Diagnostic Work-Up and Etiology in Ischemic Stroke in Young Adults: Before and Now

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Abstract

Unlike in the elderly, causes of ischemic stroke in young adults (15-45 years) are diverse. Non-atherosclerotic arteriopathy -dissection of the extra cranial arteries, migraine, drugs, vasculitis, premature atherosclerosis, cardioembolism, hypercoagulable states and cerebral venous thrombosis are the most relevant. Over time, the etiological diagnosis of ischemic stroke in young patients has changed significantly as a result of the improvement in diagnostic workup and the emergence of new risk factors, particularly drug abuse. Current diagnostic investigations allow the identification of specific cardiac, vascular and coagulation abnormalities previously undetectable. Thus, while 3 or 4 decades ago more than half of patients were diagnosed with uncertain etiology, currently less than 20% are diagnosed with cryptogenic stroke, and half of those with two or more identified potential causes. Specific etiologies, such as non-atherosclerotic vasculopathy, large-artery atherosclerosis, cardioembolism and haematological disorder, are demonstrated in the majority of patients. The scope of the present manuscript is to review the current state of the art, underlying the improvements with respect to the past.

Keywords: Ischemic stroke; Diagnostic work-up; Etiology; Young adult

Introduction

Ischemic stroke in young adults (15-45 years) is relatively frequent, accounting for more than 10% of all first ischemic strokes). Its causes are heterogeneous and while it generally has a good prognosis, it has a significant socioeconomic impact, including functional deficits and financial costs [1-19].

An accurate etiological diagnosis is crucial for preventing new episodes and additional functional deficits.

Currently, the most frequent causes of ischemic stroke in young adults are cardioembolism, premature atherosclerosis, dissection of extracranial arteries, migraine, drugs and hypercoagulable states [11,12,15,17]. However, it has not always been like this, as previously undetermined etiology was by far the most prevalent. Although still common, undetermined etiology is now less frequent as a result of diagnostic improvements [12,15,16].

Observation over time has demonstrated more accurate identification of the causes for ischemic stroke in the young, primarily through changes in epidemiological conditions and improvements in diagnostic tests [15].

Diagnostic Workup: New Technical Tools, New Diagnoses

Previous series studies of young adults with ischemic stroke cite undetermined as the most frequent etiology, identified in more than 35% of patients [7-11]. Nevertheless, the improvement in diagnostic workup has changed this panorama (Table 1).

Diagnostic workup has changed dramatically over the last 3-4 decades (Figure 1). Since 1990s, procedures such as transesophageal echocardiography, hypercoagulability testing and magnetic resonance have been included in the systematic diagnostic protocol for stroke in young adults [10-15].

Cerebral Magnetic Resonance Imaging (MRI)

This technique has allowed significantly improved diagnosis with respect to isolated cranial CT scanning. Magnetic resonance imaging (particularly diffusion-weighted MRI) offers the best sensitivity and spatial resolution and plays an important role in the diagnostic approach of young adults with stroke. It is the optimal neuro-radiological technique to confirm ischemic origin, to determine the location and the extent of the lesion, to verify the patency of major neck and intracranial arteries and to exclude eventual underling pathologies [20].

Transesophageal Echocardiography

This technique shows abnormalities (sources of cardioembolism)

	n	% Athero-thrombotic	% Cardio-embolism	% Other specific causes	% Undeter-mined
Adams et al. [8]	329	18	18	30	34
Carolei et al. [7]	333	33	24	8	35
Kitner et al. [11]	428	16	21	31	32
Varona et al. [15]	272	25	17	22	36
Bogousslavsky et al. [5]	202	8	23	46	23
Kwon et al. [12]	149	38	18	27	17
Rasura M et al. [16]	394	14	34	28	24
Putaala J el al. [17]	1.008	21	20	26	33

Table 1: Causes of ischemic stroke in young adults in the main series.

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in many patients in whom transthoratic study is normal. The importance of transesophageal echocardiography in the etiological evaluation of stroke in young adults has been widely demonstrated. The diagnosis of patent foramen ovale (PFO) is especially relevant, since paradoxical embolism through a PFO is a relatively commonly identified mechanism of stroke in young adults. However, due to the high prevalence of this condition in the general population (20%) and the frequent identification of other causes of stroke in many patients with PFO and stroke, we must be cautious in interpreting and handling PFO when detected [21-25].

Paradoxically, the improvement in cardiac imaging techniques has not provided an increase in the number of patients diagnosed with cardioembolism (Figure 2), since, in many cases, the detected cardiac abnormalities are of low risk for emboli (an incidental finding more than the origin of stroke) or coexisted with others causes of stroke (undetermined etiology due to multiple possible etiologies). Moreover, the incidence of rheumatic valve disease, prior most significant cause of cardioembolism has dramatically decreased over the last few decades.

Vascular Imaging Studies

(Like extracranial artery doppler sonography, arteriography and magnetic resonance vascular imaging). These are useful to demonstrate premature atherosclerosis or non-atherosclerotic arteriopathy, including specific vascular abnormalities [20,25].

