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ABSTRACT

Background and purpose Stroke in young individuals is a serious public health burden. This study aimed to characterise the various phenotypes of ischaemic stroke in a young urban population (≤50 years old) using the ASCOD classification system, which assigns a score to five stroke categories: atherosclerosis, small vessel disease (SVD), cardioembolism, other and dissection. Within each category, a numerical score represents the degree of causality attributed to the stroke.

Methods This retrospective study cohort was composed of patients from an urban tertiary care academic centre. Cases were selected by searching Get With the Guidelines database for adults ≤50 years old with ischaemic stroke. The study sample included 175 ischaemic strokes in 157 patients, with 16 subjects re-infarcting. Using retrospective chart review, each stroke was scored according to the ASCOD classification system. Multivariable logistic regression analyses were performed to explore each ASCOD category's association with causal risk factors.

Results Of possible causal mechanisms, defined as receiving a grade 1 or 2, a cardiovascular aetiology was most prevalent (25.7%), followed by SVD (22.3%), and closely by atherosclerosis (21.1%). Of general phenotypes, defined as receiving a grade 1 or 2 or 3, atherosclerosis was the most prevalent (51.4%), followed by SVD (47.4%), cardioembolism (42.3%) and other (35.4%). 31.6% of all strokes were of unclear aetiology. Subjects between 45 and 50 years old were more likely to develop a cardioembolic or SVD stroke when compared with subjects <45 years old.

Conclusion This study took a novel approach to ASCOD phenotyping, allowing several observations: (1) In patients with advanced atherosclerosis receiving the score A1, the vast majority had systemic atherosclerosis in multiple vascular territories; (2) the cardiac score C2(6), defined as a radiographic pattern highly suggestive of a central embolic source, may overestimate the prevalence of true cardiac disease; (3) incidental laboratory findings may detect some underlying pathology, but causality to the stroke is unlikely.

INTRODUCTION

While stroke is predominantly a disease of the elderly, in the past decade, ischaemic stroke has disproportionately affected young adults. There is an increasing rate of stroke in young people under 55 years old, which is a serious public health burden. Studies indicate that post stroke, one-half of stroke in the young (SITY) patients do not return to work and have poor functional recovery.[1] SITY patients have a longer time period for potential reinfarction; consequently, secondary prevention is crucial. However, it is unclear whether the aetiology of SITY is similar or different to stroke in the elderly. Currently, there is a lack of consensus guidelines on maximising secondary prevention in young adults with stroke. A rigorous and comprehensive approach should investigate causal mechanisms underlying SITY for appropriate treatment, prognosis and secondary stroke prevention.

The following cohort was obtained from an academic urban tertiary care hospital that serves Northern Philadelphia, one of the poorest regions in the USA. Eighty-five per cent of patients are covered by government programmes, including 31% by Medicare and 53% by Medicaid. In this cohort, young individuals comprised 10.2% of all patients with ischaemic stroke in a 4-year period. The proportion of SITY from our study population is higher than that reported in other cohorts, such as 2% in L'Aquila, Italy,[2] 5% in a meta-analysis[3] or 8% in Northern Manhattan.[4] This may be explained be a high prevalence of vascular risk factors in Northern Philadelphia, including widespread hypertension and diabetes,[5] increased rates of drug and alcohol abuse,[6] and a predominantly African-American population.

This retrospective study aimed to characterise the various phenotypes of ischaemic stroke in an economically disadvantaged population, using the ASCOD classification system. Furthermore, the association between known risk factors (ie, age, hypertension, diabetes, etc) and specific ASCOD categories (atherosclerosis, small vessel disease, etc) was investigated. Our purpose was a descriptive analysis of the stroke aetiologies and risk factors most prevalent in a young urban population.

METHODS

Selection and description of participants

A total of 1924 cases of ischaemic stroke were retrospectively identified from an urban tertiary care centre by searching *Get With*

the Guidelines database from January 2011 to December 2014. The following criteria were applied: (1) age ≥18 and ≤50 at stroke onset; (2) discharge diagnosis of ischaemic stroke. Ischaemic stroke was defined as acute focal neurological deficits lasting >24 hours with brain imaging corresponding to symptomatology.

A total of 175 ischaemic strokes met the inclusion criteria. Patients with repeat infarcts were counted more than once into the study. A repeat infarct was defined as a new vessel occlusion in a different vascular territory or new diffusion restriction. Enlarging infarcts or recrudescence of previous strokes were not considered a repeat infarct.

MRI-negative strokes were defined as a persistent deficit without radiological evidence of infarction and were also included. Transient ischaemic attacks (TIAs) were excluded.

