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Clinical/Scientific Notes

Implantable Venous Access System for Apomorphine Infusion in Complicated Parkinson's Disease

Subcutaneous infusion of apomorphine for 12 hours per day is an effective means of controlling on–off fluctuations and dyskinesias in patients with advanced Parkinson's disease (PD) resistant to other treatment.[1,2] However, this technique requires reinsertion of the injection needle into the skin of the abdominal wall at least daily. Twenty-five percent of such patients develop unsettling and distressing skin reactions at the injection site, and many of these patients increasingly find that the absorption of apomorphine becomes unpredictable and unreliable. We describe an alternative to subcutaneous delivery of apomorphine, namely, intravenous infusions through a conventional catheter completely implanted into the superior vena cava, as is used for chemotherapy for cancer.

The device (Port-A-Cath, Pharmacia Inc, Milan, Italy) is a totally implantable system composed of a silicone rubber diaphragm housed in a titanium port connected to a polyurethane catheter. Under local anesthesia, the catheter is inserted through a small skin incision under the clavicle into the left suclavian vein (in right-handed patients) and is then maneuvered into the superior vena cava under radiologic control. The proximal end of the catheter is then attached to the titanium port which is embedded in a small subcutaneous pocket under the chest wall. Access is gained by puncturing overlying skin and the rubber diaphragm with a specially designed needle attached to a programmable pump (Cronopar, Canè, Turin, Italy) which delivers 10 mg/mL apomorphine at an appropriate rate (5–10 mg/hr) sufficient to maintain the patients ''on'' and mobile throughout the infusion. In addition, for optimum benefit, such patients required oral levodopa (approximately 300–600 mg per day in two to four doses). The infusion pump also has a bolus function which can be used to deliver extra doses of apomorphine, if required; an advantage of the intravenous route is that such boluses of apomorphine take effect within minutes. Another advantage is that the dose of apomorphine required for both the infusion and the boluses is less than that needed using the subcutaneous technique resulting in cost savings. Patients should be checked for clotting factors and cardiac function. The rubber diaphragm can be punched up to 3000 times. In practice, the use of this technique in patients with Parkinson's disease required changing the needle every 15 days, which can be done by patients or caregivers themselves. At the same time, the system should be flushed with saline and heparin.

We have treated seven patients with advanced PD using this technique for periods of 1–13 months. They were chosen because they had previously been successfully managed with subcutaneous apomorphine infusion but developed problems with skin and unreliable responses. Switching to the intravenous route restored a predictable response to apomorphine infusion in all cases. Before implantation the patients had been receiving 6.18 mg/hr (standard deviation [SD] 1.73) and after implantation they required 4.25 mg/hr (SD 0.84). We have encountered no problems with this technique; theoretically, there is a risk of infection and thrombosis. However, with careful attention to antisepsis and the use of regular heparin flushing of the system, these have not proved to be a problem so far. Provided long-term safety for this technique can be shown, it may turn out to be the best way of delivering apomorphine infusion in patients with advanced PD.

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Hemifacial Spasm in Parkinson's Disease

Hemifacial spasm (HFS) is a disorder characterized by involuntary clonic contractions or twitches on one side of the face. The pathophysiological basis for HFS that has been proposed is that compression of the facial nerve by normal or abnormal vascular structures at its exit from the brain stem induces abnormal excitation of motoneurons in the facial nerve nucleus.[1] Recently, we have encountered patients with Parkinson's disease (PD) in whom HFS was present. We present

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clinical data suggesting that the coexistence of the two disorders does not appear to be a chance phenomenon but rather that the abnormal brain stem function in patients with PD contributes to the generation of HFS.

Eight patients (three men and five women) with PD and HFS were studied. The age was 68.0 ± 6.7 years (mean ± standard deviation [SD]; range, 60–81 yrs). Their disabilities were not severe and their Hoehn-Yahr stages were 2–3 (mean ± SD: 2.4 ± 0.5). The diagnosis of idiopathic PD was made clinically on the basis of the following criteria: the presence of at least two of the classic symptoms of PD (akinesia, rigidity, rest tremor, and postural instability), the absence of severe orthostatic dysregulation, ataxia, dysmetria, pyramidal signs, or oculomotor disturbance. All patients responded well to levodopa. They had been regularly followed up by us at 1- to 3-month intervals. The brain computed tomography or magnetic resonance image of the patients revealed no cerebrovascular disorders (leukoaraiosis, lacunar infractions) that could potentially induce parkinsonism, atrophy, or degenerative changes in the cerebellum, brain stem, or basal ganglia. The symptomatic features of HFS in our patients were typical. The hemifacial spasm began in the orbicularis oculi muscle and gradually spread to other muscles on the ipsilateral side of the face including the platysma. The paroxysms of HFS were not rhythmic but irregular and were induced by voluntary movements of the face. There was no rhythmic twitching or grimacing suggesting that they did not have facial myoclonus or dystonia, which is occasionally seen in multiple system atrophy. As has been reported, patients with PD occasionally have blepharospasm or Meige's syndrome.[2] However, in our patients, facial spasm was observed only on one side of the face. Moreover, blink reflex studies were performed in five of the patients, and revealed unilateral synkinetic response between the orbicularis oculi and oris muscles in all five, supporting the diagnosis of HFS. Seven patients had HFS involving the right side, and in one patient the left side of the face was involved. Usually, there is an asymmetric appearance of PD symptoms, and the patients in our study also had asymmetric symptoms from the onset of the disease. Interestingly, in seven of the eight patients, HFS occurred on the side predominantly affected by the parkinsonian symptoms. Moreover, all the patients had noted that the HFS and the parkinsonism developed almost simultaneously. Therefore, it appears possible that a relationship exists between the development of HFS and parkinsonian symptoms.

The pathologic basis of HFS and PD are clearly different: the former is caused by neurovascular compression and the latter is caused by degeneration of dopaminergic neurons in the substantia nigra. However, both disorders have been reported to have, in common, abnormal brain stem functioning as reflected by increased excitability of the reflex blink mechanism. Clinically, a less habituation of blinking, induced by tapping the glabella, known as Myerson's sign, is well known in PD patients. In addition, the reflex blink hyperexcitability has been electrophysiologically demonstrated in the PD patients.[3] The exact mechanism underlying the blink reflex hyperexcitability in PD still remains undetermined; however, recent reports have revealed that the basal ganglia output to the brain stem plays a crucial role in the modulation of blink reflex excitability.[4] Similarly, the blink reflex hyperexcitability has also been demonstrated in HFS, even on the non-affected side.[5] Our speculation is that the abnormal brain stem function in PD, which is the cause of the reflex blink hyperexcitability, may trigger or exert a facilitatory influence on the generation of HFS.

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Hemiparkinsonism-Hemiatrophy With Brain Hemihypoplasia

Hemiparkinsonism was first described as a tardive complication of body hemiatrophy by Klawans in 1981[1] (hemiparkinsonism-hemiatrophy syndrome [HPHA]). The condition can be characterized by the association of other symptoms and signs: early and premedication hemidystonia, variable response to levodopa treatment, and contralateral brain atrophy. The literature contains eight reports on a total 36 cases in recent years.[1–8] Although diagnostic criteria have been proposed by Buchman[2] and Giladi,[4] these 36 patients are rather heterogeneous. Some studies[5,7] compared HPHA with unilateral idiopathic Parkinson's disease (IPD) in terms of functional metabolism. [^{18}F]Fluorodopa ([^{18}F]dopa) and positron emission tomography (PET) studies showed that severe and asymmetric abnormalities in presynaptic dopaminergic activity affected both illnesses,[7] whereas [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET showed that a reduction in glucose metabolism at the nigrostriatal level occurred in HPHA alone.[5,7] In another study, [^{18}F]fluoroethylspiperone ([^{18}F]FESP) PET revealed a normal binding of postsynaptic striatal dopaminergic receptors in one patient affected by HPHA despite the poor response to levodopa treatment.[5]

In the present report, we describe neurophysiological findings for and functional imaging of dopaminergic nigrostriatal

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pathways in a patient with an HPHA-like syndrome. The most interesting findings were the association of a brain hemihypoplasia (and not hemiatrophy) contralateral to the side affected by parkinsonism and the presence of eye movement abnormalities. We discuss the classification of this particular condition in the HPHA syndrome group.

Case Report

A 45-year-old, right-handed man was seen in 1990 for postural and rest tremor, both confined to the left arm. Family and personal history were unremarkable. In particular, the patient was born after an uncomplicated pregnancy and delivery, and there was no history of brain injury or exposure to toxins and medications associated with parkinsonism. General examination showed congenital left hand and foot phalange hypoplasia. There was evidence of left hand postural and rest tremor with slight ipsilateral cogwheeling rigidity and bradykinesia (Hoehn and Yahr scale I).[9] Dystonia or signs of pyramidal, sensory, or mental impairment were not detected. Anticholinergic drugs were given (6 mg biperidene) without improvement. During the next 2 years, the patient worsened remarkably, and he developed a slight rigid-bradykinetic contralateral syndrome with axial involvement (Hoehn and Yahr scale III).[9] Levodopa/benserazide at a dosage of 100/25 mg was administered at up to 250 mg four times a day for 6 months with slight and transient response.

Routine hematochemical, electrocardiogram, and chest x-ray were within normal limits. Hand and foot x-ray detected a hypoplasia of the distal phalanges on the left side. Autonomic cardiovascular function, which was screened by means of tilt table, handgrip, deep breathing, 30–15 and Valsalva tests was normal.

Tremor was studied by means of electromyographic (EMG) recording from four different muscles of the upper limbs (biceps brachii, triceps brachii, finger extensors, and finger flexors) to analyze agonist-antagonist patterns. EMG activity was present during rest and postural position, both in the proximal and in the distal muscles examined; brief synchronous bursts in agonist and antagonist muscles were interrupted by alternating EMG activity. This pattern was similar for rest and postural tremor of the left arm, except for the burst frequencies, which were 6–8 Hz at rest and 8–11 Hz during postural position (against gravity). No tremor was observed in the right arm. Additionally, long latency responses (LLR) were evaluated in accordance with Deuschl and Lücking[10] with recordings from the abductor pollicis brevis muscle during rest and slight voluntary contraction following stimulation of the radial nerve sensory fibers at the wrist. No LLRs were recorded from the abductor pollicis brevis muscle during rest. In contrast, such responses were obtained during slight contraction, and they showed two components, namely LLRI and LLRII in the affected side, whereas only LLRII was recorded in the unaffected side.

Basal rest EEG showed non-constant alpha activity at 9–10 c/s over the occipital areas of both the hemispheres with partial reaction to eye opening. Hyperventilation for 3 min and intermittent light stimulation did not modify the basal EEG pattern. Slow theta waves (4–5 Hz) recurred sporadically or in brief sequences over the temporo-occipital areas with right-sided prevalence.

We evaluated both reflexive saccades and triangular ramp smooth pursuit eye movements by means of the bitemporal electrooculographic technique. We detected a saccadic hypometria (lower normal limit: 0.87) which was slight for rightward (mean value: 0.85) and more pronounced for leftward saccades (mean value: 0.76); this asymmetry proved to be significant ($t = 2.4$; $p = 0.021$). Saccadic latency (upper normal limit: 316.8 ms) was normal for rightward saccades (mean value: 286.78 ms) and markedly delayed for leftward saccades (mean value: 413.07 ms); this asymmmetry proved to be significant too ($t = 4.3$, $p < 0.001$). Smooth pursuit target velocity-performance index relationship (the performance index expresses a ratio between eye movement after saccade removal and target movement) showed borderline values in both directions. Performance index values showed a slight asymmetry ($F[1.36] = 3.94$; $p = 0.055$) in that they were lower for left to right (mean value: 0.51) than for right to left (mean value: 0.58) movements. Pattern reversal visual-evoked potentials, brain stem auditory-evoked potentials, and short latency somatosensory-evoked potentials (SSEP) obtained by stimulation of both median and tibial nerves were all normal.

Magnetic resonance imaging (MRI) scan was performed. A sequence of 128 coronal oblique T1-weighted FFE images perpendicular to the long axis of the temporal lobe was obtained and transferred to a SUN Gyroview-HR workstation (Philips, Holland) and analyzed with a CAMRA S400 Allegro application (ISG Technologies Inc) by segmentation techniques and automatic volumetric reconstruction. The anatomic guidelines were fixed according to anatomy atlas.[11] Volumes were measured in cubic centimeters as absolute volume and, for the lobes, as percentage of total brain volume. A skull and encephalic asymmetry with hypoplasia of the right side was detected (frontal lobe: right/left 0.775 [range in age-matched control subjects: 0.95–1.05], temporal lobe: right/left 0.896 [1.03–1.05], parieto-occipital area: right/left 0.943 [1.05–1.08]). The right lateral ventricle was smaller than the contralateral (Fig. 1). A bilateral mild cortical atrophy was detectable. Regional cerebral perfusion was assessed using ^{99m}Technetium-bicisate dihydrochloride (^{99m}Technetium N, N″-1,2-ethylene-diylbis-L-cisteine diethyl ester dihydrochloride [^{99m}Tc-ECD]) and single photon emission computed tomography (SPECT).[12] A single-head rotating gamma camera (Toshiba 901 ASA, Japan) equipped with a low-energy, high-resolution collimator was used. Transaxial sagittal and coronal slices were reconstructed with a standard backprojection algorithm. SPECT study showed a global hypoperfusion of the right hemisphere (Fig. 2).

