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### Hyperventilation-Enhanced Chorea as a Transient Ischaemic Phenomenon in a Patient with Moyamoya Disease

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#### Introduction

Moyamoya disease is a relatively rare and eventually underdiagnosed cerebral vasculopathy of unknown aetiology, which is characterised by progressive bilateral narrowing or occlusion of the terminal portion of the internal carotid artery and the proximal part of the anterior and middle cerebral artery, with the concomitant development of an abnormal meshwork of basal collateral vessels. The disease may also involve the posterior circulation, most commonly the posterior cerebral artery. The first symptoms usually become clinically evident and diagnosis is made during childhood or in young adult life. Epileptic seizures, migrainous headaches, transient ischaemic attacks or ischaemic strokes in children and haemorrhagic strokes in adults are the cardinal initial manifestations of this uncommon cerebrovascular disease [1–4]. Involuntary movements, such as dyskinesia, chorea or hemiballismus [1, 5], behavioural disturbances [6], neuropsychological deficits and mental deterioration [7] have rarely been described. Moyamoya disease has to be distinguished from the secondary moyamoya syndrome, which occurs mostly unilaterally and is associated with a series of other diseases [1, 8, 9]. The clinical differentiation is not easy since the symptoms of both entities are similar. Moyamoya disease has been predominantly described in Japan and other Asian countries [1, 2]. Smaller case series from the United States, Canada and Europe indicate a significantly lower incidence and prevalence of moyamoya disease outside Japan [10–12]. Another typical difference is that the distinction between childhood and adulthood cases that characterises the Japanese moyamoya disease is less clear in western populations. We describe a case of moyamoya disease with choreatic movements, which get dramatically enhanced by hyperventilation.

#### Case Report

A 28-year-old Caucasian woman reported involuntary movements of the extremities. The movements were brief, irregular and more prominent on the right side of the body. She had first noted these abnormal movements during and after coitus about 1 year before presentation in our department. In the meantime, similar phenomena were also observed during jogging or walking up the stairs. They had become more frequent and intensive. They were all

obviously provoked by conditions of hyperventilation and they all ceased after a few minutes of resting. In several cases, these episodes were accompanied by numbness on the right half of the body. From the age of 5, the patient had suffered from typical migraine attacks, which had become more frequent and severe since adolescence. She was not on any kind of medication and her family history was free of movement disorders or cerebrovascular diseases.

