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Clinical/Scientific Notes

Reversible Leucopenia Related to Olanzapine

The so-called atypical neuroleptics represent a new class of antipsychotic drugs that only rarely cause extrapyramidal side effects. Therefore, they have proved valuable not only for the treatment of schizophrenia, but also for drug-induced psychosis in parkinsonian patients.[1]

Unfortunately, the use of clozapine, the first atypical neuroleptic, has been limited by agranulocytosis that occurs in approximately 0.6% of patients.[2] In contrast, the new substance olanzapine has not been related to hematologic adverse events in any of the 2500 patients who were evaluated in five large clinical trials.[3] Recently, however, prolongation of clozapine-induced leucopenia has been reported in three patients who received olanzapine immediately after clozapine had been discontinued.[4] We report on two patients who developed reversible leucopenia while being treated with olanzapine.

Patient 1

A 56-year-old woman with L-dopa-responsive parkinsonism and dementia, presumably resulting from diffuse Lewy body disease, was treated with 15 mg olanzapine per day for L-dopa-induced psychosis. Her white blood count (WBC) was 5200 μL before treatment was initiated. After 4 months her leucocytes started to decrease falling to a minimum of 2400 μL within 4 weeks. Subsequently, olanzapine was tapered off over 4 weeks which resulted in a recovery of her WBC reaching 4600 μL 1 week after olanzapine was discontinued. When psychosis recurred a few days later, 12.5 mg clozapine mg per day was started in another hospital which provoked another reversible decrease of her WBC to 2900 μL. Her antiparkinsonian medication included levodopa and pergolide; in addition she took donezepil for dementia. Her general medical status was normal; extensive laboratory studies did not reveal any concurrent illness.

Patient 2

A 58-year-old man with idiopathic Parkinson's disease was treated for L-dopa-induced psychosis with 150 mg clozapine per day. Before initiation of neuroleptic therapy, his WBC was 4000 μL. After 6 weeks of treatment, there was a continuous decrease of leucocytes to 2900 μL over a period of 2 weeks. Clozapine was discontinued and his WBC recovered to 3800 μL within 1 week. When L-dopa-induced psychosis recurred 2 years later, 5 mg olanzapine per day was started without prior blood testing. The patient's WBC was 3200 μL after 3 and 6 weeks of treatment, 3700 μL after 6 months, and fell to 2100 μL after 13 months. When olanzapine was discontinued, his WBC returned to 4150 μL within 2 weeks.

This patient may have had a preexisting hematologic disorder because for 5 years his platelets had been between 99,000 μL and 174,000 μL and his hemoglobin had been in the low normal range between 12.8 and 14 g/dL. When treated with olanzapine, he had a further decrease of his hemoglobin to 10.9 g/dL. Extensive investigations, including immunologic studies and bone marrow cytology, were normal and failed to reveal a specific cause. His medication comprised levodopa and tolcapone.

These case histories demonstrate that olanzapine may, in fact, cause reversible leucopenia. No hematologic, infectious, or nutritional factors causing leucopenia were observed in our patients. Although levodopa may rarely induce leucopenia, this seems to be an unlikely explanation in our patients because both had been treated with levodopa for several years before they were exposed to olanzapine. Moreover, both had a normalized WBC when olanzapine was stopped while levodopa was continued. None of the other concomitant drugs is known to induce leucopenia. Both patients also developed leucopenia when treated with clozapine suggesting a similar pathogenetic mechanism. This appears to be not surprising with regard to the similar chemical structure of the two substances. However, previous evidence in 32 patients with transient leucopenia resulting from clozapine suggested that treatment with olanzapine would not cause a recurrence.[5] Similarly, two patients with agranulocytosis caused by typical and atypical (risperidone) neuroleptics were successfully treated with olanzapine.[6] The pathogenesis of olanzapine-related leucopenia may be multifactorial as suggested by our second patient who had hematologic abnormalities before treatment but became leucopenic only when exposed to clozapine and later olanzapine.

The clinical implications of olanzapine-induced leucopenia are still unclear because our patients remained asymptomatic and their WBC recovered as soon as olanzapine was discontinued. On the other hand, development of agranulocytosis under prolonged exposure cannot be excluded. In conclusion, parkinsonian patients with previous clozapine-related leucopenia or concurrent hematologic disease may run an increased risk of developing olanzapine-induced leucopenia. Under these circumstances, it may be advisable to monitor the white blood count at weekly intervals during the first 4 weeks and later monthly.

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Possible Tardive Dystonia Resulting From Clozapine Therapy

Clozapine (CLZ) is considered to be an "atypical" antipsychotic drug because it does not induce dose-related catalepsy in rodent models[1] and is associated with a low incidence of acute extrapyramidal syndromes in people.[2] This non-neuroleptic pharmacologic profile distinguished CLZ from all other currently available antipsychotic agents. Tardive dyskinesia and its variants, including tardive dystonia, are delayed-onset drug-induced movement disorders associated with the use of traditional neuroleptic agents which, unlike parkinsonism, acute dystonia, or akathisia, are chronic, difficult to treat, and can result in permanent disability.[3] In keeping with the non-neuroleptic character of this drug, there have been few reports in the literature implicating CLZ as a cause of tardive dyskinesia[2,4,5] and no convincing reports of tardive dystonia. As a result, it is generally considered to have little or no potential to cause tardive syndromes.[4]

These unique features in combination with CLZ's antipsychotic efficacy have led to its frequent use in schizophrenic patients resistant to other neuroleptic medications and may make CLZ the treatment of choice for those patients with existing tardive dyskinesia. Low-dose CLZ is now the standard of care for patients with Parkinson's disease who have drug-induced psychosis.[6] It has also been reported as an effective treatment for tardive dyskinesia, tardive dystonia, and tremor.[6] With the increasing popularity of CLZ use in these settings, the issue of its potential association with tardive syndromes likewise grows in importance. Clearly, a well-documented case of tardive dystonia resulting from CLZ treatment would be of great interest. We report what we think is the first well-documented case of probable tardive dystonia associated with CLZ monotherapy.

Case Report

This patient is a 37-year-old non-Ashkenazic left-handed man with a history of chronic paranoid schizophrenia since the age of 16. He was initially evaluated at the Albany Medical Center Movement Disorders Clinic in October of 1996, at the age of 36, for a 4-year history of involuntary turning of head to the left. He had been treated with numerous neuroleptic medications from 1975–1990 including loxapine, haloperidol, trifluoperazine, fluphenazine, thioridazine, chlorpromazine, and molindone. At times he experienced mild parkinsonism which was effectively treated with low doses of benztropine. However, he specifically denied having involuntary movements such as of the tongue, mouth, face, or neck during this period. His mother was present for this evaluation and confirmed this. In 1990, he was switched to CLZ because of breakthrough psychosis. CLZ was effective in controlling his psychosis and has remained his exclusive antipsychotic treatment since that time.

Two years after starting CLZ he began to experience involuntary turning of his head to the left. His symptoms began gradually and progressed over time. He has occasionally experienced superimposed spasms which jerk his head to the left but there has been no pain. There have been no other involuntary movements. The turning can be improved by putting his hand on his left cheek but there has been no sleep benefit noted. Medical history is significant for adult-onset diabetes. There was a history of polysubstance abuse including alcohol, marijuana, and cocaine, but there has been no exposure to these substances in the last 11 years (7 years prior to the onset of his neck symptoms). There is no family history of dystonia or other neurologic problems. His medications at the time of his evaluation were 825 mg CLZ per day, 4 mg trihexyphenidyl per day, 100 mg metformin per day, and 10 mg glyburide per day.

On examination in October 1996, he was alert and cooperative but there was loosening of thought processes and magical thinking. His general examination was unremarkable. While seated, at rest, he had left torticollis of 60–70°, mild left laterocollis, and superimposed spasmodic head movements jerking his head to the left (see the videotape). Muscle palpation revealed hypertrophy of the right sternomastoid, right levator scapulae, and left splenius capitis muscles. The latter two muscles were also tender. He had difficulty rotating his head to the right past midline. There was no sign of head or neck trauma. There were no Kayser-Fleischer rings. There were no other involuntary movements or signs of parkinsonism. The remainder of his neurologic examination was normal.

An attempt to treat his dystonia with up to 3 mg trihexyphenidyl three times a day was unsuccessful because of lack of benefit and memory impairment. He has had no other treatments. A full chemistry profile, liver functions, serum ceruloplasmin, and thyroid functions were all normal.

Discussion

We think this case represents the first well-documented example of new-onset dystonia occurring in the setting of chronic

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CLZ monotherapy. The diagnosis of tardive dystonia can be made in this case based on the following criteria created by Burke et al in 1982[3]: (1) the presence of chronic dystonia (4 years in our patient); (2) a history of antipsychotic drug treatment preceding (<2 months) or concurrent with the onset of dystonia; (3) exclusion of known causes of secondary dystonia by appropriate clinical and laboratory evaluation; and (4) a negative family history of dystonia. One might argue that this patient developed dystonia as a direct result of chronic exposure to numerous typical neuroleptic medications prior to CLZ use. However, the fact that the patient was on CLZ monotherapy for a full 2 years prior to the onset of dystonic symptoms makes this extremely unlikely. Burke et al used the cut-off of 2 months between onset of symptoms and last exposure to the suspected medication in their original report[3] and later extended it to 3 months in a follow-up report[7]; however, even these arbitrary cut-offs may be too inclusive. It is possible that the previous neuroleptic exposure did result in long-term functional dopamine receptor abnormalities through chronic dopamine receptor blockade. This could have created a sensitizing or priming effect on this patient's striatum. Thus, CLZ exposure alone may not be sufficient to cause dystonia. It may be necessary for the substrate of an abnormal striatum to already be in place.

