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A Population-Based Study of the Prevalence of Fatigue After Transient Ischemic Attack and Minor Stroke

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Background and Purpose—Fatigue is common after stroke and can be attributable to the increased physical effort associated with severe neurological deficits; however, its presence in those with little motor deficit raises the possibility of confounding by other factors, such as comorbidity, anxiety, and medication. To control for such factors and determine the extent of stroke-specific fatigue, we compared patients with minor stroke who had little or no residual neurological deficit with patients with TIA; both groups had undergone similar investigations and treatment.

Methods—The prevalence of fatigue 6 months after TIA or minor stroke was assessed in consecutive patients using the Chalder fatigue scale in a population-based incidence study (Oxford Vascular Study). Patients were included if they were independent in self-care Barthel Index (≥18/20) and without major cognitive impairment (Mini-Mental State Examination ≥24/30). Stroke severity at baseline was assessed with the National Institute of Health Stroke Scale (NIHSS). Other potential causes of fatigue were assessed including anxiety, depression, recent life events, medication, and abnormalities in biochemistry or hematologic tests.

Results—Seventy-six participants had minor stroke (mean age, 74.1 years; 42 men) and 73 had TIA (mean age, 72.5 years; 40 men). At 6-month follow-up, median Barthel Index score was 20 (interquartile range, 20–20) in both groups. However, fatigue was more common after stroke than TIA (56% vs 29%; OR, 3.14; 95% CI, 1.51–6.57; $P=0.0008$). This difference was present both in patients with modified Rankin score of 0 at 6 months (23.8% vs 10.3%) and patients with modified Rankin score ≥1 (69.2% vs 48.6%), and remained more frequent in stroke patients after adjustment for potential confounders. Within the group of patients with stroke, the prevalence of fatigue increased with initial stroke severity (87% NIHSS ≥4 vs 48% NIHSS ≤3; $P=0.0087$); however, stroke patients with initial NIHSS of 0 were still more fatigued than patients with TIA (57% vs 29%; $P=0.015$).

Conclusions—The prevalence of fatigue after minor stroke is higher than after TIA, suggesting that it is not simply a consequence of the stress of a recent acute cerebral event, comorbidity, medication, or other potential confounders. The high levels of fatigue in stroke patients without neurological impairment suggest it has a central origin rather than being the result of increased physical effort required after stroke. **(*Stroke*. 2009;40:757-761.)**

Key Words: fatigue ■ stroke ■ transient ischemic attack

Fatigue is a common and important cause of long-term morbidity after stroke.[1] The prevalence of fatigue after stroke varies with time since the event and with population types and sampling (hospital, community, and outpatient); estimates range between 38% and 68%.[2–8] Although fatigue is important to patients[9,10] and clinicians,[8,11] research has been limited,[4,12,13] partly perhaps because of difficulties in measurement and in disentangling the numerous potential causes.[1,3,14]

Both physical and mental factors contribute to fatigue. Poststroke fatigue is associated with depression,[2,6,12] motor impairment,[2,15] physical deconditioning,[8,16] reduced health-related quality of life,[2,6] and increased mortality.[4] However, fatigue has also been reported in patients who are not depressed and have little motor impairment,[4,5] and it is uncertain whether other factors, such as the stress of a cerebral event, comorbidity, and medication, may also contribute. To control for such factors, and to determine the extent of stroke-specific fatigue, we compared patients with recent minor stroke vs patients with a recent TIA and no neurological deficit; both groups had undergone similar investigations and treatment. To our knowledge there are no previously published data on the prevalence of fatigue in unselected patients with TIA and no population-based studies.

Materials and Methods

The study was nested in the Oxford Vascular Study, a population-based study of all acute vascular events, including TIA and stroke, in Oxfordshire, UK. The methods of Oxford Vascular Study have been

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described previously,[17] and direct assessment has shown that case-ascertainment is near complete.[18] All cases were reviewed by a neurologist to confirm the diagnoses, which were based on standard criteria.[19] A detailed clinical assessment was performed, including the NIHSS score.[20] Ethical approval for Oxford Vascular Study and related substudies was obtained from the local ethics committee.