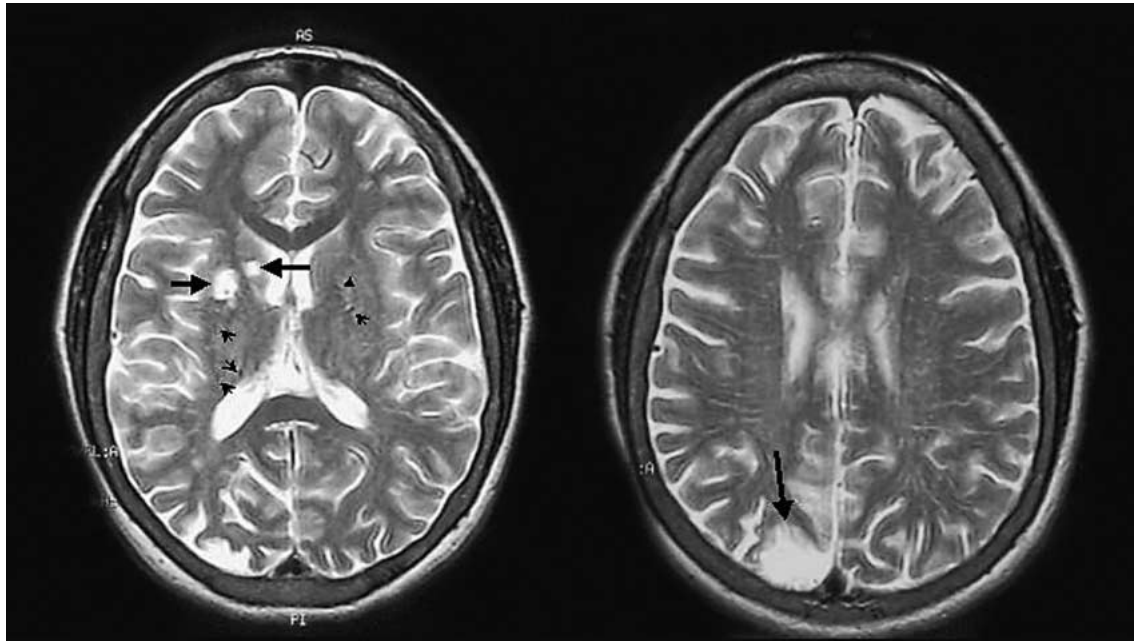
The orientating neurological examination revealed no pathological findings. However, bilateral fine wavering movements of the hand and fingers, the neck and the shoulder girdle were seen after careful observation in the supine resting position or on active posture conditions. Forced hyperventilation of about 15 s enhanced these movements dramatically. They became more prominent on the right side presenting typical choreatic characteristics, including leg and arm as well as the neck and face. She was at no time able to control these movements. She also reported numbness of the entire right half of her body. During hyperventilation and several minutes afterwards and while the choreatic movements still persisted, the patient made a frightened impression. Her speech was silent and slightly dysarthric. However, she remained fully alert and followed accurately orders of all kind. All these symptoms resolved completely almost 10 min after terminating hyperventilation. Repeated short periods of forced hyperventilation led to identical episodes. General physical and neuropsychological examinations were normal.

The EEG disclosed left hemispheric slow waves, which increased as a 'build up' phenomenon with the appearance of delta-waves during hyperventilation. Magnetic resonance imaging (MRI; T<sub>2</sub>-weighted images) showed ischaemic lesions in the right basal ganglia and the right hemispheric parieto-occipital cortex and the immediate subcortical structures, as well as bilateral enlargement of the lenticulostriatal arteries (fig. 1).

Digital subtraction angiography showed a complete occlusion of the supraclinoidal part of both internal carotid arteries. A rich collateral network was seen. It involved the ophthalmic arteries and pial collaterals arising from the external carotid arteries. The anterior and middle cerebral arteries were opacified via leptomeningeal collaterals. The same pattern with hypertrophy of meningeal vessels and collaterals arising from both posterior cerebral arteries and reaching the basal ganglia was seen in the posterior circulation (fig. 2).

Transcranial Doppler revealed low flow velocities (30–35 cm/s) in the middle cerebral artery (depth 55 mm). This finding is in accordance with the angiographically documented, more proximally localised occlusive disease. During forced hyperventilation, a marked increase in the flow velocity up to 55 cm/s was documented, indicative of vasoconstriction. As the maximum increase in registered flow velocity was reached, the patient presented the above-described choreatic movements. This constellation was reproduced identically on three occasions.

B-mode Doppler examination of the extracranial portion of the carotid and vertebral arteries revealed no atherosclerotic lesions or signs of wall dissection. Transthoracic echocardiography, 24-hour



**Fig. 1.** T<sub>2</sub>-weighted axial MRI showing ischaemic lesions in the basal ganglia, the parieto-occipital cortex and the immediate subcortical structures of the right hemisphere (arrows) and bilaterally enlarged lenticulostriatal arteries with characteristic signal void (arrowheads).

blood pressure and heart rate monitoring also revealed normal findings. Baseline blood tests, platelet sedimentation rate, C-reactive protein, protein C, protein S, antithrombin III, fibrinogen, plasminogen levels and activated protein C resistance were all within normal range. Antibody screening including p-ANCA, c-ANCA, ANA, AMA, ASMA, anti-ds-DNA, ACA and anti-TPO was negative. These findings practically excluded all possible causes of moyamoya syndrome and established the diagnosis of moyamoya disease.