Another diagnostic consideration is that this patient developed idiopathic cervical dystonia coincidentally while taking CLZ. Although this is possible, such a coincidence should be considered unlikely. However, it is interesting to note that the clinical features of this patient's dystonia seems to be more typical of idiopathic cervical dystonia than tardive dystonia involving the cervical region; that is, this patient had predominant rotational torticollis without retrocollis, dystonic involvement of other areas, or coexisting orobuccal-lingual dyskinesia. These latter features were found to be more common in patients with tardive dystonia by Kang et al.[7] In our own retrospective clinical comparison of idiopathic and tardive cervical dystonia, retrocollis was present in 60% of tardive and only 25% of idiopathic cervical dystonia patients. Extracervical involvement was also more common in the tardive group (65% versus 21%).[8] Of course these clinical features are not exclusive to either group and cannot be used to make a diagnosis in individual cases. The criteria set out by Burke et al[3] should be applied with equal rigor to all patients with dystonia whether they are exposed to typical or atypical neuroleptic agents.

We could find only two previous reports of possible tardive dystonia associated with CLZ use. In 1994, Dave[9] reported a patient who experienced recurrent oculogyric crises on CLZ. Although oculogyric crisis is considered to be part of the spectrum of tardive dystonia, this patient had previously experienced the same symptoms while taking perphenazine, calling into question the relationship of these symptoms to CLZ treatment. In addition, episodes of oculogyria only occurred in this patient while on antipsychotic medications and each episode responded dramatically to anticholinergic medication. Thus, it is possible that this was a case of recurrent acute dystonia rather than true tardive dystonia. In 1996, Peacock et al[10] reported the onset of "mild finger dystonia in the form of splaying of one or more fingers in a fixed position, mainly seen when the patient(s) were walking . . ." in one of 100 patients treated chronically (>5 years) with CLZ. However, without videotape confirmation this case is also difficult to interpret. Given the rarity of these reports, it would be reasonable to conclude that the incidence of tardive dystonia in CLZ-treated patients will be low. In individual cases, it may be an idiosyncratic reaction resulting from an underlying genetic susceptibility or occult basal ganglia injury. Reporting of similar cases hopefully will lead to a more accurate understanding of the incidence of this potential side effect of CLZ therapy.

Legend to the Videotape

Six years after beginning clozapine monotherapy and 4 years after the onset of cervical dystonia, the patient has left spasmodic torticollis and mild left laterocollis.

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SSRI-Induced Reversal of Levodopa Benefit in Two Patients With Dopa-Responsive Dystonia

Dopa-responsive dystonia (DRD) is an inherited primary dystonia with childhood onset usually involving the feet; it is more common in females.[1,2] Patients can have diurnal variation of symptoms and parkinsonism rather than dystonia which can be a feature in some with an older age of onset.[1,2] The gene for DRD has been mapped to the long arm of chromosome 14. The

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condition results from mutations coding for the enzyme GTP1 cyclohydrolase which catalyzes the first step in the tetrahydrobiopterin (BH4) synthesis pathway resulting in reduced concentration of neopterin and dopamine.[3] Fluorodopa PET studies suggest that the nigrostriatal pathways are intact.[4] Neuropathologic and biochemical studies in one case have confirmed normal nigral dopaminergic cells, decreased nigral pigment cells, severe reduction of dopamine in the caudate and putamen, and reduced striatal tyrosine hydoxylase activity.[5] DRD patients have an excellent response to low-dose levodopa and do not develop dyskinesias or fluctuations on long-term follow up.[2] Fluoxetine, a serotonergic reuptake inhibitor (SSRI), and venlafaxine, a selective serotonergic and non-adrenaline reuptake inhibitor (SNRI), are thought to be generally safe and not have the common extrapyramidal side effects known to occur with dopamine-blocking neuroleptic drugs. We report the unexpected reversal of levodopa benefit in two patients with DRD who received fluoxetine and venlafaxine, respectively, as mood elevators.

Case 1

This 34-year-old woman had developed dystonia of her left foot and torticollis in childhood. Her mother and her 7-year-old daughter also had childhood-onset leg dystonia which had responded dramatically to levodopa. The patient had complete resolution of her presenting symptoms from childhood on levodopa treatment. Currently, she was seen on a yearly basis showing no dystonia symptoms. At that time she was taking two tablets of Sinemet plus (DuPont Pharmaceuticals Ltd, Herts, UK; 100 mg levodopa and 25 mg carbidopa) three times a day. Recently, her general practitioner prescribed 20 mg fluoxetine once a day for stress and low mood. While on holiday, 5 days after starting fluoxetine, she felt a pulling sensation in her neck and developed torticollis to the right. Over the next 2 days her left ankle started to invert, initially on walking but then persistently. By the ninth day she felt a tendency for her right foot to also invert. Her clinical state had reverted to "just like it was at onset" before levodopa treatment. During this period she continued taking her Sinemet at the same dosage without the usual benefit. On the ninth day, on the advice of a local doctor, she stopped taking fluoxetine and within 2 days the dystonia began to improve and resolved completely in approximately 1 week. Since then, she continues to take Sinemet plus at her usual dose and was found to have no persistent neurologic signs on examination.

Case 2

This 32-year-old woman developed a limp in her right leg and dystonia of her right foot at the age of 5 years. She had a clear diurnal variation of her symptoms. By the age of 16 she began to get similar symptoms in her left foot which was severe enough to prevent her from participating in any sports at school. At 16 she developed tremor and rigidity affecting both arms and her handwriting was affected. She was started on one tablet of Sinemet LS (50 mg levodopa and 12.5 mg carbidopa) twice a day with complete resolution of her symptoms. In December 1997 she developed a low mood, and her general practitioner prescribed venlafaxine. Within 4 days after starting the drug, she felt a trembling of all her limbs and her dystonia returned with severe inturning of her right foot. She was not seen by a medical practitioner and discontinued the venlafaxine on her own. Within 2 or 3 days she felt better with the dystonia resolving in approximately 1 week. During this period she was continuing to take Sinemet as before. On examination there were no persistent signs.

Discussion

This is the first report of fluoxetine and venlafaxine making the symptoms of dopa-responsive dystonia reappear by reversing the benefit of levodopa. There have been numerous reports of SSRIs, when used alone or in combination with other antipsychotics, inducing movement disorders.[6–13] Dave reported blepharospasm, lip tremor, foot and trunk dystonia without buccolingual or choreoathetotic movements in a middle-aged woman after 4 weeks of fluoxetine therapy.[6] Others have noted extrapyramidal symptoms after prolonged (7 months to 2 years) therapy with fluoxetine,[9,10] and there is growing literature about different movement disorders resulting from SSRI treatment.[11–14] Different mechanisms have been cited by different authors to explain the extrapyramidal symptoms resulting from SSRIs, including inhibition of dopamine release,[11] impaired cytochrome CYP1A2, CYP2D6, and CYP3A4 activity,[10,15,16] and activation of Sigma receptors in the rubrocerebellar circuit.[17] However, venlafaxine has minimal or no inhibitory effect on CYP1A2, CYP2C9, CYP2D6, and CYP3A4 in vivo.[18] CYP inhibition may affect the metabolism of numerous drugs with potentially serious consequences. Another possibility is that SSRIs may be interacting with the levodopa metabolism.[14] Whatever the mechanism, the reversibility of signs in our patient suggests that the mechanism is probably related to a critical level of dopamine. Serotonergic pathways originating from dorsal raphe nucleus to substantia nigra have been described.[19] Bouchard et al. suggested that serotonin uptake blockers may inhibit metabolic production or release of dopamine.[11] Acute and repeated doses of fluoxetine lower the concentration of dopamine in the striatum, hippocampus, and frontal cortex.[20] In support of this hypothesis and analogous to our patient, there is growing literature about patients who developed parkinsonism de novo[14] or whose preexisting parkinsonism worsened on SSRI treatment.[12–13,21] Improvement of the parkinsonian features when discontinuing these drugs is also recognized.[11,21] In conclusion, we would urge caution in using SSRIs in patients with DRD because SSRIs can make the dystonia symptoms reappear despite continuing levodopa treatment.

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Paroxysmal Dyskinesia and Gonadal Sex Hormones

Paroxysmal dyskinesias (PD) comprise a fascinating group of movement disorders of which two forms have been discerned: paroxysmal kinesigenic choreoathetosis (PKC) and paroxysmal nonkinesigenic dystonic choreoathetosis (PNKDC), whether induced by exertion or hypnogenic. In either case, the disorder can be familial or sporadic and idiopathic or secondary.[1,2]

While sex hormones appear to exert an influence on basal ganglia function, in experimental models they act diversely on dopamine transmission.[3]

We present a patient with familial PKC who experienced dramatic worsening both in frequency and severity of episodes following noretisterone and gestrinone treatment.

Case Report

This 35-year-old woman was diagnosed with PKC at age 13. She is the second of four sisters who are likewise affected, one of whom still experiences attacks. The other two sisters had spontaneous remissions.

Since onset, dystonic attacks presented in clusters lasting 2–3 days once or twice per year, with up to three daily episodes. This pattern remained unchanged until age 30 when her symptoms remitted spontaneously.

Seven months before consultation, a large left ovarian cyst secondary to endometriosis was detected by echography. She underwent unilateral oophorectomy followed by hormonal treatment with 5 mg noretisterone acetate per day for 2 months followed by 5 mg gestrinone per week for 4 months. No hormonal level was performed prior to supplementation.

After 2 months on hormones, attacks reappeared with increasing frequency reaching 50 episodes per day after 6 months of treatment.

