Original Paper

Aggressive Medical Care in Young Chinese Patients with Ischemic Stroke of Undetermined Etiology: A Retrospective Study

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Key Words

Medical care · Undetermined etiology · Young stroke patients

Abstract

Objectives: This study aimed to investigate the clinical and angiographic characteristics of ischemic stroke of undetermined etiology in young Chinese adults and to observe the effects of medication on their long-term outcomes. **Methods:** A total of 179 consecutive young patients with ischemic stroke of undetermined etiology were retrospectively analyzed for clinical and angiographic characteristics, laboratory tests, the choice of drug treatment, and follow-up outcomes. Any predictive power for recurrent stroke and new lesions or aggravated stenosis was analyzed. **Results:** 170 patients were clinically followed up for a median of 25 months (range, 4–92), and 65 patients with 114 lesions had angiographic follow-up for a median of 7 months. A total of 53 patients were enrolled in a routine medical management (RMM) group, and 117 were treated with corticosteroids plus RMM (aggressive medical management, AMM). Kaplan-Meier survival analysis revealed that differences in the 2-year cumulative stroke-free rate and in the 18-month cumulative worsening and/or new lesion-free rate between the RMM and AMM groups were significant ($p < 0.05$). Multivariate and Cox regression analyses revealed that the choice of drug therapy and erythrocyte sedimentation rate were associated with recurrent stroke, that AMM was independently associated with a decreased risk of worsening lesion, and that worsening lesion was the only independent predictor of recurrent

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stroke. **Conclusion:** Compared with RMM, AMM is more efficacious in the prevention of secondary ischemic stroke and progressive arterial lesions among young adults with ischemic stroke of undetermined etiology.

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Introduction

Ischemic strokes occurring in patients aged <45 years have been considered relatively rare events, accounting for up to 12% of all ischemic strokes [1]. Compared to old patients, young stroke patients have more diverse etiologies, and the etiologic frequency of ischemic stroke in young patients differs around the world [2, 3]. The proportion of ischemic strokes of undetermined etiology is 30–70% among young patients in different countries and regions, which is significantly higher than in elderly stroke patients [4].

Although stroke occurs at a relatively lower annual incidence rate in young adults, it has a relatively higher public health impact because of direct socioeconomic and associated indirect costs [5, 6]. This phenomenon is especially striking in China, as it is a developing country with a population of >1.3 billion and an uneven development of regional economies. Until now, published studies on young adults suffering from stroke mainly focused on its clinical subtypes, the distribution of stroke etiologies, prognosis, and associated cerebrovascular disease risk factors [7] and rarely referred to its medication and angiographic characteristics. In the present study, we attempted to retrospectively review the incidence of ischemic stroke of undetermined etiology among young Chinese patients (aged 18–45 years) as well as their clinical and angiographic characteristics. Meanwhile, we compared the efficacy of aggressive (AMM) and routine medical management (RMM) in clinical and angiographic outcomes.

Materials and Methods

Patients

This study was approved by the ethics committee of our institution, and written informed consent was obtained from all patients and their families.

The Nanjing Stroke Registry Program (NSRP) [8] is a program conducted in mainland China, which contains a variety of information including demographic, clinical, and imaging data as well as laboratory tests. Ischemic stroke patients aged <45 years were recruited from the NSRP between March 2005 and March 2012, and their medical records were reviewed to exclude those who presented with determined etiologies such as atherosclerosis, cardiac disease, etc. Finally, a total of 179 eligible young patients with ischemic stroke were enrolled, and their baseline data, drug management, and angiographic and clinical follow-up outcomes were retrospectively collected and analyzed.

Medication

All eligible patients received RMM as follows: (1) antiplatelet therapy (aspirin 100 mg/day, clopidogrel 75 mg/day, or a combination of both); (2) a cholesterol-lowering agent (statins such as atorvastatin or rosuvastatin) unless there were drug contraindications, and (3) intravenous administration of penicillin G (9.6–14.4 million units per day for 10–14 days) or oral azithromycin therapy (0.5 g per day for 5 days) for patients allergic to penicillin.

