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Clinical/Scientific Notes

Dopa-Responsive Parkinsonism Secondary to Right Temporal Lobe Haemorrhage

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Abstract: A 46-year-old man developed a symmetrical parkinsonian syndrome 7 weeks after large right temporal intracerebral haemorrhage resulting from a ruptured arteriovenous malformation. His signs included bradykinesia, rigidity, start hesitation, and poor postural reflexes, without a resting tremor. He also had signs of a Parinaud's syndrome. Computed tomography and magnetic resonance imaging of the brain demonstrated changes in the right temporal lobe associated with the haemorrhage but no abnormality of the basal ganglia or midbrain. Levodopa therapy produced a dramatic improvement within a few days of commencement. We postulate that the parkinsonism resulted from midbrain compression secondary to transtentorial herniation. Although parkinsonism is a rare complication of lobar intracerebral haemorrhage, it is important to recognise as it may be potentially treatable. © 2002 Movemement Disorder Society

A number of causes of parkinsonism have been identified, including drug exposure, trauma, lacunar disease, infection, and metabolic disturbance.[1] There have also been reports of parkinsonism associated with midbrain haemorrhage,[2,3] compression of the brain by hydrocephalus,[4] chronic subdural haematomas,[5] and intracranial neoplasms.[6,7] We describe a case of parkinsonism following a right temporal lobe haemorrhage.

Case Report

We report on the case of a previously healthy 46-year-old man, with no premorbid evidence of parkinsonism on routine medical examination. He was not on any medications and was working as a physical education teacher. He presented with a severe headache followed by a seizure, decreased level of consciousness (Glasgow Coma Score, 6), a dilated right pupil, and a left hemiparesis. Computed tomography (CT) scan of the brain showed a large right temporal intracerebral haemorrhage measuring 5 × 5 × 3 cm with 6 mm of midline shift, associated with transtentorial herniation. An urgent right temporal craniotomy was performed. The haematoma was evacuated and a small arteriovenous malformation nidas was found and excised.

Once his acute medical condition had stabilised (after approximately 4 weeks), he was transferred for ongoing intensive rehabilitation. At the time of admission to the rehabilitation facility, he had a tracheotomy, indwelling catheter, and was receiving nasogastric feeds. He was intermittently drowsy, but able to obey simple one-step commands consistently. He had mild left hemiparesis (grade 4/5), a left homonymous hemianopia, and a Parinaud's syndrome with impaired vertical upward gaze associated with convergence–retraction nystagmus on attempted convergence, and small, unequal pupils reactive to accommodation but not light. His tone was normal at this point. He required the assistance of two people to transfer and stand. He had delayed information processing, dysphonic speech, and delayed initiation of both the oral and pharyngeal phases of swallow.

Over the next 3 weeks, as he became more alert and started to mobilise, it became evident that he had parkinsonian features including symmetrical bradykinesia and rigidity, reduced facial expression, reduction in spontaneous blink rate, and a soft, monotonous voice. His posture was flexed and he had start hesitation, freezing, and festination. He had poor postural reflexes, with retropulsion and propulsion. There was no resting tremor. Muscle strength, deep tendon reflexes, and sensation were normal. Left homonymous hemianopia and signs of Parinaud's syndrome persisted. He required moderate assistance with activities of daily living and stand-by supervision to mobilise and transfer. His nasogastric tube had been removed, and he was tolerating thin fluids.

He was commenced on levodopa/carbidopa therapy (100/25) twice daily. Within 6 days, there was a dramatic improvement in his symptoms and a noticeable reduction in his bradykinesia and rigidity. He was alert, communicating well with no dysphonia, and was independent in showering, dressing, and grooming. His gait parameters improved, and he was able to jog 60 metres and run up and down stairs. Levodopa therapy was increased to three times a day and he was discharged home after an 8-week period of hospitalisation.

A magnetic resonance imaging (MRI) scan of the brain showed hyperintense signal in the right temporal lobe in the area of previous intracerebral haemorrhage (T2-weighted images). There was no mass lesion or hydrocephalus. No abnormality was seen in the midbrain or the basal ganglia, in particular, the striatum or globus pallidus (Fig. 1).