Several consultations at that time led to a diagnosis of a psychogenic movement disorder for which no therapy was given.

The patient then discontinued gestrinone treatment and 1 month later sought advice at our Neurology Clinic. The frequency of attacks had dropped to 10 daily lasting only a few seconds. The episodes were invariably triggered by sudden movement such as rising from a chair after being seated for a while or when commencing to walk after waiting at a traffic light. Quite often, attacks were heralded by an odd sensation in her left foot. She was able to abort the crises by changing foot position. Dystonic postures usually began on the left side in either foot or arm. Episodes were so severe as to cause postural instability compelling her to grasp someone to avoid falling. There was no loss of consciousness.

Both neurologic examination and brain magnetic resonance imaging were unremarkable. Ictal electroencephalogram/video recording was normal. The introduction of 300 mg phenytoin per day resulted in complete remission.

Discussion

As in our patient, PKC attacks commonly start at puberty and tend to decrease with advancing age.[1] However, acute worsening at age 35 without any triggering factor is an unusual feature. Exacerbation of PKC episodes followed the introduction of hormone therapy, which ameliorated on discontinuation. This strongly suggests a cause-and-effect relationship.

Our patient received 6 months of hormone therapy including noretisterone for 2 months and gestrinone for 4 months. Like noretisterone, gestrinone is 19-nor derivative tested as a contraceptive because of its antiprogestational and antigonadotrophic actions by inhibiting hypophyseal peaks of LH and FSH, thus inducing endometrial atrophy without affecting physi-

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ological levels of ovarian estrogens. Noretisterone acetate and gestrinone do not modify estrogen levels.[4–6]

The pathophysiology of PKC remains speculative but basal ganglia dysfunction has been strongly advocated. In this regard, female sex hormones are inclined to interact with dopaminergic function particularly in patients in whom there is clinical evidence of basal ganglia impairment.[7,8] The mechanism of action of sex hormones in experimental models leads to contradictory findings disclosing both dopaminergic and antidopaminergic effects.[3,9] Whereas an epileptic cause of PKC is believed to be unlikely,[10] an analogy in this case could be drawn with catamenial epilepsy in which an altered estrogen/progesterone ratio enhanced the susceptibility to seizures.[11,12]

Curiously enough, while chorea secondary to oral contraceptive use has often been documented, a careful search of the literature failed to disclose any case of PKC either induced or triggered by sex hormone therapy.

Our patient shares striking similarities with contraceptive-induced choreas including: (1) development of a basal ganglia disorder in a clinical setting; (2) triggered by exogenous administration of sex hormones; (3) time elapsing until onset of dyskinesia within the range of 2–6 months; and (4) prompt improvement within 1–4 weeks of discontinuing hormonal therapy. These features are also shared by chorea gravidarum in which the hormonal changes are endogenous.

This case report again demonstrates that alterations of the gonadotrophic hormones may exacerbate preexisting movement disorders, including PKC.

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Digoxin-Induced Chorea in a Child

Chorea in children that is not related to Sydenham's chorea is an uncommon occurrence. We report a 7 year old who developed two episodes of reversible asymmetric generalized chorea resulting from digoxin toxicity.

Case Report

A 7-year-old girl with a history of a severe congenital heart defect, polysplenia, and aplastic left kidney presented with abnormal movements. Her heart defect consisted of a complete atrioventricular canal with a common atrium and a history of AV and sinus nodal dysfunction. She had undergone pacing for atrial flutter and multiple cardiac surgeries. The most recent surgery was mitral valve replacement 4 years ago. She was healthy until approximately 2 weeks before presentation when she developed left-sided incoordination. She was falling to the left side and had involuntary movements of that side. This progressed to the point that she would not use her left hand. Subsequently, she began having intermittent dysarthria. She did not have any numbness, bowel or bladder difficulties, diplopia, dizziness, nausea or vomiting, recent rash, sore throat, or fever. There was no history of emotional lability. She had a transient headache for 1 day after the onset of symptoms. She had a history of two seizures as an infant related to the cardiac surgery but was not currently on any anticonvulsants. Her medications included 0.125-mg digoxin tablets twice a day, 40 mg sotalol hydrochloride twice a day, ½ tsp trimethoprim sulfamethoxazole suspension once a day, 2 mg crystalline warfarin sodium once a day, and 5 mg captopril three times a day. She had been on these medications for over 18 months but her digoxin preparation had been changed from liquid to tablets shortly before her symptoms began. Family medical history was significant only for a mother with a history of seizures. There was no family medical history of chorea or other movement disorders.

On examination she was alert and oriented. She had multiple surgical scars on her chest and abdomen. Heart examination showed a grade II/VI systolic murmur with a mechanical click at the end of S2. There was no hepatosplenomegaly, clubbing, or cyanosis. Neurologic examination revealed normal repetition, naming, and calculations. She had dysarthria with varying speech volume. Cranial nerves II–XII were intact. Strength was difficult to evaluate secondary to the severe motor impersis-

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tence on the left but no frank weakness was noted. Milkmaid's grip was present on the left. Deep tendon reflexes were trace to 1+ and symmetric. Plantar responses were downgoing. She had irregular nonrhythmic random jerky movements predominantly of the face, tongue, left arm, and leg. Occasional choreic movements were also noted on the right. Cerebellar examination showed difficulty with finger to nose and heel to shin secondary to the choreiform movements. There was no tremor or frank dysmetria. There was no nystagmus. Gait was slightly wide-based and interrupted occasionally by a choreiform/hemiballistic movement causing her to stagger slightly (see the videotape).

Computed tomography (CT) of the head was normal. Magnetic resonance imaging (MRI) could not be done secondary to the pacemaker. The echocardiogram showed a hypokinetic left ventricle with no vegetations or clots on the mural surface or on the prosthetic mitral valve. Laboratory work-up included: WESR 2 mm/hr (normal 0–20 mm/hr); PT 19 (control 10.9–13.3 sec); PTT 43.8 sec (control 23.8–34 sec); TSH 1.58 UIU (normal 0.4–4.7 UIU/ml); T4 9.2 μg/dL (normal 4.8–11.2 μg/dL); ANA negative initially with repeat 1+ homogeneous; anti-double-stranded DNA antibody 7% binding (normal <20%); anticardiolipin 8.3 gpl (normal <23 gpl) and 2.2 mpl (normal <11 mpl); anti-DNAaseB 1:85 (normal <1:170); ASO titer 122 IU (normal 0–199 IU); anti-hyaluronidase <1:256 (normal <1:256); and digoxin level 3.8 ng/mL (normal 0.8–2.0 ng/mL).

The digoxin was held and repeat level 3 days later was 1.47 ng/mL. With the lower level, she had almost complete resolution of symptoms over 3 days. However, at discharge, she was given her original dose of digoxin and the symptoms returned after 4 days. She was reexamined 10 days after discharge and was noted to have recurrence of chorea, predominantly left-sided, but less severe than originally. Her digoxin level at that time was 2.47 ng/mL. Subsequently, her dose of digoxin was lowered and symptoms resolved again. At follow up she had no further chorea and her digoxin level was 1.27 ng/mL.

Discussion

Drug-induced chorea is rare in children. Chorea resulting from digitalis toxicity has never been reported in children. Only two adult cases linking chorea to digoxin intoxication have been reported. In one patient, hemichorea was present[1] and in the other, generalized chorea occurred in the postoperative phase of an aortic dissection repair.[2] In both cases, the chorea lasted several days. Sydenham's chorea is the most common childhood chorea. In this patient, there was no clinical history or serologic evidence supportive of a streptococcal infection. Other causes of chorea, such as systemic lupus erythematous and thyrotoxosis, were also ruled out. Although drug toxicity is considered a generalized insult, the presentation with predominantly hemichoreic movements suggests a lateralizing lesion. Hemichorea has been reported with other "generalized" insults such as Sydenham's chorea,[3,4] phenytoin toxicity,[5,6] oral contraceptive-induced chorea,[7] and thyrotoxicosis.[8] Whether a predisposing unilateral abnormality of the basal ganglia, such as a vascular injury, set the stage for a predominantly unilateral presentation of a global problem can only be speculated on. It is possible that a silent insult to the basal ganglia could have occurred during one of her surgeries. However, there was no evidence for any basal ganglia abnormalities on the patient's CT scan of the head. An MRI would have been useful to better evaluate the possibility of underlying ischemic lesions, but was unobtainable because of the presence of a pacemaker.

Chorea occurs in approximately 11% of children following cardiac surgery using cardiopulmonary bypass with hypothermia.[9] This chorea presents within 7 days of surgery. Selective injury to the globus pallidus is noted in autopsied cases.[10] Because our patient had no recent surgery, postsurgical chorea is an unlikely explanation for her symptoms. However, the history of previous surgeries may have predisposed her to manifest chorea if a second insult occurred. The resolution of her symptoms with the waning of her digoxin level and the recurrence of symptoms with the reinstitution of digoxin at high levels are consistent with digoxin being the etiology of her chorea.

The source of our patient's intoxication is speculative. Digoxin absorptions are preparation-dependent. Although the elixir typically has a higher bioavailability (70–85%) than the tablet form (60–80%),[11] the change in preparation may have contributed to her intoxication because no other factors could be identified. Common early signs of digoxin toxicity are fatigue, anorexia, nausea and vomiting, and central nervous system dysfunction manifested by visual disturbances, delirium, and seizures. Arrhythmias may also occur. It is unclear why our patient had no other symptoms of digoxin toxicity.

