Limb-shaking transient ischaemic attacks in patients with internal carotid artery occlusion: a case-control study

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Limb-shaking is a specific clinical feature of transient ischaemic attacks that has been associated with a high-grade stenosis or occlusion of the internal carotid artery. The aim of this study was to describe the clinical characteristics of limb-shaking in patients with internal carotid artery occlusion and to investigate whether patients with limb-shaking have a worse haemodynamic state of the brain than patients with internal carotid artery occlusion without limb-shaking. We included 34 patients (mean age 62 ± 7 years, 82% male) with limb-shaking associated with internal carotid artery occlusion without limb-shaking. We included 34 patients (mean age 62 ± 7 years, 82% male) with limb-shaking associated with internal carotid artery occlusion and 68 sex- and age-matched controls with cerebral transient ischaemic attack or minor disabling ischaemic stroke associated with internal carotid artery occlusion, but without limb-shaking. We investigated clinical characteristics, collateral pathways on contrast angiograms and carbon dioxide-reactivity measured by transcranial Doppler. The results showed that limb-shaking usually lasted less than 5 min and was often accompanied by paresis of the involved limb. Compared with controls, patients with limb-shaking more frequently had symptoms precipitated by rising or exercise (odds ratio 14.2, 95% confidence interval 4.2–47.9), more frequently had recurrent ischaemic deficits after documented internal carotid artery occlusion (but before inclusion in the study) (odds ratio 8.2, 95% confidence interval 2.3–29.3), more often had leptomeningeal collaterals (odds ratio 6.8, 95% confidence interval 2.0–22.7), and tended to have a lower carbon dioxide-reactivity (mean 5% ± 16 versus 12% ± 17; odds ratio 0.97 per 1% increase in carbon dioxide-reactivity, 95% confidence interval 0.94–1.00). In conclusion, limb-shaking transient ischaemic attacks in patients with internal carotid artery occlusion can be recognized by their short duration, are often accompanied by paresis and precipitated by rising or exercise and are indicative of an impaired haemodynamic state of the brain.

Keywords: transient ischaemic attack; stroke; carotid artery diseases; haemodynamics

Abbreviations: EC/IC = extracranial/intracranial; ICA = internal carotid artery; MCA = middle cerebral artery; TCD = transcranial Doppler; TIA = transient ischaemic attack
Introduction

Several case reports have described limb-shaking as a rare clinical feature of transient ischaemic attacks (TIAs) (Firlik et al., 1996; Leira et al., 1997; Niehaus et al., 1998; Zaidat et al., 1999; Kiechl et al., 2002; Schulz and Rothwell, 2002; Cheshire and Meschia, 2006; Kiechl et al., 2007). Limb-shaking has been characterized by brief, jerky, coarse, involuntary movements involving an arm or leg (Fisher, 1962; Baquis et al., 1985) and has been associated with high-grade stenosis or occlusion of the internal carotid artery (ICA). Small observational studies have shown impaired cerebral blood flow or cerebrovascular reserve capacity in patients with limb-shaking and ICA stenosis or occlusion in comparison with normal controls (Yanagihara et al., 1985; Levine et al., 1989; Tatemi et al., 1990; Firlik et al., 1996; Baumgartner and Baumgartner, 1998). Whether patients with ICA stenosis or occlusion with limb-shaking have a worse flow state of the brain than patients with ICA stenosis or occlusion without limb-shaking is unknown. Since the large extracranial-intracranial (EC/IC) bypass trial showed no benefit of EC/IC bypass surgery for prevention of stroke in patients with an ICA occlusion (The EC/IC Bypass Study Group, 1985), several studies have suggested that EC/IC bypass surgery may be of benefit in a subgroup of patients with impaired cerebral perfusion (Grubb et al., 1998; Garrett et al., 2009). In that perspective, it may be important to recognize limb-shaking on the basis of the history and to investigate whether this specific subtype of TIA is associated with haemodynamic impairment. The purpose of this study was to describe the clinical characteristics of limb-shaking in patients with TIA or moderately disabling stroke associated with an occlusion of the ICA and to investigate whether patients with limb-shaking have a worse haemodynamic state of the brain than patients with symptomatic ICA occlusion without limb-shaking.