Over the next 4 months he developed some difficulty turning in bed, and had early morning symptoms that interfered with his function. He did not experience any motor fluctuations during the day. A nocturnal dose of controlled-release levodopa/carbidopa (200/50) was added and his morning levodopa/carbidopa dosage was increased to 250/25, with satisfactory clinical outcome. It is now 2 years since his intracerebral haem-

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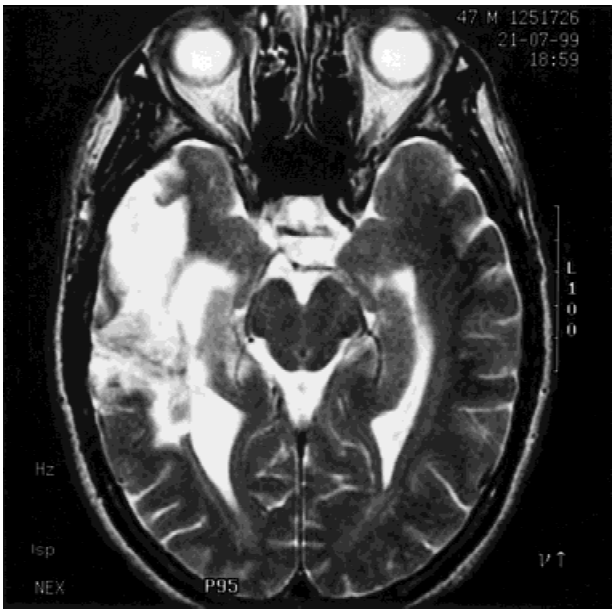

FIG. 1. Magnetic resonance imaging scan of the brain (T2 weighted) showing hyperintense signal of the right temporal lobe in the area of previous intracerebral haemorrhage. There was no mass lesion, hydrocephalus, or abnormality in the midbrain or basal ganglia.

orrhage. His symptoms are stable on 750 mg of levodopa per day. He remains dopa-responsive, with attempted reductions in levodopa dose resulting in increased parkinsonian symptoms. A levodopa dose cycle was performed recently, after withdrawal of levodopa for 12 hours. This demonstrated improvement in his left hand Peg time (a test of hand function involving the insertion and removal of pegs from a board with holes) from 25 to 21 seconds (normal, 15 seconds), 3 hours after a single dose of 200/50 levodopa/carbidopa. His gait time to walk 10 metres improved from 6.0 to 4.3 seconds (normal, 4.0 seconds). The features of Parinaud's syndrome are improving, but remain.

Discussion

This patient's parkinsonism was discovered in the immediate aftermath of a large haemorrhage into the right temporal lobe. Prior to the haemorrhage he was healthy, working as a physical education teacher. Routine medical examination by his general practitioner had not detected any signs or symptoms of pre-existing parkinsonism. The question arises as to whether the parkinsonism resulted from the haemorrhage or whether the haemorrhage unmasked as yet asymptomatic idiopathic Parkinson's disease.

Parkinsonism is frequently associated with loss of neurones in the zona compacta of the substantia nigra in the midbrain,[8] although there are some forms of parkinsonism where the main pathology is postsynaptic and the substantia nigra is left intact. There is good evidence in this patient that the temporal lobe expansion associated with the haemorrhage caused compression of the midbrain, as he developed a Parinaud's syndrome, a sign of tectal plate dysfunction. It follows that damage may also have been done to the substantia nigra directly by compression or by interference with its blood supply.

There have been a number of reports of parkinsonism due to mass effect from subdural haematomas, supratentorial tumours, and hydrocephalus. Curran and Lang[4] found parkinsonism arising from hydrocephalus in nine cases which responded variably to medical and surgical therapy. The authors' proposed mechanism of hydrocephalic parkinsonism was dysfunction in the nigrostriatal pathway and/or the cortico-striato-pallido-thalamo-cortical circuit, due to mass effect or ischaemia caused by the ventriculomegaly.

It is possible that the lesion in the secondary cases of parkinsonism in whom the response to levodopa is poor lies not in the substantia nigra but in the basal ganglia to which it projects, particularly the corpus striatum. Reduced blood flow to the basal ganglia in hydrocephalus has been demonstrated on CT using 99mTc-hexamethylpropylenamine oxime.[10] The blood supply of the basal ganglia is derived from the pallidal branches of the anterior choroidal artery to the globus pallidus, and branches of the lenticulostriate artery to the head of the caudate and putamen. Lindenberg[11] proposed that anterior choroidal artery compression against the rostral tentorium occurred in swelling of the cerebral hemispheres. The basal ganglia may be more vulnerable to pressure-causing hypoperfusion because they are supplied by non-anastomosing end-arterioles. The cells of the striatum are also thought to be susceptible to ischaemia by virtue of their high metabolic rate.

