F Moriwaka, K Tashiro
School of Psychological Science, Health Sciences University of Hokkaido, Sapporo, Japan

Correspondence to: Dr I Yabe, Department of Neurology, Hokkaido University School of Medicine, N-15 W-7, Kita-ku, Sapporo 060-8638, Japan; yabe@med.hokudai.ac.jp

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Combination of thalamic Vim stimulation and GPi pallidotomy synergistically abolishes Holmes' tremor

The recent report of Kim *et al*,[1] who demonstrated that stereotactic surgical ablation of the thalamic nucleus ventrointermedius (Vim) markedly improved Holmes' tremor in a patient with midbrain tumour, corroborated our earlier findings.[2] In their patient, Vim thalamotomy alleviated tremor in both the distal and proximal segments of the upper extremity.[1] However, controversy continues to surround the advisability of using this procedure for proximal tremors because the placement of larger lesions carries increased risks and the somatotopy of the proximal or truncal muscles remains obscure in the human Vim.[3–5] Here we present a patient with a pontine haemorrhage in whom the combination of thalamic Vim deep brain stimulation (DBS) and globus pallidus internus (GPi) pallidotomy abolished Holmes' tremor.

This 53 year old right-handed man with a history of essential hypertension suddenly developed right hemiparesis and cerebellar ataxia in February 2000. He was admitted to a hospital where radiological examinations showed a left upper brainstem haemorrhage (fig 1A). His neurological state gradually improved. However, in October 2001 a coarse, slowly progressive tremor arose in his right upper extremity. It was severely disabling and he could not use his right arm. He was admitted to our hospital in December 2001.

On admission, he was alert and oriented. His speech was mildly dysarthric and slurred. There was palatal tremor. Mild hemiparesis with increased stretch reflexes and Babinski sign were noted on the right side. There were mild deficits of position, vibratory sense, and superficial sensation of light touch and pain in his right upper and lower extremities. Dysmetria was more pronounced on the right. Because of severe truncal and gait ataxia, he could not remain upright without support; he was unable to walk even with assistance. There was coarse and severe tremor in the right upper extremity. It persisted at rest and its amplitude increased during maintenance of a fixed posture and intentional voluntary movements. It rendered the right arm useless and prevented him from feeding and caring for himself. He was exhausted because of the severe tremor that persisted throughout his waking hours.

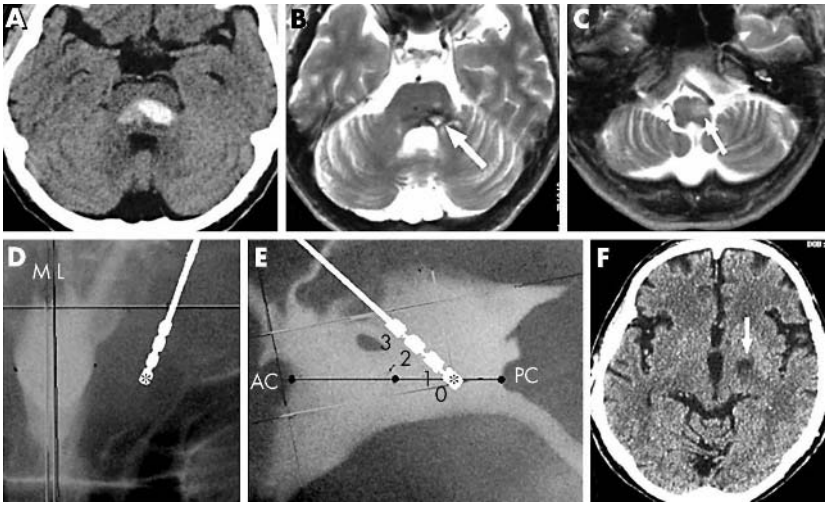

Figure 1 (A) Computed tomography (CT) scan showing a haematoma in the pontine tegmentum. (B, C) Axial views of T2-weighted magnetic resonance images at chronic stage (22 months after onset) demonstrating a haemosiderin ring around the lesion in the pontine tegmentum (B, arrow) and a high signal intensity area in the left inferior olivary nucleus indicating hypertrophic olivary degeneration (C). (D, E) Location of the electrode superimposed on the frontal (D) and lateral (E) view of a selective third ventriculography. The target point is indicated by the asterisk. (F) CT scan demonstrating the coagulative lesion made by the left GPi pallidotomy (arrow). The CT scan was carried out 10 days after pallidotomy. AC, anterior commissure; PC, posterior commissure; ML, midline.

Surface electromyograms showed rhythmic grouping discharges of 3.6 Hz in the right forearm muscles. His preoperative score on the Tremor Rating Scale (TRS)[6] for his right upper extremity (Part A, score 5) was 11. Magnetic resonance imaging (MRI) study (December 2001) showed a haemosiderin ring around the lesion in the left pontine tegmentum (fig 1B). On T2-weighted images, a high signal lesion was seen in the left inferior olive, as consistent with the hypertrophic olivary degeneration (fig 1C). As sequential pharmacotherapy using clonazepam (3×0.5 mg/day) and benserazide/levodopa (3×25/100 mg per day) was only slightly effective, he was referred for surgery. Prior informed consent was obtained from the patient and his family.

