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Stroke in Young Patients: Etiopathogenesis and Risk Factors in Different Age Classes

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Key Words
Stroke · Large-vessel disease · Small-vessel disease · Cardioembolism · Young patients

Abstract
The aim of our study was to evaluate the etiopathogenesis and the vascular risk factors in a consecutive series of patients with juvenile ischemic stroke. We enrolled 273 patients (158 males and 115 females), aged between 16 and 49 years, with ischemic cerebrovascular events (ICVE), including transient ischemic attack (TIA) or stroke, referred to our neurology ward between January 1994 and December 2001. Our protocol included medical history, cardiac and neurological examinations, assessment of risk factors and laboratory tests. The instrumental assessment included transthoracic echocardiography (70%), transesophageal echocardiography (60%), conventional angiography (30%), MR angiography (30%), cranial computed tomography (100%) and brain MRI (48%). The ICVE was a stroke in 60% of the cases, a reversible ischemic neurologic deficit in 14% and a TIA in 26%. Thirty-three patients were aged less than 29, 59 were aged between 30 and 39 and 181 between 40 and 49. The percentage of females was higher in patients aged less than 29 while males were prevalent in the 4th and 5th decade. The patients were subtyped according to etiopathogenesis. A large-vessel disease (LVD) was diagnosed in 43 patients (16% of the cases), mostly in patients aged more than 40 years (36 cases). A small-vessel disease (SVD) was found in 48 patients (17% of cases), mostly in patients aged more than 40 years (41 cases). A cardioembolic stroke (CE) was diagnosed in 66 patients (24% of the cases). In the majority of the cases, the cardiopathies were at low-uncertain embolic risk: patent foramen ovale (PFO, 39 cases, in 8 patients associated with an atrial septal aneurism), atrial septal aneurism (12 cases) and myxomatous mitral valve prolapse (3 cases). Stroke due to other causes was found in 51 patients (19% of the cases). Arterial dissection, more frequently involving the carotid region, was diagnosed in 35 patients. Coagulopathies and vasculitis were found in 5 and 6 patients, respectively. Stroke of unknown etiology was found in 65 patients (24% of the cases) with a homogeneous distribution among decades. Our study highlights the role of minor cardiac sources of embolism and arterial dissection in the etiology of juvenile ischemic stroke, whereas coagulopathies and vasculitis are less relevant. LVD and SVD were relevant only in the 5th decade.

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Introduction

Ischemic stroke in young people is fairly uncommon, its annual rate ranging from 6 to 20 per 100,000 [1]. Studies on juvenile stroke are heterogeneous, particularly regarding the inclusion criteria [2]. Despite extensive diagnostic investigations in young stroke victims, the etiology remains unknown in almost one third of the cases [3]. To gain further insight into the etiopathogenesis of juvenile stroke, we analyzed a large consecutive hospital-based series of young adults (aged less than 49 years) with ischemic stroke, with particular focus on the etiologic subtype and the vascular risk profile in the various groups.

Patients and Methods

We included 273 patients (158 males and 115 females) with transient ischemic attack (TIA) or stroke, aged less than 49 years (mean age 41.7 ± 7.45 years), who had been admitted to our neurological ward between January 1994 and December 2001. TIA was defined as a focal neurological deficit resolving completely within 24 h; stroke was defined as a focal neurological deficit of sudden onset that persisted beyond 24 h in surviving patients [4].

Medical history and vascular risk factors were recorded on a dedicated computerized schedule. Hypertension was diagnosed with systolic or diastolic values over 140/90 mm Hg or in the presence of a specific therapy. Hypercholesterolemia was diagnosed in the presence of a fasting total cholesterol level >240 mg/dl or in the presence of a specific therapy. Diabetes was diagnosed according to current accepted criteria [5].

Diagnostic workup included a chest radiogram, an ECG and routine blood tests. If necessary, detailed immunologic screening (antinuclear, anti-DNA and anti-ENA antibodies, P-ANCA, C-ANCA) was performed (in 54% of the patients), and some emerging risk factors, including lipoprotein(a) and homocysteine plasma levels, were determined (in about 70% of cases).