The levodopa responsiveness in this case supports our pathophysiological hypothesis that the parkinsonism was due to midbrain rather than basal ganglia compression, with midbrain impairment further confirmed by the patient's Parinaud's syndrome. The effect of levodopa in parkinsonism is thought to depend on release of dopamine in the corpus striatum, normally a function of the nigrostriatal tract. Where the disease process affects the basal ganglia, as in progressive supranuclear palsy and multiple system atrophy, levodopa is usually ineffective.

The development of bilateral and symmetrical corticospinal features in the context of a unilateral temporal lobe haemorrhage is unusual. However, Defer and colleagues described this phenomenon previously in a similar case of bilateral parkinsonism following a unilateral midbrain haemorrhage.[3] That report attributed it to bilateral innervations between the basal ganglia, and of crossed nigrostriatal connections, which have been found in monkeys, rats and possibly in humans. This is the also the most feasible explanation for our findings.

Although parkinsonism is a rare complication of lobar intracerebral haemorrhage, it is important to recognise, as it is potentially treatable. We believe this is the first reported case of parkinsonism as a complication of an intracerebral haemorrhage occurring outside the midbrain.

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Thalamic Stimulation for Midbrain Tremor After Partial Hemangioma Resection

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Abstract: We describe a patient with disabling medication-resistant midbrain tremor developed after partial hemangioma resection, who responded to deep brain stimulation of the thalamus. © 2002 Movement Disorder Society

Midbrain tremor is a distinct but uncommon clinical entity caused by a lesion involving the cerebellar outflow pathways or the area around the red nucleus. Although the red nucleus is often involved, destruction of the nucleus is not required for the syndrome to occur.[1,2] Midbrain tremor is typically described as a combination of rest, postural, and kinetic tremor.[2] The kinetic tremor is the most severe tremor and often causes marked disability. It has also been labeled as Holmes' tremor, rubral tremor, thalamic tremor, myorhythmia, and Benedikt's syndrome.[3] The consensus statement of the Movement Disorder Society on tremor recommended the use of the term Holmes' tremor for this condition.[3] They recommended the use of the following criteria for the diagnosis of Holmes' tremor: (1) rest and intention tremor with sometimes irregular presentation and presence of postural tremor in many patients (the tremor may not be as rhythmic as other tremors); (2) slow frequency, usually less than 4.5 Hz; and (3) if the time that the lesion occurred can be identified, a variable delay (usually 4 weeks to 2 years) between the lesion and first occurrence of the tremor is usual. The reason the term Holmes' tremor was suggested is because many cases of such tremor have been described with lesions outside the classic locations. We use the term midbrain tremor here because it is still more widely recognized. There are multiple causes of midbrain tremor, including infarction, contusion, tumor, abscess, and demyelination.[2] Medical symptomatic management of midbrain tremor is usually unsuccessful. Stereotactic surgery such as thalamotomy[4] and pallidotomy[5] has been reported to improve tremor in some cases. Deep brain stimulation (DBS) of the ventral intermediate (VIM) thalamic nucleus is currently considered an effective form of treatment for the control of essential tremor (ET) and tremor secondary to Parkinson's disease (PD).[6] Thalamic DBS is occasionally used to treat tremor secondary to various other diseases, and variable outcomes have been reported with its use for other tremors.[7,8] In the Unites States, thalamic DBS is approved by the Food and Drug Administration for treatment of ET and PD tremor, and its use for other forms of tremor is considered to be off-label or experimental use.

We report on a patient with midbrain tremor resulting from a midbrain cavernous hemangioma treated with thalamic stimulation. This patient had marked functional and symptomatic improvement in her tremor that persisted for the 2 years of follow-up.

Case Report

This 45-year-old woman with a partially resected midbrain cavernous hemangioma presented with a severe left-sided tremor. Approximately 22 years previously, the patient started having episodes of headaches and periodic left-sided weakness. These episodes occurred infrequently. Three years before presentation, she had repeated episodes and developed an enlarged right pupil; hence, she underwent surgery to partially remove the hemangioma in the right cerebral peduncle. The patient was stable for 3 months after surgery and then developed a tremor in her left hand that progressively worsened. She had mild difficulty walking. She denied any tremor in her right hand; she could not perform any motor activities with her left hand. She complained of mild weakness on the left side of her body. She denied any numbness. She had been taking carbidopa–levodopa and trihexyphenidyl and felt that it improved her tremor approximately 30%. The patient had been tried on multiple other medications including benzodiazepines, dopamine agonists, baclofen, and higher doses of carbidopa–levodopa. The patient either had no benefit or adverse effects from these medications.