Stroke evaluation

All patients were initially evaluated by a neurologist with a complete medical history and physical examination. Initial studies included brain CT and MRI, routine blood biochemistry and vascular studies of intracranial and extracranial arteries (magnetic resonance angiogram (MRA), computed tomography angiography (CTA), carotid duplex, transcranial Dopplers, angiography). Patients received a 12-lead ECG with a routine transthoracic echocardiogram; selective patients underwent transoesophageal echocardiogram. Cardioembolism was screened using ASCOD definitions of cardiac pathology, including ejection fraction <35%, atrial fibrillation >60 s, left atrial thrombus, endocarditis and so on. At the neurologist's discretion, patients also received a hypercoagulability work-up (antithrombin III, factor V Leiden and prothrombin mutations, protein C and S deficiencies, antiphospholipid antibodies). If a high clinical suspicion for cardiac source of embolism was present without evidence of structural heart disease, a loop recorder was placed.

The hospital electronic database was used to collect patient data, which included pertinent medical history, hospitalisations, laboratory studies and imaging studies. A vascular neurologist, senior neurology resident and medical student then scored each stroke using the ASCOD phenotyping. The team adjudicated ASCOD scoring as a consensus.

ASCOD classification description

Previous methods of describing stroke aetiology focused on a single casual risk factor. The ASCOD phenotyping method describes all concurrent risk factors with varying degrees of causation. The ASCOD classification system represents five primary stroke aetiologies: atherosclerosis, small vessel disease (SVD), cardioembolism, other and dissection.[7] Within each aetiology, a numerical score represents the degree of causality attributed to the stroke. The scores are defined as 1, likely causal; 2, uncertain if causal; and 3, unlikely causal, but disease present. The score is determined by a combination of vascular imaging, brain imaging, cardiac studies, laboratory results and medical history. For instance, for atherosclerosis, A1 is carotid stenosis >50%, A2 is carotid stenosis between 30% and 50%, and A3 is the presence of atherosclerosis in any vascular territory. For more details on the specific criteria, please refer to the original paper 'The ASCOD phenotyping of ischaemic stroke' by Amarenco *et al*.

A score of 0 indicates no disease, and a score of 9 indicates incomplete work-up. Each stroke receives a score in all five categories, for example, A1-S2-C0-03-D9 (atherosclerosis (likely causal), SVD (possibly causal), cardioembolism (absent), other (absent), dissection (incomplete work-up)). Thus, ASCOD allows a detailed understanding of the unique stroke to each individual patient.

In this study, a novel approach was taken to ASCOD phenotyping. Typically, scorers adopt the higher grade, that is, A1+A3 would be considered A1. However, all grades present were included in this study. For example, a patient with severe atherosclerosis both ipsilateral (A1) and contralateral (A3) to the infarct, in addition to an aortic plaque (A2), would be considered A1+A2+A3, not only A1. The authors believed this would be a more inclusive method to capture all abnormalities present, rather than just the more severe pathology.

Statistical analysis

Data were expressed as frequencies and percentages for categorical variables and mean±SD (or range or quartile range) for continuous variables. Multivariable multinomial logistic regression analyses were performed on the ASCOD classifications to explore its association with other potential predictors or confounding variables. All the variables were entered into the model a priori without any specific selection, first by introducing age, sex, hypertension, smoking and diabetes, and second by adding blood lipids. However, none of the blood lipid variables showed significant predictive abilities for the ASCOD groups and hence were subsequently dropped. The adjusted ORs with their 95% CIs are reported in table 3. P values less than 0.05 were considered statistically significant. SAS V.9.3 (SAS Institute, Cary, North Carolina, USA) was used for all the data analyses.

RESULTS

The study sample included 175 ischaemic strokes in 157 patients. Sixteen subjects (10.2%) experienced one reinfarction, and 2 of those 16 had two reinfarctions. Patients ranged from 20 to 50 years old, with 58.6% men and 41.4% women. The cohort's underlying risk factors are detailed in table 1: 65.0% had hypertension, 40.8% had diabetes, 33% had hyperlipidaemia and 61.8% were smokers.

