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Clinical/Scientific Notes

Cabergoline Plasma Concentration Is Increased During Concomitant Treatment with Itraconazole

Jakob Christensen, MD,[1,2]* Erik Dupont, MD,[2] and Karen Østergaard, MD, DMSci[2]

[1]*Centre for Clinical Pharmacology, University of Aarhus, Aarhus, Denmark*
[2]*Department of Neurology, Aarhus University Hospital, Aarhus, Denmark*

Abstract: We report on 2 patients with idiopathic Parkinson's disease who experienced marked improvement in symptoms following the addition of itraconazole to current cabergoline treatment. Plasma levels of cabergoline were analyzed in one of the patients and increased to approximately 300% during treatment with itraconazole, which paralleled major clinical improvement. © 2002 Movement Disorder Society

Key words: Parkinson's disease; cabergoline; itraconazole; cytochrome P-450; drug interactions

To our knowledge, an interaction between cabergoline and itraconazole has not been reported previously. We describe 2 patients treated with cabergoline who exhibited marked decrease in their parkinsonian symptoms during pulse treatment with itraconazole.

Cabergoline is a relatively selective dopamine D2 agonist used for the treatment of Parkinson's disease.[1–4] Cabergoline is probably well absorbed after oral dosing but the absolute bioavailability is unknown.[5] The drug undergoes extensive first-pass metabolism and the majority is excreted as metabolites in the bile and feces.[1,5] The metabolites are not believed to be pharmacologically active.[5] Results of current in vitro studies indicate that the metabolism of cabergoline is mediated via the cytochrome P-450 system (CYP) and that the subtype principally responsible for the metabolism is CYP3A4.[6] Peak plasma concentrations of cabergoline are achieved 1 to 2 hours after dosing, and the drug is extensively distributed into body tissues, including the brain.[1,5] The elimination half-life of cabergoline is relatively long (65–115 hours), providing stable effects over time; however, there is considerable variation among patients.[1,5]

Itraconazole is a triazole used as a local and systemic antifungal agent.[7] It is a potent inhibitor of CYP3A4 and significantly increases plasma concentrations of several orally administered drugs that are metabolized by CYP3A4.[8–14]

*Correspondence to: Jakob Christensen, MD, Centre for Clinical Pharmacology, Department of Pharmacology, The Bartholin Building, Aarhus University, 8000 Aarhus C, Denmark.
E-mail: Jakob@farm.au.dk

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Patient 1

A 65-year-old, Caucasian man with idiopathic Parkinson's disease (PD) presenting with rigidity and tremor of the right upper and lower extremities was admitted to the outpatient clinic. Symptoms had emerged 4 years earlier, and at the time of admission he was treated with selegiline (Eldepryl; Oprion, Espoo, Finland) in monotherapy, which relieved some of his symptoms. The decision was made to give additional treatment with the dopamine agonist cabergoline (Cabaser; Pharmacia, Copenhagen, Denmark). The patient's treatment was titrated to a maintenance dose of selegiline 5 mg twice daily and cabergoline 4 mg once a day. Symptoms at these dosages consisted of light to moderate parkinsonian symptoms on the right side of the body, slurred speech, immobility of the face, and imbalance. It was observed that the patient had fungal infection in the toenails of both feet, for which treatment with itraconazole (Sporanox; Janssen-Cilag, Birkerød, Denmark) 200 mg was given twice daily for 1 week.

At the clinical visit at the end of itraconazole treatment, the patient reported subjective improvement in his condition, with facilitated movements, decreased tremor, and normalization of speech. He further reported mouth dryness, improved mood, and erotic dreams. The improvement was also clearly evident in the clinical investigation, although parkinsonian symptoms in right-sided extremities were still present. The improvement was still evident after an additional week following discontinuation of itraconazole, although less marked. The effect was assessed using items 18 to 31 on the Unified Parkinson's Disease Rating Scale.[15] The scores are shown in Figure 1. The improvement gradually decreased during the weeks after the patient stopped itraconazole treatment. The improvement reemerged following two additional 1-week periods of treatment with itraconazole of identical dose and duration separated by 3 weeks' treatment pause but was not further assessed.

To monitor the cabergoline treatment, blood samples were collected prior to, during, and after itraconazole treatment (Fig.

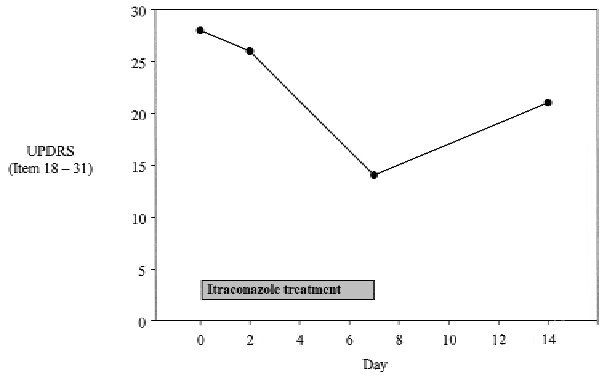

FIG. 1. Unified Parkinson's Disease Rating Scale (UPDRS) score for Patient 1 before, during, and after treatment with itraconazole. Only items 18 to 31 of UPDRS were assessed.

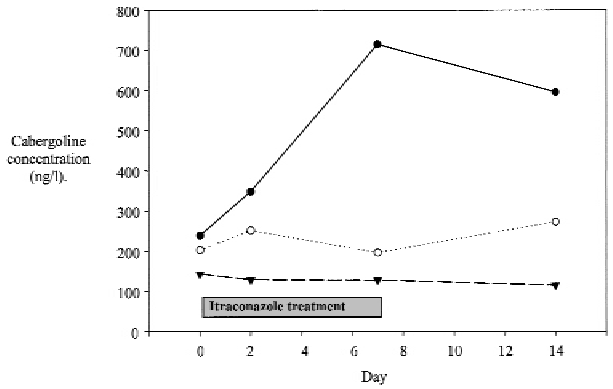

FIG. 2. Concentration of cabergoline in 3 patients during a 14-day period. Blood samples were collected in the morning (8.30–10.30 AM) prior to cabergoline dosing (trough levels). Patient 1 had additional itraconazole treatment, which was initiated on day 0. Steady state was reached for all patients prior to day 0. Samples were collected from Patient 1 during the first of three pulse treatments with itraconazole (2 × 200 mg daily). Concomitant treatment with itraconazole resulted in a marked increase in the plasma concentration of cabergoline. Treatment for patients and controls was as follows: Patient 1 (●), cabergoline (Cabaser) 4 mg at 1 PM and selegiline (Eldepryl) 5 mg at 8 AM and 1 PM. Control Patient 1 (○), carbidopa 25 mg/levodopa 100 mg (Sinemet) three times daily at 6:30 AM, 12:30 PM, and 6:30 PM, and cabergoline (Cabaser) 4 mg at 12:30 PM. Control Patient 2 (▼), selegiline (Eldepryl) 10 mg at 7 AM and cabergoline (Cabaser) 3 mg at 7 PM.

2). The cabergoline plasma concentration was determined using a validated liquid chromatography tandem mass spectrometry assay.[16,17] In brief: Plasma samples were mixed with the internal standard (cabergoline labelled with $^2H_5$) and after extraction were injected into the liquid chromatography system. Chromatographic separation was achieved using a μBondapack C18 analytical column (Waters Corp., Milford, MA). Cabergoline and internal standard were detected using an API 3000 tandem mass spectrometer (PE-Sciex, Toronto, Canada). The calibration curve was linear over the range 2.00 to 100 ng/L. The lower limit of quantification was 2.00 ng/L. Total accuracy was 108.0%, 106.0%, and 104.6%, respectively, for the 2.00 ng/L, 20.0 ng/L, and 80.0 ng/L quality control standard concentrations. Total assay precision expressed as coefficients of variation was 12.8%, 9.2%, and 11.0%, respectively, for the same quality control standard concentrations.[17]

The plasma concentration of cabergoline was increased to approximately 300% during itraconazole treatment, which paralleled the improvement in the patient's clinical condition. The plasma concentration of cabergoline remained increased (>200%) 1 week after itraconazole treatment had stopped, which was in accordance with the maintained improvement in clinical condition at that time.

As part of the clinical control, blood samples were collected from 2 additional PD patients who did not take other drugs besides their usual antiparkinsonian medication. The medical treatment of these 2 patients was as follows: Control Patient 1, carbidopa 25mg/levodopa 100 mg (Sinemet; Merck, Sharp, and Dohme, Glostrup, Denmark) three times daily and cabergoline 4 mg once a day; Control Patient 2, selegiline 10 mg once a day and cabergoline 3 mg once a day. For comparison, the results of the cabergoline analyses of these 2 patients are included in Figure 2. There seemed to be little variation in cabergoline concentration over time when patients were kept on a fixed dose. The clinical condition of the 2 patients did not change significantly between clinical visits.

Patient 2

A 41-year-old Caucasian woman diagnosed with PD experienced increasing parkinsonian symptoms over a 4-year period. Symptoms consisted of significant bilateral rigidity most pronounced in the left extremities. She also presented with tremor and bradykinesia localised to the left side, and her gait was shuffling with poor swinging of the left arm. She received the following drug treatment: carbidopa 12.5 mg/levodopa 50 mg (Sinemet, Merck, Sharpe, and Dohme) six times daily, entacapone (Comtess; Oprion) 200 mg six times daily, selegiline (Eldepryl, Oprion) 5 mg twice daily, and cabergoline (Cabaser) 2 mg twice daily. Her general practitioner prescribed itraconazole (Sporanox, Janssen-Cilag) 200 mg twice daily for 1 week, for the treatment of fungus in the toenails. After 3 days of itraconazol treatment, the patient experienced symptoms of overdose in the form of hyperkinesia of the extremities and consequently reduced her medication, taking only the morning doses of each of the four drugs. Despite this dramatic reduction in dose, her usual parkinsonian symptoms practically disappeared during days as well as nights and without any side effects for the following week, but relapsed gradually 4 to 5 days after discontinuation of itraconazole treatment. Her subjective experience was verified by clinical examination.

She reinstituted her usual treatment, but the astonishing clinical improvement was repeated following two additional periods of itraconazole treatment of identical dose and duration.

Discussion

The marked improvement in the condition of the 2 Parkinsonian patients during treatment with itraconazole was striking. We suggest that the mechanism behind this improvement might have been a decrease in metabolism of cabergoline during concomitant itraconazole treatment. This suggestion is likely from a theoretical point of view, as cabergoline is metabolized in vitro via CYP3A4, which is specifically inhibited by itraconazole. Furthermore, this is supported by the major increase in cabergoline concentration during itraconazole treatment found in Patient 1, which paralleled the clear clinical improvement.

Both patients received selegiline, which is also susceptible to metabolism via the cytochrome P450 system. However, itraconazole treatment has recently been shown not to influence selegiline metabolism, making significant involvement of CYP3A4 in the metabolism of selegiline unlikely.[18]

In conclusion, an interaction between itraconazole and cabergoline was suspected in our 2 patients. The mechanism behind this interaction is believed to be an itraconazole-mediated inhibition of cabergoline metabolism via CYP3A4. The finding raises the possibility that other drugs known to inhibit or induce drug metabolism via CYP3A4 may influence the cabergoline

plasma concentration, resulting in an altered response to treatment.

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Entacapone-Induced Hepatotoxicity and Hepatic Dysfunction

Alexander Fisher, MD,[1] James Croft-Baker, MBBS, MRCP,[1] Michael Davis, MBBS, FRACP,[1,2] Patrick Purcell, MBBS,[3] and Allan J. McLean, MBBS (Hon I), BMed Sci (Hons I), PhD, FRACP, AFACHSE[1,2,4]*

[1]Department of Geriatric Medicine, The Canberra Hospital, Canberra, Australia
[2]Canberra Clinical School of the University of Sydney Canberra, Australia
[3]Therapeutic Goods Administration, Canberra, Australia
[4]National Ageing Research Institute, University of Melbourne, Royal Melbourne Hospital, and Melbourne Health, Melbourne, Australia

Abstract: We describe 2 patients with Parkinson's disease who developed hepatotoxicity associated with the use of entacapone, a novel, mainly peripheral acting inhibitor of catechol-D-methyltransferase. Hepatotoxicity resolved rapidly with discontinuation of the drug. Analysis of causality in a further case initially linked to entacapone exposure was confounded by conflicting serial adverse reaction reports. © 2002 Movement Disorder Society

Key words: hepatotoxicity; entacapone; COMT inhibitors

Entacapone is a potent, selective, reversible inhibitor of catechol-*O*-methyltransferase (COMT), principally active in the periphery. This novel drug is used as a beneficial adjunct to levodopa–dopa decarboxylase therapy in Parkinson's disease. It is found to be well tolerated, with most adverse effects being related to enhancement of dopaminergic activity, including dyskinesias, nausea, orthostatic hypotension, sleep disturbance, confusion, and hallucinations.[1–3] Hepatotoxicity, including fulminant hepatitis and three deaths among 60,000 patients, was a serious adverse event associated with the use of tolcapone, a COMT inhibitor preceding entacapone. Tolcapone was removed from the market in Europe and Canada and restricted in many other countries, including the United States. In contrast, significant liver toxicity has not been reported in some 80,000 entacapone-treated patients. It has been concluded that hepatotoxicity observed with tolcapone is not a class effect of COMT; consequently, no laboratory monitoring is required for entacapone.[2,4–7] We report in detail the first case of entacapone-induced hepatotoxicity together with summary data of 2 other cases reported to the Australian Adverse Drug Reaction Advisory Committee (ADRAC).

Case Report

A 76-year-old, Caucasian woman was admitted to hospital after a fall that resulted in fractured right pubic ramus. She had

*Correspondence to: Allan J. McLean, National Ageing Researach Institute, PO Box 31, Parkville, Victoria 3052, Australia. E-mail: a.mclean@nari.unimelb.edu.au

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a history of Parkinson's disease (diagnosed 6 years previously), long-standing hypertension, and osteoarthritis. Three weeks before admission, she was started on entacapone (200 mg five times/day) because of increased frequency of falls in the preceding months. The week before admission she developed nausea, anorexia, and generalised malaise. The patient had no history of liver disease, excessive alcohol use, exposure to blood products, intravenous drug use, and denied risk factors for acquisition of viral hepatitis. She had never smoked, and there was no family history of liver disease. Liver function tests done 2 years earlier as part of a general medical assessment were normal. Long-standing medications included levodopa 200 mg/benserazide 50 mg four times daily, amiloride 5 mg/hydrochlorothiazide 50 mg OD, verapamil 40 mg once daily, and rofecoxib 25 mg b.i.d. On admission to the hospital, there was a parkinsonian tremor without focal weakness, scleral icterus, and mild right upper quadrant tenderness, but no rebound tenderness or hepatomegaly was detected. The heart size was at the upper limit of normal and lung fields were clear on plain chest X-ray. Laboratory tests showed a total bilirubin of 40 mmol/L (normal, 2–20); alanine aminotransferase (ALT), 104 U/L (normal, 5–55 U/L); γ-glutamyltransferase (GGT), 328 U/L (normal, 12–43 U/L); alkaline phosphatase (ALP), 238 U/L (normal, 20–110 U/L); and lactic dehydrogenase (LDH), 1,565 U/L (normal, 300–500 U/L). Albumin and prothrombin time were normal at 34 g/L (normal, 33–50 g/L) and 12 seconds (normal, 9–15 seconds), respectively. The serologic studies for viral, autoimmune, and metabolic liver disease, as well as full blood count, electrolytes, amylase, lipase, and tumour markers (a-fetoprotein, carcinoembryonic antigen, b-human chorionic gonadotrophin, CA-125) were normal. Abdominal ultrasonogram was normal. Liver function tests continued to worsen with a peak on the fourth day when GGT reached 487 U/L, ALT 116 U/L, ALP 293, but total bilirubin returned to normal (14 mmol/L). The possibility of an adverse drug reaction was considered on the second hospital day and entacapone, in view of its recent introduction, was discontinued. According to prescriber recommendation, the dose was halved for 2 days before stopping to avoid abrupt withdrawal. The last dose of entacapone was on the 4th hospital day. From the 7th day after admission, nausea disappeared, appetite improved, and liver function tests improved: ALT returned to a normal level on day 14, ALP and GGT 4 weeks later, and total bilirubin stayed at a normal level. A summary of laboratory data is shown in Table 1. The patient refused the offer of a supervised rechallenge test.

ADRAC Database

An initial search of the ADRAC database disclosed two cases of possible hepatotoxicity associated with entacapone. A 73-year-old woman with a history of parkinsonism was admitted to hospital when she became confused and febrile some 6 weeks after commencing entacapone at a dose of 800 mg daily. Her other medications included donezipil, selegeline, carbergoline, doxepin, levodopa, and prothiaden. She was found to have mildly increased liver function tests, decreased haemoglobin, and raised erythrocyte sedimentation rate. Gamma glutamyl transferase peaked at almost nine times the upper limit of normal, and her ALP reached 2.5 times the upper limit of normal. Her symptoms resolved immediately when all medications except levodopa and clonazepam were withdrawn. The other case involved an 83-year-old man reported initially to have suffered "worsening liver failure" and recurrent syncope 5 weeks after commencing entacapone 200 mg daily. His other medications included levodopa/benserazide (200/50 combination), frusemide (furosemide), celecoxib, moclobemide, warfarin, perindopril, and atorvastatin. His previous history also included stroke, deep venous thrombosis, hypothyroidism, impaired renal function, and myocardial function. His GGT was reported as remaining elevated (four to five times the upper limit of normal) for at least 2 months after entacapone was ceased. Direct contact from Novartis management after the initial electronic posting of this publication required an important amendment of the history to include a 40-year history of alcoholism and hepatic cirrhosis. A subsequent case update from Novartis involved biochemical data retrieved retrospectively, indicating that elevated GGT levels had preceded the initial exposure to entacapone.

Discussion

Drug-induced liver disease accounts for between 10% and 50% of instances of elevated liver enzymes in adult patients. The incidence is increasing, reflecting an increased number of reactions to new medications.[8,9] Tolcapone, a COMT inhibitor, is a recognised cause of hepatotoxicity.[4–7] Entacapone has been found to be a safe drug, which does not cause hepatotoxicity in experimental studies[10,11] and human trials,[4,5,7,12] including postmarketing surveillance.[2,3] However, clinical experience with entacapone is still limited. It is worth noting that, for some drugs, hepatotoxicity was discovered several decades after they became available.[13]

TABLE 1. *Dynamics of liver chemistries in a patient receiving entacapone for 3 weeks before and after discontinuation of the drug*

Laboratory values (normal)	Day of discontinuation of entacapone							
	−3	−2	−1	0	3	5	7	35
ALT (5–55 U/L)	104	84	104	116	116	69	29	12
GGT (12–43 U/L)	328	280	425	487	394	328	262	111
ALP (20–110 U/L)	238	168	275	293	210	176	156	132
Bilirubin (2–20 mmol/L)	40	9	16	14	10	9	8	8
LDH (300–500 U/L)	1565	NA	NA	NA	1365	1278	707	NA
ALT/LDH	0.07	NA	NA	NA	0.08	0.05	0.04	NA
ALT/ALP	0.44	0.50	0.38	0.39	0.55	0.39	0.19	0.9

ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase; LDH, lactic dehydrogenase; NA, not available.

We report here on 2 cases of acute liver dysfunction in association with entacapone therapy in two women, 73 and 76 years of age. Older age and female gender are known factors that predispose to hepatotoxic reactions.[9] These 2 patients had no known chronic liver disease, and the laboratory tests did not show other causes of liver dysfunction except the use of entacapone. After entacapone was discontinued, the liver dysfunction resolved in our patient, indicating a drug-induced hepatotoxicity. Similar recovery was reported for the female patient on the ADRAC database. The other case on the ADRAC database had significant apparent errors or omissions in initial reports of clinical history and biochemistry, confounding existing analyses of causation.

