Movement Disorders
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Clinical/Scientific Notes

Clozapine Replacement by Quetiapine for the Treatment of Drug-Induced Psychosis in Parkinson's Disease

Drug-induced psychosis (DIP) occurs in 5% to 8% of patients with Parkinson's disease (PD)[1,2] and is probably the most important risk factor for nursing home placement among patients with PD.[3] Although a decrease in anti-PD medication may relieve psychosis, patients may experience reduced motor ability as a result. Atypical antipsychotic (AA) agents, such as clozapine, olanzapine, and risperidone, are increasingly being used for the treatment of DIP in PD.

While clozapine is useful in this situation, there have been reports of worsened parkinsonism among patients with PD who have DIP and are receiving risperidone and olanzapine.[4–7] Moreover, a recent article has seriously questioned risperidone's atypical nature.[8] The frequency of extrapyramidal symptoms (EPS) with risperidone or haloperidol treatment have been noted to be comparable, even among neuroleptic-naive non-PD patients experiencing a primary psychosis in this study.[8] Clozapine is considered the "gold standard" atypical antipsychotic drug for the treatment of DIP in PD at this time because of results from two double-blind, placebo-controlled trials and multiple open-label trials,[2] but the risk of agranulocytosis and the cumbersome white blood cell monitoring limit its use. Quetiapine is the newest atypical antipsychotic that shows promise for treating DIP in PD.[9–11] It has the closest pharmacologic resemblance to clozapine among the AA but lacks the risk for agranulocytosis. Like clozapine, quetiapine has a greater affinity for 5-HT_{2A} than dopamine D_2 receptors.[12,13] Its effect on parkinsonism and prolactin levels (predictive of EPS occurrence) has been indistinguishable from placebo in trials of patients with schizophrenia.[14,15] However, cataracts occurred in chronic dog studies. Although no definite causal relationship linking quetiapine to lenticular changes has been established, lens examination by slit lamp or other appropriate methods is recommended at the initiation of treatment and at 6-month intervals thereafter.[16]

Our initial experience in clozapine switch-over to quetiapine among psychiatrically stable patients with PD who have DIP was not encouraging.[9] Only three of eight patients with PD who were on clozapine were successfully switched to quetiapine. We hypothesized that the rapid titration and the shorter overlap period between clozapine and quetiapine might have been contributing factors to the high failure rate. Nonetheless, only one patient had increased tremors. All other patients who were unable to tolerate the switch-over did not experience a decline in motor function.[9]

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We now report our findings on clozapine replacement by quetiapine on 15 additional patients using a slower titration schedule with a wider overlap period.

Methods

Fifteen patients (eight men and seven women) with presumed idiopathic PD, defined by the presence of three of four cardinal features (tremor at rest, rigidity, bradykinesia, gait and balance dysfunction; and a positive initial response to L-dopa) were studied. All patients had a history of DIP (according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [DSM-IV] criteria) but were psychiatrically stable.

All patients were assessed at baseline and reassessed at 4 and 8 weeks after clozapine was totally discontinued using the Brief Psychiatric Rating Scale (BPRS), Mini-Mental Status Examination (MMSE), Unified Parkinson's Disease Rating Scale (UPDRS parts 1, 2, and 3), Hoehn and Yahr staging (H-Y), and Clinical Global Impressions Scale (CGIS) by the same examiner. Starting at baseline visit, the daily clozapine dose was reduced by 6.25 mg per week for 2 weeks, 12.5 mg per week for the next 2 weeks, then 25 mg per week thereafter until the drug was discontinued. Quetiapine was started at the same baseline visit at 12.5 mg per day for 1 week and increased weekly by 12.5 mg per day until the patient was no longer on clozapine. If the baseline dose of clozapine was 6.25 mg per day, 1 week of overlap with 12.5 mg quetiapine was given prior to clozapine discontinuation.

The titration schedule was strictly adhered to. The duration of the titration period ranged from 1 to 10 weeks depending on the initial clozapine dose. After the titration period, quetiapine adjustment was permitted, such as lowering the drug dose to improve orthostasis or increasing the nighttime dose to improve sleep, as long as the patient remained psychiatrically stable.

An open-ended, nonstandardized weekly telephone interview was performed on all patients and their caregivers/spouses to assess for compliance, recurrence of hallucinations or delusions, and side effects. Anti-PD medications were kept fixed during the cross-over period. Any patient who remained on quetiapine without worsened psychosis or parkinsonism was considered a treatment success. Another follow-up telephone interview was performed after 12 months on all patients (and their caregivers) who successfully switched over to quetiapine to assess the tolerability and continued efficacy of the drug.

