N-Terminal Pro–Brain Natriuretic Peptide (NT-proBNP) Levels are Increased in Patients With Transient Ischemic Attack Accompanied by Nonfocal Symptoms

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Background—Transient nonfocal neurological symptoms may serve as markers of cardiac dysfunction. We assessed whether serum N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, a biomarker of cardiac disease, are increased in patients with transient ischemic attack (TIA) accompanied by nonfocal symptoms and in patients with attacks of nonfocal symptoms (transient neurological attack [TNA]).

Methods and Results—We included 15 patients with TNA, 69 with TIA accompanied by nonfocal symptoms, 58 with large-vessel TIA, 32 with cardioembolic TIA, and 46 age- and sex-matched healthy control participants. Serum NT-proBNP levels were determined within 1 week after the attack. We compared log-transformed NT-proBNP levels of patients with cardioembolic TIAs and mixed or nonfocal TNAs, with those of patients with noncardioembolic TIAs as a reference group. Adjustments for age, sex, atrial fibrillation, and a history of nonischemic heart disease were made with a multiple linear regression model. Compared with large-vessel TIA (mean 14.2 pmol/L), mean NT-proBNP levels were significantly higher in patients with TIA accompanied by nonfocal symptoms (40.5 pmol/L, \(P=0.049\)) and with cardioembolic TIA (123.5 pmol/L; \(P=0.004\)) after adjustments for age, sex, atrial fibrillation, and a history of nonischemic heart disease. Patients with TNA also had higher mean NT-proBNP levels (20.8 pmol/L, \(P=0.38\)) than those with large-vessel TIA, but this difference was not statistically significant.

Conclusion—NT-proBNP levels are increased in patients with TIA accompanied by nonfocal symptoms. (J Am Heart Assoc. 2015;4:e002072 doi: 10.1161/JAHA.115.002072)

Key Words: cardiac origin • nonfocal symptoms • N-terminal pro–brain natriuretic peptide • transient neurological attacks • transient nonfocal neurological symptoms

The increased risk of stroke and coronary heart disease in patients with transient ischemic attack (TIA) is well known. Transient neurological attacks (TNAs) are attacks of transient (<24 hours) nonfocal neurological symptoms. TNAs are generally considered more benign, but a recent study in unselected patients aged ≥55 years suggested that patients with TNAs or patients with TIAs accompanied by nonfocal symptoms are at particularly high risk of cardiac events.\(^1,2\) Consequently, transient nonfocal symptoms may serve as markers of cardiac dysfunction.

N-terminal pro–brain natriuretic peptide (NT-proBNP) is an important biomarker of cardiac disease that is increased in patients with heart failure and atrial fibrillation.\(^3,4\)

In this study, we aimed to assess whether serum NT-proBNP levels were increased in patients with transient nonfocal symptoms.

Methods

Patients were derived from the Erasmus Stroke Study (ESS), which registered patients with cerebrovascular diseases who were admitted to the Erasmus University Medical Center Rotterdam from 2005 to 2010. The ESS also includes population-based control participants, mostly friends and spouses of patients.

We included all patients with TNA, TIA accompanied by nonfocal symptoms, cardioembolic TIA, and TIA with
large-vessel etiology who were admitted between March 2007 and October 2009 and 46 age- and sex-matched stroke-free control participants. Cardioembolic and large-vessel TIsAs were defined with the TOAST (trial of ORG 10172 in acute stroke treatment) classification.5

TIA was defined as a focal neurologic deficit of sudden onset lasting <24 hours without signs of recent infarction on acute brain imaging. Nonfocal symptoms were defined as decreased consciousness, confusion, unsteadiness, jerking, nonrotatory dizziness, visual phenomena, cardiac or vegetative signs, paresthesia, and bilateral weakness. Attacks with a nonvascular pathogenesis like typical migraine aura, epileptic insult, hypoglycemia, drug intoxication, traumatic injury, and Ménière’s disease were excluded. All events and etiology of TIA were diagnosed by an experienced stroke neurologist without knowledge of NT-proBNP results.

The blood samples were collected from a peripheral vein within 1 week, with a median of 2 days to allow clotting. The samples were then centrifuged for 15 minutes at 15,000 g, and the serum was isolated and stored at −80°C until analysis. NT-proBNP levels were measured with an electrochemiluminescence immunoassay (Roche Diagnostics). All participants provided informed consent. The study was approved by the medical ethics committee and research board of the Erasmus Medical Center.