The mechanism whereby digoxin induces chorea is unknown. Digoxin crosses the blood brain barrier and up to 5% of a dose in steady state can be found in the central nervous system.[12] In high doses, digitalis increases the sympathetic outflow from the central nervous system. Because the basal ganglia and related structures do not play an active role in the sympathetic nervous system, it is unlikely that this is the mechanism involved. Digitalis has estrogenic activity, producing gynecomastia in men,[13] causing cornification of the vaginal squamous epithelium in postmenopausal women,[14] and directly binding to estrogen receptors in animal models.[15,16] Research suggests that estrogen acts directly on the basal ganglia and plays a regulatory role in the dopamine system.[17] Therefore, one can hypothesize that digoxin may produce chorea through the estrogenic effects in a mechanism similar to that suspected for oral contraceptive-induced chorea. However, the mechanism of digoxin toxicity-induced chorea has yet to be elucidated.

Legend to the Videotape

The videotape shows random, jerky, arrhythmic movements affecting the left arm and leg more than the right. At times, more violent, ballistic movements are seen in the trunk and left lower extremity. She appears fidgety and has semipurposeful movements.

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Complex Hyperkinesias Ipsilateral to Right Frontoparietal Cortical Infarction

Although rare, a certain number of motor phenomenon have been observed in the upper limb ipsilateral to cerebral infarction. These include an instinctive grasp reaction first noted by Hecaen et al in 1957,[1] a utilization behavior,[2] and hyperkinetic motor behaviors recently described by Ghika et al.[3] We report the case of a patient who developed highly complex hyperkinesias of the right arm, contralateral to a left hemiplegia resulting from a right middle cerebral artery infarction that spared the basal ganglia.

Case Report

This 75-year-old, right-handed, hypertensive woman of Polish origin was admitted in our ward for acute left hemiplegia. Two months previously, she developed a rapidly regressive left brachiocephalic hemiparesis. The work-up at that time had shown normal computed tomography scans and a 70% stenosis of the right internal carotid artery on Doppler examination. The patient refused thromboendarterectomy and was discharged to her home, her neurologic examination having returned to normal. In particular, neuropsychologic testing done on the day of discharge showed no abnormalities. This time she developed acute left hemiplegia, left homonymous hemianopia, and total left hypoesthesia without anosognosia or hemiasomatognosia. The patient was confused during the first few days after symptom onset. Cerebral computed tomography (CT) on the day of admission was normal. Ten days later, a repeat CT scan showed a fresh infarction in the territory of the right middle cerebral artery with hypodensities in the prefrontal ascending frontal and ascending parietal sulci. Another CT scan performed 1 month after admission was unchanged. Magnetic resonance imaging (MRI) performed 2 months after stroke onset confirmed the extent of the frontoparietal infarction with total sparing of the underlying ganglia (Fig. 1). Electroencephalography showed bilateral frontal slow waves without any epileptic foci.

From the first day of admission this patient had stereotypical involuntary movements of the right arm limited to her right hemispace. When seated, the patient seized the wheeled table in front of her and rocked it in a to-and-fro motion that lasted for hours (see videotape segment 1). When in bed, she ceaselessly handled either the knob located above her or her bedposts (see videotape segment 2), rang her call-bell compulsively, and moved a rag on her bedside table with stereotypical rotational movements. These involuntary movements persisted during sleep, her right hand constantly fingering the buttons of her nightshirt. She was conscious of these movements when someone drew her attention to them and explained they could not be prevented, that her hand "did not obey her any more," that it had become "electronic," and that all these movements "were a necessity." Sometimes she asked that her right hand be bound to her, but in general she was indifferent to these movements. Once an object was seized, the patient was only able to relinquish it after having received several orders to do so, but then quickly took it up again after some hesitation. The removal of the handled object did not induce anxiety. These involuntary movements ceased when the patient engaged in voluntary activity; she could feed and wash herself normally despite her left hemiplegia. The presence of a pen and writing pad triggered a hypergraphic behavior, of which the patient was conscious, in which she only used the right part of the sheet of paper, was unable to write in straight lines, and showed a graphic awkwardness when compared with writing done before this current stroke (Fig. 2). The patient did not express any desire to communicate and semantic contents were poor. There were some misspellings partially as a result of her Polish origin, perseverations in both spontaneous and copied writing, and some paragraphias. There was no echographia. In addition to this hypergraphia, there was a stereotypical handling of the pen

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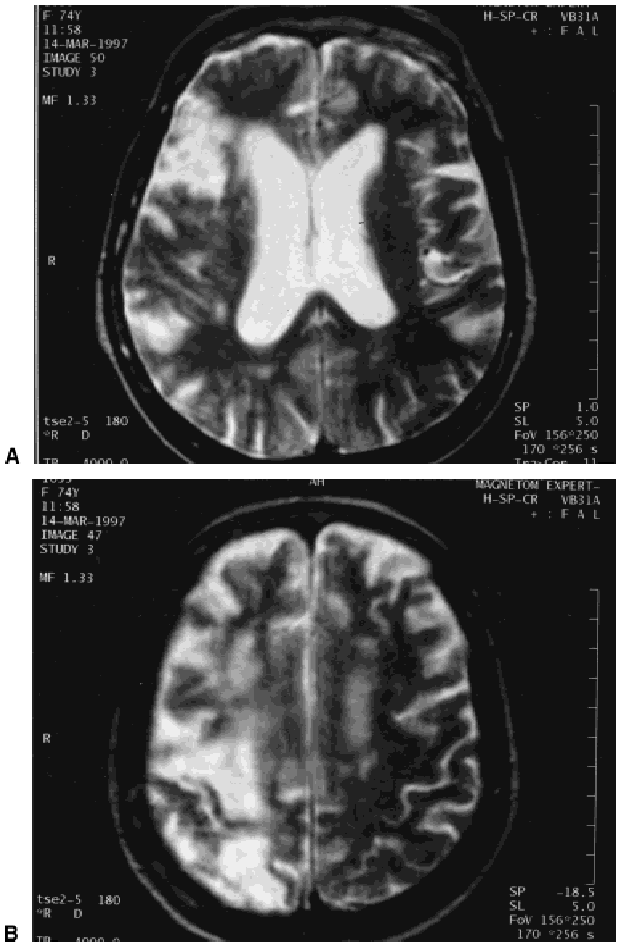

FIG. 1. Axial MRI in spin echo T2 performed 2 months after the present stroke onset shows the right frontoparietal ischemia with hypersignals in the right lateral prefrontal region (**A**) and the right frontoparietal region (**B**).

when someone asked her to stop writing (see videotape segment 4). All other linguistic functions were normal. There were no obsessive-compulsive personality traits. She also had some frontal signs with a grasp reflex and an instinctive grasp reaction of the right hand triggered by tactile and visual stimulations in her right hemispace. There was a utilization behavior without an attempt at imitation; when someone gave her a glass and a pitcher of water, she filled the glass and although not thirsty, repeatedly drank from it (see videotape segment 3).

This same sort of utilization behavior was observed with a pair of sunglasses, a comb, and a pair of scissors and some paper. On neuropsychologic testing, she was unable to reproduce Luria's graphic or gestural series and showed many perseverations. Fifty-seven percent of perseverations were noted during the Wisconsin test. Mini-mental state score was 24. Schenkenberg's test showed left unilateral space neglect. There was no apraxia of any kind, no visual agnosia, and no sign of interhemispheric disconnection.

These involuntary movements were observed during the entire 3-month course of her hospitalization. They became intermittent during the last 15 days, and she was discharged to a nursing home. The patient died 4 months later of a third stroke involving the entire right hemisphere and the left occipital lobe after an emergency operation for acute angiocholitis. Permission for autopsy was refused by her family.

Discussion

This patient had involuntary movements of the right hand consisting of an instinctive grasp reaction, as defined by Seyffarth and Denny-Brown[4] in 1948, integrating phenomenon of "magnet reaction and instinctive groping." She tended to seize objects located in her right hemispace. Magnani et al[5] had also observed that the phenomenon of grasping and groping of the dominant right hand in response to a visual stimulus was electively related to the right hemispace. In our observation, however, this instinctive grasp reaction was prolonged by stereotypical, compulsive movements escaping any willful control which recurred equally during sleep, an association which, to our knowledge, has not been described previously. Although these movements were felt by the patient to be completely involuntary, they could not be assimilated to an "alien hand" because of their stereotypical and ceaseless characteristics.

Hecaen et al[1] described several cases of grasping phenomena concerning the hand ipsilateral to a retrorolandic lesion, most often right-sided, sometimes with groping and searching. Mori and Yamadori[6] found a correlation between the presence of an ipsilateral instinctive grasp reaction (IGR) and an extensive

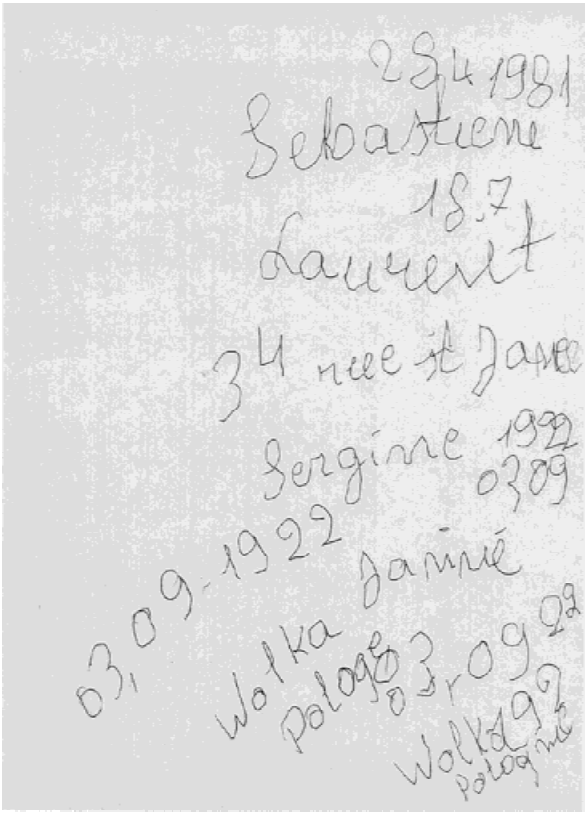

FIG. 2. Spontaneous writing in French 1 month after onset showing a tendency to use only the right part of the sheet of paper and uneven lines.

