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# Clinical/Scientific Notes

## Levodopa-Induced Ocular Dyskinesias in Parkinson's Disease

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**Abstract:** Levodopa-induced ocular dyskinesias are very uncommon. Usually they occur simultaneously with limb peak-dose choreatic dyskinesias. We report on a patient with leftward and upward deviations of gaze during the peak effect of levodopa, and hypothesize that a severe dopaminergic denervation in the caudate nucleus is needed for the appearance of these levodopa-induce ocular dyskinesias. © 2001 Movement Disorder Society.

Levodopa-induced dyskinesias (LID) are one of the most important problems in the practical management of patients with advanced Parkinson's disease (PD). More than 50% of parkinsonian patients will experience LID after 5 years of treatment with levodopa.[1] The physiopathology of LID is not completely understood. Depending on clinical presentation and chronology after a levodopa dose, LID can be classified in benefit (peak) of dose dyskinesias, diphasic (dyskinesias–improvement–dyskinesias) dyskinesias, and *off* period dyskinesias.[2] In most cases, LID involve the limbs, trunk, neck, and orofacial musculature. Disturbances in eyelid motor control, such as apraxia of eyelid opening or blepharospasm, may be seen in PD patients as a result of levodopa treatment. However, ocular dyskinesias are very uncommon.[3,4] We report on a patient with advanced PD and levodopa-induced ocular dyskinesias occurring simultaneously with generalized peak-dose chorea.

### Case Report

A 60-year-old man had gradual onset of rest tremor and rigidity in the left arm in 1975. Levodopa was started with a very good clinical response. After 3 years, he began to experience predictable motor fluctuations and peak-dose choreiform dyskinesias. These motor complications gradually worsened and eventually he developed unpredictable *on–off* fluctuations and biphasic dyskinesias. Other antiparkinsonian drugs, such as amantadine (300 mg/day), selegiline (10 mg/day), budipine (40 mg/day), and dopamine agonists (bromocriptine (30 mg/day), pergolide (up to 6 mg/day), cabergoline (4 mg/day), pramipexole (6 mg/day), and subcutaneous apomorphine (18 mg/day in three subcutaneous injections) were added to the levodopa regime without success. In the last 2 years he showed intermittent upward and leftward deviations of gaze (see Video). During the episodes he was unable to look forward and to voluntarily control the ocular movements. They appeared 2 hours after the intake of each levodopa dose and occurred simultaneously with generalized choreiform dyskinesias of moderate severity. The movements disappeared when the motor situation of the patient returned to the *off* state. There were not associated changes in pupils, nystagmus, or eyelid abnormalities. No vocalizations or other symptoms suggestive of tics were present. He is currently receiving levodopa-benserazide 800 mg/day in five doses, pramipexole 4.5 mg/day in three doses, budipine 30 mg/day in three doses, and amantadine 300 mg/day in three doses.

### Discussion

Abnormalities in the oculomotor control mechanisms of patients with PD are well recognized.[5,6] In general, the abnormalities described seem to be broadly compatible with the more general disorder of motor control (bradykinesia and hypokinesia) seen in this condition. Even ocular microtremor has been described.[7] Some of these oculomotor disturbances could be related to the pathogenetic process of the underlying disease and, at least in part, to the dopaminergic deficit. Indeed, Rascol and colleagues[8] showed that several saccade abnormalities were more severe in the advanced stages of the disease and they were improved by the administration of levodopa. By contrast, ocular dyskinesias have been very rarely reported. Shimizu and colleagues[3] described conjugate, large amplitude oscillations of gaze coinciding with the appearance of LID in other body parts. More recently, LeWitt[4] reported on two patients with intermittent upward and rightward deviations of gaze lasting for several seconds and occurring in unison with LID in the limbs. Our patient developed similar oculomotor alterations which can be considered as peak-dose dyskinesias: they occurred in the peak effect of each levodopa dose at the same time of choreic generalized dyskinesias and disappeared when the motoric effects of levodopa vanished and the patient returned to the *off* condition.

Differential diagnosis included postencephalitic parkinsonism with oculogyric crises[9] and oculogyric tics.[10–12] Our patient showed no clinical evidence of either of these two possibilities. Oculogyric crises were frequently seen in postencephalitic parkinsonism.[9] Levodopa sometimes exacerbated their severity, although continued therapy seemed to prevent their recurrence in some cases. Moreover, reported descriptions suggest that they consisted of a tonic gaze deviation of longer duration than the movements shown by our patient. In this sense, oculogyric crises seem to more resemble the conjugate gaze deviation seen in acute dystonic reactions.

A videotape accompanies this article.

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The physiopathology of ocular dyskinesias, as well as LID in other body parts, is not clear. As the abnormal eye movements coincided with dyskinesias in the limbs, it is likely that they share a common mechanism. Besides this, in the case of ocular dyskinesias, any proposed hypothesis should explain the following clinical facts: they are extremely rare, they occur simultaneously with dyskinesias in the limbs, they are not seen in isolation, and they are not seen in the early phase of the disease. One possible explanation for the characteristic features of levodopa-induced ocular dyskinesias in parkinsonian patients is that both the degree and the topographical distribution of dopamine depletion in the striatum play a crucial role in their origin.

Several data from animal and human studies suggest that nigrostriatal denervation is an obligated requirement to develop LID.[13–16] In PD, the loss of dopaminergic neurons in the nigrostriatal system results in a dorsoventral gradient of striatal denervation with greater loss of dopaminergic nerve terminals in the dorsolateral striatum than in the ventromedial part of the structure.[17,18] This gradient is related to the pattern of cellular loss in the substantia nigra pars compacta (SNpc) of parkinsonian patients, which is maximal in the ventrolateral tier (projects to the dorsal putamen) and less pronounced in the dorsal part of the nucleus (projects to the ventromedial zone of the putamen and to the caudate nucleus).[17,18] In vivo studies using PET scans have shown that [$^{18}$F]-fluorodopa uptake is severely impaired in the posterior part of the putamen of PD patients and it is less impaired in the caudate.[19] Thus, the decrease in dopamine content is lower in the caudate nucleus than in the putamen and it is well known that the caudate is the striatal portion in which the oculomotor circuit is centered.[20] The findings of Marconi and associates[21] support this hypothesis. In a detailed clinical–pharmacological study, those authors found that LID began in the foot. The foot is represented in the dorsal putamen, which receives the corticostriatal afferent fibers corresponding to the lower extremities and is the more denervated portion of the striatum.[22] After that, the concentration of dopamine increases gradually in the striatum and LID spread to other body parts, following a somatotopical order which is directly related to the degree of denervation. Therefore, it can be hypothesized that ocular dyskinesias will appear when the concentrations of dopamine in the caudate are very low. This could explain why ocular dyskinesias appear in patients with advanced PD and always follow the development of LID in the limbs and trunk. This hypothesis could also explain why ocular dyskinesias are so infrequent in PD and why they do not appear in isolation. PET scanning technology with the use of high-resolution cameras would be helpful in studying this hypothesis. The physiopathological relevance of the effects of levodopa/dopamine on other brain areas related to the control of ocular movements, such as the frontal eye fields (area 8), the substantia nigra reticulata, and some brainstem nuclei cannot be excluded and requires further investigation. These areas are closely linked to the caudate nucleus and some of them also receive dopaminergic innervation.[23]

## Legend to the Videotape

After 2 hours of intake of 200 mg of levodopa–benserazide, the patient develops generalized chorea (left arm choreic movements are shown) and upward and leftward deviations of gaze. He is unable to look forward and to voluntarily suppress the abnormal movements.

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# Levodopa-Induced Dyskinesias and Continuous Subcutaneous Infusions of Apomorphine: Results of a Two-Year, Prospective Follow-Up

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**Abstract:** Twelve patients with levodopa-induced dyskinesias were treated with continuous subcutaneous apomorphine. A markedly significant reduction in peak dose dyskinesias occurred over a two-year follow-up. © 2001 Movement Disorder Society

The beneficial role of apomorphine in the systematic treatment of Parkinson's disease (PD) has been suggested since 1951.[1] In the form of rescue injections or subcutaneous infusions, apomorphine helps patients to overcome the *off*-periods during the advanced fluctuating stage of the disease.[2–14] In recent years, the beneficial antidyskinetic (or "de-priming") effect of apomorphine monotherapy by continuous subcutaneous infusions of apomorphine has been newly demonstrated.[15] We assessed the effect of smaller amounts of apomorphine in subcutaneous infusions, administered for 2 years in fluctuating parkinsonian patients in whom the levodopa (L-dopa) daily dose was reduced.

## Patients and Methods

Twelve patients suffering from fluctuating advanced PD were followed-up for a period of 2 years. Four patients were men and eight were women, mean age 64.3 (SD = 9.2) years, mean age at onset of PD 49.8 (SD = 7.7) years. The mean duration of the disease was 14.4 (SD = 6.3) years, the mean duration of L-dopa treatment was 12.6 (SD = 5.4) years, and the mean duration of the complicated, fluctuating stage of PD was 3.6 (SD = 1.8) years. The mean total UPDRS score before the start of apomorphine treatment was 68.3 points (SD = 12.7), the mean Hoehn and Yahr scale value was 4.5 (range, 4–5). All patients were suffering from frequent *on-off* fluctuations, and from all types of L-dopa-induced dyskinesias:[16] peak-of-dose dyskinesias (n = 7), end-of-dose dyskinesias (n = 3), biphasic dyskinesias (n = 5) and *off*-period dyskinesias (n = 2). No patient received single-dose intermittent rescue injections of apomorphine before the start of treatment. The dopaminergic responsiveness was tested by an apomorphine challenge test prior to the introduction of infusion treatment.[17]

The apomorphine daily dose titration lasted basically 3 weeks, when the infusions were introduced during the stay at a hospital ward. The mean time needed to stabilize the dose in all patients was 8 weeks (range, 6–10 weeks).

The patients used at home self-scoring diaries for the self-assessment of *on-off* fluctuations, the duration of *off* periods, and the duration (and also severity) of all types of dyskinesias.[15] The patients and caregivers were instructed how to differentiate between the dyskinesia types. The self-assessment reports were then done at each outpatient visit. The motor disability was assessed by calculating the hours spent in the *off* phase during the day and it was also calculated as a percentage of the whole waking day; in the same manner the percentages of dyskinesias were calculated. Outpatient visits were scheduled monthly. Current parkinsonian status and the presence of side effects during the visit were recorded in the file. For an assessment during the outpatient visits the subscore for dyskinesias and clinical fluctuations (UPDRS IV) was adopted. Patient's caregivers and relatives were asked to come for the patient's visits and they were interviewed separately. All data were calculated and further analyzed at month 6, month 12, and month 24 of treatment and were compared with the baseline. The nonparametric Wilcoxon matched-pair test was adopted for the statistical analysis of results.

## Results

The results of the 2-year follow-ups are presented in the tables.

The mean daily dose of apomorphine (Table 1) remained essentially stable after the completion of titration phase (which has been taken as the onset for the next comparison and analysis) for the rest of follow-up period. The dose was only occasionally increased due to the worsening of a patient's parkinsonian state. No statistically significant differences were found between the mean apomorphine doses at onset, or at months 6, 12, and 24. The mean daily dose of L-dopa was slowly reduced in all patients during the first 6 months of apomorphine treatment; and the further reduction was only minimal. There was statistically significant difference between the mean daily dose of L-dopa at the onset and at months 12 ($P \geq 0.005$) and 24 ($P \geq 0.005$).

The mean value of the *off* hours (Table 2) was significantly reduced at month 6, and also at Months 12 and 24. The difference between the mean values of daily *off* hours at onset and at months 6, 12, and 24 was significant at the level of $P > 0.005$; the difference between the values at months 6 and month 12 or Month 24 was not significant.

There was also a certain reduction of *off* periods number (during the day) present. This number was found reduced at month 6 (mean 0.9/day) when compared with this number at onset of apomorphine treatment (mean 2.2/day). The difference was statistically significant only at the level of $P \geq 0.05$. There was practically no difference in this number when its mean values at months 6, 12, and 24 were compared.

The differences between the mean values of the UPDRS total score and subscores (Table 3) at onset and month 6, month 12, and month 24 were all also significant ($P \geq 0.005$). The total UPDRS score values differed significantly ($P \geq 0.005$) at months 6, 12, and also month 24. The differences between the values of UPDRS IV subscale at onset and at months 6, 12, and 24 were also significant ($P \geq 0.005$).

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**TABLE 1.** *Mean daily doses of apomorphine and L-dopa, and mean numbers of daily L-dopa intakes, calculated at onset and at months 6, 12, and 24*

| | Onset | Month 6 | Month 12 | Month 24 |
|---|---|---|---|---|
| Mean daily dose of apomorphine in continuous infusions, mg (±S.D.) | 30.8 (10.4) | 30.4 (11.9) | 30.4 (11.9) | 31.4 (12.2) |
| Mean daily dose of L-dopa, mg (±S.D.) | 1,650 (570) | 1,250 (640) | 1,150 (600) | 1,270 (750) |
| Mean number of L-dopa intakes per day | 7.5 | 6.6 | 6.9 | 7.0 |

The mean values of the daily duration of dyskinesias at the start of the titration phase and at months 6 and 12 were clearly different (Table 4). Virtually all patients suffered from peak-of-dose dyskinesia; the comparison of the percentage of dyskinetic time at onset and months 6, 12, and 24 were all statistically significant ($P \geq 0.01$); the differences between month 6 and month 12 or month 24 were not significant. The differences in the occurrence of biphasic dyskinesia at onset and at months 6, 12, and 24 were all significant ($P \geq 0.05$). The difference in the occurrence of end-of-dose dyskinesias and *off*-period dyskinesias were only just significant.

The side effects reported by patients were as follows: sleepiness in eight patients, vertigo in three patients, orthostatic hypotension in three patients, panniculitis at injection site (transient, treated by ultrasound) in one patient, rash at the injection site in one patient, and hallucinations also in only one patient.

## Discussion

The reduction of dyskinesias in our patients was achieved at the same time as the stabilization of L-dopa doses and daily doses of apomorphine, i.e., within 2–3 months. All patients showed substantial improvement in their dyskinesias by month 6. In eight patients, sustained *on* state was present during the whole day, without any *off* periods, and their parkinsonian state worsened only after withdrawal of the apomorphine. The mean number of *off* periods during the day was also reduced, but (probably due to the small numbers) the difference was significant only at the level of $P \geq 0.05$. The side effects observed in our group were practically only mild, and did not limit the apomorphine treatment in any patient.

The sustained and virtually unchanged effect of apomorphine treatment lasted the entire period of 2 years. The mean apomorphine dose, mean L-dopa dose, and the reduction of dyskinesias present at month 6 remained stable at months 12 and 24. Opposite observations were described in previous studies; worsening of the parkinsonian state during the infusions and also worsening of dyskinesias were reported.[6] Why the situation was different in our group is not completely clear. It is known that long-term levodopa treatment leads to further alterations in the balance of neuronal activity in the direct and indirect striatal outputs.[15,18,19] It has also been described that dopamine synthesis from L-dopa runs in this disease stage also in other cells that contain dopa-decarboxylase, and which normally are not equipped to store and release dopamine.[20] The dopamine level within the dopaminergic synapses then tends to fluctuate according to the plasma levodopa concentration. The result is the repeated sudden switching from the tonic phase of dopaminergic transmission in the nigrostriatal system to the phasic one, which subsequently leads to the development of motor fluctuations.[21] It has been described in rats that at least 95% of nigral cells must be lost to develop the motor fluctuations after L-dopa administration. L-dopa, administered in the continuous mode, broke up the dyskinetic periods in rat or monkey.[22–24] There is evidence also in humans that a continuous mode of dopaminergic stimulation, or rather, continuous administration of dopaminergic agents, prevented fluctuations in the patient. Such effects were described with subcutaneous infusions of lisuride and apomorphine and continuous intravenous infusions of L-dopa.[3,12,25]

To hypothesize about the pathophysiological basis of the effect of our combined treatment, one must look at the site where L-dopa and apomorphine act simultaneously. It is well-enough known that the fluctuations are a result of damage to the presynaptic as well as the postsynaptic parts of the nigrostriatal system.[26] In the generation of fluctuations and particularly dyskinesias, both presynaptic damage of nigral cells and functional changes of postsynaptic medium-sized spiny neurons are involved. This should mean that the dyskinesias should be suppressed not only by continuous apomorphine but also by combined therapy with levodopa and continuous apomorphine infusions. The dopamine depleted in striatum is substituted by peroral administration of L-dopa and the postsynaptic receptors are continuously stimulated by apomorphine. The proposed "dopamine receptor supersensitivity" might then be decreased due to this combined dopamine substitution.[27] This decrease in "receptor supersensitivity" could then cause the marked reduction of dyskinesia, particularly peak-of-dose and biphasic.

We also worked on the theory of a possible role of an

**TABLE 2.** *Mean values of* off *hours, calculated as a percentage of the waking day at onset and at months 6, 12, and 24*

| | Onset | Month 6 | Month 12 | Month 24 |
|---|---|---|---|---|
| Mean values of *off* hours during waking day, calculated as percentage (±S.D.) | 54.2 (18.3) | 13.8 (8.3) | 10.8 (5.2) | 10.9 (4.6) |

**TABLE 3.** *Mean values of UPDRS subscores and total UPDRS scores, calculated at onset and months 6, 12, and 24*

| Mean values of UPDRS subscores and total scores in points (±S.D.) | Onset | Month 6 | Month 12 | Month 24 |
|---|---|---|---|---|
| UPDRS subscore I & II | 27.8 (6.6) | 17.7 (5.7) | 17.8 (5.9) | 18.7 (6.8) |
| UPDRS subscore III | 29.7 (6.2) | 16.3 (6.8) | 15.6 (6.5) | 16.5 (7.1) |
| UPDRS subscore IV | 10.8 (1.2) | 5.4 (1.1) | 5.3 (1.2) | 5.4 (0.9) |
| UPDRS total score | 68.3 (12.4) | 39.5 (9.3) | 37.9 (8.2) | 38.1 (9.1) |

UPDRS, Unified Parkinson's Disease Rating Scale.

**TABLE 4.** *Mean values of duration of dyskinetic periods, calculated as a percentage of the waking day (±S.D.)*

| Type of dyskinesia | Number of patients | Onset | Month 6 | Month 12 | Month 24 |
|---|---|---|---|---|---|
| Peak-of-dose | 7 | 40.0 (20.8) | 17.7 (12.6) | 18.6 (10.4) | 15.6 (11.3) |
| End-of-dose | 3 | 13.3 (5.4) | 5.0 (3.4) | 0 | 0 |
| Biphasic | 5 | 36.0 (18.8) | 14.0 (7.1) | 11.0 (4.7) | 10.0 (5.0) |
| *Off*-period | 2 | 8.5 (2.0) | 4.5 (1.0) | 0 | 0 |

NMDA receptor blockade in the treatment of dyskinesias. It has been suggested that the known proximity of D2 and NMDA receptor structures in the body of striatal, medium-sized spiny neurons may be involved in that.[26,28–31] It has also been supposed that D2 receptor stimulation may block NMDA receptor system through the link between two neurotransmitter systems; thus, it might enable suppression of their ability to induce motor fluctuations.

