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Original Article

Etiologic Overlaps Based on the Brain Infarct Topography

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ABSTRACT

Background: Etiologic overlaps may occur in patients with ischemic stroke depending on the diagnostic investigations and classification criteria.

Methods: Consecutive ischemic stroke patients admitted in Mackenzie hospital, Canada from August 2003 to August 2004 underwent a standard battery of diagnostic investigations by stroke neurologists. Stroke mechanism was defined based on the Toast criteria. Stroke topography subtypes were small and large artery territory infarcts.

Results: A total of 302 stroke patients (159 female, 143 male) were registered. Small and large artery territory infarcts consisted 25.5% and 74.5% of our topography respectively. Etiologic overlaps were found in 17.5% of the patients. Cardiac source of embolism was significantly more frequent in patients with large artery territory infarcts (p= 0.002) but frequency difference of corresponing large artery atherosclerotic stenosis was not significant in these topographies (p= 0.378). Etiologic overlaps were more frequent in patients with small artery territory infarcts (p= 0.004).

Conclusion: Etiologic overlaps are frequent and should be considered for optimal management of the ischemic stroke patients.

Key words: Etiology, Mechanism, Overlap, Stroke, Coexistence

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Frequency of brain infarct etiologies depends on how throughly patients are evaluated, what lesions are accepted as potential etiology and diagnostic criteria[1].

Identification of a cardiac source of embolism is insufficent to confirm definite cardioembolic mechanism, as other possible etiologies frequently coexist, particularly in elderly patients. About 30% of atrial fibrillation associated strokes are due to intrinsic small cerebrovascular disease or atheroma of the large cerebral and neck arteries[2]. It is impossible to be sure of actual cause of an ischemic stroke if several potential causes are present in the same individual. In one-thirds of stroke patients with cardiac sources of embolism, the source is irrelevant because there is another, perhaps more likely cause of cerebral ischemia[3]. In order to treat the stroke patient effectively, the physician must identify the correct mechanism of stroke. As it is not possible to be always absolutely sure of a single true mechanism, the clinician must keep in mind that several mechanisms such as atheroembolism and cardioembolism may be simultaneously involved[4]. Attributing an infarct to a particular pathogenesis purely on the basis of its site and size is often incorrect[4]. Small emboli can occlude single penetrating arteries to cause lacunar infarcts[5]. It is clear that brain infarcts of all sizes and locations can be caused by atheroembolism and cardiombolism. We prospectively evaluated etiologic overlaps in Alberta stroke registery data bank based on topography of brain infaction.

Subjects and Methods

The study population consisted of consecutive patients with ischemic stroke admitted in

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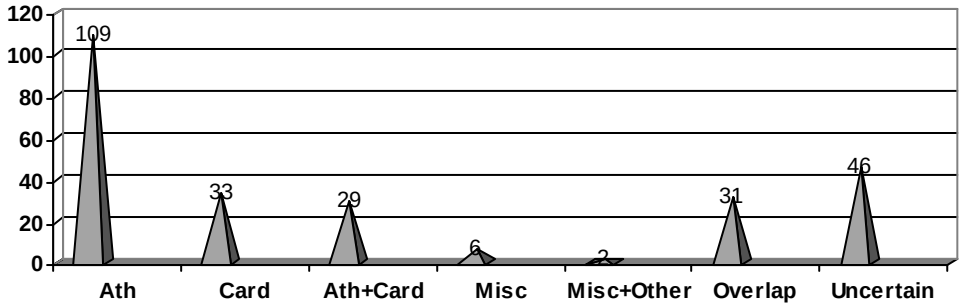
Mackenzie hospital, Canada, in a period of one year from August 2003 to August 2004. The diagnosis and etiologic investigations of stroke were made by stroke neurologists. Stroke was defined as an ischemic focal neurological deficit that persisted at least 24 hours[6].