In our patient, levels of ALT, GGT, LDH, ALP, and bilirubin were elevated 2-, 11-, 3-, 3-, and 2-fold over the upper limit of normal (ULN), respectively. In the 2 cases as initially reported to ADRAC, the ALT was elevated 3- and 5-fold, GGT was elevated 13- and 12-fold, ALP was increased 2- and 3-fold, and total bilirubin was normal. By convention, liver injury is designated hepatocellular when serum ALT level is greater than two times ULN or ALT/ALP ratio is ≥ 5. In cholestatic injury, the ALP is >2 times ULN or the ALT/ALP ratio is ≤ 2; and the injury is called mixed when ALT/ALP ratio is 2 to 5 and individual values are greater than 2 times ULN.[14] According to these criteria, the hepatotoxic injury in our patient should be classified as mixed. The female ADRAC case may be tentatively classified as hepatocellular. In some studies,[3,5] a serum ALT level >3 ULN is potentially significant and indicates monitoring. Liver dysfunction presented in the female ADRAC case had also been reported in phase 3 clinical trials in 0.5% of 603 patients receiving entacapone and 0.5% of 400 patients on placebo,[5] and in a postmarketing study in 0.9% of 218 patients and in 0% of 108 nonpatients.[5]

Our patient also had a significant rise in LDH and GGT. LDH activity is abnormal in a large number of disorders, indicating cell damage or inflammation. A massive rise in LDH and a low (<1.5) ALT/LDH ratio are characteristic features of ischaemic hepatitis,[15,16] as well as hepatocellular neoplasms. However, in our patient, there was no evidence of systemic hypotension, cardiac or renal failure, coagulopathy, or hyperglycaemia to suggest ischaemic hepatitis and no symptoms and signs of malignant disease were detected. Moreover, after entacapone was discontinued, the liver dysfunction resolved, indicating a drug-induced hepatotoxicity. The marked elevation of GGT is another important index of entacapone-associated liver injury in line with the current understanding of the physiological role of GGT in counteracting oxidative stress (by breaking down extracellular glutathione) and observations of increased free radical production and glutathione depletion in conditions with high serum GGT.[17]

We used the method of Naranjo and colleagues[18] and the Council for International Organisations of Medical Sciences (CIOMS) scale[19] to estimate the probability of hepatotoxicity associated with entacapone in our patient. In the first scoring method, the total score was 7, indicating a probable cause of hepatotoxicity. In the CIOMS scale, which appears to be the best for detecting hepatotoxicity,[14] the total score was 8, making entacapone a probable cause of hepatotoxicity. Thus, in both scales, the association between entacapone and liver injury is considered probable. In this patient, entacapone was suspected to be the causative agent associated with development of hepatotoxicity. Other coprescribed medications, including rofecoxib, were considered unlikely as causal, because they were used for several years before the event and were continued in the hospital and after discharge.

The mechanism of hepatotoxicity due to COMT inhibitors is unknown. It is thought that the most likely mechanism of tolcapone's toxicity is related to interference with mitochondrial respiration in the hepatocyte "possible because tolcapone is more lipophilic and has a greater tendency to accumulate in mitochondria than entacapone."[5] However, the 11-fold increase in GGT level in our patient indicates a possible role of oxidative stress in entacapone-induced hepatotoxicity. Entacapone (as well as tolcapone) is highly metabolized in the liver mainly by conjugation with glucuronic acid and eliminated mainly by biliary excretion. Although glucuronidation (primarily by UGT1 A9) is the most important metabolic pathway for both COMT inhibitors, entacapone has a three to four times greater rate of glucuronidation than tolcapone.[20] A reduced rate of detoxification with accumulation of a toxic compound would be expected to have enhanced susceptibility to hepatotoxicity. However, there is as yet no evidence to support such a mechanism with COMT inhibitors. Drug interaction as a cause of entacapone hepatotoxicity is unlikely, because less than 1% of the drug is oxidized by cytochrome P-450 system, it is not *O*-methylated in humans, and when combined with levodopa-dopa decarboxylase does not effect entacapone pharmacokinetics.[7] Entacapone is extensively bound to plasma proteins, mainly to albumin. Therefore, increased bioavailability (with a toxic effect) may be expected in patients with hypoalbuminaemia. This condition was not the case in our patient, who had a normal level of albumin. Our patient did not have fever, rash, arthralgias, arthritis, or hypereosinophilia to suggest a hypersensitivity or allergic mechanism. The toxicity data, the rareness of entacapone-associated hepatotoxicity, the absence of evidence of dose-relationship and reproducible animal models, as well as absence of signs of hypersensitivity or allergy all indicate that an idiosyncratic toxicity mechanism is most likely.

In conclusion, the cases presented establish a significant probability that entacapone may be hepatotoxic, particularly in older people. Although this toxic response is rare and routine monitoring of liver function tests may not be cost-effective, clinicians should be aware of the possibility of entacapone-induced hepatotoxicity. Caution should be exercised when initiating this medication, and early discontinuation should be strongly considered if significant changes in markers of liver dysfunction are detected. The sponsor in Australia lists "liver impairment" as a contraindication to the use of the drug, a prudent recommendation that should be noted and endorsed.

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Clozapine Withdrawal Symptoms in a Parkinson's Disease Patient

Theresa A. Zesiewicz, MD,[1]* Sujatha Borra, MD,[1] and Robert A. Hauser, MD[1,2]

[1]Department of Neurology, Parkinson's Disease and Movement Disorders Center, University of South Florida and Tampa General Healthcare, Tampa, Florida, USA
[2]Department of Pharmacology and Experimental Therapeutics, Parkinson's Disease and Movement Disorders Center, University of South Florida and Tampa General Healthcare, Tampa, Florida, USA

Abstract: Abrupt clozapine withdrawal can cause rebound psychosis and severe somatic symptoms in psychiatric patients. We report on the case of an advanced Parkinson's disease patient who developed myoclonus, tremor, rigidity, hyperreflexia, and stupor after abrupt clozapine withdrawal. The patient's symptoms resolved with treatment with cyproheptadine. This clinical picture suggests serotonergic rebound as an explanation for the patient's symptoms, although other pharmacological mechanisms are possible. Clozapine should be gradually withdrawn over a period of 1 to 2 weeks when possible, and abruptly discontinued only when necessary. © 2002 Movement Disorder Society

Key words: clozapine; withdrawal; rebound; serotonin syndrome

Clozapine is an atypical antipsychotic agent that effectively ameliorates hallucinations in patients with Parkinson's disease (PD) without worsening motor symptoms.[1–4] Clozapine may be discontinued due to side effects, noncompliance, or when switching to another agent.[5] Possible side effects of clozapine include agranulocytosis, hypotension, seizures, tachycardia, hyperglycemia, eosinophilia, transient fever, deep vein thrombosis, hepatitis, and anticholinergic effects.[6] In addition, there are several reported cases of clozapine-induced neuroleptic malignant syndrome, prompting clozapine discontinuation.[7,8] We report on the case of an advanced PD patient who experienced clozapine withdrawal symptoms after abrupt discontinuation, and discuss possible pathophysiological explanations and treatments.

Case Report

A 69-year-old man was diagnosed with Parkinson's disease in 1974. He initially noticed incoordination and stiffness in his left upper extremity and his symptoms responded to levodopa (L-dopa)–carbidopa therapy. Over time, his L-dopa dose was increased to as high as 1,000 mg daily. He developed visual hallucinations in 1991 that resolved after L-dopa dose reduction to 500 to 800 mg a day and the subsequent introduction of clozapine (Clozaril) 50 mg a day. The patient remained on clozapine for 10 years, and continued on L-dopa–carbidopa. He did not experience tremor or take antidepressants at any time during the course of his illness.

Ultimately, the patient's caretaker could no longer arrange for biweekly blood draws due to her own illness, and asked that her husband be taken off clozapine. She was therefore given instructions to taper the dose down and discontinue the medication over 2 weeks. Due to confusion on the part of the caregiver, however, the clozapine dose was reduced to 37.5 mg for 1 week and then discontinued on day 8. Before clozapine withdrawal, the patient's Mini Mental State Exam (MMSE) score was 25/30.

Twenty-four hours after clozapine was discontinued, the patient became confused, agitated, restless, and had difficulty performing his usual activities of daily living such as eating and dressing. The next morning, the caregiver had difficulty arousing the patient, finding that painful stimuli were necessary to induce eye opening. He was brought to the hospital and stupor

*Correspondence to: Theresa A. Zesiewicz, MD, Associate Professor of Neurology, Parkinson's Disease and Movement Disorders Center, 4 Columbia Drive, Suite 410, Tampa, Florida 33606.
E-mail: tzesiewi@hsc.usf.edu

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continued for the next several hours. In the hospital, he was found to have normal vital signs including temperature, pulse, and respirations. There were no overt signs of psychosis or sepsis. On neurological examination, he was stuporous, had a rest tremor in his left upper extremity, and exhibited increased rigidity, myoclonus and hyperreflexia in his upper and lower extremities. CT scan of the head, blood chemistries, hematological studies, urinalysis, and cerebrospinal fluid examination were normal. Electroencephalogram showed mild generalized slowing of 5 to 7 Hz.

Approximately 48 hours after onset of symptoms, the patient was treated with cyproheptadine (Periactin) 4 mg every 6 hours for possible serotonergic rebound due to clozapine withdrawal. His mental status returned to baseline and myoclonus resolved after 24 hours, and rigidity and tremor also showed mild improvement. The patient was continued on tapering doses of cyproheptadine for the next 6 days, during which his rigidity returned to baseline and tremor completely resolved.

Discussion

Clozapine is an atypical antipsychotic medication with antagonistic actions at dopaminergic, serotonergic, α-adrenergic, histaminergic, and muscarinic receptors.[9] The prevalence of clozapine withdrawal symptoms is not known. In 1994, the National Institute of Mental Health concluded that there was insufficient evidence to determine the magnitude of problems associated with abrupt clozapine withdrawal.[10] Case reports and one double-blind study have described rapid relapse of psychosis or somatic symptoms after abrupt clozapine withdrawal in psychiatric patients.[11–24] In contrast, one retrospective review of clozapine use in PD patients found no evidence of clozapine withdrawal symptoms in the 23% of patients who discontinued the drug, but the manner and timing of clozapine withdrawal was not reported.[25]

The difficulty of switching PD patients taking clozapine or olanzapine to quetiapine has been described.[26] Fernandez and associates attempted to switch 11 psychiatrically stable PD patients taking clozapine (8 patients) or olanzapine (3 patients) to quetiapine.[26] Five patients completed this transition without difficulty. Six of the 11 patients (5 on clozapine, 1 on olanzapine) switched back to their original antipsychotic drugs; crossover failures were due to confusion, erratic behavior, and increased hallucinations. In another trial, Fernandez and associates attempted to switch 15 psychiatrically stable PD patients from clozapine to quetiapine[27] and found that 12 patients made the transition without worsening of cognition or loss of antipsychotic effect. Switch-over failures were due to increased dyskinesia, tremor, and anxiety in one patient, and increased hallucinations and confusion in another. The third patient dropped out of the study due to sudden onset of transient radicular leg pains.

The etiology of clozapine withdrawal symptoms is unknown. It has been suggested that abrupt discontinuation of clozapine can cause rebound psychosis, reflecting supersensitivity of the dopaminergic limbic system.[12,28–32] Tollefson and associates conducted a randomized, double-blind trial evaluating clozapine withdrawal symptoms in 106 schizophrenic patients.[11] Patients received clozapine (mean, 464 ± 100 mg/day; maximum dose, 900 mg/day) for a minimum of 4 weeks before study entry, and clozapine was tapered during a 2- to 12-day interval by 50 mg a day to 300 mg a day. Clozapine was then abruptly discontinued, and patients were randomized to receive olanzapine or placebo for a 3- to 5-day period. Significantly more placebo-treated patients (24.5%) than olanzapine-treated patients (7.5%) experienced clozapine discontinuation symptoms ($P = 0.017$), including delusions, hallucinations, hostility, and paranoia. Whether this is a re-emergence of previously treated symptoms or a true dopaminergic rebound phenomenon is not clear.

Clozapine withdrawal can cause cholinergic rebound,[12,13,33] resulting in nausea, vomiting, diarrhea, abdominal colic, rhinorrhea, insomnia, restlessness, anxiety, agitation, headache, irritability, and diaphoresis. Similar effects have been observed after the abrupt withdrawal of anticholinergic tricyclic antidepressants such as imipramine[34,35] and low potency neuroleptics.[36,37] There is anecdotal evidence that anticholinergic medications may prevent or treat clozapine withdrawal symptoms.[13]

Our patient's symptoms of stupor, myoclonus, increased rigidity, tremor, and hyperreflexia may be explained by several pharmacological mechanisms (Table 1). Clozapine withdrawal may lead to the rapid relapse of psychosis due to dopaminergic mechanisms,[11] whereas myoclonus, tremor, and altered mental status may be indicative of serotonergic alterations. We believe that the transient appearance of tremor was part of a rebound syndrome rather than re-emergence of a previously treated symptom because the patient did not exhibit tremor earlier in his disease, and it resolved permanently after a brief course of cyproheptadine.

Clozapine is a 5-HT_{2A} antagonist, and chronic clozapine use may induce upregulation of 5-HT_{2A} receptors.[38] The addition of cyproheptadine resulted in clearing of our patient's sensorium after 24 hours and resolution of other symptoms over 1 week. Cyproheptadine[6] is a 5-HT_{2A} receptor antagonist with antihistaminic and anticholinergic properties that improves symptoms of the serotonin syndrome.[39] Mild serotonergic symptoms are often self-limited, however, and it is possible

TABLE 1. *Common symptoms of serotonin syndrome, neuroleptic withdrawal, and cholinergic rebound compared to patient's symptoms*

Clinical feature	Patient symptoms	Serotonin syndrome	Neuroleptic withdrawal	Cholinergic rebound
Consciousness impairment	Yes	Yes	Yes	Yes
Restlessness	Yes	Yes	Yes	Yes
Agitation	Yes	Yes	Yes	Yes
Psychosis			Yes	Yes
Headache			Yes	Yes
Nausea			Yes	Yes
Vomiting			Yes	Yes
Diaphoresis			Yes	Yes
Fever		Yes	Yes	
Autonomic dysfunction		Yes		
Diarrhea			Yes	Yes
Insomnia			Yes	Yes
Hyperreflexia	Yes	Yes		
Seizures		Yes		
Dystonia			Yes	
Dyskinesia			Yes	
Myoclonus	Yes	Yes		
Tremor	Yes	Yes		
Rigidity	Yes	Yes		
Akinesia	Yes			

that our patient's symptoms would have improved spontaneously without the use of cyproheptadine. Restarting clozapine would have been an alternative treatment option.

The National Institute of Mental Health recommends that clozapine should be abruptly discontinued only when necessary, and suggests gradually tapering clozapine over a period of 1 to 2 weeks when possible. Caretakers and patients should be warned that abrupt clozapine withdrawal can produce somatic and psychiatric symptoms. Patients who are withdrawn from clozapine should be monitored closely during the first week after its discontinuation.

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Hemiballism After Subthalamotomy in Patients with Parkinson's Disease: Report of 2 Cases

Chiung-Chu Chen, MD,[1,2] Shih-Tseng Lee, MD,[3] Tony Wu, MD, PhD,[2] Chi-Jen Chen, MD,[4] Chin-Chang Huang, MD,[2] and Chin-Song Lu, MD[1,2]*

[1]Movement Disorders Unit, Chang Gung Memorial Hospital and Medical College, Chang Gung University, Lin-Ko, Taoyuan, Taiwan, Republic of China

[2]Department of Neurology, Chang Gung Memorial Hospital

and Medical College, Chang Gung University, Lin-Ko, Taoyuan, Taiwan, Republic of China
[3]Department of Neurosurgery, Chang Gung Memorial Hospital and Medical College, Chang Gung University, Lin-Ko, Taoyuan, Taiwan, Republic of China
[4]Department of Diagnostic Radiology, Chang Gung Memorial Hospital and Medical College, Chang Gung University, Lin-Ko, Taoyuan, Taiwan, Republic of China

Abstract: The occurrence of persistent hemiballism after subthalamotomy for Parkinson's disease (PD) has not been described as frequently as mild or transient dyskinesia. We report on 2 patients with advanced PD who developed hemiballism and/or dyskinesia after subthalamotomy. One patient with a small lesion confined to the subthalamic nucleus (STN) developed persistent hemiballism; the other with a larger lesion involving the STN and also the zona incerta presented with a transient dyskinesia in a single limb. We conclude that a precise STN lesion might bear a potential risk of persistent hemiballism. © 2002 Movement Disorder Society

Key words: subthalamotomy; hemiballism; Parkinson's disease

Neuronal overactivity in the subthalamic nucleus (STN) is the main electrophysiological abnormality in the basal ganglia-thalamo-cortical circuit in Parkinson's disease (PD).[1] Previous investigations have demonstrated that reducing this STN overactivity using lesions or deep brain stimulation can alleviate all motor symptoms of parkinsonism in animal models[1–4] and humans.[5–14] However, complications such as hemiballism or dyskinesia[5–10,12–23] are well known and have frequently accompanied the benefit of STN lesions. Most reports[5,6,8–10,12,13,15] have suggested that subthalamotomy was safe and rarely induced severe hemiballism in PD patients. However, the size and location of subthalamotomy were rarely shown. Some reports[6,8,13] described a small subthalamic nucleotomy, but the lesions usually extended beyond the subthalamic nuclei, and the size of lesions were usually larger than expected.

We performed unilateral subthalamotomy for 3 advanced PD patients before deep brain stimulation was available to us. Two of the 3 patients developed dyskinesia on the contralateral limbs after the surgery, 1 of whom previously had unilateral pallidotomy, and the other thalamotomy. After stereotactic subthalamotomy, 1 patient developed hemiballism and the other appeared to display transient dyskinesia in the arm. We examine the relationship between the location and size of STN lesions and characteristics of the induced dyskinesia, and review the literature on dyskinesia after STN lesions in animal models of parkinsonism and human PD. Possible resolutions are considered.

Case Report

Patient 1

A 52-year-old housewife developed tremor in the left hand at age 19 years. The tremor spread slowly to involve the four limbs within the next 3 years. Neither family history of neurological disease nor any history of encephalitis or drug addiction was noted. The patient also experienced progressive clumsiness and stiffness in the left hand over the following years. Juvenile parkinsonism was diagnosed at the age of 27. The parkinsonian symptoms responded well to levodopa treatment. A survey of possible mutation of α-synuclein and parkin genes yielded negative results. Drug-induced dyskinesia appeared shortly after treatment in the left limbs and progressively worsened, despite the low dosage of levodopa. When she was 50 years old, the patient underwent stereotactic right pallidotomy in 1997 because of gait disturbance, severe motor fluctuations, and levodopa-induced dyskinesias, particularly on the left side. Not only was the rigidity and bradykinesia improved, but the dyskinesias in the left limbs was also extinguished. A subsequent left subthalamotomy (instead of pallidotomy) was arranged to improve the right-sided and axial symptoms, freezing gait, while avoiding the dysarthria possibly caused by bilateral pallidotomy.

Surgery was performed in October of 1999 using our standard protocol of CT brain scan with Brown-Roberts-Wells frame. Targeting was performed using a computer program that included a digitized version of Shaltenbrand-Wahren atlas. The sensorimotor region was also defined by microrecording. Then, an electrical coagulation lesion was made on the left STN. Postoperative magnetic resonance imaging (MRI) 3 months later confirmed a small lesion of 3 × 3 mm confined entirely to the STN (Fig. 1A). The patient's contralateral rigidity, tremor, and bradykinesia improved immediately after surgery. However, the patient developed violent choreic kicking movements mainly in the right leg and to a lesser extent in the right hand and face (see Video, Segment 1). Mild dysarthria and difficulty in swallowing were also noted. Hemiballism also appeared in sleep and did not respond to haloperidol, valproate, or clonazepam. When the patient was followed up 6 months later, the involuntary chorea had improved slightly, appearing only in the leg. At 10 months, the hemiballism was still present with only a slight improvement. The dysarthria and swallowing had also improved. Assessed on the Unified Parkinson's Disease Rating Scale (UPDRS), the *off* phase motor score improved by approximately 60% from 62 preoperatively to 25. After 10 months, follow-up was discontinued.