Currently, it is difficult to provide some more plausible explanation for the described observations in our patients' group. However, our experience may serve as an alternative possibility of a combined treatment regimen for patients with debilitating fluctuations or dyskinesias with higher risk of side effects. The relatively lower dose of apomorphine in our patients was probably the cause of a low incidence of side effects; even the psychiatric side effects, usually described in apomorphine patients, were only rare and mild. Transient hallucinations were reported only by one patient.

The interesting feature of such a combined treatment is the stability of its effect. There were no signs of tachyphylaxis. Once the beneficial effect of apomorphine had been achieved, it remained relatively stable for the entire 2-year follow-up period, together with the dose of apomorphine. This observation has been made in other groups using apomorphine monotherapy;[15,32] however, further research will be necessary to assess this stability over a longer period of time.

Another interesting finding, particularly regarding the progressive character of PD, is the persistent reduction of UPDRS value without significant apomorphine dose escalation. One possible explanation is that our group consisted of severely affected patients, with a long disease duration. The progression in these stages is usually rather slow than quick.

The neuroprotective potential of apomorphine[33–35] remains unresolved. As we mentioned in our first-year report,[36] it is uncertain how substantial the neuroprotection could be in the late, advanced stages of the disease, when apomorphine is usually administered to the patients.

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## Postural Asymmetries Following Unilateral Subthalamotomy for Advanced Parkinson's Disease

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**Abstract:** Two cases of postural asymmetrics following unilateral subthalamotomy were observed with head and body tilting to the side contralateral to the STN lesion, which corrected itself completely or partially with levodopa treatment. After subsequent contralateral STN surgery, the postural asymmetry disappeared in both patients. Possible mechanism is discussed.


Postural asymmetry is a well-known phenomenon in advanced Parkinson's disease (PD), although few publications have been devoted to this subject. Lateral curvature of the spine with corresponding inclination of the trunk frequently directs to the side of the more dopamine-deficient hemisphere.[1] Even in mild unilateral PD, electronic sensors attached to patients' feet have detected spontaneous rotation toward the hemisphere of less striatal dopaminergic activity[2]; these changes occur without the patients' awareness. Patients with infarcts or hemorrhages in the vicinity of the ventrolateral nucleus of thalamus tend to fall to the side contralateral to the lesion when standing or even sitting.[3] Acute, unilateral lesions of the lenticular nucleus can produce a similar drift or tilt away from the side of the lesion.[4] Thus, there is ample evidence that the striatal dopaminergic system exerts a powerful influence on posture, but the exact neural pathway is poorly understood.

Postural deviation to one side in PD can convert to the contralateral side with progression of the disease.[1] In monkeys made parkinsonian with 6-hydrodopamine, there was head tilting and body rotation to the side of the lesion.[5] However, head position bias and direction of spontaneous rotation were dramatically changed to the contralateral side if additional subthalamus (STN) lesions were created.[5] It appears that postural asymmetry in primates and PD can be altered depending on the structure and the location of the lesion.

For advanced PD refractory to medical management, the surgical targets include the thalamus, globus pallidus interna (GPi), and STN. As seen in previous reports, PD patients who underwent ventrolateral nucleus thalamotomy could exhibit body tilting to the side contralateral to the surgery.[6,7] Pallidotomy for PD has not yet been reported to be associated with postural asymmetry. While an STN deep brain stimulator (DBS) has been generally favored in patients,[8] STN ablation may represent a safe, technically feasible, and less costly alternative.[9–11] We have encountered two patients who developed body tilt to the side contralateral to the surgery following unilateral ablation of STN for advanced PD. Both patients had postoperative magnetic resonance imaging (MRI) confirming that the target was within the STN.

### Case Reports

### Case 1

A 62-year-old, right-handed man developed bradykinesia in 1984 at the age of 46 years, which improved with levodopa (L-dopa) treatment. He developed a disabling *on*-dyskinesia

A videotape accompanies this article.

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from L-dopa treatment beginning in 1993. A right pallidotomy was carried out in November 1996, resulting in temporary improvement in dyskinesia on the left but no benefits in the right dyskinesia. However, the benefits lasted less than 12 months. Six months prior to admission, he developed severe bilateral *off*-dyskinesia in addition to the *on*-dyskinesia. He also suffered motor fluctuations, freezing, and *off*-periods lasting more than 50% of the day. At the time of STN surgery in October 1999, he was taking 175 mg L-dopa and 37 mg benserazide (Madopar 3/4 tab of 250 mg per tablet) four times per day, 200 mg of long-acting L-dopa and 50 mg benserazide (Madopar HBS 125 mg) four times per day, and pergolide 0.25 mg three times per day. Neuropsychological tests were within the normal range. Examination during the *on* period (Video, Segment 1) revealed a Hoehn & Yahr (H&Y) stage III with mild bradykinesia and mild rigidity in the upper and lower extremities. Bilateral generalized dyskinesia persisted for more than 1 hour following the onset of on effects. The Unified Parkinson's Disease Rating Scale (UPDRS) motor section was 22; Schwab and England activities of daily living scores was 70%. He had normal erect posture without asymmetry. The pull test was negative. Examination during the *off* period (Video, Segment 2) revealed an H&Y stage IV with mask-faces and slurred, unintelligible speech. The UPDRS motor scores were 58; Schwab and England activities of daily living were 20%. Severe bradykinesia and rigidity were present in the upper and lower extremities. He could not get up from a chair nor could he walk without assistance. Pull test was positive. A stooping posture was noted with his head and neck slightly flexed but no postural asymmetry. The remainder of the neurological examination including sensory system, cranial nerves, cerebellar, and reflexes were within normal limits.

The indications for subthalamotomy were motor fluctuation, severe disability in the *off* period, and severe biphasic dyskinesia. We elected to do the more affected right hemisphere first in a staged bilateral subthalamotomy. At a trajectory of 13 mm from midline, 6 mm behind, and 6 mm below the mid-anterior and posterior commissural line, the STN size was 6 mm as determined by mapping with microelectrodes. A lesion electrode with a diameter of 1.2 mm and a 3-mm exposed tip was used (Radionics, Burlington, MA) to create a single lesion in the right STN using 70°F for 60 seconds. Five days later, a postoperative MRI was performed to confirm the location of the STN lesion and to estimate lesion volume,[12] which was 60 $mm^3$ (Fig. 1).

Immediately after surgery, and persisting for 5 months postoperatively (Video, Segment 3), the patient tilted to the left while sitting. His upper body gradually and continuously drifted to the left if unattended. He could shift back to the midline position if reminded but promptly tilted to the left again in a few minutes. He needed assistance in walking since his whole body would rotate to the left, causing him to fall. The tilting was observed only when he was in the *off* state. During the *on* state, there was no head or body asymmetry (Video, Segment 4). Five months later a left subthalamotomy was performed. His body tilting subsided even *off* L-dopa after the second surgery (Video, Segment 5).

## Case 2

The patient is a 42-year-old, right-handed woman. Her PD symptoms started in 1985 at the age of 29 years. She began with stiffness and bradykinesia of her left upper and lower extremities, which improved with L-dopa treatment. Four years later, her right side became symptomatic with bradykinesia, tremor, and rigidity. She responded well to L-dopa but developed a disabling *on*-dyskinesia with upward tilting of the head and incapacitating upward eye-rolling (Video, Segment 6), and motor fluctuation with shortening of the *on*-effects. She spent 50% of the day in the *off* state, during which she was totally dependent on a carer for her daily activities. When she was in the on state she could not stop propelling herself forward and fell several times per week. At the time of STN surgery in March 1999, her medications included 200 mg L-dopa and 50 mg benserazide (Madopar 250 mg) three times per day and long-acting L-dopa 100 mg and 25 mg benserazide (Madopar HBS 125 mg) three times per day. Examination during the *off* period (Video, Segment 7) revealed an H&Y stage IV with severe rigidity and bradykinesia bilaterally, greater on the left side. There were moderate intermittent resting and postural tremors of her right hand; these were mild on the left side. The UPDRS motor section was 89; Schwab and England activities of daily living were 20%. Her left fifth finger had a flexion deformity at the distal interphalangeal joint. She could not rise from a chair. There was a severe flexion posture, but her head and body maintained in the midline position while standing or walking. The pull test was positive. Examination during the on state revealed an H&Y stage IV with dyskinesia; UPDRS motor section was 67; Schwab and England activities of daily living were 60%. A prominent head and neck dyskinesia with both eyes deviated upward was seen. A severe flexion posture was present but no asymmetry. The pull test was negative.

Indications for subthalamotomy were severe disability with H&Y stage IV *(off)*, motor fluctuation and disabling *on*-dyskinesias. We elected to do the ablation of the more affected right STN to be followed by the left side in a staged operation. At a trajectory of 10 mm from the midline, 4 mm behind, and

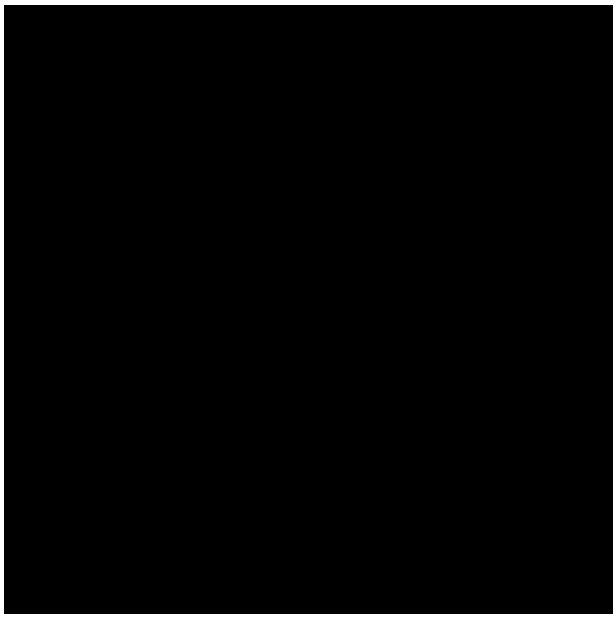

**FIG. 1.** Five days post-right subthalamotomy: coronal MRI of Case 1. Sequences used: TR, 3000, TE, 90.

6 mm below the mid-anterior and posterior commissural line, the STN size was 6.5 mm as guided by microelectrode recording. A lesioning electrode with a diameter of 1.2 mm and a 3-mm exposed tip was used (Radionics) to create a single lesion in the right STN using 75°F for 60 seconds. A postoperative MRI 1 month later showed the lesion volume was 40 $mm^3$ (Fig. 2).

Immediately after surgery, the patient was found to tilt to the left side while sitting (Video, Segment 8). The upper body gradually and continuously drifted to the left in the sitting position. She could sit and fold a piece of tissue with her left hand even in the tilted position. Walking a short distance was possible but assistance was needed because of the continued shifting of her body to the left. Tilting improved but did not disappear completely during *on* condition as compared with *off* (Video, Segment 9). One month later, a deep brain stimulator was implanted in the left STN. There was no postural asymmetry after the second surgery with DBS *on* and levodopa *off* (Video, Segment 10).

## Discussion

Our two patients were alert and aware of their instability yet appeared to neglect or ignore their bodies drifting away from the side of the lesion. There was no weakness in the extremities but the patients had difficulty in correcting body drift or preventing falls. In both patients, postural asymmetry was corrected completely or partially by taking levodopa. In addition, the asymmetry totally disappeared once the contralateral STN surgery was performed, one with thermal coagulation and the other with DBS.

In 1965 Mamo and colleagues[13] described nine patients with PD in whom there was bias of both the head and body to the side opposite the lesion after unilateral coagulation in the subthalamic region. Although the subthalamic region was named as the target for surgery, the location was probably in the vicinity of the fields of Forel and the zona incerta based on the technology available in that era. Previous studies in humans have not discussed a correlation between a subthalamic lesion and posture asymmetry, but this has been discussed in primate studies. Henderson and associates[5] reported that unilateral lesions of the STN in monkeys induced a marked contralateral head bias. Hammond and colleagues[14] reported in monkeys the appearance of contralateral head position bias and rotational asymmetry after unilateral lesioning of the STN.

**FIG. 2.** One month post-right subthalamotomy: coronal MRI of Case 2. Sequences used: TR, 6500, TE, 48.

The STN projects to the output station of the basal ganglia, GPi and SNr. The STN also projects and receives input from the pedunculopontine nucleus (PPN), which regulates locomotion. In theory, ablation of STN should reduce the hyperactivities of the GPi, SNr, and PPN. Using [$^{18}$F]fluorodeoxyglucose (FDG)/PET before and 3 months after unilateral STN ablation in six patients, Su and colleagues[15] recently reported a highly significant decrement in glucose utilization in the SNr, STN, and lateral border of the ventral GP. Another significant metabolic decrement was present in the ipsilateral pons in the vicinity of the caudal PPN.[15] In addition, following STN ablation there is a significant decrease in a previously identified PD-related metabolic covariance pattern (PDRP). PDRP expression is abnormally elevated in PD patients and correlates consistently with independent clinical measures of disease severity.[16,17] Indeed, significant reductions in abnormal PDRP expression have been recently noted with effective medical and surgical antiparkinsonian therapy.[18,19] Su and colleagues also found that surgical changes in PDRP expression differed significantly between the operated and unoperated hemispheres. Thus, stereotaxic lesioning of the STN not only reduces output to its projection targets in SNr, GPi, and PPN, but also reduces the expression of abnormal PD-related metabolic brain networks.

We speculate that the tilting to the contralateral side of STN lesion found in our patients might be related to the imbalance between operated and unoperated hemispheres as revealed in Ma's studies. In the MPTP primate[5,20] and in PD,[1,2] postural asymmetry is always toward the less dopaminergic hemisphere. Even in rodents, spontaneous rotation was found toward the side with less striatal dopamine uptake.[21] Since basal ganglia outputs from GPi and SNr are inhibitory using gamma-aminobutyric acid (GABA), we speculate that the operated side had more dopaminergic influence compared to the unoperated side. Therefore, STN-operated patients tilt toward the unoperated hemisphere. By a similar mechanism, postural asymmetry in our patients improved with an effective dosage of levodopa treatment. In non-PD patients with a striatal or thalamic lesion, body tilting to the contralateral side might have a different mechanism.

The SNr has a reciprocal connection with the deep layers of the superior colliculus (SC),[22,23] a nucleus known to be involved in the control of eye movement and orientation behavior. In MPTP-treated monkeys and in PD, the SC was found to have a reduced expression of glutamic acid decarboxylase mRNA.[24] A functional interplay is a distinct possibility between the basal ganglia and the SC in the control of some orientation behavior and postural symmetry in PD. The observed effects of STN or striatal lesions[4] on postural imbalance could also be the result of asymmetrical projection between the deep layers of the SC and SNr.

The superior colliculus has a superficial and deep layer. The deep layers of the superior colliculus receive afferents from the spinal cord, somatosensory relay nuclei, cerebellum, substantia

nigra, and brainstem reticular formation.[25] The superficial layer is concerned with detection of movement of objects in space, whereas the deeper layer is concerned with head and eye movement. Somatosensory input from the spinal cord to the SC (spinotectal fibers) is topographically organized with the head and forelimb occupying an unusually large portion,[25] which might help explain greater head and upper limb tilting.

In conclusion, unilateral STN ablation can produce postural asymmetry in PD with head and body tilting away from the side of the lesion. The asymmetry is partially reversible with levodopa treatment and completely reversible with contralateral STN surgery. We speculate that reduced SNr activities and consequently reduced projection from SNr to and from the SC is responsible for the head and body asymmetry following unilateral subthalamotomy.

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## Legends to the Videotape

**Segment 1.** Case 1: Preoperative: *on* with generalized dyskinesia.

**Segment 2.** Case 1: Preoperative: *off* state.

**Segment 3.** Case 1: Four weeks post-right subthalamotomy in *off* state, showing patient markedly tilted to the left while sitting and unable to walk.

**Segment 4.** Case 1: Four weeks post-right subthalamotomy in *on* state.

**Segment 5.** Case 1: One week post-contralateral subthalamotomy in *off* state, showing loss of postural asymmetry.

**Segment 6.** Case 2: Preoperative: *on* state.

**Segment 7.** Case 2: Preoperative: *off* state.

**Segment 8.** Case 2: One week post-right subthalamotomy in *off* state, showing patient markedly tilted to the left while sitting and unable to stand. She could walk a short distance with a tripod but her body weight continuously shifted to the left, resulting in a fall.

**Segment 9.** Case 2: Three weeks post-right subthalamotomy in *on* state, showing less bradykinesia of left side. Head and body tilted mildly to the left while sitting.

**Segment 10.** Case 2: Two weeks post-contralateral DBS implant in subthalamus; 4 days apart in two subsegments with DBS *on* and no levodopa, showing loss of postural asymmetry.

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# Life-Threatening Parkinsonism Induced by Kava-Kava

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**Abstract:** We present a 45-year-old female with severe parkinsonism induced by kava-kava. The patient, who had a family history of essential tremor, developed severe and persistent parkinsonism after 10 days of treatment with kava extract for anxiety. The symptoms improved with anticholinergics. Kava derivatives could produce severe parkinsonism in individuals with genetic susceptibility. © 2001 Movement Disorder Society.

Herbal medicines are used increasingly in western countries, but their clinical indication, efficacy, and safety are not always well established according to the usual scientific standards. Kava extracts are a tradition, as ceremonial beverages, in the South Pacific Islands for their relaxing properties, inducing a warm, pleasant and cheerful but lazy feeling. The extracts are obtained from the root and the rhizome of several subspecies of a pepper plant, *Piper methysticum*.[1]

The pharmacological properties of these compounds have been partially investigated in different European laboratories, mainly in Germany. Kava derivatives, called kavapyrones, alter dopamine concentrations in the rat nucleus accumbens.[2] There is evidence for binding to γ-aminobutryic acid (GABA)-A receptors in synaptosomal membranes from rat brain.[3] Kavapyrones inhibit in vitro noradrenaline uptake in synaptosomes from rodent cerebral cortex and hippocampus, but this effect took place at concentrations 10-fold higher than the maximal brain levels detected in mice after a bolus of 100 mg of kava extract.[4]

Kava extracts are widely sold as a symptomatic treatment for anxiety. In Germany, 547,000 units were sold in 1993[5]; sales in other European countries and North America are unknown. Double-blind, randomised, placebo-controlled trials suggest that oral kava extracts are superior to placebo for the treatment of anxiety.[6] These compounds are sold as natural drugs for the treatment of obesity-associated anxiety. Reported side effects include shortness of breath, malnutrition, liver damage, changes in red and white blood cells and platelets,[7] and a scaly rash suggestive of ichthyosis.[8] Neurological side effects of kava extracts have been previously described but are never severe or persistent. Poewe and colleagues[5] reported three patients with acute dystonic reactions and one with transient worsening of parkinsonism after short-term treatment (occasionally a single dose) of kava extracts, that disappeared with drug withdrawal and biperiden intravenously (i.v.). Almeida and colleagues[9] reported a case of semicomatose state after ingestion of alprazolam and kava in therapeutic dosages.