infarction in the territory of the right middle cerebral artery. However, this hemispheric asymmetry was not confirmed by Renzi and Barbieri[7] in their study of 491 such patients. A grasp reflex or an IGR were observed in frontal lesions, mostly median, sometimes lateral, rarely subcortical, but never in the event of retrorolandic lesions. In 1995, in a population of 210 consecutive patients with acute unilateral stroke, Ghika et al[3] described hyperkinetic motor behavior of the upper limb ipsilateral to the hemispheric lesion in 20 cases of whom 17 had a form of compulsive handling of electrocardiographic leads, venous catheters, and different parts of the bed (sheets and barriers) when awake. These movements partially resembled what we saw in this case. However, they were reported only during the acute phase of stroke and disappeared at night. Ghika et al thought these behaviors could be motor expression of the transient modifications of brain plasticity occurring immediately after an acute lesion. The complex hyperkinesias seen in our patient lasted for another 3 months in the chronic phase of stroke without any alteration of consciousness. They persisted during sleep. The hyperkinetic behaviors described by Ghika et al were reported to occur with large infarctions in the internal carotid territory always involving the internal capsule and the basal ganglia, which was not the case in our observation.

Fung et al[8] reported a distinctive movement disorder of rhythmic, stereotypical, and repetitive movements in four patients after infarction involving either the thalamus or the basal ganglia. Aside from their stereotypical and repetitive characteristics, these movement abnormalities were different from those we describe in our case. In Fung's cases, the movements were those of rhythmic scratching or rubbing of the hands and heels. They were of such persistence as to cause skin injury. Our patient's stereotypical movements involved compulsive object manipulation. The movements reported by Fung were bilateral and asymmetric and absent at night. Our patient's were strictly unilateral and persisted during sleep. In Fung's cases they appeared to occur spontaneously and could be provoked by passive movement of the limbs, something we never observed in our patient. In Fung's clinical syndrome, there was a setting of language aspontaneity, often mutism, more rarely an inappropriate repetition of words and sentences, whereas our patient spoke normally. In Fung's cases like in ours, frontal release signs with perseverations on psychomotor testing, a grasping reflex, and groping were noted. Lastly, the thalamus and the basal ganglia were spared.

These stereotypical movements of the right arm and hand were associated with hypergraphia triggered by the presence of a pen and a writing pad of which the patient was aware. They had some of the characteristics of the spatial agraphia described in right hemispheric lesions by Hecaen et al[9] and Marcie et al[10]: graphic awkwardness, writing limited to the right part of the sheet, and irregular lines. This hypergraphia also had some perseverations as seen in frontal hypergraphias. There was no echographia contrary to the graphomania described by Cambier et al.[11] The semantic contents were poor with low communication value.

The patient could not prevent herself from handling the objects placed within her range. Both this instinctive grasp reaction and this utilization behavior were integrated within the framework of an environmental dependence syndrome[12,13] with the patient being dependent on external stimulations.

We think this case of upper limb hyperkinesia is of particular note because of its mix of both frontal and right hemispheric signs. The "uninhibited" character of the motor activity was probably the result of the loss of a suppressive influence exerted by the right hemisphere onto the left one. There was, in addition, a triggered behavior more commonly found in frontal lesions. This observation underlines the importance of carefully and repeatedly inspecting the arm homolateral to a cerebral infarction, often bound for intravenous perfusion use, because it can be animated with involuntary movements.

Legends to the Videotape

Segment 1: Sitting in her armchair, the patient begins a ceaseless to-and-fro motion with the wheeled table in front of her. She can stop this behavior for only a few seconds after having been repeatedly ordered to do so, then promptly starts again.

Segment 2: The supine patient is manipulating the handle located at the top of her bed. She is virtually unable to detach her hand from it.

Segment 3: The patient grabs a glass of water from which she drinks repeatedly without being thirsty. Between two mouthfuls she continues to rotate the glass on the table in a stereotypical way.

Segment 4: The sight of a pen and a writing pad triggers a hypergraphic behavior. After having been ordered several times to release the pen, she finally puts it back on the table before immediately picking it up again, handling it in a stereotypical manner, and then starting to write again.

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The Dancing Larynx—A Variant of Palatal Tremor?

Palatal tremor (PT), previously called palatal myoclonus, is a rare movement disorder consisting of continuous rhythmic movements of the soft palate at a frequency of 20–600 per minute,[1] which are sometimes associated with synchronous movements of other brain stem-innervated muscles or even the limbs.[2,3]

We report a patient with unusual involuntary movements of the laryngeal cage with some similarities to, but also differences from, both the syndromes of palatal tremor (PT) and focal dystonia. The patient had developed spontaneous movements of the laryngeal cage following a severe febrile illness. These movements were complex and arrhythmic, and were suppressed by talking or deep breathing. On opening the mouth, the laryngeal cage movements developed into rhythmic vertical movements of varying frequency with synchronous movements of the tongue, posterior pharynx, and the palatopharyngeal arch. However, there were no accompanying movements of the uvula, the roof or posterior part of the soft palate typical of PT. By history, there was also involvement of the lower face, the right shoulder, arm, and leg, and audible clicking sounds synchronous with the movements also occurred. We propose that this atypical presentation could be a variant of palatal tremor, possibly resulting from a previous encephalitic illness, but an unusual form of focal dystonia cannot be excluded.

Case Report

A 33-year-old woman developed visible movements of her larynx 2 months after a "viral" illness with nausea, dizziness, high fever, and generalized paraesthesiae and pain. The laryngeal movements, which were initially intermittent and later became continuous, were accompanied by an audible clicking sound in her throat and moderate pain in the back of the neck. When opening her mouth, she would see her tongue moving rhythmically in the mirror. The movements persisted during sleep. Two years after the onset of the laryngeal movements, these spread to intermittently involve the right shoulder and lower facial muscles. When she was first seen 3 years after the onset of symptoms, she reported a recent episode of numbness of the right side of her neck and the right angle of her jaw, and a rhythmic clicking noise in her right ear, both of which had subsided after 2 weeks. For a short time, she and her husband had also noticed rhythmic movements of her right arm and leg, particularly at night. There was no history of drug treatment and no family history of relevance.

On examination, there were complex, partly circular, side-to-side, and vertical, arrhythmic movements of the outer larynx which were suppressed by talking or deep breathing. When she opened her mouth, the movements of the outer larynx would become rhythmic, vertical, and were synchronous to movements of the tongue, the posterior pharyngeal wall, and the palatopharyngeal and the palatoglossal arches. They were accompanied by an audible clicking sound, which appeared to be caused by the movements of the tongue and the pharynx. The frequency of these movements would vary from 60–180 per minute. The roof and posterior part of the soft palate and the uvula were still. Rapid ante- and retroflexion of the head would precipitate severe bouts of myoclonic twitching associated with a tingling sensation of the face, scalp, head, and shoulders. There was no voice tremor and the remainder of the neurologic examination was normal. Full blood count, biochemical screen, ESR, cerebrospinal fluid examination including oligoclonal bands, and brain magnetic resonance imaging (MRI) were normal.

When seen again 10 years after onset of symptoms, she reported an episode of facial movements with tonic elevation of the left and depression of the right side of her mouth, which lasted for only a few weeks. By history, the movements had spread to her chest and upper abdomen, but were not seen on examination, which was unchanged from previous visits. Auditory brain stem-evoked potentials, a repeat MRI of the brain, and a fluorodeoxyglucose PET scan were normal. In particular, no abnormalities of the inferior olives were seen. Sensory evoked potentials were increased in amplitude but of normal latency and form. Treatment with 14 mg benzhexol daily had been unsuccessful. However, 10.5 years after the onset of her symptoms, the movements and audible clicks spontaneously remitted for several months. When they recurred, they were mild and only occurred intermittently, and remained unchanged for the next 4 years.

Discussion

This patient displays many features of PT such as movements of parts of the soft palate (the palatopharyngeal and palatoglossal arches), synchronous with movements of the tongue, larynx, and pharynx, persisting during sleep. There were also audible clicking sounds synchronous with the abnormal movements. However, there are also some atypical features compared with classic PT. (1) The predominant movement disorder in this patient was of complex and arrhythmic movements of the laryngeal cage, which were suppressed by action (talk-

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ing). When the mouth was opened, they became rhythmic, and it became apparent that they were synchronous with writhing movements of the tongue and contraction of the posterior pharyngeal wall, the palatopharyngeal and, to a lesser degree, the palatoglossal muscles. (2) The movements were of varying frequency and amplitude. (3) The part of the palate which forms the roof of the palate and is elevated by the tensor veli palatini and the dorsal part of the palate, which is elevated by the levator veli palatini, did not move. The uvula, which is typically raised in PT, was not involved. (4) She also experienced sensory symptoms and sensory input (flexion of the head) triggered attacks.

These atypical features raise the differential diagnosis of focal dystonia. The complex movements of the laryngeal cage are compatible with this, with irregular, slow, and partly circular movements of varying frequency and amplitude while the mouth is closed, suppression on action and change to a faster, more rhythmic, tremulous movements when the mouth is opened. In addition, the brief (unobserved) episode of tonic contraction of facial muscles is also suggestive of a dystonic disorder. Focal dystonia of the laryngeal cage is unusual. In our patient, there was no preceding peripheral injury, use of neuroleptic drugs, or history of psychiatric disorder, all of which can cause focal dystonia of the craniocervical region.[4,5] In addition, the presence during sleep, the ear clicks, the sudden onset and the remission would be unusual for focal dystonia.