A videotape accompanies this article.

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On neurological examination her right pupil was 6 mm in size and her left pupil was 2 mm. Her right pupil was sluggishly reactive to light. There was mild ptosis of her right eye. There was decreased light touch and pinprick on the left side of her face. Gag was normal. There was mild bradykinesia during finger tapping, hand movements, and rapidly alternating movements on the left side. She also had decreased light touch, pinprick, and vibratory sensation on the left side of her body. She had normal truncal stability. She had a slightly slow gait and could heel-walk, toe-walk, and tandem-walk. There was a moderately severe resting tremor and a markedly severe postural and kinetic tremor of the left hand. She could not pour with her left hand. When attempting to write, she was unable to bring the pen to paper with her left hand. The patient's magnetic resonance imaging (MRI) scan showed a low signal intensity lesion on T1 and high signal intensity lesion on T2 with peripheral low signal intensity, consistent with a cavernous hemangioma in the right midbrain (Figs. 1 and 2). It measured approximately 1.3 cm × 1.0 cm.

In September of 1998, the patient underwent placement of a thalamic DBS system. The surgical procedure for implantation has been described in detail elsewhere.[9,10] The initial programming was performed the day after surgery, and the parameters included bipolar stimulation with an amplitude of 3.3 V, pulse width of 90 msec, and a stimulation rate of 100 Hz. With the device turned on, there was no evidence of resting or postural tremor in her left hand. She had mild kinetic tremor in her left hand. She could draw a spiral and a straight line with her left hand without resting the hand or arm on the table (Fig. 3). Approximately 1 year after surgery, the patient developed an infection over the implantable pulse generator (IPG) site and had the IPG and connection removed and was treated with antibiotics. After replacement of the IPG and connector, complete tremor control returned. Present stimulation parameters obtained 10 months after replacement (approximately 2 years after the initial surgery) include bipolar electrode selection with 3.7 V amplitude, pulse width of 90 msec, and rate of 170 Hz. The tremor characteristics when the device is turned off are essentially unchanged from baseline.

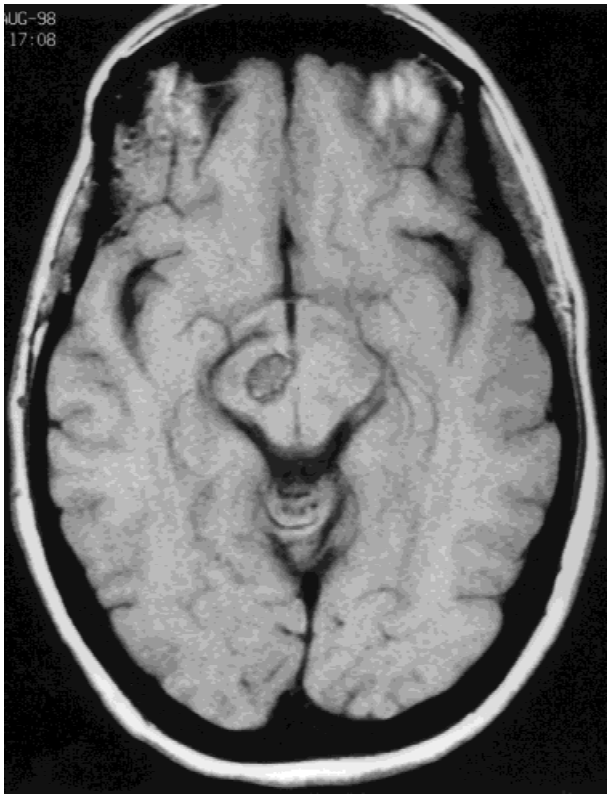

FIG. 1. Brain magnetic resonance imaging (MRI) scans demonstrating low signal intensity lesion on T1 and high signal intensity lesion on T2, consistent with a cavernous hemangioma in the right anterior midbrain.