We present a case of severe and persistent parkinsonism induced by extracts of kava-kava (*Piper methysticum*). This is the most severe complication ever reported of kava to date. Our patient developed rapidly progressive parkinsonism for 3 months after ingestion of 65 mg of kava extracts daily for 10 days.

## Case Report

A 45-year-old female was referred to our attention for a rapidly progressive parkinsonism. The patient had a family history of essential tremor affecting her mother, one sister, and a maternal cousin. She was healthy until 3 months prior to her visit, when she developed pain and stiffness in her legs followed by sadness, anxiety, and insomnia. She was seen by a psychiatrist who diagnosed depression and treated her with benzodiazepines and fluoxetine. Her symptoms continued to worsen and she developed generalised slowness. Fluoxetine was substituted for sertraline but she failed to improve and became restless.

One month prior to her visit, the patient developed hypophonia, generalised tremor, and changes in sleep behaviour. She was referred to a neurologist, and was found to have a normal mental examination, full eye movements but with slow saccades, hypophonic speech, generalised postural and tremor at rest, severe generalised rigidity in axial and apendicular muscles, severe akinesia and gait disturbance with lack of balance, and inability to walk without support by another person. Laboratory tests showed normal haematological and biochemical values including copper and ceruloplasmin, electroencephalogram (EEG), computed tomography and magnetic resonance imaging scans. She was treated with levodopa(L-dopa)/carbidopa 300/75 mg/day, and pergolide 0.75 mg/day, without improvement. She was thought to have a malignant parkinsonism and was referred to our clinic to rule out spongiform encephalopathy.

A careful review of the clinical history did not uncover any pharmaceutical compound responsible for her symptoms. The patient's husband, however, provided samples of herbal medicines that she had taken before the appearance of her clinical symptoms and that were prescribed to her for reduction of weight and treatment of her anxiety. Two to three weeks before the onset of her clinical symptoms, she had taken a compound that contains extracts of kava 65 mg/day for 10 days in addition to vitamins. One month after onset, she took manganese 2.5 mg/day for 4 days. Her clinical examination was similar to that previously described, but in addition she had severe akathisia. Her blood chemistries and EEG were again normal. A lumbar tap revealed a clear cerebrospinal fluid with normal levels of protein and cells, increased homovanillic acid (143 ng/ml; nor-

A videotape accompanies this article.

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mal values for adults in our laboratory: 47 ±2 ng/ml in healthy individuals, 21 ± 4 ng/ml in untreated parkinsonian patients, 81 ± 24 in patients treated with L-dopa). The treatment was changed to L-dopa/carbidopa 800/200 mg/day, pramipexole, 0.75 mg/day, and a single injection of apomorphine, total cumulative dose 10 mg, subcutaneous (s.c.) (divided into two injections of 5 mg, separated by a time interval of 10 minutes, after treatment with domperidone, 60 mg, per oris (p.o.), for 24 hours) without improvement. The total Unified Parkinson's Disease Rating Scale (UPDRS) I–III score was 94.

The patient was treated with biperiden, 5 mg (i.v.), and she improved quickly (Video, Segment 1). One hour later, the patient received a second injection of biperiden, 5 mg, i.v., resulting in further improvement (Video, Segment 2). She was discharged on treatment with L-dopa/carbidopa 300/75 mg/day, biperiden retard once a day, and amantadine 300 mg/day. Five days later, she was reviewed in the outpatient clinic. She had further improved, returning to normal daily activities. Mild postural and rest tremor, generalised rigidity, and akinesia were still present. Her gait was still abnormal and her face was hypomimic. The total UPDRS I–III score was now 34.

We followed up withthe patient 6 weeks later. She had returned to her normal daily activities but slowness and tremor at rest persisted. Her UPDRS score was then 27. Her treatment was maintained with the addition of pramipexole, starting with 0.25 mg/day and increasing slowly the dose up to 1.5 mg/day. Two months later, the patient returned for her last visit. Her symptoms were stable and the treatment was continued.

## Discussion

The previously reported neurological complications of kava are rare and benign.[5] Movement disorders induced by this compound usually appear with the first dose of medication and disappear quickly with drug withdrawal. The severity of this case may be related to prolonged intake of this compound for 10 days. The role of manganese in the pathogenesis of this syndrome is probably irrelevant, as the patient took a very small dose, 2.5 mg/day for 4 days, and the administration of manganese took place 1 month after the onset of the clinical symptoms, but the possibility could not be excluded that manganese increased the persistence and severity of the symptoms of this patient.

The mechanism underlying this complication is unknown, but it is probably related to blockade of dopamine receptors as shown by the lack of response to apomorphine and the high levels of homovanillic acid (HVA) in cerebral spinal fluid. Parkinsonism due to receptor blockade may improve with anticolinergics, as happened in this case. The reason for the persistence and progression of the deficit in spite of suppression of the drug is unknown. A genetic susceptibility cannot be ruled out, as this patient had three relatives with essential tremor. Family history of essential tremor was one of the risk factors identified by García Ruiz and colleagues[10] for development of parkinsonism due to calcium channel antagonists. Miryantopoulos and associates[11] described increased risk of drug-induced parkinsonism in relatives of individuals with tremor, and Hoenicka and colleagues[12] reported parkinsonism induced by small doses of neuroleptics and calcium channel antagonists in heterozygous carriers of mutations of the Park-2 gene. Therefore, it is likely that the severity of this clinical syndrome is related to genetic risk factors and that the exposure to kava may therefore trigger persistent parkinsonism in predisposed individuals.

The scientific standards that regulate prescription of pharmaceutical compounds and the requirements of efficacy and safety requested by European health authorities for the marketing of herbal or so-called "naturalistic" medicines are quite relaxed in comparison with those of most medicines. Many of these compounds are not innocent and their use should follow the same requirements as that of conventional pharmaceuticals.

## Legends to the Videotape

**Segment 1.** Clinical status of the patient prior to treatment with anticholinergics, while treated with levadopa/carbidopa 300/75 mg/day, and pramipexole 0.75 mg/day. A severe parkinsonian syndrome, with lack of balance and full but slow and hypometric ocular saccades, is present. With horizontal and vertical gaze movements, the patient is unable to suppress head thrusts.

**Segment 2.** The patient greatly improved 4 hours after the first and 3 hours after the second i.v. bolus of biperiden.

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# Late-Onset Axial Jerky Dystonia Due to the *DYT1* Deletion


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**Abstract:** We describe a 71-year-old woman who presented to the neurology department late in life with a jerky axial dystonia due to the *DYT1* GAG deletion. She recalled that her symptoms began 62 years prior to study and remained unchanged for 40 years, illustrating the broad phenotype of *DYT1* idiopathic torsion dystonia. © 2001 Movement Disorder Society.

A heterozygous three base pair GAG deletion (ΔGAG) at codon 946 of the *DYT1* gene on chromosome 9q34 is a common cause of primary torsion dystonia (PTD).[1,2] In a recent study of a large series of patients with PTD, the onset of dystonia before age 26 years was 100% sensitive for the detection of clinically affected carriers, and the onset of focal dystonia in a limb before age 24 years was highly sensitive and specific for disease due to the *DYT1* deletion both in Ashkenazi Jews and non-Jewish patients.[3] While these criteria are extremely helpful in optimizing the chance of detecting a *DYT1* deletion, potential cases may be missed if they are strictly adhered to, particularly if symptoms early in life were incorrectly diagnosed and a clear family history is not apparent.

## Case Report

A 71-year-old woman presented with a 20-year history of progressive "tremulousness," predominantly affecting her gait but with a significant appendicular component. She had been able to work as a teacher up to the age of 53 years, but in recent years the movement disorder had prevented her from riding a bicycle and latterly from leaving the house alone, leading to social isolation. An upper-limb tremor made eating and drinking difficult. Her dexterity was impaired due to coarse proximal upper limb movements on intention, and her symptoms worsened at times of stress. She had not noted any effect from alcohol, and there was no previous exposure to dopamine receptor blocking agents. Closer enquiry revealed that at 9 years of age she had developed a gait disturbance, which at the time was described as "polio." Her left leg had been stiff, she wore the toe of her left shoe-sole away, and she was unable to place her heel on the floor. Her Achilles tendons were lengthened at 14 years of age. In the 1970s, she had undergone a fibroidectomy, and following the anesthetic her movement disorder had deteriorated for 24 hours. Details of the anesthetic agents used were not available. Ten years previously she had undergone a left mastectomy and local radiotherapy for breast carcinoma, currently thought to be in remission. She had no siblings, but her mother was said to have had a tremor.

General medical examination was unremarkable. When sitting upright, the patient had a coarse, jerky tremor affecting both arms and legs. With the arms outstretched, she had an intermittent tremor, with mild dystonic posturing in the right hand. On standing, she developed paroxysmal, jerky movements of the trunk causing predominantly flexor, but occasionally extensor, posturing. She also developed dystonic movements when walking in both legs, particularly in the left foot. The movements were not present when she was supine and relaxed, nor were they present during sleep. There were no cranial nerve abnormalities, and in particular, her eye movements and palate were normal. Tone was normal, power was within normal limits, reflexes physiological and plantar responses flexor. There were no cerebellar signs. Neither L-dopa nor alcohol had an effect, but the gait disturbance moderately improved on clonazepam (0.5 mg b.i.d.). Routine hematological and biochemical investigations were normal, including a blood film. Her thyroid function and copper studies were normal. Magnetic resonance imaging (MRI) of the brain showed no significant abnormality. Molecular genetic testing[1] identified the ΔGAG in the *DYT1* gene.

## Discussion

The most interesting feature of this case is the bizarre predominantly axial myoclonic dystonia due to the ΔGAG which developed in late middle age. Classically, the *DYT1* deletion causes focal onset limb dystonia before age 26 years, followed by rapid generalization or spread to another limb but not involving the craniocervical region,[3] The disorder may, however, present in a variety of different ways, and both truncal tremor[4–6] and flexor spasms[2] have been described in patients harboring the *DYT1* ΔGAG. With hindsight, our patient's description of "old polio" almost certainly corresponds to the focal onset limb dystonia seen in 89% of European patients with PTD due to the *DYT1* deletion[2] It is, however, interesting that the dystonia neither became generalized nor involved another limb for nearly 50 years. This raises the possibility that the penetrance of the *DYT1* ΔGAG may be greater than the reported value of 30–40%[7] when families are studied over longer periods of time. Individuals studied in middle age may be misclassified as unaffected because of vague or inaccurately diagnosed symptoms in early life, as in the case of our patient. This case also illustrates the absence of a clear family history in some patients with PTD due to the *DYT1* ΔGAG. This is partly due to the markedly reduced penetrance of mutation,[7] but also due to new mutation events that have been reported on rare occasions.[8] It is also difficult to establish an accurate family history without examining the relatives. Tremor is common, and is often misdiagnosed. It is only in retrospect that the vague history of "tremor" affecting the patient's mother was thought to be significant. Although the prevalence of *DYT1* ΔGAG is low in sporadic cases of generalized PTD presenting in adult life,[6] the case we present here highlights the importance of taking a clear personal and family history in any dystonic disorder, however unusual, because the genetic diagnosis may have implications for other family members.

## Legend to the Videotape

The patient is seen walking with two sticks. She displays jerky, dystonic movements of the trunk in flexion and occa-

A videotape accompanies this article.

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sionally in extension. There is dystonic posturing evident at both feet, particularly on the left. The jerky, tremor-like movements persist in both legs when the patient is seated.

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# Riluzole Therapy in Cervical Dystonia


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**Abstract:** We conducted a 6-week open-label pilot study with blinded video rating of riluzole (50 mg twice a day) in six patients with cervical dystonia (CD) refractory to botulinum toxin A and oral pharmacological treatment. The Tsui rating scale served as primary efficacy measure and improved significantly under riluzole ($P = 0.002$). In three of six patients, the Tsui score improved by more than 30% with a greater 50% reduction in the head tremor/jerk subscore of the Tsui scale. These data suggest that riluzole may be helpful in a subgroup of patients with disabling CD refractory to other therapies.




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Idiopathic cervical dystonia (CD) is the most common form of focal dystonia.[1] While oral pharmacological treatment of CD is often unsatisfactory and limited by side effects, local Botulinum toxin type A (BtxA) injections are considered the treatment of choice for CD. However, BtxA renders only limited benefit or is not effective in 6–14% of patients, and it loses its initial efficacy in at least 3% of patients with continued use.[2,3]

The evidence of highly irregular spontaneous neuronal activity in the globus pallidus internus (GPI) in patients with CD[4] together with the observation that riluzole may regularize GPI firing activity in the MPTP-treated monkey[5] suggests that antiglutamatergic agents such as riluzole might improve clinical symptoms in patients with CD. Riluzole (2-amino-6-trifluoromethoxy benzothiazine) interferes with glutamatergic transmission and appears to have several mechanisms of action, including indirect blockade of excitatory amino acid receptor-mediated responses, inhibition of glutamate release, stabilizing of voltage-dependent sodium channels, and blockade of gamma aminobutyric acid (GABA) reuptake.[6]

We conducted a pilot study in six CD patients refractory to BtxA injections as well as oral pharmacological treatment to evaluate the efficacy and safety of riluzole in CD.

## Patients and Methods

The study was designed as a 6-week open pilot trial with blinded video rating of CD according to Tsui et al.[7] Six patients (three women, median age 50 years, median disease duration 18 years) with adult onset therapy refractory CD were included from our outpatient movement disorder clinic comprising about 90 CD patients. Patient characteristics are shown in Table 1. In four patients, neutralizing antibodies against BtxA were detected; none of the patients showed a response to three consecutive BtxA injections up to a dose of 1,200 units Dysport®. Oral pharmacological treatment including trihexyphenidyl, sulpiride, tiapride, and tetrabenazine alone or in combination had failed to improve dystonia. Riluzole was administered at 50 mg twice a day, a dose which showed the best benefit-to-risk ratio in a dose-ranging study of riluzole in ALS.[8] At the end of that period, patients were offered the opportunity to continue with riluzole (100 mg/day). At entry into this study, two patients were on constant (>1 year) trihexyphenidyl therapy (15 mg/day), and one was on tetrabenazine (75 mg/day). These medications remained unchanged throughout the study period. The remaining three patients had no concomittant medication. There was no family history of involuntary movements in any indivual. Except for dystonia and a mild bilateral action tremor in one patient, clinical examination was normal. Patient history, laboratory workup, and CT/magnetic resonance imaging (MRI) scanning excluded secondary dystonia. Informed consent was obtained from all patients.

The Tsui rating scale[7] served as primary efficacy measure. Video recording was performed using a standardized protocol before and after 6 weeks of treatment with riluzole. The videos were randomized and rated by three independent blinded movement disorder specialists. Additional efficacy measures were: Tsui subscore head tremor/jerk,[7] subjective benefit assessed by the Patient Global assessment of Change (0–100%),[9] rating of torticollis associated pain on a 4-point scale (absent, mild, moderate, severe).[10] Laboratory tests were repeated monthly by a general practitioner. All adverse experiences were recorded.

**TABLE 1.** *Patient characteristics and efficacy outcome variables after 6 weeks riluzole (n = 6)*

| Patient | Age/gender | Disease duration (yr) | Type of dystonia | BtxA neutralizing antibodies | Subjective benefit from riluzole (%) | Tsui score[1] (%) | Tsui subscore head tremor/jerk[1] (%) |
|---|---|---|---|---|---|---|---|
| A | 62/M | 19 | Irregular phasic CD + Meige-Syndrome | No | 35 | 34 | 58 |
| B | 58/M | 15 | Tremulous CD | No | 60 | 33 | 50 |
| C | 50/M | 25 | Tremulous CD | Yes | 40 | 48 | 67 |
| D | 42/W | 21 | Tremulous CD | Yes | 0 | 9 | 17 |
| E | 50/W | 13 | Tonic/tremulous CD | Yes | 0 | 22 | 33 |
| F | 42/W | 17 | Pure tonic CD | Yes | 0 | 10 | — |

[1]Median improvement by three blinded raters.
CD, cervical dystonia; M, men; W, women; BtxA, Botulinum toxin type A.

## Statistics

Within-group comparisons of the efficacy criteria were performed by Wilcoxon signed rank test. Kendall's coefficient of concordance *W* was used to assess agreement among the three blinded raters for the primary efficacy measure.

## Results

All patients completed the study. Table 1 summarizes the individual outcome variables. The median improvement at group level was as follows: (1) Tsui score, 26% ($P = 0.002$); (2) Tsui subscore head tremor/jerk, 45% ($P = 0.002$); and (3) rating of torticollis associated pain, 20% ($P = 0.07$). The interrater agreement for the Tsui rating scale was good at baseline and after 6 weeks riluzole with Kendall's range 0.77–0.72 ($P < 0.05$, each). Three patients (50%) reported initial nausea (mild), which persisted in patient E throughout the study period. In one patient, a mild elevation of liver enzymes within two times the normal level was observed.

At the end of the study period, three patients (patients A, B, and C) asked for continuation of therapy. They were maintained on riluzole 50 mg twice a day. The primary efficacy parameters as well as the Patient Global assessment of Change remained stable at two follow-up visits (weeks 12 and 24). No new side effects were reported.

## Discussion

This is the first report on riluzole in cervical dystonia. We observed clinically significant improvement of CD in three of the six patients. Furthermore, there was a significant reduction of the Tsui score by 26% at group level, which is similar to that reported by Poewe et al.[10] 4 weeks after injections of 500 units Dysport®. Finally, phasic head movements assessed by the tremor/jerk subscale of the Tsui score[7] improved by a median of 45% at group level. These findings suggest that riluzole may be an effective and well-tolerated therapy in CD refractory to BtxA injections and conventional pharmacotherapy.

This study has limitations: first, the study design was not double-blind. However, effects were assessed by three independent blinded raters who showed a good interrater agreement pre- and post-treatment. Secondly, this study was small with only six patients participating. However, we deliberately only included patients with CD refractory to conventional antidystonic therapy, representing about 7% of the CD patients regularly treated at our outpatient movement disorder clinic. It seemed appropriate to perform a pilot study in this small subgroup of patients in whom conventional therapy failed, but clearly, larger double-blind studies are needed.

The present mechanism of action for riluzole in CD is unclear. The drug was originally introduced as an antagonist of glutamatergic transmission, and antiglutamatergic actions at the basal ganglia level have been proposed to underlie riluzole's possible effects on levodopa-induced dyskinesias.[11] In dystonia, microelectrode recordings indicate that most of the GPI neurons do not exhibit a normal tonic discharge rate, but instead display irregularly grouped discharges with an increased incidence of bursting activity in dystonic tremor.[4] In addition, an increased excitatory (glutamatergic) drive from the nucleus subthalamicus (STN) on the GPI resulting in alteration in receptive field properties of GPI neurons is suggested.[4] Therefore, glutamatergic mechanisms at STN level may play a role in the riluzole-mediated regularization of GPI discharge pattern in dystonia.[5]

In conclusion, the data from our pilot study suggest that riluzole may be considered as third line therapy in patients with disabling CD refractory to BtxA and conventional pharmacotherapy. Future studies should address the assessment of potential drug efficacy at different doses and establish differential responses to riluzole in subgroups of patients with phasic and tonic CD.

