Etiologic Evaluation of Ischemic Stroke in Young Adults: A Comparative Study between Two European Centers

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Introduction: Identifying the cause of ischemic stroke in young adults is often difficult. Our objective was to compare the etiologic diagnostic strategy for ischemic stroke in young adults between 2 European centers and investigate the influence of workup variations in the diagnosed etiologies. *Patients and Methods:* We included patients aged 18-55 years admitted for ischemic stroke or transient ischemic attack to the stroke units of Santa Maria Hospital in Lisbon, Portugal, and Innsbruck University Hospital in Innsbruck, Austria, between 2014 and 2016. Etiology and diagnostic procedures were compared between centers. *Results:* We included 156 patients from Innsbruck University Hospital and 110 patients from Santa Maria Hospital. Search for intracranial large-vessel disease was performed mainly by computed tomography/magnetic resonance angiography in Innsbruck (83.9% versus 52.7%; $P < .01$) and by transcranial Doppler in Lisbon (91.8% versus 43.2%; $P < .01$). Transoesophageal echocardiography was preferred in Innsbruck for detecting paradoxical embolism (80.0% versus 68.2%; $P < .05$), whereas in Lisbon contrast transcranial Doppler was preferred (80.9% versus 3.9%; $P < .01$). For investigation of other causes, Lisbon patients were more commonly screened for thrombophilia (100.0% versus 92.3%; $P < .05$) and autoimmune disorders (91.7% versus 44.5%; $P < .01$) while in Innsbruck consultation by other specialists was more frequent (51.6% versus 10.0%; $P < .01$). No significant differences were found in etiologies between centers. *Conclusion:* The differences in diagnostic workup did not influence etiologic diagnosis. Extensive laboratory testing does not seem to influence diagnosis of stroke of other determined cause, emphasizing the importance of a clinically-oriented approach for the etiologic diagnosis of stroke in young adults.

Key Words: Ischemic stroke—young adult—etiological diagnosis—cryptogenic stroke—transcranial Doppler

Introduction

Ischemic stroke in young adults is a serious event that can cause death, lifelong disability, and decreased quality of life.[1] No less important than the acute-phase management of stroke is the prevention, control, and treatment of its underlying causes, which often differ from those of the older patient.

Epidemiological studies report an increasing incidence and proportion of young adult patients with stroke within the total stroke population.[2] Young adults also present a considerably wider etiological spectrum than older subjects.[3,4] As such, the proportion of strokes of undetermined or rare causes is much higher for young adults than for older patients.[5]

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There is no current consensus on the more effective diagnostic workup algorithm to identify stroke etiology in young adults. Three major strategies can be used: a comprehensive strategy requires a full etiological evaluation of all patients with no evident cause for their stroke; a staged workup strategy is based on regional prevalence of potential etiologies and diagnostic assessment is sequential; and a clinically-oriented and selective strategy investigates suspected disorders based on clinical hints and pretest probability. It is still unknown how different etiological strategies affect the proportion of patients to whom an etiological diagnosis is made, specifically whether they improve the diagnosis in patients who would otherwise be classified as having stroke of undetermined cause. Depending on local availability of diagnostic procedures, experience, and tradition, strategies for etiological assessment may vary between centers.[1,6,7]

In the present study, we compared the etiological diagnostic procedures in young adult stroke patients admitted to the stroke units of 2 tertiary hospitals in different European countries and analyzed how they influenced etiological diagnosis.

Patients and Methods

We conducted a retrospective and descriptive study on the diagnostic workup and etiological diagnosis of patients aged 18-55 years admitted for acute ischemic stroke or transient ischemic attack to the stroke units of Santa Maria Hospital and Innsbruck University Hospital from 1st January, 2014 to 1st May, 2016. Both hospitals have comprehensive stroke centers providing acute stroke diagnosis and treatment with stroke units, neurosurgical, neurointerventional, and neurointensive care. Exclusion criteria included patients with stroke related to major trauma, cardiac surgery, or vasospasm after subarachnoid hemorrhage. We also excluded patients with current drug addiction, severe alcohol abuse and intrahospital deaths, as such patients were not included in the Innsbruck stroke unit registry from where data were collected.

