CARDIOVASCULAR MEDICINE

Increased frequency of cardioembolism and patent foramen ovale in patients with stroke and a positive travel history suggesting economy class stroke syndrome

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Objective: To investigate the frequency of acute stroke in patients with a recent travel history and to analyse risk factors, stroke patterns and presence of a patent foramen ovale (PFO) in this patient group.

Design: One-year prospective observational study.

Setting: Single-centre study.

Methods: Enrolling all patients presenting with a first cerebral ischaemia and complementing the usual history with a standardised travel history.

Results: Of 338 patients with acute stroke, 42 had a positive travel history (PTH) (12.4%). Patients with a PTH were significantly younger (56.6 (SD 13) years) than patients (66.9 (13.2) years, $p = 0.0001$) with a negative travel history (NTH). Frequency of PFO in the PTH group (13; 44.8%) was significantly higher than in the NTH group (7; 10.8%) ($p = 0.0001$), even after patients were dichotomised into two age groups (younger and older than median of all patients: 31% v 6.1%, $p = 0.007$ and 13.8% v 4.6%, $p = 0.022$, respectively). PTH patients had fewer stroke risk factors (2.2 (1.4) v 3.3 (1.6), $p = 0.0001$) and a different risk profile with a lower frequency of diabetes (11.9% v 31.4%, $p = 0.009$), hypertension (52.4% v 78.7%, $p = 0.0001$), atrial fibrillation (7.1% v 22%, $p = 0.025$) and others (16.7% v 38.9%, $p = 0.005$). In contrast, PTH patients had significantly more cardioembolic (35.7% v 19.3%, $p = 0.023$) and cryptogenic strokes (50% v 19.9%, $p = 0.0001$) and more often ischaemia in the territory of the posterior cerebral artery (29.6% v 6.3%, $p = 0.0001$).

Conclusions: The finding that more PTH patients had a PFO and a cardioembolic stroke pattern but that fewer had other typical stroke risk factors led to the hypothesis that PFO is a risk factor for economy class stroke syndrome.

In recent years, several studies have indicated that stroke can occur due to paradoxical embolism, mostly through a patent foramen ovale (PFO).^{1–5} The risk factors for this type of stroke are the same as for deep venous thrombosis (DVT) and pulmonary embolism, namely long time immobilisation, dehydration and prolonged sitting in a small confined space with flexed lower limbs and other predisposing factors.^{2–6} Venous thrombosis and consequent pulmonary embolism after long-distance travel has been widely recognised and reported in the literature.^{6–9} Recently, some reports described a possible association between long travelling and stroke through paradoxical embolism and designated this condition “economy class stroke syndrome” (ECSS).^{10–17} On the basis of these reports, we questioned whether this clinical stroke condition can be relevant in the care of patients in a European stroke care centre. We therefore evaluated the frequency of positive travel history (PTH) in patients with acute stroke and their risk factors, stroke aetiology and stroke location. We questioned whether patients with possible ECSS would be more likely to have a PFO, a cardioembolic stroke according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria and a stroke location (such as in the posterior cerebral artery) suggesting an embolic cause.

METHODS

Patients

The Department of Neurology, University Hospital Erlangen, is a 74-bed university hospital with a five-bed acute stroke

unit since June 1999. Besides teaching, a major clinical task is acute stroke care in northern Bavaria. Between December 2002 and December 2003, a prospective observational study was undertaken enrolling all patients who presented with clinical signs and symptoms of a first cerebral ischaemia.

Clinical assessment

All patients were neurologically examined by the study neurologist (JGH) to establish the diagnosis of stroke, the clinical syndrome, and the pathological and aetiological subtype of stroke. All patients underwent neuroradiological examination. On admission, all patients underwent computed tomography (CT) to exclude cerebral haemorrhage. In 235 patients control CT (33%) or magnetic resonance imaging (MRI) (67%), including diffusion-weighted imaging technique, were performed during the course of the disease to evaluate exactly the size and location of the infarction.