**Table 1. Patient Characteristics**

| Event Type Combined (N=174) | Cardioembolic TIsAs (n=32) | TNAs (n=15) | TIsAs Accompanied by Nonfocal Symptoms (n=69) | Large-Vessel TIsAs (n=58) | Controls (n=46) | P Value |
|-----------------------------|---------------------------|-------------|-----------------------------------------------|---------------------------|----------------|---------|
| Age, y, mean (SD)           | 62 (12.2)                 | 68 (11.0)   | 61 (7.4)                                      | 63 (12.1)                 | 59 (12.8)                   | 62 (8.2) | 0.017  |
| Sex, female, n (%)          | 80 (46)                   | 10 (31)     | 7 (46)                                        | 39 (57)                   | 24 (41)                     | 23 (50) | 0.059  |
| SBP, mean (SD) mm Hg        | 148 (10)                  | 126 (19)    | 134 (21)                                      | 125 (21)                  | 131 (19)                    | —       | 0.215  |
| DBP, mean (SD) mm Hg        | 96 (11)                   | 73 (7)      | 79 (10)                                       | 72 (10)                   | 78 (11)                     | —       | 0.006  |
| Smoking, n (%)              | 102 (59)                  | 17 (53)     | 9 (60)                                        | 43 (62)                   | 33 (57)                     | 29 (63) | 0.833  |
| Positive family history, n (%) | 75 (43)                  | 11 (34)     | 6 (40)                                        | 30 (44)                   | 28 (48)                     | —       | 0.639  |
| Migraine n (%)              | 24 (14)                   | 4 (13)      | 3 (20)                                        | 16 (23)                   | 1 (2)                        | 0 (0)   | <0.001 |
| Use of OAC, n (%)           | 33 (19)                   | 20 (63)     | 1 (7)                                         | 6 (9)                     | 6 (10)                       | —       | <0.001 |
| Use of platelet aggregation inhibitors, n (%) | 93 (54) | 7 (22) | 10 (67) | 41 (59) | 35 (60) | 1 (2) | <0.001 |
| Use of antihypertensive drugs, n (%) | 97 (56) | 23 (72) | 10 (67) | 37 (54) | 27 (47) | 13 (28) | 0.002 |
| Use of antiarrhythmics, n (%) | 17 (10) | 3 (9) | 1 (7) | 8 (12) | 5 (9) | 5 (11) | 0.968 |
| Previous TIA or ischemic stroke, n (%) | 51 (29) | 13 (41) | 3 (20) | 19 (28) | 16 (28) | 4 (9) | 0.023 |
| Previous ischemic heart disease, n (%) | 34 (20) | 8 (25) | 2 (13) | 12 (17) | 12 (21) | 2 (4) | 0.110 |
| Previous nonischemic heart disease, n (%) | 40 (23) | 17 (53) | 4 (27) | 11 (16) | 8 (14) | — | <0.001 |
| Previous paroxysmal AF, n (%) | 29 (17) | 21 (66) | 0 (0) | 5 (7) | 3 (5) | 0 (0) | <0.001 |
| Other vascular disease, n (%) | 32 (18) | 9 (28) | 3 (20) | 13 (19) | 7 (12) | 2 (4) | 0.047 |

AF indicates atrial fibrillation; DBP, diastolic blood pressure; OAC, oral anticoagulant; SBP, systolic blood pressure; TIA, transient ischemic attack; TNAs indicate transient neurological attacks.

**Statistical Analysis**

Differences between patient characteristics for different event types and controls were assessed with ANOVA or chi-square test. NT-proBNP levels were normalized by logarithmic transformation. Event groups were compared with ANOVA, with patients with large-vessel TIA as a reference group. Adjustments for age, sex, atrial fibrillation, and history of nonischemic heart disease were made with a multiple linear regression model. A significance level of 0.05 was considered significant. The analysis was carried out with the Stata 12.1 statistical package (StataCorp).

**Results**

A total of 174 patients with TIA or TNA were included. Of these, 15 (9%) had TNA, 69 (40%) had TIA accompanied by nonfocal symptoms, 32 (18%) had cardioembolic TIA, and 58 (33%) had large-vessel TIA. Patients with a cardioembolic TIA were older and more often had a history of previous nonischemic heart disease and atrial fibrillation. In addition, they more often used oral anticoagulation instead of platelet aggregation inhibitors. Those with TIA accompanied by nonfocal symptoms more frequently had a history of migraine and previous TIA or ischemic stroke (Table 1).
Visual phenomena (29%) were the most common nonfocal signs, followed by nonrotatory dizziness (16%) and unsteadiness (16%), as shown in Table 2.