In June 1995, a SPECT study using [^{123}I]-2-b-carbomethoxy-3-b-(4-iodophenyl)-tropane ([^{123}I]β-CIT) was performed to evaluate dopamine transporter activity.[13] Transaxial images were acquired 24 hrs after intravenous injection of the tracer with a brain-dedicated camera (CERASPECT, DSI, Boston, MA, U.S.A.). Specific-to-nondisplaceable striatal uptake ratios were calculated by dividing the activity in the head of the caudate and putamen by that in the occipital cortex in accordance with previous studies.[14] Uptake ratios were compared with values obtained in six control subjects (mean age ± standard deviation = 62 ± 7.6).[15] A marked bilateral but asymmetric reduction of tracer uptake was observed both in caudate (right 40%, left 16% compared with control subjects) and in putamen (right 70%, left 55%; Fig. 3A). Subsequently, a PET study using [^{18}F]FESP was performed to evaluate D_2 dopaminergic activity.[16] Images were acquired for 2 hours after injection of the tracer by means of a high-resolution (4.3 mm) PET

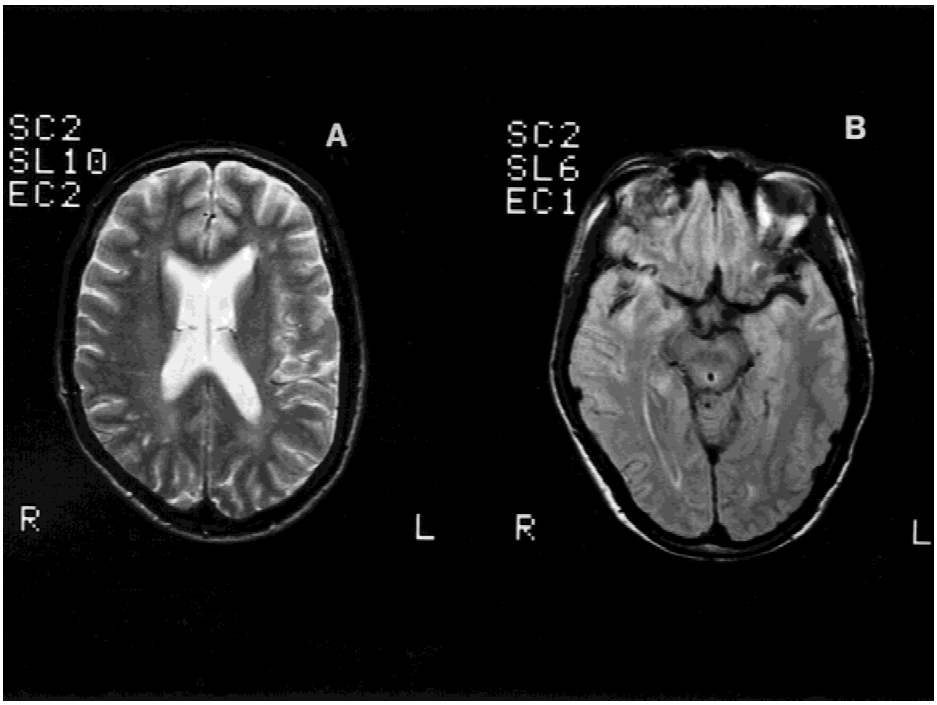

FIG. 1. (**A** and **B**) MRI (0.5 T) axial scans (T2-weighted [SE, 7 mm thick, 0.7 mm gap, TR 2500, TE 40/100]) demonstrate skull and encephalic asymmetry and a hypoplasia of the right side. There is a mild enlargement of the ventricular system with smaller right lateral ventricle and mild cortical atrophy.

tomograph (GE-advance). The images acquired between 90 and 120 min after injection were visually inspected for the presence of asymmetries. An intense and symmetric [^{18}F]FESP uptake in both caudate nuclei and putamen was observed (Fig. 3B).

Discussion

In the present case, the clinical evidence of left skeletal hypoplasia with hemiparkinsonism suggests the diagnosis of HPHA.[1–8] However, in contrast with the other 11 reports of HPHA associated with contralateral brain atrophy,[4,5,7] MRI here demonstrated a hypoplasia of the right hemisphere, ventricular system, and skull. Other morphologic and functional abnormalities, such as the hemispheric hypoperfusion, and the eye movement disorders indicated a diffuse right hemispheric involvement. The morphologic distinctions between atrophy, caused by degeneration of the fully developed nervous system, and hypoplasia, caused by an arrest of maturation of the nervous system, are not fully defined.[17] On the clinical basis, the disease progression is interpreted to be indicative of a degeneration disease. However, in the literature, the term ''cerebral hemiatrophy'' is often used to define cases of ''cerebral hemihypoplasia.''[18] Brain hemihypoplasia, in its extreme variants, has been described as ''a hemisphere in miniature.''[19] It is a rare condition that has never been observed in association with parkinsonism or other tardive extrapyramidal disorders but is generally related to congenital severe encephalopathies, intellectual retardation, and epileptic seizures.[19] In general, it is plausible to hypothesize toxic, metabolic, or infective factors as virtual causes of cerebral prenatal injury, although the etiology of this neuronal atrophy is, at present, only speculative.[19] We hypothesize that brain hemihypoplasia and contralateral skeletal atrophy with parkinsonism in our patient derived from a common cause.

Functional imaging studies with [^{123}I]β-CIT SPECT disclosed a bilateral but asymmetric presynaptic deficit resembling the pattern observed in one of three cases studied using [^{18}F]dopa and PET.[7,8] The dopaminergic loss involved both the caudate and putamen similar to the case by Lang.[8] Previous studies with [^{18}F]dopa and the dopamine reuptake site inhibitor

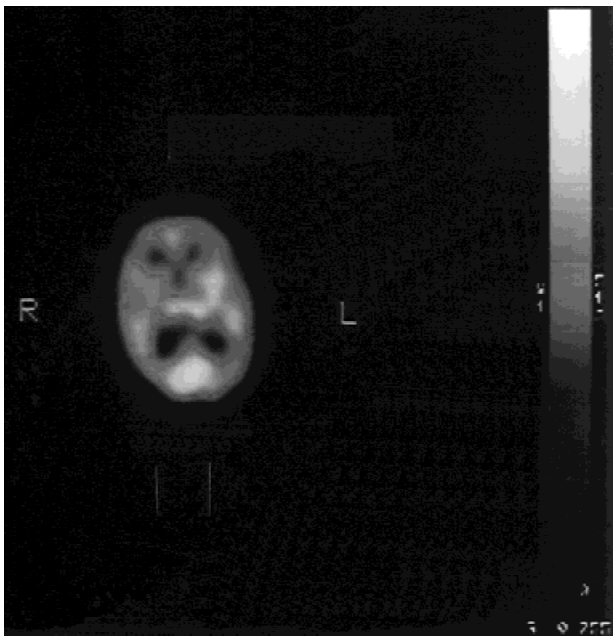

FIG. 2. ^{99m}Tc ECD SPECT shows a global hypoperfusion of the right hemisphere.

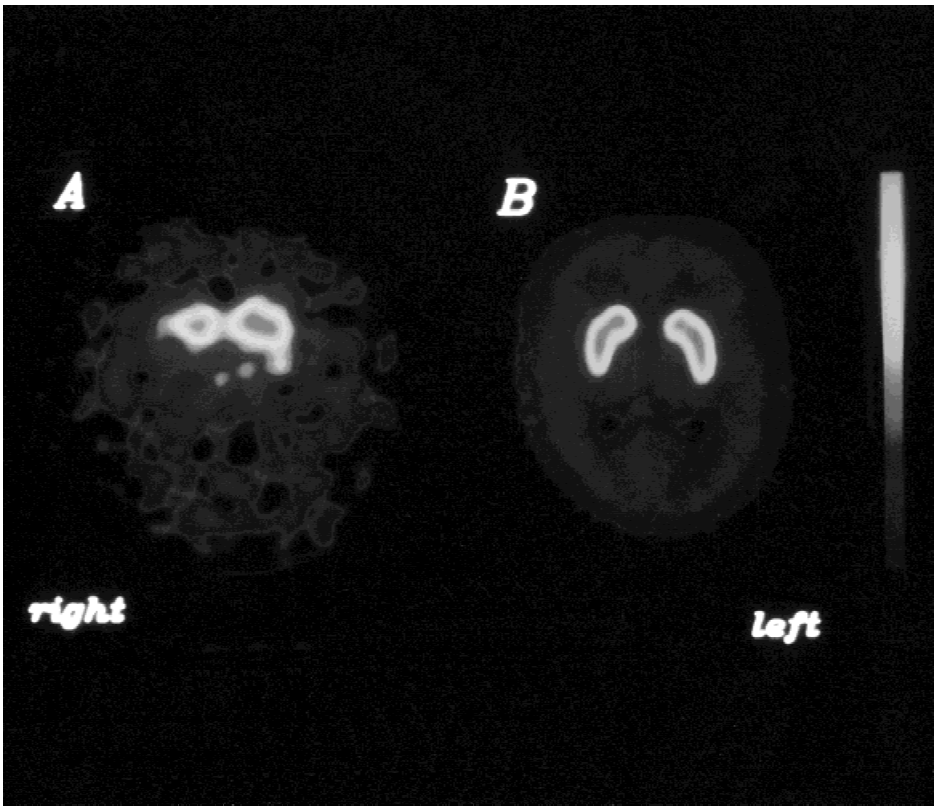

FIG. 3. (**A**) [^{123}I]β-CIT SPECT detects a mild bilateral but asymmetric reduction of tracer uptake more marked in the putamen than in the caudate (see text). (**B**) [^{18}F]FESP PET demonstrates an intense and symmetric FESP uptake in both caudate nuclei and putamen.

[^{11}C]nomifensine[20] showed that these patterns, of uniform striatal dopaminergic loss, indicate parkinsonism rather than IPD. [^{18}F]FESP PET studies, both in our patient and in the case of Przedborski,[5] showed that striatal dopamine D_2 receptors were probably spared despite the unsatisfactory levodopa responsiveness observed in both patients. In our case, levodopa treatment only lasted a few months and was stopped 3 years ago, so its pharmaphysiological effect should no longer strongly influence D_2 receptor sensitivity. However, it is possible that [^{18}F]FESP PET fails to detect pathologic reduction of D_2 receptors because of a compensatory supersensitivity which in turn is the result of chronic denervation.[21] The sparing of D_2 receptors seems to exclude the possibility of a hypoxic/ischemic pathogenetic mechanism which, according to experimental evidences, would lead to D_2 receptors' persistent decline.[22] In conclusion, we think the resistance of some HPHA patients to levodopa depends on damage of other basal ganglia or brain stem connections, such as in other Parkinson-like syndromes.[23]

^{99m}Tc-ECD SPECT showed a global hypoperfusion of the right hemisphere, which was probably subsequent to a reduction in cerebral metabolism.[24] This finding resembled observations on atypical parkinsonism[25] and on one case of HPHA.[5]

Further information about cortical and extrapyramidal impairment have been collected from neurophysiological findings. The impairment of right cortical areas located within the temporal-parietal-occipital junction may explain abnormalities in reflexive saccades and in smooth pursuit.[26] A basal ganglia dysfunction is not a likely explanation for this asymmetry despite the extrapyramidal signs in our patient being mainly located on the left side, because asymmetric distribution of eye movement abnormalities was not reported in those papers that addressed this issue in patients with unilateral Parkinson's disease.[27,28]

The high frequencies and the agonist-antagonist pattern of the tremor are atypical for IPD[29,30] without being indicative of specific extrapyramidal disorders.

In our patient, the diagnosis of secondary parkinsonism rather than IPD was justified by the early onset of symptoms, the lack of drug sensitivity, the atypical features of the left hand tremor, and the decreased right cerebral blood flow, as well as by the neurophysiological findings of diffuse encephalopathy. The absence of vegetative impairment, of cerebellar involvement, and of specific MRI findings after 5 years of follow up differentiated this from multiple system atrophy (MSA) syndromes.[31]

Przedborski et al.[7] observed that in most HPHA cases the clinical course was benign. In contrast, our patient worsened rapidly and developed an asymmetric drug-resistant parkinsonism in a few years, as Giladi[4] reported in one of 11 cases. According to the diagnostic criteria of Buchman[2] and Giladi,[4] we can classify this case as ''definite HPHA,'' because 32 of the total 36 reports[1–8] in the literature have been classified.

The most significant finding of this case relies on the presence of hemispheric hypoplasia associated with a full clinical phenotype.

Because in HPHA no pathologic data are available and the signs, clinical course, and functional imaging findings of this syndrome vary substantially from case to case, it is hard to identify a reference model. Probably different pathophysiologi-

cal mechanisms explain this phenotypic heterogeneity.[32] Perhaps the plural term HPHA ''syndromes'' defines this large group of conditions more appropriately.

In conclusion, the present report highlights the concept that brain and skeletal asymmetry are possibly associated with early-onset parkinsonism, but it confirms the heterogeneity of the clinical-instrumental patterns of these secondary extrapyramidal disorders.