All patients were followed-up at 1, 6, 12, and 24 months after the TIA or minor stroke. At the 6-month follow-up visit, a researcher assessed fatigue in all patients who fulfilled the following eligibility criteria: (1) TIA or stroke (ischemic or hemorrhagic) at baseline; (2) no recurrent stroke during first 6 months of follow-up; (3) no major nonstroke disorder (eg, cancer or acute coronary syndrome) during first 6 months of follow-up; and (4) functionally independent at 6-month follow-up: Barthel Index score ≥18/20 and Mini-Mental State Examination ≥24/30.

The following potential causes of fatigue were assessed: anxiety and depression,[21] recent life events, obesity (body mass index), thyroid function, urea and electrolytes, hemoglobin, and medication. Other potential confounders were assessed, including social circumstances, educational attainment, employment status, and ethnic origin. We also measured the modified Rankin score at 6-month follow-up.[22]

To determine whether the presence of fatigue was associated with the patients' subjective impressions of their recovery from the stroke or TIA, we also administered the Simple Questions scale for recovery from stroke at the 6-month follow-up.[23]

Fatigue was measured with the Chalder[24] fatigue scale, which has been used widely in chronic fatigue,[25] multiple sclerosis,[26] Gulf War syndrome,[27] migraine,[28] HIV,[29] and in healthy populations.[30] The score consists of 11 short questions on tiredness, energy, and the need to rest, and it does not specifically ask about "fatigue." As generally recommended, a score >3 out of 11 indicates significant fatigue.[24] Several studies have shown the score to be valid and reliable in measuring chronic fatigue.[24,31,34] Data were analyzed with the SPSS version 15.0 (SPSS Inc).

Results

Of 149 eligible participants who were approached at 6-month follow-up, all consented to the study. Seventy-three patients had minor stroke (67 ischemic) and 76 had TIA. Baseline characteristics, assessed at the time of the TIA or stroke, are shown in Tables 1 and 2. There were no significant differences in demographic characteristics, vascular risk factors, results of relevant blood tests, education attainment, social circumstances, employment status, anxiety and depression, or baseline medications. There were, however, more cases of previous stroke in the minor stroke population compared with TIA (P=0.0011; Table 1).

There were no differences at the 6-month assessment between TIA and stroke patients in medications (Table 3), Barthel Index, Mini-Mental State Examination, or anxiety and depression (Table 4). However, Chalder fatigue scores at the 6-month follow-up were significantly higher in patients with stroke than in those with TIA (P=0.0013; Figure). Significant fatigue (>3 on the Chalder fatigue scale) was more common after stroke than after TIA (56% vs 29% respectively; OR, 3.14; 95% CI, 1.51–6.57; P=0.0008; Table 4). This difference was still present after adjusting for previous stroke, living alone, and systolic blood pressure (OR, 2.85; 95% CI, 1.36–5.96; P=0.005), and when patients with previous stroke were excluded from the analysis (53% vs 30%; OR, 2.62; 95% CI, 1.21–5.70; P=0.008).

Median modified Rankin score at 6 months was 1 (interquartile range, 0,2) in stroke cases and 0 (interquartile range, 0,1) in TIA (P=0.0002). However, when the analysis of