All the patients underwent a standard battery of diagnostic investigations[6]. This included Brain CT, ECG, blood electrolytes, blood count and differential, coagulation profile, fasting blood sugar and lipid profile, duplex sonography of supra-aortic trunks, transcranial doppler and transthoracic echocardiography. A 24-hour Holter monitoring was obtained in patients with history of syncope and/or palpitation with non-diagnostic ECG [7]. Transesophageal echocardiography was performed in whom transthoracic echocardiography was non-diagnostic despite high suspicion of cardioembolism[7]. Three serial blood cultures were requested for any stroke patient with fever and heart murmur or valvular vegetation detected on echocardiography. Brain MRI and MRA were performed in suspected arterial dissection, arteriovenous malformation, or aneurysm[8]. Cardiac enzymes were measured when history or ECG evidence of recent myocardial infarction was present[8]. An extended coagulation profile (antithrombin III, protein C, protein S) was requested in patients aged <45 years without identifiable cause of stroke who had personal or family history of venous thrombosis[8]. Antinuclear and anticardiolipine antibodies were obtained in cryptogenic young (aged <45 years) stroke patients with personal or family history of venous thrombosis, recurrent miscarriage, thrombocytopenia, cardiac valve vegetations, livedo reticularis or raised sedimentation rate[7,8]. The latter was requested in suspected vasculitis patients. Brain infarcts were subtyped into Large Artery Territory (LAT) and Small Artery Territory (SAT) topographies by brain CT performed ≥48 hours of ischemic events. Topographic and etiologic diagnosis was made using Toast criteria for classification of brain infarction[9, 10]. Data on patients' demographics, clinical presentation and results of investigations were kept in a SPSS 9 software package. Fisher Exact test was performed for statistical analysis and $p<0.05$ was declared as significant.

Results

Three hundred and two ischemic stroke patients (159 female, 143 male) with mean age 64.59 years; SD= 2.80 were registered in our stroke data bank during this period. LAT and SAT infarcts were detected in 225 (114 female, 111 male) and 77 (45 female, 32 male) patients respectively. Etiologic overlaps were found in 17.5% (53/302) of overall stroke patients**.** Figure 1 represents frequency of the etiologic subtypes and their overlaps in the 225 patients with LAT infarct. Etiologic overlaps were found in 31 patients (13.7%) of this topography. In LAT group, 4 arterial dissections, 2 migraine induced strokes, 1 cerebral venous thrombosis and 1 vasculitis consisted our 8 patients with miscellaneous etiologies which had overlap with atherosclerosis and cardioembolism in 2 patients. Figure 2 demonstrates the frequency of the etiologic subtypes and their



Ath: Atherosclerosis Card: Cardioembolism Misc: Miscellaneous

Figure 1. Frequency of etiologic subtypes and their overlaps in 225 patients with large artery territory infarct

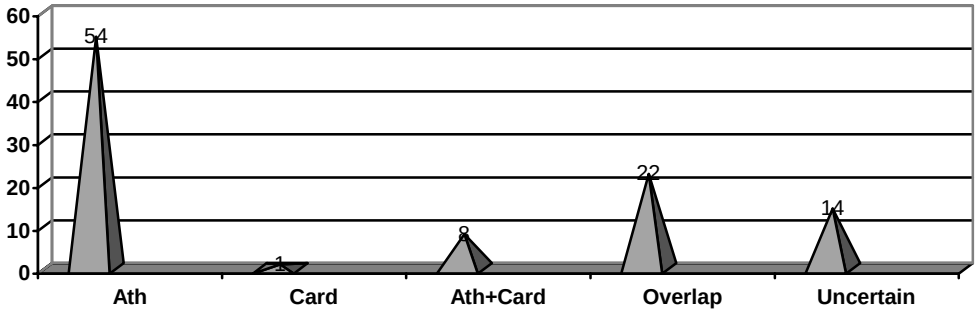


Figure 2. Frequency of etiologic subtypes and their overlaps in 77 patients with small artery territory infarct