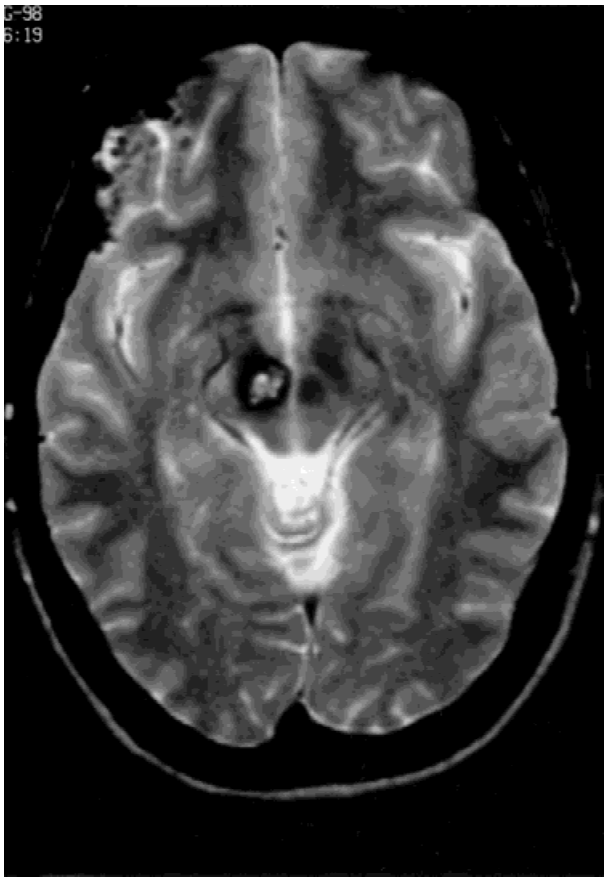

FIG. 2. Brain MRI demonstrating low signal intensity lesion on T1 and high signal intensity lesion on T2, consistent with a cavernous hemangioma in the right anterior midbrain.

Discussion

Our patient had severe tremor in her left hand in the resting, postural, and kinetic positions. The tremor was accentuated in the postural and especially the kinetic position causing marked functional disability. The patient had a midbrain lesion. Based on these characteristics, we diagnosed our patient with midbrain or Holmes' tremor. The patient also satisfied the criteria for Benedikt syndrome due to the presence of partial oculomotor palsy, cerebellar ataxia, tremor, and mild weakness. Our patient had failed multiple medication trials, and because the