Table 1. Baseline Characteristics Between Strokes and TIA

	Stroke, n=73 n (%)	TIA, n=76 n (%)	Stroke vs TIA *P*
Age, median (IQR)	74.1 (64.5, 80.0)	72.5 (62.6, 82.5)	0.83
Male	42 (58%)	40 (53%)	0.62
Previous MI	7 (10%)	3 (4%)	0.20
Previous TIA	11 (15%)	12 (16%)	1.00
Previous stroke	14 (19%)	2 (3%)	0.001
Previous PVD	4 (5%)	3 (4%)	0.72
Previous angina	7 (10%)	6 (8%)	0.78
AF	7 (10%)	13 (17%)	0.23
Carotid territory event*	43 (66%)	50 (68%)	0.86
Blood pressure			
Systolic, median (IQR)	155 (140, 171)	150.0 (130, 160)	0.05
Diastolic, median (IQR)	83.5 (75, 94)	82.5 (72, 91)	0.46
Raised BP (systolic >140, diastolic ≥90)	50 (70%)	54 (71%)	1.00
Blood tests			
Hemoglobin, median (IQR)	14.0 (12.8, 15.1)	13.7 (13.2, 14.9)	0.79
Platelet, median (IQR)	262.0 (222, 326)	255.5 (213, 286)	0.12
Sodium, median (IQR)	138.0 (135, 140)	138.5 (137, 140)	0.57
Potassium, median (IQR)	3.8 (3.6, 4.3)	3.9 (3.7, 4.3)	0.43
Urea, median (IQR)	5.9 (4.9, 8.0)	5.5 (4.9, 6.4)	0.15
Thyroid stimulation hormone, median (IQR)	1.6 (0.9, 2.2)†	1.7 (1.2, 2.3)‡	0.17
Ethnic group			0.75
White	71 (97%)	72 (95%)	
Black Caribbean	1 (1%)	1 (1%)	
Black African	1 (1%)	0 (0%)	
Asian	0 (0%)	2 (3%)	
Chinese	0 (0%)	1 (1%)	
Smoking			0.24
Never	29 (40%)	40 (53%)	
Ex-smoker	33 (45%)	29 (38%)	
Current	11 (15%)	7 (9%)	
Diabetes	6 (8%)	5 (7%)	0.76
Alcohol units, median (IQR)	2 (0, 10)	2 (0, 9.5)	0.82
BMI, median (IQR)	25.1 (23.1, 28.4)	25.0 (22.0, 29.4)	0.75

BMI indicates body mass index; BP, blood pressure; IQR, interquartile range; MI, myocardial infarction; PVD, peripheral vascular disease; AF, atrial fibrillation.

P values are for Mann–Whitney *U* test for medians and Fisher exact test for frequencies unless stated otherwise.

*Carotid event n=65; †TSH n=46; ‡TSH n=57.

Table 2. Baseline Demographic, Social, and Psychological Characteristics

	Stroke, n=73 n (%)	TIA, n=76 n (%)	Stroke vs TIA *P*
Education			0.71
Basic	47 (66%)	45 (59%)	
Further	13 (18%)	17 (22%)	
Higher	11 (15%)	14 (18%)	
Age left school, median (IQR)	15 (14, 16.5)	15 (14, 17)	0.50
Age left education, median (IQR)	15 (14, 18)*	16 (15, 20)	0.26
Social circumstances			
Living at home	66 (92%)	73 (97%)	0.16
Living alone	16 (22%)	28 (37%)	0.07
Carer	6 (8%)	2 (3%)	0.16
Marital status			0.19
Married	49 (67%)	38 (50%)	
Widowed	15 (21%)	23 (30%)	
Single	2 (3%)	1 (1%)	
Separated	5 (7%)	11 (14%)	
Partner	2 (3%)	3 (4%)	
Employment			0.25
Working full-time	11 (15%)	13 (17%)	
Working part-time	2 (3%)	7 (9%)	
Caring for home	0 (0%)	2 (3%)	
Unemployed	0 (0%)	1 (1%)	
Unable to work	3 (4%)	2 (3%)	
Retired	56 (78%)	50 (67%)	
Interviewer's perception of patient's personality			0.16
Very relaxed	4 (6%)	9 (12%)	
Fairly relaxed	33 (46%)	34 (46%)	
Average	21 (30%)	18 (24%)	
Prone to stress	13 (18%)	9 (12%)	
Patient's perception of own personality			0.24
Very relaxed	9 (13%)	7 (9%)	
Fairly relaxed	24 (33%)	24 (32%)	
Average	17 (24%)	30 (39%)	
Prone to stress	19 (26%)	14 (18%)	
Anxiety/depression at 1 month	18 (27%)†	18 (26%)	0.85

*Age left education n=68; †Anxiety and depression n=66.

fatigue was stratified by modified Rankin score at 6 months (Table 4), the excess of fatigue among patients with stroke (OR, 3.14; 95% CI, 1.51–6.57; $P=0.0008$) was present in patients with modified Rankin score of 0 (23.8% vs 10.3%; OR, 2.73; 95% CI, 0.54–14.4) and patients with modified Rankin score ≥1 (69.2% vs 48.6%; OR, 2.38; 95% CI, 0.91–6.26).