Paired *t* test or Wilcoxon signed rank test (if normality test failed because of the small sample) was used to compare the mean MMSE, BPRS, UPDRS, H-Y, and CGIS at 4 and 8 weeks with baseline.

Results

Fifteen psychiatrically stable patients with PD who have a history of DIP on an average 41.6 mg clozapine per day were

TABLE 1. *Demographics*

Patient no.	Age (yrs)	Sex	PD duration (yrs)	Hoehn and Yahr stage	Daily L-dopa dose (mg)	Daily clozapine dose (mg)	Ending quetiapine dose (mg)
1	72	M	12	2.5	500	12.5	37.5
2	79	M	13	2.0	600	25	50
3	86	F	3	3.0	0	12.5	25
4	78	F	24	4.0	1250	50	D/C
5	80	F	4	5.0	300	50	62.5
6	77	M	8	3.0	300	6.25	25
7	59	M	19	5.0	900	350	450
8	73	F	15	5.0	400	56.25	D/C
9	83	M	20	3.0	600	6.25	12.5
10	79	F	3	2.5	900	6.25	12.5
11	74	M	5	2.5	450	25	12.5
12	71	F	15	3.0	150	6.25	D/C
13	66	M	18	2.5	400	6.25	25
14	71	M	7	3.0	500	6.25	25
15	82	F	16	2.5	250	6.25	12.5
Average	75		12		517	41.6	62.5

PD, Parkinson's disease; D/C, discontinued, switched back to clozapine.

switched to quetiapine (see Table 1). Our sample had a mean MMSE score of 18 (range, 8–28).

Twelve of 15 patients made the transition without a worsening of cognition (as measured by the MMSE) or a loss of antipsychotic effect (as measured by BPRS and CGIS) at the 4- and 8-week visits after clozapine discontinuation and chose to remain on quetiapine (see Table 2). Switch-over failures were the result of increased dyskinesia, tremor, and anxiety in one patient; and increased hallucinations and confusion in another patient. The third patient dropped out of the study after a single dose of quetiapine because of the sudden onset of transient radicular pains on both legs; she refused to return for re-evaluation. Overall, side effects noted were transient and mild. Two patients became more animated and reported increased energy. None of the patients had significant worsening of parkinsonism as measured by the UPDRS motor scale, except for increased dyskinesia in one and transient worsening of tremor in four patients. The average quetiapine ending dose was 62.5 mg (range, 12.5–450 mg).

TABLE 2. *Comparison of baseline and 4-week/8-week visits (N = 14)*

	Baseline	4-week		8-week	
Test	Mean/ Median	Mean/ Median	p value	Mean/ Median	p value
MMSE	19.2*/20.5†	21†	0.19	20.5†	0.31
BPRS	27.3*/28†	25.4*	0.22	27†	0.68
CGIS	2†	2†	0.38	2†	0.88
H&Y	3†	2.8†	0.25	2.8†	6.25
UPDRS					
Part I‡	5.1*/5†	4.7*	0.56	5.5†	0.94
Part II§	20.8*/21†	19.7*	0.92	20†	0.06
Part III‖	47.2*	45.5*	0.42	44.5†	0.18

MMSE, Mini-Mental State Examination; BPRS, Brief Psychiatric Rating Scale; CGIS, Clinical Global Impressions, Severity of Illness; H&Y, Hoehn and Yahr stage; UPDRS, Unified Parkinson's Disease Rating Scale.

* Mean; using paired *t* test for comparison.

† Median; using Wilcoxon signed rank test for comparison.

‡ Mentation/behavior assessment.

§ Activities of daily living assessment.

‖ Motor assessment.

At the end of 12 months, nine of 12 patients remained psychiatrically stable on quetiapine. Four patients had a decline in motor function but only two thought it was significant enough to switch back to clozapine. One patient died of an unrelated cause.

Discussion

The results of this study are similar to other open-label trials reported and suggest that quetiapine is a useful and well-tolerated agent for the treatment of DIP in PD. Our difficulty in switching psychiatrically stable patients with PD on clozapine in an earlier study[9] seems to have been overcome with a slower titration and a longer overlap period of the two AA agents. In the previous study, clozapine replacement was done empirically. A dose of 12.5 to 25 mg quetiapine per day was added at baseline visit whereas daily clozapine dose was reduced to 12.5 to 25 mg per week. Thus, the majority of patients who were initially on 12.5 mg or less of clozapine per day did not have an overlap period with quetiapine.