Extracranial duplex ultrasonography was performed in all the patients, transthoracic echocardiography in 70% and transesophageal echocardiography (TEE) in 60%. If necessary, conventional angiography (30% of the patients) and MR angiography (30% of the patients) were performed. A cranial CT was obtained in all the patients on admission. A second CT was performed in 50% of the cases whereas 48% of the patients underwent a brain MRI. The study population was arbitrarily divided into three groups according to age ranges: 16–29 years (group 1); 30–39 years (group 2), and 40–49 years (group 3).

Stroke events were classified according to the TOAST criteria [6] as: (1) large-vessel disease (LVD); (2) small-vessel disease (SVD); (3) cardioembolism (CE); (4) other determined cause (OTH), and (5) undetermined cause (UND).

Results

Sex, age and subtype distribution are reported in table 1 and figure 1. LVD was diagnosed in 43/273 (16%) of the study patients (29 males, 14 females). Carotid arteries were involved in 33 (77%) patients (14 with occlusion and 19 with stenosis) and vertebral arteries in 10 (33%) patients (6 cases with occlusions and 4 with stenosis). SVD was diagnosed in 48/273 (17%) patients (32 males and 16 females). CE was diagnosed in 66/273 (24%) patients (27 males and 39 females). Of the 66 CE patients, 12 (18%) had a major cardiac source of embolism: atrial fibrillation (2 cases), valvular heart disease (5 cases), myocardial infarction (3 cases) and cardiac myxoma (2 cases). In 54 (82%) patients, a minor or uncertain cardiac source

Table 1. Sex distribution in the three age classes

Age classes	Total	Males	Females
<29 years	33	16	17
30–39 years	59	35	24
40–49 years	181	107	74
All patients	273	158	115

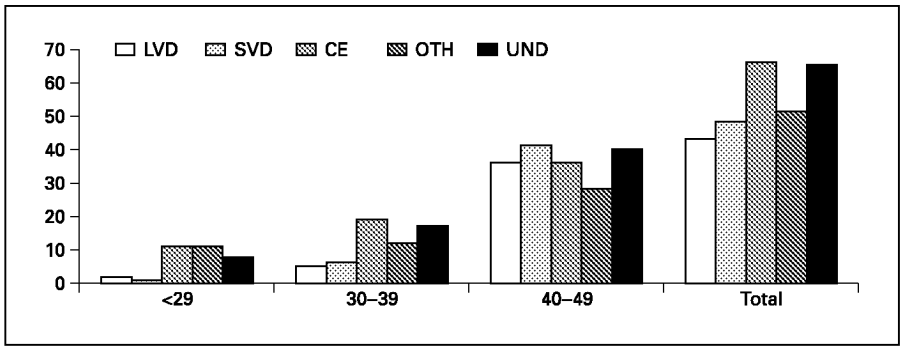

Fig. 1. Stroke subtype in the three age classes.

of embolism was found: patent foramen ovale (PFO; 39 cases: associated with an atrial septal aneurism, ASA, 8 cases), ASA (12 cases) and myxomatous mitral valve prolapse (3 cases). No patient with aortic arch plaques was found.

Stroke due to OTH was diagnosed in 51/273 (19%) patients (29 males and 22 females). Stroke causes are detailed in table 2. An arterial dissection was diagnosed in 35 (68% of the patients with OTH) patients, involving the carotid artery in 20 patients (in 2 cases bilaterally) and the vertebral artery in 14. One patient had simultaneously a carotid and vertebral dissection. With respect to coagulation disorders, high titers of anticardiolipin antibodies were found in 3 cases and LAC positivity in 2 patients (table 2). A cerebral vasculitis was found in 6 patients. Stroke of UND was diagnosed in 65/273 (24%) patients (41 males and 24 females).