Patient 2

A 59-year-old man was healthy until 1988 when he began experiencing resting tremor and stiffness in his right hand. Upon examination, rigidity, bradykinesia, and a typical pill-rolling tremor at rest, were noted in the right hand. The patient responded well to levodopa, amantadine, and trihexyphenidyl for a couple of years. However, the tremor eventually worsened and kept him from most daily activities. He underwent left thalamotomy for the intractable tremor and dominant unilateral parkinsonism in 1995. The tremor completely disappeared, and the right parkinsonism improved significantly without any complications.

A videotape accompanies this article.

*Correspondence to: Chin-Song Lu, Movement Disorders Unit, First Department of Neurology, Chang Gung Memorial Hospital, 5 Fu-Shin Street, 333 Kweishan, Taoyuan, Taiwan, Republic of China.
E-mail: c81214@adm.cgmh.org.tw

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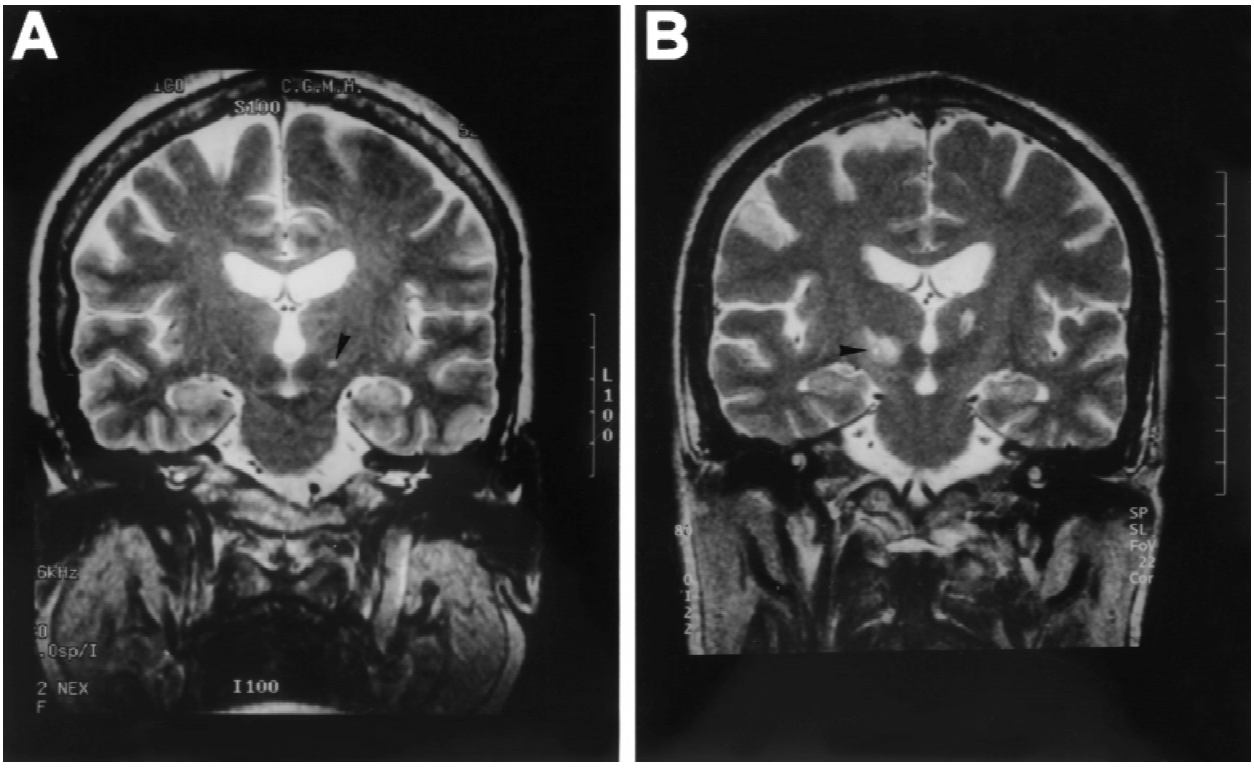

FIG. 1. Two successive coronal T2-weighted magnetic resonance imaging scans clearly depict a 3 × 3 mm well-defined lesion (arrowhead) of the subthalamic nucleus (STN) in Patient 1 (**A**), and a 9 × 6 mm lesion (arrowhead) in the STN, involving the zona incerta, in Patient 2 (**B**), postoperatively.

In 1996, he developed difficulty in walking, with problems mainly in the left leg. He fell occasionally because of propulsive walking and freezing. The *on* motor phase was short and fluctuated, although the dosage of levodopa was increased to 2,200 mg daily. He was also distressed by painful dystonia in the foot and toes during the *off* motor phase. He was scheduled for right subthalamotomy in February of 2000 for the gait disturbance, left foot painful dystonia, and major left parkinsonism. The surgical procedures resembled those described for Patient 1. An additional macrostimulation test at 1 volt, 0.06 msec, and 100 Hz induced no involuntary movement just before STN lesion. The gait and left parkinsonism markedly improved immediately after surgery. Painful dystonia was also extinguished. He developed mild chorea in the left arm 3 days later (see Video, Segment 2). The monoballism worsened slightly over the following 2 months but gradually disappeared after a short period of treatment with haloperidol and clonazepam. The patient also complained of low voice and mild dysphagia. He was evaluated 6 months after surgery by UPDRS motor score. An improvement of 47% in the *off* motor score, from 48 preoperatively to 25, was noted. His levodopa dosage was reduced to 300 mg daily. A postoperative MRI scan of the brain 2 months after surgery revealed a 9 × 6 mm lesion in the dorsolateral STN, extending to zona incerta (Fig. 1B).

Discussion

Unilateral subthalamotomy was performed in 3 advanced PD patients. Two of 3 patients developed hemiballism and/or dyskinesia. One had had a preexisting stereotactic lesion in the contralateral globus pallidus internal (GPi) and the other in the ventral intermediate nucleus (Vim). The contralateral parkinsonian features, gait disturbance and levodopa-induced dyskinesias, improved in both patients after surgery. These benefits were marked and resembled those previously reported in animal[1–4] and human[5–10,13,15] experiments. No significant dysarthria or dysphagia was observed.

Both patients developed hemiballism or dyskinesia postoperatively. Previous reports have also commonly described this complicated hemiballism or dyskinesia, which has been estimated to occur in approximately 35% of human subjects (Table 1) and 85% of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (MPTP) -treated monkeys.[1–4] The hemiballism generally commenced immediately after surgery and was often transient but rarely persistent. Therefore, its intensity varied. But hemiballism or hemichorea was reported more frequently than dyskinesia in one limb.

In primate experiments, the subthalamic nucleotomy is best demonstrated in MPTP-treated parkinsonian monkeys by injection of the excitotoxic agent, which provokes selective cell damage while sparing the surrounding fibers. The monkeys in these studies[1,4] developed hemichorea, some persistent, others transient. However, in thermocoagulation lesioning,[2,3] histological examination revealed that the lesions in half of the monkeys extended to the internal capsule, ansa lenticularis, and GPi. Dyskinesia in this study was only mild and transient in some of the animals.

In Patient 1, the hemiballism immediately appeared and persisted after surgery. An MRI brain scan revealed a small stereotactic lesion confined to the STN, which was in fact a subthalamic nucleus lesion, or restated, a subthalamic nucleotomy.

TABLE 1. *Hemiballism following subthalamotomy in patients with advanced Parkinson's disease*

Author (ref.)	Patients with H–H* (total no.)	Movement disorder	Onset (postoperation)	Persistence
Obeso et al.[21]	1 (5)	Hemiballism	7 days	Persistent[a]
Gill and Haywood[9]	1 (10)	Monoballism (foot)	NR	Transient
Alvarez et al.[5,6]	10 (16)	Hemiballism	NR	Transient
Orhan et al.[13]	1 (9)	Hemiballism	Immediately	Transient
This report	2 (2)	Hemiballism	Immediately	Persistent
		Monoballism	3 days	2 mo.

[a]The patient developed hemichorea on the seventh postoperative day secondary to an infarction involving the entire subthalamic region.

H–H, hemiballism and/or hemichorea; NR, not recorded.

Ten of 16 PD patients treated with bilateral subthalamotomy by Alvarez and colleagues[5] developed slight to moderate dyskinesia. However, another report[6] mentioned only 1, who had a large infarction and developed lesion-induced dyskinesia. The follow-up MRI scans postoperatively showed that the lesion included approximately two thirds of the STN and part of the dorsal region that extended above the nucleus. In Patient 2, a mild and transient arm dyskinesia or monoballism appeared 3 days after surgery. However, a larger lesion extended beyond the dorsolateral STN to the zona incerta. In fact, the lesion involved the STN and adjacent structures in the subthalamic region. Alvarez and associates[6] also reported that most of their 10 patients did not develop hemiballism, because the lesions were large and extended beyond the subthalamic nucleus. Gill and Heywood[8] successfully administered bilateral subthalamotomy in 2 patients without causing any abnormal movement. MRI showed that both the lesions extended beyond the STN itself.

In 1992, Burnett and Jankovic[7] conducted ventrolateral thalamotomy to alleviate the persistent hemiballism induced by a miss during a previous subthalamotomy operation. Krauss and Mundinger[24] also suggested that the zona incerta and the thalamic Vim are the appropriate surgical targets in the treatment of hemiballism. Tsubokawa and coworkers[25] also successfully treated posthemorrhagic hemiballism by thalamic stimulation. Pallidotomy has been widely reported effectively to abolish hemiballism.[5,12,26–28]

Subthalamotomy in Patient 2 of this report, as well as in other humans, failed to cause persistent hemiballism, perhaps because the lesion involved the pallidothalamic projection, which mimicked a pallidotomy effect. Lozano's[29] hypothesis further corroborates the finding that a lesion involving part of the subthalamic nucleus but also the pallidofugal pathways reduces the driving from STN to the reticulata and the globus pallidus, and treats the anticipated chorea by producing a pallidal outflow lesion.

Conclusion

We conclude that, in the limited scope of this study of advanced PD patients, subthalamotomy effectively alleviated parkinsonian features. However, it would appear that with subthalamotomy, if it is a sine qua non subthalamic nucleotomy, the risk of hemiballism after the surgery may outweigh the benefit of increased motor improvement for advanced PD patients. If lesions extend beyond STN to the neighboring subthalamic fasciculus and/or lenticular fasciculus, the subthalamic nucleotomy combined with subthalamic area lesion may have the effect of diminishing the possibility and severity of hemiballism.

We suggest that subthalamotomy is effective in advanced PD patients. However, it might bear a potential risk of persistent hemiballism. The surgery should be carried out by an experienced surgeon in highly selective conditions.

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Legends to the Videotape

Segment 1. Patient 1: Recording severe gait disturbance and freezing before surgery. The violent choreic kicking movements mainly appear in the right leg and to a lesser extent in the right hand and face postoperatively after overnight off medication.

Segment 2. Patient 2: Recording dyskinesia after operation in the left arm, dominantly in the proximal part after 12 hours off medication.

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Transient Mania with Hypersexuality After Surgery for High-Frequency Stimulation of the Subthalamic Nucleus in Parkinson's Disease

Luigi Michele Romito, MD,[1] Michele Raja, MD,[1]
Antonio Daniele, MD, PhD,[1] Maria Fiorella Contarino, MD,[1]
Anna Rita Bentivoglio, MD, PhD,[1]
Annalisa Barbier, MPsych,[1] Massimo Scerrati, MD,[3]
and Alberto Albanese, MD[1,4]*

[1]*Istituto di Neurologia, Università Cattolica del Sacro Cuore, Rome, Italy*
[2]*Servizio Psichiatrico, Ospedale S. Spirito, Rome, Italy*
[3]*Istituto di Neurochirurgia, Università Cattolica del Sacro Cuore, Rome, Italy*
[4]*Istituto Nazionale Neurologico Carlo Besta, Milan, Italy*

Abstract: Among 30 Parkinson's disease patients who received high frequency stimulation of the subthalamic nucleus, 5 developed remarkable disorders of mood or sexual behavior after the implant. We describe 2 men who developed mania and hypersexuality a few days after the implant that lasted for some months and then gradually disappeared spontaneously. © 2002 Movement Disorder Society

Key words: high frequency stimulation; Parkinson's disease; subthalamic nucleus; UPDRS

High frequency stimulation (HFS) of the subthalamic nucleus (STN) markedly improves the motor symptoms of Parkinson's disease (PD) and reduces the requirement for dopaminergic therapy.[1–3] The possible neuropsychological and behavioral effects of this technique, however, have not been defined completely.[4,5] Persistent or transient emotional states induced by HFS have been described recently in patients who received STN implants. A persistent depressive disorder unmodified by changes in stimulation settings was described in 4 PD patients who underwent bilateral STN HFS.[6] Transient major depression was reported in a woman with PD when HFS was delivered to the left substantia nigra, 2 mm below the STN.[6] By contrast, transient episodes of involuntary laughter were induced by STN stimulation in 2 men with PD.[7,8] Similarly, a transient euphoric state with laughter, induced by high voltage stimulation, was reported in 2 PD patients who received bilateral STN HFS.[6]

Among the 30 PD patients treated successfully in the Gemelli hospital by bilateral STN HFS, 5 developed remarkable disorders of mood or sexual behavior after the implant. A 61-year-old man who had suffered from major depression after the death of his wife developed a transient euphoric state after the implant. A 57-year-old woman, with a history of hypomania during youth, experienced a marked increase of sexual drive, which gradually appeared in the first month after the implant, lasted for about 18 months, and then gradually disappeared. A 54-year-old man with a 10-year history of PD, with no previous history of psychiatric disorders, 2 months after the implant gradually developed manic symptoms and an increase of sexual interest, which gradually subsided 6 months later. Finally, 2 men affected by young-onset PD developed remarkable manic symptoms and changes in sexual behavior, which began a few days after the implant and lasted for some months, gradually disappearing spontaneously.

The latter 2 cases, described in some detail here, met the diagnostic criteria for manic episode.[9]

Patients and Methods

Quadripolar leads were implanted bilaterally in the STN under stereotactic guidance as described previously.[2] Stimulation was applied 24 hours a day. The patients were formally assessed 1 week, and 1, 3, 6, and 12 months after the implant in their best *on* state and in the practically defined *off* condition[10]

*Correspondence to: Alberto Albanese, Istituto Nazionale Neurologico, via G. Celoria, 11 I-20133 Milano, Italy.
E-mail: alberto.albanese@rm.unicatt.it

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with the Unified PD Rating Scale (UPDRS) motor score.[11] Activities of daily living (ADL) were assessed by the ADL score of the UPDRS and the Schwab and England scale. The total levodopa-equivalent daily dose (LEDD) was calculated.[2] After the implant, antiparkinsonian medication was reduced to the lowest possible dose and stimulation was increased progressively. On each follow-up assessment, the stimulation settings were adjusted until the best overall clinical response was obtained. Behavioral and neuropsychological evaluations were carried out in all the patients treated with STN HFS, preoperatively and 3, 6, and 12 months after the implant, according to the after procedure. Cognitive assessment was carried out using a neuropsychological test battery[12]; the patients remained in the *on* period during cognitive assessment. Mood and anxiety were evaluated by means of Zung's self-rating scales for depression and anxiety[13]; the patients received structured psychiatric interviews to detect behavioral or psychiatric problems. Historical or ongoing psychiatric disorders were classified according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.[9]

Patient 1

A 52-year-old, right-handed man presented with an 11-year history of severe rigid–akinetic PD with moderate resting tremor that responded poorly to medication (levodopa [L-dopa] 400 mg/day, pergolide 5 mg/day). Before surgery, in the *off* state, UPDRS motor score was 60, and ADL score was 31.

There was a personal and family history of psychiatric disorders. At age 26 years, the patient suffered from a major depressive episode during his father's terminal illness. One of his sisters also presented an episode of major depression in her youth, which was treated successfully with antidepressants.

The patient received a bilateral STN implant in July 1999. Postoperative imaging confirmed that contact 1 of the right lead was in the right STN, while contact 0 of the left lead was in the left STN. Immediately after electrode placement and in the absence of STN stimulation, there was a dramatic improvement in the parkinsonian motor symptoms that lasted for about 7 days, probably due to transient functional inactivation of STN. Three days after the implant, preliminary STN stimulation was started. Compared to preoperative assessment, UPDRS motor score were improved by 67%, 55%, and 83%, respectively at 3, 6, and 12 months, while ADL score improved by 71%, 87%, and 86.8%, respectively (Table 1). Wearing-off phenomena and *on*-state dyskinesias disappeared. All antiparkinsonian medication was discontinued 1 month after surgery. Stimulation settings remained unchanged from the second month on (Table 1). Neuropsychological testing during follow-up showed no significant changes compared to preoperative performance. No noticeable change was detected in neuropsychological tests assessing attention, as compared to preoperative performance.

Two days after the implant (1 day before the initiation of STN stimulation) the patient developed a manic syndrome, characterized by inflated self-esteem and grandiosity, marked increase in goal-directed activities. This led to purchase of unneeded items, decreased need for sleep, planning of hazardous business investments, and flights of ideas. In addition, sexual desire, sexual fantasies, and sexual activity increased. These changes interfered significantly with the patient's social life and relationships.

Despite a lack of aptitude for, or interest in, religion, he began to spend much of his time writing poems on religious themes. He also became prodigal, purchasing books of every sort, and planned to open an artistic workshop or a tourist centre in the south of Italy. He began driving his car in a reckless manner, or as he himself described it "at the rhythm of rock and roll." Although he was not on dopamine agonists, he had frequent spontaneous erections and his sexual desire increased "like when I was twenty." At the same time, mood lability and quarrelsomeness developed, and he became irritable, litigious, and over-reactive. His appetite decreased and he lost 5 to 6 kg. Although his mood was steadily elevated, he also showed increased empathy for the suffering of others and a tendency to cry. Positive psychotic symptoms, such as hallucinations, delusions, catatonia, and conceptual disorganization did not occur. He could turn the generator on and off using a magnetic switch. When he turned off stimulation, which he did for less than 1 hour because of resurgence of motor impairment, there was a marked worsening of parkinsonian motor symptoms, but the manic symptoms did not resolve. Changes in the stimulation settings immediately affected motor abilities, but did not have any obvious effect on mood or behavior.

A diagnosis of manic episode was made. In agreement with the spouse, the patient was followed up very carefully and no pharmacological treatment for manic symptoms was prescribed. Three months later, the manic symptoms began to subside and eventually disappeared completely. Twelve months after the implant, the patient showed some reduction of initiative but no notable impairment in everyday life.

TABLE 1. *Levodopa equivalent daily dose, energy delivered and clinical evaluations observed in 2 patients*

	Before implant	1 week	1 mo	3 mo	6 mo	12 mo
Patient 1						
Levodopa-equivalent daily dose (mg)	900	760	0	0	0	0
Energy delivered (Watt $\times 10^{-6}$)	—	0.69	1.56	1.65	1.65	1.65
UPDRS motor score	60	22	20	20	27	10
UPDRS ADL score	31	—	2	9	4	4
Patient 2						
Levodopa-equivalent daily dosage (mg)	1800	1000	400	400	0	0
Energy delivered (Watt $\times 10^{-6}$)	—	0.30	0.86	1.94	1.92	2.16
UPDRS motor score	61	—	16	16	18	15
UPDRS ADL score	37	—	4	4	3	4

UPDRS, Unified Parkinson's Disease Rating Scale; ADL, activities of daily living.

Patient 2

This 42-year-old man had a 15-year history of severe PD, with resting and postural tremor and marked rigidity that could not be controlled adequately by drug treatment (L-dopa, 1,200 mg/day; pergolide, 6 mg/day). Before surgery, in the practically defined *off* state, UPDRS motor score was 61, and ADL score was 37 (Table 1).