In addition, all patients received a thorough clinical, laboratory, cardiological and neuro-sonological examination including transcranial Doppler sonography. According to our internal guidelines, which are based on the European Stroke Initiative guidelines, transthoracic and transoesophageal echocardiography (TOE) were performed in the case of

Abbreviations: CT, computed tomography; DVT, deep venous thrombosis; ECSS, economy class stroke syndrome; MRI, magnetic resonance imaging; NTH, negative travel history; PFO, patent foramen ovale; PTH, positive travel history; TOAST, Trial of Org 10172 in Acute Stroke Treatment; TOE, transoesophageal echocardiography

presumed cardioembolic stroke.¹⁸ In 94 patients, therefore, both contrast transcranial Doppler and contrast TOE were performed to search for a PFO.⁵⁻¹⁹ Stroke aetiology was classified according to TOAST criteria.²⁰ To locate the stroke, all CTs or MRIs were seen by a neurologist with extensive neuroradiological experience (MD) blinded to the clinical data. Strokes were classified into four subtypes according to location: the middle or anterior cerebral artery; the posterior cerebral artery; the brainstem and cerebellum; and lacunar stroke (modified according Bamford *et al*²¹).

A standardised questionnaire complemented the routine history by asking about travel during the four weeks preceding the onset of stroke. In case of a positive answer, the patient was interviewed in detail about the type of travel. A PTH was defined as travel, mainly in a sitting position, for at least 4 h in a plane, car, bus or train.⁹⁻²² All patients with a PTH underwent additional thrombophilic screening to analyse antithrombin activity, concentrations of protein S and protein C, and the presence of prothrombin gene mutation G2010 A, factor V Leiden mutation and lupus anticoagulant.

Statistical analysis

To determine differences in the frequency of PFO, stroke risk factors, TOAST criteria and stroke location in both groups (stroke patients with PTH and stroke patients with a negative travel history (NTH)) we applied the χ^2 test. To compare the influence of age on the frequency of PFO and the total number of stroke risk factors in both patient groups, we used the Mann-Whitney test. Data were analysed with the SPSS statistical package (V.12.0; SPSS Inc, Chicago, Illinois, USA). A value of $p < 0.05$ was considered to be significant.

RESULTS

We identified 338 patients with a first ever cerebral ischaemia during the observation period (149 women and 189 men;

mean age 65.6 (SD 13.6) years. Table 1 shows baseline characteristics of the study population.

Forty two patients had a PTH and 296 had an NTH. Of the patients with PTH 14 (33.3%) travelled by car, 20 (47.6%) by bus and 8 (19.1%) by plane. The median delay between travel and the onset of stroke was seven days (mean 9.2 (SD 6.7) days).

The frequency of PFO in the PTH group (13 of 29 (44.8%)) was significantly higher than in the NTH group (7 of 65 (10.8%)). The morphology of the PFO was not, however, exactly estimated. Nevertheless, in three patients with PTH and PFO and in one patient with NTH and PFO, a hypermobile atrial septum combined with a slight interatrial septum aneurysm was assumed on the basis of the echocardiographic findings. Mean age was significantly lower in the PTH group (56.6 (SD 13) years) than in the NTH group (66.9 (SD 13.2) years). The two groups were stratified on the basis of this age difference by dichotomising the factor age (younger than and older than the median of the entire study population). In both age groups, significantly more PTH patients had a PFO ($p = 0.007$, $p = 0.022$).

A larger proportion of patients with acute stroke and a PTH were men ($p = 0.03$). Regardless of the sex, however, PTH patients had a higher frequency of PFO than the NTH patients (for women $p = 0.005$; for men $p = 0.009$).

The number and profile of risk factors were differed between the groups. The PTH group had a lower total number of risk factors (mean 2.2 (1.4)) than the NTH group (mean 3.3 (1.6), $p = 0.0001$). Analysis of the risk profile showed that fewer PTH patients were smokers ($p = 0.035$) or had hypertension ($p = 0.0001$), atrial fibrillation ($p = 0.025$), diabetes ($p = 0.009$) or other risk factors ($p = 0.005$). In addition, more PTH patients had cardioembolic ($p = 0.023$) and cryptogenic strokes ($p = 0.0001$) and fewer of them had small-vessel disease ($p = 0.0001$). Regarding neuroradiological findings, on the basis of control CT or MRI, ischaemia in

Table 1 Characteristics of patients with and without a history travel preceding a stroke