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## X-Linked Dystonia ("Lubag") Presenting Predominantly with Parkinsonism: A More Benign Phenotype?

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**Abstract:** "Lubag," or Filipino X-linked dystonia, typically presents with either pure dystonia (that inexorably becomes generalized) or combined dystonia–parkinsonism. We report on three cases of Lubag presenting with isolated parkinsonism without dystonia or late-onset dystonia and a slower course. 

Filipino X-linked dystonia–parkinsonism (XDP) or "Lubag" is a rare genetic movement disorder that was first recognized in the Philippines, particularly in the islands of Panay.[1] In the native Panay dialect, dystonic posturing of the disease is referred to as "Lubag" if the movements are intermittent, or "Wa'eg" when sustained. Lubag usually affects men in their fourth or fifth decade, and can manifest as early as adolescence.[2] In reviewing the phenotype of 42 individuals previously reported with Lubag, six patients (14%) were noted to have definite parkinsonism (presence of any two of the following five signs: resting tremor, bradykinesia, rigidity, loss of postural reflexes, and shuffling gait); one individual had probable parkinsonism (presence of either resting tremor or bradykinesia alone), and eight patients (19%) had possible parkinsonism (presence of only one of the five parkinsonian signs).[3] Of note, these parkinsonian Lubag patients also had multifocal or concurrent multifocal or generalized dystonia. We report on three cases of Lubag presenting predominantly with parkinsonism for several years, with dystonia developing late in the course in one patient.

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### Methods

To confirm that the three cases presented were carriers of the XDP haplotype, we performed polymerase chain reaction (PCR) amplification of microsatellite markers in and around the previously reported segregating region, spanning approximately 400 kb.[4] The markers used were DXS7117, DXS6673E 3′, ZNF261, DXS10017, DXS10018 and DXS559. The primer sequences were as previously described with the exception of the marker ZNF261, which was amplified using primer pair ZNF REP F 5′ -fam CTGGAGGAGAAAGAGAGAGAGAG-3′ and ZNF REP R 5′-TTCTCCCTGAGTCTTCCTGC-3′. PCR amplification was performed in a 25 -μl reaction containing 200 μM dNTPs, 10 pmol of both the forward and reverse primers, 1× the manufacturers reaction buffer (Qiagen, Chatsworth, CA), 25 ng genomic DNA and 0.2 units of *Taq* DNA polymerase. The reactions were run on a Hybaid thermal cycler using a touchdown program which consisted of an initial 5-minute denaturation at 96°C followed by 40 cycles of annealing (65°C for all primers except DXS10018 and DXS7117 which were run at 60°C) for 30 seconds, extension at 72°C for 30 seconds and denaturation at 96°C for 30 seconds. After the fourth cycle, the annealing temperature decreased by 0.5°C per cycle for 20 cycles and then remained constant (10°C lower than the initial annealing temperature) for the remaining cycles. A 1:10 dilution of these products was then electrophoresed on an ABI377XL and the fragment sizes analyzed (*Genescan* and *Genotyper* software, Perkin Elmer Applied Biosystems, Oak Brook, IL). In addition to these cases, we also amplified and analyzed these markers in genomic DNA from CEPH family 1331, individuals 01 and 02 to facilitate accurate allele size calling.

### Results

#### Case Descriptions

*Case 1.* J.V. is a 34-year-old male Filipino from Manila whose mother hails from Capiz, a province in the Panay Islands. J.V. developed a kinetic tremor of the right hand at age 21 years. At age 29 years, a left-hand kinetic tremor was noted as well. Mild bradykinesia developed a year later. The family history was remarkable for the following reasons: an older brother developed tremor at age 48 years; a maternal uncle presented with tremor and generalized dystonia beginning at age 40 years; a first cousin of the patient's mother exhibited tremor and slowness of movements and was diagnosed with Parkinson's disease (PD) at age 50 years, and a maternal male first cousin presented with generalized dystonia, with onset at age 40.

On examination 13 years after the onset of symptoms, J.V. had the following findings: mild masked fascies; no resting tremor; mild terminal tremor of the right (R) upper extremity (UE) and left (L) UE; rigid tone which was mild to moderate in

both UEs and L lower extremity (LE), and moderate to severe in the neck and RLE; mild asymmetric (left worse than right) breakdown of alternating motion rate (AMR) on finger tapping, closing/opening of the hands, and hand tapping; severe breakdown of foot tapping bilaterally; and normal gait, balance, and speech.

J.V. was initially diagnosed by his family physician as suffering from an overlap syndrome of PD and essential tremor (ET). He was started on selegiline, trihexyphenidyl, and propranolol treatment, resulting in some improvement of his symptoms. After several months of therapy, he decided to discontinue all medications, resulting in worsening of symptoms. He was then prescribed varying doses of levodopa, with subjective improvement of his tremor and bradykinesia.

Fourteen years after onset of symptoms, J.V. continues to have isolated parkinsonism (without dystonia) that is moderately responsive to levodopa. The motor United Parkinson's Disease Rating Scale (UPDRS) in the *off* state was 41; this improved to 33 on 100 mg/day levodopa, and to 27 on 900 mg/day levodopa. No levodopa-associated dyskinesias were noted. He remains gainfully employed as a bank employee.

*Case 2.* R.G. is a 42-year-old male Filipino from Iloilo in the Panay Islands. At age 40 years, he presented with a right foot tremor. At age 41 years his handwriting started to deteriorate, and his walking became slower. No abnormal twisting or posturing was reported. The family history was suggestive of an X-linked recessive disorder: an older brother (onset at age 45 years) and five maternal uncles (brothers of the patient's mother) developed generalized dystonia.

On examination 2 years after the onset of symptoms, R.G. had the following findings: mild dysarthria, hypomimia, stooped posture, retropulsion, bradykinesia, and micrographia; mild resting tremor of the right foot, and mild rigidity of the RUE and RLE; mild reduction in AMRs bilaterally on finger tapping, hand tapping, closing/opening of the hands, and foot tapping, and moderate reduction in armswing bilaterally (R worse than L).

R.G. was initially prescribed biperiden 1 mg/day and clonazepam 1 mg/day with minimal improvement of his symptoms. Six months later, selegiline 5 mg/day was added with no further improvement. Subsequently, the patient was maintained on 600 mg/day of levodopa with significant control of his tremor and bradykinesia. The motor UPDRS score before levodopa treatment was 34; this improved to 19 on 600 mg/day of levodopa.

Three years after onset of symptoms, R.G.'s parkinsonism had worsened but continued to be responsive to levodopa. At this point, blepharospasm and right hand posturing were noted. Discontinuation of levodopa for a few days resulted in worsening of his tremor and bradykinesia, but persistence of his dystonia. He remains employed as an office worker.

*Case 3.* G.A. is a 41-year-old male Filipino who hails from Capiz in the Panay Islands. At age 39 years, he began to experience stiffness of his neck and trunk, progressive slowing of ambulation, bilateral hand tremors, and difficulty with handwriting. No twisting or posturing was noted. The family history was pertinent for generalized dystonia and tremors in a maternal uncle (brother of the patient's mother).

On examination 2 years after onset of symptoms, G.A. presented with the following findings: mild to moderate dysarthria, hypomimia, stooped posture, terminal tremor of both UEs, shuffling gait, retropulsion, difficulty on arising from a seated position, and bradykinesia; moderate breakdown of AMRs on finger tapping, closing/opening of hands, hand tapping, and foot tapping; moderate to severe rigidity of the neck and limbs (worse in LEs), and markedly reduced armswing bilaterally.

G.A. was prescribed clonazepam 1.5 mg/day plus biperiden 3 mg/day, with some subjective relief of his symptoms. Levodopa treatment was contemplated, but was deferred because of financial limitations.

Two and a half years after onset of symptoms, the patient still presented with pure parkinsonism without dystonia. He continues working as a chauffeur.

## Results of Genetic Testing

We have confirmed that the three cases examined here possess the disease segregating haplotype found in 20 clinically evaluated XDP cases[5] and in 34 previously reported cases.[4]

## Discussion

Lubag has been noted to present with either pure dystonia, or dystonia with parkinsonism.[1–3] Although Lubag was initially referred to as "X-linked recessive dystonia," the terminology was later modified to "X-linked dystonia-parkinsonism" because about 14% manifest with definite parkinsonism (i.e., two or more parkinsonian features), and as many as 36% present with one or more parkinsonian signs. However, isolated parkinsonism, with clinical features similar to PD can be the presenting and predominant phenotype, as demonstrated by the three cases described here. All suffered from "definite parkinsonism," without dystonia 2½, 3, and 14 years after onset of symptoms. Only one of these three has developed dystonia during our longitudinal follow-up, at the third year of disease. It is possible that the patients' medications were masking the dystonia (e.g., Case 2 was taking clonazepam, and Case 3 was taking clonazepam and biperiden). However, this is considered unlikely, since the dystonia in Lubag is only partially responsive to anti-dystonia therapy.[1,3] Interestingly, unlike dopa-responsive dystonia,[7] the dystonia in Lubag is not alleviated by levodopa.[1,3] In fact, levodopa may exacerbate dystonia in Lubag patients.[2] Thus, we consider it unlikely that levodopa was suppressing the dystonia in the two patients described above treated with this drug.

Isolated parkinsonian symptoms have been previously noted to precede the onset of symptoms in Lubag.[3] Specifically, 10% of the 42 patients reported by Lee and colleagues[3] exhibited a fine pill-rolling tremor at onset, while 33% had a coarse resting or postural tremor. All these individuals inevitably and inexorably developed dystonia according to that report, although the time of development of dystonia from onset of parkinsonism was not stated. In a previous description of Lubag,[1] five of 28 patients presented with tremor. Although the onset of dystonia in these five cases was not specified, all had multi-focal or generalized dystonia by the fifth year of disease. Wilhelmsen and colleagues[6] described four generations of a Filipino kindred with Lubag, in which three affected men presented with pure parkinsonism, one of whom was examined at the onset of symptoms, the other two of whom were examined 2 and 19 years after onset of symptoms, respectively.[6] The response of these three individuals to levodopa was not specified.

Positron emission tomography (PET) findings in three affected male Lubag patients with dystonia (the predominant symptom) and parkinsonism consisted of selective reduction in striatal glucose metabolism, but normal [$^{18}$F] fluorodopa up-

take, suggesting that the extrapyramidal manifestations are metabolically localized postsynaptically to the striatum.[8] These PET data are further supported by the neuropathological findings of neuronal loss and multifocal mosaic pattern of astrocytosis restricted to the caudate and lateral putamen in one affected Lubag patient with generalized dystonia and parkinsonism.[9] In a separate report, [$^{18}$F] fluorodopa PET in an affected male with moderately severe parkinsonism and dystonia showed reduced striatal uptake, consistent with presynaptic nigrostriatal involvement.[2] Thus, it appears that, by PET analysis, Lubag patients may either have postsynaptic striatal involvement, or presynaptic nigrostriatal affection. The first group may represent the huge majority of Lubag patients with pure dystonia or combined dystonia-parkinsonism from the early stages; this group does not respond to levodopa. The second subset may represent the fewer patients with pure parkinsonism for a considerable number of years, with dystonia setting in late in the course; this group appears to be more levodopa-responsive. The cases we described above may fall under the second group. Fluorodopa PET studies as well as neuropathological examination of the brains of these parkinsonian Lubag patients may help confirm this.

The cases presented in this paper serve to highlight the importance of suspecting Lubag in any adult Filipino male presenting with tremor or parkinsonism and a family history of tremor, parkinsonism, or dystonia in any maternal male relative. Not uncommonly, these patients (and their other parkinsonian male relatives, especially those residing outside the Philippines) are misdiagnosed as suffering from PD or ET. Case 1 is testimony to this, as he was originally diagnosed with a "PD-ET overlap syndrome," while his maternal uncle was diagnosed with PD. The symptoms, particularly the tremor, may start asymmetrically in one limb in Lubag, like PD. With the development of other parkinsonian signs including bradykinesia, shuffling gait, rigidity, hypomimia, micrographia, and postural instability, the differentiation from PD becomes even more difficult. The parkinsonism in Lubag patients has been previously believed to be unresponsive to levodopa. In the series of 28 patients described by Lee and colleagues,[1] only one patient had a partial response to levodopa. In a larger series of 42 patients later characterized,[3] four were treated with levodopa, but none had any noticeable improvement. In contrast, two of the three patients we described were treated with levodopa with a moderate, sustained response. Fourteen years after onset of symptoms, Case 1 remains employed and fully ambulatory. The other two patients were only mildly disabled by their parkinsonism 2½ and 3 years after onset of symptoms. In contrast, about two-thirds of reported Lubag patients presenting with dystonia early in the course with or without parkinsonism would have developed generalized symptoms and significant disability by their fifth year.[3] The onset and progression of disability was not different between dystonia patients with and without parkinsonian features. Thus, the phenotype of predominant parkinsonism with late-onset dystonia in Lubag appears to be associated with a slower progression and later onset of disability. These patients may remain functional and gainfully employed for a longer period compared with those who develop dystonia before or concurrently with the parkinsonism. This may be, in part, due to the responsiveness of the parkinsonism to dopaminergic drugs, particularly levodopa.

Our observations suggest that there may be a milder phenotype of Lubag with moderately levodopa-responsive parkinsonism being the predominant symptom, and with dystonia developing late in the course. In Lubag patients with parkinsonism, a trial of levodopa is worthwhile. Also, one should keep a high level of suspicion for Lubag in men of Filipino descent and typical Parkinson's disease. Family history is not always reliable, and a negative family history does not necessarily rule out Lubag, especially considering that it is X-linked recessive.

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# Encephalomyelitis with Rigidity Complicating Human Immunodeficiency Virus Infection


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**Abstract:** A 34-year-old man with human immunodeficiency virus type 1 (HIV-1) presented with axial rigidity, painful

spasms, and delayed hemiparesis and dementia. Cerebrospinal fluid analysis showed no antiglutamic acid dehydrogenase antibodies but viral genome from Epstein-Barr virus was detected by polymerase chain reaction. Clinical features and possible viral aetiology of progressive encephalomyelitis with rigidity are briefly discussed.

Progressive encephalomyelitis with rigidity is a rare condition characterised by progressive rigidity of both limbs and axial muscles, painful myoclonus and spasms associated with long tract and brainstem clinical signs.[1] The neuropathological basis of this syndrome is a subacute encephalomyelitis which primarily affects grey matter.[2] The aetiology remains mostly unknown. A paraneoplastic aetiology has been confirmed in some cases.[3] An infectious aetiology has been suggested[4] but was proven in only one case of C hepatitis with detection of virus genome in the brain.[5] We describe a patient co-infected with human immunodeficiency virus type 1 (HIV-1) and Epstein-Barr virus (EBV) developing an encephalomyelitis with predominant axial rigidity.

## Case Report

A 34-year-old, Afro-Caribbean patient with HIV-1 infection (stage B3) presented in July 1998 with a one-month history of abdominal contractions and difficulty walking. HIV-1 infection had been diagnosed 6 years prior to study. Serology for human-T-cell lymphotropic virus type 1 (HTLV-1) was negative. The patient had refused anti-retroviral therapy and in July 1998 an immunodeficiency with 160 CD4 T cells appeared and HIV-1 plasma load was 5.4 log copies/ml.

The patient presented spontaneous painful contractions of abdominal muscles predominantly on the right side and severely enhanced during active or passive movements. These symptoms induced lumbar hyperlordosis and inflexion of the trunk to the right associated with stiffness of the proximal parts of the right arm and leg during standing and walking. Examination of muscular tone in the limbs, deep tendon reflexes and cranial nerves was normal. Electromyography (EMG) at rest showed spontaneous spasms in the right and left rectus abdominis muscles. These were more prominent on the right side and enhanced while standing (Figure 1). CT-scan and magnetic resonance imaging (MRI) of the brain were normal. Cerebrospinal fluid (CSF) analysis showed 14 leukocytes, raised protein level (up to 1.09 g/L) and normal glucose level. Microbiologic studies of the CSF were negative. Antibodies against glutamic acid decarboxylase (GAD) were negative in serum and in CSF. Other autoantibodies against islet cells and against neurons (Hu, Yo, Ri, CV2) were absent. No antinuclear, anti-DNA, anticardiolipin antibodies nor autoantibodies to Sm, Sm/RNP, Ro (SS-A), La (SS-B) antigens were found in serum. Intravenous clonazepam (2 mg) aborted the spasms and normalised walking within 30 minutes. The patient was treated with oral clonazepam (3 mg/day) with partial but significant improvement.

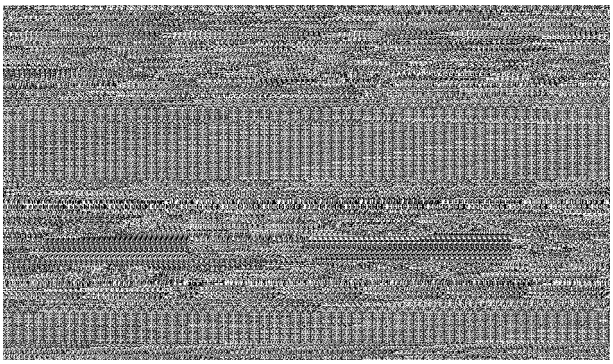

**FIG. 1.** EMG recording of spontaneous spasms from the right rectus abdominis at rest (**A**) and while standing (**B**) using surface electrodes.

On further admission in October 1998 the patient had painful continuous axial stiffness which only partially responded to clonazepam. His clinical status progressively worsened with severe immunodeficiency (43 CD4 T lymphocytes and 5.67 log copies of HIV-1/ml of plasma). In January 1999 he developed an acute right weakness. Neurological examination showed axial rigidity with increased tone of abdominal muscles, right hemiparesis, hyperreflexia, right Babinski sign, bilateral palmo-mental reflexes, and cognitive impairment. Cranial CT-scan showed three left capsulothalamic and lenticular hypodensities not enhanced by contrast. CSF analysis showed 19 leukocytes (98% polynuclear neutrophil), 1.32 g/L of protein and normal glucose. Detection of viral genome from EBV in the CSF by polymerase chain reaction (PCR) was positive whereas cytomegalovirus (CMV), herpes types 1-2-6 and herpes zoster PCR were negative. EBV serology (Elisa) was positive for IgG but not IgM. Untreated with antiretroviral therapy, in December 2000 he had a severe immunodeficiency (33 CD4 T cells and 7.57 log copies of HIV-1/ml of plasma). His neurological status (see Videotape) and CT-scan were unchanged. EMG showed continuous activity in the right and left rectus abdominis (Figure 2) and proximal muscles of the right arm and leg (biceps brachialis, quadriceps femoris, gluteus medius).