In March 1999 he received a bilateral STN implant. Postoperative imaging confirmed that contact 0 of the right lead was in the right STN and contact 1 of the left lead was in the left STN. Immediately after electrode placement and in the absence of stimulation there was a remarkable improvement of motor symptoms, which lasted for 9 days. Two days after the implant intermittent STN stimulation was started. The voltage was increased gradually over a period of 3 months (Table 1). Motor symptoms greatly improved under stimulation; in particular, wearing-off phenomena, *off*- and *on*-state dyskinesias disappeared. Compared to baseline, at 3, 6, and 12 months UPDRS motor score respectively improved by 74%, 70%, and 75%, and ADL score by 89%, 92%, and 89% (Table 1). L-Dopa was reduced to 400 mg daily one week after the operation and all antiparkinsonian medication was stopped four months later. Neuropsychological testing during follow-up showed no postoperative changes in cognitive functioning. No noticeable change was detected in neuropsychological tests assessing attention, as compared to preoperative performance.

The patient had no personal or family history of psychiatric disorders except for alcohol abuse in his father. A tendency to cry and to be moved by trivial events, without mood changes, was noted some years before the implant.

The patient's manic symptoms started to develop 3 days after implant and few hours after the first STN stimulation session. He developed inflated self-esteem, labile mood and irritability, marked increase in goal-directed activities, increased sexual desire and sexual fantasies, and non-customary sexual behavior (inappropriate seductive behavior toward female medical staff and indiscriminate sexual encounters). His life changed markedly and, for the first time in several years, he resumed work and went on a journey with his wife. He wrote the manuscript for a short book about his experience with PD, started using a computer, and resumed his university course in astrophysics, which he had abandoned 15 years previously. His mood disturbance was associated with marked impairment of social relationships, as reported by his wife. He had no psychotic signs. A manic episode was diagnosed, but no medication was prescribed. The patient was carefully followed up with the cooperation of his wife.

When stimulation was discontinued, the parkinsonian motor symptoms worsened strikingly, but no changes in mania could be detected. The patient could not stand being without stimulation for more than few hours. When the stimulation settings were changed, motor signs were immediately affected, but the manic state persisted and no acute behavioral changes were observed. Six months after implant the mania started to abate and by 8 months there were no residual manic symptoms.

Discussion

The mood disorders observed in these 2 patients fulfilled the diagnostic criteria for a manic episode.[9] In both cases, the episode started soon after the observation of motor improvement after the implant, lasted for some months, and disappeared gradually. Both have been followed up for a total of 12 months, during which time there has been no recurrence of the symptoms. In both patients, mania was associated with remarkable motor improvement and resolved spontaneously, while the motor improvement persisted. The patients have not received any specific psychiatric treatment, which has allowed to observe the natural course of mood changes after STN implant. Attention did not appear to be affected by mania in these patients. The 3-month postoperative neuropsychological assessment of Patient 1, who showed the most severe manic symptoms, was carried out when the manic symptoms began to subside. In Patient 2, the manic symptoms began to subside 6 months after the implant; the 3-month postoperative assessment showed no change even on neuropsychological tests assessing attention, as compared to preoperative performance.

To our knowledge, this is the first report of a manic disorder in PD patients after the surgical procedure of bilateral STN HFS. Surgery is immediately suspected of being involved in inducing manic symptoms in these cases. Either the procedure, or the stimulation, or both, may have played a role in the appearance of manic symptoms. It is remarkable, however, that, although the motor condition had a strict time relationship with STN stimulation, this could not be demonstrated with manic symptoms. Reduction or discontinuation of STN stimulation for a matter of minutes caused immediate worsening of the motor condition, but did not influence behavior. Thus, the surgical procedure of lead implantation may have induced a reversible dysfunction of some neural cortical-subcortical circuits involved in mood, which could not be corrected by reducing stimulation for a short while. There was no morphological evidence of frontal damage on postoperative MRI scans, and the surgical procedure was identical to that of other patients who had no mood disturbance. The patients received dopaminergic treatment until the day before surgery; this was gradually reduced afterwards. In Patient 1, complete withdrawal was attained by the first month after implant, whereas in Patient 2 this occurred 4 months after the implant. It is remarkable, that in Patient 2 the manic symptoms lasted longer than in Patient 1.

Dopaminergic treatment before the surgical implant was well-tolerated by both patients in the present series. It is possible that the effects of STN implants added up to those of dopaminergic treatment, thus causing mood changes. In keeping with this, it has been demonstrated that STN HFS and dopaminergic treatment produce similar motor effects.[2] A synergy between dopaminergic treatment and HFS of the globus pallidum has also been observed in a patient who suffered from recurrent manic episodes shortly after the implant.[14] Other factors that may be related plausibly to the development of manic symptoms include the exact point of electrode placement, the anatomical variations in the STN region[6] and individual predisposition, such as a history of a mood disorder.

These clinical observations on PD patients receiving STN HFS provide an intriguing glimpse of the neural circuits possibly involved in depressive and manic disorders. We wonder whether cases were observed with a poor surgical outcome, in whom mania or psychotic depression occurred. Such observation could support a specific role of the surgical procedure or of other anatomical structures in generating mood changes, thus answering to some of the questions that are posed here.

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Steele-Richardson-Olszewski Syndrome in a Patient with a Single C212Y Mutation in the Parkin Protein

Blas Morales, MD,[1] Armando Martínez, MD,[2,3] Isabel Gonzalo, PhD,[3] Lidice Vidal, PhD,[3] Raquel Ros, PhD,[3] Estrella Gomez-Tortosa, MD,[3,4] Alberto Rabano, MD,[3] Israel Ampuero, PhD,[3] Marina Sánchez, PhD,[4] Janet Hoenicka, PhD,[3] and Justo García de Yébenes, MD[3,4]*

[1]*Hospital Universitario, San Cecilio, Granada, Spain*
[2]*Hospital Clínico Universitario S. Carlos, Madrid, Spain*
[3]*Banco de Tejidos para Investigaciones Neurológicas, Madrid, Spain*
[4]*Fundación Jiménez Díaz, Madrid, Spain*

Abstract: Steele-Richardson-Olszewski syndrome (SROS) is a neurodegenerative disorder of unknown aetiology, most frequently sporadic. Familial cases of SROS have been described. An intronic polymorphism of the tau gene is associated with sporadic SROS and mutations of the tau gene are present in atypical cases of SROS. The role of tau has been excluded in other families with pathology proven SROS, suggesting that this syndrome may have multiple causes. An 82-year-old patient, father of 3 children with autosomal recessive juvenile parkinsonism due to combined heterozygous mutations of the parkin gene, developed clinical features of SROS 2 years before death. The diagnosis was confirmed by pathology. He carried the C212Y mutation of the parkin gene and was homozygous for the A0 polymorphism and for the H1 haplotype. The role of parkin in the processing of tau is discussed. © 2002 Movement Disorder Society

Key words: Steele-Richardson-Olszewski syndrome; tau gene; parkin; PARK2

Steele-Richardson-Olszewski syndrome (SROS) was initially described as a combination of clinical findings characterized by akinesia, supranuclear gaze palsy, rigidity, axial dystonia, gait disturbance and fronto-limbic dementia, and pathological abnormalities including neuronal loss, gliosis and presence of neurofibrillary tangles and neuropil threads, mainly in basal ganglia, diencephalon, brainstem, and frontal and temporal lobes.[1] SROS was soon renamed as progressive supranuclear palsy (PSP) and many investigators began to consider PSP as a new neurodegenerative disease.

The cause of SROS or PSP is unknown but toxic and infectious etiologies have been considered, based upon the pathological similarities with post-encephalitic Parkinsonism, metal poisoning and with the Parkinson–dementia complex of Guam.[2–7] Because of the coexistence of cerebrovascular disease in some cases a vascular mechanism was also postulated.[8–9] Atypical cases with characteristic pathological findings, but an incomplete clinical syndromes, have been described previously.[10]

Until recently PSP was considered a sporadic disorder, despite a small number of reports suggesting familial clustering.[11–19] The gene responsible for the familial cases is unknown. Mutations of the tau gene were excluded in the majority of the families with familial PSP[19,20] but there are some reports describing PSP-like syndromes in patients, occasionally members of families with typical frontotemporal dementia, with mutations of the tau gene.[21–23] In addition, in sporadic

A videotape accompanies this article.

*Correspondence to: Justo Garcia de Yebenes, MD, Department of Neurology, Fundación Jiménez Díaz, Avda. de Reyes Católicos, 2., Madrid 28040. Spain. E-mail: jgyebenes@fjd.es

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cases there is evidence for higher prevalence of the polymorphism A0 and the haplotype H1 than in the control population.[24–27] Thus, with the available data, the most likely explanation for this paradox is that SROS is a syndrome of multiple etiology that could be triggered by several genetic or environmental factors rather than a single entity with a unique cause. In support of this idea we present a patient with clinical and pathological features of PSP and a single C212 mutation of parkin protein.

Case Report

Patient.

The patient was the father of 6 sons, 3 of whom had typical autosomal recessive Parkinson's disease (PD), with age at onset in the third decade of life, very good response to levodopa (L-dopa), and early development of fluctuations. The 3 affected children were combined heterozygous carriers of the previously unreported mutations V56E and C212Y.[28] The other 3 children were asymptomatic, one of them had a single V56E mutation, the second had normal Park2 genes and the third was not available for molecular study.

The patient did not describe any environmental risk factors for parkinsonism. He had a clerical job, retired at the age of 65 without complaints of neurological disease and lived with his wife until her death, when he was 78. At that time the family decided he should go to a nursing home, not for medical reasons, but for housekeeping requirements. When we visited him at age 82, he denied any neurological complaints. During the interview he remained indifferent. When asked about tremor he said that he did it voluntarily. He confessed having problems swallowing and difficulty with gait and balance. He said he could not read because of blurred vision. His neurological examination showed an apathetic, thin, but well-nourished, gentleman with intermittent postural and at rest tremor in both hands, severe ophthalmoparesis in all directions of the gaze, mostly downwards, and lack of balance with a tendency to fall backwards (see Video). The patient was invited to an office visit at the nearest university neurological department but he never attended the appointment. During the following months the patient's gait difficulty and dysphagia worsened. Six months after our visit to his nursing home he developed aspiration pneumonia and died.

The brain was extracted and split by a midline sagittal section, the left half was frozen and the right half kept in formalin for histopathological studies. DNA was extracted from the brain and analyzed for mutations of the Park2 gene, tau gene, and polymorphisms and haplotypes of tau. The following brain areas were embedded in paraffin: cerebral cortex (from the frontal, temporal, parietal and occipital lobes, according to the CERAD protocol), cingulate gyrus, calcarine cortex, nucleus basalis of Meynert, posterior hippocampus, amygdaline nucleus, caudate putamen, lenticular nucleus, thalamus, subthalamic nucleus of Luys, mid brain including sections through the substantia nigra and the III cranial nerve nucleus, pons, medulla, cerebellar cortex and dentate nucleus and superior vermian cerebellar cortex. Sections of 7 μm thickness were cut and stained with haematoxiline–eosine, Gallyas stain, and methenamine–silver. Immunohistochemical studies were performed with antibodies against α-synuclein (Santa-Cruz Biotechnology, Santa Cruz, CA), tau (Novocastra, Newcastle upon Tyne, UK), ubiquitin (Dako, Copenhagen, Denmark) and glial fibrillary acid protein (GFAP, Dako). The immunoreactivity was detected using the strepto–avidin–biotinylated horseradish peroxidase complex (ABC-System-Dako) and visualized with 3–3 diaminobenzidine (DAB-Sigma, St. Louis, MO).

Results

Macroscopic Examination.

The weight of the brain was 1,100 g. The macroscopic examination of the brain showed moderate atrophy of the frontotemporal lobes and superior cerebellar vermis and less remarked atrophy of the parietal lobe. The coronal sections of the brain and brainstem showed moderate enlargement of the lateral cerebral ventriculi, atrophy of the pallidum and atrophy and loss of pigment in the substantia nigra as well as atrophy of the brainstem tegmentum (Fig. 1).

Histological Findings.

The most relevant lesions were characterized by neuronal loss, gliosis, and cytoskeletal abnormalities in several neuronal nuclei and glial cells (astro and oligodendrocytic), such as neurofibrillary tangles (NFT), oligodendrocytic coiled bodies (OCB), and neurophilic threads (NPT) showed by the silver technique of Gallyas and by immunostaining with tau antibodies (Table 1). The substantia nigra showed a severe neuronal loss and marked astrogliosis (Fig. 2). Abundant free neuromelanin pigment was present in the neuropil and many neurons showed globoid NFT, strongly positive with the Gallyas technique and immunoreactive to tau but not to ubiquitin. There were, also, many NPT and some OCB. Immunostaining with α-synuclein and ubiquitin antibodies did not show Lewy bodies in any of the brain areas studied.

Similar lesions were observed in other nuclei including striatum, pallidum, nucleus basalis of Meynert, subthalamic nucleus of Luys, pontine and III cranial nerve nuclei (see Table 1), though the density of NFT, OCB, and NPT was less marked in the thalamus. Tufted astrocytes were present in most subcortical areas such as striatum, pallidum, substantia nigra, red nucleus, thalamus, midbrain, dentate nucleus, insula, but not in the nucleus basalis of Meynert. These tau-positive astroglial structures could be also observed in other regions such as the insular cortex, hippocampus and the entorhinal cortex, but with less marked density in the neocortical areas. Immunoreactivity to tau was present in many residual neurons with argyrophilic inclusions in the substantia nigra, mid brain tegmentum and other brain areas. The globus pallidus, the subthalamic nucleus and, with less intensity, the striatum presented severe gliosis. The superior vermian cerebellar cortex presented moderate loss of Purkinje cells and proliferation of the Bergmann's glia. Methenamine–silver stains showed the presence of diffuse amyloid plaques in most brain areas, more abundant in the temporal and parietal cortex. Neuritic plaques were sparse and no vascular amyloid was present.

Molecular Analysis.

DNA was extracted from the patient's brain. Analysis of the Park2 gene by single strand conformation polymorphisms followed by sequencing showed that the patient was an heterozy-

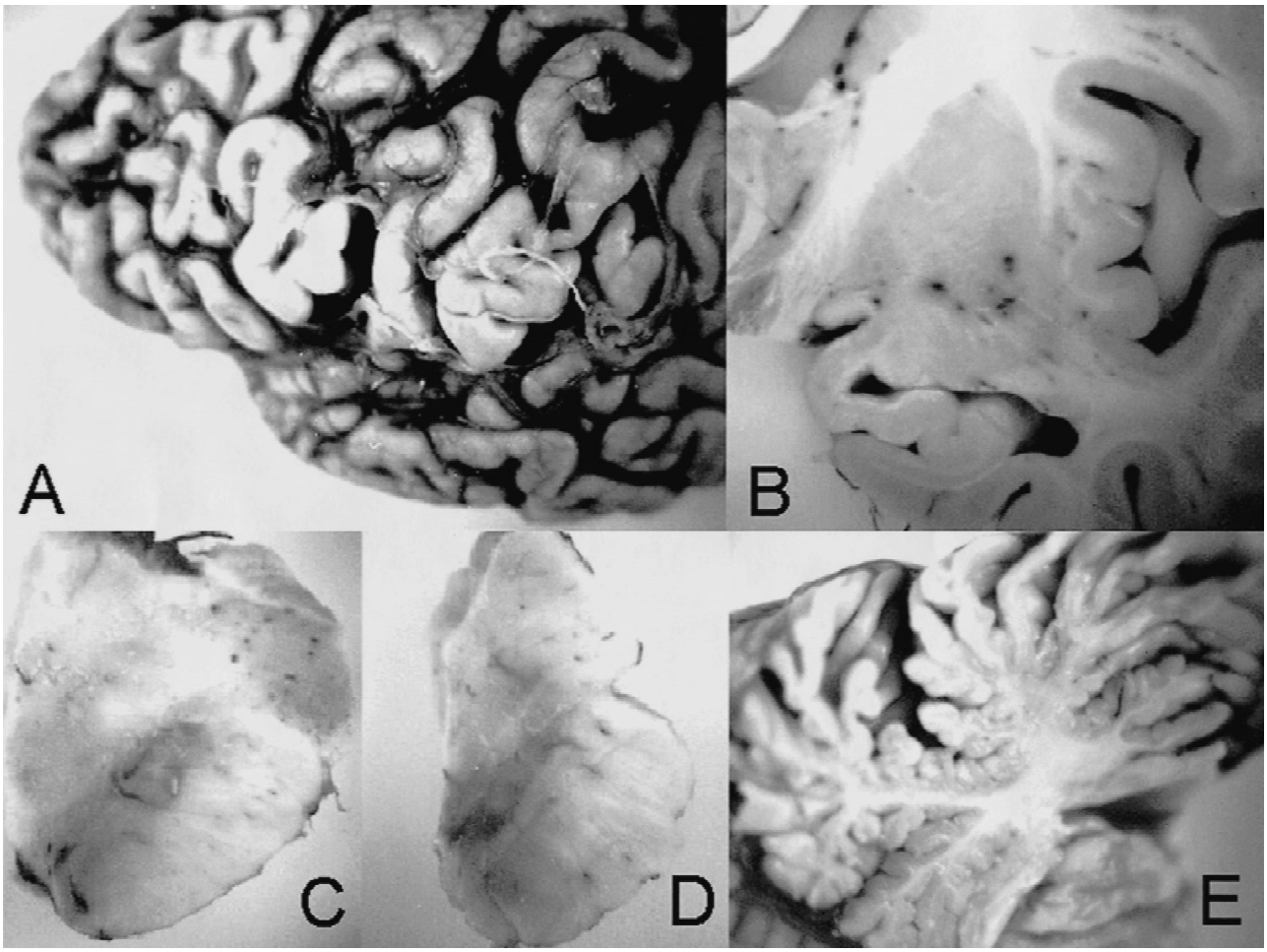

FIG. 1. Macroscopic findings in the patient's brain. **A:** Lateral view of the left hemisphere showing atrophy of the cerebral circumvolutions and enlargement of the cerebral sulci in the frontal and temporal lobes. **B:** Coronal section of the brain at the level of the basal ganglia. There is evidence of pallidal atrophy and mild enlargement of the left lateral cerebral ventricle. **C**, **D:** Sections through the upper (C) and lower (D) midbrain showed atrophy and depigmentation of the substantia nigra. **E:** Section through the cerebellum showing midline atrophy of the cerebellar lamellae, more marked in the superior cerebellar vermix.

gous carrier of a mutated Park2 gene at 736 G-A that produces a G212Y mutation. The analysis of the tau gene showed a haplotype H1/H1 and absence of mutations in exons 9 to 13. Analysis of tau isoforms obtained from the patient's brainstem, pallidum, thalamus and cerebellum showed a mixed pattern of 3 and 4 repeats isoforms, similar to controls (data not shown).

Discussion

We present a patient, heterozygous carrier of C212Y, a previously unreported mutation of the Park2 gene, with clinical and pathological features of PSP. The diagnosis of PSP was made according to international criteria.[10,29–32] The characteristic pathology is consistent with a variable combination of neuronal loss, gliosis, neurofibrillary tangles, neuropilic threads and tau-immunoreactive glial lesions in several brain areas including the cerebral cortex, basal ganglia and the brainstem.[10,29] Other NFT-associated disorders may present lesions that have to be distinguished from typical PSP changes. In our case, although some neuritic plaques were present in associative neocortical regions, they showed a low density and did not fulfilled CERAD criteria for Alzheimer's disease. Similarly, no definite histological criteria for the diagnosis of corticobasal degeneration (CBD) were present in this case. No ballooned neurons were observed in the cortex, and neuronal basophilic and small tau (+) inclusions were also absent in our case. On the basis of the most reliable criteria for the neuropathological diagnosis of PSP, i.e., the presence of a high density of NFT in basal ganglia and brainstem, together with numerous astrocytic tufts and coiled bodies at a cortical and subcortical level, our case was classified morphologically as typical PSP. SROS could be sporadic or familial. Some of the last cases are related to mutations of the tau gene.[21–23] Mutations of the tau gene, however, were excluded in other familial cases of PSP,[19,20] suggesting that there may be multiple causes of this disease. The role of the tau gene in sporadic cases of PSP has been underlined by the higher prevalence of the polymorphism A0[24–27] and the allele H1 in PSP than in the control population. That polymorphism could, in fact, be a risk factor for other

TABLE 1. *Histological findings in different brain areas*

Brain area	NL	NFT	Gliosis	OC	TA	NPT
Frontal lobe	–	–/+	–	++	+++	++
Temporal lobe	–	–	–	+	++	+
Parietal lobe	–	–	–	++	+	+
Occipital lobe	–	+	–	+	+++	+
Hippocampus	+	+	–	+	+	++/+++
Thalamus	+/++	+	–	++	++	+/++
Pallidum	++/+++	++	+++	+++	++	+++
Striatum	++	++	+/++	++	+++	++
Nucleus basalis (Meynert)	–/+	++	–	+++	–	+++
Subthalamic nucleus	+++	++	+++	+++	+	+++
Dentate nucleus	–/+	–	–	++	++	++
Substantia nigra	+++	+++	++	+	–	+++
III cranial nerve nucleus	+/++	+/++	–	+++	++	++
Pontine nuclei	+++	+++	–	++	+	++

Abnormalities were evaluated according to the following semiquantitative scale: –, absent; +, present but rare; ++, common; +++, very abundant.