#### Discussion

We report the case of a Caucasian female with moyamoya disease. Diagnosis was made at the age of 28 and relied on the typical vascular imaging findings. The visualised bilateral intracranial occlusive vascular disease with the presence of the characteristic meshwork of fine-calibre collateral vessels (moyamoya = puff of smoke) allows the certification of the diagnosis of moyamoya disease. The absence of other concomitant diseases, such as protein C, protein S and plasminogen deficiency, vasculitis, systemic lupus erythematosus, Sjögren syndrome, thalassaemia, sickle cell disease atherosclerosis, dissections and infectious diseases, exclude the alternative of moyamoya syndrome.

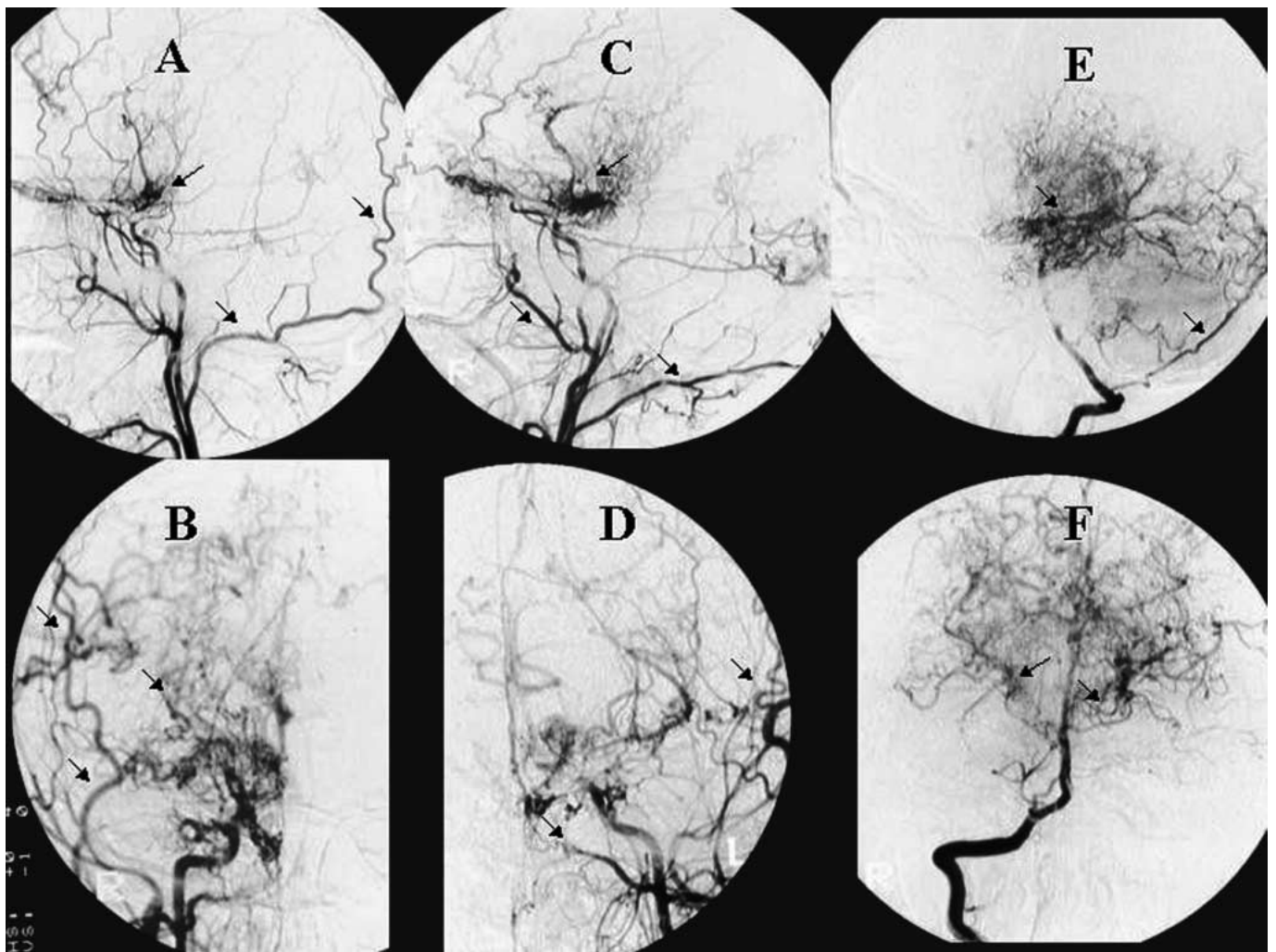
In the present case, the patient reported having had migrainous headaches since the age of 5, which were later accompanied by visual field defects leading to the diagnosis of complicated migraine. Similar phenomena are typical first manifestations of moyamoya disease in children [1, 3, 13], which however get usually underestimated because of the little awareness of the disease among neurologists and paediatricians. This was obviously the case in our patient. We assume that the reported headaches were the initial manifestation of this in Europe and Greece highly uncommon disease, which was not