ASCOD distribution

Possibly causal phenotypes were defined as receiving grade 1 or 2 (table 2). Of possibly causal phenotypes, a cardiovascular aetiology was most prevalent (C1+C2=25.7%),

Table 1 Demographic data of young adults with ischaemic stroke

	N	Mean	Median	SD	Q1	Q3	Minimum	Maximum
Continuous variables								
Age	157	43.44	46.00	6.29	41.00	48.00	20.00	50.00
NIHSS	151	5.51	4.00	5.35	2.00	7.00	0.00	26.00
Homocysteine	150	10.68	9.75	4.64	7.90	12.00	3.30	38.20
HbA1c	152	7.28	6.00	2.64	5.40	8.50	4.30	14.70
T.Chol	155	182.57	172.00	57.09	150.00	202.00	92.00	415.00
HDL	155	39.59	38.00	11.66	31.00	46.00	12.00	84.00
TG	155	150.34	120.00	112.27	84.00	176.00	18.00	804.00
LDL	151	110.98	107.00	41.55	86.00	129.00	35.00	303.00
Binary variables								
Gender, male	58.6% (92)							
Gender, female	41.4% (65)							
HTN	65% (102)							
Diabetes	40.8% (64)							
HLD	33.1% (52)							
Smoking	61.8% (97)							

Binary variables expressed as % of total population (N).
HbA1C, glycated haemoglobin; HDL, high-density lipoprotein; HLD, hyperlipidaemia; HTN, hypertension; LDL, low-density lipoprotein; N, number of subjects; NIHSS, National Institutes of Health Stroke Scale; Q1, first quartile; Q3, third quartile; T.Chol, total cholesterol; TG, triglyceride.

followed by SVD (S1+S2=22.3%), and closely by atherosclerosis (A1+A2=21.1%). Only 6.3% of strokes had a possible cause in the 'other' category. The least prevalent possibly causal phenotype was dissection at 1.7%.

Aside from grades 1 and 2, almost half of the population scored A3 (46.3%), and almost a third scored O3 (30.9%). One-fourth of strokes received S3; similarly, approximately one-fourth of strokes received C3. 'Unclear aetiology' was defined as a stroke lacking a grade of 1 or 2, suggesting an undetermined causal mechanism. In this cohort, 31.6% of all strokes were of unclear aetiology.

General phenotypes were defined as receiving grade 1 or 2 or 3. Of general phenotypes, atherosclerosis was the most prevalent (51.4%), followed by SVD (47.4%), cardioembolism (42.3%) and other (35.4%). Dissection was the (2.3%) least common general phenotype.

Table 3 shows the possibly causal phenotypes that overlapped, defined as receiving grade 1 or 2 in two separate aetiologies. Moreover, 5.71% of strokes had both A and C and 3.43% of strokes had both S and C. 'Other' had no overlap with any other aetiology, and atherosclerosis and SVD had no overlap.

ASCOD phenotype association with risk factors

Table 4 demonstrates whether specific risk factors were predictive of grade 1 ASCOD phenotypes. Two significant associations were discovered: subjects 45 and older were more likely to develop a C1 or S1 stroke when compared with subjects younger than 45. Gender, hypertension, diabetes or smoking did not predict the odds of an A1, S1, C1 or O1 stroke in this cohort. Additionally, no significant associations were found between risk factors and possibly causal ASCOD phenotypes (grades 1+2).

Specific ASCOD grade breakdown

Table 5 details the specific pathologies within each ASCOD grade. Of individuals receiving C1, there was one individual with endocarditis, two cases of atrial fibrillation,

Table 2 Distribution of ischaemic strokes by ASCOD phenotype

	1	2	3	0	9	1+2	1+2+3
Atherosclerosis	16.0% (28)	5.7% (10)	46.3% (81)	48.6% (85)	13.7% (24)	21.1% (37)	51.4% (91)
SVD	11.4% (20)	10.9% (19)	25.1% (44)	52.6% (92)	0.0%	22.3% (39)	47.4% (83)
Cardiac	12.0% (21)	14.3% (25)	22.3% (39)	54.8% (96)	2.9% (5)	25.7% (45)	42.3% (74)
Other	5.7% (10)	0.6% (1)	30.9% (54)	45.7% (80)	22.3% (39)	6.3% (11)	35.4% (62)
Dissection	1.7% (3)	0.0%	0.6% (1)	97.1% (170)	0.6% (1)	1.7% (3)	2.3% (4)

Data expressed as % of total population (N).
SVD, small vessel disease.