In the Innsbruck University Hospital data were extracted from a web-based stroke unit registry, whereas in Santa Maria Hospital data were collected from the stroke unit registry and discharge notes.

Apart from basic demographic data, we collected risk factors for stroke in the young adult[1] as well as all diagnostic procedures performed for etiologic diagnosis. We also included dermatologic and ophthalmologic counseling for assessment of possible inflammatory, infectious and genetic diseases or retinocerebral arteriopathies, and possible skin vasculitis, respectively. We classified causes of stroke into atherothrombosis, small-vessel disease, cardioembolism, other determined cause, and undetermined cause according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system.[8] Patients with isolated patent foramen ovale were considered as having stroke of undetermined cause. For the other determined causes, we further specified the final etiological diagnosis.

Independent samples Student t test was used to compare continuous variables between groups, whereas Pearson's chi-squared test was performed for categorical variables. For low-frequency categorical variables, Fisher's exact test was used. Clinical scales were compared with nonparametric tests (Mann-Whitney test). For all statistics tests, $P < .05$ was considered significant.

Ethic and informed consent were not required under Austrian and Portuguese law, as this project relies on a retrospective analysis of hospital data.

Results

A total of 265 patients was enrolled, 155 from Innsbruck University Hospital and 110 from Santa Maria Hospital. Age, sex, and the distribution of stroke risk factors were similar in both groups, except for dyslipidemia which was significantly more frequent in Innsbruck (71.8% versus 29.1%; $P < .001$), as shown in Table 1.

All diagnostic testing was done during the same hospitalization. The frequency of diagnostic procedures is described in Table 2.

Table 1. *Demographics and stroke risk factors*

	Innsbruck (n = 155)	Lisbon (n = 110)	*P* value
Male	97 (62.2%)	63 (57.3%)	
Age	49 [42-52]	47 [40-51]	
Hypertension	59 (37.8%)	54 (49.1%)	
Diabetes	10 (6.4%)	12 (10.9%)	
Smoking	69 (44.2%)	58 (52.7%)	
Dyslipidemia	112 (71.8%)	32 (29.1%)	<.001
Use of oral contraceptives*	7 (11.8%)	10 (21.3%)	
Pregnancy/puerperium*	2 (3.4%)	1 (2.1%)	
Migraine	11 (7.1%)	5 (4.5%)	

Data are n (%).
*% refer to the total of women.

Table 2. *Ancillary diagnostic procedures*

	Innsbruck (n = 155)	Lisbon (n = 110)	*P* value
Brain imaging			
CT	99 (63.9%)	105 (95.5%)	<.001
DWI	141 (91.0%)	97 (88.2%)	
Extracranial vessel imaging			
Carotid ultrasound	137 (88.4%)	103 (93.6%)	
MR/CT angiography	78 (50.3%)	17 (15.5%)	<.001
Cervical MRI with fat supression	45 (29.0%)	13 (11.8%)	<.001
Intra-arterial angiography	15 (9.7%)	10 (9.1%)	
Intracranial vessel imaging			
MR/CT angiography	130 (83.9%)	58 (52.7%)	<.001
Transcranial Doppler	67 (43.2%)	101 (91.8%)	<.001
Heart evaluation			
Holter monitoring	109 (70.3%)	78 (70.9%)	
TTE	22 (14.2%)	46 (41.8%)	<.001
TEE	124 (80.0%)	75 (68.2%)	<.05
Other imaging procedures			
Tanscranial Doppler with contrast	6 (3.9%)	89 (80.9%)	<.001
Leg ultrasound	51 (32.9%)	29 (26.4%)	
CSF examination	14 (9.0%)	17 (15.5%)	
Laboratory tests			
Screening for ANAs/ANCAs	69 (44.5%)	100 (91.7%)	<.001
Screening for ilicit drugs	3 (1.9%)	1 (.9%)	
Screening for HIV	62 (40.0%)	89 (81.7%)	<.001
Screening for syphilis	64 (41.3%)	102 (93.6%)	<.001
Screening for neurotropic viruses	9 (5.8%)	7 (6.4%)	
Screening for thrombophilia	143 (92.3%)	110 (100%)	<.05
Evaluation by other specialist*	80 (51.6%)	11 (10.0%)	<.001
Monogenic disorder screening			
Fabry's disease	14 (9.0%)	3 (2.7%)	<.05
MELAS	0 (.0%)	0 (.0%)	
CADASIL	0 (.0%)	1 (100.0%)	
Thrombophilia	7 (4.5%)	3 (2.7%)	