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Brain Stem Cystic Astrocytoma Presenting With ''Pure'' Parkinsonism

Although degenerative or idiopathic Parkinson's disease accounts for most cases of parkinsonism, reports of parkinsonian syndromes secondary to intracranial mass lesions are increasing. Husag et al.[1] and Polyzoidis et al.[2] reviewed, respectively, 75 and 49 cases of brain tumors and secondary parkinsonism. We found that almost all the 22 cases reported in the last 12 years were the result of supratentorial mass lesions that resulted in compression or distortion of basal ganglia,[3–7] whereas midbrain infiltration or compression was rare. Moreover, in the latter instance, the parkinsonian syndrome was usually associated with other neurologic signs and was not the main neurologic manifestation.[2,8]

We report the case of a young woman in whom a mild parkinsonian syndrome was the major clinical manifestation of a brain stem cystic astrocytoma.

Case Report

A 39-year-old woman was initially observed in the Department of Internal Medicine of our School of Medicine because of palpitations and a history of occasional vertigo. A general physical examination was unremarkable. Laboratory data, including thyroid hormones, were normal. Electrocardiograph, radiographs of the cervical spine, extracranial duplex sonography, and vestibular function tests revealed no abnormalities. She was then seen by a neurologist who diagnosed an extrapyramidal syndrome characterized by hypomimia, discrete bradykinesia of the right hand (difficulty in buttoning clothes and slowing of finger tapping), micrographia, occasional tremor of right and left limbs at rest, and absence of right arm swing during walking. There was mild bilateral rigidity which was more evident in the left arm. The patient scored 15 on the Unified Parkinson's Disease Rating Scale (UPDRS)—Section III.[9] Muscle strength was preserved. Tendon reflexes were normal and symmetric. Plantar responses were flexor. There was no evidence of papilledema or cranial nerve involvement. Gait was normal. Right-side propulsion during closed-eye walking was observed on one occasion. No cerebellar dysfunctions or sensory deficits were found. A levodopa test[10] did not alleviate symptoms.

Magnetic resonance imaging (Fig. 1) revealed a round cystic lesion (1.8 × 1.8 × 2.2 cm) which was hypointense in T1- and hyperintense in T2-weighted images. The lesion filled the left pontomesencephalic region of the brain stem and extended to the left superior cerebellar peduncle. After administration of gadolinium-GTDA, a small enhancing nodule was visible in the lower part of the cyst; there was no enhancement of the cyst wall.

A cystic astrocytoma of the brain stem was diagnosed, and the patient was admitted to the Department of Neurosurgery. A microsurgical technique was used to incise the ventricular floor and a small amount of yellow fluid was removed from the cyst; then a tumor nodule measuring a few millimeters was removed from the lower part of the cyst wall. Finally, a small silastic catheter was inserted between the cyst and the fourth ventricle to avoid closure of the cyst. The histologic diagnosis was a pilocytic astrocytoma.

In the postoperative period, the patient had ataxic gait which gradually regressed in the following weeks. Two weeks after the operation, the cyst was no longer visible on a computerized tomographic scan (Fig. 2). Two months after surgery the patient was able to walk unassisted. The patient no longer had vertigo or resting tremor; bradykinesia of the right hand, rigidity, and hypomimia had regressed during the pre-

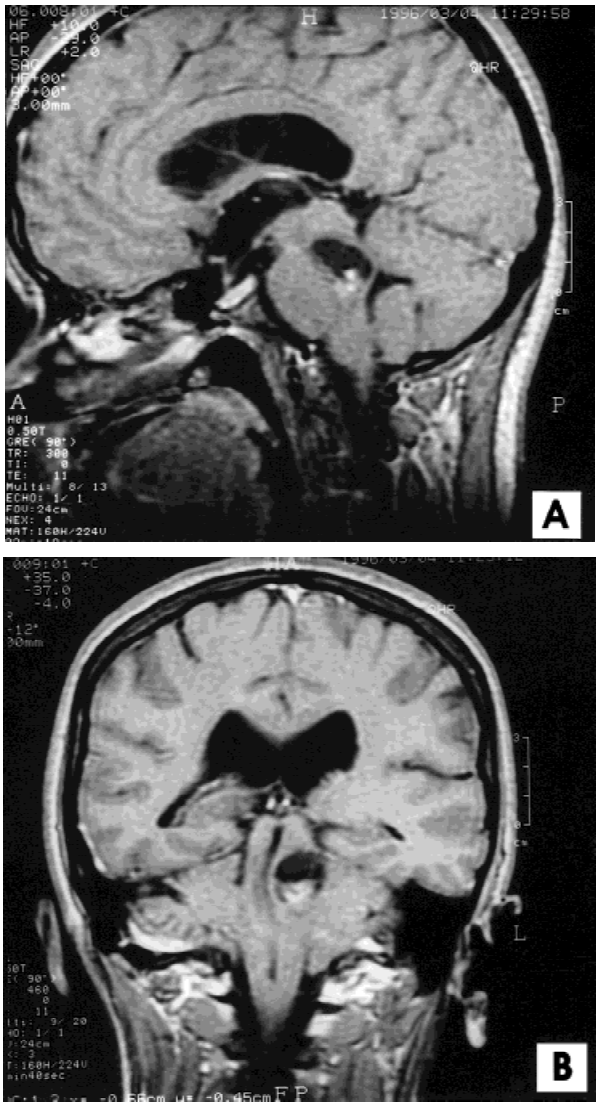

FIG. 1. Preoperative magnetic resonance imaging. T1-weighted sagittal (**A**) and coronal (**B**) images, after administration of paramagnetic contrast (Gadolinium-GTDA): round cystic hypointense lesion filling the left pontomesencephalic region of the brain stem; an enhancing nodule is visible in the lower part of the cyst.

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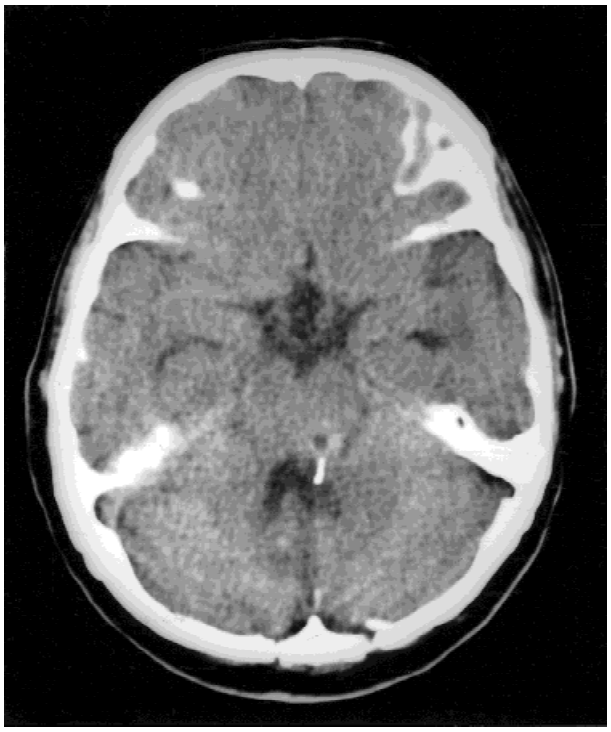

FIG. 2. Postoperative computerized tomographic scan, axial section after contrast administration: disappearance of the cyst; a small catheter is visible between the collapsed cystic cavity and the fourth ventricle.

operative period. The right arm swing reappeared. The UPDRS—Section III score was 5.

Discussion

Intracranial mass lesions that cause parkinsonism are usually located in the supratentorial compartment.[1–3,6,11,12] Forty-two of the 49 cases reviewed by Polyzoidis and colleagues had supratentorial brain tumors and seven had infratentorial lesions,[2] which is a ratio of 6:1. Of the 22 cases reported during the last 12 years reviewed by us, only one had an infratentorial tumor,[13] whereas the remaining 21 were associated with supratentorial mass lesions.[3,5,6,11,12,14–22] Meningiomas[1,3,5,6,12,18,20] and gliomas[14,17,19,22] accounted for most supratentorial lesions inducing parkinsonism; subdural hematomas,[23] ependymomas,[7] craniopharyngiomas,[24] and pituitary adenomas[25] were more rare.

Three pathogenic mechanisms have been proposed to explain parkinsonism associated with supratentorial mass lesions: (1) lesion of striatal postsynaptic cells secondary to mechanical pressure or intrinsic involvement of the basal ganglia[4,7]; (2) impairment of the striatal output to the supplementary motor area[6,22]; and (3) compression and/or distortion of nigrostriatal pathways.[14,24]

Infratentorial tumors, both cerebellar[26,27] and brain stem neoplasms,[2,8,13] are rarely associated with secondary parkinsonism. In such cases, compression and/or infiltration of the midbrain could damage the nigral dopaminergic neurons or their axons.[13]

More than a century ago, Blocq and Marinesco[8] first described the autoptic finding of an olive-sized tubercoloma of the cerebral peduncle that involved the substantia nigra causing secondary parkinsonism; this was the first indication that this region played a role in the etiology of parkinsonism. More recently, Gherardi et al.[13] described postmortem findings of a brain stem lymphoma associated with parkinsonism; the tumor had infiltrated the substantia nigra causing neuronal loss, thus resulting in the extrapyramidal syndrome. In our case, it appears that compression of the substantia nigra by the tumoral mass was responsible for the parkinsonism.

The signs and symptoms of brain stem tumors are usually caused by enhanced intracranial pressure, pyramidal tract, and/or cranial nerve involvement[28]; extrapyramidal signs are rare but they are generally masked by the former. Ours is the first report of a brain stem cystic astrocytoma giving rise to a ''pure'' parkinsonian syndrome. Thus far, in patients with intracranial tumors, tremor and rigidity has involved the contralateral side[4,6,24] or, less frequently, the same side.[21] In our patient, symptoms were contralateral to the lesion, but rigidity unexpectedly prevailed on the ipsilateral side.

Consistent with other reports,[6,21,24] our patient was not levodopa-responsive, although a partial regression of symptoms has been described in parkinsonism secondary to a brain tumor.[22,29] Clinical findings can regress after tumor resection[2,4]; however, in our patient tremor disappeared but a degree of bradykinesia and rigidity remained.

Brain tumors are an uncommon cause of parkinsonism. However, because extrapyramidal symptoms may be the only clinical finding of a cerebral mass (this study),[1,3,5,20] neuroimaging should be considered not only for those patients who exhibit atypical clinical presentation or poor response to levodopa therapy, but for all parkinsonian patients at the time of diagnosis.

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Postoperative Parkinsonian Tremor in a Patient With a Frontal Meningioma

Symptomatic parkinsonism may result from a number of causes, in particular, exposure to dopamine receptor antagonists such as neuroleptics. Intracranial neoplasms represent an uncommon cause of parkinsonism (with or without resting tremor). Krauss et al.[1] reported an incidence of 0.3% in a prospective evaluation of 907 patients with supratentorial tumors. Patients with hypokinesia combined with tremor and/or rigidity or isolated rest tremor and tumors not infiltrating the basal ganglia and the thalamus were included. To verify the diagnosis of a tumor-induced movement disorder, the authors required a temporal relationship between onset of symptoms and diagnosis of the tumor and the demonstration of postoperative improvement. To our knowledge, transient parkinsonian tremor appearing during postoperative recovery from removal of a supratentorial tumor has not been recognized. We report a case 1 month postoperatively who had a frontal meningioma who presented with isolated transient pill-rolling resting tremor that spontaneously disappeared after 8 weeks.

Case Report

In July 1996, this woman presented with a series of three tonic-clonic grand mal seizures at the age of 59 years. She was initially seen by a consultant neurologist who reported no focal deficit. A cranial computed tomography (CT) scan, however, revealed a frontal tumor arising from the anterior falx with homogeneous contrast enhancement. There was marked perifocal edema extending into the subcortical white matter. The CT changes were suggestive of a meningioma; the patient was then referred to the University Department of Neurosurgery, Innsbruck, for further assessment and therapy. The diagnosis of falx meningioma was confirmed by both angiography and magnetic resonance imaging scan (Fig. 1). The tumor was removed August 13, 1996, following endovascular embolization; postoperative recovery was unremarkable except for deep vein thrombosis of a lower extremity which was treated appropriately. The patient was given 200 mg carbamazepine three times a day and discharged after 3 weeks. On September 19, 1996, the patient was admitted to her local hospital because of another grand mal seizure. Neurologic examination several days later revealed intermittent resting and postural tremor variably affecting the arms and legs uni- or bilaterally. There were no further signs of parkinsonism and the remaining neurologic examination was unremarkable except for inconsistent hemihypesthesia on the left side. The patient was referred to the Department of Neurology, Innsbruck, for further assessment. Neurologic examination was entirely normal except for inter-

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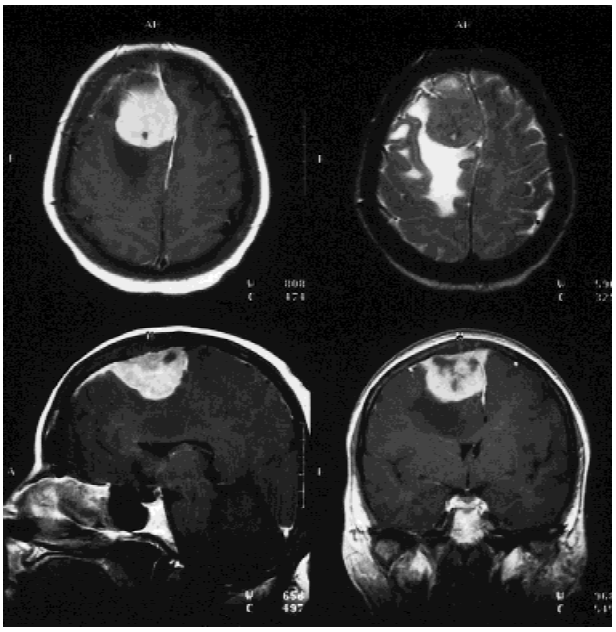

FIG. 1. T1-weighted MRI scan showing a right-sided frontoparietal meningioma with areas of low density corresponding to focal calcification. The tumor is surrounded by a large perifocal edema resulting in considerable midline shift and compression of lateral ventricles.

mittent resting tremor of moderate amplitude which variably affected the right or left arm and both legs (see videotape segment 1). A routine electroencephalogram was reported as abnormal with diffuse theta activity and right-sided paroxysmal slow waves in anterior leads. Cranial CT scan showed a mainly right-sided frontoparietal hypodensity at the site of tumor resection (Fig. 2). Dopamine transporter function measured by ^{123}I-β-CIT SPECT scanning was within the low normal range (delta total 3.12; controls 4.52 ± 1.42 [mean ± 1 standard deviation]). In contrast, ^{123}I-IBZM-SPECT scanning was abnormal with bilaterally reduced striatal/cerebellar (s/c) ratios (s/c ratio right 1.65, left 1.60; controls 1.78 ± 0.12 [mean ± 1 SD]. ^{99m}Tc-ECD-SPECT scanning showed bilateral, mainly right-sided hypoperfusion corresponding to structural imaging. There were no other areas of hypoperfusion. A trial of levodopa treatment offered to the patient was rejected, however, tremor intensity was mild and did not result in significant handicap. In June 1997, the patient was seen again for follow up. She reported that her tremor had slowly resolved by mid-December 1996 after approximately 8 weeks and there had been no further seizures. Neurologic examination was entirely normal (videotape segment 2). A repeat CT scan revealed a smaller right-sided frontal parasagittal defect without definite residual edema. Dopamine D2 receptor binding had returned to normal (s/c ratio right 1.71, left 1.79; controls 1.78 ± 0.12 [mean ± 1 SD]).