NL, neuronal loss; NFT, neurofibrillary tangles; OC, oligodendrocyte coils; TA, tufted astrocytes; NPT, neuropilic threads.

neurodegenerative disorders, such as PD,[24,33–35] suggesting a relation between tau and the proteins that play a role in PD.

Tau protein is a key element of the neuronal cytoskeletal system. Tau pathology has been described in many neurodegenerative disorders including Alzheimer's disease, PSP, and frontotemporal dementia with parkinsonism and disinhibition. In AD there is no evidence of genetic abnormalities of tau and the involvement of this protein in the disease process is considered to be due to posttranslational changes. In frontotemporal dementia, linked to chromosome 17, the disease is caused by mutations of the tau gene, most frequently in the exons 9 to 13, inherited with autosomal dominant pattern.[36,37] There are reports of patients with mutations of the tau gene with phenotypes intermediate between PSP and frontotemporal dementia.[22]

The cause of PD is unknown in most cases. Mutations of the α-synuclein gene are only responsible for very few families with PD from Europe.[33] α-Synuclein is one of the main components of the typical histopathological inclusion lesions in PD, the Lewy body. Lewy bodies and synuclein-immunoreactive dystrophic neurites are present in the brain of the majority of the patients with sporadic PD. Other types of PD are not related to synuclein abnormalities. Some of these phenocopies including familial cases with mutations of the Park2 gene,[39] and sporadic cases of postencephalitic parkinsonism and manganese poisoning, are characterized by neurofibrillary degeneration with prominent pathology of protein tau.

The most frequent genetic cause of parkinsonism is autosomal recessive juvenile parkinsonism related to mutations of the Park2 gene. These mutations include a variety of gene defects such as deletions of one or more exons, truncated proteins or missense mutations.[40,41] This form of parkinsonism was first described in Japan and initially considered to be restricted to that country. The first cases of this disease were characterized by early onset of parkinsonian symptoms, during childhood or adolescence, excellent response to L-dopa and early development of fluctuations. When the genetic defect was discovered it was found that the typical early-onset Japanese cases were produced by homozygous deletions of one or more exons of Park2 gene.[39] More recently it has been shown that parkinsonism related to Park2 mutations is present worldwide, that it may appear in children, young adults and presenile patients; that the clinical symptoms are indistinguishable from typical idiopathic PD in many cases and that the gene defect is variable.[40,41] There are few pathology studies in patients with Park2 mutations. In the initial reports the pattern of lesions was characterized by neurofibrillary tangles and argyrophilic astrocytes restricted to the substantia nigra, locus coeruleus, red nucleus, and posterior hypothalamus.[42,43] One case reported recently presented more widespread distribution of lesions involving the cerebellar cortex, the dentate nucleus, subthalamic nucleus and the caudate and putamen.[44] This last case may be a transitional form between typical parkin pathology and our patient where, as in typical PSP, there was a much more extensive pathology and where the involvement of the pallidum is more severe than that of the striatum. In some of the more recent pathological reports,[43,44] as in our case, there was evidence of tau deposition, mostly in the basal ganglia and brainstem, in a pattern more similar to PSP than to frontotemporal dementia with parkinsonism linked to mutations of the tau gene.

In addition to mutations and polymorphisms of the tau gene other proteins that play a role in the processing of this protein may cause tauopathies, such as PSP. Different factors involved in the proteasome-dependent ubiquitin pathway decrease the proteasome function in some tauopathies.[45,46] It has been reported recently that parkin is an ubiquitin ligase component, E3, of the ubiquitin-proteasome dependent protein degradation pathway.[47] It is considered that genetic abnormalities that impair the normal function of parkin disturb the processing of other proteins. There is no clear explanation, however, about the mechanism through which, mutations of parkin produce neurofilament pathology with abnormal tau immunoreactivity in the damaged brain areas. It is possible that abnormalities of parkin protein induce abnormal processing of tau. Levels of parkin and ubiquitin in the brain of this patient were not modified when compared to control cases (data not shown), meaning that up- or downregulation processes do not occur if normal function of parkin is affected. We observed a decreased proteolysis of unphosphorylated tau and an increase in tau phosphorylation, by Western blot analysis (Sanchez et al., in press), in the brain samples from this patient. The reduction of tau degradation is compatible with a parkin function failure in patient's brain samples. Moreover, if tau molecules are proteolyzed to a lesser extent, their turnover is decreased, and they could be more easily modified. The augmented lifetime of the protein could also produce its accumulation, phosphorylation and further aggregation. In fact, a correlation between the level of tau phosphorylation and its proteolysis, has already been reported.[46] The observation that a higher level of tau phosphorylation results in a decrease of tau proteolysis, has also been illustrated.[46]

In most patients with autosomal recessive PD caused by mutations of the Park2 gene the pathology is restricted to the substantia nigra and the clinical symptoms are those of autosomal recessive PD. In our patient, however, other brain areas were involved and the clinical symptoms and pathological findings were much more likely those of SROS. It is unknown whether the H1/H1 genotype is a risk factor that, in the presence of deficient parkin function, predisposes to more extensive

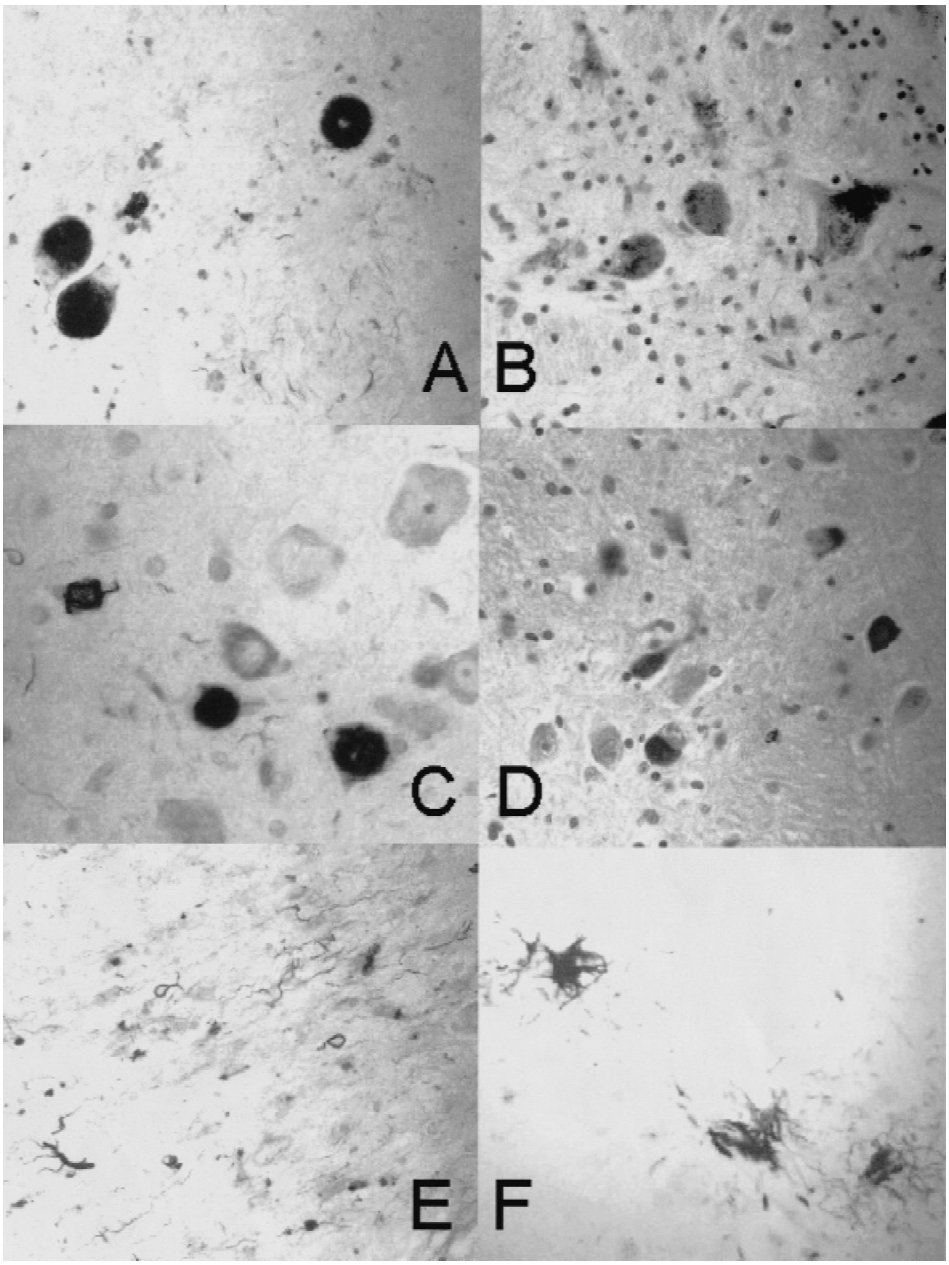

FIG. 2. Histological findings in the patient brain. **A**, **B:** Neurofibrillary tangles in the pigmented neurons of the substantia nigra stained with the technique of Gallyas (A) and tau protein immunocytochemistry (B). **C**, **D:** Pontine nuclei with neurons stuffed with neurofibrillary tangles revealed by the technique of Gallyas (C) and tau protein immunocytochemistry (D). **E:** Microphotograph of the internal pallidum showing argyrophilic neurophilic threads and coiled bodies (Gallyas stain). **F:** Microphotograph of the dentate nucleus of the cerebellum showing tufted astrocytes (Gallyas stain). Magnification ×400.

tau pathology. Other studies have suggested that there is an inter-relation between tau and parkinsonism. Several studies have shown that tau polymorphisms play a role in PD.[33–35] We propose that mutation of parkin may play a role in tau processing and produce PSP in predisposed individuals. This study suggests that clinical and pathological findings, compatible with PSP, may be present in patients with parkin mutations. We do not have a clear explanation for the fact that in this patient's family the members affected by combined heterozygous mutations C212Y and V56E developed typical autosomal recessive juvenile PD, whereas this patient presented with typical SROS at age 82. We could speculate, however, that severely reduced parkin function by mutation of the Park2 gene in both chromosomes produces important and early disturbance of protein processing in the proteasome whereas a single mutation of parkin produces only partial and late disturbance of this func-

tion, restricted to only some proteins. The target proteins may depend on the individual risk factors, such as the polymorphisms of the particular protein in each individual. In this case, the partial parkin deficiency, related to the C212Y mutation, associated with the PSP risk factor H1/H1 would trigger PSP. Late onset of the symptoms could be related to the partial deficiency of the protein and to the fact that the H1/H1 haplotype leads to overexpression and aggregation of 4-repeat tau, an isoform that appears in the brain late in life.[48] Recent studies provide evidence for the role of parkin in the ubiquitination of α-synuclein.[49] Total deficiency of parkin function by homozygous or combined mutations of Park2 genes may produce autosomal recessive juvenile PD, whereas partial deficit of parkin function may be insufficient to produce abnormalities of the synuclein processing, but may cause abnormal processing of other proteins as tau in individuals at risk, and late onset of the clinical symptoms, as in the case reported here. With a single case we can not rule out that PSP and parkin mutation are unrelated, but because the prevalence of these disorders is low,[50] it would of interest to look for heterozygous mutations of the Park2 gene, or even polymorphisms, in individuals with PSP. That study should be multicentric to collect an informative number of individuals.

If it could be proven that PSP could be related to a partial deficit of parkin function, it would be possible to consider that this syndrome may be related to a variety of genetic and environmental causes. We believe it would be more appropriate to return to the eponym SROS because it enhances the multifactorial etiology of this syndrome.

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Legend to the Videotape

Examination of the patient at home. Note tremor in the hands, abnormal eye movements, namely in the vertical plane, lack of stability, akinesia and apathy.

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Hemichorea as an Initial Manifestation of Moyamoya Disease: Reversible Striatal Hypoperfusion Demonstrated on Single Photon Emission Computed Tomography

Yoon-Ho Hong, MD,[1] Tae-Beom Ahn, MD,[1] Chang Wan Oh, MD,[2] and Beom S. Jeon, MD, PhD[1]*

[1]Department of Neurology, Clinical Research Institute, Seoul National University Hospital, SNUMRC, College of Medicine, Seoul National University, Seoul, South Korea
[2]Department of Neurosurgery, Clinical Research Institute, Seoul National University Hospital, SNUMRC, College of Medicine, Seoul National University, Seoul, South Korea

Abstract: We describe a case with unilateral moyamoya disease that showed progressive hemichorea as an initial manifestation. Single photon emission computed tomography showed perfusion defect in the contralateral basal ganglia although magnetic resonance imaging was unremarkable. Hemichorea improved along with normalization of perfusion after bypass surgery, suggestive of striatal hypoperfusion as the cause of hemichorea. © 2002 Movement Disorder Society

Key words: hemichorea; moyamoya disease; SPECT

Moyamoya disease is a chronic cerebral vasculopathy of unknown etiology, characterized by unilateral or bilateral stenoocclusion of internal carotid artery at the supraclinoid portion together with abnormal net-like collateral vessels in base of brain.[1,2] Initial symptoms manifest as a transient ischemic attack, cerebral infarction, and intracranial hemorrhage, or occasionally as epileptic seizures. An ischemic event is the usual clinical presentation in a childhood moyamoya, whereas the

*Correspondence to: Beom S Jeon, MD, PhD, Department of Neurology, Seoul National University Hospital, 28 Yongon-Dong Chongno-gu, Seoul, 110-744, South Korea. E-mail: brain@snu.ac.kr

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hemorrhagic stroke is more common in an adult patients.[2] As a presenting feature of moyamoya disease in a child, chorea has been described rarely.[3–5] We are aware of one case reported previously of a choreiform movement as a presenting symptom in an adult.[6] In that case, the authors concluded the movements represented pseudochoreoathetosis due to a parietal lobe infarction resulting in a cortical sensory loss.

We report on an adult patient with unilateral moyamoya disease who developed hemichorea as an initial manifestation. Although magnetic resonance imaging (MRI) was normal, single photon emission computed tomography (SPECT) showed perfusion defect in the basal ganglia. After a superficial temporal artery to a middle cerebral artery (STA-MCA) bypass surgery, the perfusion defect resolved and the hemichorea gradually disappeared.

Case Report

A 20-year-old woman was evaluated for slowly progressive right hemichorea involving the face, arm, and leg. The choreic movement was nearly continuous although transiently suppressed by actions such as grasping or holding objects with her right hand. She had been in good health until 6 months prior, when she suffered an acute febrile illness accompanied by a sore throat and general malaise for a few days. Four months later she first noticed the subtle choreic movement starting in the right hand. The movement steadily worsened and spread to the right arm, leg and then the face over the ensuing 2 months. During the same period, her personality changed. She became easily annoyed and showed aggressive behavioral outburst. She denied prior use of neuroleptics and oral contraceptives. She had no family history of involuntary movements.

Physical examination was unremarkable except for the hemichorea. She was mildly inattentive without cognitive impairments. There was no weakness. Sensory examination including pain, temperature, light touch, proprioception, and vibration was intact. Graphesthesia, stereognosis, and two-point discrimination were normal. Routine blood tests and specialized tests including thyroid function test, antistreptolysin O, antistreptokinase antibody, rheumatoid factor, lupus anticoagulant, antiphospholipid antibody, antinuclear antibody, anti dsDNA, antineutrophil cytoplasmic antibody, anti-Ro/La antibody, echocardiography, and electroencephalography were all normal.

MRIs showed a few scattered high signal intensity lesions in the left centrum semiovale (Fig. 1a), but the basal ganglia was unaffected (Fig. 1b). Transfemoral cerebral angiogram (TFCA) showed near complete occlusion at the supraclinoid portion of the left internal carotid artery (ICA), which was accompanied by fine basal collaterals (Fig. 1c). [99mTc]-HMPAO brain SPECT showed perfusion defect in the left basal ganglia and decreased vascular reserve in the left frontal lobe after acetazolamide administration (Fig. 2a,b).

Two weeks after admission, the patient underwent left STA-MCA bypass. Choreic movements and the personality changes improved over the next few weeks. Postoperative TFCA, four months after surgery, demonstrated patent bypass flow. Follow-up SPECT showed now normal perfusion in the left basal ganglia, but the vascular reserve in the left frontal lobe remained decreased (Fig. 2c,d).

Discussion

Hemichorea or hemiballism can be produced reliably by selective lesions of the subthalamus or subthalamo-pallidal pathways.[7] Most likely mechanism involved is the loss of subthalamic excitation in the medial pallidum, followed by the disinhibition of the thalamic neurons. Hemichorea has also been reported with lesions in caudate nucleus, putamen, globus pallidus, and parts of the thalamus, presumably due to an underactivity of striatopallidal indirect pathway.[8] Subcortical white matter lesions sparing basal ganglia or the subthalamic nucleus have been described as a cause of hemichorea, but the pathophysiological relationship remains questionable.[9,10] Functional imaging was not performed in these prior studies so that abnormalities of the basal ganglia could not be completely excluded.

Recent investigations showed the pathophysiological corre-

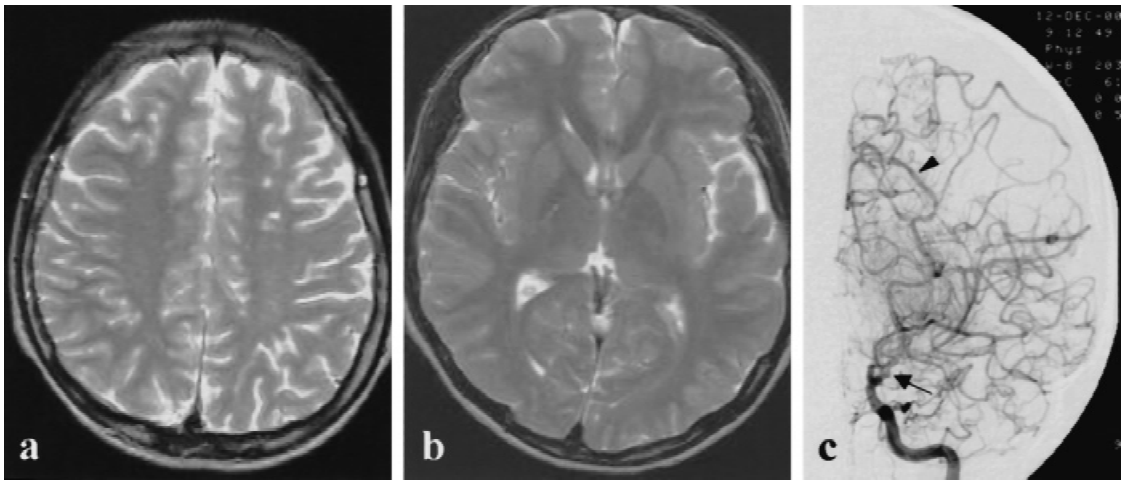

FIG. 1. T2-weighted MR imaging showing multiple small high signal intensity lesions in the centrum semiovale in the left frontal lobe (**a**). There was no basal ganglia lesion (**b**). Left internal carotid angiogram (**c**), anteroposterior projection, demonstrating near complete occlusion of ICA at the supraclinoid portion (arrow). Note the fine scanty basal collaterals suggestive of moyamoya vessels, and the leptomeningeal collateral flow from the PCA (arrowhead).

lation between the functional abnormalities in the basal ganglia and choreic movements even without visible lesions on conventional MRI or computed tomography. In Sydenham's chorea, positron emission tomography or SPECT showed variable imaging features reflecting transient neuronal dysfunction in the striatum or thalamus.[11–13] Perfusion defect in the basal ganglia was demonstrated on ictal SPECT in a case of paroxysmal kinesigenic choreoathetosis.[14] It was also reported in juvenile primary antiphospholipid syndrome and parietal watershed infarction.[15,16]

In the present case, we speculate that the hemodynamic compromise caused the functional imbalance in the striatum and resulted in underactivity of the indirect pathway leading to hemichorea. Marked improvement of hemichorea with normalization of the basal ganglia perfusion after the bypass surgery suggests the basal ganglia hypoperfusion was responsible for the genesis of hemichorea rather than the frontal lobe lesions. It also suggests the reversible nature of ischemia-induced functional imbalance in the striatum. Interestingly, our patient showed remarkable improvement in emotional lability and behavior after surgery. Disinhibition and more frequently abulia, which are features of frontal lobe damage, have been seen in some patients with basal ganglia lesion.[17–19] Thus, behavioral disturbance in our patient could be understood as an epiphenomenon of striatal dysfunction and would be an another evidence supporting the reversibility of ischemia-induced striatal dysfunction.