Abbreviations: ANAs, antinuclear antibodies; ANCAs, antineutrophil cytoplasmic antibodies; CADASIL, cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy; CSF, cerebrospinal fluid; CT, computed tomography; DWI-MRI, diffusion weighted magnetic resonance imaging, HIV, human immunodeficiency virus; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MR, magnetic resonance; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Data are n (%).

*Ophthalmology and dermatology.

The following significant differences were found:

1) Assessment of intracranial large vessel disease: subjects from the Austrian center were significantly more often evaluated by computed tomography (CT)/magnetic resonance (MR) angiography (83.9% versus 52.7%; $P < .001$), whereas Portuguese subjects were preferentially investigated by transcranial Doppler (91.8% versus 43.2%; $P < .001$).
2) Evaluation of extracranial large vessel disease: the Austrian group resorted more frequently to CT/MR angiography (50.3% versus 15.5%; $P < .001$), particularly cervical T1-weighted MR imaging with fat suppression sequence for detection of intramural hematoma indicative of acute dissection (29.0% versus 11.8%; $P < .001$).
3) Assessment of cardioembolic sources: transoesophageal echocardiography (TEE) was more often performed among Austrian subjects (80.0% versus 68.2%; $P < .05$), while transthoracic echocardiography was instead more frequently used in Lisbon (41.8% versus 14.2%; $P < .001$), as well as screening for right-left shunt with transcranial Doppler with bubble contrast (80.9% versus 3.9%; $P < .001$).
4) Detection of other determined causes of stroke: screening for antinuclear antibodies and antineutrophil cytoplasmic autoantibodies (91.7% versus 44.5%; $P < .001$), HIV (81.7% versus

40.0%; $P < .001$), syphilis (93.6% versus 41.3%; $P < .001$), and thrombophilia (100% versus 92.3%; $P < .05$) was significantly more frequent in Lisbon. On the other hand, consultation of other specialties for assistance in diagnostic workup (eg, dermatology, ophthalmology) was a more common practice in Innsbruck when compared to Lisbon (51.6% versus 10.0%; $P < .001$).

Considering the TOAST classification groups, there was no statistically significant differences between the 2 centers (Chart 1).

Stroke of undetermined cause made up approximately half of cases in both groups, comprising 50.9% of patients in Lisbon and 47.7% in Innsbruck. As shown in Table 3, acute arterial dissection was diagnosed in 12.9% of patients in Innsbruck and 10.0% in Lisbon, making up the majority of strokes of other determined causes (90.9% and 78.6%, respectively). Antiphospholipid syndrome and other disorders of coagulation were found only in .6% patients in Innsbruck and 1.8% in Lisbon.

Discussion

In this retrospective study, the use of 2 different diagnostic workup strategies did not influence diagnosis of stroke etiologies. We can thus conclude that for our study population, extensive laboratory tests as routine workup measures do not seem to influence the diagnosis of other determined causes of stroke.

Due to a lack of defined clinical guidelines, the current approach to young adults with newly diagnosed stroke is mainly based on clinical experience and judgment. Diagnostic testing for stroke etiology envisions not only establishing a diagnosis but also reducing stroke recurrence.

The initial study objectives were accomplished. Even though our findings regarding stroke etiology are consistent with published literature,[6,9-11] the diagnostic investigations in both centers diverge slightly, particularly in what concerns laboratory evaluation.