There was no significant difference in the antipsychotic effects of quetiapine versus clozapine as measured by the BPRS and the CGIS at 4 or 8 weeks. Moreover, there was no change in mentation (as measured by the MMSE, UPDRS part 1), activities of daily living (UPDRS part 2), and parkinsonism (UPDRS part 3) at the end of the trial. We think the increase in dyskinesia in one patient and transient tremor worsening in four patients are a result of withdrawal of clozapine's antidyskinetic[17,18] and antitremor effects.[19,20]

The 12-month follow up allowed us to assess quetiapine's long-term tolerability and efficacy. Seventy-five percent of patients who successfully switched over remained psychiatrically stable on quetiapine. However, 33% had increased parkinsonism by 12 months, half of whom switched back to clozapine. Nonetheless, because repeat UPDRS motor assessment, BPRS, and CGIS were not performed, mild increases in parkinsonism,

worsening of cognition, or loss of antipsychotic effect may not have been captured in the 12-month patient and caregiver telephone interview.

In conclusion, quetiapine appears to be an effective and well-tolerated alternative to clozapine among psychiatrically stable patients with PD who have a history of DIP and who want to change their antipsychotic medication. The success rate for such a cross-over increases with a more gradual titration schedule.

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References

1. Friedman JH. Levodopa-induced psychosis. *Neuropharmacology* 1991;14:283–295.
2. Fernandez HH, Friedman JH. The role of atypical antipsychotics in the treatment of movement disorders. *CNS Drugs* 1999;11:467–483.
3. Goetz CG, Stebbins GT. Risk factors for nursing home placement in advanced Parkinson's disease. *Neurology* 1993;42:2227–2229.
4. Rich SS, Friedman JH, Ott BR. Risperidone versus clozapine in the treatment of psychosis in six patients with Parkinson's disease and other akinetic-rigid syndromes. *J Clin Psychiatry* 1995;56:566–559.
5. Jimenez-Jimenez FJ, Tallon-Barranco A, Orti-Pareja M, Zurdo M, Porta J, Molina JA. Olanzapine can worsen parkinsonism. *Neurology* 1998;50:1183–1184.
6. Friedman JH, Goldstein SM. Olanzapine in the treatment of dopamimetic psychosis in patients with Parkinson's disease. *Neurology* 1998;50:1195–1196.
7. Molho ES, Factor SA. Worsening of motor features of parkinsonism with olanzapine. *Mov Disord* 1999;14:1014–1016.
8. Rosebush PI, Mazurek MF. Neurological side effects in neuroleptic-naive patients treated with haloperidol or risperidone. *Neurology* 1999;52:782–785.
9. Fernandez HH, Friedman JH, Jacques C, Rosenfield M. Quetiapine for the treatment of drug-induced psychosis in Parkinson's disease. *Mov Disord* 1999;14:484–487.
10. Juncos JL, Evatt ML, Jewart D. Long Term effect of quetiapine fumarate in parkinsonism complicated by psychosis. *Neurology* 1998;50(suppl 4):A70–71.
11. Parsa M, Bastani B. Quetiapine (Seroquel) in the treatment of psychosis in patients with Parkinson's disease. *Neuropsychiatry* 1998;10:1–4.
12. Saller CF, Salama AL. Seroquel: biochemical profile of a potential atypical antispychotic. *Psychopharmacology (Berl)* 1993;112:285–292.
13. Carey G, Bergamn J. Discriminative stimulus effects of proposed atypical antipsychotics in clozapine-trained squirrels and monkeys [Abstract]. *Behav Pharmacol* 1994;5:114.
14. Small JG, Hirsch SR, Arvanitis LA, Miller BH, Linic CG. Quetiapine in patients with schizophrenia. A high and low-dose double blind comparison with placebo. *Arch Gen Psychiatry* 1997;54:549–557.
15. Arvanitis LA, Miller BG, Seroquel Trial 13 Study Group. Multiple fixed doses of 'Seroquel' (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry* 1997;42:233–246.
16. *Physicians' Desk Reference*, 54th ed. Montvale, NJ: Medical Economics Company, Inc, 2000:252–253.
17. Bennett JP Jr, Landrow ER, Schuh LA. Suppressors of dyskinesia in advanced Parkinson's disease. II: increasing daily clozapine doses suppress dyskinesias and improve motor symptoms. *Neurology* 1993;43:1551–1555.
18. Bennett JP Jr, Landrow ER, Schuh LA. Suppressors of dyskinesia in advanced Parkinson's disease: moderate daily clozapine doses provide long-term dyskinesia reduction. *Mov Disord* 1994;9:409–414.
19. Friedman JH, Koller WC, Lannon MC, et al. Benztropine versus clozapine for the treatment of tremor in Parkinson's disease. *Neurology* 1997;48:1077–1081.
20. Bonuccelli U, Ceravolo R, Salvetti S, et al. Clozapine in Parkinson's disease tremor: effects of acute and chronic administration. *Neurology* 1997;49:1587–1590.