Materials and methods

Patients

Between 1995 and 2008 we collected data from 313 patients with TIA or minor ischaemic stroke with, at most, moderately disabling cerebral or retinal ischaemic symptoms (modified Rankin scale ≤ 3) (Banks and Marotta, 2007) associated with ICA occlusion, who were referred to the Department of Neurology, University Medical Centre Utrecht, The Netherlands. All patients had been symptomatic in the 6 months prior to the time of referral. Data, including the presence of limb-shaking, had been collected prospectively by two vascular neurologists (L.J.K. and C.J.M.K.). Limb-shaking was defined as brief, jerky, coarse, involuntary movements of an arm or leg or both (Baquis et al., 1985). All patients were specifically asked for these symptoms of limb-shaking, and if present they were interviewed in detail about the duration, frequency and location of the limb-shaking, the presence of weakness accompanying the limb-shaking, and for precipitating factors such as rising, exercise, coughing, a meal, hyperextension of the neck, transition from a cold to warm environment or taking anti-hypertensive medication. In addition, we documented whether additional cerebral or retinal ischaemic symptoms (retinal infarction or transient monocular blindness) were present.

The protocol for the current study was prepared after collection of all data, but before the analysis was performed. For each patient with limb-shaking we randomly selected two controls, matched for sex and age, who had presented during the same period with cerebral TIA (lasting < 24 h) or moderately disabling ischaemic stroke (modified Rankin scale ≤ 3) associated with ICA occlusion, but who had not reported limb-shaking. The ICA occlusion was demonstrated by the absence of filling of the ICA by contrast angiography, or in one patient by absence of flow in the ICA on magnetic resonance angiography. The degree of an additional stenosis in the contralateral ICA, ipsilateral external carotid artery or vertebral artery was measured according to the North American Symptomatic Carotid Endarterectomy Trial criteria (Fox, 1993). Patients with an ICA occlusion caused by a dissection or a radiation-vasculopathy were not included. In patients and controls, we investigated the presence of vascular risk factors as listed in Table 2. The mean arterial blood pressure was calculated by two times the diastolic pressure plus the systolic pressure divided by 3, and expressed in mmHg. All patients underwent MRI or CT of the brain to investigate the presence of a symptomatic infarct. Infarcts were considered symptomatic if the location corresponded with the patients’ symptoms and were classified as territorial, watershed, large subcortical or lacunar (diameter ≤ 15 mm) (Damasio, 1983).

Collateral blood flow

Patients had contrast angiography to confirm the ICA occlusion and to visualize the collateral blood flow patterns. Collateral blood flow pathways were studied for the symptomatic hemisphere. We considered collateral blood flow via the ophthalmic artery as present if selective catheterization of the common carotid artery showed filling of intracranial arteries distal to the carotid siphon via the external carotid artery. Collateral pathways via the anterior communicating artery or the posterior communicating artery were considered present if these collateral pathways showed filling of the anterior or middle cerebral artery (MCA) branches ipsilateral to the symptomatic ICA occlusion. Leptomeningeal collaterals were considered present if pial branches from the posterior cerebral artery extending as far as the vascular territory of the MCA or anterior cerebral artery (beyond the usual posterior cerebral artery territory) were visualized on the angiogram after selective catheterization of one of the vertebral arteries (Fig. 1) (Brozzi et al., 2003).

Transcranial Doppler CO2-reactivity

Transcranial Doppler (TCD) was performed with measurement of the CO2-reactivity to investigate cerebrovascular reserve capacity. Details of this protocol have been described before (Klijn et al., 2000). The CO2-reactivity after carbogene inhalation was the relative change in blood flow velocity in the MCA and expressed as a percentage. A CO2-reactivity of < 20% was considered abnormal, since this value corresponds with the mean CO2-reactivity minus two times the standard deviation (SD) in normal controls (Klijn et al., 2001).

Data analysis

We compared clinical characteristics, vascular risk factors, the presence and type of cerebral infarcts, the presence of a stenosis or occlusion in the contralateral ICA, external carotid artery or vertebral arteries, collateral blood flow pathways, and CO2-reactivity between patients with and without limb-shaking and expressed differences as odds ratios (ORs) with 95% confidence intervals (CIs). In a subgroup-analysis, patients with limb-shaking TIAs were compared with control patients.
with TIAs without limb-shaking (excluding control patients with ischaemic stroke). We used logistic regression analysis to study the effect of the time interval between the patient’s last ischaemic symptoms and the CO₂-reactivity measurement on the association between limb-shaking TIAs and CO₂-reactivity and expressed this adjusted association as OR per 1% increase in CO₂-reactivity. Finally, we assessed the relationship between CO₂-reactivity and leptomeningeal collaterals by a multivariable regression model. The study was approved by the institutional review board of the University Medical Centre Utrecht.