Prevalence of fatigue increased with severity of the initial stroke (87% at NIHSS >3 vs 48% at ≤3; OR, 6.96; 95% CI, 1.30–49.25; $P=0.0087$). However, patients with stroke who had an NIHSS score of 0 in the acute phase were still more fatigued at 6-month follow-up than those with TIA (57% vs 29%, respectively; OR, 3.19; 95% CI, 1.10–9.34; $P=0.015$).

Table 3. Medications Between Strokes and TIA

	Stroke, n=73 n (%)	TIA, n=76 n (%)	Stroke vs TIA *P*
Before event			
Antiplatelet	37 (51%)	29 (38%)	0.14
Warfarin	4 (5%)	6 (8%)	0.75
Antihypertensive	47 (64%)	39 (51%)	0.14
Beta-blocker	21 (29%)	23 (30%)	0.86
Statin	20 (27%)	15 (20%)	0.33
At 6 mo			
Antiplatelet	60 (82%)	69 (91%)	0.15
Warfarin	6 (8%)	7 (9%)	1.00
Antihypertensive	56 (77%)	52 (69%)	0.28
Beta-blocker	21 (29%)	22 (29%)	1.00
Statin	64 (88%)	64 (84%)	0.64

To determine whether the presence of fatigue was associated with the patients' subjective impressions of their recovery from the stroke or TIA, we asked the "Simple Questions."[23]

Patients who felt that they had not made a full recovery were significantly more likely to be fatigued than those who had made a full recovery (37/51 vs 30/103; $P<0.0001$), and although patients with stroke were more likely than those with TIA to state that they had not fully recovered (Table 4), the association between lack of subjective recovery and fatigue was still present when the analysis was confined to those with stroke only (33/44 vs 10/32; $P<0.0001$).

Discussion

This population-based study of fatigue in consecutive cases of minor stroke and TIA is the first to our knowledge to report data on the prevalence of fatigue in TIA patients. Previous studies[3,32] have often specifically excluded patients with TIA. One of the strengths of our study is the comparison of TIA and minor stroke cases. Even though the study was confined to patients who had relatively minor strokes with sufficient recovery to be independent in self-care, patients with minor stroke reported significantly higher levels of fatigue at 6-month follow-up than those with TIA. This difference was independent of measured potential confounders for fatigue, including anxiety, depression, recent life events, relevant blood tests, and medication, suggesting that the excess of fatigue in patients with minor stroke reflected a causal association. Although fatigue can be related to the increased physical effort associated with severe neurological deficits, our stroke patients had little or no motor deficit, suggesting that their excess of fatigue compared with TIA patients was attributable to central mechanisms.

Other studies have also reported high rates of fatigue during follow-up after stroke. In a Swedish study of all community and hospital first-ever strokes, Appelros et al[33] found that 53% reported fatigue at 1 year after stroke, which is consistent with our rate of 56% at 6 months. Also

Table 4. Functional Scores, Simple Questions, Modified Rankin Score, NIHSS, and Anxiety/Depression at 6 Months

	Stroke n (%)	TIA n (%)	Stroke vs TIA *P*
Chalder, median (IQR)	4 (0, 7)	1 (0, 4)	0.0013
Excluding cases with previous stroke			
Chalder, median (IQR)	4 (0, 7)	1.5 (0, 4)	0.008
All cases			
Fatigue (Chalder >3)	41 (56%)	22 (29%)	0.0008
Excluding cases with previous stroke			
Fatigue (Chalder >3)	31 (53%)	22 (30%)	0.008
Barthel, median (IQR)	20 (20, 20)	20 (20, 20)	0.16
MMSE, median (IQR)	27 (26, 29)	27.5 (26, 29)	0.48
Simple Questions			
Need help at 6 mo	7 (10%)	1 (1%)	0.030
Have problems at 6 mo	43 (60%)	8 (11%)	<0.0001
Made a full recovery at 6 mo	32 (44%)	71 (93%)	<0.0001
Modified Rankin score, median (IQR)	1(0,1)	0 (0,1)	0.0002
NIHSS by fatigue			
NIHSS ≥4	13 (87%)		
NIHSS ≤3	28 (48%)		0.0087
NIHSS=0	13 (57%)	22 (29%)	0.015
Anxiety/depression at 6 mo	20 (30%)*	20 (27%)	0.85

MMSE indicates Mini-Mental State Examination.