Posttraumatic Tremor and Arnold Chiari Malformation: No Sign of Compression, But Cure After Surgical Decompression

Cases of delayed or acute posttraumatic, therapy-resistant tremor have been previously described.[1–4] The onset is usually delayed (weeks to months/years), but they may also begin rapidly (within hours). Careful neuroradiologic examination may reveal small lesions, often in the deep brain areas, or a herniation of the midbrain and the cerebellar structures with a con-

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comitant compression of these structures.[1] Although a number of drug therapies[2] or neurosurgical lesions[4] have yielded relief in some patients, others have had the tremor for years regardless of treatment. Common to the whole spectrum of posttraumatic tremor disorders is the fact that the mechanism of tremor usually remains unexplained, even when a rationally fitting lesion is found.[1–4] We describe a patient with unusually disabling tremor after minor head trauma. There was no brain damage or compression attributable to the tremor, but an innocent-appearing Arnold-Chiari malformation was present. There was dramatic relief of the symptoms after surgical intervention.

Case Report

A previously healthy 13-year-old boy was admitted to the hospital because of an abnormal gait and confusion. Earlier on the same day he had fallen in a water slide. He slid down on his back with his feet forward. He had a blackout of approximately 10 seconds after the fall. He stood immediately but never straightened his hips, making him walk in a peculiar manner. Whole-body tremors began in the emergency room 1.5 hours after the fall. During the first few days he reported double vision. He had mild nystagmus, exaggerated patellar reflexes, and a slight dysphagia. The neurologic examination was otherwise normal. The tremor affected first the hip flexors and spread to the arms with relative sparing of the head and face muscles. It was strong enough to shake the whole body and the bed at a rate of 3–5 Hz at rest. Both the rate and the amplitude of the tremor increased considerably with movement. The patient could not walk or use his hands. The tremor was continuous during wakefulness but absent during sleep throughout the 4 months that the symptoms lasted.

Head and spine magnetic resonance imaging with different sequences (T1, T2, and Flair) revealed only a type 2 Arnold-Chiari malformation (ACM-2, Fig. 1). There were no signs of compression or tissue damage, the spinal cord was not tethered, and the cervical vertebrae seemed to be normal. Single proton emission computerized tomography (1 month after the trauma) showed a slightly decreased perfusion of the right temporobasal area and decreased binding of the CIT labeling (dopamine transport) in the right putamen: These findings had disappeared on follow up 3.5 months later. The electroencephalogram was initially normal. After 1 month there was a rhythmic slow activity (4–5 Hz) in the right posterior areas in the beginning of the registration session. However, it was replaced by a symmetric alpha activity (8–9 Hz) later during the registration. Somatosensory evoked responses could not be elicited initially but were normal on later examinations. Other electrophysiological investigations, including motor evoked potentials by transmagnetic stimulation, visual, somatosensory, and brain stem auditory evoked potentials, were all normal. Other investigations, a large number of regular laboratory tests and metabolic investigations, including serum ceruloplasmin, were normal.

The possibility of a conversive etiology was evaluated several times. Pediatric psychiatric investigation and care to support the patient and his family were instituted. No psychogenic mechanism could be established. Factors suggesting a psychogenic origin (inconsistent symptomatology, selective disabilities, multiple other somatizations, psychiatric disease, and so on)[5] were not unambiguously present. Hypnosis was finally tried but led to no relief of the tremor.

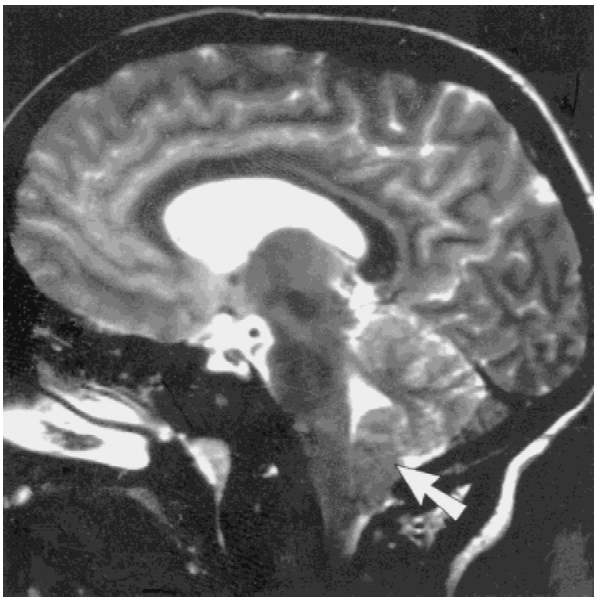

FIG. 1. This MRI image shows the herniation of the brain stem and the cerebellum into the foramen magnum. Although the herniation seems tight, with no cerebrospinal fluid around the brain stem, no changes in signal intensity (that is, no sign of compression) are visible.