	Travel history		p Value
	Positive (n = 42)	Negative (n = 296)	
Men/women	30 (71%)/12 (29%)	159 (54%)/137 (46%)	0.03
Age (years)	56.6 (13)	66.9 (13.2)	0.0001
Number of stroke risk factors	2.2 (1.4)	3.3 (1.6)	0.0001
Hypertension	22 (52.4%)	233 (78.7%)	0.0001
Diabetes	5 (11.9%)	93 (31.4%)	0.009
Dyslipoproteinaemia	20 (47.6%)	156 (52.7%)	NS
Atrial fibrillation	3 (7.1%)	65 (22%)	0.025
Smoking	15 (35.7%)	127 (42.9%)	0.0349
Other	7 (16.7%)	115 (38.9%)	0.005
TOAST criteria			
Large-artery atherosclerosis	2 (4.7%)	32 (10.8%)	NS
Small-vessel atherosclerosis	2 (4.7%)	101 (34.1%)	0.0001
Cardioembolic	15 (35.7%)	57 (19.3%)	0.023
Undetermined/cryptogenic	21 (50%)	59 (19.9%)	0.0001
Concurrent	2 (4.7%)	43 (14.5%)	NS
Stroke location*	n = 27	n = 208	
Territory of MCA or ACA	14 (51.8%)	111 (53.4%)	NS
Territory of PCA	8 (29.6%)	13 (6.3%)	0.0001
Brainstem and cerebellum	2 (7.4%)	32 (15.4%)	NS
Lacunar stroke	3 (11.1%)	52 (25%)	NS
PFO examination (TOE and c-TCD)	n = 29	n = 65	
Detected PFO	13 (44.8%)	7 (10.8%)	0.0001
Detected PFO in age < median	9 (31%)	4 (6.1%)	0.007
Detected PFO in age > median	4 (13.8%)	3 (4.6%)	0.022
Detected PFO in men	9 (31%)	3 (4.6%)	0.009
Detected PFO in women	4 (13.8%)	4 (6.1%)	0.005

Data are mean (SD) of number (%).

*On the basis of control computed tomography or magnetic resonance imaging.

ACA, anterior cerebral artery; c-TCD, contrast transcranial Doppler; MCA, middle cerebral artery; PCA, posterior cerebral artery; PFO, patent foramen ovale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; TOE, transoesophageal echocardiography.

the posterior cerebral artery was more common in patients with a PTH ($p = 0.0001$).

In the patients with PTH, thrombophilic screening showed the presence of heterozygote factor V Leiden mutation in one patient.

With regard to secondary prevention, treatment of the patients with PFO was individually discussed with the cardiologists at our institution. Decisions on interventional PFO closure were based on similar criteria to those mentioned in the recent article by Landzberg and Khairy.²³ None of our patients had a high-risk PFO. All patients in our cohort have therefore been treated conservatively, according to our national stroke care guidelines, and received platelet inhibitors.

DISCUSSION

The most important findings of this study are that, irrespective of their age, significantly more patients with a PTH had a PFO. In addition, patients with a PTH had a significantly lower total number of risk factors as well as a different risk factor profile. Moreover, the stroke pattern in patients with a PTH differed significantly indicating a higher frequency of cardioembolic and cryptogenic strokes.

The current observational study is the first to investigate prospectively a possible association between travel history and stroke in a large series of patients. For the association between travel history and stroke, the term “economy class stroke syndrome” has been introduced in the literature. Until now, 14 single cases of ECSS have been reported. PFO was detected in all but one patient and fewer typical stroke risk factors were present. All patients had the stroke after a long-distance flight.^{10–17} Travel-related stroke is assumed to be under-recognised in the clinical setting and under-reported in the literature.^{10–13}

Paradoxical embolism of thrombus, fat and air through a PFO is a well-recognised pathophysiological mechanism of stroke.^{1–2} A right to left shunt can occur at rest and during coughing, after the release of a Valsalva manoeuvre and with raised right atrial pressure after a pulmonary embolism, chronic lung disease and right ventricular failure, or even sexual activity and some other Valsalva-like activities.^{1–2, 24} A further proposed mechanism is the formation of a clot within the PFO canal from where it can embolise.¹ The prevalence of PFO ranges from 10–38% depending on the investigated population and the method used.²⁵ Recent studies suggest an association between PFO and cryptogenic stroke—that is, a stroke in which no clear source of embolus has been identified.^{1–3} The main risk factor in this condition is the development of a symptomatic or an asymptomatic venous thrombosis. Several risk factors for venous thrombosis are known, such as venous stasis, endothelial lesion, chronic venous insufficiency, obesity, dehydration, cancer, heart insufficiency and pregnancy.²² Several hypercoagulation abnormalities predispose to venous thrombosis but are not more commonly found in patients with stroke and a PFO.²⁵ This was also the case in our cohort of patients with PTH and indicates that the other named risk factors for venous thrombosis may be more prominent in the evolution of a paradoxical embolism.