Results

Of the 313 patients with symptomatic ICA occlusion, 34 (11%) reported limb-shaking. The characteristics of limb-shaking are shown in Table 1. The duration of limb-shaking was shorter than 5 min in the majority of patients. Most patients reported multiple episodes of limb-shaking. The arm was more frequently involved than the leg. In almost one-third of patients the arm and leg shook simultaneously. Most patients demonstrated shaking of their whole limb and not just the hand or foot. During or following limb-shaking, 28 (82%) of the 34 patients noticed a transient paresis of their arm or leg. In 14 (41%) patients, limb-shaking occurred subsequent to precipitating factors such as rising, exercise or coughing (Table 1). Table 2 shows the characteristics of the patients with limb-shaking and of controls. The presence of vascular risk factors was similar in patients with limb-shaking and controls, except for a history of hypertension that we found more often in patients with, than in those without, limb-shaking TIAs (OR 4.3, 95% CI 1.5–12.5). All patients with limb-shaking also reported symptoms other than limb-shaking; 27 (79%) patients had additional TIAs without limb-shaking (reported symptoms, isolated or combined, were paresis of a limb in 24, sensory symptoms in 12, dysphasia in 6 and dysarthria in 2 patients), and seven (21%) patients had additional permanent deficit caused by a minor ischaemic stroke characterized by isolated or combined symptoms of paresis of a limb in six, sensory symptoms in one, and dysphasia in four patients. In the control group, 22 (32%) patients had presented with cerebral TIA and 46 (68%) patients with ischaemic stroke. Compared with controls, patients with limb-shaking more frequently presented with TIAs than with ischaemic stroke (OR 8.1, 95% CI 3.0–21.4), and more
often had additional retinal ischaemic symptoms (OR 3.6, 95% CI 1.2–10.6). Precipitating factors that may compromise cerebral perfusion, such as rising or exercise, were more often—but not always—present in patients with limb-shaking than in controls (OR 14.2, 95% CI 4.2–47.9). Patients with limb-shaking TIAs more frequently had recurrent ischaemic deficits after documented ICA occlusion (but before inclusion in the study) than control patients without limb-shaking (OR 8.2, 95% CI 2.3–29.3). Patients with limb-shaking less often had an infarct on their MRI or CT compared to controls (OR 0.2, 95% CI 0.1–0.6) and more often a stenosis or occlusion in one of the vertebral arteries (OR 4.0, 95% CI 1.5–10.4). Patients with limb-shaking were seven times more often dependent on leptomeningeal collaterals than controls (OR 6.8, 95% CI 2.0–22.7, Table 3). We found a CO2-reactivity <20% ipsilateral to the ICA occlusion in 24 (83%) patients with limb-shaking and in 43 (68%) patients without limb-shaking (OR 2.2, 95% CI 0.7–6.7). On average, CO2-reactivity in patients with limb-shaking (mean 5% ± 16) tended to be lower than in those without limb-shaking (mean 12% ± 17; OR 0.97 per 1% increase in CO2-reactivity, 95% CI 0.94–1.00). The median time interval between the most recent symptom and the CO2-reactivity measurement was 18 (range 0–140) days in patients with limb-shaking and 57 (range 0–206) days in patients without limb-shaking. After adjustment of the OR for this time interval, the finding of a lower CO2-reactivity in patients with limb-shaking TIAs lost significance in comparison with controls (adjusted OR 0.98 per 1% increase in CO2-reactivity, 95% CI 0.95–1.01).

In the subgroup analysis of patients with limb-shaking TIAs in comparison with control patients with TIAs without limb-shaking (excluding control patients with ischaemic stroke) leptomeningeal collaterals were more frequent in patients with limb-shaking (21 of 25, 84%) compared with patients without limb-shaking (6 of 16, 38%; OR 8.8, 95% CI 2.0–38.1). The mean CO2-reactivity in patients with limb-shaking TIAs was significantly lower than the mean CO2-reactivity in patients with TIAs without limb-shaking (5% ± 16 versus 17% ± 18; OR 0.96 per 1% increase in CO2-reactivity, 95% CI 0.92–0.99). Also in this subgroup analysis, the association between limb-shaking and a low CO2-reactivity was dependent on the time interval (adjusted OR 0.96 per 1% increase in CO2-reactivity, 95% CI 0.93–1.00).