In summary, onset of hemichorea and improvement after bypass surgery correlated with basal ganglia perfusion status in SPECT studies, suggestive of perfusion deficit as the cause in

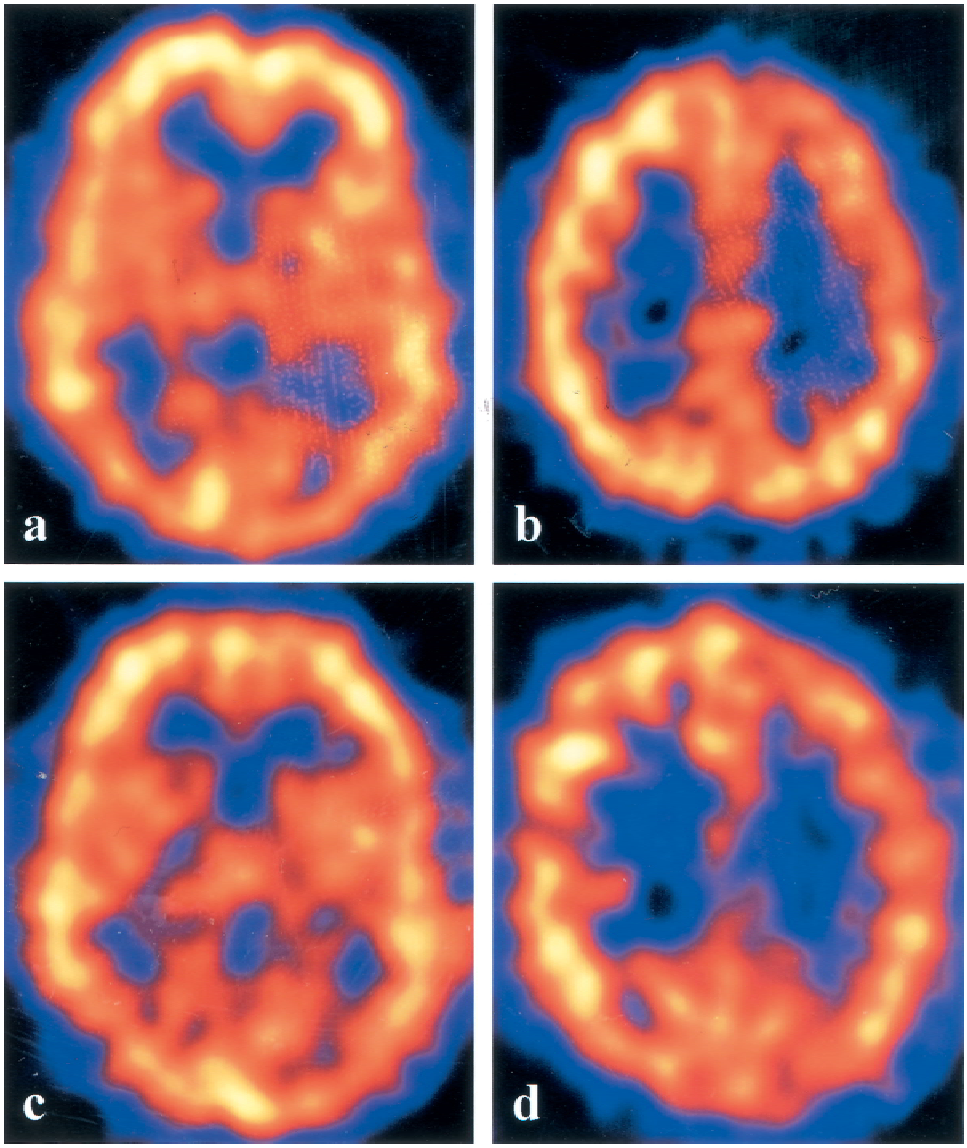

FIG. 2. [99mTc]-HMPAO brain basal (**a**) and post acetazolamide SPECT (**b**) showing perfusion defect in the left basal ganglia and decreased vascular reserve in the left frontal lobe. Postoperative follow-up basal (**c**) and post acetazolamide SPECT (**d**) demonstrated no significant perfusion defect in the left basal ganglia and little change of vascular reserve in the left frontal lobe.

our patient. The bypass surgery might have played an important role in the restoration of blood supply and achieving a functional balance of the striatum. Our case suggests a functional image may play an important role in documenting focal abnormality that may be amenable to treatment.

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Unilateral Pallidal Stimulation for Segmental Cervical and Truncal Dystonia: Which Side?

Francisco Escamilla-Sevilla, MD,[1]*
Adolfo Mínguez-Castellanos, MD,[1]
Ventura Arjona-Morón, MD,[2]
José María Martín-Linares, MD,[1]
Juan Carlos Sánchez-Álvarez, MD,[1]
Angel Ortega-Morenoa, MD,[1]
and Teresa García-Gómez, MD[1]

[1]*Movement Disorders Unit, Department of Neurology, Virgen de las Nieves Hospital, Granada, Spain*
[2]*Movement Disorders Unit, Department of Neurosurgery, Virgen de las Nieves Hospital, Granada, Spain*

Abstract: We present a 24-year-old man with idiopathic segmental cervical and truncal dystonia of juvenile onset. His condition improved after unilateral stimulation of the internal globus pallidus ipsilateral to the contracting sternocleidomastoid muscle. © 2002 Movement Disorder Society

Key words: deep brain stimulation; pallidal stimulation; GPi; stereotactic and functional neurosurgery; cervical dystonia; sternocleidomastoid muscle

The internal globus pallidus (GPi) target has yielded the best outcomes in stereotactic surgery for generalised dystonia or incapacitating cervical dystonia refractory to medical treatment.[1–3] Whether ablation or stimulation is used, the improvement is generally delayed.[2–8] Most investigators recommend a bilateral approach for the treatment of generalized[6–11] and cervical[4,12–14] dystonia, although there are reports of different degrees of improvement in axial dystonia after unilateral surgery of the GPi.[8] We present a patient with idiopathic segmental cervical and truncal dystonia who showed a marked and sustained improvement after unilateral pallidal stimulation ipsilateral to the contracting sternocleidomastoid muscle (SCM). The value of the contracting SCM to indicate the side for stereotactic surgical intervention is discussed.

Case Report

A 24-year-old man of non-Jewish origin and with no relevant family history or consanguinity was referred to our unit in 1998 for the presurgical assessment of an idiopathic segmental cervical and truncal dystonia. At 16 years of age, he noticed involuntary cervical torsion movements to the left and backward. There was a slow clinical progression for a few years until the onset of a fluctuating dorsal hyperextension that incapacitated

A videotape accompanies this article.

*Correspondence to: Francisco Escamilla-Sevilla, Servicio de Neurología, Hospital Virgen de las Nieves (CRT), Carretera de Jaén s/n, 18013 Granada, Spain.

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him for daily life activities. His clinical symptoms then stabilised in this situation. Blood analysis, copper metabolism, acanthocyte determination, and brain magnetic resonance imaging studies were all normal. He underwent various drug regimens with trihexyphenidyl, tetrabenazine, pimozide, levodopa, baclofen, and benzodiazepines but with no satisfactory results, either because of lack of response or adverse effects. Type A botulinic toxin was injected at the local cervical level, but the patient developed resistance to this drug. At the time of presurgical assessment, he was receiving 15 mg of trihexyphenidyl daily.

Results of the general examination were normal, and no Kayser-Fleischer ring was detected. Neurological examination showed a severe painless retrocollis and torticollis to the left, of intermittent intensity, with hypertrophy of the right SCM, left trapezius and left splenius muscles, and a tendency to dorsal opisthotonus. Scores on preoperative Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS)[15] were 17 on the dystonia movement scale (maximum = 120) and 5 on the disability scale (maximum = 30). The Tsui[16] torticollis rating scale score was 18 (maximum = 27; see Video, Segment 1). The patient gave his informed consent to undergo bilateral pallidal stimulation.

Surgical Procedure

In April of 1999, two quadripolar electrodes for deep brain stimulation (model 3387; Medtronic, Minneapolis, MN) were implanted into bilateral GPi. The intervention was performed under general anaesthesia because of the intensity of abnormal movement. The Cosman-Roberts-Wells stereotactic system was used, the intercommissural line was determined from computed tomography images, and GPi coordinates were defined using the Schaltenbrand and Wahren atlas[17] (3 mm in front of the midpoint of the intercommissural line, 6 mm below that line, and 20 mm from the midline). The electrodes were attached to the skull and connected to a provisional external lead. The localization of the electrodes was checked radiologically. Unilateral and bilateral stimulation tests were then carried out on the different contacts at frequencies of 25 to 185 Hz, evaluating the clinical effect after 5 minutes of connection. We observed no adverse effects. One week after the first intervention, two pulse generators (Itrel II 7424; Medtronic) were implanted into subclavicular regions under general anaesthesia.

Clinical Outcome

The patient has had no complications related to the surgery. Bilateral stimulation tests were carried out on each pair of contacts at multiple frequencies, followed by evaluation of the patient several hours later. The following clinical effects were observed after monopolar stimulation on contact 1 of each electrode: at 185 Hz, there was a slight worsening of the dystonia, and at 25 Hz, the dorsal control was somewhat improved. We set a programme of bilateral and continuous stimulation at a frequency of 25 Hz, with pulses of 90 μsec width and 3-V amplitude. After 1 month of this stimulation, there was an evident progressive improvement in the truncal dystonia, although there were no changes in the cervical dystonia (BFMDRS[15] showed 10 points on the dystonia movement scale). Because of the evident delayed improvement, the stimulation was continued for a further 5 months, but with no resulting major benefit. We then decided to perform prolonged unilateral stimulation tests using the same parameters. With stimulation of the right GPi, there was progressive improvement in the cervical and truncal dystonia, evident after 1 month and maximum at 3 months. At 6 months of unilateral stimulation, 1 year after the surgery, the trihexyphenidyl treatment was withdrawn and an improvement in the patient's quality of life and daily life activities was documented.

At the evaluation after 18 months of continuous right stimulation, there remained only a mild left laterocollis with head tremor. BFMDRS[15] score was 1 on the dystonia movement scale and 0 on the disability scale. The Tsui[16] Torticollis rating scale score was 4 (see Video, Segment 2). In view of the possibility of spontaneous remission, the stimulation was disconnected with the informed consent of the patient. At 1 week, there was a progressive worsening of the dystonia. After reconnection of the system, the patient returned to the above situation. The patient was then offered a new treatment with prolonged stimulation of only the left GPi but refused consent. The patient has remained in this situation to date and leads a normal life.

Discussion

Our patient, who presented idiopathic segmental cervical and truncal dystonia, showed an evident and sustained improvement after the unilateral stimulation of the GPi ipsilateral to contracting SCM.

We do not consider the improvement to be due to a placebo effect because it was not achieved until 7 months after the unilateral stimulation surgery. It seems unlikely that there was a spontaneous remission of the dystonia because it had progressed for 8 years without clinical variations and there was a progressive recurrence of symptoms after disconnection from the generator.

In recent years, the GPi has been considered the surgical target with best outcomes in the treatment of dystonia, especially of idiopathic dystonia.[1–8] We selected this target for our patient, although we recognised that we could not be sure which part of the GPi we were stimulating.

Various investigators have considered bilateral procedures in generalised or cervical dystonia because of the bilaterality of the process or its axial component.[4,6–9,13] Kumar and colleagues found that simultaneous bilateral stimulation achieved greater improvement than did unilateral stimulation.[10] Neuronal activity is anomalous in each GPi [5,6,10,18,19] but can be asymmetrical, with the most affected side coinciding with a more depressed activity of the contralateral pallidus.[6] There are reports of cases in which improvement was obtained with unilateral procedures on the thalamus[23–25] or GPi.[26] Although our intervention was initially bilateral, the patient showed improvements with unilateral stimulation of the pallidus ipsilateral to the contracting and hypertrophied SCM muscle.

In unilateral thalamotomies, the selection of the side for the intervention is controversial.[27] The contralateral side to the contracting SCM was proposed by Cooper,[28] whereas the ipsilateral side was indicated by others.[24,25,29,30] Hassler and Dieckmann assumed that head turning is induced by the pallidothalamic system, because stimulation of the pallidothalamic system increases the electromyographic activity of the ipsilateral SCM muscle during stereotactic surgery, whereas destructive lesions of this system in patients with spasmodic torticollis cause relaxation of the overcontracted SCM muscle on the

ipsilateral side.[24,25] There is further evidence of ipsilateral predominance in the innervation of the SCM muscle. In cats, Kavaklis and associates demonstrated an increase in the discharge rate of most motoneurons of the ipsilateral SCM muscle and a decrease in the rate of those of the contralateral muscle using a repeated train of pulses on the globus pallidus-entopeduncular nucleus.[22] In humans, weakness of the SCM muscle is known to occur ipsilateral to the hemispheric dysfunction in hemiplegic patients and during the Wada test in candidates for epilepsy surgery.[20,21] Although this muscle may be a true marker of laterality in cervical dystonia, there have been reports of improvements applying thalamotomy[28] or pallidal stimulation[25] contralateral to the contracting SCM muscle.

In the present case, we do not know what would have happened with a prolonged stimulation of the left GPi or why stimulation of the right GPi was superior in cervical and truncal control in comparison with bilateral stimulation. Nevertheless, these observations suggest the presence of an interference when both GPi are stimulating, indicating an interrelationship between them.

Both the mechanism by which the stimulation effect is produced and the optimal parameters to be applied have yet to be defined. We achieved improvement using 25-Hz frequency and a pulse width of 90 μsec. Kumar and coworkers and Muta and colleagues obtained maximum improvements in generalised dystonias using frequencies of 50 to 60 Hz, although they selected greater pulse widths (500–1,000 μsec).[10,14] Others have documented improvements with frequencies of 130 to 185 Hz.[4,12,13,25]

Unilateral stimulation can be effective in patients with cervical dystonia who fail to respond satisfactorily to bilateral pallidal stimulation and should be started on the side ipsilateral to the contracting SCM muscle.

Legends to the Videotape

The video recording shows the patient in a baseline state and 2 years after the surgery.

Segment 1. Presurgical assessment. Idiopathic segmental cervical and truncal dystonia of juvenile onset.

Segment 2. Two years after surgery. Improvement in segmental cervical and truncal dystonia with unilateral stimulation of the GPi ipsilateral to the contracting sternocleidomastoid muscle.

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Further Case of Paroxysmal Exercise-Induced Dystonia and Some Insights into Pathogenesis

Michael H. Barnett, MD,[1] Paul R. Jarman, PhD,[1] Simon J.R. Heales, PhD,[2] and Kailash P. Bhatia, FRCP[1]*

[1]*National Hospital for Neurology and Neurosurgery, Institute of Neurology, Queen Square, London, United Kingdom*
[2]*Department of Clinical Biochemistry, Neurometabolic Unit, National Hospital, Queen Square, London, United Kingdom*

Abstract: Cerebrospinal fluid (CSF) analysis of pterin and monamine metabolites was performed before and after an attack in a patient with paroxysmal exercise-induced dystonia. A twofold increase in CSF homovanillic acid and 5-hydroxyindoleacetic acid after an attack was measured. This finding lends support to the hypothesis that increased dopaminergic transmission contributes to the clinical features of the hyperkinetic movement disorders. © 2002 Movement Disorder Society

Key words: paroxysmal exercise-induced dystonia; dopamine; cerebrospinal fluid; homovanillic acid; hydroxyindoleacetic acid

Paroxysmal exercise-induced dystonia (PED) is the least common of the hyperkinetic movement disorders and is characterized by intermediate duration attacks of dystonia precipitated by prolonged muscular exertion.[1] We present a further example of sporadic PED and discuss the potential role of altered monamine metabolism in the pathophysiology of the condition.

Case History

A 21-year-old salesman presented with an 18-year history of stereotypic episodic involuntary movements. His motor milestones were delayed, having not walked until the age of 3.5 years, before which he had propelled himself on his bottom using his arms. At the age of 3 years, his parents noted episodes of clumsiness and jerking involving the upper limbs, and he frequently fell from his chair at playschool. A diagnosis of epilepsy was made and sodium valproate was administered without significant benefit.

At the age of 5 years, he began to have attacks of "wobbliness." It became apparent that most episodes were triggered by exercise such as walking and that the exercised body part was primarily involved in the subsequent attack. The involuntary movements began during exercise and lasted between 10 minutes and several hours, most attacks resolving within 15 to 30 minutes. The legs were most often affected, and the patient was prevented from walking during an attack by large, sometimes violent, ballistic movements. Lack of sleep and fatigue invariably predisposed the patient to an attack, even with trivial exercise. There was no apparent relationship to the consumption of tea or coffee. Food diminished but did not abort attacks, and alcohol had no effect.

In recent years, the jaw has been involved after eating, there have been several episodes of prolonged hiccupping, and two episodes have resulted in a tight sensation in the pharynx transiently, preventing swallowing or speaking. There have been rare nocturnal episodes that have awakened the patient with thrashing movements of the legs. In addition, an increased frequency of daytime exercise-induced attacks has markedly interfered with the patient's mobility, and he now travels with a wheelchair in case of an attack. The attacks have continued despite sequential therapeutic trials of carbamazepine, ethosuximide, and acetazolamide. A short trial of levodopa appeared to markedly exacerbate the abnormal movements.

Learning difficulties were apparent at primary school, and a diagnosis of dyslexia was made. There was no history of migraine or other past illnesses. A paternal great grandfather may have suffered from epilepsy, but there was no family history of a movement disorder.

Slowed tongue movements were noted on examination. The interictal neurological examination was otherwise entirely normal. During an attack precipitated by walking (see Video), large-amplitude, irregular ballistic movements of the legs, arms, trunk, and neck, were seen and gradually subsided over 60 minutes.

Full blood count, screen for acanthocytes, thyroid, and liver function tests were normal. Genetic analysis for the SCA mutations 1, 2, 3, 6, and 7 were negative. Lumbar puncture yielded clear cerebrospinal fluid (CSF) under normal pressure with normal protein, glucose, and cell counts. No CSF oligoclonal bands were detected. Volumetric magnetic resonance imaging of the brain was normal. Results of electroencephalograms performed before and immediately after an attack were normal.

CSF Pterin and Monoamine Metabolism

CSF pterin and monamine metabolites, measured before and 1 hour after an attack precipitated by walking, are shown in Table 1. There was a greater than twofold increase in both homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) after the attack. Biopterin metabolites, including neopterin, dihydrobiopterin, and tetrahydrobiopterin (BH4), remained essentially stable.