## Discussion

The patient developed a long-lasting axial muscle rigidity. This rigidity in the setting of continuous resting muscular activity may be due to tetanus, encephalomyelitis, corticobasal degeneration, focal lesions of the spinal cord, or the stiff man syndrome.[2] Tetanus was excluded. The diagnosis of stiff man syndrome of autoimmune origin was initially considered despite asymmetry of the symptoms and CSF pleiocytosis.[1] However, the absence of anti-GAD antibodies which are detected in 98% of cases of true stiff man syndrome[6] effectively excluded this diagnosis. During the course of the disease, the appearance of right hemiparesis, cognitive dysfunction and lesions of the deep grey matter supported the diagnosis of encephalomyelitis associated with rigidity.[1] We were unable to exclude a struc-

A videotape accompanies this article.

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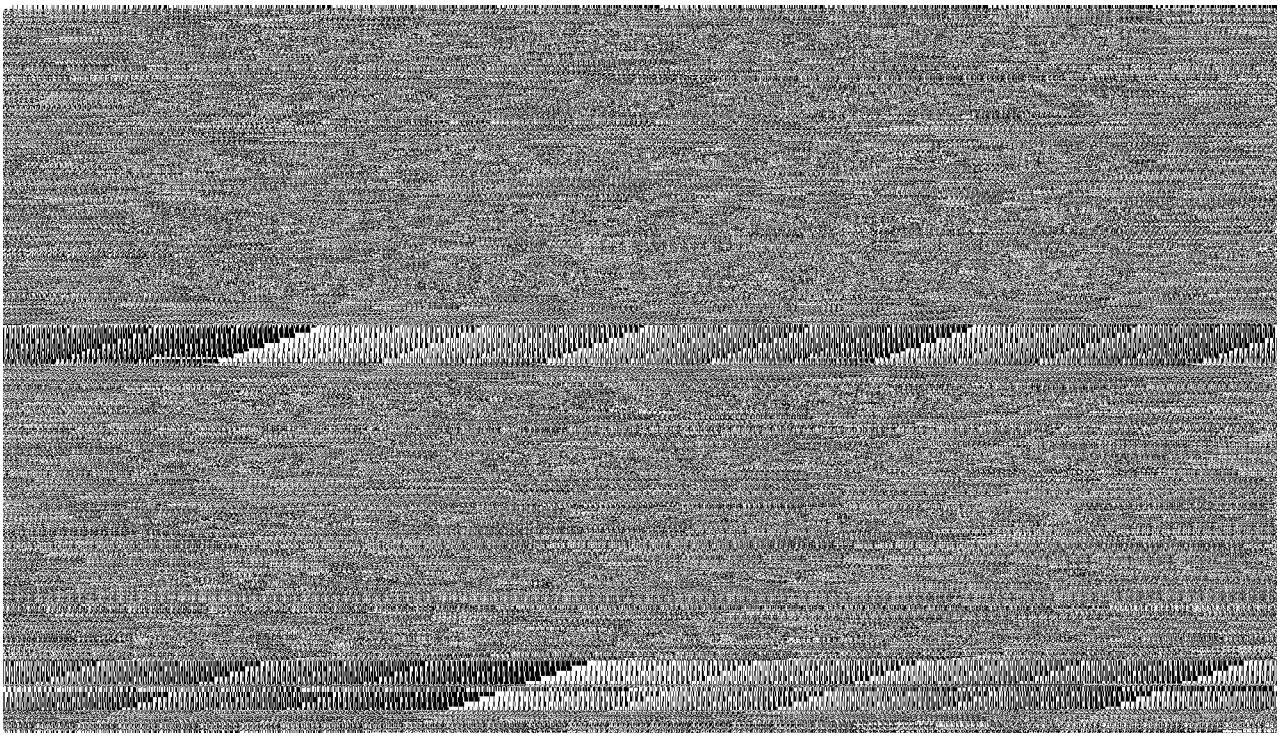

**FIG. 2.** EMG recording (surface electrodes) from the right and left rectus abdominis, at rest lying down, showing continuous activity during 500 consecutive msec.

tural spinal cord lesion because the patient declined spinal MRI on several occasions.

Encephalomyelitis with rigidity is a subacute or chronic encephalomyelitis of the grey matter with predominant involvement of spinal cord and brainstem.[1] EBV is known to produce encephalomyelitis with preferential involvement of grey matter,[7] and particularly basal ganglia.[8] In the present case the CT-scan and the detection by PCR of EBV mRNA in the CSF suggest that EBV is responsible for the patient's symptoms. Our patient represents the second case of encephalomyelitis with rigidity due to a proven viral infection of the central nervous system.[5]

## Legend to the Videotape

Patient recorded in December 2000 showing axial and right predominant rigidity during walking and laying down.

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# Improvement of Severe Trunk Spasms by Bilateral High-Frequency Stimulation of the Motor Thalamus in a Patient With Chorea-Acanthocytosis


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**Abstract:** We report on a patient with a severe form of chorea-acanthocytosis, intractable to medical treatment, who benefited

from bilateral high-frequency stimulation (HFS) of the posterior ventral oral nucleus of the thalamus. The frequency of trunk spasms dramatically decreased after surgery and the clinical benefit remained stable 1 year later. However, no clear effect was observed on dysarthria nor on hypotonia, which always impaired gait. We propose that HFS of the motor thalamus is a potential treatment for choreic or truncal dystonic symptoms whenever hypotonia is not the main feature of the syndrome. 

Chorea-acanthocytosis is a rare autosomal-recessive disorder linked to chromosome 9q21[1] and characterized by progressive neurodegeneration and abnormal red-cell morphology.[2,3] The clinical signs begin in the third or fourth decade with a hyperkinetic syndrome predominating in the orofacial region with dysarthria, chorea, hypotonia, epilepsy, and neuropathy.[4,5] Treatment remains symptomatic and is based on neuroleptics. We report on the case of a patient with a severe form of chorea-acanthocytosis, intractable to medical treatment, who benefited from bilateral high-frequency stimulation (HFS) of the posterior ventral oral nucleus (Vop) of the thalamus. As far as we know, it is the first report of an axial choreic syndrome improved by deep brain stimulation (DBS).

## Case Report

The patient was a 43-year-old man who exhibited violent trunk spasms (Video, Segment 1), associated with a major hypotonia, oromandibular dystonia, and a clinical neuropathy. Dysarthria was so severe that his speech was unintelligible. He was bedridden and totally dependent. Spasms disappeared during sleep. His Marsden and Schachter choreic rating scale[6] was 54 of 60 and his Barthel score[7] 15 of 100 before surgery. The patient presented three general epileptic seizures at the beginning of the disease and was treated thereafter by sodium valproate (1.5 g/day) and phenobarbital (50 mg/day). The disease has progressively worsened over a 12-year period and high-dose neuroleptics (haldoperidol, 25 mg/day) were of little effect.

MRI showed an atrophy predominating in the caudate nucleus and putamen. Biological investigations revealed acanthocytosis associated with increased creatine kinases and transaminases. Blood samples of the patient and his family (a sister was affected) were used for a genetic study of chorea-acanthocytosis in which a linkage of the disease to the 6-cM region of chromosome 9q21 was demonstrated (Family CA, Patient 2.7).[1] Other laboratory tests were normal. Electromyographic investigation indicated the existence of neurogenic signs in several lower limb muscles. Motor and sensory nerve conduction studies were normal. Typical lesions of neurogenic atrophy were found on muscular biopsy. Polygraphic electromyographic recordings performed in several muscles of the axis and lower limbs were performed. They showed trunk spasms of 3–12 seconds duration (average 5.2 ± 2.9 seconds) separated by periods of low electrical activity reflecting the severe hypotonia of the patient between spasms (Fig. 1A). A trunk spasm score (i.e., number of spasms per min) was calculated during the 15 min of continuous recording, the patient being fully awake. The clinical state of the patient was so dramatic that he and his wife chose to pursue a trial of DBS. The procedure was approved by the local ethical committee.

Under general anesthesia, two electrodes (Model 3387; Medtronic, Minneapolis, MN) were stereotactically and bilaterally implanted into the posterior Vop of the thalamus. The surgery was performed using a Talairach stereotactic frame and a fixed face/profile orthogonal radiologic system (distance, 5 m). The anterior commissure–posterior commissure (AC–PC) was determined on ventriculography. Radiological control at the end of surgery (Fig. 2A and B) showed that the lower plot (plot O) was positioned right 12 mm and left 13 mm lateral to the AC–PC line, right 9 mm and left 8 mm rostral to the posterior commissure, and right 0 mm and left 2 mm above the AC–PC line. Figure 2C, D shows the location of electrode plots with respect to a superimposed map of thalamic nucleii from the Schaltenbrand and Wahren Atlas,[8] whose scale was adapted to the ventriculographic landmarks (AC–PC line). It indicates that the right electrode was slightly rostral and located near the nucleus ventro-oralis anterior (VOA) nucleus, whereas the left electrode was situated in the external part of the Vop nucleus. Two pulse generators were internalized (Model 7425; Medtronic, Minneapolis, MN) and monitored with a continuous stimulation. The initial setting with a monopolar stimulation was as follows: 3.5 V at both sites; 160 Hz; pulse width, 90 μsec. After different attempts, it was found that the best combination of active plots was on the right-side plots 1, 2, and 3, and on the left-side plots 1 and 2. Voltage intensity was reduced to 1.5 V on the right and 2.0 V on the left 6 months after surgery without loss of the clinical benefit.

Postoperative testing showed a progressive improvement in choreic movements (Video, Segment 2). At 3 months, the patient was able to read and use a pencil to write. He asked to be allowed to eat unaided, although he was still clumsy due to hypotonia and needed help in cutting food. These activities were totally impossible before surgery. His Barthel index increased to 35 of 100 and his Marsden and Schachter choreic score decreased to 34 of 60. No clear effect was observed on hypotonia, which always impaired gait, nor on dysarthria. Electromyographic recordings of several trunk and limb muscles revealed that spasms frequency had decreased from 4.9 ± 0.1 to 1.4 ± 1.0 spasms/minute 3 months after surgery ($P = 0.0047$, *U*-test). The patient was seen at 6 months after surgery (Video, Segment 3) and his clinical state continued to improve. The trunk spasm score calculated from electromyographic recordings remained stable (1.2 ± 1.6 spasms/minute). Examples of integrated EMG (stimulator on) are shown in Figure 1B. Nine months after surgery, the patient was able to walk between parallel bars (Video, Segment 4). His clinical state was unchanged 1 year after surgery. He had one epileptic seizure 6 months after surgery in a period during which stimulator settings had remained unchanged for 3 months. Haloperidol treatment was decreased to 15 mg/day 1 year after surgery.

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A videotape accompanies this article.

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**FIG. 1.** Electromyographic recording of several axial muscles. **A:** Before surgery direct electromyographic recordings were performed in several axial muscles. LPV, lumbar paravertebral muscle; DPV, dorsal paravertebral muscle; CPV, cervical paravertebral muscle; Trp, Trapezius. Scale bar = 1 second. Spasms of variable duration were observed. They were separated by a period of electric silence associated clinically with a severe hypotonia. **B:** Three months after surgery integrated and filtered electromyographic recordings were performed in order to suppress the stimulation artefacts. Scale bar = 8 seconds. A discrete arm movement (asterisk) is recorded but no truncal spasm.

## Discussion

The genetic determinants of chorea-acanthocytosis and Huntington chorea are different, but both are associated with choreic symptoms, trunk spasms, hypotonia, and an atrophy of the caudate nucleus and putamen. In the current model of hyperkinetic movement disorders, chorea is associated with hyperactivity in the so-called "indirect striato-pallidal pathway," leading to hypoactivity in the internal pallidum.[9] Pallidal outputs to the thalamus are thus decreased and the resulting overactivity of the thalamus may account for the involuntary choreic movements generated in premotor cortex areas. Our result shows that HFS of the motor thalamus is able to significantly reduce the rate of axial choreic movements. Because we did not use intraoperative electrophysiology in this case, we do not know whether the positive effect of HFS was due to a decrease in the neuronal discharge frequency of thalamic neurons or to the regulation of their firing pattern. Nevertheless, if one accepts that HFS might have a similar effect as lesions even though the mechanism is different, then these data are in agreement with reports indicating that thalamotomy is effective in the treatment of various forms of hyperkinetic syndromes including chorea,[10] dystonia,[11–13] hemiballismus,[14] or levodopa-induced dyskinesia.[15] Recently, an improvement of choreiform movements was reported in two children with disabling disorders due to intracerebral hemorrhage or cerebral palsy.[16] The lack of effect on hypotonia in our patient suggests that hypotonia may be subserved through projections from the internal pallidum to the brainstem. These projections, presumably to the pedonucleopontine nucleus, bypass the thalamus and might therefore not be influenced by DBS. Hence, we propose that HFS of the motor thalamus might be a potential treatment for

**FIG. 2.** Location of the stimulation electrodes according to the ventriculographic landmarks. **A:** Sagittal radiography showing the location of electrode plots with respect to the anterior commissure (AC)–posterior commisure (PC) line. **B:** Frontal radiography. **C** and **D:** Enlargement of A and B with a superimposed mapping of the thalamic nucleii from the Schaltenbrand and Wahren Atlas (1977). Scale of the atlas was adapted to the ventriculographic landmarks.

choreic or truncal dystonic syndromes when hypotonia is not the main feature of the syndrome.

## Legends to the Videotape

**Segment 1.** Severe choreic syndrome involving the trunk and the four limbs at rest and in supine position. Sitting and standing are impossible. The spasms were so violent in this segment that the patient broke the armchair on which he was lying during the videotape.

**Segment 2.** Three months after surgery. The rate of trunk spasms has dramatically decreased by hypertonia still impairs arm movement.

**Segment 3.** Continued improvement after 6 months.

**Segment 4.** At 9 months the patient was able to walk between parallel bars.

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# Intracortical Inhibition Is Reduced in a Patient with a Lesion in the Posterolateral Thalamus

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**Abstract:** We describe a patient who developed a complex movement disorder following an ischemic lesion in the right posterolateral thalamus. Transcranial magnetic stimulation showed a shortening of the cortical silent period and deficient cortico-cortical inhibition using paired magnetic pulses on the affected side, indicating reduced effectiveness of intracortical inhibitory mechanisms. © 2001 Movement Disorder Society.

Lesions of the thalamus, subthalamic structures, internal capsule, and adjacent thalamic connections with basal ganglia and cerebellum give rise to a spectrum of motor syndromes that includes hemiballism, hemidystonia, choreoathetosis, tremor, ataxia, asterixis, paroxysmal dystonia, and hemiparesis.[1,2] Lesions involving the ventrolateral thalamus are well known to cause a combination of ataxia, hemiparesis, and sensory loss (ataxic hemiparesis and its variants).[1,3–6] However, apart from asterixis and isolated tremor,[2,3,7,8] movement disorders have rarely been described. This is surprising, because the ventrolateral thalamus receives major inputs from the basal ganglia and projects to motor and premotor cortex. In contrast, there are a number of reports of patients who developed abnormal movements after posterior or posterolateral thalamic lesions outside the ventrolateral motor relay nuclei,[2,7,9,10–22] the reason for which is not clear. We describe a patient with a complex, disabling movement disorder after infarction in the territory of the posterior choroidal artery involving the posterolateral thalamus. Transcranial magnetic stimulation (TMS) findings in this patient demonstrated a reduction of intracortical inhibitory mechanisms.

A videotape accompanies this article.

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## Case Report

A 27-year-old, right-handed man had experienced sudden onset of severe occipital headache followed by left hemianopia, hemiparesis, and sensory loss at the age of 15 years. At that time, a computer tomography of the brain showed a small hypodense lesion in the right thalamus. A magnetic resonance image, taken in 1998, demonstrated an approximately 1-cm focal lesion in the right posterolateral thalamus corresponding to the territory of the posterior choroidal artery, compatible with an old ischemic lesion (Fig. 1). This lesion was highly circumscribed and lay outside the ventrolateral thalamic motor relays.

One year after the insult, his hemianopia and sensory loss had resolved completely and power was normal. However, 3 months after the insult, while the hemiparesis gradually improved, a marked postural and action tremor became evident in his left arm that persisted over the following years. At the time of admission to our hospital neurological examination was normal apart from his movement disorder. At complete rest there was no tremor. Slight muscular tension produced a fairly regular low-frequency tremor of the left arm that increased on distraction. Postural tremor was present both in the left arm and left leg. Tremor amplitude increased when the arm was held outstretched. Tremor became very severe with arm movements, especially when the hand approached a target, so that the patient was unable to perform fine manual tasks with the left hand. Arm posture was dystonic, particularly affecting the upper arm and shoulder, and there were superimposed myoclonic jerks, most prominent when the patient attempted to write with his left hand. He was walking with reduced arm swing on the left.