In a multivariable analysis including the factors leptomeningeal collaterals and CO2-reactivity, the significant relationship between leptomeningeal collaterals and limb-shaking (OR 7.0, 95% CI 1.7–28.4) remained, as well as the trend for a lower CO2-reactivity in patients with limb-shaking TIAs in comparison with those without limb-shaking (OR 0.96 per 1% increase in CO2-reactivity, 95% CI 0.92–1.00). This trend was no longer apparent after adjustment for the time interval between the last symptoms and TCD (adjusted OR 0.97 per 1% increase in CO2-reactivity, 95% CI 0.92–1.01).

**Discussion**

This study shows that limb-shaking in patients with ICA occlusion usually lasts less than 5 min, is often accompanied by paresis of the involved limb and is often, but not necessarily precipitated by activities that may compromise cerebral perfusion such as rising, exercise or coughing. In comparison with patients with ICA occlusion without limb-shaking, patients with limb-shaking are about seven times more often dependent on leptomeningeal collaterals and tended to have a lower CO2-reactivity. Compared with controls with TIAs without limb-shaking and no ischaemic stroke, the patients with limb-shaking TIAs had a significantly lower mean CO2-reactivity. The time period between the last symptoms and the CO2-reactivity measurement was shorter in patients with than in those without limb-shaking (OR 0.96 per 1% increase in CO2-reactivity, 95% CI 0.92–1.00).
Compared with previous small case series of 5–12 patients (Baquis et al., 1985; Yanagihara et al., 1985; Baumgartner and Baumgartner, 1998), we were able to identify a relatively large group of patients with limb-shaking. We confirmed that limb-shaking TIAs occur in about 10% of patients with occlusion of the ICA (Bogousslavsky and Regli, 1986). The underlying mechanism of limb-shaking is unclear, but most studies suggest that the shaking movements are caused by transient focal cerebral ischaemia (Baquis et al., 1985; Yanagihara et al., 1985; Tatemichi et al., 1990; Firlik et al., 1996; Baumgartner and Baumgartner, 1998; Salah Uddin, 2004). Limb-shaking TIAs may resemble epileptic seizures but can be distinguished by a normal level of consciousness, precipitation of symptoms by specific circumstances that may lower cerebral blood flow in patients with ICA occlusion, such as rising or exercise, the absence of tonic contractions or a march of symptoms, no involvement of the face or trunk, and no epileptic discharges on an EEG (Yanagihara et al., 1985; Baumgartner and Baumgartner, 1998; Schulz and Rothwell, 2002). Various other hyperkinetic movements such as hemidystonia and hemichorea-hemiballism have also been described in relation to TIA or stroke (Ghika-Schmid et al., 1997; Shimizu et al., 2001; Kim, 2001; Salah Uddin, 2004), but they are exceedingly rare with a prevalence of 1% in acute stroke (Ghika-Schmid et al., 1997). In addition, those hyperkinetic movement disorders seem to be related to an ischaemic lesion in the basal ganglia or thalamic nuclei in the majority of patients (Ghika-Schmid et al., 1997; Kim, 2001), whereas a specific location of cerebral ischaemia in patients with limb-shaking has not been found thus far.

Previous studies concluded that limb-shaking TIAs are likely to be caused by a low flow state of the brain and not by emboli, based on diminished vasomotor reactivity by TCD (Tatemichi et al., 1990; Baumgartner and Baumgartner, 1998; Niehaus et al., 1998) and cerebral blood flow by Xenon inhalation (Yanagihara et al., 1985; Tatemichi et al., 1990). However, of patients with ICA occlusion in general, 12% had an exhausted and 29% a diminished CO$_2$-reactivity when investigated by TCD.