The significantly more frequent use of transcranial Doppler in Lisbon and CT/MR angiography in Innsbruck for diagnosis of intracranial large-vessel disease did not influence the diagnosis of this etiological subtype in our study. This is in accordance with the similar diagnostic yield of transcranial Doppler imaging and CT/MR angiography for intracranial stenosis already reported in previous studies.[12]

Heart evaluation for detection of cardioembolic sources was also performed differently. The Austrian group relied mostly on TEE for detection of cardioembolic and proximal aortoembolic sources. On contrast, the Portuguese group resorted to transthoracic echocardiography for structural heart evaluation and transcranial Doppler with bubble contrast for investigation of right-to-left shunt.

While TEE is widely considered the gold standard for diagnosing patent foramen ovale,[13] previous reports state contrast transcranial Doppler to be an alternative with

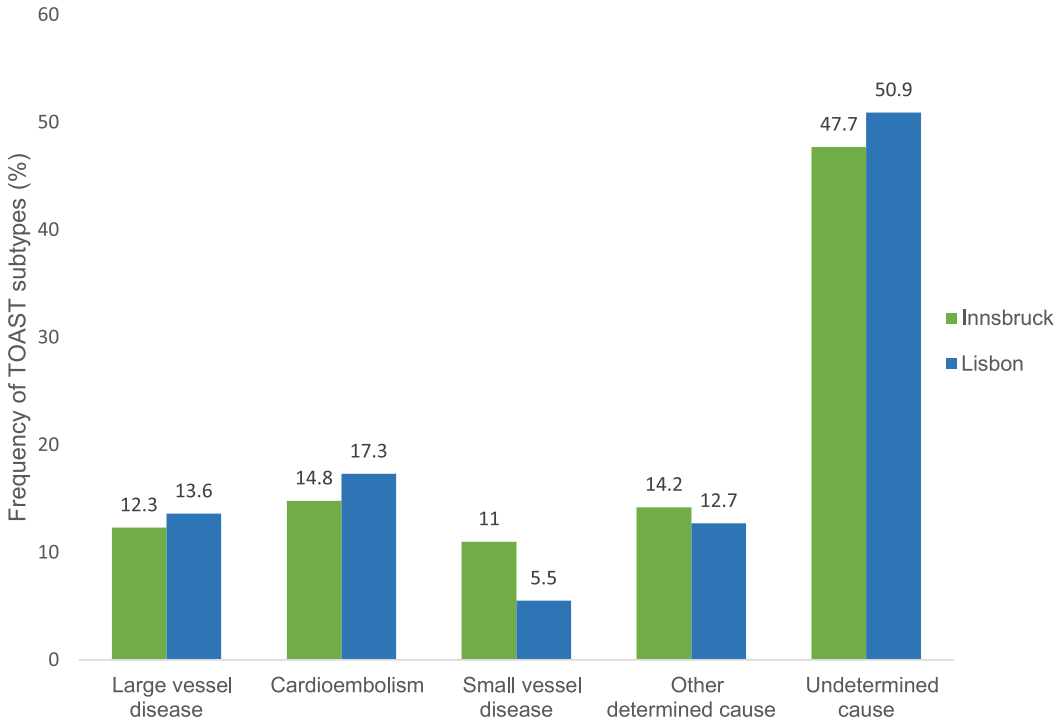

Chart 1. *Aetiology according to TOAST classification.*

Table 3. *Other determined causes of stroke*

	Innsbruck (n = 155)	Lisbon (n = 110)	*P* value
Acute arterial dissection	20 (12.9%)	11 (10.0%)	
Antiphospholipid syndrome	0 (.0%)	1 (.9%)	
Other disorders of coagulation	1 (.6%)	1 (.9%)	
Other	1 (.6%)	0 (.0%)	

Data are n (%).

similar diagnostic accuracy for detection of paradoxical embolism.[14-16]

Furthermore, the more frequent performance of Holter monitoring among Portuguese subjects for detection of arrhythmias did not influence etiological diagnosis.