Vascular risk factors according to stroke subtype are reported in figure 2. Hypertension was present in 92/273 (34%) patients (40% in LVD, 69% in SVD, 17% in CE, 16% in OTH and 35% in UND). Smoking was present in 107/273 (39%) patients (53% in LVD, 50% in SVD, 27% in CE, 33% in OTH and 25% in UND). Hypercholesterolemia was present in 47/273 (17%) patients (23% in LVD, 29% in SVD, 5% in CE, 14% in OTH and 20% with UND). Diabetes mellitus was present in 13/273 (5%) patients (7% in LVD, 10% in SVD, 5% in CE, 2% in OTH and 1.5% in UND). The prevalence of hypertension was higher in SVD (69%) than in other subtypes. The difference was significant with respect to LVD ($p = 0.01$), CE ($p = 0.001$), OTH ($p = 0.001$) and UND ($p = 0.0015$). Smoking was more frequent in LVD (53%) and SVD (50%), but a significant difference was evident only for SVD with respect to CE ($p = 0.022$). Diabetes was more common in SVD (10%) and LVD (7%), but there were no significant differences among the various subtypes. Hypercholesterolemia was more frequent in SVD (29%), LVD (23%) and UND (20%), and the difference was significant with respect to CE ($p = 0.001$) but not with OTH.

Regarding the topography of cerebral infarctions, the carotid region was involved in 141/273 (52%) patients while the vertebrobasilar region was affected in 98/273 (36%). In 32 (12%) patients, no lesion was found despite extensive investigations.

Among the 141 patients with carotid stroke, 18 had a global middle cerebral artery (MCA) infarction, 77 a partial MCA infarction, 38 a deep MCA infarction (including 8 cases with striatocapsular infarction), 8 an infarction in the anterior cerebral artery. Among the 98 patients with vertebrobasilar ischemic cerebrovascular events (ICVE), we found 13 patients with global posterior cerebral artery infarction, 16 with thalamic infarction, 39 with cerebellar infarction and 10 with brainstem infarction.

Table 2. Other determined causes of stroke

Arterial dissection	35
Vasculitis[a]	6
Antiphospholipid syndrome[b]	5
CADASIL	1
MELAS	1
Postradiation arteriopathy	1
Pseudoxantoma elasticum	1
Sneddon's syndrome	1
Total	51

CADASIL = Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MELAS = lactic acidosis and stroke-like symptoms.

[a] Primary central nervous system vasculitis in 1 case, panarteritis nodosa in 2 cases, systemic lupus erythematosus in 3 cases.

[b] Anticardiolipin antibodies in 3 cases and lupus anticoagulant positivity in 2.

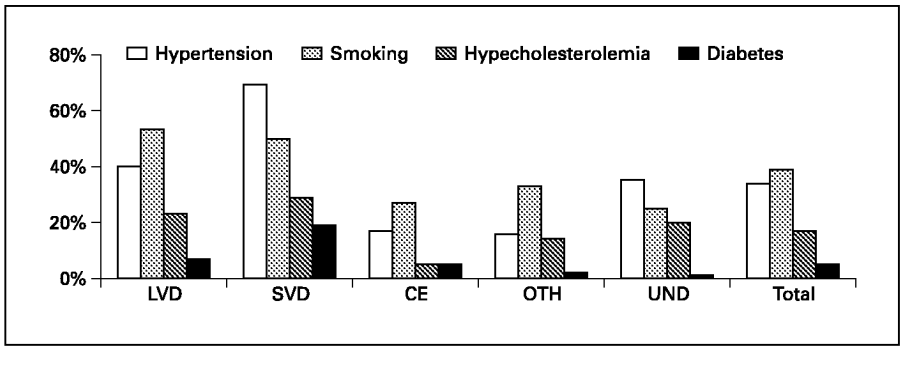

Fig. 2. Frequency of vascular risk factors in ICVE subtypes.