The participants who provided written informed consent then received corticosteroid therapy (AMM) as follows: high-dose methylprednisolone pulse therapy (1,000 mg/day i.v.) for 5 days followed by oral prednisone sequential therapy (1 mg/kg/day) for at least 3 months. If clinical symptoms improved and no stroke recurrence was noted, prednisone was continued on an alternate day regimen and was ultimately tapered to 20 mg/day and stopped within 3 months. At the same time, participants were treated with gastric acid suppressors, potassium, and calcium. During the course of steroid therapy, if transient ischemic attack (TIA)

or ischemic stroke recurred, or if worsening stenosis or a new lesion was detected, patients in the AMM group were encouraged to start taking immunosuppressive medications such as azathioprine or cyclophosphamide, whereas patients in the RMM group were encouraged to undergo corticosteroid treatment.

Laboratory Assays and Routine Tests

The following laboratory examinations were performed in all patients: complete blood counts, clinical chemistry parameters, thrombophilia markers including proteins C and S and antithrombin III, homocysteine, lupus anticoagulant and anticardiolipin antibodies, antinuclear antibody spectrum, antineutrophil cytoplasmic antibodies, serum immunoglobulin assay, rheumatoid factor, antistreptolysin O (ASO), complement 3 (C3), erythrocyte sedimentation rate (ESR), and C reactive protein (CRP).

All participants received routine tests including a chest X-ray, various neuroimaging (brain CT or MRI scan and angiography) and cardiac tests such as electrocardiography and contrast and/or transthoracic echocardiogram and/or transesophageal echocardiogram performed to exclude certain cryptogenic heart diseases such as patent foramen ovale.

Angiographic Procedure

Digital subtraction angiography (DSA) included intra- and extracranial portions of bilateral carotid and vertebrobasilar systems. According to a previous report [9], the angiographic procedure was performed on a DynaCT angiography machine (AXIOM Artis dTA; Siemens Healthcare, Erlangen, Germany) at the interventional center of our department. Briefly, under local anesthesia, a 5-Fr cerebral guiding catheter (Envoy; Cordis, Fremont, Calif., USA, or Guider Soft Tip XP; Boston Scientific, Natick, Mass., USA) was passed into the common or internal carotid artery (ICA) and the subclavian or vertebral artery through a 5-Fr femoral arterial sheath. Baseline angiography was performed to assess all vascular lesions. Each angiogram was reviewed by a neuroradiologist and a neurologist. The stenosis rate of the extracranial vessels was calculated according to the North American Symptomatic Carotid Endarterectomy Trial criteria, and the stenosis degree of the intracranial arteries was evaluated using the WASID technique. Mild, moderate, and severe stenosis was defined as 30–49, 50–69, and 70–99% diameter stenosis, respectively. All the 179 patients underwent DSA assessment, and in 95 of them a total of 169 stenotic arteries ($\geq 30\%$) were found.

Clinical and Angiographic Follow-Up

All participants were scheduled for a clinical follow-up or a complete telephone interview at 1, 3, 6, and 12 months and yearly thereafter if they had no recurrence. All patients with significant arterial stenosis were scheduled for an angiographic follow-up at 6 months after the first registration, or earlier in the case of either recurrent TIA or ischemic stroke. Patients with recurrence of stroke or TIA required DSA reevaluation. The degree of stenosis on CT or MR angiography was based on the interpretations by the staff neuroradiologists. In patients whose noninvasive imaging findings were ambiguous or suggested progressive stenosis, DSA was performed. Compared to the initial angiography, a target lesion having an increase in the degree of stenosis of $\geq 10\%$ or developing total occlusion was regarded as worsening stenosis, a lesion with a decrease in the degree of stenosis of $\geq 20\%$ or total disappearance was defined as lessening lesion, and a newly verified arterial stenosis $\geq 30\%$ was defined as a new lesion.

End Points

The main end points were composite clinical outcome events including nonfatal stroke and death from all causes, and the secondary end points were angiographic outcomes including worsening stenosis and new lesions. Recurrent ischemic symptoms were defined as new episodes of TIA or acute ischemic stroke.