Discussion

A number of patients with rest tremor and other signs of PD as presenting features of frontal meningiomas or other supratentorial neoplasms have been reported; however, in most instances, tremor improved or disappeared postoperatively.[1] This postoperative improvement has been regarded as necessary for establishing a causal relationship between the appearance of rest tremor and other signs of parkinsonism and supratentorial tumors. In contrast to previous reports, our patient developed a transient rest and postural tremor only 4 weeks postoperatively. At this stage, CT imaging revealed a marked, mainly right-sided frontoparietal hypodensity that subsequently resolved to a smaller frontoparietal defect. The initially marked hypodensity may have been partly related to residual peritumoral edema or disturbed venous drainage. In addition, IBZM SPECT scanning initially showed a bilateral reduction of dopamine D2 receptor binding that subsequently normalized with disappearance of the tremor.

The pathophysiological mechanism leading to the postoperative tremor observed in our case remains uncertain. Carbamazepine treatment was initiated 3 weeks before the onset of resting and postural tremor. In contrast to frequent reports of asterixis,[2–4] rest tremor is not a recognized side effect of carbamazepine treatment. A number of PET studies using 18F-fluorodopa reported an association of isolated rest tremor and abnormal striatal 18F-fluorodopa uptake suggesting a forme fruste of Parkinson's disease (''benign tremulous PD'').[5] The appearance of isolated rest and postural tremor in our patient may therefore represent postoperative unmasking of underlying PD. However, both the lack of additional parkinsonian features during follow up as well as the absence of dopamine transporter dysfunction would dispute this assumption. We therefore suggest that perioperative factors such as local ischemia, disturbed venous drainage, or diffuse hypoxia related to events associated with general anesthesia may have caused impaired nigrostriatal transmission bilaterally leading to the transient rest and postural tremor in our patient. Hypoxic downregulation of dopamine D2 receptors has been reported in experimental ani-

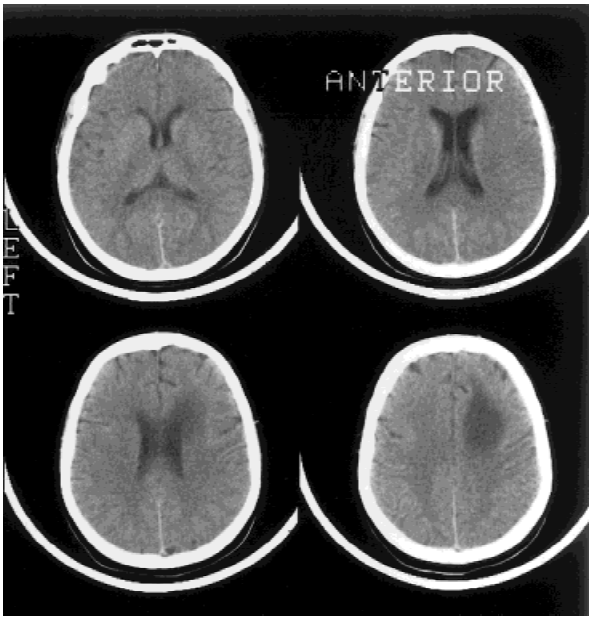

FIG. 2. Postoperative CT scan with reversed sides compared with Figure 1 showing a mainly right-sided sharply demarcated frontoparietal hypodensity at the site of tumor resection. The hypodensity may be partly related to residual peritumoral edema or disturbed venous drainage.

mal models of ischemia.[6] This finding may explain the observed downregulation of striatal dopamine D2 receptors in our patient.

Legends to the Videotape

Segment 1: This segment shows the patient with intermittent resting tremor of moderate amplitude which variably affected the right or left arm and both legs 4 weeks after resection of a frontal meningioma. No other signs of parkinsonism were present.

Segment 2: This segment shows the patient 9 months later after spontaneous resolution of the tremor which disappeared approximately 8 weeks after resection. There are no abnormal signs on neurologic examination.

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Focal Tremor Following Striatal Infarct—A Case Report

It is exceedingly rare to develop an isolated tremor following a striatal lesion. We describe a patient with a coarse resting tremor of his left hand associated with a focal ischemic lesion of the right caudate nucleus and putamen.

Case Report

This 50-year-old man was admitted for treatment of bacterial pneumonia. In addition to his respiratory illness, he also stated that 10 months previously he suddenly developed an involuntary movement of his left arm which had persisted to the present time. His medical history included chronic alcohol abuse, diabetes mellitus, hypertension, and peripheral vascular disease.

The pertinent findings on neurologic examination were largely confined to the motor system. At rest he had a continuous 3.5 Hz tremor of the left hand. The movement consisted

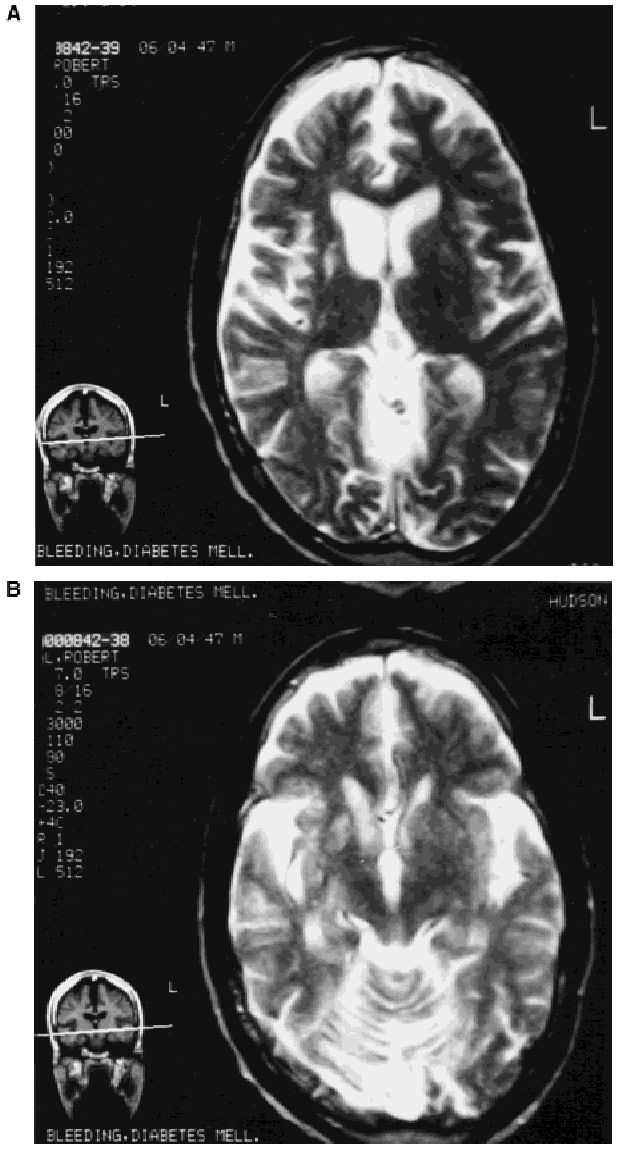

FIG. 1. (**A** and **B**) T2-weighted MRI demonstrating an infarct in the right caudate and putamen with resulting dilatation of the lateral ventricle. Diffuse cerebellar atrophy is also noted.

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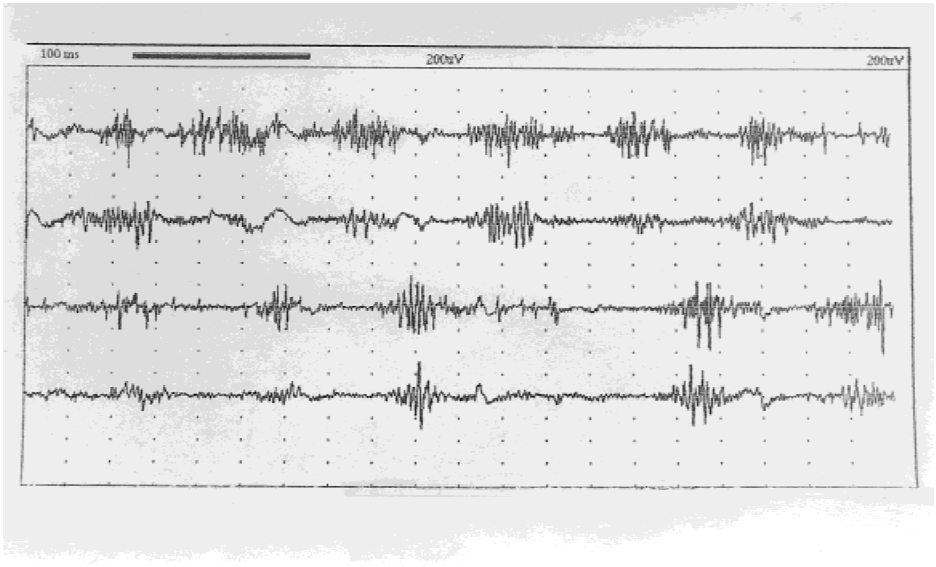

FIG. 2. EMG recorded from surface electrodes demonstrating simultaneous activation of flexor (rows 1 and 3) and extensor (rows 2 and 4) muscles of the left forearm at a rate of approximately 3.5 Hz. Divisions are 0.1 sec (horizontally) and 200 μv (vertically).

predominantly of flexion and extension of the thumb and first two fingers. During periods of tremor, the third and fourth fingers were usually maintained in a flexed posture, although the hand could be easily opened passively and the fingers could extend when the tremor ceased. A callus was present in the palm as a result of the constant movement of the fingertips on the palm surface. The tremor largely disappeared when the hand was sustended or when the index finger was brought to the nose. He could not inhibit the tremor voluntarily but it disappeared when he lightly gripped the mattress as well as during sleep. Strength, tone, and reflexes were normal. Light touch was subjectively decreased in the left hand but position, vibration, pain, stereognosis, and graphesthesia were intact. Gait was also intact.

A computed tomography (CT) scan of the brain showed focal enlargement of the frontal horn of the right lateral ventricle suggesting an underlying infarct of the striatum. This was confirmed on a magnetic resonance imaging (MRI) scan which demonstrated a 1 × 1.5 × 1 cm infarct involving the caudate nucleus and the anterior putamen (see Fig. 1). A moderate degree of diffuse cerebellar atrophy was also present.

When the patient was seen at 4 months' follow up, the tremor was unchanged. There was still no evidence of rigidity or bradykinesia. The gait remained intact. An electromyographic recording of the tremor was performed at that time that demonstrated simultaneous activation of the flexors and extensor groups of the forearm at a rate of 3.5 Hz (Fig. 2). A medication trial was suggested but the patient declined and did not return for further visits.

Discussion

Although movement disorders have been described following striatal lesions, they are most frequently of the dystonic,[1] hemichoreic, or hemiballistic type.[2,3] Tremors are infrequent following lesions of the striatum although lacunar infarctions of this area are often found at autopsy and on imaging studies. It is unclear why this patient developed a severe tremor whereas the majority of patients with lesions that appear similarly placed do not. Perhaps a particular combination of striatal structures must be damaged to produce tremor. Alternatively, it may require the addition of a lesion in some other pathway, for example, in the brain stem, which may have been too small to be detected. This patient had evidence of diffuse cerebellar atrophy on MRI scanning most likely secondary to chronic ethanol ingestion. Although this was asymptomatic, it conceivably might have modified the clinical response to the striatal lesion. In addition, this patient could have had a latent form of idiopathic Parkinson's disease in which the occurrence was accelerated by a lesion that further decompensated his nigrostriatal system.