Cervical vessel dissection is one of the most common causes of stroke in young adults.[17] T1-weighted MR angiography with fat suppression sequence, now considered the procedure of choice for diagnosis of arterial dissection,[18] was more commonly performed among Austrian patients but no significant difference was reported in the diagnosis of acute arterial dissection or other determined causes of stroke. The overall low percentage of patients submitted to this exam suggests its use as a confirmatory procedure.

Laboratory screening for vasculitis and connective tissue disorders, syphilis, HIV, and thrombophilia was performed in the vast majority of Lisbon patients, confirming its use as part of the regular battery of tests for evaluation of stroke in the young adult. This had no influence in the diagnostic yield for other determined causes of stroke when compared to Austrian patients. These results are backed up by previous reports[19-21] that state unrestricted thrombophilia testing to be unnecessary due to the uncertain association between inherited thrombophilia and arterial thrombosis. The role of immunologic screening in young stroke patients is also questionable, with the exception of testing for antiphospholipid syndrome which should be undertaken in case of clinical suspicion.[20,22]

The more frequent consultation of other specialists (usually dermatologists and ophthalmologists) in Innsbruck did not result in a higher detection of systemic illnesses with potential to cause stroke.

Despite some differences, both stroke units followed a selective and clinically oriented investigational approach, with use of second line tests based on clinical hints and findings of first line exams.

Strengths and Limitations

This is the 1 of the first studies that thoroughly characterizes the diagnostic workup of stroke in young adults and compares it between 2 tertiary stroke centers in different countries. The relatively short time-frame in which patients were included confers homogeneity to the samples given the unlikely development of new diagnostic procedures during this period.

The comparison of samples from 2 different countries can, however, be by itself a source of bias due to the rise of potential confounding factors such as different prevalence of stroke causes and risk factors. Data retrieval was also undertaken differently in 2 centers. In Innsbruck, data were retrieved from a stroke registry which did not include patients with current drug addiction, severe alcohol abuse, or intrahospital deaths.

Owing to time and logistical constraints, it was not possible to conduct a prospective study and therefore we had to resort to a retrospective analysis of already available information. Retrospective studies have well-known bias, including incomplete and missing data and interobserver and between center variation in the definition of registered variables. The retrospective design had, however, the advantage of not changing clinical practice, which could probably happen in a prospective study, unless all investigators were blinded to the objectives of the study.

The sample size was not large enough to analyze third line ancillary diagnostic procedures, as such tests were performed in a minority of patients and no specific conclusions can be drawn.

The application of TOAST criteria as a means to classify patients may lead to an overestimation of undetermined stroke. A recent study from Göckal et al[23] demonstrates that both CSS (Causative Classification of Stroke System) and ASCO (Atherosclerosis, Small vessel disease, Cardiac source, Other cause) systems reduce the number of young adult stroke patients assigned to the undetermined etiology category when compared to TOAST.

As already reviewed in previous studies,[7,11,24] a case-by-case evaluation and a selective and clinically oriented investigational approach probably constitute the best strategy to investigate stroke in young adults. A comprehensive battery of tests applied to every patient regardless of clinical features is thus highly questionable.

Prospective comparative studies with larger samples are needed to better characterize the optimal diagnostic workup in stroke patients and study the cost-effectiveness of different diagnostic strategies. As part of the etiologic investigation is often conducted after patient discharge, future studies should also address diagnostic workup performed in outpatient follow-ups.

Conclusions

The variations regarding the diagnostic workup between the 2 centers did not influence the diagnosis of stroke etiologies. We conclude that extensive laboratory tests as routine workup measures do not seem to influence the diagnosis of other determined causes of stroke, thus emphasizing the important role of a selective and clinically oriented approach in which decisions are based on clinical hints and pretest diagnostic probability. Further studies are still needed to explore the optimal diagnostic workup strategy for young patients with stroke.

Conflicting Interests

The authors declare that there is no conflict of interest.

Contributions

B.C.P. and J.F. designed the study and analyzed the data. B.C.P. collected the data and wrote the manuscript and was assisted by J.W., S.K., T.T., P.C., T.P.M., C.F., and J.F. All authors have critically reviewed the final draft of the manuscript and have given final approval for the version submitted.

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