Despite the unusual phenomenology, this syndrome may therefore belong to the spectrum of PT. In PT, particularly the symptomatic form, extrapalatal muscles may be involved and the palatal movements may affect different parts of the soft palate to varying degrees. The tensor veli palatini is characteristically involved in essential PT (giving rise to ear clicks[6,7]) and the levator veli palatini in symptomatic PT, but not essential PT, both resulting in elevation of the uvula, which was not seen in this patient.[8] Our patient also had a clicking sound, but it was located in her throat, and on examination the origin of these clicking sounds appeared to be the movements of the tongue and pharynx rather than the soft palate. However, the tensor veli palatini muscle may nevertheless also have been involved because she had ear clicks for a while, which were different from the continuous clicking sound associated with her laryngeal movements. However, no electrophysiological recordings were made, and therefore the involvement of specific muscles remains speculative.

Could this be a psychogenic movement disorder? PT subject to voluntary control has been described.[10] However, the complexity and the velocity of the laryngeal movement, as well as the extent of the movement disorder, makes this less likely. Additionally, the movements were present during sleep and there were no other features suggesting a psychogenic movement disorder.

The underlying mechanism of PT, which is thought to be an oscillatory firing of neurones in the inferior olives in the symptomatic form and the same or another pacemaker in the brain stem in the essential form of PT,[2,9] may also have caused the rhythmic laryngeal movements in our patient. However, in neither of these two types, to our knowledge, has a predominant laryngeal cage movement disorder, as seen in our patient, been described as yet.

We propose that these atypical movements of the laryngeal cage represent an atypical variant of palatal tremor, possibly resulting from an encephalitic illness, but an unusual focal dystonia cannot be completely excluded.

Legend to the Videotape

The patient exhibits violent and complex (side to side, circular, and vertical), arrhythmic movements of the outer larynx, which disappear during speaking. When the patient opens her mouth, the movements become rhythmic, albeit of varying frequency and amplitude, and are synchronous with movements of the tongue, pharynx, and the palatopharyngeal and palatoglossal arch. The uvula and the roof of the palate remain still.

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A Geste Antagoniste Device to Treat Jaw-Closing Dystonia

One of the most impressive features of dystonia is its frequent ability to improve with tactile maneuvers or sensory

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tricks. These gestures are a classic hallmark of the condition and when present can be dramatically effective. Termed geste antagoniste, or antagonist gesture, the tactile stimulation is not always antagonistic or opposite to the direction of the dystonia. In a true sensory trick, the tactile stimulation is light and would be ordinarily insufficient to counteract the force of the dystonic muscular contraction. Many of these gestures (for example, touching the chin or back of the head in a patient with torticollis) temporarily ameliorate the condition[1] but are not practical as treatments because the dystonia usually returns as soon as the trick ends. We present a professional French hornist who developed task-specific jaw-closing dystonia that spread to involve speaking and drinking. We constructed a dental prosthetic device that mimicked his sensory trick and returned his speech and drinking nearly to normal.

Case Report

A 43-year-old professional French horn player was referred to the Columbia-Presbyterian Center for Dystonia with difficulty playing the horn, speaking, and drinking.

His natural ability on the horn was evident immediately after beginning his studies, and at age 20 he began performing in a major symphony orchestra. He had never experienced previous difficulty playing the horn and regularly performed up to 6 hours per day 6 days per week. His medical history was notable for moderate obesity, diabetes mellitus, hypertension, and alopecia universalis developing at age 20. There was no history of diarrhea or painful muscle spasms. He was of Ashkenazi Jewish background and had no family history of dystonia. There was no exposure to neuroleptics or antiemetics. Imaging studies were not performed.

Fifteen months prior to evaluation at our center, after a particularly heavy period of playing, he took 3 weeks of vacation. Returning to play, he noted that his embouchure (the set pattern of facial muscles used to approach the mouthpiece) did not feel comfortable. Within 2 months he noticed that while playing, his jaw would not open when he attempted to take a deep breath. Efforts to alter his playing style, increase his daily practice, or abstain completely from playing did not help his condition. Trials of massage, acupuncture, and chiropractic therapy were also unhelpful. He gradually developed an involuntarily clenching of his teeth when playing accompanied by the sensation that his tongue was pressing against his teeth. Nine months after the onset of symptoms, playing became so uncomfortable that he was forced to retire from performing. Over the next 3 months dystonia spread to involve drinking and speech. Putting a cup of liquid to his lips or attempting to speak immediately triggered involuntary jaw closure. This ceased as soon as he stopped talking or drinking. He discovered the sensory trick of holding a small piece of food between his left upper and lower molars, which improved the clarity of his speech. Throughout the course of his illness, he had no difficulty opening or closing his jaw to eat, chew, or swallow. There was also no pain in the jaw or face aside from a feeling of progressive tightness in his masseters after prolonged speaking.

Neurologic examination was entirely normal except for prominent hypertrophy of the masseters, jaw-closing dystonia, and slight left-sided perioral dystonia. As demonstrated in the videotape, movements of the lips, cheeks, and jaw were unimpaired. When attempting to speak, his jaws immediately clenched together and his lips slightly pulled in. There was slight involuntary separation of the lips on the left, although he was unaware of this. Jaw closure ceased as soon as he stopped talking, only to recur when he began to speak. Similar (although less dramatic) movements were triggered by drinking from a cup and by playing the French horn. By placing a straw or a piece of plastic between his left rear molars, his speech and drinking became instantly nearly normal. The effect of placing the sensory stimulus on the right side of the mouth was far less effective.

Given his marked improvement with a sensory trick, we constructed a dental prosthesis to fit over two lower molars of the left jaw preventing jaw closure by 3 mm (see Fig. 1). A second identical prosthesis was constructed to fit the right lower jaw for symmetry. Using the prostheses, his speech and drinking became instantly nearly normal. He was even able to play the French horn wearing the prosthetics without the sensation of jaw tightness. After removing the prostheses, jaw closing was briefly attenuated, although it eventually returned. Thirty minutes after wearing the device, he began to experience mild jaw tightness at rest. He was treated with botulinum toxin injections to the masseters, although he continued to use the prosthetics.

Discussion

We present a dramatic example of focal task-specific dystonia responsive to a sensory trick. The etiology of task-specific dystonia is unknown. Among musicians, a history of trauma, change in technique, or increase in demands of performance often precedes the onset of dystonia.[2] Although our patient was of Ashkenazi Jewish background, there was no family history of dystonia. The occurrence of two unusual illnesses (dystonia and alopecia universalis) in the same individual is intriguing but probably coincidental. Jaw-closing dystonia could be mistaken for sustained myotonia. However, our patient had none of the cardinal systemic features of myotonic dystrophy, and his involuntary jaw closure was task-specific. Painful muscle spasms affecting the jaw occur in Satoyoshi syndrome accompanied by alopecia universalis and diarrhea.[3] However, these patients usually have painful spasms that occur at random in multiple body regions and may persist in sleep.[3] Inverse masticatory muscle activity can mimic jaw-closing dystonia; however, these patients typically have signs of cranial nerve dysfunction and usually have an underlying structural lesion.[4,5]

We previously reported two French horn players with task-specific dystonia of the lower face ("embouchure dystonia").[2] Few other examples of this disorder have been described in detail, possibly because the condition is not recognized or because affected musicians simply do not seek the attention of an experienced neurologist. Most wind and brass players with task-specific lower cranial dystonia have abnormal movements of the lips and tongue, sparing the jaw.[6,7] Sensory tricks are usually absent in these patients. Our patient's dystonia was unusual in that it predominantly involved the jaw and responded dramatically to a sensory trick.

Several studies have shown that blocking or changing sensory input from muscle afferents can improve dystonia. Injection of lidocaine or ethanol into a muscle blocks muscle spindle afferents without causing weakness. This technique transiently improves writer's cramp[8] and oromandibular dystonia.[9] In people, muscle spindle afferents are abundant in jaw-closing muscles (temporalis, masseters, and medial pterygoid) and nearly absent in muscles that open the jaw (lateral pterygoid,

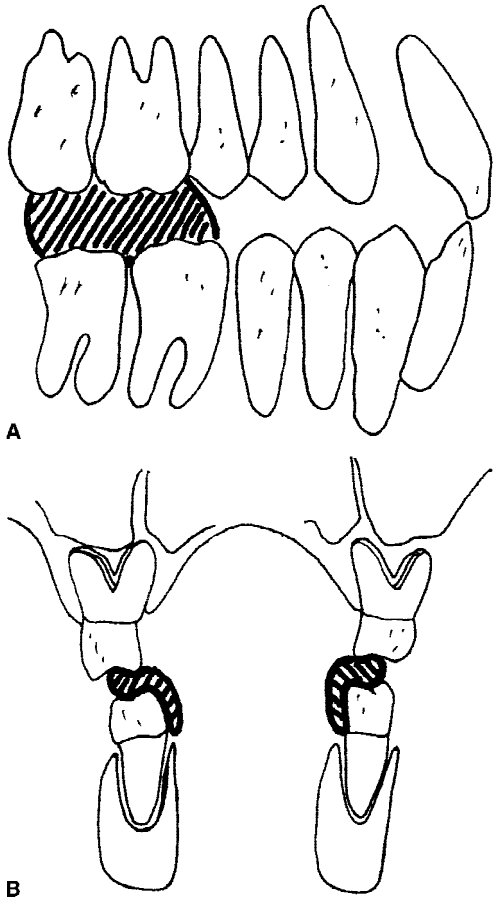

FIG. 1. (**A**) A sagittal view displays the oral prostheses that cover the first and second molars (**B**). A ball clasp between the molars helps secure the device to the teeth. A coronal view demonstrates how each prosthesis extends onto the lingual tooth surface for increased retention. The anterior teeth are not covered, allowing for normal tongue movement and position. The prostheses are balanced for even contact in the closed mouth position.

mylohyoid, and digastric).[10] This may explain why patients injected for oromandibular dystonia derive the most benefit from muscle spindle blockade when the predominant dystonic movement is jaw closure.[9] It has also been shown that muscle spindles and receptors of the temporomandibular joint stimulate masseter contraction, whereas periodontal receptors have an inhibitory effect.[11]

How does our patient's prosthesis improve his dystonia? We did not perform an electrophysiologic study because of concerns of patient comfort, and thus cannot comment definitively on the pattern of muscle activation. However, the dental prosthesis we devised extended only 3 mm above the molars and probably did not simply prevent occlusion of his jaws. We postulate instead that the device activated periodontal receptors (inhibiting firing of the masseters) by modulating central control of jaw closing. Although we did not attempt it, injection of our patient's masseters with lidocaine (inhibiting the excitatory muscle spindle afferents) might have had the same effect.