Table 2: Characteristics of patients with symptomatic ICA occlusion with (n = 34) and without (n = 68) limb-shaking, matched for age and sex

<table>
<thead>
<tr>
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<th>Limb-shaking group (n = 34)</th>
<th>Control group (n = 68)</th>
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<tbody>
<tr>
<td>Mean age (years ± SD)</td>
<td>62 ± 7.6</td>
<td>62 ± 7.3</td>
</tr>
<tr>
<td>Male</td>
<td>28 (82%)</td>
<td>56 (82%)</td>
</tr>
<tr>
<td>Cigarette smoking in the last 5 years</td>
<td>29 (85%)</td>
<td>49 (72%)</td>
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<tr>
<td>Hypertension</td>
<td>29 (85%)</td>
<td>39 (57%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>30 (88%)</td>
<td>60 (88%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (18%)</td>
<td>17 (25%)</td>
</tr>
<tr>
<td>History of ischaemic stroke (&gt;6 months ago)</td>
<td>7 (21%)</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>History of ischaemic heart disease</td>
<td>9 (27%)</td>
<td>19 (28%)</td>
</tr>
<tr>
<td>History of peripheral vascular disease</td>
<td>14 (41%)</td>
<td>23 (34%)</td>
</tr>
<tr>
<td>History of vascular disease in first-degree relative</td>
<td>26 (77%)</td>
<td>43 (63%)</td>
</tr>
</tbody>
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**Clinical features**
- Cerebral TIA without limb-shaking
  - 27 (79%)$^b$
  - 22 (32%)
- Ischaemic stroke
  - 7 (21%)
  - 46 (68%)
- Additional retinal ischaemic symptoms
  - 10 (29%)$^b$
  - 7 (10%)
- Ischaemic symptoms after documented occlusion
  - 31 (91%)$^b$
  - 38 (56%)
- Precipitating factors$^d$
  - 16 (47%)$^b$
  - 4 (6%)
- Mean arterial pressure (mmHg ± SD)
  - 112 ± 15
  - 116 ± 16

**Infarcts**
- Symptomatic infarct$^e$
  - 16/33 (48%)$^b$
  - 54/68 (79%)
- Territorial
  - 3 (19%)
  - 19 (35%)
- Watershed, cortical
  - 6 (38%)
  - 19 (35%)
- Watershed, deep
  - 0 (0%)
  - 2 (4%)
- Large subcortical
  - 3 (19%)
  - 5 (9%)
- Lacunar
  - 4 (25%)
  - 9 (17%)

**Cerebropetal arteries**
- Contralateral ICA occlusion
  - 5/34 (15%)
  - 12/68 (18%)
- Contralateral ICA stenosis 50–99%
  - 7/34 (21%)
  - 27/68 (40%)
- Stenosis >50% or occlusion ipsilateral of ECA
  - 6/33 (18%)
  - 8/67 (12%)
- Stenosis >50% or occlusion of vertebral artery
  - 15/27 (56%)$^b$
  - 15/63 (24%)

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$^a$ Defined as a blood pressure >160/95 mmHg or the current use of anti-hypertensive medication.

$^b$ Comparison patients with and without limb-shaking, P < 0.05.

$^c$ Defined as patients with either a history of hyperlipidaemia, patients on drugs because of hyperlipidaemia or patients with levels of cholesterol, triglycerides, or high density lipoprotein cholesterol beyond the normal ranges.

$^d$ In 14 patients the limb-shaking was precipitated by activities that may compromise cerebral perfusion, in two patients only additional TIAs without limb-shaking were precipitated by rising. In the control-group symptoms were precipitated by rising in two patients and by exercise in two patients.

$^e$ 94 patients had an MRI scan of their brain, seven patients a CT scan and in one patient a recent CT or MRI scan could not be performed.

ECA = external carotid artery.
b CO2-reactivity is expressed as OR per 1% increase in CO2-reactivity.
we only classified the symptomatic infarcts, whereas patients with ICA occlusion often have asymptomatic ischaemic lesions in the deep watershed area.

Fourth, the current study inevitably had some element of retrospective ascertainment of the data, as it was not yet designed at the beginning of the prospectively collected series of patients with a symptomatic ICA occlusion. Fifth, we did not perform an inter-observer study with respect to the clinical diagnosis of limb-shaking. This might have influenced the frequency of limb-shaking in our series, although we strictly defined the criteria for this diagnosis before inclusion of patients. Finally, we did not perform EEG in all patients to confirm the absence of epileptic discharges at the time of limb-shaking.

In conclusion, we have further characterized the clinical features of limb-shaking TIAs that may improve their recognition by clinicians. Our results indicate that patients with an ICA occlusion and limb-shaking have a particularly impaired flow state of the brain compared with patients with ICA occlusion without limb-shaking. Whether the presence of a similar clinical feature such as limb-shaking can be used to identify the patient who might benefit from a revascularization procedure remains to be determined.

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