Polymyographic recordings from outstretched left forearm muscles revealed a postural tremor at 3.5 Hz, which was alternating in antagonist muscles. It increased in amplitude during movement without changing frequency (data not shown). Sensory evoked potential studies from median and tibial nerve were normal. Transcranial magnetic stimulation (TMS), carried out at complete rest when no involuntary movements were present, revealed normal active and relaxed thresholds for EMG responses in the right and left first dorsal interosseus muscles (right arm, 35% of stimulator output when active, 44% relaxed; left arm, 36% active, 44% relaxed). However, the cortical silent period (SP) elicited by suprathreshold TMS during a 20% maximum voluntary contraction was much shorter in duration in the left arm (81 ± 7 msec) than in the right arm (136 ± 13 msec), even though the motor-evoked potentials were of similar size (2 ± 0.3 mV in the left arm; 1.7 ± 0.7 mV in the right arm) (Fig. 2A). Short latency cortico-cortical inhibitory connections were investigated with paired TMS pulses, one of which being the test (control) stimulus, the other a conditioning pulse preceding the test pulse by 1–6 msec.[23] The intensity of the conditioning shock was set at 5% of maximum stimulator output below the active motor threshold, whereas the intensity of the test (control) shock was larger and sufficient to produce a motor-evoked potential (MEP) of 0.5 mV peak-to-peak amplitude in relaxed first dorsal interosseus muscle. The area under the curve (AUC) of the nonrectified MEPs following paired pulses was expressed as a percentage of the AUC of the control MEP. Test pulses alone and paired pulses with different interstimulus intervals (1–6 msec) were applied in a pseudorandom fashion. A conditioning pulse given at 1–5 msec before the test

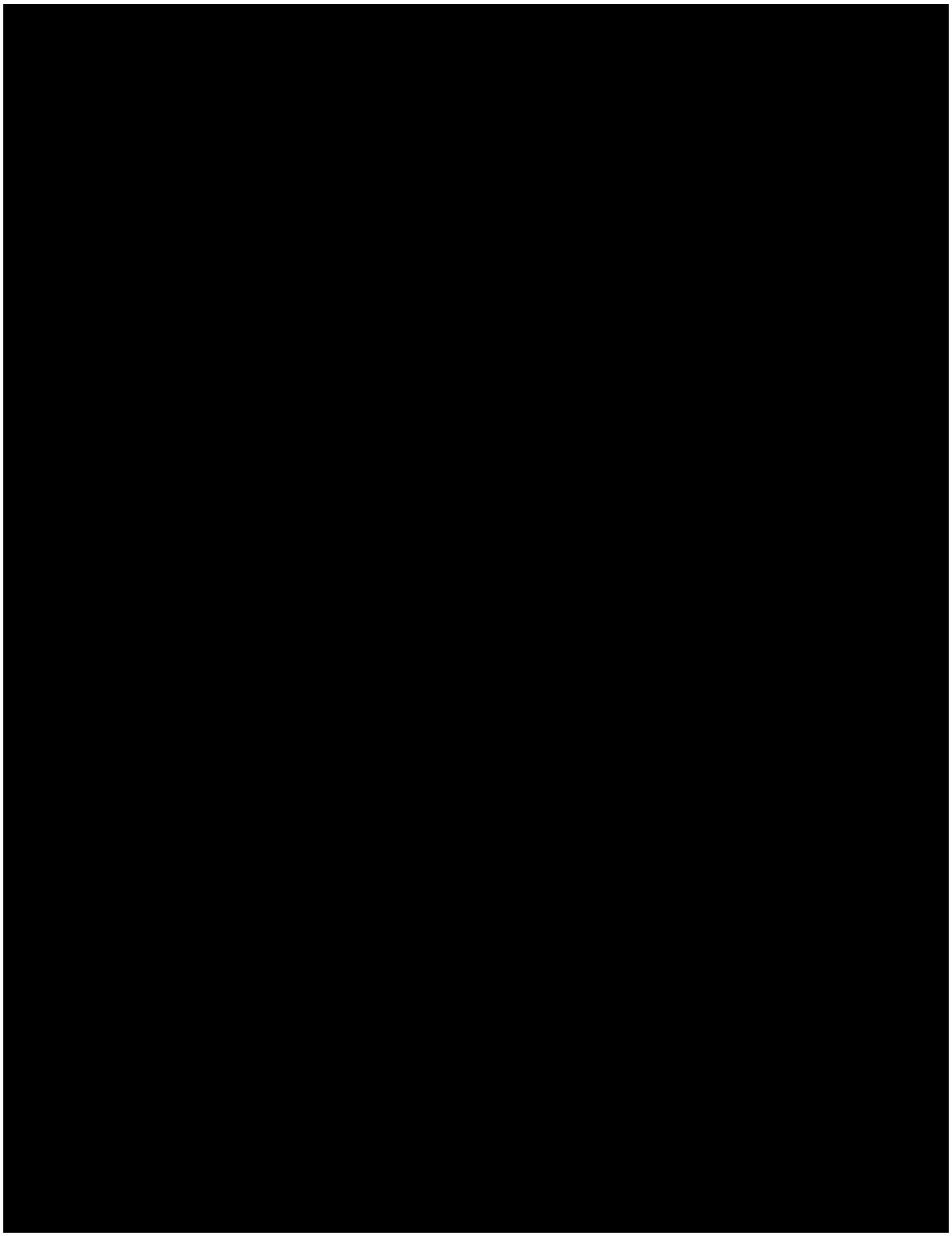

**FIG. 1.** Magnetic resonance image of the brain showing an approximately 1-cm focal lesion in the right posterolateral thalamus corresponding to the territory of the posterior choroidal artery. On the T2-weighted image (**top left**) the lesion appears hyperintense. It is hypointense on T1-weighted images (**top** and **bottom right**) and there is no contrast enhancement after i.v. gadolinium application (**bottom left**). These findings are compatible with an old ischemic infarct.

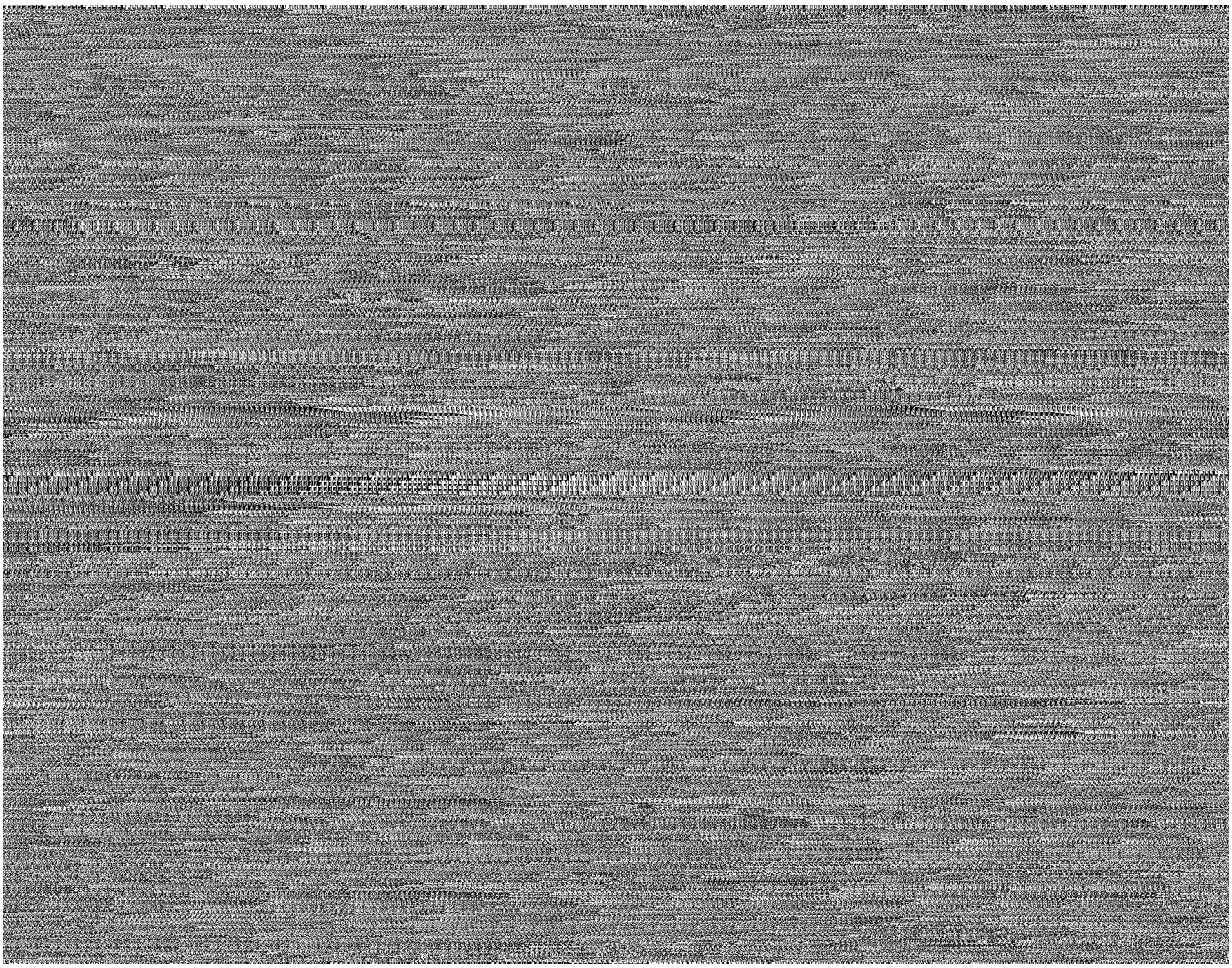

**FIG. 2.** **A**: Superimposed raw data traces (four trials) showing electromyographic silent periods in the contracting (20% of maximum voluntary contraction) right and left first dorsal interosseus (FDI) muscle. Cortical stimulus intensity was adjusted to evoke a muscle response in active muscle with an amplitude of approximately 2 mV peak-to-peak (1.7 mV ± 0.13 SD and 2 mV ± 0.3 S.D. in right and left first dorsal interosseus muscle, respectively). The silent period duration is significantly shorter in the left FDI muscle ($P < 0.005$, paired Student's *t*-test). **B**: Raw data of the ipsilateral cortico-cortical inhibition in the right and left relaxed FDI muscle of the patients. Each trace is the mean of five responses. The upper traces are the responses to test stimulus alone and the lower traces are the responses to the conditioned test stimulus at interstimulus intervals of 1–6 msec. At 4 and 5 msec interstimulus intervals (ISI) there was significantly less inhibition in the left FDI ($P < 0.005$, paired Student's *t*-test). **C**: Tremor frequency (Hz) after the delivery of cortical stimulus as a function of magnetic stimulus intensity. The tremor frequency correlates significantly with the stimulus intensity (linear correlation coefficient, $r = 0.97$; $P < 0.005$). T = active motor threshold. **D**: Average (10 trials) rectified forearm extensor EMG signals collected for 2.5 seconds before and 2.5 seconds after a magnetic brain shock at five different stimulus intensities. The magnetic brain stimulus is given in the middle of each trial, but at random times with respect to the phase of ongoing tremor. Note that bursts of rhythmic EMG activity are averaged out and EMG amplitudes are small in the first half of the trace, which is caused by phase cancellation. In contrast, EMG bursts of higher amplitude are clearly discernible in the second half of the trace after the stimulus, indicating synchronization of tremor by TMS. The frequency of EMG bursts is increased at the highest stimulus intensity. T = active motor threshold

stimulus resulted in a normal reduction of the AUC of the MEP on the unaffected right side. At interstimulus intervals of 4 and 5 msec there was significantly ($P < 0.005$) less reduction of the AUC on the affected left side as compared with the right (Fig 2B). In addition, we found that single TMS shocks could reset the phase of ongoing tremor when the arm was held outstretched (Fig. 2D). The frequency of tremor immediately after resetting was usually slightly higher than at baseline. The larger the intensity of stimulation used to produce resetting, the more the frequency increased (Fig. 2C).

## Discussion

This patient suffered from an infarction affecting the right posterolateral thalamus. In view of the history it is possible that the underlying cause was migraine, but this remains uncertain. He recovered from the initial left-sided hemiparesis and hemianopia. However, several months later he developed a severe, coarse, and irregular postural, kinetic, and intention tremor with dystonic posturing of the affected limb and superimposed myoclonic jerks. Similar clinical syndromes have recently emerged

as being rather typical for patients with posterolateral thalamic lesions.[2,9,10–22] The underlying pathophysiology is as yet unclear.

TMS demonstrated a shortened SP on the affected as compared with the unaffected side in our case. In contrast, von Giessen and colleagues[24] reported a prolongation of SP in patients with focal thalamic lesions. The reason for this discrepancy is unclear. We also found a reduction of cortico-cortical inhibition on the affected side using paired-pulse TMS. Although both this finding and the shortening of the SP would be in keeping with the interpretation that intracortical inhibitory mechanisms were reduced on the affected side, it has to be borne in mind that SP and cortico-cortical inhibition are likely reflecting separate mechanisms.[25] Moreover, cortico-cortical inhibition is altered in a number of different conditions[26] and therefore has to be regarded as a relatively nonspecific measure of cortical excitability. Nonetheless, it is interesting to note that similar to our case a reduction of cortico-cortical inhibition has also been reported in patients with abnormalities in the basal ganglia-ventrolateral thalamus-frontal cortex loop.[27,28] On MRI images, the lesion in our patient appeared to be confined to the posterolateral thalamus. The initial presentation with hemiparesis and hemisensory symptoms is compatible with damage to the adjacent internal capsule and ventrolateral thalamic nuclei. MRI performed many years after the acute event might have underestimated the extent of the original lesion. The deficits of intracortical inhibition we have observed could thus be due to lasting, albeit subtle, damage of the basal-ganglia–ventrolateral-frontal cortex loop.

Alternatively, this loop might have been affected indirectly by damaged nuclei in the posterior thalamus projecting onto nuclei in the ventrolateral thalamus. One candidate would be the reticular nucleus that lies within the lesion in this case. The thalamic reticular nucleus projects to various thalamic nuclei and receives collateral input from thalamocortical and cortico-thalamic fibers.[29,30] Disconnection of ventrolateral thalamic relay nuclei from the thalamic reticular nucleus has been shown to produce abnormal rhythmicity in disconnected neurons, presumably due to disinhibition.[31] This in turn is likely to alter activity in thalamo-cortical projections. Interestingly, TMS could reset our patient's tremor and modify its frequency. This is reminiscent of parkinsonian tremor[32] in which abnormal rhythmicity of the thalamic reticular nucleus has been proposed.[33] Because the reticular nucleus projects to different thalamic motor nuclei in parallel, a lesion in the posterolateral thalamus involving the reticular nucleus could disturb different thalamo-cortical loops and consequently lead to a complex movement disorder, as in our case, rather than to pure tremor or dystonia.

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## Legend to the Videotape

When the patient is sitting relaxed with his hands on his knees there is very slight rest tremor in the left hand. On distraction (counting backwards from a hundred) he develops an irregular mainly pro/supination, coarse, and slow tremor of the left arm. Its amplitude increases when holding out the arm and on finger-nose testing. The tremor involves proximal and distal muscles. There are superimposed myoclonic jerks, especially when he is trying to rest his left arm on his left knee again. Walking is normal. While standing, holding out the arm and opening/closing his fingers, myoclonic jerks become particularly noticeable in the left pectoralis muscle. Fine finger movements on the left are clumsy. He is unable to write because of severe myoclonic jerks.

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## Focal Pathological Startle Following Pontine Infarction

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**Abstract:** A 36-year-old male developed an acute right-sided weakness due to left-sided pontine infarction. Two months later, he first noticed sudden right elbow flexion in response to a loud unexpected noise. Detailed electrophysiological assessment was performed. A large, short-latency (median 39 msec), synchronous electromyographic discharge occurred in the right biceps brachii electrodes following a 50-msec, 120-dB 1-kHz tone burst, with habituation only with very short (30-second) interstimulus intervals. Less synchronous activity at longer latencies was present both in a number of right-sided arm muscles at rest and on the clinically unaffected side during a tonic voluntary contraction. We discuss possible underlying mechanisms and our reasons for considering this a focally enhanced startle response. Our report broadens the range of expression of acquired startle disorders. © 2001 Movement Disorder Society.

An intense, unexpected stimulus, particularly sound, evokes a stereotyped startle response in normal humans and animals.[1–5] The initial reaction involves eye closure, facial grimacing, neck flexion and abduction and flexion of the arms.[1,2] The muscles of the legs are usually not involved[3,4] and the response rapidly habituates with repeated presentation of the same stimulus. Electromyographic study of the normal startle reflex reveals polyphasic responses at latencies shorter than normal voluntary reaction times (typically 60 msec or longer onset latency in biceps).

Abnormalities of the startle reflex may be subdivided and include simple exaggerated startle (normal latencies, reduced habituation) and hyperekplexia (reduced thresholds and habituation, often with characteristic short latency responses to tap in the mantle region). The latter syndrome, often hereditary, is associated with particularly short response latencies.[6] Sound-induced muscle jerks are not unique to startle, however, and are seen in some cases of reticular reflex myoclonus (RRM)[7,8] and can also be psychogenic.[9]

We report here on a case that falls within the spectrum of pathological conditions resembling startle, but differing from previously reported cases in several important respects. Following infarction confined to the left ventral pons, our patient developed focal sound-sensitive jerks in the right arm, which we have investigated neurophysiologically. Both the focal nature of the clinical abnormality and the short latency of the response are unusual but our observations suggest that this is part of the spectrum of acquired startle disorders.

### Case Report

A previously healthy 36-year-old, right-handed man woke one morning with severe right hemiparesis (grade 0/5 distally, 2–3/5 proximally), including involvement of right facial muscles. There was mild dysarthria, but no dysphasia or sensory abnormality. A cerebral computed tomography (CT) scan performed acutely was normal. Cerebral magnetic resonance imaging (MRI) performed 1 week after onset showed a probable infarct in the left ventral pons with some extension across the midline and a haemorrhagic component. He had a history of cigarette smoking (approximately 15/day) and of moderately heavy alcohol consumption (approximately 100 g/day). His serum cholesterol was elevated (6.9 mmol/L). There was no other relevant history. Normal results were obtained for most investigations aimed at identifying a cause for the stroke, including magnetic resonance angiography, trans-oesophageal echocardiography, and procoagulant blood tests. Carotid and vertebral duplex scanning showed a small soft flattened plaque in the bulb of the right common carotid artery.

With inpatient rehabilitation, he made steady improvement and after 4 months was able to walk independently, write slowly with his right hand, and perform all activities of daily

A videotape accompanies this article.

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living independently. One year after onset, he was able to return to computer programming part-time.

He first noticed jerking of his right arm in response to unexpected, loud sounds while he was an inpatient, about 2 months following the stroke. A tray was dropped nearby and his right arm jumped. The predominant movement was elbow flexion. The ward was usually fairly quiet and he was uncertain whether he had been exposed to an equivalent stimulus prior to then. Upon discharge home, he continued to experience this problem, without substantial change. Sounds such as the telephone ringing, a car backfiring or an unexpected shout produced sudden elbow flexion. Were he to be holding a full cup, glass, or jug at such times the contents would often spill. The introduction of baclofen 4 months after his stroke as treatment for spasticity had no influence upon these involuntary movements.

On examination 9 months after his stroke, the findings were as follows. A typical right hemiparetic gait was observed with circumduction of the leg and flexion of the arm. There was moderate right arm and leg spasticity with brisk right-sided tendon jerks, but a flexor plantar response. Mild distal weakness (4+/5) was found for both the right arm and leg and fine finger movements were slow and clumsy. There were no cerebellar or sensory abnormalities. In response to an unexpected tone burst, there was visible contraction of right biceps brachii associated with elbow flexion (see Video). Elbow flexion appeared of greater amplitude when the arm was raised and consequently biceps was tonically activated. Abnormal movements could not be evoked by any other type of stimulus, including tapping on the face or chest, tapping or pricking of the arms or hands, and electrical stimulation of the median nerve.

A repeat cerebral MRI scan was performed 9 weeks after onset to investigate the possibility of an underlying lesion, such as a vascular malformation, to explain the stroke. No such lesion was demonstrated. This scan revealed a small region of cerebral spinal fluid (CSF) density confined to the left side of the ventral pons at the midpontine (middle cerebral peduncle) level (Fig. 1).

Brainstem auditory evoked responses and somatosensory evoked potentials to median and tibial nerve stimulation were performed in a standard manner and showed no abnormality.