The most effective treatment for oromandibular dystonia is injection of botulinum toxin. In experienced hands, the success rate for significant improvement is as high as 60%.[12] Botulinum toxin injections are well tolerated, and side effects of excess weakness or dysphagia are uncommon. Dental prosthetics cannot replace botulinum toxin injections, and indeed many patients have used dental devices in vain after receiving a misdiagnosis of temporomandibular joint dysfunction. However, as many as 33% of patients with oromandibular dystonia have sensory tricks that improve their symptoms.[13] We suggest that a sensory trick should be sought in all oromandibular dystonia patients, particularly those whose primary abnormality is jaw closing. Patients who demonstrate a significant benefit from a sensory trick, either elicited by history or discovered in examination, might benefit from a geste antagoniste prosthesis. This approach is an inexpensive risk-free alternative or complement to botulinum toxin injections, and may significantly improve the quality of life of some patients with oromandibular dystonia.

Legend to the Videotape

The patient is able to open and close his jaw, pucker his cheeks, and whistle without difficulty. When speaking, his jaws immediately close producing moderate dysarthria. This is nearly completely relieved by holding a straw or plastic pipette tip between his left molars. The prosthetic devices are displayed in the tape, showing the ball clasp and extension onto the lingual tooth surface. When he inserts the prosthetics, his speech instantly becomes nearly normal, mimicking the effect of the straw and pipette.

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Treatment of Facial and Orolinguomandibular Tardive Dystonia by Botulinum Toxin A: Evidence of a Long-Lasting Effect

Tardive dyskinesias are a relatively common side effect of certain neuroleptic treatments. Among these disorders, dystonic dyskinesias involving facial and orolinguomasticatory muscles are most frequently encountered.[1] Drug treatment of these disorders often provides little benefit. In these cases, treatment with botulinum toxin A (BTX-A) offers a potentially useful therapeutic alternative.

In recent years, only a few case reports have been published examining the effect of BTX-A treatment for tardive dyskinesias.[2–6] Féve et al reported successful treatment of 12 patients with laryngeal dystonia.[7] Tarsy et al reported successful treatment of tardive dyskinesias in an open-label study.[8] In these reports,[2–8] the effect of BTX-A lasted for the standard period seen in various movements disorders, usually 2–3 months. Only one report briefly mentioned the long-term effect of BTX-A in two patients with tardive dystonia.[9] We report the successful treatment of four patients with chronic tardive dystonic dyskinesia syndrome affecting the facial and orolinguomasticatory muscles, with an extraordinary long-lasting effect of BTX-A treatment in two of them.

Case Reports

Case 1

A 43-year-old woman had been treated with chlorprothixene for 60 months after experiencing an isolated paranoid schizophrenic episode (see videotape segment 1). Sixty-one months after beginning continuous treatment, she experienced a "strange feeling" around her eyes and symmetric paresthesias in the lower part of her face. After several weeks, frequent blinking developed, and after another 2 months she had a blepharospasm which symmetrically affected both parts of the orbicularis oculi muscle. After another 2 months, the perioral muscles were also affected (the dyskinesia had obtained the full characteristics of Meige's syndrome). The neuroleptic drug treatment regimen was not changed and only biperidene was added to therapy. Anticholinergic treatment using biperidene was unsuccessful, however, and therefore trials with tiapridal and then with sulpiride were begun. Again, no signs of improvement of tardive symptomatology were observed. On referral to our movement disorders center, her condition was confirmed as Meige's syndrome affecting mainly the periorbital muscles. Neurologic examination showed no other abnormality. Electromyographic (EMG) polymyography showed synchronous and symmetric bilateral dystonic contractions of the orbicularis oculi muscle, frontalis, corrugator supercilii, orbicularis oris, and depressor anguli oris muscles. The value of the AIMS[10] score prior to BTX-A treatment was 24 points. Anticholinergics and atypical neuroleptics (biperidene and tiapridal) were removed from treatment 4 weeks prior to beginning BTX-A injections, but the treatment with chlorprothixene was continued.

The patient was treated with BTX-A (Dysport, Speywood Pharmaceuticals, Ltd, Berkshire, U.K.) injected into the periorbital portions of both orbicularis oculi muscles. Application into the lower facial musculature was avoided because of known complications of the applications in these sites.[11] The patient was followed up every 4 weeks for 2 years. The injections were repeated when the effect of previous treatment had disappeared. During follow up, the required interval between treatment sessions lengthened substantially. The mean duration of the beneficial effect was 192 days (approximately 6 months); there were two treatment sessions per year. The mean dose of injected BTX-A in one treatment session was 120 MU; the total amount of BTX-A administered in 1 year was 240 MU. At the end of the follow-up period, the AIMS score was 10, that is, there was apparent and sustained improvement of greater than 60%.

Case 2

A 70-year-old woman had been treated for reactive depression with perphenazine for 5 years (see videotape segment 2). Thirty-five months after beginning neuroleptic treatment, she abruptly began to display orolinguomandibular dyskinesias which interfered with normal chewing, swallowing, eating, and drinking. She was treated with biperidene and sulpiride without any substantial effect and then was referred to the movement disorders center.

On examination, she displayed marked irregular dystonic dyskinesias involving mainly the lingual and masticatory muscles resulting in involuntary movements of the mandible and tongue and bruxism. Mild dystonic features were also apparent in the periorbital region, and during a 2-week examination period she developed blepharospasm. During the examination, she displayed lateral and upward eye rotations, probably also of dystonic origin. No other neurologic abnormalities were present. EMG polymyography revealed irregular dystonic contractions in the orbicularis oculi muscle, orbicularis oris muscle, masseter muscle, pterygoideus medialis and lateralis muscles, geniohyoid muscles, and in the platysma muscle. Sulpiride and biperidene were withdrawn from therapy and assessment of dyskinesias using the AIMS score was performed. The AIMS score prior to BTX-A treatment was 36 points.

The patient was treated with consecutive injections of BTX-A into both parts of the orbicularis oculi muscle (120

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MU), masseter muscle (160 MU), pterygoideus medialis (100 MU) and lateralis (100 MU) muscles. A hollow, Teflon-coated Dantec (Copenhagen, Denmark) 27G needle was used for injections into both pterygoid muscles, which were reached extraorally using retromandibular access. Follow up entailed an examination every 4 weeks for 2 years. Injections were repeated when the effect of previous treatment had worn off. The most interesting feature in the treatment of this patient was the almost complete disappearance of lingual dyskinesias although BTX-A was not injected into the tongue muscles. Tongue dyskinesias were substantially decreased even when only the masseter muscles were injected. The mean duration of the beneficial effect of BTX-A was 96 days, the number of treatment sessions in 1 year was three to four, the mean amount of BTX-A injected in one treatment session was 430 MU, and the total amount of BTX-A injected during 1 year was 1460 MU. At the end of the follow-up period, the AIMS score had declined to 15, a decrease of 55%.

Case 3

A 28-year-old man had been treated with haloperidol, chlorpromazine, and fluphenazine for 24 months for repeated schizophrenic attacks (see videotape segment 3). After 6 months, he had neck pain and paresthesias around his mouth and orofaciolingual dyskinesias developed after another month. To avoid relapse of his schizophrenia, neuroleptic treatment was not interrupted, and tiapridal and biperidene were consecutively added to his therapy. After failure to respond to these drugs, he was referred to our center. On examination, he showed marked orofaciomandibular dystonia and mild cervical dystonia. EMG polymyography revealed involuntary dystonic activity in depressor anguli oris, orbicularis oris, and risorius muscles bilaterally, and dystonic activity in both trapezoid muscles. Both biperidene and tiapridal were withdrawn from treatment prior to BTX-A injections. The AIMS score prior to BTX-A treatment was 32 points. The patient was treated with BTX-A injected into four sites of the orbicularis oris muscle and into two sites of the trapezoid muscles bilaterally. The patient was followed up every 4 weeks for 2 years. Injections were repeated when the effect of previous treatment had begun to wear off. There was almost complete diminution of dyskinesias despite the fact that only two of the affected pairs of muscles were treated. The mean duration of beneficial effect was 92 days, the number of treatment sessions in 1 year was three to four, the mean dose of injected BTX-A in one treatment session was 230 MU, and the total amount of injected BTX-A in 1 year was 840 MU. At the end of the follow-up period, the AIMS score was 17, that is, an improvement of greater than 50%.