Mean NT-proBNP levels differed significantly among event groups (Figure). Mean NT-proBNP levels were similar in the reference group of patients with large-vessel TIAs and in healthy control participants (14.2 pmol/L versus 9.3 pmol/L; 95% CI −0.343 to 1.657 pmol/L; \( P=0.193 \)). Compared with the reference group, the mean NT-proBNP level was significantly higher in patients with cardioembolic TIA (123.5, 95% CI 0.157–0.807 pmol/L; \( P=0.004 \)) and in patients with TIA accompanied by nonfocal symptoms (40.5, 95% CI 0.001–0.349 pmol/L; \( P=0.049 \)) after adjustment for age, sex, atrial fibrillation, and a history of nonischemic heart disease. Patients with TNA also had higher NT-proBNP levels than the reference group, but this difference was not statistically significant (20.8, 95% CI −0.436 to 0.168 pmol/L, \( P=0.38 \)).

Our results provide further proof that transient nonfocal symptoms may be associated with cardiac disease. In line with earlier studies, high NT-proBNP was significantly related to TIA or stroke with cardiac origin.\(^6\)\(^{-11}\) As far as we know, this study is the first that assessed NT-proBNP in patients with TIA accompanied by nonfocal symptoms and TNA.

Our study has some limitations. First, the study comprised a small number of patients, thus we were not able to perform subgroup analyses based on type of nonfocal symptoms. Second, the group of patients with TNA may compose a selected group of patients. Patients with TNA do not always consult a physician, and they will not always be referred to the outpatient clinic. Third, because neurologists are conditioned to look for focal symptoms, nonfocal symptoms may have been missed. Consequently, patients with TIA accompanied by nonfocal symptoms could have been included in the group of patients with cardioembolic origin and large-vessel disease.

The blood samples were drawn within the first week after the attack. This may explain the lower levels of NT-proBNP found in our study compared with previous studies that assessed NT-proBNP on admission.\(^7\)\(^{-9}\)\(^{11}\) We considered a multivariable analysis to correct for all other significant differences among the comparison groups. Of these significant differences, only increased age, previous heart failure, and previous atrial fibrillation can cause elevated levels of natriuretic peptide.\(^4\)

At present, it is unclear how transient nonfocal symptoms should be managed in clinical practice. Transient nonfocal symptoms might be warning signs of cardiac dysfunction. Cardiac rhythm and conduction disorders, heart failure, or ischemic heart disease may lead directly to nonfocal symptoms by causing a sudden reduction in cerebral blood flow or indirectly cause them by anxiety-induced hyperventilation.\(^12\)\(^{13}\) Furthermore, cardiac arrhythmia or a fall in blood pressure may cause a sudden reduction in blood flow in a stenosed extracranial or intracranial artery, resulting in nonfocal symptoms or a combination of nonfocal and focal changes. Our findings underscore this hypothesis.

Conclusions

NT-proBNP levels are increased in patients with TIA accompanied by nonfocal symptoms. Further research into the

Table 2. Types of Nonfocal Symptoms

| Nonfocal Symptoms (n=153) | n (%) |
|--------------------------|------|
| Decreased consciousness | 9 (6) |
| Jerking and/or twitching | 1 (1) |
| Confusion or amnesia     | 18 (12) |
| Unsteadiness during attack | 24 (16) |
| Nonrotatory dizziness    | 25 (16) |
| Visual phenomena during attack | 45 (29) |
| Cardiac or vegetative signs | 10 (7) |
| Paraesthesia during attack | 17 (11) |
| Bilateral weakness during attack | 3 (2) |

Discussion

In this study, we found that NT-proBNP levels were increased in patients with TIA accompanied by nonfocal symptoms and in those with cardioembolic TIA. Patients with TNA also had higher NT-proBNP levels, but this was not statistically significant.

Figure. Mean NT-proBNP levels in various event groups. NT-proBNP indicates N-terminal pro–brain natriuretic peptide; TIA, transient ischemic attack; TNA, transient neurological attack.
cardiac origin of transient nonfocal neurological symptoms is necessary.

Disclosures
None.

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