In our review of the recent literature, we located only two reports of tremors associated with isolated striatal lesions. Dethy and colleagues[4] described an intermittent 5–6 Hz resting tremor of large amplitude which developed 3 months after a pure motor stroke. MRI demonstrated a contralateral ischemic lesion in the left centrum semiovale and the caudate nucleus. Kim[5] described two patients with delayed-onset hand tremor associated with an infarction of the caudate nucleus. One of these patients bore some similarity to ours in that she had a 4–5 Hz tremor with flexion-extension movements of all the fingers at the metacarpophalangeal joints that appeared at rest and diminished with action. CT scan demonstrated a cerebral infarct of the contralateral caudate and anterior portions of the internal capsule and putamen.

The differential diagnosis of rest tremor includes rubral tremor, dystonic tremor, psychogenic tremor, and parkinsonism. Rubral tremor was discarded because the tremor was largely absent on sustention and intention. The rhythmicity of the movement and the absence of dystonic posturing of the hand made the diagnosis of dystonic tremor unlikely. The history and clinical findings were not suggestive of psychogenic disease. Although the resting tremor led us to consider Parkinson's disease in the differential diagnosis of our patient, we think this possibility is unlikely. The tremor was coarse and the frequency somewhat slower than that seen in parkinsonism. In addition, other features of parkinsonism, including rigidity, bradykinesia, and gait disorder, had not developed after almost a

year since onset of severe tremor. Another interesting feature was the formation of a callus in the palm from the constant contact of fingers and palm surface, a finding we have never seen previously.

Our case demonstrates that focal striatal lesions may play a role as a cause of unilateral resting tremor, particularly when it occurs in the presence of atypical features.

Legend to the Videotape

This 50-year-old man has a 3.5 Hz continuous resting tremor of the left hand which is associated with an isolated lesion of the right caudate nucleus and putamen on MRI scan.

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Cortical Tremor Secondary to a Frontal Cortical Lesion

Tremor is a recognized feature of frontal lobe tumors.[1–4] This case suggests that this may sometimes be the result of a rhythmic cortical myoclonus. Cortical tremor is a rare tremulous movement disorder with the electrophysiological characteristics of cortical reflex myoclonus. Most cases are idiopathic or secondary to diffuse brain pathology, and lesion localization is generally not possible.[5,6] We report a case of cortical tremor secondary to a focal brain lesion in whom tremor bursts were of unusually long duration. The case highlights the importance of the electrophysiological characterization of tremors resulting from frontal lobe pathology.

Case Report

A 76-year-old man had a generalized tonic-clonic convulsion with loss of consciousness in February 1997. He was in good health until approximately 2 years previously when he noticed slight weakness on his left side. On examination he had a mild hemiparesis, spasticity, and increased tendon reflexes on the left, and an extensor left plantar reflex. There was no tremor or sensory loss. A computed tomography scan of the head revealed a right frontal space-occupying lesion with prominent contrast enhancement (Fig. 1). He was treated with 300 mg phenytoin per day and the tumor was excised a few days later. Pathologic examination confirmed an angioblastic meningioma. Immediately after the operation, his left hemiparesis temporarily deteriorated. He could raise his left arm and leg but could not carry out any fine manual tasks. His left arm and hand assumed a flexed posture. Both increased spasticity and Gegenhalten rigidity were present. A tremor of the upper limbs also became apparent. On the left it was present at rest and aggravated by posture and action, particularly isometric contraction. There was no clear stimulus sensitivity. The left hand was too shaky to hold a spoon or a bowl. On the right, there was a smaller amplitude postural tremor. There was no loss of sensory functions, including graphesthesia and stereognosis, and the hand was not apraxic. The muscle power gradually recovered to the preoperative level but the tremor persisted 1 year later.

Electromyography (EMG) was recorded with pairs of surface electrodes on the wrist flexors and extensors while at rest and with the arms outstretched. The EMG was filtered with a bandpass of 50–1000 Hz. Synchronous rest and postural tremors were recorded with a rate of approximately 7 Hz. The EMG burst duration was 80–100 ms (Fig. 2).

Electric stimulation with a constant-voltage square-wave pulse of 200 μsec duration was delivered at 1 Hz to the median nerve at the wrist and to the posterior tibial nerve at the ankle. C3′ and C4′ (2 cm posterior to C3 and C4, respectively) electrodes were used for the recording of somatosensory-evoked potentials (SEPs) from the contralateral upper limb. Cz′ (2 cm posterior to Cz) electrodes were used for the recording of SEPs from the lower limbs. Fz was used as the reference electrode. The latencies and waveforms of the earliest cortical SEPs were normal in all limbs. However, the peak-to-peak amplitude of the P25-N33 wave was 8.7 μV for the left upper limb (Fig. 3A). This was significantly larger than that on the right side (4.7 μV) and fulfilled criteria for ''giant SEPs.''[7] The amplitude of the P39-N48 wave was 4.0 μV following stimulation of the left lower limb. Although not beyond the normal upper limit,[8] this also was larger than that recorded from the contralateral limb (1.6 μV).

A long-latency double C-reflex was recorded from the left abductor pollicis brevis (APB) with an onset latency of 41.6 ms. It was absent on the right side (Fig. 3B). Back-averaging of electroencephalogram (EEG) activity before the tremor bursts was not performed.

Discussion

The term cortical tremor was first coined by Ikeda et al.[5] They described two patients who had the clinical manifesta-

A videotape accompanies this article.

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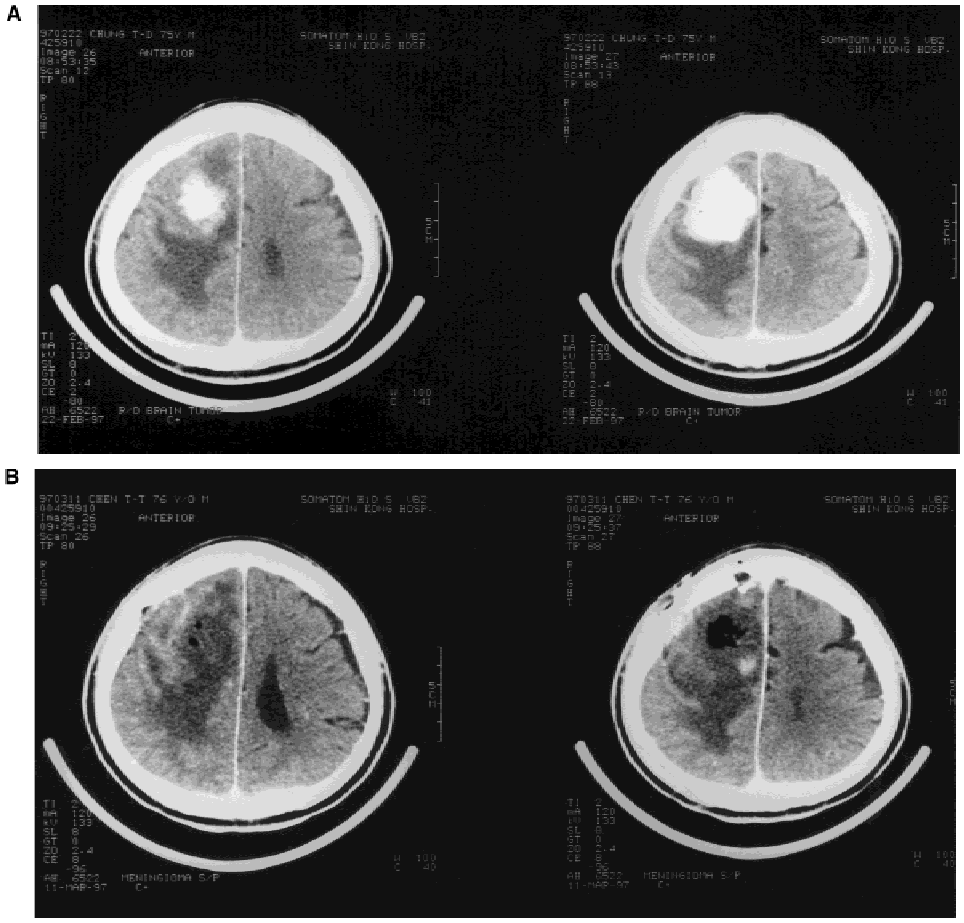

FIG. 1. (**A**) Head CT with contrast enhancement shows a well-defined space-occupying lesion with prominent enhancement over the right frontal cortex, centered around the middle frontal gyrus. Perifocal edema with mass effect is evident. (**B**) Head CT after surgical operation shows a cavity secondary to excision of the tumor. There is still prominent perifocal edema 10 days after surgery.

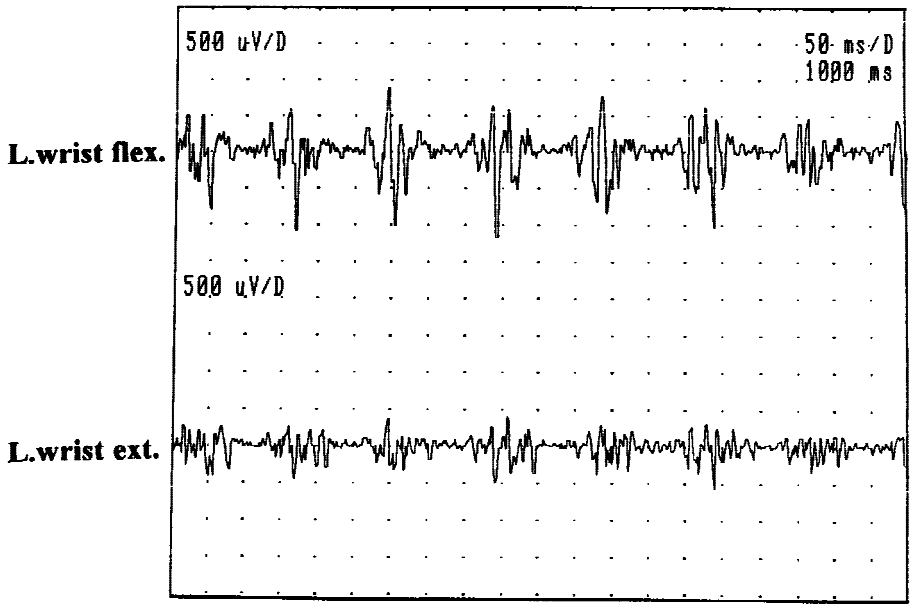

FIG. 2. Surface EMG recording from the left wrist flexors and extensors with the arm outstretched. It shows rhythmic synchronous discharges from the muscles with a frequency of 7 Hz. The EMG burst duration was 80–100 msec.

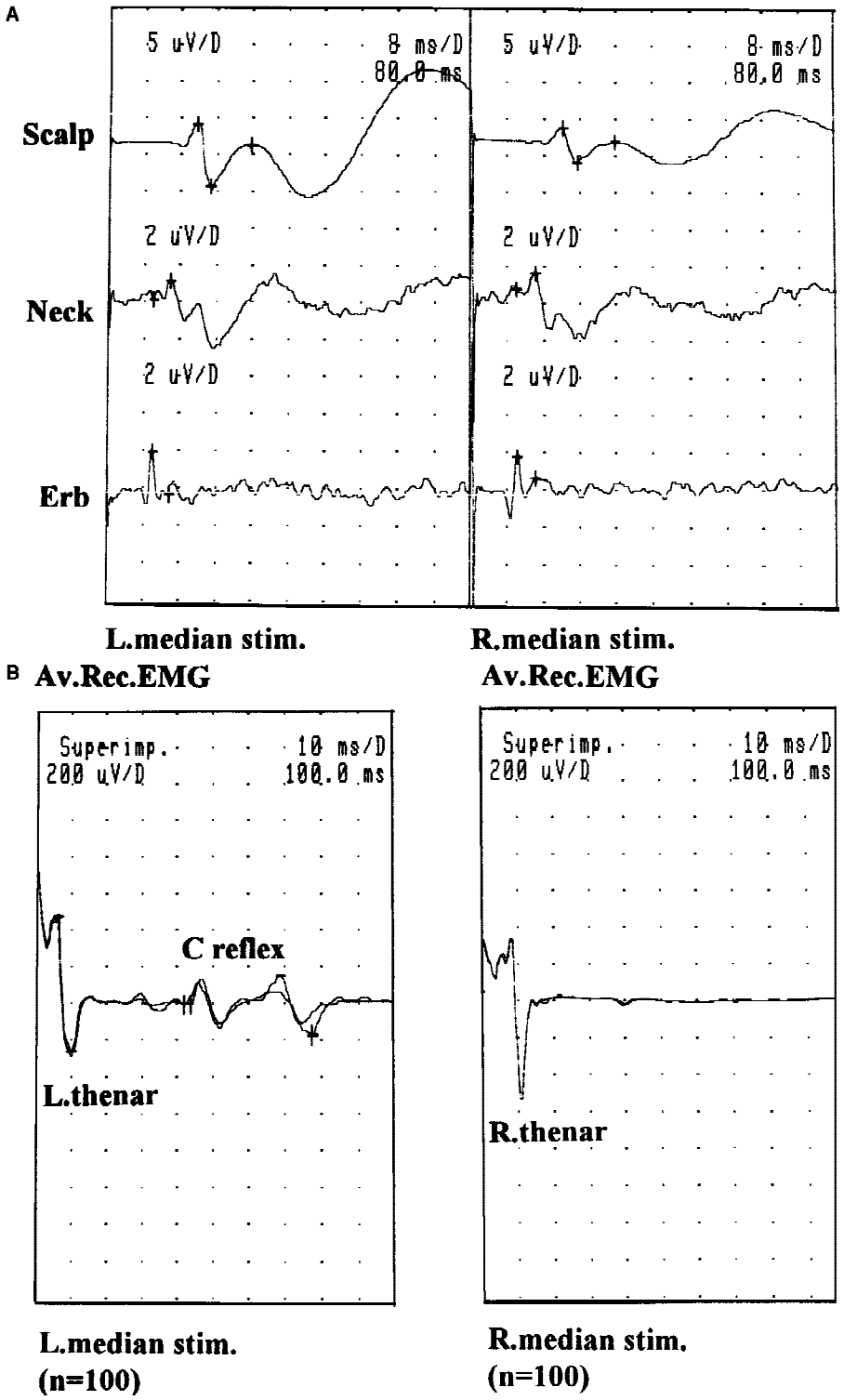

FIG. 3. (**A**) Somatosensory-evoked potentials (SEPs) from the upper limbs. The peak-to-peak P25-N33 amplitude of the cortical SEP was 8.7 μV for the left upper limb. This fulfilled the criteria for ''giant SEPs.'' The P25-N33 amplitude on the right was 4.7 μV. (**B**) A long-latency double C-reflex is recorded from the left abductor pollicis brevis (APB) with an onset latency of 41.6 msec. It was absent on the right side.