suspected and investigated by the treating paediatrician. As proved by means of MRI, this young patient had also suffered from clinically silent ischaemic strokes, which are also typical for juvenile onset moyamoya disease [1, 3].

The patient was forced to visit a neurologist at the age of 28 due to the newly observed and rather aggravating involuntary choreatic movements. The differential diagnostic thought of paroxysmal dyskinesias, such as paroxysmal kinesigenic or dystonic choreoathetosis, paroxysmal exercise-induced dystonia could not be supported because of the relatively late symptom onset [14].

A typical characteristic of these uncommon movement disorders was their occurrence after short-lasting intensive body exercise. They were all obviously provoked by repeated conditions of hyperventilation and they all ceased after several minutes of resting. These facts could suggest an underlying ischaemic pathophysiology induced by hyperventilation-mediated vasoconstriction of intracerebral arteries supplying the basal ganglia and a subsequent hypofunction of the striatal indirect pathway [15]. A similar case of singing-induced choreatic movements in a moyamoya patient from Korea has recently been reported [16]. Hyperventilation-induced limb-shaking transient ischaemic attacks have also been attributed to a similar pathogenic mechanism, which however caused hypoperfusion of the frontoparietal cerebral cortex in a Korean patient with moyamoya disease [17].

This hypothesis of hyperventilation-induced hypocapnia leading to vasoconstriction of small cerebral vessels was supported by the simultaneous presentation of intensive choreatic movements and the hyperventilation-mediated increase in cerebral blood flow velocity in branches of the middle cerebral artery, as documented by means of transcranial Doppler recording during resting and forced hyperventilation. There is, however, an atypical phenomenon, which is difficult



**Fig. 2.** Lateral (**A, C**) and anterior-posterior (**B, D**) carotid angiogram demonstrating complete occlusion of both internal carotid arteries. The pathognomonic vascular network moyamoya at the basal ganglia (arrowheads) can be seen. An extensive network of collaterals (arrows) is described and involves the ophthalmic arteries and pial collaterals arising from the external carotid artery. Lateral (**E**) and anterior-posterior (**F**) angiogram of the right vertebral artery shows the same pattern with hypertrophic leptomeningeal vessels and collaterals (arrows) and the typical vascular network moyamoya at the basal ganglia (arrowheads).

to explain. The right-sided prominence of the clinical features was ipsilateral to the ischaemic lesions demonstrated on MRI. That means that the observed symptoms cannot be attributed to the visualised parenchymatous defects. We can only assume that left-sided insufficiency of basal collaterals occurring under conditions of hypocapnia-induced vasoconstriction is the cause of the right lateralisation of the symptoms. This hypothesis is supported by the left hemispheric slow waves as a build-up phenomenon in the EEG during hyperventilation. These changes have been previously described in patients with moyamoya disease and appear to be related to a focal reduction in perfusion reserve, which is caused by hyperventilation-induced vasoconstriction [18]. The collateral supply of the basal ganglia in the right hemisphere should then be more stable, although

there are ischaemic lesions, which seem to be clinically silent. This could be a probable explanation for this side difference.