P values are for Mann–Whitney *U* test for medians and Fisher exact test for frequencies unless stated otherwise.

*Anxiety and depression n=67.

consistent with our findings, they also found that rates of fatigue were positively correlated with the NIHSS score ($P=0.004$).[33]

Previous studies have also demonstrated a positive relationship between fatigue and increased modified Rankin score at the time of assessment.[3,32,33] However, in our study even stroke patients with a modified Rankin score of 0 were more fatigued than patients with TIA. Furthermore, even stroke patients with initial NIHSS score of 0 (ie, very minor strokes at onset) still reported more fatigue than TIA patients. Similarly, fatigue is often considered to be a symptom of depression, although previous studies are conflicting.[11,14,16,32,33] However, the majority of patients in our study felt fatigued without depression. It is therefore likely that fatigue and depression are separate, albeit overlapping, constructs.

Our study does have some limitations. First, there is no gold standard for the measurement of fatigue.[32,34,35] However, the Chalder fatigue scale has been used previously in studies of patients with neurological conditions[36] and has been shown to be valid and reliable in multiple different disease states[25–29] and in the general population.[30,37] Rates of fatigue, defined as a Chalder score >3, of 10% to 18% have been reported in healthy younger populations, increasing to 22% in the general population older than 60[38,39] Thus, our stroke patients were more fatigued than would be expected in the general population of a similar age, whereas the TIA patients were probably not. Second, we only assessed some of the potentially confounding factors at baseline, such as blood tests, soon after the TIA or stroke, whereas we measured fatigue at 6-month follow-up. However, several other potential confounders, such as medication, anxiety, depression, and physical functioning, were measured at the 6-month follow-up. Third, anxiety and depression were not measured in any great detail; therefore, future studies using more sensitive measures would be appropriate. Fourth, our stroke patients were more likely to have had a previous stroke than the TIA patients. However, the excess of fatigue was still seen in incident strokes and all stroke patients were independent in self-care, even though they had experienced a previous event. Finally, we tried to use TIA patients as nonstroke controls to determine whether there might be central mechanisms consequent on having a stroke underlying fatigue and to minimize the various sources of confounding discussed, but we did not have MR brain imaging in all cases. Therefore, we cannot separate those TIA cases with and without a clinically appropriate cerebral infarct, or those with asymptomatic previous infarction. However, we found significant differences between minor strokes and TIA despite this limitation. It is possible that rates of fatigue would have been even lower in TIA patients with no infarction.

In conclusion, the prevalence of fatigue after minor stroke is higher than after TIA, suggesting that it is not simply a

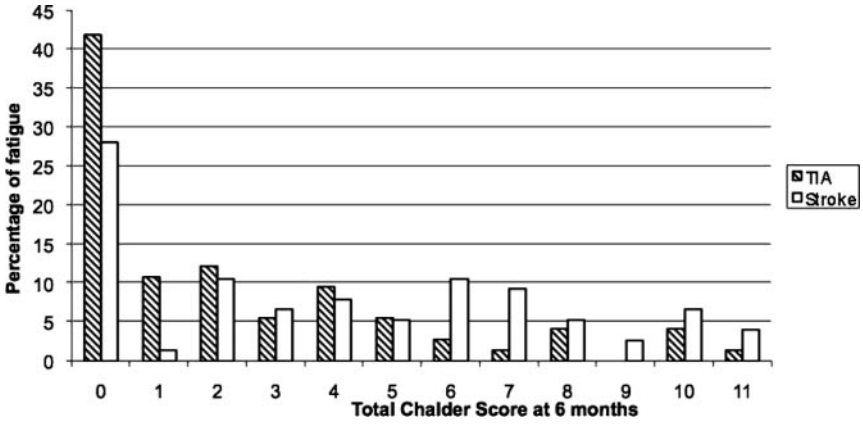

Figure. Comparison of Chalder fatigue score in TIA and minor stroke.

consequence of the stress of a recent acute cerebral event, comorbidity, medication, or other potential confounders. The high levels of fatigue in stroke patients without neurological impairment suggest it has a central origin rather than being the result of increased physical effort required after stroke. Monitoring fatigue and identifying interventions such as centrally acting pharmacological interventions may be an appropriate avenue for future study and may improve outcomes.

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Disclosures

None.

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