Case 4

A 53-year-old woman had been treated for more than 9 years with haloperidol, clozapine, perphenazine, and tiapridal for schizophrenia (see videotape segment 4). After 93 months of treatment, she reported slight involuntary movements of her jaw and slight involvement of her tongue. After another 3 months, she experienced orolinguomandibular dyskinesias which strongly interfered with speech, chewing, and swallowing. She was treated with tiapridal and sulpiride without substantial effect. Because of abrasions of the gums caused by teeth grinding, she developed gingival defects and her teeth were completely removed. The patient was not able to wear dental prostheses. At the time of referral to our center, she was continuously losing weight (10 kg in 2 months) because of discomfort during eating and drinking caused by the gingival defects.

On neurologic examination, she showed no additional neurologic abnormality. EMG polymyography showed significant involuntary dystonic activity present bilaterally in masseter, pterygoideus lateralis, and medialis muscles, and less pronounced activity in the orbicularis oris muscles. There was also dystonic activity in geniohyoid and mylohyoid muscles. Treatment with sulpiride and tiapridal was terminated prior to BTX-A injections, whereas treatment with clozapine and perphenazine continued. The AIMS score prior to BTX-A therapy was 33.

BTX-A injections were administered into the masseter muscle bilaterally (300 MU) and into pterygoideus medialis (100 MU) and lateralis (100 MU) muscles bilaterally using the same technique as in case 3. The patient was followed up for 2 years. There were only two treatment sessions with an intervening interval of 6 months, and the effect after the second treatment session lasted 18 months. Currently, the value of the patient's AIMS score is still 3 points, an improvement of almost 100%.

Discussion

There were two types of interesting therapeutic responses observed in these four patients. In the patients in cases 2 and 3, disappearance of tardive dyskinesias in all affected muscle groups was noted after consecutive BTX-A injections, injected into only a subset of affected muscles during each treatment session. The reason for injecting only certain muscles was to prevent severe asphyxia, dysphagia, and dysphonia which occasionally occur after BTX-A injections into muscles of the upper throat and tongue. This effect was most prominent in case 3 in which oromandibular and lingual tardive dystonia disappeared although only trapezoid muscles were injected. In case 2, bilateral injection of masseter muscles substantially suppressed dyskinesias in the noninjected lingual muscles. The effect of the injections into all affected muscle groups lasted at least 3 months, the same period as was seen in directly injected muscles. Currently, no satisfactory explanation for this distant effect has been presented. Simple distant effect resulting from the spread of toxin into the nearby muscles has to be taken into account; nevertheless, in our patients it is less probable because of EMG guiding of all injections. In 1968, Rondot et al reported suppression of tremor in an entire limb by anesthetizing only one muscle group.[12] Similar results were also described in recent reports concerning BTX-A treatment of tardive dyskinesias.[2,4,6] Impressively, tardive akathisia was found to be suppressed following injection of cervical muscles.[6] The authors concluded that injection of cervical muscles induced this beneficial effect on a poorly understood feedback mechanism.

A second type of therapeutic response was observed in cases 1 and 4. In addition to a dramatic improvement of tardive symptomatology, an unusual prolongation of the beneficial effect of BTX-A injection was observed in the patient described in case 1. In case 4, severe tardive dyskinesias completely disappeared after two treatment sessions. To date, symptoms have not reappeared. It is hypothesized that feedback mechanism is involved causing a change in the central mechanism of

tardive dystonia. With respect to the effects of BTX-A on tics, it has been suggested by Lang[13] that the toxin might "relieve the subjective urge to perform an abnormal movement" through a peripheral mechanism, as was previously suggested also by Shulman et al.[6] Currently we cannot explain this distant site phenomenon and the unusual duration of the effect. Some evidence suggests an affectation of the central dystonic mechanism in patients treated with BTX-A possibly caused by suppression of proprioceptive input from muscle spindles through Ia afferents, inducing a decrease in muscle activity in nontreated muscles. A similar mechanism was recently described by Priori et al[14] in patients with limb dystonia, in patients with cervical dystonia,[15] and by Pirtošek[16] in three patients with various extrapyramidal disorders. We think this phenomenon of alleviation of symptoms at sites distant from those injected might provide a useful model for studying and formulating the treatment of patients with tardive dyskinesias and deserves further evaluation in a larger cohort of patients. However, the less probable possibility of the natural remission of tardive dystonia in these patients also has to be considered.

Legends to the Videotape

Segment 1: Patient 1 before and after BTX-A treatment. The first part of this segment was recorded prior to BTX-A treatment; the second part was recorded 24 months later when the effect of the last BTX-A injection lasted 6 months.

Segment 2: Patient 2 before and after BTX-A treatment. The first part of this segment was recorded prior to botulinum toxin treatment; the second part was recorded 12 months later when the effect of the last BTX-A injection lasted 3 months.

Segment 3: Patient 3 before and after BTX-A treatment. The first part of this segment was recorded prior to botulinum toxin treatment; the second part was recorded 12 months later when the effect of the last BTX-A injection lasted 3 months.

Segment 4: Patient 4 before and after BTX-A treatment. The first part of this segment was recorded prior to botulinum toxin treatment; the second part was recorded 24 months later when the effect of the last BTX-A injection lasted 18 months.

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Tourette Syndrome: Another Cause of Movement Disorder of the Ear

Caviness et al[1] described patients with ear dyskinesias whose clinical and electrophysiological characteristics were consistent with dystonia. More recently, Chaudhuri and colleagues[2] reported two more patients with a similar movement disorder and coined the term "moving ear syndrome" to label this dyskinesia. We report one of our patients who demonstrates that Tourette's syndrome (TS) is a potential cause of movement disorders of the ear.

A videotape accompanies this article.

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Case Report

This 14-year-old boy was delivered vaginally at term after an uneventful pregnancy. Although there was mention of a brachial plexus injury during delivery, this did not cause any lasting sequelae. His developmental milestones were normal and the medical history was unremarkable. At age 10, however, he began repeatedly to attempt to touch the radial border of the forearm with the ipsilateral thumb as well as bring the medial borders of the scapulae together. Shortly thereafter, the repertoire of his dyskinesias expanded, including excessive blinking, torsion movements of the neck, vertical ("yes–yes" pattern) head jerking, blowing on the fingers, knocking the fingers on the table, and tensing of the abdominal wall. Along with these movements, the patient produced an involuntary vocalization characterized by simple guttural sounds. Approximately 2 years after the onset of the first abnormal movements, the patient started to move his ears. Similar to the other tics, the ear dyskinesia did not cause any meaningful functional disability and was not preceded by any particular local sensation, its intensity was increased by emotional stress, and the patient was capable of suppressing it voluntarily for a short period of time. The type and frequency of the movement disorders and vocalizations waxed and waned. Simultaneously with these tics, the patient developed an irresistible tendency to count objects. Because of a decline in academic performance, he was referred to the Movement Disorders Clinic of the Federal University of Minas Gerais for neurologic evaluation. His mother mentioned that during childhood she presented with "mild nervous tics" which went into remission spontaneously. There was, however, no other family history of movement disorders or behavioral abnormalities. When evaluated at age 14, there was no evidence of attention deficit hyperactivity disorder but the patient mentioned the occurrence of persistent arhythmomania. On neurologic examination, there were abrupt bursts of clonic neck movements characterized by vertical head jerking as well as repetitive, slow (1–0.5 movements per second), anterior–posterior displacements of the external ear which were more noticeable on the right side (see the videotape). On request, the patient was able to interrupt all abnormal movements. The only other abnormal finding was the presence of repetitive coughing. No palatal or other form of myoclonus was observed.

Discussion

The phenomenology displayed by our patient is entirely diverse from the features of the subjects reported by others: onset in adult life; slow, sinuous, patterned, and prolonged spasms, occasionally associated with superimposed jerks or local pain; electromyographic recordings showing bursts of a long duration and intermittent rhythmic discharges.[1,2] Based on these findings, Caviness et al[1] concluded that the "unusual dyskinesias" of their patients most likely corresponded to dystonia. Another patient presenting with an ear movement disorder was described by Kirk and Heilman.[3] Although these authors stated that the dyskinesia was myoclonus, the similarities with the patients reported by others[1,2] and the lack of palatal myoclonus, as well as of clinical or imaging evidence of brain stem dysfunction, instead suggest that their patient also had ear dystonia. Lack of rhythm, presence of voluntary suppressibility, and the association with dyskinesias in other areas are features of the ear movement disorder displayed by the patient reported here which is consistent with tics.[1] Furthermore, he meets the currently established criteria for TS: onset in the first two decades of life, multifocal motor tics, at least one phonic tic, fluctuating course, and no other explanation for these findings.[4] The coexistence of obsessive-compulsive behavior, present in approximately 50% of patients with TS, and learning disorder further support this diagnosis.[5] We would like to stress that ear tics are not common because, among 79 patients with TS followed up in our institution, this is the only subject who presents with such a dyskinesia. Furthermore, to our knowledge, the only other possible mention of ear tics was provided by Keshavan[6] who described 10 "ear wigglers." None of the patients met the criteria for TS and the author labeled the movement disorder as "hysterical tics" and "compulsive tics" in two and five subjects, respectively. Although Keshavan did not elaborate further on the diagnosis of the others, he emphasized a possible psychogenic nature of their movement disorder.

In conclusion, our patient illustrates the notion that the so-called "ear moving syndrome" is not synonymous with focal dystonia and that TS should be considered in the differential diagnosis of ear dyskinesias.

Legend to the Videotape

This is a patient with phonic and multifocal motor tics. The latter also involve the ear.

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