Discussion

In this study, we describe the etiopathogenetic findings in 273 patients with stroke or TIA aged less than 49 years admitted to our neurological ward over a period of 8 years. As expected, most of them were aged 40–49 years, according to the increase in arteriosclerotic vascular disease with age [2, 3, 7–15].

In our study, 58% of the young ischemic stroke patients were males, a percentage similar to that reported by other studies in western countries (44.1–58.9%) [2, 8, 10–13], but lower than those performed in eastern ones (71.4–75.2%) [14]. According to other studies [16], female gender slightly predominates in patients aged less than 29 years, whereas the proportion of males becomes predominant beginning from the 4th decade.

Concerning stroke subtype, LVD and SVD were rare in younger patients. As expected, its prevalence was negligible in the 15- to 29-year age range, rare in the 30- to 39-year age range and became relevant only in the 40- to 49-year age range. Indeed arteriosclerosis (including both large-vessel atheromatosis and small-vessel arteriolosclerosis) has been associated with stroke more often in patients over 40 years of age [7, 8, 17].

The number of patients with LVD and SVD was similar (16 and 17%, respectively). The percentage of LVD is generally higher in western countries [10] while SVD is higher in US Blacks [9] and Taiwanese [15]. A growing body of data suggests that there are important differences in the distribution of occlusive vascular disease between races: atherosclerosis of large extracranial arteries is more prevalent among Caucasians whereas occlusive disease of the intracranial arteries more often develops in Blacks and Orientals [18].

The significant increase in LVD and SVD observed in the 40- to 49-year age group and the frequency of risk factors suggest that arterial degenerative alterations occur earlier than expected in patients with a 'high-risk' vascular profile. Thus, in patients with LVD and SVD, the prevalence of hypertension, diabetes, smoking and hypercholesterolemia was significantly higher compared to CE and OTH. Moreover, the risk profile was similar between LVD and SVD except for hypertension, which was significantly higher in SVD according to its role favoring occlusion of the perforating arteries. As a result, although hypertension is the major risk factor for cerebrovascular disease, its role is strongly preponderant in SVD.

A cardioembolic mechanism was present in about one fourth of the patients. It was the most frequent mechanism in patients aged less than 39 years, while its proportion slightly decreased in those aged 40–49 years. Our data are in agreement with most of the previous reports in which the proportion of CE subtypes ranged from 14 to 32.7% [2, 3, 7–15].

In most of the 66 patients with CE, we found minor cardiac sources of embolism. A PFO was found in about two thirds of the cases of the CE subtype, and it was complicated by an ASA in about one fifth of the cases. Previous studies [19] and a recent meta-analysis [20] reported a significant association of PFO and ASA with ischemic stroke only in patients <55 years. In a recent study, we found a higher incidence of PFO and ASA only in patients with non-lacunar infarction [21]. In the present study, the diagnosis of PFO was reached by employing a contrast TEE, suggesting its importance as a diagnostic tool in young stroke patients.

The relevance of PFO is more significative considering the lack of evidence about the actual therapeutic options (anticoagulants, antiplatelet drugs and percutaneous closure) and the conflicting results of two larger randomized studies [22, 23].

No patients were found having aortic atheromatosis but only patients without LVD, SVD and OTH were submitted to TEE. Nonetheless, the link between aortic atheromatosis and stroke has been reported only in patients aged >60 years [24].

In contrast to some studies [10] but in agreement with others [2], the incidence of prostheses and rheumatic valvular heart disease was low in our series. This finding is presumably related to the geographic distribution of rheumatic heart disease, which is more frequent in developing than in western countries. Moreover, in the large series conducted by Bogousslavsky and Pierre [2], valvular heart disease was less important than mitral valve prolapse and PFO.

Atrial fibrillation was present in only 2 patients, i.e. less than 0.7% events in our series. In western countries, atrial fibrillation is rare in the first 5 decades but increases with age particularly in the 8th decade. Interestingly, in 2 patients with atrial myxoma, the cerebral ischemic event was the unique manifestation of the cardiopathy. As expected [25], patients with CE showed a lower risk profile with respect to SVD and LVD groups.