Table 1. Frequency rate of etiologic mechanism in 302 stroke patients

Etiologic Mechanism	LAT (225)	SAT (77)	Total (302)
Ath	109	-	109
SAA	-	40	40
Ath + SAA	-	14	14
Card	33	1	34
Card + Ath	29	4	33
Card + SAA	-	4	4
Misc	6	-	6
Misc + Ath	1	-	1
Misc + Card	1	-	1
Uncertain	46	14	60
General Overlap	31	22	53

Ath: Atheroembolism SAA: Small Artery Atherosclerosis
Card: Cardioembolism Misc: Miscellaneous

overlaps in 77 patients with SAT infarct. If we consider presence or absence of the corresponding large artery atherosclerotic stenosis as subdivisions of atherosclerotic etiology in SAT group, 22.6% (14/62) of our SAT infarct patients with atherosclerotic mechanism had both of these subdivisions. Overlaps between atheroembolism, cardioembolism and small artery atherosclerosis were found in 22 patients (28.5%). In other words, 27.7%(18/65) of our patients with symptomatic large artery atherosclerotic stenosis and 12.5% (9/72) of those with cardiac source of embolism had SAT infarct. Cardioembolism was significantly more frequent in LAT topography, (p=0.002). Frequency difference for corresponding large artery atherosclerotic stenosis between SAT and LAT topographies was not significant (p= 0.378). Etiologic overlaps were significantly more frequent in patients with SAT topography, (p= 0.004). Table 1 illustrates frequency rate of etiologic mechanisms in 302 stroke patients.

Disscusion

Stroke without identifiable cause formed 20.4% of LAT and 18.2% of SAT infarcts in our patients. About 40% of ischemic stroke patients in Adams et al series had cryptogenic stroke[9]. Using the TOAST trial criteria 15% of the patients remained without a clear subtype classification[10]. In Oxford stroke registry series 50% of cerebral ischemic events were probably due to thromboembolic complication of atheroma, 25% to atherosclerotic small vessel disease, 20% to cardioembolism and 5% to miscellane-

ous causes[11]. In our registry series, overlap of cardioembolic and atherosclerotic etiologies was found in 12.8% of LAT and 10.4% of SAT infarcts. There may be the problem of two or even more competing causes for cerebral ischemia in an individual patient, if it is the case, one must concentrate on the treatable one.

In German stroke data bank, concurrent etiology was included as an independent entity for the frequent situation in which a patient had two or more stroke etiologies, and it could not be determined which of them was causative. 5.9% of patients in Geman stroke data bank had concurrent etiologies[12]. In about 10% of stroke patients evidence of both atherosclerosis and cardioembolism were found [13, 14, 15]. 8% of Mast et al cardioembolic stroke series[16] and 12.5% of our patients with cardiac source of embolism had SAT infarcts. Although small deep infarcts and lacunar syndromes can be caused by cardioembolism, artery-to-artery atheroembolism and miscellaneous causes[17,18]; multiple small deep infarcts are infrequently due to these mechanisms in the absence of previous or coexistent LAT infarcts [18, 19]. When a small deep infarct occurs in an elderly hypertensive patient with a cardioembolic source, it is uncertain weather the infarct is due to cardioembolism or atherosclerotic cerebrovascular disease. The presence of associated diffuse white matter changes or multiple pure lacunes support an intrinsic subcortical vasculopathy[16]. Due to small diameter and vertical original angle of small penetrating arteries, cardioembolism makes less frequent infarcts in their territories[19]. The main reason for more etiologic overlaps in SAT than LAT infarcts is subdivision of atherosclerotic mechanism in our SAT infarct group. Indeed the same individuals were susceptible to both atherothrombosis of large and medium-sized arteries and small vessel disease, but one becomes symptomatic before the other[20].

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