Numerous, symptomatic pharmacologic treatments, including clonazepam, diazepam, propranolol, a combination of levodopa and carbidopa, benzhexol, tizanidin, dexamethasone, phenytoin, and gabapentin, were ineffective.

When there was no recovery at 4 months, a neurosurgical decompression of the posterior fossa was performed despite the absence of any imaging or neurophysiological sign of compression. Anesthesia, with a combination of penthanyl, thiopenthal, and rocurone, lasted 1 hour. A fragile posterior arch of C1 (anomalic or posttraumatic) was removed. The cerebellar tonsils looked normal. One day after the operation the tremor began to decrease in the hands, and on the fifth day the patient was ambulatory and using his hands. One year later no neurologic abnormality was observed.

Discussion

The previously reported ACM-associated tremors (two children[6,7] and one lioness[8]) did not have a history of head trauma. Some patients with posttraumatically diagnosed ACM without concomitant tremor have also been reported.[9] In our patient it is likely that there was a preexisting, asymptomatic ACM, but the trauma caused an acute worsening of the brain stem function. This view is supported by the number of transient ACM-associated clinical symptoms seen in our patient (nystagmus, reflex exaggeration, double vision, and dysphagia).[10]

Nevertheless, our patient is the first to present with a combination of posttraumatic tremor and ACM. This is also the first reported case to show relief of the tremor after surgical decom-

pression. Although the definitive neurobiologic mechanism remains unclear, our patient provides support for a causal link between the ACM or upper cervical pathology and the tremor. We think the mechanism of the tremor was hyperextension of the neck with herniation and stretching of the midbrain and cerebellum into foramen magnum. Surgical decompression is normally successful only if there is radiologic or electrophysiological evidence of brain stem or cerebellar compression. However, no obvious compression was present in our patient; the transient slight hypoperfusion in the temporobasal areas was regarded as being clinically nonsignificant. Likewise, the initial, transient slow rhytmicity in the electroencephalogram recording was not attributable to any specific brain structure or related to the tremor, because it disappeared while the tremor continued during registration.

This case emphasizes the concept that posttraumatic symptoms should be primarily considered organic rather than conversion symptoms. Presently available magnetic resonance imaging or electrophysiological techniques may not reveal all functional disturbances in the brain stem or cerebellum. While more sensitive methods of investigation are awaited, this case reminds us that neurosurgical decompression may sometimes be indicated purely on the basis of the clinical symptoms coupled with suspicion.

Legends to the Videotape

Segment 1 shows the patient 3 weeks after the accident. The tremor remained essentially the same throughout the period of 4 months before surgery. During the time of this video recording the patient was receiving 3 × 20 mg propranolol per day. He shows a disabling postural tremor, which was worsened by any action. While the tremor was clearly present in all parts of the body, there was a distal predominance in the limbs during voluntary movements.

Segment 2 shows the patient 3 weeks after surgery on no medications. Note the virtually complete resolution of the tremor during both the whole body movements (walking) and the fine motor movements (eating and writing). The well-healed wound in the neck after surgery is shown. Note also the weakness (resulting from the period in the wheelchair) of the lower limb muscles during climbing of the steps.

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References

1. Louis ED, Lynch T, Ford B, Greene P, Bressman S, Fahn S. Delayed-onset cerebellar syndrome. *Arch Neurol* 1996;53:450–454.
2. Biary N, Cleeves L, Findley L, Koller W. Post-traumatic tremor. *Neurology* 1989;39:103–106.
3. Johnson SLJ, Hall DMB. Post-traumatic tremor in head injured children. *Arch Dis Child* 1992;67:227–228.
4. Krauss JK, Mohadjer M, Nobbe F, Mundinger F. The treatment of posttraumatic tremor by stereotactic surgery. *J Neurosurg* 1994; 80:810–819.
5. Koller W, Lang A, Vetere-Overfield B, et al. Psychogenic tremors. *Neurology* 1989;39:1094–1099.
6. Cammalleri R, D'Amelio M, Gangitano M, Raimondo D, Rossetti M, Camarda R. Monosymptomatic presentation of type I Arnold-Chiari malformation: report of two cases. *Ital J Neurol Sci* 1994; 15:57–60.
7. Nakae Y, Tamaki H, Maekawa K. Stereotypical lower-limb movements of a child with Arnold-Chiari malformation. *Dev Med Child Neurol* 1993;35:540–548.
8. Shamir MH, Horowitz IH, Yakobson B, Ofri R. Arnold-Chiari malformation in a captive African lion cub. *J Wildl Dis* 1998;34: 661–666.
9. Mampalam TJ, Andrews BT, Gelb D, Ferriero D, Pitts LH. Presentation of type I Chiari malformation after head trauma. *Neurosurgery* 1988;23:760–762.
10. Pollack IF, Pang D, Kocoshis S, Putnam P. Neurogenic dysphagia resulting from Chiari malformations. *Neurosurgery* 1992;30:709–719.