#### *Conclusion*

Chorea is a comparatively rare clinical feature of moyamoya disease and moyamoya syndrome, which in few cases seems to be the initial manifestation leading to the diagnosis [5, 15, 16, 19, 20]. This case demonstrates the need to include this uncommon pathological entity in the differential diagnosis of juvenile or adult onset chorea. Although rare and perhaps underdiagnosed, moyamoya disease should not be considered as an exotic diagnosis and should be regarded as a differential diagnostic alternative especially in atypical neurological syndromes occurring in children and young adults. It

also points out the possibility of an underlying transient ischaemic pathophysiology that would explain the described choreatic movements, which could be induced by insufficiency of the collateral arteries supplying the basal ganglia after hyperventilation- and hypoxia-mediated vasoconstriction.

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### A Case of Hemiparkinsonism following Ischemic Lesion of the Contralateral Substantia nigra: A PET Study

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#### Introduction

Parkinsonism associated with focal lesions localized in the substantia nigra (SN) has rarely been reported [1–3]. Careful investigation of such patients can provide important information to facilitate understanding of the pathophysiology of parkinsonian features such as tremor at rest and cogwheel rigidity. Moreover, positron emission tomography (PET) can be used to determine the pathophysiology of nigrostriatal dopaminergic function of patients with SN lesions. We report a 71-year-old woman with hemiparkinsonism whose brain magnetic resonance imaging (MRI) demonstrated ischemic lesion of the contralateral SN and neighboring regions. A PET study showed denervation of the presynaptic nerve terminals together with supersensitivity of the postsynaptic nerve terminals in the ipsilateral striatum. These results account for parkinsonian features of the present patient, such as tremor at rest and cogwheel rigidity, as well as the effectiveness of levodopa.

#### Case Report

A 71-year-old right-handed woman was admitted for evaluation of tremor at rest of the left hand in July 2001. She had noticed weakness in her left leg 7 years earlier, followed by recovery within 1 month. Around 2 months later, she noticed tremor in her left hand, which persisted for 7 years. There was no relevant history of trauma, encephalitis, or manganese intoxication, and there were no current medications. Physical examination did not demonstrate abnormality other than a mild systolic murmur. Neurological examination demonstrated tremor at rest, mild postural tremor, and cogwheel rigidity in the left extremities, which was more evident in the arm. Deep tendon reflexes in the lower extremity were slightly brisk, but plantar reflexes were flexor. Gait, cerebellar signs, and sensory and autonomic symptoms were unremarkable. The following investigations showed normal or negative results: routine biochemistry, hematology, urinalysis, serological tests, cerebrospinal fluid, chest roentgenogram, and electrocardiogram. Head-up tilt test was normal. Surface electromyography showed a 4.5-cps rhythmic reciprocal discharge showing tremor. T<sub>2</sub>-weighted sequence (TR 3500, TE 112) of brain MRI demonstrated a high-intensity area in the right midbrain, right pons, and right middle cerebellar peduncle (fig. 1A). T<sub>1</sub>-weighted sequence (TR 500, TE 20) with and without gadolinium enhancement and diffusion-weighted imaging were unremarkable. The lesion did not change over an 18-month observation period. The patient has been treated with 200 mg/day of levodopa/carbidopa and has shown a positive and stable response until now.

The viability of presynaptic and postsynaptic dopamine neurons was evaluated by PET with [<sup>11</sup>C]-labeled 2β-carbomethoxy-3β-(4-fluorophenyl)-tropane (CFT) and [<sup>11</sup>C]-labeled raclopride (RAC), respec-

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