Table 3 ASCOD phenotype overlap

Phenotype combination	% of total strokes, (n)
A1+A3	12.57 (22)
A1/A2+S1/S2	0.57 (1)
A1/A2+C1/C2	5.71 (10)
A1/A2+O1/O2	0 (0)
S1/S2+C1/C2	3.43 (6)
S1/S2+O1/O2	0 (0)
C1/C2+O1/O2	0 (0)
Unclear aetiology	31.60

Overlap between stroke phenotypes is demonstrated as % of all strokes.

one heart transplant and the remaining individuals had an ejection fraction <35%. Of individuals who received a C2, the vast majority were C2(6), defined as 'no direct cardiac source identified, but multiple brain infarction, repeated either bilateral or in two different arterial territories (…) and/or evidence of systemic emboli'.[7]

Of individuals receiving O1, three individuals had moyamoya, two individuals had systemic lupus and one individual had metastatic thyroid cancer compressing the vertebral artery. Of individuals who received an O3, 10 had an elevated antiphospholipid antibody and 15 had elevated homocysteine. Moreover, 12.6% of all strokes had additional laboratories to suggest abnormal hypercoagulability, as specified in the Methods section.

DISCUSSION

This study took a novel approach to ASCOD phenotyping in a young, urban population by including all grades of causality within each aetiology, and within each grade, examining the stroke aetiologies in detail. The results yielded several patterns, depending on how ASCOD grades were combined. For possibly causal phenotypes, the most prevalent categories were cardioembolism, SVD and atherosclerosis, respectively. In contrast, for general phenotypes, the order of prevalence shifted to atherosclerosis as the most common category, followed by SVD and cardioembolism.

Atherosclerosis as the most prevalent general phenotype may be attributed to the high percentage of A3 (46.3%). Even in this young cohort, almost half of strokes showed at least a minimal level of atherosclerosis. Sirimarco *et al* demonstrated that A3 conferred a similar risk profile as A1 in a 3-year follow-up study for reinfarction, non-fatal cardiac events and death from a vascular cause.[8] Those results illustrate the need for aggressive control of atherosclerosis, even at an early stage without clinical symptoms. Furthermore, in this cohort, nearly 80% of A1 strokes had a concomitant A3 grade (12.6% of all strokes), suggesting that atherosclerosis is present at additional sites beyond the vessel supplying the infarct. Because this subset of patients with ischaemic stroke had systemic, rather than local, atherosclerosis, it was surprising to find a low overlap of atherosclerosis (A1/A2) with cardiac pathology (C1/C2). This result challenges the notion that intracranial and extracranial atherosclerosis share a similar pathophysiology to that of cardiac atherosclerosis. Interestingly, while research supports using carotid intima–media thickness as a marker for future cardiac events,[9] this association is not always as strong in black individuals, suggesting this surrogate marker may be racially dependent.[10 11]

Cardioembolism as the most prevalent possibly causal phenotype may be explained by 10.3% of all strokes receiving a C2(6). In the ASCOD criteria, C2(6) is defined as multiple brain infarcts in two vascular territories suggesting embolisms, with no identified cardiac pathology. This definition is comparable with embolic stroke of unknown source (ESUS).[12] Key to the ESUS definition is an embolic origin that is not necessarily cardiac and also includes carotid/vertebral plaques,

Table 4 Multivariate adjusted associations of risk factors with phenotypes scoring a '1' grade

	Atherosclerosis (A1)	SVD (S1)	Cardioembolic (C1)	Other (O1)
Female	2.50 (0.95 to 6.62) p=0.065	0.85 (0.26 to 2.76) p=0.785	1.12 (0.40 to 3.11) p=0.834	1.78 (0.43 to 7.38) p=0.427
Age 45–50 vs <45	1.58 (0.59 to 4.26) p=0.363	4.15 (1.0716.13) p=0.040*	3.44 (1.12 to 10.62) p=0.032*	0.248 (0.051.30) p=0.099
Hypertension	0.94 (0.32 to 2.79) p=0.910	1.48 (0.39 to 5.70) p=0.568	1.44 (0.45 to 4.66) p=0.539	3.80 (0.6821.41) p=0.130
Diabetes	1.06 (0.37 to 3.05) p=0.913	1.16 (0.35 to 3.78) p=0.809	0.89 (0.30 to 2.61) p=0.828	0.46 (0.10 to 2.11) p=0.318
Smoking	1.58 (0.55 to 4.54) p=0.399	0.86 (0.28 to 2.68) p=0.795	0.57 (0.21 to 1.54) p=0.269	1.07 (0.26 to 4.44) p=0.930

Values are expressed as OR (95% CI) with p value below.
Strokes not receiving a one grade were used as a reference category.
*Indicates a significant p value.