Lazarus' Sign in Brain Death

Brain death (BD) is the irreversible loss of function of the brain, including the brain stem.[1,2] Criteria for the diagnosis of BD require complete unresponsiveness, apnea, and absent brain stem reflexes.[1,3,4]

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BD patients may have spontaneous and reflex movements, some of which are considered spinal reflexes.[5–7] Extension-pronation movements, plantar responses, muscle stretch reflexes, abdominal reflexes, and undulating toe flexion sign are some that have been reported.[5–8] The most dramatic movement described is the "Lazarus' sign."[9]

We describe and show on videotape a brain-dead patient with Lazarus' sign to illustrate the characteristics of this phenomenon. This patient is part of a series reported elsewhere.[7]

Case Report

A 42-year-old man was admitted to the hospital as a result of impaired consciousness. His medical history was unremarkable. He was eating when he had sudden neck pain and fell to the floor. When admitted to the intensive-care unit he was comatose. He was intubated and on a ventilator for respiratory support. On neurologic examination 12 hours later, there were no motor responses to noxious stimuli to the sternum or limbs. Brain stem reflexes were absent, including pupil responses to light; oculocephalic, oculovestibular, and corneal reflexes; grimacing to painful stimuli; and pharyngeal and tracheal reflexes. Spontaneous respiration was absent for 10 minutes during repeated apnea testing. A 30-minute electroencephalogram (EEG) was recorded from eight scalp electrodes at 3 μV/mm gain, high-frequency filter at 70 Hz, and time constant at 0.3 seconds. Interelectrode distance was at least 10 cm. The EEG was isoelectric (Fig. 1). Thus, the patient met criteria for BD as established by the American Academy of Neurology guidelines for determining BD.[1] A computed tomography scan of the head showed a large, right pontocerebellar hemorrhage (see the videotape segment).

Six hours later, his examination and another EEG remained unchanged. At that time, a complex sequence of movements was noticed. After appropriate written consent from the patient's family we recorded these movements on videotape. On passive flexion of the neck, both upper limbs were raised with flexion of the left arm at the elbow. There was slight internal rotation and adduction of the shoulders and pronation of the forearms. Subsequently, both arms crossed on the patient's chest while there was dystonic-like posturing of the hands with extension and abduction of the fingers, more pronounced on the left side. A few seconds later, the hands proceeded down to the lower abdomen. On repetition of passive neck flexion, the patient raised both arms, extended them at the elbows, pronated the forearms, and exhibited dystonic-like posturing of the hands for approximately 3 seconds before returning them to rest on his lower abdomen. Variations included flexion of the left arm with subsequent extension at the elbow on passive neck flexion. With repetition of neck flexion, this pattern extinguished and only slight flexion of the arms was observed. The patient also had a tonic neck reflex. When his head was passively turned to the right, there was flexion of the left upper limb. No other movements or responses were seen in his limbs or abdomen, even when painful stimuli were applied.

Discussion

BD is a state that includes absence of cortical functions and brain stem reflexes. It ends with cardiac arrest, usually occurring within 24–48 hours. In the past, the presence of any type of spontaneous or reflex movement challenged the diagnosis of BD.[3]

Ivan et al.[5] studied 52 subjects with BD and found some forms of spinal reflexes in 75%. Jorgensen et al.[6] reported the presence of deep tendon reflexes of the limbs in one third of a series of 63 patients. Twenty-one patients had extension/pronation of the arm and forearm in response to cutaneous stimulation. In 1982, Mandel et al.[10] reported a 28-year-old man with BD who spontaneously had extension movements of