Data Analysis

Continuous data are expressed as mean $\pm$ standard deviation (SD), and categorical data are presented as numbers and percentages. A χ^2 test and one-way ANOVA analysis were performed for multiple comparisons when appropriate. Kaplan-Meier analysis and a log-rank test were performed to detect the differences between the two groups for the time to any neurological event (ischemic stroke and/or TIA) and lesion change. By employing stepwise regression analysis, all variables were investigated to screen for those factors which were related to recurrent stroke and progressive original stenosis or new lesions. The entry and removal probabilities of the stepwise selection were 0.05 and 0.1, respectively. A p value < 0.05 was considered statistically significant. All analyses were performed with SPSS version 15.0 (SPSS Inc., Chicago, Ill., USA).

Table 1. Patient characteristics

Characteristics	Total (n = 179)	No DSA follow-up (n = 114)	DSA follow-up (n = 65)
Age, years	37.6±6.2	37.0±6.4	38.5±5.4
Male sex	34 (74.9)	85 (75.6)	49 (75.4)
Follow-up, months			
Median (range)	24 (0–92)	24 (0–85)	24 (6–92)
Mean ± SD	31.5±24.2	31.5±24.5	31.4±23.8
Blood examination			
ESR (>10 mm/h)	34 (19.0)	23 (20.2)	11 (16.9)
C3	30 (16.3)	18 (15.8)	12 (18.5)
CRP (>15 mg/l)	41 (22.9)	24 (21.1)	17 (26.2)
IgM	14 (7.8)	7 (6.1)	7 (10.8)
IgA	19 (10.6)	11 (9.6)	8 (12.3)
IgG	38 (21.2)	23 (20.2)	15 (23.1)
ASO (>20 IU/ml)	24 (13.4)	16 (14.0)	8 (12.3)
Qualifying events			
TIA	40 (22.3)	28 (24.6)	12 (18.5)
Ischemic stroke	139 (77.7)	86 (75.4)	53 (81.5)
No stenosis	84 (46.9)	84 (73.7)	0 (100)
Lesions, n	162	48	114
Lesion location			
Anterior circulation	113		
Extracranial ICA	47 (29.0)	14 (29.2)	33 (28.9)
Intracranial ICA	17 (10.5)	4 (8.3)	13 (11.4)
Middle cerebral artery	45 (27.8)	11 (22.9)	34 (29.8)
Anterior cerebral artery	4 (2.5)	2 (4.2)	2 (1.8)
Posterior circulation	49	46	
Posterior cerebral artery	4 (2.5)	2 (4.2)	2 (1.8)
Basilar artery	5 (3.1)	2 (4.2)	3 (2.6)
Vertebral artery	40 (24.7)	13 (27.1)	27 (23.7)
Mean degree of stenosis, ± SD ^a	78.37±12.07	79.09±12.07	76.67±12.00
Treatment			
RMM	55 (30.7)	38 (33.3)	17 (26.2)
AMM	124 (69.3)	76 (66.7)	48 (73.8)

Data are expressed as numbers with percentages in parentheses unless otherwise indicated.

^a The degree of stenosis was determined by the WASID method.

Results

Baseline Characteristics

Between March 2005 and March 2012, data of 458 consecutive young patients with ischemic stroke (aged 18–45 years) were extracted from the NSRP, and 179 (39.1%) of them were diagnosed with ischemia of undetermined etiology. The baseline patient characteristics are presented in table 1. The mean age of all participants was 37.6 ± 6.2 years, and 134 (74.9%) of the patients were males. The qualifying events before enrolment were cerebral infarction (77.7%) and TIA (22.3%). A total of 55 (30.7%) patients were assigned to the RMM group and 124 (69.3%) to the AMM group.