tions of an essential tremor but with the electrophysiological characteristics of a cortical reflex myoclonus. Toro et al. subsequently reported three patients with postural tremor and another seven patients with ''stereotyped involuntary rhythmic movements when attempting to execute a sustained isometric muscle contraction,'' all of whom had some electrophysiological evidence of cortical myoclonus.[6]

The etiology in these cases included Baltic myoclonus, Lafora body disease, progressive myoclonic epilepsy, and anoxia.[5,6] In addition, familial cortical tremor has recently been recognized.[9] However, many cases remain idiopathic.[5,6] Our patient had a predominantly unilateral cortical tremor as a result of a focal brain lesion. The tremor was present with sustained posture and was aggravated by action and isometric muscle contraction. The tremor frequency was 7 Hz, similar to that reported by Oguni et al.[10] The EMG burst duration was 80–100 ms. This is substantially longer than the short burst duration reported by Ikeda et al. and Toro et al.[5,6] Thus the tremor in our case was similar to an essential tremor, both clinically and electromyographically. However, the clinical history and the presence of giant SEPs suggested a cortical origin for the tremor. Similar EEG findings are seen in many cases of epilepsia partialis continua, but the movement disorder in our case had the appearance of a regular tremor rather than myoclonus, and EMG bursts were longer than usually seen in epilepsia partialis continua of cortical origin.[11]

Myoclonic activity can arise in either the motor or the sensory cortex in cortical myoclonus. Magnetoencephalographic analyses suggest a source in the sensory cortex is more common.[12] Enhanced excitability of the motor cortex alone may be enough to generate cortical reflex myoclonus and long loop reflexes but no enlarged SEP is found under such circumstances.[13] The giant SEPs of cortical reflex myoclonus are generated in the primary sensory cortex.[14,15] This local hyperexcitability may be the result of direct injury or secondary to disinhibition elsewhere.[16] In all previously reported cortical tremor cases and in most cases of cortical reflex myoclonus, the jerking has been either idiopathic or secondary to diffuse brain pathology, and the cause of local hyperexcitability has remained obscure.

The cortical tremor in this case can be attributed to focal pathology. The meningioma was located over the right frontal cortex centered over the medial premotor area. Although perifocal edema and mass effect extended somewhat posteriorly, the tremor developed only after the surgical removal of the brain tumor, contemporaneous with a deterioration in motor function without sensory deficit, suggesting direct injury to the frontal cortex. The tremor continued thereafter. Therefore, while diffuse pathology may result in multifocal or diffuse cortical hyperexcitability, an isolated unilateral frontal cortical lesion may also lead to a predominantly unilateral rhythmic limb movement with enlarged SEP amplitudes. This suggests that the sensory cortex normally may be under some inhibitory influence from the ipsilateral frontal motor cortex, and that the loss of such inhibition may be important in the pathophysiology of cortical tremor.

Tremors secondary to frontal brain tumors have been well documented in the literature.[1–4] These are clinical observations and no electrophysiological study has been reported. Tremor is thought to be the result of secondary involvement of the basal ganglia, either through direct mass effect or vascular insufficiency. However, the size of some of the frontal lobe tumors associated with tremor has been small and insufficient to exert such changes.[4] This case suggests that some tremors secondary to frontal lobe tumors may be the result of rhythmic cortical myoclonus.

Legend to the Videotape

The patient has a postural and action tremor of the left hand. Tremor increases while trying to hold a spoon and also while performing isometric contraction against resistance. There is also a mild rest tremor. On the right, there is a smaller amplitude postural tremor.

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Dystonia; a Central Nervous System Presentation of Sjögren's Syndrome

Central nervous system (CNS) involvement has been reported in approximately 10–20% of patients with Sjögren's syndrome, a multisystem autoimmune disorder characterized by dryness of the eyes (keratoconjunctivitis sicca) and mouth (xerostomia).[1,2] A variety of CNS manifestations, such as aseptic meningoencephalitis, seizures, and optic neuropathy, have been described.[2]

We report the first patient with Sjögren's syndrome and dystonia of the left hand and foot, which completely disappeared after immunosuppressive treatment and may therefore be the result of antibodies against neuronal antigens in the right striatum.

Case Report

A previously well 36-year-old man presented with painless fixed dystonic posture of the left hand with hyperflexion of the left third to fifth fingers and wrist. There were no numbness, paraesthesia, infection, discoloration, or autonomic disorders. The left index finger and thumb were completely normal. The patient also had dry eyes and a dry mouth. On examination, the left third to fifth fingers were in flexion but could be passively extended. The patient could not actively move these fingers. No muscle atrophy or other neurologic abnormalities were observed. The left foot showed slight inversion with internal rotation.

Additional examinations revealed keratoconjunctivitis based on absent tear production as evaluated by the Schirmer test and abnormal rose bengal staining of the cornea. Serum antinuclear autoantibodies (titer 1: 256) were detected by immunofluorescence, but anti-double-stranded DNA (by the Chrithidia Luciliae test and Farr assay) and other disease-specific autoantibodies (by immunoblotting) such as anti-Ro or anti-La were negative. Histologic examination of a sublabial salivary gland biopsy showed a focus score of 1.0 (one lymphocytic foci per 4 mm^2). Immunohistologic examination of the plasma cells revealed 64% IgA-containing cells. On the basis of these findings, the diagnosis of Sjögren's syndrome was made according to Vitali et al.[3]

Magnetic resonance imaging (MRI) of the brain showed no abnormalities. However, the I^{123}-iodobenzamide (IBZM) single photon emission computed tomography (SPECT) showed decreased right striatal uptake (ratio striatum: occipital cortex on the left 1.53, and on the right 1.41; mean normal value ± 2 standard deviation = 1.66 ± 0.16) indicating loss of D_2 receptors in the right striatum.

Treatment with 60 mg prednisone daily was started, and after 2 weeks the dystonia disappeared. Follow-up IBZM-SPECT 10 months later showed normal availability of D_2 receptors in the right striatum (ratio left 1.53 and ratio right 1.69). Reduction of the prednisone dose by 10 mg every 2 weeks led to recurrence of the dystonia at a dosage of 30 mg/day. Adding azathioprine had no effect on the dystonia. Replacing azathioprine with 100 mg cyclophosphamide daily with 20 mg prednisone daily resulted in the resolution of the dystonia.

Discussion

Central nervous system manifestations are not frequently observed in Sjögren's syndrome.[2,4] In nearly half of the patients with central nervous system involvement, anti-Ro (SS-A) antibodies are present.[4,5] We describe a patient with Sjögren's syndrome who also had dystonia of the left hand and foot. Treatment with high doses of corticosteroids was associated with resolution of symptoms. Isolated CNS vasculitis can be successfully treated with corticosteroids. Also, cyclophosphamide, in contrast to azathioprine, seems to be effective in CNS vasculitis.[6]

MRI of the brain, especially on the T2-weighted images, has shown abnormalities in a majority of patients with Sjögren's syndrome and active neuropsychiatric manifestations.[7] However, in a minority it is normal, as in our patient.

Central nervous system vasculitis has been demonstrated in patients with central nervous system manifestations associated with Sjögren's syndrome by cerebral angiographic appearance, and by histopathologic examination of meningeal and parenchymal blood vessels.[7,8] In our patient, IBZM-SPECT showed D_2 receptor loss in the right striatum, compatible with the clinical signs.[9] Theoretically, local CNS vasculitis as a result of Sjögren's syndrome could decrease striatal perfusion and induce striatal cell dysfunction which manifests by D_2 receptor loss and dystonia. However, MRI showed no striatal abnormalities, suggesting that functional change may occur before structural defects, as also proposed in cerebral systemic lupus erythematosus (SLE).[10] The beneficial effect of the immunosuppressive therapy (corticosteroids and cyclophosphamide) is also in favor of reversible striatal cell dysfunction. Three patients have been described with Sjögren's syndrome and parkinsonism.[11–13] Immunosuppressive treatment was beneficial in only one.[11–13] However, MRI showed white matter lesions in these patients[11–13] which, in view of our patient, suggest that the effect of therapy may depend on site and severity of neuronal cell loss.

Although vasculitis remains the simplest explanation, regional striatal normal or hypermetabolism in patients with SLE-related striatal dysfunction[14,15] supports the suggestion that in SLE, focal neurologic dysfunction is not caused by vascular occlusion, but results from antibodies to neuronal antigens in SLE,[10,16] a mechanism which may also be operative in our patient.

In conclusion, our patient showed that focal dystonia can occur in Sjögren's syndrome and can completely resolve with immunosuppressive treatment. However, on the basis of this

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single case, it is not possible to say whether the association is causative or coincidental.

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Shoulder Girdle Dyskinesia Associated With a Thalamic Infarct

Isolated infarcts confined to the thalamus may lead to a variety of clinical syndromes including pure sensory stroke,[1] complete and incomplete hemisensory syndromes,[2] sensorimotor stroke,[3] Dejerine Roussy syndrome,[4] hemichorea hemiballismus,[5] asterixis,[6] hemidystonia,[7] focal dystonias,[8] and paroxysmal dyskinesias.[9,10]

This report describes a patient who developed an unusual focal rhythmic dystonia limited to the left shoulder girdle following a sensory stroke as a result of infarction of the right posterior thalamus. It could be dramatically provoked by application of sensory stimuli to the affected region. It responded to treatment with clonazepam.

This is the first reported case of a symptomatic shoulder girdle dyskinesia. A videotape is provided depicting the interesting observations.

Case Report

This 58-year-old man was seen for evaluation of involuntary movements affecting his left shoulder girdle. His neurologic illness started 16 months ago when he developed an acute-onset sensory event involving the left half of his body. This was characterized by a feeling of ''heaviness'' left of midline extending from the middle of the neck to the knee including the upper extremity. This perception of heaviness was more dense over a zone covering the scapula and ridge of the shoulder.

Eight months later he developed involuntary movements involving the left shoulder girdle. They consisted of rhythmic retraction of the scapula and mild elevation of the shoulder. He had made a curious observation that the movements were markedly exaggerated when he wore his shirt. Removal of the shirt would immediately reduce the severity. He claimed that the ''touch'' of the shirt to the scapular region was the cause of such worsening. Over the next 8 months, until he presented to us, the involuntary movements became more severe and affected the motor activities of his left arm. There was no history of trauma to the head or to the affected part.

He was 160 cm tall and weighed 54 kg. His blood pressure was 150/96 mm Hg. General examination was unremarkable except for a large cafe-au-lait spot over the right costal margin and a scar from previous abdominal surgery for a duodenal ulcer.

Neurologic examination was unremarkable except for the focal dyskinesia. The dyskinesia was limited to the left shoulder girdle. At rest it was characterized by rhythmic retraction and elevation of the scapula toward the spine. Over-contraction of the rhomboids could be visibly appreciated during each such

A videotape accompanies this article.

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movement. The movements worsened with action. It also worsened dramatically on application of stimuli to an area of the skin overlying the scapula. Response to stimulus was not modality-specific. Touch, pain, or vibration were equally effective. Touching the same region with the patient's opposite hand could worsen the dyskinesia. It could also be provoked by hyperventilation for approximately 2 minutes. There was no habituation. It could not be provoked by active or passive movements of any other part of the body. There was no associated pain.

The videotape demonstrates the features of the focal dyskinesia, its response to voluntary movements and various sensory stimuli (see videotape segments 1–3). Response to clonazepam therapy is also shown (videotape segment 4). See the legends to the videotape for more details.

Electromyographic (EMG) studies performed with surface electrodes using the rhomboids and trapezius demonstrated rhythmic, repetitive bursts of prolonged EMG activity lasting approximately 3 seconds separated by periods of relative silence lasting approximately 400 msec. Application of a stimulus to the dyskinetic region lead to immediate crowding of three to four such bursts with disappearance of the interburst period (Fig. 1). Electroencephalography was normal.

Computer-assisted tomographic scan (CAT) of the head revealed a small infarct of the posterior part of the right thalamus. This was confirmed and better delineated by a magnetic resonance imaging (MRI) scan of the brain (Fig. 2).