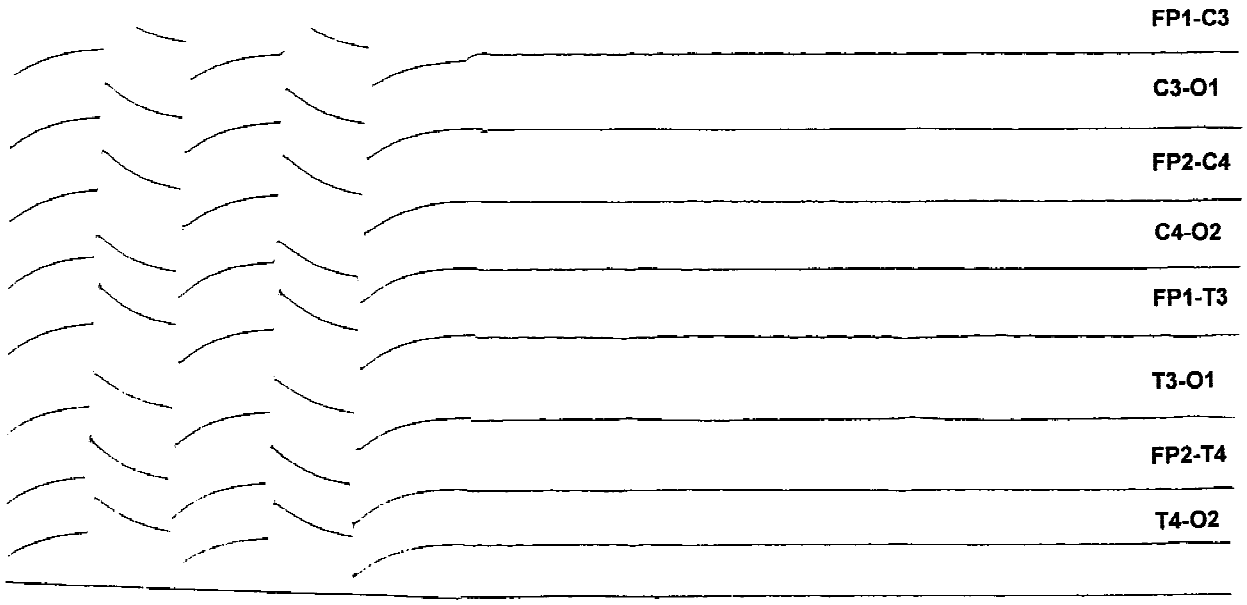

FIG. 1. Isoelectric scalp electroencephalogram.

both upper limbs, hands held in a praying position, and arms flexed at the elbow followed by abduction movements of the arms, separation of the hands, and falling of the arms alongside the torso. There was also flexion/extension of the lower limbs as well as walking-like movements. The authors added that these movements could also be elicited by applying noxious stimuli to the extremities, by flexion of the neck, or by plantar stimulation. This was the first report of these types of movements. Subsequently, Ropper et al.[9] reported the presence of the classic "Lazarus' sign" in five patients with BD after the ventilator was disconnected or during apnea testing. Typically, the sequence of movements lasted for several seconds and included bilateral arm flexion to the chest, shoulder adduction, and hand-raising above the chest or moving up to the neck. The fingers sometimes held dystonic postures. The hands then crossed or touched and finally proceeded down to the bed. In two patients, passive flexion of the neck elicited a jerk that raised the four limbs off the bed. Historically, Lazarus was the brother of Mary and Martha of Bethany and a friend of Jesus Christ. According to the New Testament, Christ raised Lazarus from the dead, thus the sign of the patient moving while brain dead. Jordan et al.[11] reported on a 63-year-old man with BD who, a few minutes after termination of respiratory support, crossed both arms over his chest and began to sit up. This spontaneous movement lasted approximately 15 seconds before he resumed the horizontal position. Later, Heytens et al.[12] also reported a case of Lazarus' sign in a brain-dead patient during nonhypoxic apnea testing, although with a repetitive pattern lasting approximately 1 hour and with associated arterial hypertension, tachycardia, and facial flushing. Other cases of Lazarus' sign were also reported either following respiratory support removal or on neck flexion.[13–18] Most cases involved movements of the upper limbs only, although some also had lower limb motion, such as flexion at the hips and knees,[10,15,16] flexion of the trunk,[11] or shallow and irregular respiration movements.[13,15]