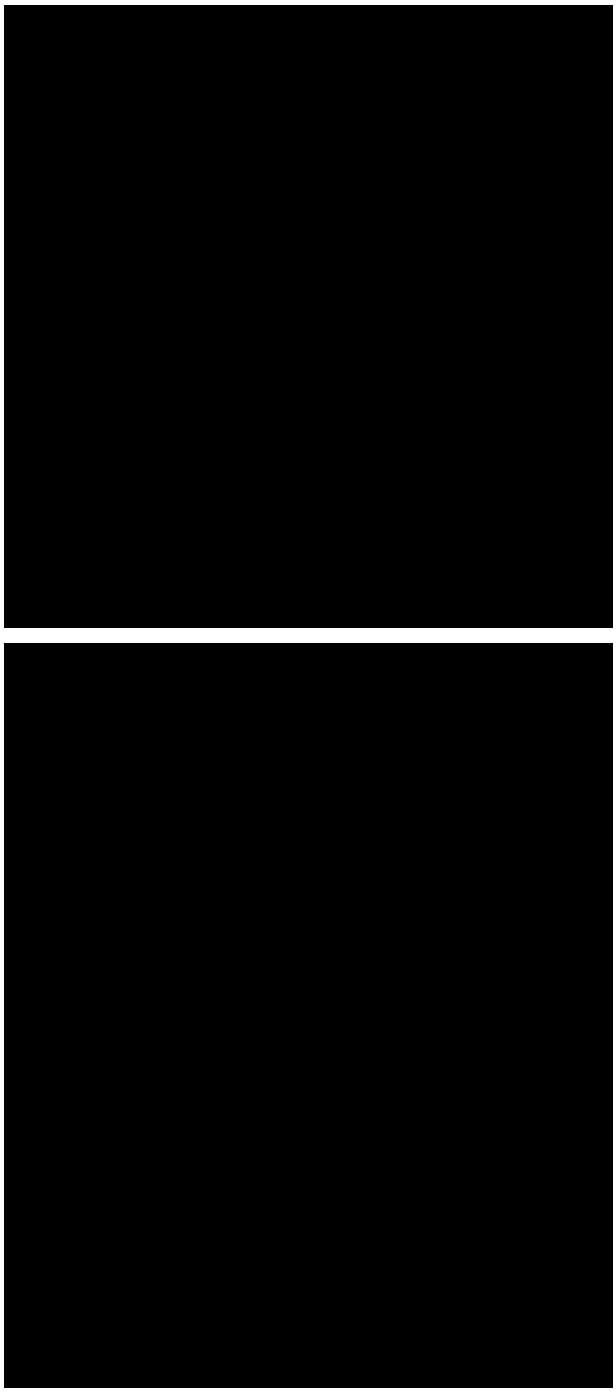

**FIG. 1.** T1-weighted magnetic resonance imaging (MRI) scans from 9 weeks following presentation. **A:** A sagittal view to the left of midline. **B:** An axial view at the midpontine level. A circumscribed region of cerebral spinal fluid (CSF) density is present in the left ventral midpontine region, consistent with an area of postinfarction porencephaly.

## Methods

Tone bursts of 1 kHz, 50-msec duration and 120 dB (ISO) were delivered binaurally through calibrated headphones (TDH49, Telephonics, Farmingdale, NY). Stimuli were delivered unpredictably, approximately every 4 minutes, unless otherwise stated. Pairs of surface electrodes were placed 6 to 8 cm apart over muscles to be studied. Surface electromyographic (EMG) signals were bandpass filtered (8–1,600 Hz) and acquired using Sigavg software (Cambridge Electronic Design, Cambridge, U.K.) at a sampling rate of 5,000 Hz.

In the first set of trials (n = 4), the patient sat relaxed in a comfortable chair while EMG was recorded from orbicularis oculi (OrbOc), sternocleidomastoid (SCM), biceps brachii (biceps), and tibialis anterior (TA) bilaterally. A further set of trials studied the habituation of the right biceps response at various stimulation intervals. Surface EMG was recorded from right biceps, SCM, and OrbOc, and the standard acoustic stimulus was delivered unpredictably, with interstimulus intervals of approximately 4 minutes, 1 minute, or 30 seconds (n = 8 of each). The distribution of the response within the right upper limb and right-sided cranial nerves was studied in detail using surface EMG recorded from right abductor pollicis brevis (APB), flexor carpi radialis, extensor carpi radialis, biceps, triceps, SCM, masseter and OrbOc (10 runs).

The effect of background contraction of muscles was also examined. In one series of trials, the right biceps was relaxed while the left biceps was activated (8 runs), with the aim being to determine whether increasing motoneuronal excitability would result in responses in left biceps. We also recorded from biceps, SCM, APB, and TA bilaterally while these muscles were tonically active (4 runs). Because fatigue developed rapidly during contraction of right-sided muscles, we instructed the patient to activate his muscles approximately 4 minutes after the previous stimulus and then delivered the stimulus unpredictably over the following minute.

Cortical magnetic stimulation was performed using a MagStim Model 200 (MagStim, Dyffed, Wales) stimulator and circular coil, recording with surface electrodes over biceps brachii bilaterally.

## Results

Typical responses obtained during relaxation are shown in Figure 2. A high amplitude (up to 2.5 mV), biphasic response occurring at short latency was always recorded over the right biceps. In contrast, during relaxation, no responses were recorded in the left biceps or in either TA muscle. Responses were also recorded in OrbOc bilaterally in all trials and in SCM bilaterally in most trials. The responses in these muscles generally comprised a highly polyphasic burst of EMG activity rather than the synchronous biphasic volley observed for the right biceps. The onset latencies for responses in all three of these muscles showed quite large variations between trials. The range and median onset latencies were: right OrbOc 20–50 (37) msec; right biceps 27–48 (39) msec; right SCM 28–72 (39) msec. Using the trials in which responses were clearly present in the two muscles being compared (trials with muscles relaxed only), there was no difference in onset latency between right SCM and right biceps (Student's *t*-test, $P = 0.29$, $n = 19$) while the onset was earlier for right OrbOc than right biceps ($P < 0.005$, $n = 27$). There was little habituation of the right biceps response with the interstimulus intervals of 4 minutes or 1 minute, but marked attenuation of the response amplitude occurred when stimuli were presented at 30-second intervals. The distribution of the response in the right upper limb and cranial nerves is shown in Figure 3. A small response in masseter was recorded in two of 10 trials, with onset latency 4 and 8 msec after biceps, respectively. Responses in triceps and forearm muscles occurred in nine of 10 trials and followed the response in biceps by no more than 10 msec. In eight of 10 trials, a response was seen in APB. This response occurred at relatively long latency and showed very wide temporal jitter between trials (61–131 msec). The interval separating the onset of the responses in biceps and APB varied between 28 and 98 msec. In the three trials in which the APB response commenced

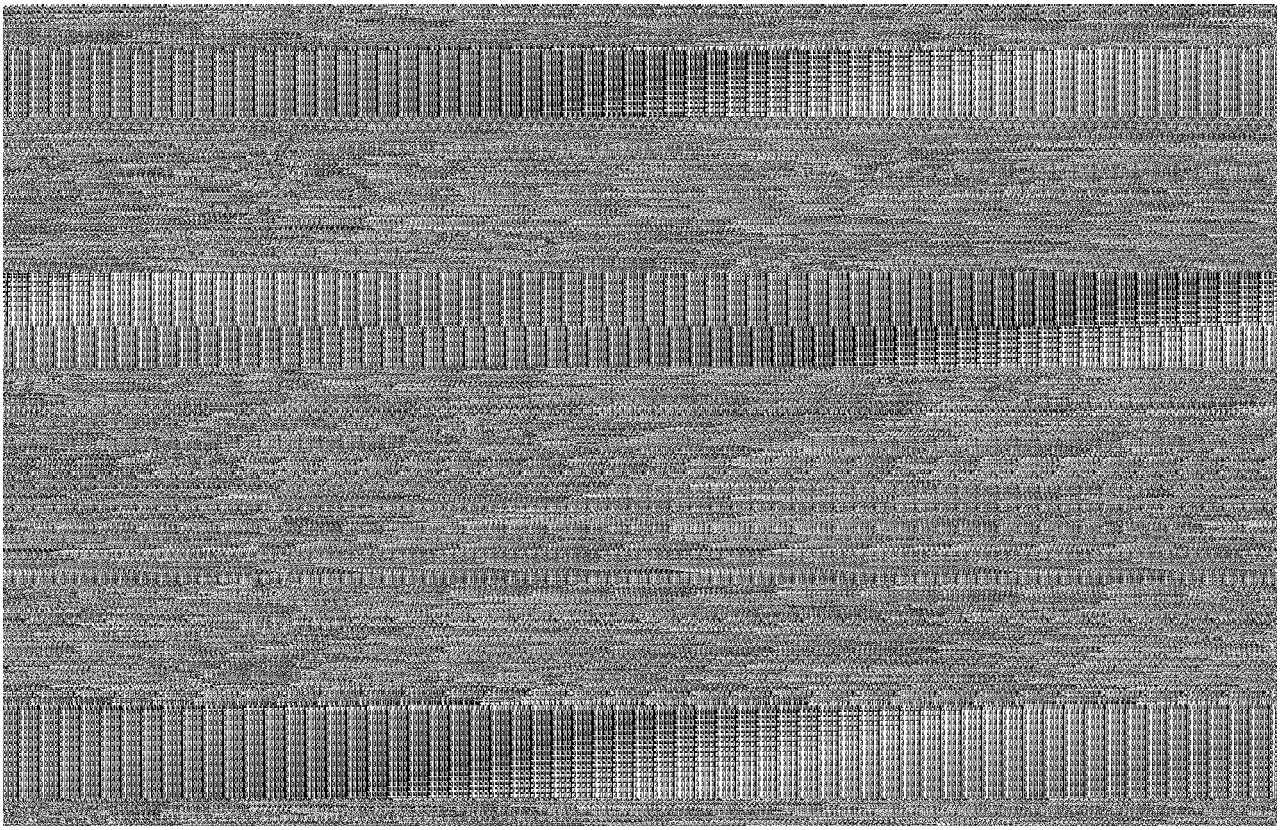

**FIG. 2.** Responses to a binaural 1-kHz, 120-dB, 50-msec duration tone burst, presented at least 4 minutes after the preceding pulse. Responses in relaxed muscles from both right and left sides are shown: orbicularis oculi (Orb Oc); sternocleidomastoid (Scm); biceps brachii (biceps); tibialis anterior (Tib Ant). Onset latencies are indicated with arrows. A large biphasic response is evident in the right biceps. No response occurred in the left biceps.

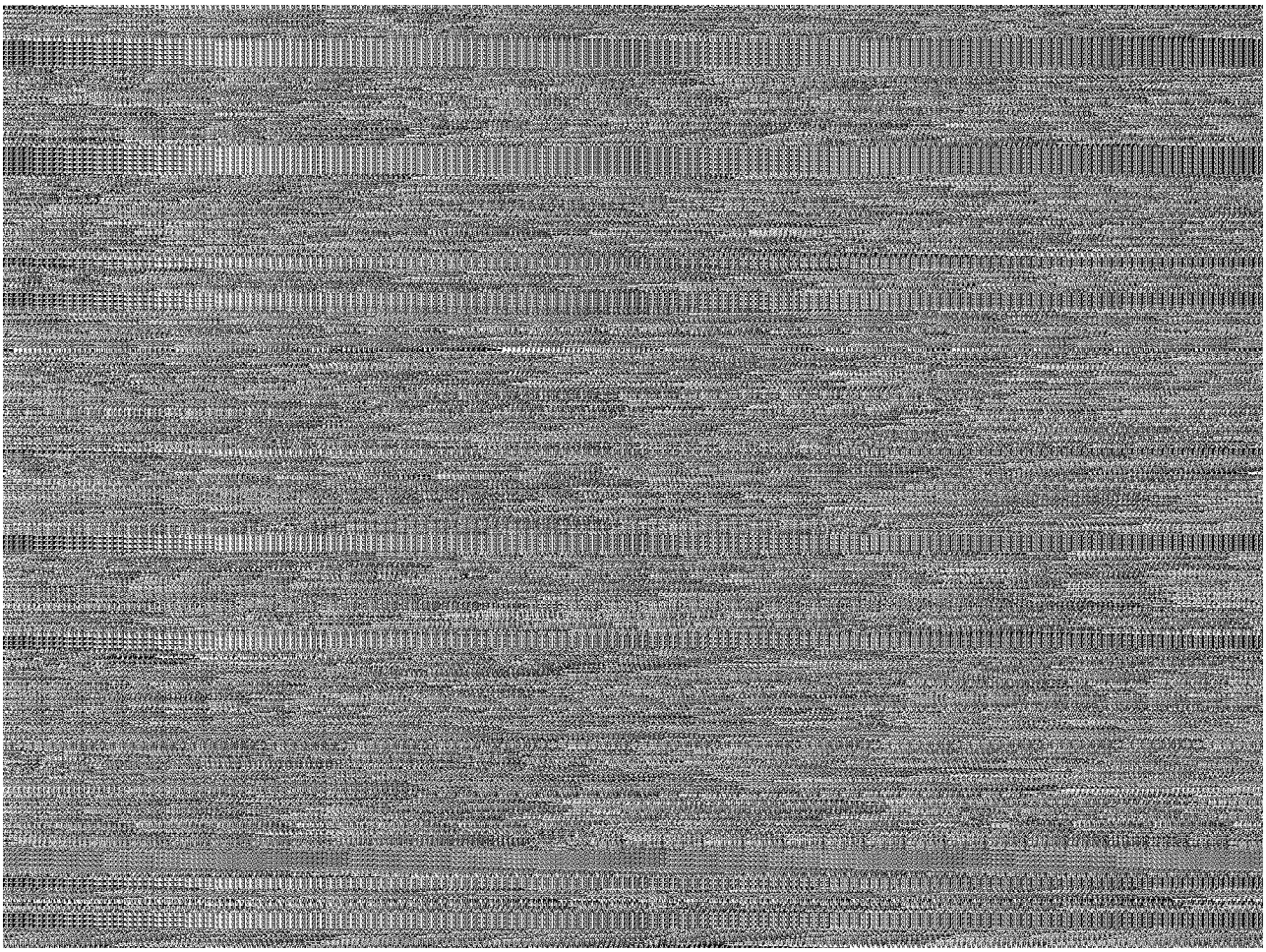

**FIG. 3.** Responses in right-sided arm and cranial nerve muscles to a binaural 1-kHz, 120-dB, 50-msec duration tone burst, presented at least 4 minutes after the preceding pulse (a separate trial in each column). Muscle names are abbreviated as follows: orbicularis oculi (Orb Oc); sternocleidomastoid (Scm); masseter (Mass); flexor carpi radialis (FCR); extensor carpi radialis (ECR); abductor pollicis brevis (APB). Onset latencies are indicated with arrows.

before 100 msec (61, 69, and 71 msec onset latency, respectively) there was a further burst of EMG activity commencing after 100 msec.

In contrast to the results obtained during relaxation, a small but definite excitatory EMG response was recorded in the left biceps during background muscle activation in three out of eight trials (Fig. 4). This response occurred at similar latency (1 to 9 msec later) to the response recorded concurrently in right biceps, but was always of much smaller amplitude. A period of inhibition of left biceps EMG activity followed the initial excitatory response or occurred in the absence of an excitatory response (as illustrated). No responses occurred in left APB despite background activation. While no excitatory responses were observed in either TA, in several trials there was a period of inhibition of EMG activity in left TA (Fig. 5). With background activation of right- and left-sided muscles, three of the four trials showed a double-peaked response in right biceps, a pattern never observed with the muscle relaxed. For these three trials, the onset latencies were 27, 27, and 29 msec, respectively, amongst the shortest we recorded (one response of latency 27 msec was also recorded with the muscle relaxed). Three of the four trials also showed an initial right APB response at relatively short latency (64, 66, and 67 msec, respectively), in each case followed by a second EMG burst commencing after 100 msec (Fig. 5). This pattern of APB response was seen in only three of 10 trials when the muscle was relaxed (see above). During the bilateral activation, responses in the left biceps were both more consistent (occurring in all four trials) and occurred at shorter latency than with left-sided activation alone.

The threshold for a response in the relaxed left biceps following magnetic stimulation was 45% of maximum output (B side up). Following stimulation at 65% intensity (five trials), the onset latency ranged from 14.0 msec to 14.8 msec and the peak to peak amplitude from 1.5 mV to 4.7 mV. No clear responses were recorded in the relaxed right biceps at stimulus intensities up to 90% of maximum output (A side up; stimulus artifact was prohibitive above this level). A small response, possibly to the sound of the coil discharging, was recorded in four of five trials at 90% intensity when the right biceps was

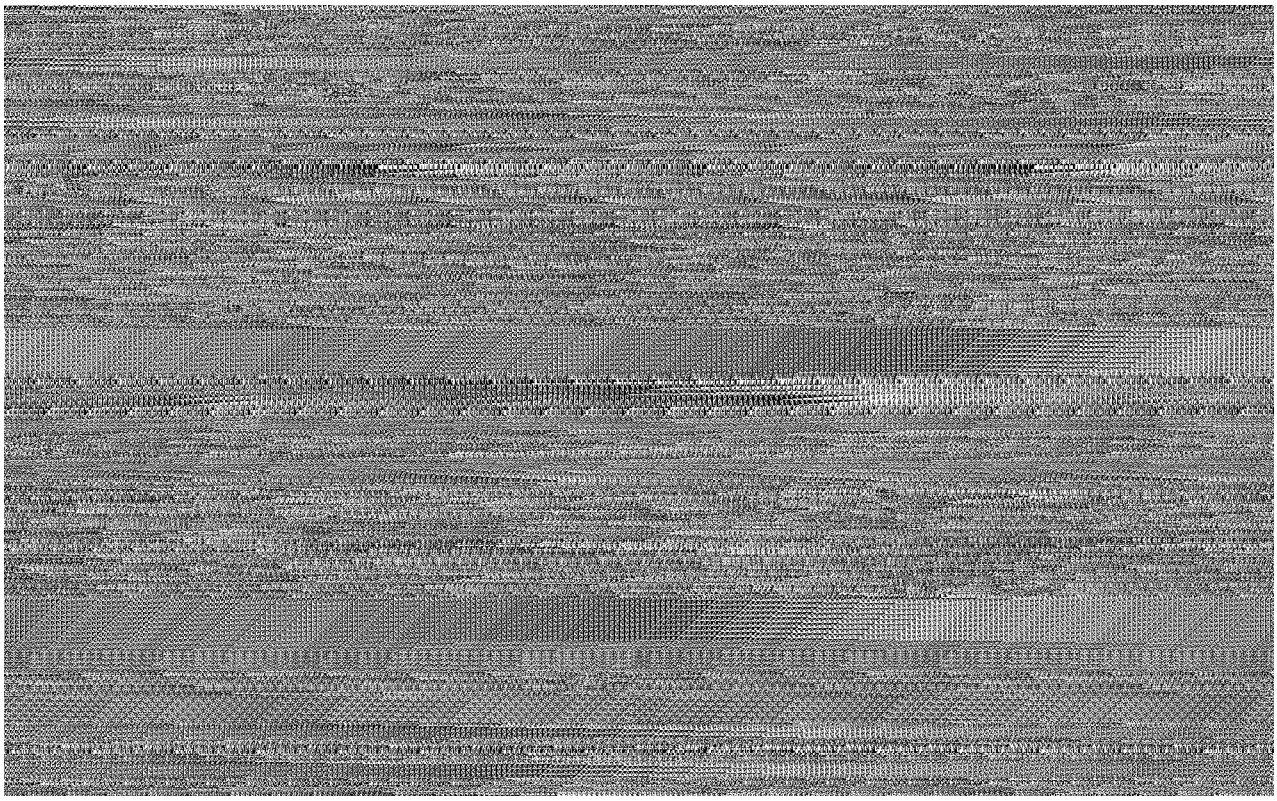

**FIG. 4.** Responses to a binaural 1-kHz, 120-dB, 50-msec duration tone burst (a separate trial in each row). The right biceps is relaxed while the left biceps is tonically contracted. Latencies are indicated with arrows. In the upper row (trial 8), the left biceps recording shows a low-amplitude excitatory response followed by a period of inhibition. The lower trace (trial 5) shows only a period of inhibition of background electromyographic (EMG) activity. The right biceps shows large synchronous activity throughout. Intertrial intervals: 4–5 minutes.

tonically contracted. The onset latency ranged from 20.6 msec to 41.2 msec and the amplitude from 0.5 mV to 1.1 mV.

