whether ischemic stroke increases DSA risk, compared to other conditions such as subarachnoid hemorrhage¹⁵.

DSA may be safer in younger patients without diffuse vasculopathy than in older individuals^{12,15}. However, risk-benefit ratios should be considered and invasive procedures should be avoided whenever additional information does not substantially contribute to definition of diagnosis and treatment. Therefore, DSA in stroke in the young must be more clearly defined. These preliminary findings emphasize the need to enhance identification of sources of embolism and the importance of an integrated clinical/radiological approach. Due to small sample size of this study, we performed a descriptive analysis of the data. Therefore, we do not know if the results of this study may be externally generalized. However, the findings of this study encourage future prospective studies involving larger number of patients to determine in which cases DSA is more likely to have a relevant impact on definition of ischemic stroke etiology and treatment in young patients.

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