Discussion

Altered dopaminergic transmission is well recognized in Parkinson's disease and the dystonic syndromes, in particular dopa-responsive dystonia. More recently, the protein encoded by the DYT1 gene, which is mutated in primary torsion dystonia, has been localized to the dopaminergic neurons of the substantia nigra pars compacta by immunohistochemistry.[2] The pathophysiology of the hyperkinetic movement disorders is unknown. Familial paroxysmal dystonic choreoathetosis has, however, been linked to a locus on the long arm of chromosome 2,[3,4] and in a single patient with this condition, increased levels of metabolites of dopamine (HVA) and serotonin (5-HIAA) were present in the CSF during an attack.[5] This finding lends support to the hypothesis that increased dopaminergic

A videotape accompanies this article.

*Correspondence to: Dr. Kailash Bhatia, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom. E-mail: k.bhatia@ion.ucl.ac.uk

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TABLE 1. *Comparison of CSF pterin and monamine transmitter metabolites before and after attack*

CSF metabolite	Before attack	1 hr after attack	Normal values (nmol/L)
Total neopterin	6	7	7–65
Tetrahydrobiopterin	18	19	9–39
Dihydrobiopterin	2.6	3.2	0.4–13.9
Homovanillic acid	86	196	71–565
5-HIAA	44	97	58–220

CSF, cerebrospinal fluid; 5-HIAA, 5-hydroxyindoleacetic acid.

transmission contributes to the abnormal movements seen in these disorders. We report on a similar twofold increase in CSF HVA and 5-HIAA after an attack in a patient with PED, and propose that, at least at a biochemical level, these two conditions may share a common pathophysiological mechanism. Our patient also had a history of marked exacerbation of his movement disorder after commencing levodopa therapy.

The essentially normal pterin profile before and after the attack in our patient is of interest. Changes in the CSF biopterin concentration may reflect ongoing demands for dopamine synthesis or indeed synthesis activity.[6] Failure to detect an increased concentration of CSF BH4 in this patient may relate to the intermittent nature of the attacks. Alternatively, changes in BH4 metabolism may not be reflected in CSF sampled 1 hour after an attack.

Although dramatic, these results represent a single observation and, therefore, must be interpreted with caution. The potential confounding effect of exercise and diet on CSF dopaminergic metabolites is unknown. In addition, the specimens were collected on separate days, although they were taken at approximately the same time. CSF analysis in further patients with hyperkinetic movement disorders may clarify the role of the altered monoaminergic transmission in the pathogenesis of these disorders.

Legend to the Videotape

Large-amplitude dystonic movements of the upper and lower limbs and trunk induced by walking.

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Forty-One-Year Follow-Up of Childhood-Onset Opsoclonus-Myoclonus-Ataxia: Cerebellar Atrophy, Multiphasic Relapses, and Response to IVIG

Michael R. Pranzatelli, MD,[1]* Elizabeth D. Tate, FNP, MNC,[1] Marcel Kinsbourne, MD,[2] Verne S. Caviness, Jr., MD, PhD,[3] and Bibhuti Mishra, MD[4]

[1]The National Pediatric Myoclonus Center, Departments of Neurology and Pediatrics, Southern Illinois University School of Medicine, Springfield, Illinois, USA
[2]New School University and Tufts University, Winchester, Massachusetts, USA
[3]Massachusetts General Hospital, Boston, Massachusetts, USA
[4]Temple University, Philadelphia, Pennsylvania, USA

Abstract: We report on an adult with opsoclonus-myoclonus-ataxia syndrome experiencing widely spaced neurological relapses, who was followed for 41 years. His responses to treatment are described. © 2002 Movement Disorder Society

Key words: ACTH; cerebellar ataxia; dancing eyes; IVIG; Kinsbourne syndrome; myoclonus

Opsoclonus-myoclonus-ataxia syndrome, though rare, affects children and adults. Despite age-related differences in the tumor types found in paraneoplastic cases, the clinical features are similar, and both adults and children may be steroid-responsive. Because the autoantibodies reported in adults are seldom found in children with opsoclonus-myoclonus-ataxia, the biological relation between the childhood-and adult-onset groups is unknown. Although opsoclonus-myoclonus-ataxia is a monophasic disorder in some children,[1] in others it is not, as indicated by relapses with illnesses. There has been little long-term follow-up into adulthood. We report on an adult with widely spaced neurological relapses, who was followed for 41 years, and describe his responses to treatment.

Case Report

The patient is a 42-year-old, African-born, Indian male who was diagnosed in England at 11 months of age with opsoclonus-myoclonus-ataxia 1 week after DPT immunization and apparent viral illness. He was a patient of Dr. Paul Sandifer, at one point seen by Lord Brain, and was the third case in Dr. Marcel Kinsbourne's original study.[2] Opsoclonus was a presenting sign. Myoclonus not only made his limbs unable to

A videotape accompanies this article.

*Correspondence to: Prof. Pranzatelli, The National Pediatric Myoclonus Center, SIU School of Medicine, PO Box 19658, Springfield, IL 62702. E-mail: mpranzatelli@siumed.edu.

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reach their targets, but it interfered with his ability to swallow and he lost his ability to sit. For at least 6 months he was bedridden, required a feeding tube, and he remained hospitalized for 1 year. There were no seizures. Both opsoclonus and myoclonus were completely suppressed by ACTH, beginning at 60 IU daily, and later by corticosteroids, which were tapered over 11 years. He began to speak at age 3 and learned to walk, but had slow speech and never achieved normal comprehension. Recovery of function was substantial but not complete. The remission lasted 10 years.

At age 22 years, the patient developed a flu-like illness with acute ataxia severe enough to confine him to a wheelchair within 3 weeks. His relapse was so unexpected that he was evaluated for other etiologies of ataxia, such as demyelinating disease. Neurological abnormalities included gait ataxia, limb dysmetria, but no opsoclonus, reflex abnormality, or weakness. Although he could stand with feet together, he wasn't steady and preferred them to be 6 to 8 inches apart. His speech was slightly dysphonic with a tendency to run together syllables of large words. He displayed irregular saccades with quickly attenuating nystagmus to horizontal gaze in either direction. Rapid alternating movements were slow. IQ testing showed borderline intelligence to mild mental retardation. Neuropsychological testing showed deficits in frontal function with poor understanding of concepts, low visual motor ability, poor impulse control, and disinhibition. A head computed tomography (CT) scan showed mild cerebellar atrophy, particularly of the vermis. He was treated with 30 IU ACTH daily, which was tapered over 5 years, and physical therapy. Although he improved greatly, he did not return to his previous level of function.

Three years later, he developed an acute duodenal ulcer and uveitis of the left eye, which were thought to be steroid-induced and were treated successfully. An abdominal CT scan with specific attention to the suprarenal or adrenal area was negative for tumors. He had occasional vascular headaches, allergies, and required corrective lens for astigmatism. A spectral mapping of the electroencephalogram (EEG) was normal. He took diazepam and desipramine to manage stress that seemed to decrease his energy level.

Between the ages of 22 and 31 there were at least three other illness-induced relapses. On one occasion he became too ataxic to walk. Again he responded to increases in ACTH. Head MRIs also showed cerebellar atrophy and slight cerebral sulcal prominence. An EEG was normal.

The patient came to the National Pediatric Myoclonus Center at 36 years of age (see Videotape). He exhibited a pancerebellar syndrome, the main feature of which was gait ataxia, with inability to perform tandem walking or to stand on one foot without holding on. He drank from a cup without spilling and used a spoon well with either hand. Truncal titubation and action myoclonus were minimal and opsoclonus was absent, but his saccades were irregular. Handwriting was labored and poor (Fig. 1). Finger and foot tapping were slow and sequential finger movements were awkward. He had finger agnosia and acalculia, but no left–right confusion, aphasia, or apraxia. Touch and position sense were intact. Deep tendon reflexes were brisk with crossed adductors, but plantar responses were flexor. Strength was slightly decreased. Speech, like mental processing, was slow but fluent, although he was affable and engaging. He was seronegative for anti-Hu, anti-Ri, and anti-Yo autoantibodies. ESR, T4, TSH, CMP, and CBC were all normal with the exception of mildly increased cholesterol of 232 and triglycerides of 264. Lyme antibody testing was negative. Head MRI showed significant cerebellar atrophy, which was most severe in the vermis (Fig. 2).

We recommended using intravenous immunoglobulins (IVIG) rather than steroids. He received a monthly infusion of 2 g/kg for 6 months. The improvement in ataxia was immediate and dramatic, with only transient headache as a side effect. His gait became steadier and he felt more confident in performing activities of daily living. As a result, he has continued on IVIG for 5 years, receiving treatments 6 months of each year when he is in the US. His family felt he improved in cognitive as well as motor function since being on a regular IVIG program. The IVIG dose was reduced to 1.5 g/kg.

Within the last few years he contracted malaria during his travels. In addition to chloroquine, he received IVIG. In a few days, he was up and about, a much quicker recovery than expected, and without relapsing neurologically.

The youngest of 3 children, the patient married at the age of 35, speaks four languages, drives in Africa, and sometimes jogs or swims. A brother and sister are in good health. He was schooled in the United States from age 8 to 24, acquiring the English language at the age of 12. After completing high school, he took some business and computer classes. The patient uses a computer but cannot do mathematics. He enjoys painting as a hobby. By mid-afternoon he becomes very fatigued and must take a nap. He has difficulty persevering with most tasks, and despite vocational planning and counseling, has not been able to work or live independently of the family.

Discussion

Our patient is one of the first reported cases of childhood opsoclonus-myoclonus-ataxia. Not only did he have relapses, indicative of a multiphasic disorder, but he has remained responsive to ACTH or corticosteroids. At the time of his first major relapse, there was nothing in the literature to suggest that such late events were possible in childhood-onset opsoclonus-myoclonus-ataxia. He is similar to a woman described in a recent case report,[3] who presented with opsoclonus-myoc-

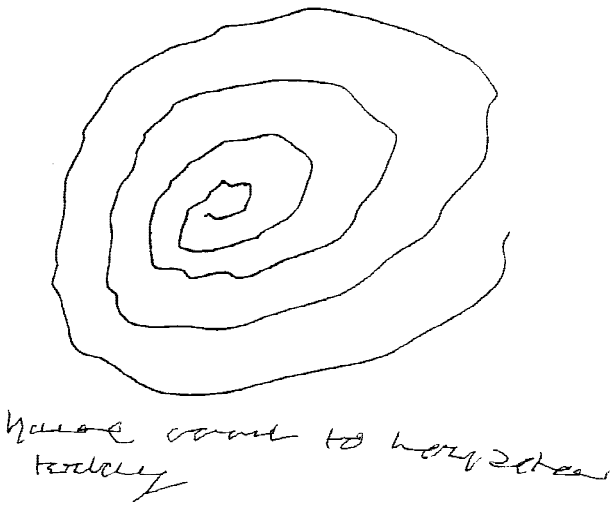

FIG. 1. Handwriting sample and Archimede's spiral at age 36 years. The patient was instructed to write "I have come to the hospital."

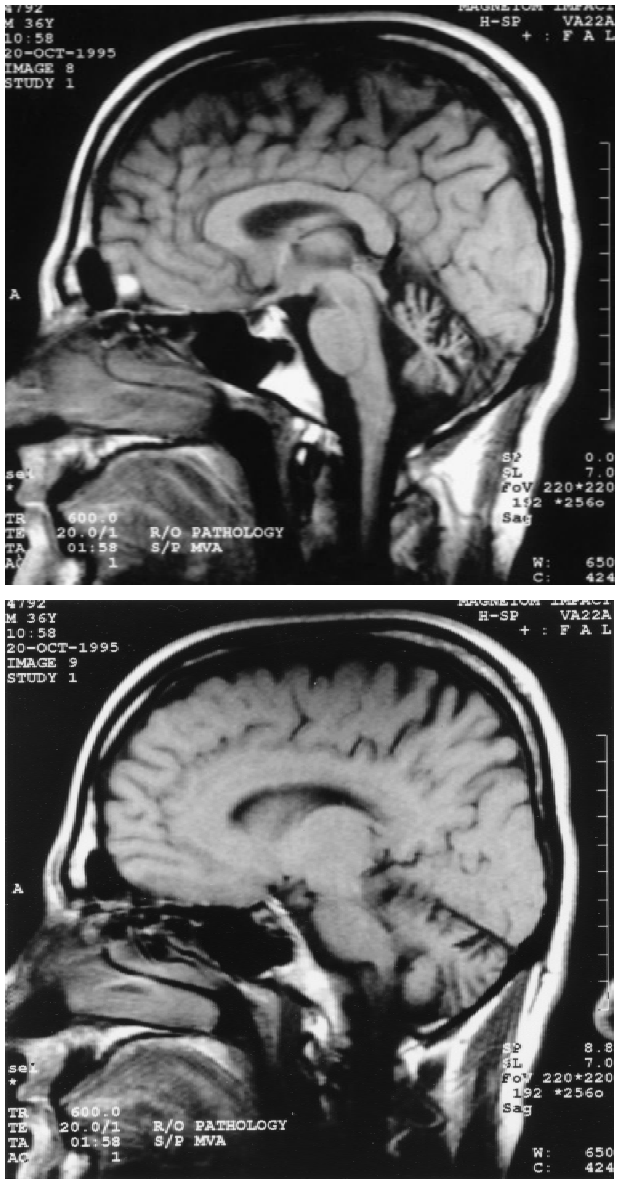

FIG. 2. Head magnetic resonance imaging scan. Sagittal, T1-weighted image in the plane of the cerebellar vermis (top) and cerebellar hemisphere (bottom).

lonus-ataxia at 20 months and relapsed with subacute cerebellar ataxia at 29 years of age. Just as she had responded well to corticosteroids as a child, remaining on betamethasone for 6 years, she improved on them as an adult. In 3 of 5 other patients with childhood opsoclonus-myoclonus-ataxia followed into adulthood, 4 of whom had reduced cognitive function and language capabilities, symptoms still worsened with episodes of minor illness.[4]

Our study substantiates the existence of a protracted, lifelong, steroid-responsive syndrome and furthers the observation by demonstrating IVIG-responsiveness and cerebellar atrophy. Collectively, these reports indicate that prolonged follow-up is necessary to achieve a true picture of the incidence of relapse. Our patient was doing so well one might have thought relapse was unlikely. Perhaps a predictor of relapse was the severity of his initial presentation, which is more severe than usual, but not rare. Some infants with profound hypotonia do require a feeding tube. A high incidence of relapses has been reported in cases in which neuroblastoma is found.[5] The duration of treatment illustrates how long children with the disorder are kept on ACTH or steroids to avoid relapse.

The clinical significance of our observations depends on the veracity of the diagnosis. How certain can we be that the relapses during adulthood were a recrudescence of the initial disorder and not a nonspecific effect of illness or the appearance of some other disease? Our patient's worsening was more severe than expected from a stressor-induced mechanism and it did not improve until immunotherapy was instituted. His neurological manifestations did change over time, from opsoclonus and myoclonus to more predominant ataxia, behavioral, and cognitive impairment, but such a transition has been reported previously.[6] As to other diseases, relapsing remitting multiple sclerosis can be considered, but the clinical features were dissimilar and the MRI was not diagnostic despite four decades of illness. This patient had no optic neuritis, internuclear ophthalmoplegia, or posterior column related findings. There were no demyelinating lesions. Vasculitis was ruled out by laboratory screening. Metabolic disorders do not respond to immunotherapy, tend not to be confined to a single system over multiple decades, typically do not cause opsoclonus-myoclonus-ataxia, and tested negative in this patient. We believe that other plausible disorders have been ruled out and the evidence fits best with relapses due to the underlying immunological disorder of opsoclonus-myoclonus-ataxia.

Cerebellar involvement is a key feature of childhood opsoclonus-myoclonus-ataxia and may even contribute to cognitive impairment.[7] Cerebellar atrophy, however, is uncommon early in the course of the disorder. There have been two reports of cerebellar vermis lesions in children with opsoclonus-myoclonus.[8,9] Biopsy or autopsy reports in these cases and another child without atrophy showed Purkinje and granular cell loss with gliosis.[10] Two of the children had ganglioneuroblastoma and at least 1 had been treated with chemotherapy. Greater involvement of the vermis in opsoclonus-myoclonus-ataxia is in keeping with its principal cerebellar manifestations of gait impairment and truncal titubation.

If cerebellar atrophy is a late feature of the disorder, why is its appearance delayed, whereas in paraneoplastic cerebellar degeneration (PCD), a different disorder affecting adults, it is an early and requisite finding?[11] There are several possible explanations, none of which have been confirmed in the absence of an animal model and the paucity of post mortem studies. It may have to do with the antigen or antigens and the nature or magnitude of the autoimmune response they trigger. Although significant cytotoxic injury might be expected to produce early atrophy, other types of injury, such as apoptosis, might not. Alternatively, an immunologically-induced neurophysiological derangement in opsoclonus-myoclonus-ataxia resulting in cerebellar overactivity could lead to gradual trophic changes, much in the same transsynaptic way that olivary degeneration occurs in palatal tremor.[12] Increased cerebellar blood flow identified by PET is associated with several forms of tremor, but there is no direct evidence that cerebellar hyperactivity causes tremor.[13] A more worrisome and likely explanation is that the initial cerebellar injury is sublethal but ongo-

ing and cumulative. If this is the case, early, more specific and effective immunotherapy will be necessary to prevent the atrophy.

IVIG is being embraced more and used at higher doses since first reported as a treatment for opsoclonus-myoclonus-ataxia.[14] Case reports suggest that children benefit from 1 g/kg/day.[15,16] Our patient was fortunate in responding to three different, separately administered therapeutic agents which may work through different mechanisms.[1]

Because the patient presented several years before an association was made between opsoclonus-myoclonus-ataxia and neuroblastoma,[17] it is unclear if he had neuroblastoma. Despite modern imaging technology and increased awareness of the need to screen for neuroblastoma, diagnostic difficulties continue to plague clinicians due to the tumor's tendency toward spontaneous regression and the flu-like symptoms that have so often suggested a viral etiology in children later shown to have a tumor. In as many as half of the reported cases, no tumor is found despite repeated nuclear medicine scans or body CT. All that can be said is that he did not harbor three of the autoantibodies found in a minority of patients with a paraneoplastic syndrome.

The capacity of patients to respond for years to ACTH without loss of efficacy indicates a lack of tolerance or receptor down-regulation. This is of interest to models of pro-opiomelanocortin receptors, at which ACTH may bind,[18] and should be an important clue to the mechanism of ACTH's action in opsoclonus-myoclonus-ataxia.

Our patient adds to the profile of neuropsychological dysfunction in opsoclonus-myoclonus-ataxia. His cognitive abilities were not uniform, as he seemed to have islands of preserved function surrounded by deficits. Finger agnosia and acalculia, although short of a Gerstmann's syndrome, suggest dominant hemisphere dysfunction. The pattern of abnormalities we reported previously in opsoclonus-myoclonus-ataxia was compatible with subcortical dysfunction.[19] A cognitive–affective syndrome has been described in adults with lesions involving the posterior lobe of the cerebellum and the vermis.[20] These individuals have impairment of executive functions, spatial cognition, personality changes, and language deficits. How much of the cognitive impairment in children with opsoclonus-myoclonus-ataxia can be attributed to cerebellar involvement remains a fundamental question.

Note added in proof

Since this manuscript was submitted for publication, Hayward and colleagues [J Pediatr 2001;139:552–559] reported that cerebellar atrophy occurred in children with opsoclonus-myoclonus-ataxia and neuroblastoma several years after onset. These cases support our assertion that cerebellar atrophy in opsoclonus-myoclonus-ataxia of pediatric onset is caused by the paraneoplastic disorder.