The complex movements that our patient displayed are similar to those described by the previous reports mentioned above. This complex sequence of movements was named the "Lazarus' sign"[9] and is thought to be spinal in origin.[6,9,15–17] It was suggested that this phenomenon may be the result of hypoxic stimulation of neurons in a cervical spinal cord isolated from rostral brain regions, because it has been reported after the respirator was shut off, during apnea testing, or when on arterial hypotension.[9,13,15] In fact, some authors prefer to reserve the term "Lazarus' sign" for this motor phenomenon when seen in BD patients after cessation of artificial ventilation.[16] However, our patient, as well as others,[10,12,16,18] exhibited this phenomenon without being hypoxic. In our case, passive flexion of the neck elicited Lazarus' sign. Passive neck flexion, as well as other noxious stimuli, has also been reported to trigger this complex sequence of movements,[10,14,16] suggesting that stimulation of the cervical spinal cord in a brain-dead individual may also induce this phenomenon. Mechanical extension of spinal roots, compression of the spinal cord, or sensory input phenomena may have a relationship to Lazarus' sign.[17]

Further electrophysiological, functional imaging, or flow studies can help elucidate the nature of Lazarus' sign. Because of the practical and legal implications, neurologists need to identify this unusual movement.

Legend to the Videotape

The patient is a 42-year-old man who met criteria for brain death following a large pontocerebellar hemorrhage. In the first 24 hours, a complex sequence of movements was observed.

The videotape shows the patient displaying a sequence of complex movements on passive flexion of the neck: both upper limbs are raised while there is flexion of the left arm at the elbow. There is slight internal rotation and adduction of the shoulders and pronation of the forearms. Subsequently, both arms cross on the patient's chest while there is dystonic-like posturing of the hands with extension and abduction of the fingers, more prominent on the left side. A few seconds later, the hands proceed down to the lower abdomen.

On repetition of passive neck flexion, the patient raises both upper limbs. There is arm extension at the elbows, pronation of the forearms, and dystonic movements of the hands for approximately 3 seconds before their return to rest on the lower abdomen. Later, the videotape shows variations, including flexion of the left arm with subsequent extension at the elbow on passive neck flexion. With repetition of neck flexion, this pattern extinguished. Only slight flexion of the arms was observed.

Finally, the videotape shows the tonic neck reflex. When the head is passively turned to the right, there is flexion of the left upper limb.

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References

1. Practice parameters for determining brain death in adults. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1995;45:1012–1014.
2. Wijdicks EFM. Determining brain death in adults. *Neurology* 1995;45:1003–1011.
3. Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. a definition of irreversible coma. *JAMA* 1968;205:337–340.
4. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Guidelines for the determination of death. *JAMA* 1981;246:2184–2186.
5. Ivan LP. Spinal reflexes in cerebral death. *Neurology* 1973;23: 650–652.
6. Jorgensen EO. Spinal man after brain death. The unilateral extension-pronation reflex of the upper limb as an indication of brain death. *Acta Neurochir (Wien)* 1973;28:259–273.
7. Saposnik G, Bueri JA, Mauriño J, Saizar R, Garretto NS. Spontaneous and reflex movements in brain death. *Neurology* 2000;54: 221–223.
8. McNair NL, Meador KJ. The undulating toe flexion sign in brain death. *Mov Disord* 1992;7:345–347.
9. Ropper A. Unusual spontaneous movements in brain death patients. *Neurology* 1984;34:1089–1092.
10. Mandel S, Arenas A, Scasta D. Spinal automatism in cerebral death [Letter]. *N Engl J Med* 1982;307:501.

11. Jordan JE, Dyess E, Cliett J. Unusual spontaneous movements in brain-dead patients [Letter]. *Neurology* 1985;35:1082.
12. Heytens L, Verlooy J, Gheuens J, Bossaert L. Lazarus sign and extensor posturing in a brain-dead patient. *J Neurosurg* 1989;71: 449–451.
13. Urasaki E, Fukumura A, Itho Y, et al. Lazarus' sign and respiratory-like movement in a patient with brain death. *No To Shinkei* 1988;40:1111–1116.
14. Turmel A, Roux A, Bojanowski MW. Spinal man after declaration of brain death. *Neurosurgery* 1991;28:298–302.
15. Urasaki E, Tokimura T, Kumai JI, Wada SI, Yokota A. Preserved spinal dorsal horn potentials in a brain-dead patient with Lazarus' sign. *J Neurosurg* 1992;76:710–713.
16. Awada A. Automatismes réflexes inhabituels après mort cérébrale. *Rev Neurol (Paris)* 1995;151:586–588.
17. Nokura K, Yamamoto H, Uchida M, Hashizume Y, Inagaki T. Automatic movements of extremities induced in primary massive brain lesion with apneic coma. *Rinsho Shinkeigaku* 1997;37:198–207.
18. Dequin PF, Hazouard E, Huguet M, Delplace C, Tayoro J, Giniès G. Signe de Lazare après mort encéphalique [Letter]. *Presse Med* 1998;27:1102.