Table 5 ASCOD grade breakdown

C1	Significant cardiac pathology and single infarct	Left ventricle EF <35%		
	7.4% (13)	2.3% (4)		
C2	Left ventricle apical akinesia and decreased EF	No cardiac pathology but multiple infarcts		
	4.0% (7)	10.3% (18)		
O1	Moyamoya disease	Systemic lupus		
	2.9% (5)	2.3% (4)		
O3	Abnormal hypercoagulability laboratories (see Methods)	Homocysteinemia <40 µmol/L	Antiphospholipid AB <100 GPL units	Thrombocytosis <800 000/ mm^3
	12.6% (22)	8.6% (15)	5.7% (10)	2.9% (5)

Within each ASCOD grade, specific pathologies were quantified.
EF, ejection fraction.

aortic atheromas and rare variations of the circle of Willis. Consequently, the true incidence of cardioembolism as a causal mechanism may have been overestimated using the ASCOD classification scheme in this cohort. Similarly to the recommendations for cryptogenic stroke, additional high-quality trials should investigate whether the C2(6) patient subgroup would benefit from systemic anticoagulation or antiplatelet therapy.[13]

The authors were interested by the substantial number of O3 grades (30.9%), most of which were assigned due to incidental laboratory findings, such as an elevated homocysteine or positive antiphospholipid titre. Perhaps these findings were inflammatory markers resulting from the stroke or simply incidental laboratories. Wolf, a creator of the ASCOD phenotyping system, stated the aim of ASCOD was to best characterise the patient at the moment of the ischaemic stroke and document all abnormalities present.[14] Whether these abnormalities are causal, incidental or a result of the stroke is left to the scorer's discretion.

Multivariate logistic regression demonstrated that in this study population, subjects 45 and older were more likely to develop a cardioembolic or SVD stroke (C1 or S1) than subjects younger than 45. This suggests that the 'young' cohort may segregate into two extremes, the very young and the older young. A similar statistical model used by Jaffre *et al* found several more associations, including cardioembolism with age and also atherosclerosis with age, smoking, diabetes, hypertension and SVD with age and hypertension.[15] Reasons why this study cohort failed to replicate Jaffre *et al*'s findings include a high baseline prevalence of hypertension, diabetes and smoking, masking the risk factors' impact. Furthermore, this study's variables were coded categorically rather than continuously; using the numerical values may have yielded a more sensitive detection of the various associations. In this cohort, the absence of the risk factor's predictive value for stroke phenotype questions the use of stroke classification systems. However, as Elkind writes in a recent editorial, determining stroke aetiologies is valuable for prognostication.[16] In a study comparing various scoring systems for stroke (ASCOD, TOAST, CCS), regardless of the classification system, cardioembolic strokes were associated with a decreased 90-day survival rate, a larger infarct area and a more severe deficit, as compared with other stroke aetiologies.[17]

Comparisons with other young cohorts reveal both similarities and differences. The sifap1 study (Stroke in Young Fabry Patients) found SVD (29.2%) and other (16.5%) as the most prevalent possibly causal mechanisms, although this study included TIAs and had a higher age cut-off of 55.[18] In contrast, the Helsinki Young Stroke Registry revealed cardioembolism (19.6%) and dissection (15.4%) as the most common stroke mechanisms.[19] The lower incidence of atherosclerosis in the Helsinki cohort can be explained by a healthier baseline population with lower incidence of obesity, hypertension, diabetes and smoking. A more analogous population to this study is the Northern Manhattan Study (NOMAS), with multiple vascular risk factors and a high incidence of African Americans and Hispanics. The findings of this study were in line with NOMAS, which also had high levels of undetermined aetiology and a low incidence of cardioembolic strokes.[4]

This study had several limitations, including the high percentage of incomplete work-up, which was attributed to the rigorous application of ASCOD criteria for the 9 grade. Furthermore, this cohort had risk factors unique to a low socioeconomic area, so the results may not be generalisable to other regions. Other characteristics impacting stroke risk that merit further investigation include drug and alcohol abuse, nutrition and environmental stressors. Additionally, this statistical analysis included repeat strokes (up to three strokes in one patient), which may have over-represented aetiologies in recurrent strokes such as untreated atrial fibrillation or moyamoya disease.

In summary, this study used the ASCOD phenotyping system to describe aetiologies and their level of causality to ischaemic stroke in individuals <50 years old. In this urban cohort, the findings emphasise cardioembolism

as the leading possibly causal mechanism and atherosclerosis as the leading general phenotype. As we have attempted to demonstrate, the significance and implications of a stroke classification system are not limited to its original definition. Ultimately, ASCOD scoring is a dynamic process and can be applied to an individual stroke to personalise secondary prevention and analysed on a population level to detect patterns of risk factors.

Contributors MP conceived the project and implemented data collection tools and performed the initial data collection. AL and GL organised the data, performed ASCOD scoring, drafted and revised the paper. DY helped build statistical models for data analysis and interpretation.

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