In January 2002, a quadripolar DBS electrode (Model 3387; Medtronic Inc., Minneapolis, MN, USA) was implanted in the left thalamic Vim nucleus with the aid of MRI, third ventriculography, and microelectrode guidance, as previously described.[2] The optimal target was determined to be 7 mm posterior and 14.5 mm lateral to the midpoint of the anterior to posterior commissure (AC–PC) line, and on the AC–PC line. The most ventral contact was placed precisely on the target point (fig 1D, E). As stimulation tests, performed for 5 days, confirmed the beneficial effects of DBS, a programmable pulse generator (Soletra, Model 7426; Medtronic Inc.) was implanted. His postoperative course was uneventful.

After extensive trials, stimulation was carried out using contacts 0 and 1 (fig 1D, E). The optimal stimulation parameters were determined to be 160 Hz frequency, 90 μsec pulse width, and 2.9 V and 3.4 V amplitude at the first and final session. Stimulation with amplitude exceeding 3.4 V induced unpleasant electrical paraesthesia on the right side of his face and right upper extremity. Under optimal stimulation, the tremor was markedly alleviated in the distal part of his right arm: the TRS score for his upper extremity tremor (Part A, score 5) was reduced to 6. Upon discontinuation of stimulation, the distal tremor reappeared immediately and returned to the preoperative state. The proximal tremor of his right arm was unresolved.

After discharge, he visited our outpatient department once a month. In January 2003, he complained of gradual worsening of the remaining proximal tremor; the distal tremor remained completely suppressed by thalamic Vim stimulation. We discussed GPi pallidotomy[5] and obtained informed consent prior to the procedure.

In April 2003, left GPi pallidotomy was performed according to the method we described previously.[7] The optimal target for the posteroventral part of the GPi was determined to be 2 mm anterior and 20 mm lateral to the midpoint of the AC–PC line, and 1 mm dorsal to the floor of the third ventricle. After creating a test lesion (42 ℃, 60 sec), a permanent anatomical lesion was made by heating the electrode tip to 72 ℃ for up to 70 sec. The electrode was moved in 2 mm increments in the medial, lateral, and dorsal directions, and the lesioning process was repeated to increase the overall size of the lesion (fig 1F). GPi pallidotomy completely abolished his proximal tremor. However, it produced only a small effect on his distal tremor and discontinuation of Vim stimulation resulted in its reappearance at almost the preoperative level. Without stimulation, the TRS score for his upper extremity tremor (Part A, score 5) was 5. The combination of Vim stimulation and GPi pallidotomy had synergistic effects in abolishing Holmes' tremor in our patient. The therapeutic benefits remain unchanged at the time of writing and the TRS score for his upper extremity tremor (Part A, score 5) is 0. His palatal tremor did not respond to Vim stimulation and pallidotomy and remains unresolved.

Stereotactic Vim surgery, either thalamotomy or thalamic stimulation, is a mainstay in the surgical treatment of parkinsonian or essential tremors.[8] Its efficacy in tremor suppression is superior to that of pallidotomy in parkinsonian patients. However, as evidenced by our case, it does not always produce satisfactory results in patients with Holmes' tremors, particularly with respect to their proximal tremors. The basal ganglia outflow pathway from the GPi exerts a direct influence on not only the thalamus but also the brainstem motor centres such as the pedunculopontine nucleus related to the mesencephalic tegmental field that controls the axial and proximal appendicular musculature via the descending reticulospinal tract. Therefore, unlike thalamic surgery, which interrupts the thalamocortical output that controls distal appendicular musculature via descending corticospinal and corticobulbar tracts, GPi pallidal surgery influences the control of otherwise inaccessible axial and proximal muscles. This may be the reason why GPi pallidotomy produced a marked alleviation of the proximal tremor in our patient. Due to the limited efficacy of thalamic Vim surgery on proximal tremors, the use of other or additional surgeries with greater effects—for example, pallidal surgery[5] or subthalamic area stimulation,[9] should be considered for the treatment of Holmes' tremor.

S Goto, K Yamada

Department of Neurosurgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

Correspondence to: S Goto, MD, PhD, Department of Neurosurgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto 860-8556, Japan; sgoto@kaiju.medic.kumamoto-u.ac.jp

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No association of the mitochondrial DNA A12308G polymorphism with increased risk of stroke in patients with the A3243G mutation

There is a striking phenotypic variability among patients with the A3243G $tRNA^{Leu(UUR)}$ gene mutation of mitochondrial DNA (mtDNA), the most common heteroplasmic mtDNA mutation. It is responsible for ~80% of cases of MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes), and is also associated with several other phenotypes including maternally inherited diabetes and deafness (MIDD) and chronic progressive external ophthalmoplegia (CPEO).[1]

Only 50% of patients carrying the A3243G mutation have stroke-like episodes[1 2] and the reason for this clinical variability remains poorly understood. Although the percentage level of the A3243G mutation in clinically relevant tissues appears to be important, this relationship is far from clear.[1] High percentage levels of the A3243G mutation in muscle are associated with stroke-like episodes, but approximately one in five patients harbouring >80% A3243G in muscle remain stroke free,[1] suggesting that additional environmental and genetic factors may influence the phenotypic expression of this mutation.