Blood examination was normal in the majority of the patients; only some had increased serum levels of IgG (20.2%), IgM (7.3%), and IgA (10.1%), ESR (18.4%), CRP (22.9%), and ASO (12.8%), or decreased C3 levels (15.6%). A total of 84 (46.9%) patients had no DSA-

Table 2. Clinical and angiographic outcomes during follow-up

End points	RMM (n = 53)	AMM (n = 117)	HR			
			unadjusted	p	adjusted	p
Clinical follow-up, months						
Median (range)	22 (4–85)	31 (6–92)	–6.61345 ± 3.90507 (–14.32279–1.09589) ^a	0.092		
Mean ± SD	28.6 ± 22.7	35.2 ± 24.0				
Mean age ± SD, years	39.0 ± 5.5	37.1 ± 6.2	–1.93162 ± 0.98747 (–0.1783–3.88107) ^a	0.052		
Clinical outcomes						
Recurrence	10 (18.9)	2 (1.7)	0.082 (0.018–0.375)	0.001	0.04 (0.008–0.211)	0.000
Angiographic outcomes	43	71	0.211 (0.077–0.578)	0.002	0.160 (0.053–0.485)	0.001
Progression	9 (20.9)	4 (5.6)				
Improvement	10 (23.3)	44 (62.0)				
No change	17 (39.5)	22 (31.0)				
New lesion	7 (16.3)	1 (1.4)				
DSA follow-up time, months						
Median (range)	8.0 (4.5–20)	7 (4–18)	–0.31952 ± 0.580994 (–0.83164 to 1.47068) ^a	0.583		
Mean ± SD	8.2 ± 3.4	7.9 ± 2.8				

Values are presented as numbers with percentages in parentheses unless otherwise indicated. Recurrence: cerebral infarction or TIA. Adjusted: adjusted by all the variables presented in table 1 using Cox proportional hazard analyses.

^a t value = mean ± SE with 95% CI in parentheses.

verified intra- or extracranial artery stenosis (degree of stenosis <30%). We found a total of 162 significant lesions (degree of stenosis ≥30%) in 95 patients: 113 (69.8%) located in the anterior circulation and 49 (30.2%) in the posterior circulation. The mean baseline degree of stenosis was 76.78 ± 14.44% (table 1). The baseline demographic, laboratory, clinical, and lesional characteristics (location of the lesion and stenosis rate) were comparable between the two medical treatment groups (data not shown).

Clinical and Angiographic Outcomes during Follow-Up

Of the 179 patients, 9 (5%; 2 RMM and 7 AMM cases) were lost to follow-up after discharge. Their baseline variables were not different from those of the patients who were followed up (data not shown). Thus, 170 patients could be followed up clinically: 53 RMM and 117 AMM cases. The mean and median clinical follow-up time was 28.6 ± 22.7 and 22 months (range, 4–85) for the RMM group and 35.2 ± 24.0 and 31 months (range, 6–92) for the AMM group, respectively (table 2).

Clinical follow-up outcomes are shown in table 2. No fatal complications or deaths occurred in this study. Recurrent neurological events (TIA and cerebral infarctions) occurred in 12 cases: 2 (1.7%) in the AMM group and 10 (18.9%) in the RMM group. The composite stroke rate was 6.7% (12/179). Of these cases, 11 (91.7%) were attributed to worsening original stenosis or new lesions. The 2-year cumulative stroke-free survival rate was 86.3 ± 2.9% in the whole study population, 71.5 ± 2.2% in the RMM group, and 92.6 ± 2.4% in the AMM group, and the difference was significant (log-rank test, $\chi^2 = 7.459$, $p = 0.006$) (fig. 1a).

A median DSA follow-up of 7 months (range, 4–20) was available for 65 patients (68.4% of the 95 patients with significant arterial stenosis) with 114 lesions, and 105 patients with 48 lesions were not followed up by DSA. The baseline characteristics of patients with and

Table 3. Clinical variables at baseline vs. risk of stroke recurrence during clinical follow-up