## Discussion

Had we only recorded the response in this patient's right biceps muscle, the short duration and highly synchronous nature of the EMG activity may have led to a provisional diagnosis of a form of myoclonus. Although startle is arguably a type of myoclonus, it is not usually classified as such. The distinguishing clinical features of our patient were the fact that sound was the only effective stimulus, the enhancement by unexpectedness, and the presence of habituation, albeit reduced. The exaggerated responses were not simply due to increased motoneuronal excitability on the side of the stroke, as a weak contraction on the other side resulted in only a small response; the main disturbance therefore must be before the motoneurons. The latency of the excitation in biceps brachii and its synchronous nature indicates that the responses are not simply enhanced startle (meaning a lower threshold or impaired habituation to a startling stimulus). Thus we have used the term "focal pathological startle." While the focal nature of the abnormality was not absolute, it was a striking clinical feature (see Video).

Evidence from animal studies[5,10] and observations of patients[4] strongly suggest that the response to startle is mediated via brainstem structures and is conducted to the cord by a nonpyramidal, probably reticulospinal, pathway. Consistent with a nonpyramidal pathway, our patient had large responses in biceps to startle but mimimal responses to magnetic motor cortical stimulation over the contralateral hemisphere. The giant neurons of the nucleus reticularis pontis caudalis appear to have particular importance in mediating startle, and lesions of the pons have been reported as causes of enhanced startle and acquired hyperekplexia.[11,12] However, cortical lesions have also been reported to cause increased startle responses. Voordecker and colleagues[13] found that four of 10 patients who were studied within 3 to 5 days of the onset of acute hemiplegic stroke showed an "obvious reflex movement" in the plegic arm in response to startle. Interestingly, the changes were best seen in the biceps. They deduced that the likely mechanism was one of disruption of tonic descending cortical inhibition of brainstem structures. Denny-Brown[14] had previously found lateralised, stimulus-sensitive myoclonus in monkeys following lesions of the contralateral cortex, thalamus, or a lesion of the ventral part of the pons. Denny-Brown concluded that the changes were due to interruption of a descending inhibitory projection, which crossed the midline in the region of the mid- to caudal pons. The study of our patient suggests that such a corticoreticular pathway must lie in close relation to the descending pyramidal fibres in the pons, given the restricted nature of the lesion. As the reticulospinal tract is predominantly

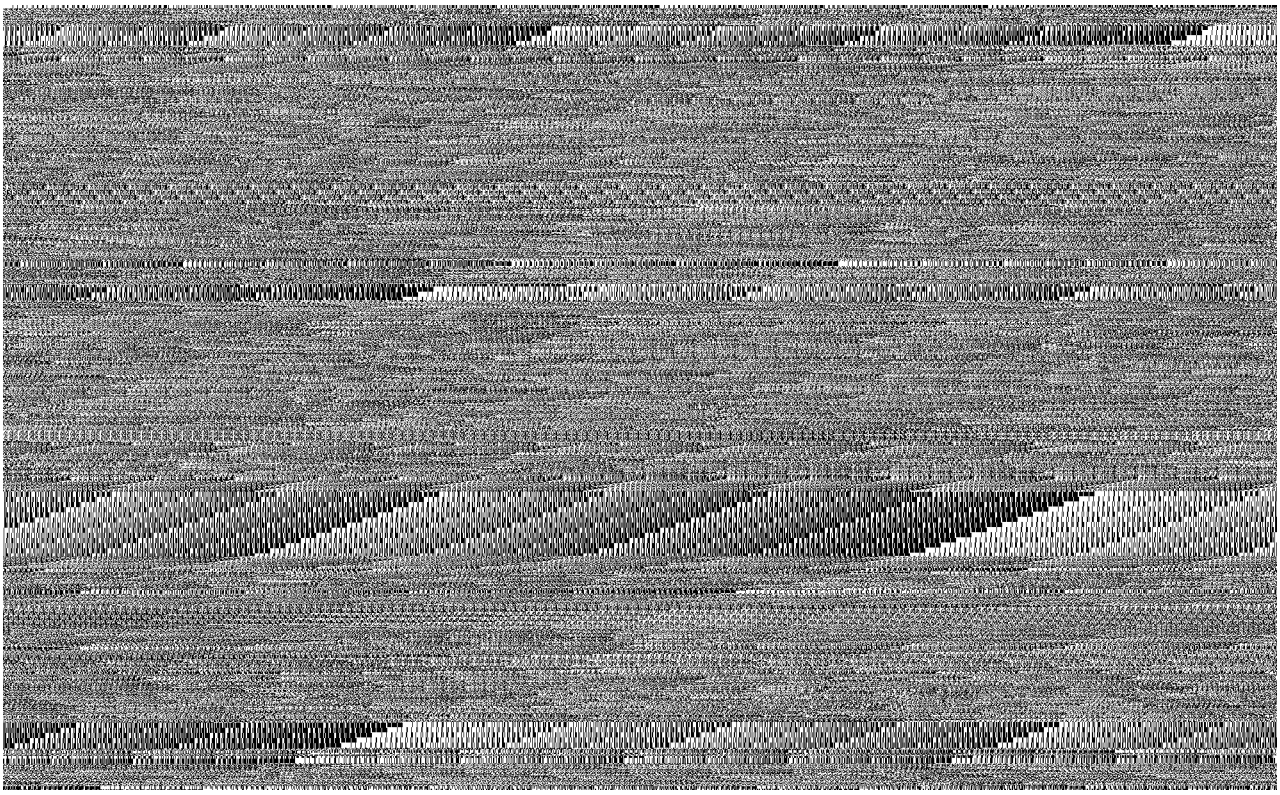

**FIG. 5.** Responses during bilateral tonic activation to a binaural 1-kHz, 120-dB, 50-msec duration tone burst, presented at least 4 minutes after the preceding pulse (a separate trial in each column, right-sided muscle above the corresponding left-sided one). Time of stimulus delivery is shown by vertical dashed lines. Responses are shown for the following tonically contracted muscles: biceps brachii; abductor pollicis brevis (APB), tibialis anterior (TA). Latencies are indicated with arrows. The excitatory responses in both biceps muscles appear bipeaked, while the excitatory responses in right APB showed early and late components. Purely inhibitory responses are evident in left TA.

ipsilateral,[15] the descending projection interrupted in our patient must cross the midline shortly below the level of the lesion.

What do our observations tell us about the nature of the descending pathway mediating startle, most likely reticulospinal? We confirmed the presence of disproportionately long latency to intrinsic hand muscles, previously reported for startle pathways.[4] The relatively selective involvement of biceps suggests a degree of somatotopy of the efferent pathway; the same population of descending neurons clearly cannot have similar connections with widely varying pools of motoneurons. There were both excitatory and inhibitory descending influences, usually occurring in that order, and while the projection was predominantly ipsilateral, weaker crossed effects were also evident. In the cat, startle-responsive reticulospinal fibres arising from the nucleus reticularis pontis caudalis and nucleus gigantocellularis have very rapid conduction velocities and usually evoke excitation followed by inhibition.[16] Voluntary activation facilitated the involuntary EMG responses. The finding that activation of muscles bilaterally resulted in more consistent and shorter responses in left biceps than purely left-sided activation suggests that voluntary activity facilitated the startle activity at a brainstem rather than a spinal level. The majority of the corticoreticular pathway arising from areas 4 and 6 in the cat projects ipsilaterally.[17] Our observations thus raise the possibility of both excitatory and inhibitory descending corticoreticular projections; presumably the lesion in our patient predominantly affected the descending (crossed) inhibitory pathway.

An unexpected aspect of our findings was the recruitment order. The latency to the biceps muscle was repeatedly shown to be the same or earlier than that for the sternocleidomastoid muscles. Relative recruitment order of muscles remains a strong indicator of the likely source of involuntary movements. If the discharges to all muscles originate simultaneously from a single site, and have the same conduction velocity, then the muscles closest to the anatomical site of the abnormality will always be the first activated. Other muscle groups will follow in sequence rostrally and caudally from the source throughout the neuraxis. The initial activation of the sternocleidomastoid muscle was crucial evidence for a lower brainstem site of origin for reticular reflex myoclonus.[7] Similarly, apart from the blink response, the normal startle reflex usually appears first in the sternocleidomastoids.[4] In our case, either the central latency is particularly short for the biceps muscle, or faster-conducting pathways must have been recruited which project to it, in order to explain its short latency. Both these mechanisms have been postulated as possible causes of the progressive shortening of latency which occurs in hereditary hyperekplexia in response to increasing stimulus intensity.[6]

We have shown that startle can be focally enhanced, with short latency and brief, highly synchronised activity. The term

"startle" appears appropriate when sound is the most effective stimulus, and there is evidence of habituation. Hyperekplexia is associated with additional features, including responses to taps and tonic spasms, and we therefore prefer to avoid this term. Reticular myoclonus is usually associated with more disturbed physiology, with a broad range of effective stimuli, loss of habituation (including even the presence of facilitation between successive stimuli),[8] and spontaneous discharges. In general, latencies are shortest and the activity most synchronous for reticular myoclonus, but the clinical features, rather than strict recruitment order or central conduction velocities, appear to be the most useful in the classification of these disorders.

**Acknowledgments:** We thank Dr. Kati Watson for translation from French into English. This research was supported by the National Health and Medical Research Council of Australia.

## Legends to the Videotape

**Segment 1.** The patient is seen sitting with headphones in position. One of the authors, standing behind the patient, was able to trigger a 50-msec, 120-dB 1-kHz tone at unexpected intervals. Twitches are clearly visible in the right biceps in response to the tone initially, but habituate to repeated presentations of the stimulus at short intervals. On electromyography (EMG), the twitches corresponded to a synchronous EMG burst in biceps (Fig. 2).

**Segment 2.** Approximately 9 minutes later. The biceps twitches are again evoked by the stimulus. The size of the response is larger when the subject holds his arms up in front of him. Similarly, electromyographic (EMG) recordings during weak tonic activation showed a double-peaked response in the right biceps at short latency (Fig. 5). Clinically, the muscle jerking remained confined to the right elbow.

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# Objective Tinnitus Associated with Essential Laryngeal Myoclonus: Report of Two Cases

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**Abstract:** We report on two patients with an objective tinnitus. In the first one, the objective tinnitus was unique as it was due to bilateral rhythmic contractions of the vocal cords. In the second, the objective tinnitus arose from Eustachian tube contractions and was associated with up and down movements of the larynx. In both patients, the abnormal laryngeal movement shared most of the characteristics of palatal or palatolaryngeal myoclonus and was thought to be laryngeal myoclonus. Its origin remained essential as all the investigations were negative. © 2001 Movement Disorder Society.

Objective tinnitus is, by definition, audible to the examiner. It is a rare condition that usually results from vascular pulsations or muscular contractions. In the latter situation, it has been mainly reported in palatal myoclonus,[1] middle ear myoclonus,[2,3] or the association of both.[4] In middle ear myoclonus, the tinnitus is usually unilateral and due to contractions of the tensor tympani and/or stapedial muscles.[2,3] The diagnosis of middle ear myoclonus relies on otoscopy, impedance audiom-

A videotape accompanies this article.

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etry, and often can only be confirmed by sectionning the tensor tympani and stapedial muscle tendons.[2–4] In palatal myoclonus, the objective tinnitus is usually bilateral and arises from Eustachian tube movements mostly due to tensor veli palatini muscle contractions.[1] Local injections of botulinum toxin is the best therapeutical approach.[5] Here, we present two unusual cases in whom the objective tinnitus was associated with abnormal laryngeal movements and in one case arises from these movements.

## Case Reports

### Case 1

A 27-year-old man without medical history was first referred in March 1993 because he complained of hearing a noise similar to the sound produced by castanets in both ears. This noise had started 1 year before and was initially intermittent but it had become permanent. It was easily heard without amplification at a distance of a few meters from the patient. The noise was not alleviated by sleep and was particularly troublesome for his wife. Laryngological examination revealed bilateral rhythmic contractions of the vocal cords hitting together at a rate varying from 80 to 170 beats per minute. The movements of the vocal cords were synchronous with the noise and temporarily halted during phonation but resumed immediately upon cessation of the phonation. There was no definite movement in other muscles, in particular, the soft palate and the tympanic membrane. Neurological examination was unremarkable. Pure tone audiometry and brainstem auditory evoked responses were normal. Brain magnetic resonance imaging (MRI) was normal. All other investigations, including cerebrospinal fluid examination, visual and somatosensory evoked potentials as well as electroencephalography, remained negative.

The patient was recalled in May 2000. He had no other symptom apart from the objective noise that had become intermittent and was no longer disabling. Interestingly, the patient could voluntarily stop or provoke it by contracting the pharyngolaryngeal musculature. He could also stop it by performing a brief external laryngeal compression. Laryngological examination confirmed the contractions of the vocal cords after a voluntary provocation. There were no simultaneous movements of the soft palate, tympanic membrane, or Eustachian tube on nasofibroscopy. Neurological examination was otherwise unremarkable. Pure tone, speech, and impedance audiometry were normal.

### Case 2

A 33-year-old woman, with a previous history of ulcerohemorrhagic recto-colitis, became aware of permanent audible clicks in both ears 2 months prior to her referral in January 2000. The sound was similar to the noise produced by the snapping of two fingernails against one another. It could be heard using a double stethoscope to connect with the external auditory canals of the patient. Its rate was approximately 80 beats per minute and was not synchronous with heart pulse. External examination revealed up and down rhythmic movements of the larynx. Laryngoscopy confirmed up and down movements of the larynx with no abnormal movement of the vocal cords. Nasofibroscopy revealed synchronous rhythmic contractions of both Eustachian tubes. These contractions were located inferiorlateral to the Eustachian tube and directed upwards. Examination of the soft palate with mouth opened was negative. Movement of the tympanic membrane was absent on otoscopic examination. There was no other neurological deficit or abnormal clinical findings. Pure tone, speech, and impedance audiometry were normal. Electroencephalography and brain MRI were normal. The patient was put sequentially on clonazepam, carbamazepine, and trihexyphenidyle without any relief. Botulinum toxin injection was proposed but she refused this option. She was recalled in January 2001. Audible clicks were still present but by intermittence they could spontaneously disappear within a few minutes.

## Discussion

Our two patients complained of an objective tinnitus associated with obvious laryngeal movements, consisting either of vocal cord contractions (Case 1) or up and down laryngeal movements (Case 2). Rare observations have been reported of an objective tinnitus associated with contractions of the vocal cords[6,7] or up and down laryngeal movements.[8–10] In these observations, the objective tinnitus was ascribed to muscular contractions of the Eustachian tube, since the laryngeal movements were constantly associated with palatal and Eustachian tube contractions.[6–10] Associated middle ear myoclonus was absent.[7,8] In our two cases, middle ear myoclonus was unlikely, as the objective tinnitus was not lateralized to one ear and movements of the tympanic membranes were not observed. In Case 2, the laryngeal up and down movements of the larynx were associated with a synchronous movement of the Eustachian tube that was responsible for the objective tinnitus.[8] This latter movement is probably due to contraction of the levator veli platini muscle, as it was located inferiorlateral to the Eustachian tube and directed upwards.[11,12] Curiously, it was not seen during transoral examination, but this condition has been reported to suppress the palatal movement[10] and thus can be sometimes less reliable than nasofibroscopy. In Case 1, there was no movement of the palate and Eustachian tube. Consequently, we believe that the objective tinnitus was directly due to contractions of the vocal cords, which, to the best of our knowledge, has not been previously reported. In this patient, the term "objective tinnitus" could be controversial if the abnormal noise was produced by the larynx. However, the noise in an objective tinnitus can be generated in the ear and in the surrounding region as well, the topographical limits of which have never been clearly defined. For example, in objective vascular tinnitus, the surrounding region involves the vascular structures of both head and neck.[13] This is the reason why we have proposed the term "objective tinnitus" in this patient.

An isolated abnormal rhythmic laryngeal movement is a very rare condition.[14] In most cases, this movement is associated with palatal movements, of which it is only one component.[1,6–9,15,16] There are rare observations of abnormal palatolaryngeal movement due to a cortical epileptic process[16] or a peripheral nerve lesion.[9] In most cases, abnormal palatolaryngeal movements refer to the well-known concept of palatal myoclonus, recently also designated as palatal tremor.[1,5] Palatal myoclonus can be symptomatic or essential. Involvement of the larynx, either in its inner or outer part, is possible in both forms, although it is more frequent in symptomatic cases.[1] Symptomatic palatal or palatolaryngeal myoclonus is due to a brainstem and/or a cerebellar lesion in the olivary-dentatorubro pathways, inducing an inability to inhibit the firing of

cranial nerve motor nuclei.[1,2] It is associated with a medical history of organic disease of the central nervous system and symptoms and signs of brainstem and/or cerebellar dysfunction. In more than 80% of cases, the presenting complaints are related to the underlying neurological disease, and audible ear clicks are reported in 8% of the patients only.[1] Essential palatal or palatolaryngeal myoclonus is a different entity, as there is no related neurological disease, and continuing audible ear clicks are the presenting complaint in 90% of the patients.[1] Spontaneous improvement or recovery as well as voluntary control of the movement have been reported.[1,8,17,18] Case 2 is a form of essential palatolaryngeal myoclonus in the absence of any neurological disorder and, as expected, the presenting complaint is ear clicks due to Eustachian tube movements.[1,8] Case 1 is unique because the movement was limited to the vocal cords. The classification of this movement disorder is difficult but, interestingly, it shares several features with essential palatal myoclonus, including the frequency of muscle jerks, a spontaneous improvement, and the possibility to be voluntarily controlled.[1,17,18] In addition, movements of the vocal cords resembling those of our patient can be observed in palatolaryngeal myoclonus.[6,7] Thus, we believe that this case could be a particular form of essential and isolated laryngeal myoclonus.

## Legends to the Videotape

The sound was recorded with a microphone placed in the room, enabling us to hear the sound for the first patient. The sound was not recorded for the second patient.

**Segment 1.** Case 1. Laryngoscopy with a flexible fibroscope in March 1993. Rhythmic movements of the vocal cords.

**Segment 2.** Case 1. Nasofibroscopy and laryngoscopy in May 2000. Rhythmic movements of the vocal cords after a voluntary provocation. No associated movements of the Eustachian tube.

**Segment 3.** Case 2. External recording of the throat in February 2000. Up and down rhythmic movements of the larynx.

**Segment 4.** Case 2. Laryngoscopy in February 2000. Up and down rhythmic movements of the larynx. No movements of the vocal cords.

**Segment 5.** Case 2. Nasofibroscopy of the left Eustachian tube in February 2000. Rhythmic movements of the Eustachian tube.

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