Stroke due to OTH was diagnosed in 51 patients (19%) and represents the more common subtype in patients aged less than 29 years. The most common cause was arterial dissection, representing 35 cases, a percentage slightly lower than that reported by Bogousslavsky and Pierre [2] and Gautier et al. [26] but higher than that of others [3]. More than half of the cases were aged 40–49 years. According to recent data [27], arterial dissection mainly

involves the carotid region. Two patients were found having bilateral internal carotid dissection and 1 patient had simultaneously a carotid and vertebral dissection, suggesting a structural defect in the arterial wall as a predisposing factor. In most of the patients, the dissection occurred spontaneously because major traumatic events were reported in only 2 patients. The number of dissections could be even higher using the current neuroradiological techniques (axial neck MRI, contrast MR angiography, digital subtraction angiography). Particularly vertebral dissection may be underdiagnosed due to the small diameter of the artery, and the difficulty to distinguish between dissection and congenital dysplasia. Furthermore, the clinical manifestation of vertebral dissection may be represented by a cervicocephalic pain without other signs (for example, cranial nerve involvement in vertebral dissection is less frequent than in carotid dissection).

In our casuistic, most of the patients with arterial dissection were aged 40–49 years. Considering that atherosclerosis is a relevant cause of stroke in this age class, we highlight the importance of a distinction between these two arterial pathologies, also with respect to the different therapeutic and prognostic options.

In this study, ICVE related to vasculitis was found only in 6 patients. Hematologic disorders were rare, including 5 patients with antiphospholipidic syndrome. The negligible role of coagulopathies may be due to the fact that we have not evaluated inherited thrombophilic conditions systematically. Nonetheless, deficiencies in antithrombin III, protein C, protein S, as well as factor V and II mutation are considered as risk factors for venous thrombosis but not for arterial stroke [28].

Our data are similar to those reported by Adams et al. [10] and to the studies performed in Korea [14] and in northern Sweden [11]. In contrast to other series [2], we did not found cases with migraine stroke.

The incidence of ICVE due to undetermined etiology (24% of the patients without differences among the three age classes) was slightly higher than in other series [2, 8, 10, 26]. This difference can be partially related to the lack of an exhaustive diagnostic assessment: indeed, we did not perform a complete battery of examinations in every patient, selecting diagnostic studies on a case-by-case basis and specific investigations, such as digital subtraction angiography and TEE, were only performed in selected cases. Interestingly, the vascular risk profile of stroke patients with UND was similar to that of those with LVD and SVD, suggesting that many of these patients may have an occult arteriopathy.

Few studies on juvenile stroke have considered the infarct topography [2, 29]. In agreement with our study, Bogousslavsky and Pierre [2] found an involvement of carotid and vertebrobasilar territories in 61 and 31% of the patients, respectively. We found a higher incidence of posterior circulation infarcts, particularly of cerebellar and thalamic infarction. The high number of posteroinferior cerebellar artery infarctions may be due to the inclusion of patients with suspect vertebrobasilar TIA. It is well known that transient vestibular symptoms may be due to an undiagnosed ischemia of the posteroinferior cerebellum. The recent growth of MRI implementation in the diagnostic assessment of ischemic stroke may have improved the diagnosis of vertebrobasilar stroke.

The present study has a few limits. First, our study cohort was composed of patients aged less than 49 years, while most other studies comprised patients aged less than 45 years. Second, the inclusion of TIA events might have determined the enrollment of patients with non-vascular events (actually, this issue is reduced considering that more than half of the TIA patients showed a congruous ischemic lesion during neuroimaging). Third, during the long study period, the diagnostic workup has partially changed as new techniques and laboratory investigations became available and validated. MR angiography, for example, was not performed in the first years of the study. In our opinion, these limits do not substantially affect the significance of our study, in which a considerable number of patients has been homogeneously evaluated in a single neurological ward.

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