The patient was started on clonazepam with an initial dose of 0.5 mg/day which was gradually stepped up. As the dose reached 4 mg/day, there was significant control of the dystonia despite the sensory stimulus. He tolerated the dose well. With an intention to observe the effect of carbamazepine, it was planned to withdraw clonazepam. This was done with consent of the patient. This led to reappearance of the dystonia. Doses of up to 600 mg/day carbamazepine could not control the dystonia. Clonazepam was reintroduced in a dose of 4 mg/day with good relief.

Discussion

This patient developed a delayed-onset left shoulder girdle dyskinesia following infarction of the right posterior thalamus.

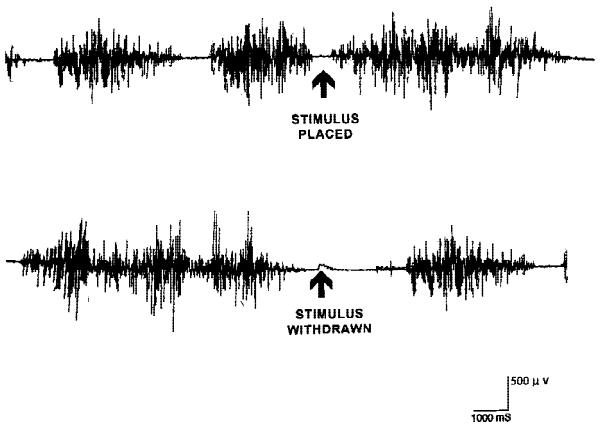

FIG. 1. Surface EMG recording from the left rhomboids. Prolonged bursts of EMG activity lasting approximately 3 seconds separated by periods of relative silence lasting 400 msec are seen at rest. Note the crowding of such bursts in response to stimulation.

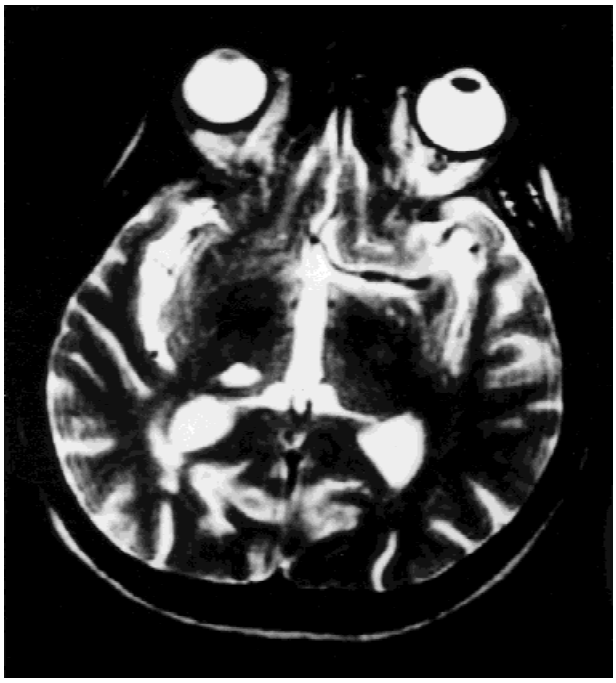

FIG. 2. MRI scan showing a small infarct in the posterior part of the right thalamus.

The localized slow, sinuous, prolonged spasms associated with rhythmic, repetitive bursts of prolonged EMG activity are strongly suggestive of rhythmic dystonia.

Recently Caviness et al.[11] reported cases of focal dyskinesias involving unusual sites. Their paper includes five cases who presented with rhythmic focal dystonia involving the shoulder girdle. The involvement was bilateral in three cases and unilateral in two cases. Neuroimaging studies, including CT scan and MRI, did not show any lesion in the brain or spinal cord. The present case had a similar focal dyskinesia. However, a few important differences could be noted. In the cases described by them, the focal dyskinesia could be suppressed or abolished by voluntary movement of the involved limb, whereas in the present case it was exaggerated by such a voluntary movement. Their cases were not stimulus-sensitive whereas the present case demonstrated stimulus-sensitive behavior. Drug treatment, including clonazepam, was not effective in their cases whereas there was good improvement with clonazepam in the present case. Lastly, no structural lesion could be demonstrated in their cases whereas a contralateral posterior thalamic infarct was detected in the present case. This last finding makes this case outstanding and possibly explains the other differences noted.

Two cases of paroxysmal dyskinesia associated with a thalamic infarct have been described in the past.[9,10] In both these cases the dystonia, which involved one half of the body, worsened promptly with voluntary movements of the affected limbs. The case described by Nijssen and Tijssen[10] also showed provocation of the dyskinesia by sensory stimulation of hyperpathic skin regions. In both of these cases the infarct was located in the posterolateral part of the thalamus as seen in the present case. This region receives spinothalamic fibers, medial meniscus, pallidal afferents, and cerebellothalamic fibers.[12]

One of the unique features of dystonic movements is that they can be diminished by tactile or proprioceptive ''sensory tricks'' (gestes antagonistes).[13] The mechanism of this phenomenon is not known. Our patient shows a reversal of the gestes phenomenon. The case reported by Nijssen and Tijssen[10] also exhibited a similar phenomenon. This observation may point to the possible involvement of the posterior thalamus in inducing the gestes phenomenon through a higher order modulation of the dystonia. A critical lesion of this region possibly reverses the gestes phenomenon. However, the development of an abnormal reflex pathway leading to the stimulus-sensitive behavior cannot be ruled out.

The successful control of the dyskinesia with clonazepam therapy, which is seen in this case, was also observed in the case described by Sunohara et al.[9] Their case had a significantly low level of 5-HIAA in lumbar cerebrospinal fluid which rose to normal after 5-HTP or clonazepam therapy. This suggests that there was inhibition or loss of presynaptic serotonergic neurons or serotonin production which is found in the human thalamus. A similar mechanism can be postulated in the present case leading to thalamofrontal disinhibition, in turn leading to the appearance of focal dyskinesia.

Legends to the Videotape

Segment 1: This segment demonstrates the focal dystonia. The left scapula is rhythmically retracted and elevated toward the spine. It also shows the outline of the ''stimulus-sensitive'' zone. Any stimulus applied within this zone would immediately accentuate the dystonia.

Segment 2: This segment demonstrates the effect of placing a napkin across the stimulus-sensitive zone. Picking up a glass of water with the right hand is easily possible. A similar act with the left hand is grossly affected as a result of worsening of the dystonia leading to backdrawing of the left arm. Removal of the stimulus suddenly ''releases'' the arm for easy action.

Segment 3: This segment demonstrates the effect of placing the tip of a plastic rod within the stimulus-sensitive zone. The tip was 3 mm in size. It could provoke the dystonia as effectively as seen in segment 2. Withdrawing the stimulus suddenly allows the arm to perform the task easily.

Segment 4: This segment demonstrates the effect of clonazepam. With a dose of 4 mg clonazepam per day the patient could perform the same task as seen in the previous segments despite having a stimulus placed over the stimulus-sensitive zone.

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Risperidone is Effective in Severe Hemichorea/Hemiballismus

Hemichorea (HC) and hemiballismus (HB) are usually of vascular etiology, including ischemia, infarction, hemorrhage, and vascular malformations.[1] Hyperglycemia and hypoglycemia can also lead to HC/HB, presumably through vascular mechanisms as well. Although most patients recover spontaneously from vascular HC/HB within 2–4 weeks, in severe cases, HC/HB can be debilitating and irreversible. When the movements are persistent or interfere with function, patients may respond well to antidopaminergic agents. Conventional neuroleptics, particularly haloperidol, perphenazine, and chlorpromazine, are especially effective in controlling severe, debilitating HC/HB.[1–3] Elderly patients, however, are particularly susceptible to developing neuroleptic-induced extrapyramidal symptoms (EPS), particularly tardive dyskinesia (TD) and parkinsonism.

Risperidone is an atypical neuroleptic with potent serotonin-S2 and secondary dopamine-D2 receptor antagonist properties.[4] Although risperidone can also cause TD and parkinsonism,[5] the prevalence of EPS with risperidone is much lower compared with conventional neuroleptics.[6] We report two cases of severe HC/HB, one of which had limited response to conventional neuroleptics, that were effectively treated with risperidone.

Case 1

An 82-year-old hypertensive woman had sudden onset of mild confusion and drowsiness, was diagnosed with nonketotic

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hyperglycemia (blood sugar = 500 mg/dL) in the hospital, and was discharged on an oral hypoglycemic agent (glucotrol). A month later, she developed involuntary, continuous, jerky movements of the right leg that gradually worsened over 3–4 days. The movements were partially suppressible for a few seconds, disappeared during sleep, and were of such severity as to cause excoriations and bruising of the right leg. Walking was significantly impaired. The patient was not taking neuroleptics or antiemetic drugs. There was no family history of any movement disorder.

On examination at the Mayo Clinic 11 days after onset of the abnormal movements, severe, continuous HC/HB was seen in the right leg (videotape segment 1). The rest of the neurologic examination was unremarkable. Patchy areas of skin erythema, excoriations, and superficial hematomas were also seen in the same leg. Although the patient would also move the left leg, she mainly used that leg to calm down the movements in the right leg.

On the day of consultation at the Mayo Clinic, extensive serologic tests, including blood sugar, electrolytes, liver function tests, thyroid stimulating hormone, parathyroid hormone, anticardiolipin antibodies, antinuclear antibodies, rapid plasma reagin, blood smear, complete blood count, and erythrocyte sedimentation rate, were normal. Cerebrospinal fluid (CSF) analysis was normal. Brain magnetic resonance imaging (MRI) showed symmetric, increased T1 and T2 signal in the basal ganglia bilaterally, small lacunes in the right and left thalami, and increased T2 signal in the periventricular white matter and subcortical white matter bilaterally. MRI of the cervical and thoracic spine showed normal spinal cord signal.

The patient was treated unsuccessfully with the following drugs individually up to the maximum tolerated doses: maximum of 6 mg trihexiphenidyl per day, maximum of 1.5 mg clonazepam per day, and maximum of 7.5 mg olanzapine per day. She was then tried on up to 6 mg perphenazine per day with only partial improvement of the leg movements. She was finally placed on risperidone, initially at 1 mg twice a day, then 1 mg three times a day 3 days later. She experienced complete resolution of her HC/HB within 2 days of receiving 3 mg risperidone per day (videotape segment 2). Her walking was markedly improved and was back to its pre-chorea state. At 1, 3, and 6 months post-initiation of risperidone, gradual tapering and discontinuation of risperidone was attempted with prompt recurrence of the leg movements. Thus, since 6 months after starting risperidone, the patient has been maintained on a dose of 1 mg twice a day with complete control of the HC/HB. On follow up 11 months after initiating risperidone, the patient has had no extrapyramidal signs or symptoms from risperidone.

Case 2

A 96-year-old woman without any significant medical problems presented with subacute onset of involuntary, intermittent, fidgety movements of the right hand. Two months later, after receiving spinal anesthesia for rectal prolapse surgery, the movements of the right upper extremity became more severe, continuous, and started affecting the proximal right upper limb as well as the distal and proximal right lower limb. The movements were partially suppressible for a few seconds and would disappear during sleep. The patient did not take neuroleptics or antiemetic drugs. There was no family history of any movement disorder.

On examination at the Mayo Clinic 11 months after onset of the abnormal movements, the patient presented with severe HC/HB of the right arm and right leg as well as mild impairment of walking (videotape segment 3). The rest of the neurologic examination was unremarkable.

Serologic tests done at various times from the onset of movements, including fasting blood sugar, electrolytes, liver function tests, thyroid stimulating hormone, complete blood count, and antinuclear antibodies, were normal. Brain MRI showed mild diffuse cerebellar and cerebral atrophy which was more pronounced in the left temporal lobe and left cerebellar hemisphere. Cerebral magnetic resonance angiography was normal.

Before being seen at the Mayo Clinic, the patient was previously tried unsuccessfully on a maximum of 6 mg trihexiphenidyl monotherapy per day, 2.5 mg procyclidine monotherapy per day, and combined treatment with 2.5 mg procyclidine per day and 1 mg clonazepam per day. On being seen at the Mayo Clinic, the patient was then started on 1½ mg risperidone tablet once a day, and the dose was increased by ½ tablet every 3 days on a three-times-a-day basis. On reaching a dose of 2½ tablets per day (2.5 mg per day), the patient experienced at least 95% improvement of her movements. On reexamination 2 months after starting risperidone, the patient had no choreiform movements at rest and had some mild, intermittent choreiform movements of the right upper limb when talking or concentrating (videotape segment 4). The patient said that on risperidone, she only develops the abnormal limb movements when she gets excited or nervous. Walking was also improved. No extrapyramidal signs or symptoms were seen on examination at 2 months post-initiation of risperidone.

Discussion

Traditionally, severe or disabling HC/HB is treated with conventional high-potency neuroleptics (like haloperidol and perphenazine), which have a high incidence of parkinsonism and TD. Dopamine depleters, like tetrabenazine and reserpine, may be effective in treating chorea.[7,8] Unlike tetrabenazine, reserpine has been reported to cause TD as well.[9] Valproate is effective in Sydenham's chorea, but its efficacy in hemichorea-hemiballism is variable.[10,11] Clozapine, an atypical neuroleptic, may benefit HC/HB but necessitates weekly complete blood count determinations because of a high incidence of lymphocytopenia or thrombocytopenia.[12] Other atypical neuroleptics, like olanzapine and quetiapine, are rarely associated with EPS and may be alternative medications for HC/HB.[13] Anticholinergics are at times prescribed by some physicians for HC/HB but often do nothing but worsen the symptoms.