	Total (n = 170)	Recurrence (n = 12)	p
Mean age ± SD, years	37.7 ± 6.0	39.9 ± 5.0	0.180
Sex			
Male	128 (75.3)	8 (66.7)	0.339
Female	42 (24.7)	4 (33.3)	
Blood examination			
ESR (≥10 mm/h)	29 (17.1)	5 (41.7)	0.034
C3	30 (17.6)	2 (16.7)	0.643
ASO (≥20 IU/ml)	21 (12.4)	1 (8.3)	0.548
CRP (≥15 mg/l)	39 (22.9)	3 (25.0)	0.548
IgM	13 (7.6)	1 (8.3)	0.628
IgA	18 (10.6)	1 (8.3)	0.630
IgG	38 (22.4)	2 (16.7)	0.472
Qualifying events			
TIA	134 (78.8)	12 (100.0)	0.052
Ischemic stroke	36 (21.2)	0 (0.0)	
Treatment			0.000
RMM	53 (31.2)	10 (83.3)	
AMM	117 (68.8)	2 (16.7)	

Data are expressed as numbers with percentages in parentheses unless otherwise indicated.

Fig. 1. Kaplan-Meier curves for cumulative incidence of neurological events (TIA or ischemic stroke; **a**) and cumulative worsening lesions (progressive original stenosis or new lesions; **b**).

without DSA follow-up were similar (table 1). Out of the 65 patients, 17 (15.4%) were found to have 21 (13.2%, 21/114; table 4) progressive stenoses and/or new lesions. Using Kaplan-Meier analysis, the cumulative 18-month progressive and/or new lesion-free rate was $38.2 \pm 1.45\%$: $15.6 \pm 1.34\%$ in the RMM and $73.1 \pm 1.43\%$ in the AMM group (log-rank test, $\chi^2 = 11.513$, $p = 0.001$) (fig. 1b).

The baseline characteristics of the subsets of patients with and without recurrent stroke were further compared (table 3). Our data showed that the choice of drug treatment and the

Table 4. Lesion variables vs. risk of worsening lesions during angiographic follow-up

Lesion characteristics	Total (n = 114)	Worsening lesions (n = 21) ^a	p
Anterior circulation	80 (70.2)	13 (61.9)	0.430
Extracranial ICA	24 (21.1)	4 (19.0)	
Intracranial ICA	20 (17.5)	5 (4.8)	
Middle cerebral artery	34 (29.8)	4 (42.9)	
Anterior cerebral artery	2 (1.8)	0 (0.0)	
Posterior circulation	34 (29.8)	8 (38.1)	
Posterior cerebral artery	2 (1.8)	0 (4.8)	
Vertebral artery	27 (23.7)	7 (28.6)	
Basilar artery	5 (4.4)	0 (0.0)	
Mean degree of stenosis ± SD, %	73.59 ± 20.26	71.43 ± 25.30	0.614
Recurrence	12 (10.5)	11 (52.4)	0.000
Treatment			0.000
RMM	43 (37.7)	16 (76.2)	
AMM	71 (62.3)	5 (23.8)	

Data are expressed as numbers with percentages in parentheses unless otherwise indicated.

^a Worsening lesions include progressive original lesions (n = 13) and new lesions (n = 8).

ESR were significantly associated with recurrent stroke (AMM vs. RMM: OR = 0.075, 95% CI, 0.016–0.355, $p = 0.001$; ESR vs. no ESR: OR = 3.988, 95% CI, 1.169–13.605, $p = 0.027$), whereas other variables were not. Using stepwise multivariate Cox regression analysis, AMM (crude HR = 0.082, 95% CI, 0.018–0.375, $p = 0.001$) was associated with a reduced risk of recurrent stroke and elevated serum levels of ESR (crude HR = 3.933, 95% CI, 1.247–12.404, $p = 0.019$) were associated with an increased risk of recurrent stroke. Furthermore, according to the χ^2 test and multivariate Cox regression analysis, RMM was associated with worsening lesions including progressive or new arterial stenosis (AMM vs. RMM: OR = 0.128, 95% CI, 0.043–0.384, $p = 0.000$), and AMM was independently associated with a decreased risk of worsening lesions (crude HR = 0.211, 95% CI, 0.077–0.578, $p = 0.002$). In addition, worsening lesions were the only independent predictor of recurrent stroke (after adjusted for all factors shown in table 3: HR = 35.000, 95% CI, 4.483–273.259, $p = 0.001$).