In this study, we defined a PTH as travel of at least 4 h in duration in mainly a sitting position, including plane, bus, car and train travelling. This definition of PTH is part of the definition of “traveller thrombosis” according to the guidelines of the phlebological and angiological societies of Austria, Germany and Switzerland and was used in previous studies.^{7–9, 22–26} Pathophysiologically, venous stasis in the sitting position is considered the main risk factor for developing thrombosis.⁹ This condition is well recognised to have a role not only in air travel but also in all other types of

travel and even in situations with prolonged sitting.²⁷ In addition, during long-distance air travel, cabin-related low humidity, dehydration and relative hypoxia may aggravate the hypercoagulable state.¹²

Some limitations may apply to the current study. Classification of the patients according to TOAST criteria might have been more exact if all patients had undergone high standard MRI. For logistic reasons and limitations of MRI capacities, however, we had to restrict the performance of control imaging.

At first glance, the percentage of cardioembolic strokes (35.7%) according to the TOAST criteria in the PTH group may seem lower than expected. However, this rate is still significantly higher than the percentage of cardioembolic strokes in the NTH group (19.3%). Moreover, on the basis of the 27 patients who underwent control brain imaging, the percentage of presumably territorial strokes goes up to about 80%. Our finding of about 30% infarctions in the PCA territory may be a further hint of the embolic nature of PTH-associated strokes. Cals *et al*²⁸ describe that infarctions in the territory of the PCA are mostly due to embolism.

We cannot prove that an actual paradoxical embolism was the cause of stroke in all patients with stroke, a PTH and PFO. The high percentage of PFO per se—probably the most important prerequisite for paradoxical embolism—does, however, favour this assumption. We omitted an investigation of these patients with ultrasound and laboratory tests for the presence of DVT because it is known from the literature that lack of evidence of a DVT does not necessarily diminish the likelihood of paradoxical embolism.²⁹ Otherwise it is known that after long-distance travelling, 4.5–10% of patients develop DVTs that remain mostly asymptomatic.^{30–31}

A further concern may be whether the patients also had had a pulmonary embolism. From reports of ECSS in the literature, only the four patients reported on by Lapostolle *et al*¹⁵ had a pulmonary embolism and a stroke together; the other reported patients had isolated strokes. In their series, however, Lapostolle *et al*¹⁵ recruited patients who had a pulmonary embolism and a stroke during the flight or shortly afterwards. Others—that is, patients with isolated strokes or strokes occurring later—were not included in this analysis. Furthermore, in patients with a PFO, pulmonary embolism can be speculated to occur less often and to be less severe if the embolus can escape into the arterial system. Thus, we assume that pulmonary embolism is not a prerequisite to diagnosing stroke through paradoxical embolism.

The results of our study might have been influenced by a selection bias. Patients with a PTH were younger and more of them were men. These features of the PTH group are probably explained by the general observation that younger people and men travel more often and longer often due to leisure activities and professional obligations. After dichotomisation of all patients according to age and sex, however, the frequency of PFO was increased in patients with PTH and stroke in comparison with patients with stroke and NTH. We assume therefore that this selection bias is not responsible for the findings.

Another possible bias of our study is that a TOE was not performed in all patients to search for a PFO. We always decided by consensus with the cardiologists of our institution whether to perform a TOE. According to our internal clinical guidelines, which are based on European Stroke Initiative guidelines, TOE is recommended only for patients with a presumed cardioembolic stroke if transthoracic echocardiography findings are not definite.¹⁸ For a considerable number of our patients, results of non-invasive transthoracic echocardiography were sufficient for clinical stroke care. Still, invasive TOE was necessary for almost a third (28%) of all patients. Furthermore, we consider it unlikely that a selection

bias has influenced our results, as the above mentioned clinically oriented diagnostic approach was applied for all patients, irrespective of PTH or NTH.

In conclusion, the findings that our patients with stroke and a PTH more often had a PFO and a cardioembolic and cryptogenic stroke pattern, but less often other typical stroke risk factors, led to the hypothesis that PFO is a risk factor for travel-associated stroke. This assumption applies to travelling not only by plane but also by bus, car or train. In the context of increasing globalisation, travel may be recognised as a potential risk factor for the occurrence of stroke. The medical community is increasingly directing its attention to this field of travel-related disease.³² In our study, however, it is hard to establish a direct cause and effect association between travel and stroke in individual patients. Epidemiological studies testing our hypothesis may therefore give further insight into the magnitude of this problem. In case of a plausible indication for closure of PFO, interventional techniques are now available to safely and effectively prevent secondary presumed paradoxical embolisms.^{23 33 34}

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