To our knowledge, this is the first report stating the efficacy of risperidone in severe HC/HB. In a comparative study investigating the prevalence of EPS in 106 patients treated with clozapine,[41] risperidone,[23] or conventional antipsychotics,[42] akathisia and parkinsonism were seen twice as often in patients treated with traditional neuroleptics compared with risperidone.[6] TD can also occur in risperidone-treated patients but often in doses of 6 mg per day or more.[5,14] Our two cases demonstrated prompt and significant improvement of their HC/HB even at low doses (3 mg per day or less), and the first case has had no signs of TD even at 11 months post-initiation of risperidone. Since the introduction of risperidone in 1993, and after over 12 million patient-months of exposure to the drug in

more than 1100 patients, one study has reported the annual incidence of TD with risperidone (at doses of 7.6–9.4 mg per day) to be 0.3% compared with 5–10% for conventional neuroleptics.[15]

The dopamine supersensitivity hypothesis cannot adequately explain the time course of neuroleptic-induced TD or its persistence despite discontinuation of the offending drug. Some authors theorize that neuroleptics enhance striatal glutamatergic neurotransmission by dopamine receptor blockage, resulting in neuronal damage as a consequence of oxidative stress and lipid peroxidation.[16,17] Risperidone potently blocks both serotonin 5HT-2[4] and dopamine D2 receptors.[18] Although haloperidol and risperidone are both potent dopamine D2 receptor blockers, the latter may have a lower incidence of EPS because of its strong 5HT-2 receptor antagonism and more gradual dopamine D2 receptor occupancy.[18] Furthermore, risperidone is often effective as an antipsychotic and antichoreic agent at doses lower than what usually lead to EPS and TD. Because elderly individuals are particularly prone to developing neuroleptic-induced TD, risperidone should be given at the lowest effective dose and the shortest period necessary, especially in patients who have been previously treated with other dopamine receptor blockers.

In summary, we report two cases of severe HC/HB refractory to other medications that responded promptly and significantly to risperidone. Because risperidone has not been reported to produce TD at low doses (less than 6 mg per day), and because TD develops less often with risperidone compared with conventional neuroleptics, low-dose risperidone should be considered as first-line therapy for persistent, disabling HC/HB.

Legends to the Videotape

Segment 1: Case 1 before treatment with risperidone. Note the severe hemichorea/hemiballismus of the right leg. The patient mainly uses the left leg to quiet down the movements in the right leg. Walking was severely impaired.

Segment 2: Case 1 on risperidone. There is complete resolution of hemichorea/hemiballismus of the right leg. Walking is markedly improved.

Segment 3: Case 2 before treatment with risperidone. Note the severe hemichorea/hemiballismus of the right arm and right leg. Walking is mildly impaired.

Segment 4: Case 2 on risperidone. While talking, the patient has some mild chorea of the right arm and right foot. At rest, there are no movements visible. Walking also appears improved.

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Acetazolamide-Responsive Periodic Ataxia Induced by Amiodarone

Amiodarone is an anti-arrhythmic drug with known side effects on the cardiopulmonary system, which is liable to induce peripheral neuropathy[1] but not central nervous system (CNS) toxicity, because of its amphophilic chemical structure.[2] Rare CNS toxicity, reported by national formularies,[3] include optic neuritis, tremor, pseudotumor cerebri, vertigo, nightmares, drowsiness, and headache. One case report in the literature,[4]

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not in English, describes cerebellar disturbances consisting of vertigo and non-paroxysmal ataxia.

We describe a peculiar side effect of amiodarone, consisting of cyclic episodes strictly resembling periodic ataxia,[5,6] appearing in a patient 5–6 months after the administration of the anti-arrhythmic drug. These episodes were long mistaken and unsuccessfully treated for myasthenia than for the sporadic variant of acetazolamide-responsive periodic ataxia,[6,7] and successfully treated for 3 months with acetazolamide until interruption and then reintroduction of amiodarone administration showed the real cause.

Case Report

This 67-year-old retired bank clerk had episodic ataxia and dysarthria during the last 18 months, appearing everyday at approximately 10:00–11:00 AM and approximately 5:00–7:00 PM, lasting approximately 1–3 hours, followed by complete remission. Ten years previously, he had a myocardial infarction with a residual right bundle branch block; 6 months before the ataxic episodes had begun, he had episodes of ventricular tachyarrhythmia. Amiodarone tablets at a dosage of 200 mg and administered at 8 AM was the chosen treatment. For the gait disturbance and the dysarthria, he had been treated for 2 months with 60 mg piridostigmine four times a day without any effect.

His family history was negative for familial periodic ataxia; no history of neurologic disorders was detected among paternal or maternal relatives. Neurologic examination between attacks was normal, and the diagnostic conclusion was that the disturbance might be psychogenic. The patient was, however, required to provide a tape recording of his voice during the ataxic episodes; his recorded voice was evidently dysarthric and scanned, same as in paroxysmal-periodic ataxia, thus addressing further evaluations.

We could observe this patient during ataxic episodes. Each episode consisted of a broad-based ataxic gait with latero- and retropulsion, dysarthric and scanned speech, and modest dysmetria to finger-to-nose or finger-to-finger test. Eye movements were normal during the ataxic episode.

Video electroencephalogram recordings between and during attacks were normal. Electromyography of vasti medialis, gastrocnemii, flexor carpi ulnaris, and extensores comunii digitii during the attacks were also normal.

Laboratory investigations, including blood count, glucose, electrolytes, levels of urea, creatine, calcium, uric acid, plasma and urine aminoacid, plasma protein electrophoresis, vitamins E and B12, red cell folate, piruvate, and lactate were normal between and during attacks.

Genomic DNA was tested for detection of the mutation of SCA (spino-cerebellar ataxia) type-1 locus on chromosome 6p and SCA3 on chromosome 14 q. CAG repeats excluded abnormal alleles compatible with SCA1-SCA3 mutations.

Brain stem and somatosensory evoked responses, audiograms, caloric tests, electronystagmography, and rotational tests were normal. T1-, T2-weighted 1.5 tesla magnetic resonance imaging of the brain showed minor leukoencephalopathy with only three hyperintense areas evidenced by T2 images in frontal (one) paratrigonal (two) white matter, all smaller than 4 mm^2.

Acetazolamide at a dosage of 125 mg twice a day was administered for 2 weeks and then increased to 250 mg twice a day. During the first 2 weeks the patient had only four attacks of ataxia; in the following months he experienced only one episode of ataxia-dysarthria lasting for 1 hour; and during 3 months of acetazolamide treatment, he experienced only one episode of scanned dysarthric speech.

Within 2 days of acetazolamide withdrawal his ataxic episodes reappeared with the same daily timing as before. Two weeks after acetazolamide withdrawal, amiodarone was, however, discontinued at the patient's insistence even though a diagnosis of sporadic acetazolamide-responsive ataxia had been considered as definitive at the time, because the morning/afternoon pattern of ataxia seemed unrelated to amiodarone administration. With amiodarone withdrawal, ataxic episodes disappeared in 15 days and did not recur in the next 2 months. At the end of the 2 months amiodarone was reintroduced with the same daily schedule as before; periodic ataxic gait and dysarthria reappeared in 10 days. The same morning/afternoon pattern as before overtly appeared after 14 days, thus leading to final discontinuation of the anti-arrhythmic drug. Ataxic episodes did not recur in the following year, not even when 0.5 g procainamide hydrochloride four times a day was administered for further episodes of paroxysmal ventricular tachycardia.

Discussion

The paroxymal periodic ataxia observed in our patient reproduced the pattern observed for periodic ataxia, a disease described as ''often unrecognized.''[5,8]

Recent articles attempt a classification of periodic ataxias into four forms: one is periodic ataxia with choreoathetosis and dystonia not responding to acetazolamide, a second one is familial periodic ataxia consisting of episodes of gait ataxia and dysarthria and, inconstantly, of eye movement abnormalities transmitted in a strictly dominant pattern, responding to acetazolamide. a third one is periodic ataxia with myokymia, variably responding to acetazolamide, and the last is periodic ataxia resulting from different metabolic or anatomic abnormalities.[8]

Furthermore, few sporadic cases of episodic ataxia have been described, only some responding to acetazolamide treatment.[5–7]

Recent studies suggest that familial periodic ataxia is the result of pH variations of the cerebellar structures,[8] and that mutations of the K channel encoding genes might explain the symptoms.[9,10]

The patient described here responded dramatically to acetazolamide treatment but could not be classified into the different forms of periodic ataxia or, likely, of other disorders currently considered in the differential diagnosis of periodic ataxia, like basilar artery migraine, multiple sclerosis, and so forth. His periodic ataxic episodes had a morning/afternoon pattern that was apparently unrelated to the early morning amiodarone intake, but with amiodarone discontinuation-reintroduction the periodic ataxia disappeared and reappeared with a timing (10–15 days) compatible with the drug long half-life of 30 days.[2] Reporting this peculiar form of CNS toxicity induced by amiodarone might add to the understanding of possible adverse effects of this drug and focus the attention of other researchers to inconsistent patterns of neurologic abnormalities that could be mistaken for psychogenic abnormalities or mistreated following the most likely diagnostic procedures.

The fact that acetazolamide effectively abolished the periodic ataxia induced by amiodarone might also suggest caution

when evaluating the effects of acetazolamide or when interpreting its effects for diagnostic purposes. This drug came back into interest because of its therapeutic efficacy in periodic ataxias[5,7] but was already used in the treatment of epilepsies[11] of essential tremor,[12] even of tremor induced by valproate.[13]

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Melatonin-Induced Withdrawal Emergent Dyskinesia and Akathisia

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone that is commonly used for sleep induction.[1,2] Acute exogenous administration of melatonin has produced sedation, fatigue, self-reported vigor, confusion, and a reduction in body temperature in healthy subjects.[3] No serious long-term side effects have been reported from chronic use of melatonin, and, as a result, it is considered a safe "drug." Herein, we report a case of withdrawal emergent dyskinesia and akathisia after chronic melatonin treatment was stopped.

A 22-year-old woman, of Ashkenazi origin, with spastic diplegia resulting from cerebral palsy and severe mental retardation had insomnia for the past 6 years. Melatonin at a dosage of 5 mg was given at 8 PM for the past year with good response.

Recently, melatonin was stopped because of repeated vomiting. One week later, still without melatonin, the patient gradually developed involuntary lip-smacking movements and tongue protrusion with extreme restlessness, moaning, and shouting. These symptoms continued for 2 weeks accompanied by marked worsening of insomnia.

At that stage, we examined her and noticed repeated involuntary contraction of the orbicularis oris imitating sucking and rapid extrusion of the tongue. In addition, the woman was restless, could not sit still, and was shouting, moaning, and grunting.

On examination we also noticed severe mental retardation, dysarthria, and spasticity with bilateral pyramidal signs. Routine laboratory studies were all normal.

The patient's history was negative for exposure to neuroleptics during the previous 6 months except for one injection of 10 mg metoclopramide HCL, which was given for repeated vomiting and which caused acute dystonic reaction in the form of "locked jaw." No family history of dystonia or any other neurologic disorders were reported.

With the diagnosis of withdrawal emergent syndrome, melatonin was readministered in gradually increasing doses. Two days after a dose of 5 mg was reached, the involuntary movements disappeared along with an improvement in her agitated state and insomnia. A month later, another episode of abdominal pain and vomiting made the parents discontinue melatonin again. Within 2 days, identical involuntary lip and tongue movement reappeared with akathisia. Melatonin at a dosage of 5 mg was readministered and all symptoms disappeared the next day. No antiemetic drugs were given during these episodes as well.

Suspecting we were facing a case of melatonin-induced withdrawal emergent syndrome, we slowly stopped melatonin over a period of 2 months. The woman is free of any movement abnormalities for more than 6 months.

The appearance of lip and tongue dyskinesias with akathisia secondary to withdrawal of dopamine receptor blockers agents (DRBAs) is called tardive syndrome.[4] However, the appearance of these symptoms after acute withdrawal of melatonin, the disappearance of symptoms when melatonin was readministered on two occasions, and the successful withdrawal from melatonin when it was stopped gradually are compatible with the diagnosis of melatonin-induced withdrawal emergent syndrome.[4] Orobuccolingual dyskinesia is rarely if ever seen in withdrawal emergent syndrome which is classically seen as generalized chorea, mostly in children.

The history of acute dystonic reaction secondary to metoclopramide might have been a warning sign for neuroleptic hypersensitivity, but the relationship between the two reactions is still poorly understood and has not been confirmed in other studies.

Melatonin is known for its hypnotic effect. However, it also

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has been shown to inhibit the release of dopamine from the hypothalamus[6] and striatum[7] in experimental animals and was suggested to have neuroleptic properties.[8]

Furthermore, Sandyk[9] has suggested that reduction of melatonin secretion in association with depression may contribute to the development of tardive syndrome in patients with affective disorders treated with neuroleptics.

The biochemical cascade at the level of the basal ganglia, which might relate to melatonin-induced withdrawal emergent, is unknown but the presence of melatonin receptors in human substantia nigra and striatum[10] is additional supportive evidence for the possible role of melatonin in withdrawal emergent syndrome.

Melatonin-induced withdrawal emergent syndrome has never been reported before.

This case raises important question regarding the dopamine-blocking effect of melatonin. As DRBA, melatonin should be used with caution because of the risk for the development of tardive syndrome, a disease that can cause serious morbidity with a low remission rate. Melatonin should be used with special caution for patients with organic brain damage like this case.

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