Among the 65 patients (21 in the RMM and 44 in the AMM group) who had a DSA follow-up, only 17 (26.2%) were detected to have worsening lesions including progressive original and new lesions (table 4). Among them, 5 were from the AMM group; however, only 2 patients presented with recurrent symptoms. Figure 2 shows typical angiograms of 3 cases before and after treatment with corticosteroids. The patients with progressive stenosis, new lesions, or clinical recurrence were advised to start azathioprine or cyclophosphamide therapy and had no recurrence of stroke (fig. 3a–c). A total of 12 patients in the RMM group had worsening lesions (fig. 3d–f), and 3 received stent placement for progressive stenosis with recurrent stroke.

Discussion

In our study, we found no definite stroke risk factors in all participants aged 18–45 years, in spite of extensive clinical and laboratory investigations. Although some patients had abnormal serum levels of IgG, IgM, IgA, ESR, CRP, C3, or ASO, none of them met the diagnostic

Fig. 2. a, b Imaging from a 37-year-old man diagnosed with acute brainstem and cerebellar infarction. **a** Initial angiogram showing a total occlusion at the root of the right vertebral artery (arrow) and not detecting the distal vasculature. **b** After corticosteroid therapy for 6 months, the angiogram showed a 50% stenosis in the proximal right vertebral artery (lower arrow) with good distal vasculature imaging (upper arrow). No clinical recurrence occurred during the 3-year follow-up. **c, d** Imaging from a 35-year-old man presenting with recurrent TIA in the anterior circulation. **c** Angiogram showing an 85% stenosis in the M1 segment of the right middle cerebral artery (arrow). **d** Angiogram showing no significantly changed lesion after treatment with corticosteroids for 6 months. However, the patient was asymptomatic.

criteria of autoimmune system diseases such as systemic lupus erythematosus, Takayasu's disease, Behçet's disease, Sjögren's syndrome, rheumatoid arthritis, and primary central nervous system vasculitis, etc. In our study, the proportion of patients with strokes of undetermined etiology was 39.1%, which is higher than that reported in a study from Taiwan (23.5%) [10] and similar to that reported in other studies (31–62% in young adult patients) [3, 11].

The proportion of male patients (74.9%) was much higher than that in previous studies of cerebral infarction in young adults [4, 12]. Except for ESR, there were no other differences between male and female patients. Furthermore, the frequency of lesions in the posterior circulation was lower and similar to that reported in other studies on young stroke patients [1, 13]. More than 50% of the lesions in our study were located in the intracranial arteries,

Fig. 3. **a–c** Imaging of a 39-year-old woman who presented with right cerebral infarction and who, in the process of corticosteroid reduction, developed recurrent TIA in the same vascular territory. Subsequently, she received azathioprine therapy, and no recurrence developed in the ensuing clinical follow-up. **a** Initial angiogram showing a mild stenosis at the root of the right middle cerebral artery (arrow). **b** Angiogram showing worsening original stenosis in the right middle cerebral artery after corticosteroid therapy for 4 months (arrow). **c** Angiogram showing no significant stenosis in the same artery after azathioprine therapy for 1.5 years. **d–f** Imaging from a 33-year-old woman with frequent episodes of TIA in the distribution of the left middle cerebral artery who refused to receive corticosteroid therapy. **d** Initial angiogram showing a 95% stenosis in the M1 segment of the left middle cerebral artery (arrow). **e** Angiogram showing a subtotal occlusion of the same lesion after RMM for 6 months (white arrow). **f** Angiogram showing a total occlusion of the left middle cerebral artery after 18 months (arrow).

which is consistent with previous reports showing that Asian patients have relatively higher occurrence rates of intracranial atherosclerotic lesions than White patients.