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Hereditary Chin Trembling: A New Family with Exclusion of the Chromosome 9q13-q21 Locus

David A. Grimes, MD,[1,2]* Fabin Han, MD,[1] Dennise Bulman, PhD,[1] Mary Lou Nicolson, RN,[3] and Oksana Suchowersky, MD[3]

[1]Ottawa Health Research Institute, Ottawa, Canada
[2]Parkinson's Disease and Movement Disorders Clinic, Ottawa, Ontario, Canada
[3]The University of Calgary, Movement Disorders Clinic, Calgary, Alberta, Canada

Abstract: Hereditary chin trembling is a rare autosomal dominant condition that has been linked to chromosome 9q13-21 in one kindred. We describe a four-generation family with this condition and, using linkage analysis, have excluded the 9q13-21 region as causing the chin trembling in this family. © 2002 Movement Disorder Society

Key words: hereditary chin trembling; linkage analysis; chromosome 9q13-21

Hereditary chin trembling (OMIM 190100) is an autosomal dominant condition that has been reported in fewer than 25 families.[1] It is characterized by paroxysmal, often rhythmic up-and-down movements of the chin and the lower lip. The episodes last from seconds to hours and may be triggered by emotion, anxiety, or may occur without apparent precipitants. The condition typically becomes manifest in infancy or in early life, and the episodes tend to reduce in frequency with advancing age.[2] Jarman and colleagues[3] in 1997 identified linkage to markers on the long arm of chromosome 9 in one family and defined an ~2.1 cM interval on chromosome 9q13-21. They described a second family not linked to this region, but to date no further genetic information has been described for this condition. We report here on a new family with hereditary chin trembling and exclude the previously linked locus at 9q13-21 in our family.

Subjects and Methods

This study was approved by the Conjoint Medical Ethics Committee, University of Calgary. All individuals were examined by a movement disorder specialist (O.S.) and, after signing a written consent, had blood drawn for DNA extraction. DNA was prepared by standard procedures. A total of 11 core individuals were genotyped for this study (Fig. 1). Genotypes were generated for microsatellite markers D9S1806, D9S1822, D9S1876, D9S175 (see Table 1) linked to the known chromosome 9q13-q21 locus. After polymerase chain reaction amplification, alleles were electrophoretically separated and scored on an automated DNA sequencer (Li-Cor, Lincoln, NE). Two-point linkage analysis was performed using MLink from the *Linkage v. 5.1* software program.[4] An autosomal dominant model of transmission was used, with a disease penetrance of 90% and a disease allele frequency of 0.0001 with the recombination fractions assumed to be equal for men and women. Marker allele frequencies were taken from Marshfield/CEPH when available, but otherwise were assumed to be equal.

This family has been followed up in the Movement Disorders Clinic at the University of Calgary since 1994. Subject III-2 was originally referred at the age of 15 years because of trembling of his chin, which had been present since infancy.

Review of the family history showed numerous other family members (age range, 13–74 years) with similar symptoms (Fig. 1). All were aware of quivering of the chin with onset in infancy. The quivering varied in severity and frequency among the family members, with some having essentially a constant quivering of the chin, and others noting intermittent quivering occurring several times per day. The quivering was exacerbated by fatigue and stress. All family members felt embarrassed by this quivering as they would be frequently teased, and people would think that they were about to cry. The family was otherwise healthy. Neurological examination was normal outside of quivering of mentalis muscles bilaterally in affected family members. A diagnosis of hereditary chin trembling was made. Several family members started on botulinum toxin A injections in 1995, which they have continued since. They receive between 5 and 10 units of botulinum toxin type A in total, divided equally between the two mentalis muscles. All have had an excellent response with complete resolution of the chin quivering, lasting 3 to 4 months with no side effects. There has been no loss of benefit over the 7 years of repeat injections.

Results and Discussion

We evaluated this family for the possibility that the disease was linked to chromosome 9q13-q21. Two flanking recombinant markers, D9S1806 and D9S175, plus two nonrecombinant markers (D9S1822, D9S1876) based on the original linkage report[3] were used to cover this 4 cM region (see Table 1). All markers within this region yielded significant negative (<-2.0) logarithm of odds scores at $\theta = 0.0$; therefore, we could exclude this area as causing the trembling chin our family.

Hereditary chin trembling has been described in the literature using many different terms, including "hereditary geniospasm,"[3] "hereditary quivering of the chin,"[5] and "familial trembling of the chin."[6] Recently, it has been suggested that a better term would be hereditary chin myoclonus, because the abnormal involuntary movement is related to quick jerks of the mentalis muscle, the burst duration is brief (10–25 msec) and because there are pauses between the individual jerks.[7] Botulinum toxin has been reported to be a useful treatment for the over activity of the mentalis muscle.[8] In this family, the efficacy of this treatment option has been shown to persist over an extended period of 7 years, with no increase in dose or loss of effectiveness. The clinical characteristics of our family are typical of other families reported in the literature, including the family linked to 9q13-q21. The chin trembling appeared to be inherited in our family in an autosomal dominant pattern with very high penetrance. There were no obiligate gene carriers in

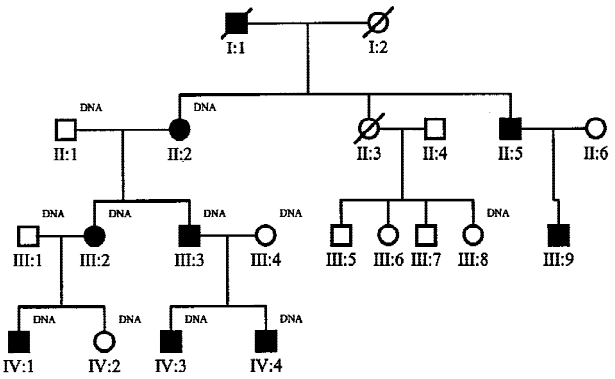

FIG. 1. Pedigree of family with hereditary chin trembling. Filled symbols indicates individuals with chin trembling. "DNA" indicates DNA obtained. Slashed symbols represent deceased individuals.

*Correspondence to: D.A. Grimes, The Ottawa Hospital, Civic Campus, 1053 Carling Avenue, Ottawa, Canada, K1Y 4E9.
E-mail: dagrimes@ottawahospital.on.ca

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TABLE 1. *Two-point LOD Scores between chromosome 9q13-q21 markers and hereditary chin trembling*

Locus	Marker	Distance[a] (cM)	Lod score at theta values						
			0.0	0.01	0.05	0.1	0.2	0.3	0.4
9q13	D9S1806	66.32	–4.01	–0.89	–0.24	–0.00	0.17	0.19	0.13
locus	D9S1822	66.86	–9.29	–2.25	–0.92	–0.41	–0.01	0.12	0.11
	D9S1876	67.93	–4.21	–2.79	–1.44	–0.88	–0.39	–0.17	–0.06
	D9S175	70.33	–9.34	–2.27	0.94	0.43	0.02	0.11	0.11

[a]Distances are given in Kosambi, sex-averaged centimorgans based on Marshfield genetic map (1998).

the family but whether asymptomatic gene carriers exist will have to wait until the specific genetic mutation in this family is discovered. The exclusion of the chromosome 9 q13-q21 locus further demonstrates that genetic heterogeneity exists with this condition and that further linkage studies will be required to identify other chromosomal regions that can cause similar phenotypes.

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Holmes' Tremor and Neuroparacoccidioidomycosis: A Case Report

Hélio A.G. Teive, MD,* Alessandra Zanatta, MD, Francisco M.B. Germiniani, MD, Sérgio M. Almeida, MD, PhD, and Lineu C. Werneck, MD, PhD

Movement Disorders Unit, Service of Neurology, Hospital de Clínicas, Federal University of Paraná, Curitiba, Pr, Brazil

Abstract: We report on a case of neuroparacoccidioidomycosis that presented with a midbrain mass lesion associated with Holmes' tremor. The difficulties of pharmacological treatment of such tremor are emphasized.

Key words: neuroparacoccidioidomycosis; Holmes' tremor; Benedikt syndrome

Paracoccidioidomycosis is a chronic infectious disease that may present with neurological signs/symptoms. Involvement of the central nervous system (CNS) with paracoccidioidomycosis (PCM) was first described in 1919.[1,2] PCM must always be considered in the differential diagnosis of both meningoencephalitis and expansive CNS lesions in endemic areas.[1–3] We report on a case of PCM that presented with a midbrain mass lesion associated with Holmes' tremor.

Case Report

A 34-year-old man was admitted in September 1995, complaining of gradual onset of right hemiparesis as well as diplopia. He had a previous history of systemic hypertension, smoking, and alcoholism. There were no abnormal findings on general physical examination, but upon neurological examination, a complete paralysis of the right III cranial nerve, grade IV muscle strength, spasticity, dysmetria, and dysdiadochokinesia on the left side were found.

A chest X-ray showed a fibrotic pulmonary pattern. A cranial computed tomography (CT) scan showed an expansive lesion affecting the midbrain (right side), with contrast enhancement. The HIV test was negative. Mycological examination of sputum disclosed several sprouting yeast cells, morphologically compatible with *Paracoccidioides brasiliensis*, which was later confirmed by bronchial lavage.

A lumbar puncture was performed, and the study of the cerebrospinal fluid disclosed a protein of 51 mg/dl, glucose 85 mg/dl, leukocytes 0.3/mm^3 and no erythrocytes. A presumptive diagnosis of neuroparacoccidioidomycosis (NPCM) associated with pulmonary PCM was made, and the patient was treated with intravenous trimethoprim/sulfamethoxazole (TMP/SMX) for 15 days. He was discharged on oral TMP/SMX with an improvement of both muscle strength and the paralysis of the III cranial nerve.

A videotape accompanies this article.

*Correspondence to: Hélio A.G. Teive, Rua General Carneiro 1103/102, CEP: 80.060-150, Curitiba, Paraná, Brazil.
E-mail: hagteive@mps.com.br

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He was admitted, once again, 2 months later, because of a left hand tremor with rest, intentional, and postural components, as well as a dystonic posture of the left hand (see Video, Segment 1). A new cranial CT scan showed that the lesion had increased in size (Fig. 1). He was then treated with amphotericin B (total cumulative dose, 1.5 g). A CT scan 1 month after treatment showed no remaining lesions, and the mycological test results were negative. An initial therapeutic test with levodopa (125 mg t.i.d.) for the tremor was later followed by the use of clonazepam (8 mg/day) and trihexyphenidyl 15 mg/day, all with no significant improvement. Later, on no medication, the patient had a spontaneous resolution of symptoms.

Discussion

PCM is a systemic mycosis caused by *Paracoccidioides brasiliensis*, a dimorphic, yeastlike fungus, which is endemic in Brazil. CNS involvement can take one of two forms: the most common is a granulomatous lesion, and the second rare form is an inflammatory meningeal reaction, which characterizes either acute or chronic basilar meningitis. The combination of both forms can be found in 23% of patients.[1–3]

CNS compromise in PCM varies from 9.6 to 45%.[1,2] Most patients with CNS involvement have a disseminated disease that is easily identifiable. The lungs are probably the most frequent primary source for secondary disease, with hematogenous or lymphatic spread.[1,2] Nonetheless, some patients with generalized PCM have no CNS compromise, which leads us to believe that immunological reactions in some patients favor the CNS involvement.[1–3]

Holmes' tremor (HT) was initially described by Benedikt,[4] Holmes,[5] and Souques and colleagues.[6] It is also known as static cerebellar tremor, *hiperkinesia volitionnelle* or myorhythmia, mesencephalic tremor, and rubral tremor.[7] The traditional terms rubral tremor and mesencephalic tremor can be misleading, because of a greater number of lesions outside these locations with similar clinical features.[8–10]

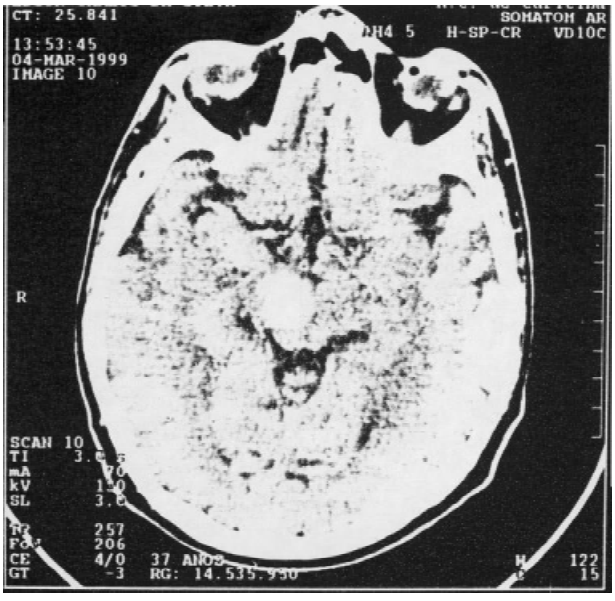

FIG. 1. Cranial computed tomography scan demonstrated an expansive lesion, with contrast enhancement, in the right side of the midbrain.

Recently, Deuschl and associates established the following criteria for the diagnosis of HT: (1) resting and intention tremor with sometimes irregular presentation; (2) postural tremor can also be found in many patients; (3) the tremor is not as rhythmic as other tremors; (4) slow frequency (usually less than 4.5 Hz); and (5) a typical delay (usually 4 weeks – 2 years) between the time when the lesion occurred (e.g., cerebrovascular lesion) and the onset of tremor.[8]

The anatomical location of the lesion can be diverse, involving the superior and external part of the red nucleus, rubrothalamic pathways, the central tegmental tract, the superior cerebellar peduncle, and the substantia nigra.[9,10]

Some investigators emphasize a secondary lesion with retrograde degeneration of the dorsal tegmental pathway, cerebellar peduncle, and hypertrophic degeneration of the olive.[7] These anatomical findings are compatible with a dopaminergic denervation of the striatum that can play a role in the pathogenesis of Holmes' tremor, which is supported by the sporadic reports of response to levodopa in rubral tremor.[9–11]

Remy and coworkers evaluated this hypothesis by analyzing positron emission tomographic scans with $^{[18]}$F-fluorodopa uptake in 6 patients with a contralateral tremor after a peduncular lesion. Their results show an important compromise of the nigral dopaminergic system in rubral tremor that seems to be independent of postsynaptic dopaminergic pathways.[11]

Propranolol, valproate, clonazepam, levodopa, and anticholinergic drugs have all been used in the treatment of HT with variable results, but no convincing therapy for Holmes' tremor is available and gradual spontaneous improvement may occur.[9,10]

We report on a patient with Benedikt's syndrome, with Holmes' tremor secondary to midbrain granulomatous NPCM. We emphasize the difficult pharmacological treatment of such tremor, which disappeared spontaneously, after the resolution of the NPCM granuloma after treatment with amphotericin.

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Legend to the Videotape

The patient presents with a left hand tremor with rest, intentional, and postural components, associated with a focal dystonia of the hand. Note spasticity in the left lower limb and dysmetria in the left arm.

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Oculo-Auricular Phenomenon Secondary to Vestibular Dysfunction

Adriano Jiménez-Escrig, MD, PhD,[1]*
Juan M. San-Millan, MD, PhD,[2] and Manuel Barón, MD, PhD[3]

[1]S. de Neurología, Hospital Ramón y Cajal, Madrid, Spain
[2]S. de Neuroradiología, Hospital Ramón y Cajal, Madrid, Spain
[3]U. de Neurología, Hospital Fundación Alcorcón, Universidad de Alcalá, Madrid, Spain

Abstract: The oculo-auricular phenomenon consists of coactivation of the ocular rectus lateralis and the posterior muscles of both ears (transverse auriculae and obliquus auriculae muscles). This coactivation produces a bilateral curling of auricles during extreme lateral gaze that can be observed in as much as an 80% of the normal population. We herein describe a 26-year-old man who presented a transient oculo-auricular phenomenon in the course of a vestibular vertigo. © 2002 Movement Disorder Society

Key words: oruloauricular phenomenon; vertigo

According to Heuser,[1] the recognition of an associated movement of auricle and eyes in humans must be ascribed to Wilson (1908), who reported that extreme lateral gaze can induce a perceptible movement of the upper part of both ears, which are then turned backward. Following works called this movement the oculo-auricular phenomenon. This auricle movement, generated by the activity of the retroauricular muscles of the external ear (transverse auriculae and obliquus ariculae muscles) can be observed in 40% to 80% of normal individuals during extreme lateral gaze.[2] Vestibular or midbrain disorders can disturb this reflex, but this finding has seldom been reported. Furthermore, a transiently appearing oculo-auricular phenomenon is even less frequently documented. We herein describe a patient who developed a transient oculo-auricular phenomenon during a peripheral vestibular disorder.

Case Report

A 26-year-old man, without previous remarkable medical history, developed a 39°C fever, cough and throat soreness that resolved spontaneously in 1 week. In the following days, he presented instability and dizziness that forced him to rest for 4 days. At this time, his general practitioner consulted the neurologist because he had observed, while exploring the nystagmus, that the patient made auricle movements. These movements were imperceptible to the patient but had been noticed by his relatives during spontaneous ocular movements.

General physical examination was normal, and the neurological examination performed when the vertigo and auricle movements were in resolution (5th day of vertigo), showed left beating nystagmus that was seen with gaze deviation to the right and left (third degree nystagmus), a slight deviation of gait to the right, and bilateral slow tonic auricle movements synchronic with the fast phase of the nystagmus. Ocular fundus, hearing, strength, reflexes, sensibility, and cerebellar exploration were normal. The vertigo resolved 1 week later. At this time, the patient had normal findings upon neurological examination, and the auricle movements were very occasionally present, and at a much lower amplitude. Results of cranial magnetic resonance imaging were normal.

Discussion

Coactivation of muscles of external ear and eye is a common phenomenon in mammals.[3] The oculo-auricular phenomenon is a reflex mechanism between the ipsilateral nerve abducens (rectus lateralis muscle) and both motor facial (retroauricularis muscles) nerves. It is a physiological and bilateral phenomenon, usually rudimentary in humans.[4] Structures implicated are projections between the superior colliculus and the contralateral pontine paramedian reticular formation to the ipsilateral and contralateral facial nuclei, by means of interneurons located in the paralemniscal ipsilateral area.[5,6] In addition to the automatic and tonic co-contraction of the involuntary retroauricularis muscles in conjugate lateral gaze, several other physiological ways to trigger this co-contraction have been described such as talking, chewing, swallowing, and straining. Co-contraction may be registered also during involuntary inspiration. Finally, in nervous individuals, irregular involuntary contraction of the retroauricularis muscles can serve as a measurement instrument of the involuntary somatomotor system, i.e., the degree of anxiety.[1] Investigation of the other cranial nerves has shown that, occasionally, electromyographic activity of the transverse auricular muscle is present also during vestibular stimulation.[7]

The phenomenon can be observed clinically by the presence of bilateral curling of the pinna in forced lateral gaze or by polygraphic register.[8] With this, unilateral abolition could be observed in peripheral facial lesions or central pontine disorders. In a large clinical and neurophysiological study performed by Urban and colleagues, with electromyogram of the transverse auricular muscle of 25 healthy volunteers and 1,186 pa-

A videotape accompanies this article.

*Correspondence to: Adriano Jiménez-Escrig, S. de Neurología, Hospital Ramón y Cajal, 28034 Madrid, Spain.
E-mail: adriano.jimenez@hrc.es

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tients, they found bilateral coactivation with lateral gaze in 96% and ocular convergence in 65% of subjects.[2] In patients with various brainstem diseases such as multiple sclerosis or ischemic disorders, there was an absence of activity in muscles of one or both ears during lateral gaze in one or both directions. The most frequent abnormality reported in this series was absence of transverse auricular muscle activity homolateral to the lateral ocular gaze. However, apparition of a transient oculo-auricular phenomenon secondary to a vestibular abnormality has not been reported previously.

The patient had an acute vertigo with clinical data and neuroimaging that point to a peripheral vestibular origin. We believe that this patient is one of the normal subjects in the population who has a prominent oculo-auricular phenomenon. Oculo-auricular phenomenon is seen more clearly during saccades; in this case, the fast phases of the nystagmus, because saccades depend on high frequency, high intensity burst of activity in neurones, and extra-ocular muscles. During this high-intensity activity in extra-ocular nuclei neurones, there is also more chance to achieve higher recruitment of facial nerve motor neurones, producing a visible oculo-auricular phenomenon. These movements of auricle can be mistaken for a movement disorder, but it must be considered a benign condition, more prominent in some subjects than in others; it does not compel further exploration.

Legends to the Videotape

Segment 1. The patient has horizontal nystagmus, with synchronic auricle contractions. Detailed images of ocular and auricular movements are shown (note that these images are sequential, not simultaneous).

Segment 2. After the vertigo has resolved, the ocular movements are normal and the auricle movements have almost disappeared.

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