One possibility is that background mtDNA sequence variation influences phenotype. There is a well-recognised association between the mtDNA genetic background (or haplogroup) and the risk of developing visual failure in another mtDNA disorder, Leber's hereditary optic neuropathy,[3] and a similar mechanism may influence the incidence of stroke-like episodes in patients harbouring the A3243G mutation. Intrafamilial clustering of clinical phenotypes in A3243G patients would indirectly support a role for the mtDNA background, though our own clinical experience suggests that there is significant clinical variability between families.

Pulkes *et al* have previously reported an increased risk of stroke associated with the presence of a homoplasmic, polymorphic (A12308G) variant in 48 patients with the A3243G mutation.[2] The A12308G polymorphism, which is located in the second mitochondrial tRNA gene encoding leucine ($tRNA^{Leu(CUN)}$), occurs with a frequency of 21% in a population of European origin and defines the mtDNA super-haplogroup U/K together with two other polymorphisms (A11467G and G12372A). As haplogroup U has also been reported to be a risk factor for sporadic occipital stroke in patients with migraine,[4] these observations could have profound implications for our understanding of mitochondrial genotype and its relationship to the clinical phenotype. Here we report on the investigation of the A12308G polymorphism in a larger group of well-characterised, unrelated A3243G index cases.

Methods

We carried out a large, multicentre study to investigate the A12308G polymorphism in a group of 107 unrelated family index cases harbouring the A3243G mutation. The patients (>95% Caucasian) were from England, Germany, USA, Australia, and Finland. All presented to a neurology clinic, where stroke-like episodes were diagnosed clinically by experienced neurologists based upon a characteristic clinical history and brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI)[5]; in all cases, a molecular diagnosis of the A3243G mutation was made at a centre with expertise in the investigation of patients with mtDNA disorders.

To investigate the A12308G and G12372A polymorphisms, a 249 bp fragment spanning this mtDNA region was polymerase chain reaction (PCR)-amplified using a forward primer (5′ GATTGTGAATCTGACAACAGAGG CTT 3′; nt 12164–12189) and a reverse primer (5′ GGTTAACGAGGGTGGTAAGGATG 3′; nt 12412–12390). Amplified products were purified and sequenced using BigDye terminator cycle sequencing chemistries on an ABI 377 automated DNA sequencer (Applied Biosystems, Warrington, UK).

Results

The A12308G polymorphism was present in 32 of the 107 patients, while 56 had a history of stroke-like episodes. Nine of the 56 patients with a history of a stroke and 23 of 51 patients without stroke were shown to harbour the A12308G polymorphism. Every patient with the A12308G polymorphism also harboured the G12372A variant, indicating that they belong to the same mtDNA super-haplogroup U/K.

As shown in fig 1, our study alone revealed an apparent negative association between stroke-like episodes and the A12308G polymorphism, an observation in direct contrast to the positive association found by Pulkes *et al*.[2] Meta-analysis of all available data however, including the present study (n = 107) and the published study of Pulkes *et al*[2] (n = 48), revealed that 16 of the 77 patients with a history of a stroke and 25 of 78 patients without stroke harboured the A12308G polymorphism. This did not show a statistically significant association between the A12308G polymorphism and stroke-like episodes ($\chi^2 = 2.53$, p = 0.112).

Discussion

The aim of our study was to examine whether a previously described association between the A12308G polymorphism and an increased risk of stroke in patients with the A3243G mutation[2] was reflected in a larger study group. In agreement with previous reports, 52% of our patients experienced stroke-like episodes[1 2] and 30% harboured the A12308G polymorphism, confirming that our cohort of

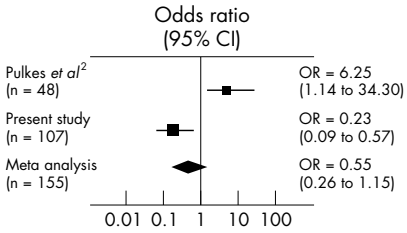

Figure 1 Meta-analysis showing odds ratios (OR) and 95% confidence intervals (CI) for the original study by Pulkes *et al*,[2] the data generated by this study, and the combined dataset including both studies. The squares represent the OR, with the size proportional to the study size. The horizontal lines show the CI for the OR. The diamond shows the OR for the combined dataset with CI that overlap 1, indicating a non-significant result.