Despite the fact that 30% of all ischemic strokes have an unknown etiology, to date no information is available for special drug therapy and secondary prevention protocols for young patients with ischemic stroke of unknown etiology. Thus, these patients are usually treated according to guidelines that are applicable to patients with defined risk factors. According to the international and Chinese stroke association guidelines on ischemic stroke, all patients in the present study were provided a comprehensive treatment including lifestyle changes, risk factor management, antiplatelet therapy, and statin medication, regardless of the lipid levels. For the patients with symptomatic ICA stenosis ($\geq 50\%$), carotid endarterectomy or carotid angioplasty and stenting were recommended [14–16]. However, although intracranial stenting has been used in symptomatic patients with intracranial atherosclerotic stenosis in many neurological intervention centers, the results of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial challenge this approach [17, 18]. Furthermore, except for high complication and morbidity rates associated with percutaneous transluminal angioplasty and stenting, in-stent restenosis after intracranial stenting is an option which cannot be ignored. Some studies reported that in-stent restenosis tended to occur more often in young male patients [19, 20]. In our

cohort study, despite the fact that most patients had symptomatic ICA stenosis and/or intracranial atherosclerotic stenosis, all participants were young with undefined stroke risk factors and the majority of them were males. Therefore, endovascular interventions were not the first choice for them.

In view of the fact that some patients had abnormal serum levels of inflammation- or immunology-related parameters but did not meet the diagnostic criteria for vasculitis or autoimmune diseases, we presumed that inflammatory or immunological reactions might play a potential role in the course of vascular damage and underline the etiology of stroke. Based on this hypothesis, we attempted to treat some young stroke patients with corticosteroids (dexamethasone and/or prednisone) in accordance to the therapeutic protocol of vasculitis. In our study, the composite stroke recurrence rate was similar to that found in previous reports (3–15%). Although the baseline data on admission between the RMM and AMM group were similar, during the mean 33 months of clinical follow-up, the patients in the AMM group had a significantly lower clinical recurrence rate (1.7 vs. 18.9%) as well as progressive and new lesion rate (5.6 vs. 1.4% and 20.9 vs. 16.3%, respectively). Consistently, results from the Cox regression analysis showed that AMM could reduce the risks of clinical and angiographic end points, but the elevated serum levels of ESR might increase the risk of stroke recurrence. In addition, worsening lesion (progressive original or new arterial stenosis) was an independent predictor of recurrent stroke. In the AMM group, 2 patients experienced clinical recurrence and 5 had progressive artery stenosis. They received azathioprine therapy for 1 year no stroke occurred and the original lesions improved. Patients treated with corticosteroids did not undergo angioplasty or stenting, whereas 3 patients in the RMM group received endovascular interventions for aggravation of arterial stenosis and frequent recurrence of cerebral infarction and/or TIA. Since corticosteroids themselves have anti-inflammatory and suppressive immunological actions, our results suggest that inflammatory or immunological mechanisms did play a role in our patients, especially in those with elevated serum ESR.

This is a hospital-based direct comparison between young patients with ischemic stroke of unknown etiology treated with a routine and an aggressive protocol admitted to a single center. As a retrospective study with a relatively small sample size, there are several potential limitations. Firstly, angiographic follow-up was not available in all patients. In particular, fewer patients were reevaluated by DSA in the RMM group than in the AMM group, which may limit the statistical power and bias our results. Secondly, because treatment allocation between routine and corticosteroid therapy was not randomized, this may potentially influence the rate of progressive and/or new lesions or recurrent stroke. In the end, in view of the drawback of the retrospective study, some variables, such as the time interval between symptom onset and treatment and the characteristics of target lesions were not consistently or uniformly ascertained, which may influence patients' clinical outcomes or the angiographic outcomes of lesion arteries. This limitation may have led to an underestimation of asymptomatic events and other potential confounders in the comparison.

Conclusion

Based on our observation, we suggest that, although young patients with ischemic stroke may have more favorable long-term outcomes than elderly patients, when a young patient presents with ischemic stroke without risk factors – despite lifestyle changes, antiplatelet therapy, and statin therapy – corticosteroids may be recommended for preventing recurrent stroke and new arterial or worsening lesions.

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Disclosure Statement

The authors declare that they have no competing interests.

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