Extensive Coagulation Testing

One of the cornerstones in the improvement in etiological diagnosis due to its ability to identify molecular and/or genetic disorders associated with hypercoagulable states such as antiphospholipid antibodies syndrome or prothrombin gene mutation. However, as nongenetic lab test may be unreliable in acute phase of stroke, the most reliable studies use genetic testing to identify patients with inherited thrombophilia [18,26].
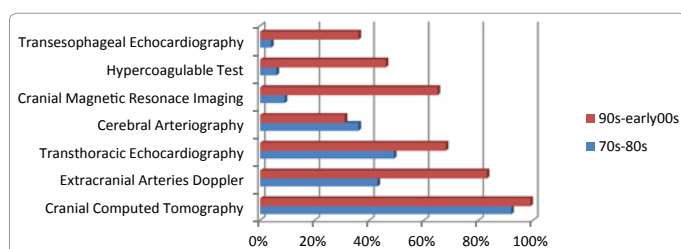

Figure 1: Etiological diagnostic workup performed on patients, according to admission period, based on data of study of Varona et al. [14].
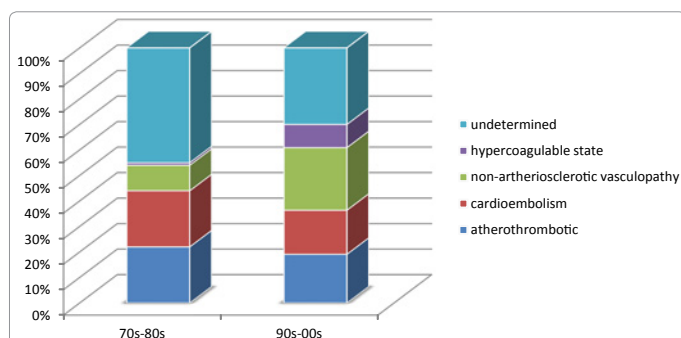

Figure 2: Etiology of ischemic stroke in young adults according evaluation period prior/after 1989, based on data of study of Varona et al. [13,14].

Etiological Diagnosis

With the standardized use of these procedures, a clear improvement has been made in the etiological diagnostic accuracy (Figure 2). As a result, as the percentage of patients with undetermined etiology has dramatically fallen since 1970-80s, the identification of specific causes (non-atherosclerotic vasculopathy and hypercoagulable state) has increased remarkably [15].

Additionally, and according to TOAST criteria [27-29], the pattern of sub-classification of uncertain etiology has changed significantly over time from incomplete evaluation to negative complete evaluation and multiple contributing factors. This is a very important issue. As uncertain etiology is a very heterogeneous stroke subtype in which causes cannot be determined with any degree of confidence we must be able to subclassify and separate the 3 components of undetermined etiology (Table 2), taking into consideration the different prognoses and management protocols [30]. Although other stroke classifications, such Baltimore-Washington-Cooperative Young Stroke Group [31-32] exits for young stroke, the TOAST criteria are the most widely used since their inception in 1993.

More extensive knowledge about infrequent entities such as Fabry disease, hypercoagulable states and mitochondrial diseases and about increasing cardiovascular risk factors like recreational drugs and obesity-prediabetes-metabolic syndrome has contributed to the improvement in diagnostic accuracy.

What about Migraine?

There is a recognized association between migraine (with or without aura) and ischemic stroke, especially among women taking oral contraceptives and in association with other conditions like patent foramen oval and smoking [33-35]. However, prior to any diagnosis of migraine-related stroke (expanded definition of migrainous infarction, including patients with migraine without aura) we must first exclude other coexisting conditions, as up to 75% of young adults with stroke and migraine also have other specific causes of ischemia [36,37]. Studies have contradictory findings as some show stable percentages over time [15] while others suggest a decrease with diagnostic improvement [10].

The Future New Biomarkers

In the last two decades great efforts in research have been focussed in new biomarkers. Emerging novel risk factors such as hyperhomocysteinaemia and thrombophilia may account for up to 20% of all strokes [38]. In this setting, recent studies have shown novel lipid and lipoprotein biomarkers associated with the risk of ischemic stroke, such as baseline triglycerides, very low-density lipoprotein (VLDL) size, and intermediate-density lipoprotein (IDL) particle number, suggesting new therapeutics targeting [39].

Furthermore, molecular lab testing like proteomics offers great promise for the discovery of biomarkers in the etiological diagnosis of cardiovascular disease and stroke. Some of the identified proteins may be therapeutic targets or biological markers for stroke diagnosis and prognosis [40-42].

Conclusions

Improvements in diagnostic workup and advances in knowledge about new risk factors and infrequent entities have led to a remarkable increase in the percentage of patients diagnosed with specific causes of

1) large-vessel atherosclerosis
2) small-vessel disease
3) cardioembolism (due to medium or high risk cardiac embolic source)
4) other specific etiology, including non-atherosclerotic vasculopathies (dissection of extracranial arteries, migraine, inflammatory vasculopathy associated with illicit drugs, infections, connective tissue disease...) and hypercoagulable states
5) undetermined etiology, which was further classified into 3 subtypes 5.a) two or more possible causes identified (undetermined, multiple possible etiologies); 5.b) negative evaluation after exhaustive etiological diagnostic workup which excluded atherothrombotic, lacunar, cardioembolic or specific etiologies; the complete workup includes: cerebral imaging studies as computed tomography (CT) scanning or magnetic resonance imaging, echocardiography, extracranial cerebrovascular Doppler studies, a hemostatic test and arteriography, if needed (undetermined, complete evaluation or unknown etiology) 5.c) incomplete evaluation.

Table 2: Diagnostic categories for ischemic stroke. TOAST criteria.

ischemic stroke. Currently a concrete cause is identified in more than 70-80% of patients, whereas in the seventies it was possible in less than 50% of patients.

Procedures such as transesophageal echocardiography, hypercoagulability testing, and magnetic resonance are the cornerstone tools for these improvements, and we must use them in young adults with ischemic stroke to optimize accurate diagnosis and thus appropriate prevention strategies.

However, a significant percentage of patients continue to be diagnosed with undetermined etiology even after extensive evaluation. Thus we must strive further to improve diagnostic evaluation in order to further identify appropriate secondary prevention therapy and to provide proper prognostic assessments.

Acknowledgment

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