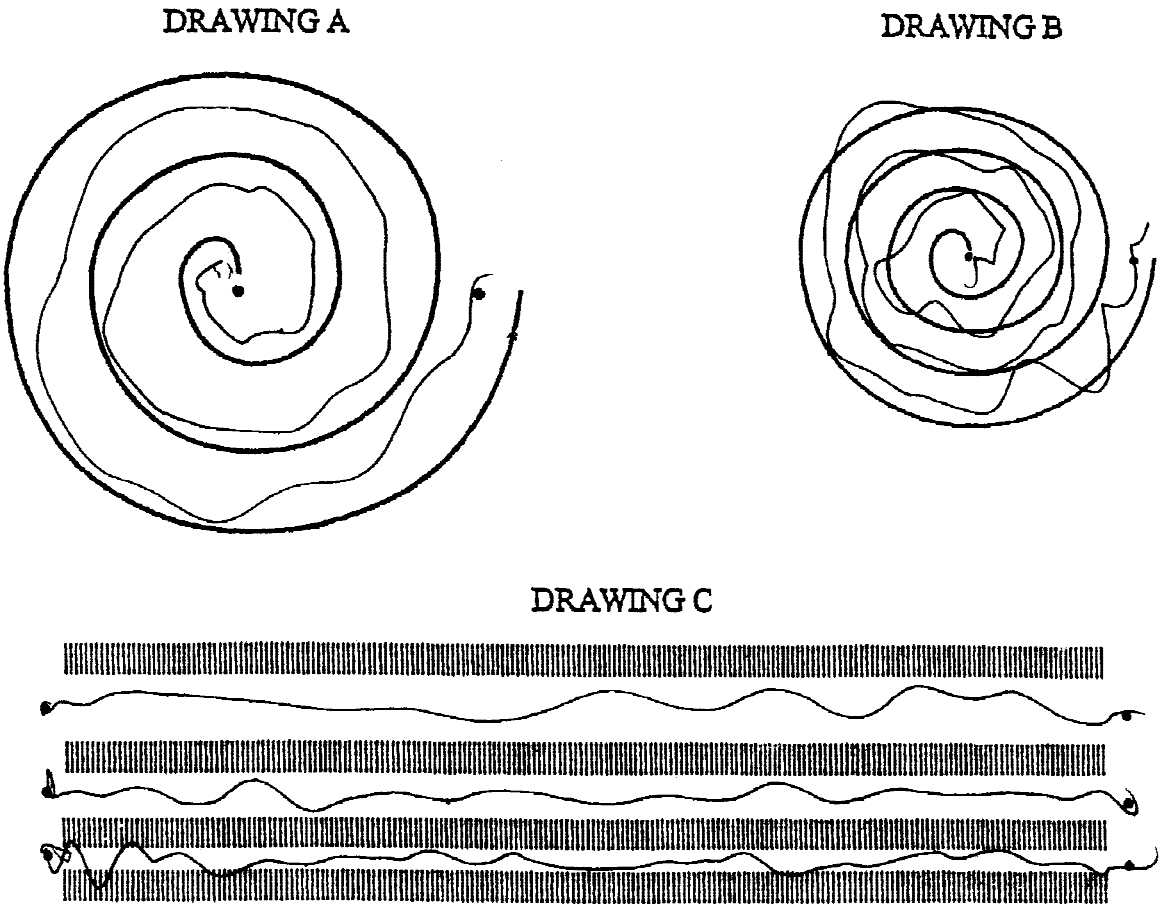

FIG. 3. The patient could not draw before surgery or bring the pen to the paper. After surgery with the deep brain stimulation turned on, samples of the patient's drawings without resting the hand or arm on the table are shown.

tremor was disabling, DBS of the thalamus was considered in this patient.

Andrew and colleagues[4] reported eight cases with post-traumatic tremor treated with thalamotomy. Three patients had resting tremor, seven patients had postural tremor, and eight patients had kinetic tremor. After thalamotomy, none of the patients had resting or postural tremor; however, seven patients had improvement of kinetic tremor. Our patient did not have post-traumatic tremor; however, her tremor was also mainly of the postural and kinetic form.

Tremor can arise due to lesions of the cerebellum, superior cerebellar peduncle, inferior olivary nucleus, central tegmental tract, substantia nigra, and thalamus.[11] Experimental data in monkeys[12,13] have shown that involvement of the rubro-olivo-cerebello-rubral loop results in postural tremor. It has also been shown clinically and by positron emission tomography (PET) studies that postural and rest tremor occur when the nigrostriatal system is involved.[14] Our patient had some response to carbidopa–levodopa therapy, suggesting involvement of the nigrostriatal system. The tremor pathways have an intermediate point in the VIM nucleus of the thalamus; hence, deep brain stimulation of the VIM nucleus could be effective for midbrain tremor.[11] There are potential risks of device-related events with DBS. In our experience in patients undergoing DBS of the thalamus for various types of tremor, 34% of patients have required additional surgical procedures due to lead revisions or replacements, IPG replacements, and system explants. Although thalamotomy is another option, deep brain stimulation appears to have fewer complications and is more efficacious than thalamotomy for essential tremor.[15] Another potential drawback of DBS of the thalamus for this type of tremor concerns coverage for the procedure by insurance companies, because this is not an approved indication. We did not have any problems obtaining third party coverage for this procedure in our patient; she continued to have disabling tremor, despite trials of multiple medications.

Geny and associates[16] described a 33-year-old man who developed severe postural cerebellar tremor due to cavernous angioma in the right cerebellar peduncle. Similar to our patient, this patient also reported improvement in tremor after thalamic stimulation. Although there are risks of surgery and device-related complications, these cases suggest that thalamic stimulation should be considered in patients with midbrain tremor who have major social and functional disabilities when non-surgical approaches fail.

Legends to Videotape

Segment 1: Patient before surgery. Tremor in the left hand in the resting, postural, and kinetic positions is shown.

Segment 2: One day after surgery and after the thalamic stimulator was programmed. The patient has no tremor in the resting position and reappearance of the tremor when the stimulator is turned off.

Segment 3: Patient approximately 2 years after surgery. The Improvement is seen in the tremor in the rest, postural, and kinetic positions with the thalamic stimulator on, and the reappearance of the tremor when the stimulator is turned off.

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Frequency of DYT1 Mutation in Early-Onset Primary Dystonia in Italian Patients

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Abstract: Thirty Italian patients with sporadic, early-onset, primary dystonia were screened for the DYT1 mutation. Five patients were positive (mean age at onset, 8 years); two had the typical phenotype, two a generalised dystonia also involving the cranial muscles, and one a segmental dystonia. In the other 25 patients (mean age at onset, 7.7 years), dystonia was generalised in 22 patients and remained segmental in three. Our results indicate the role of DYT1 mutation in Italian patients and confirm clinical and genetic heterogeneity of early-onset primary dystonia. © 2002 Movement Disorder Society

Primary dystonia is a clinically and genetically heterogeneous syndrome consisting of dystonic movements and postures with no identifiable cause.[1,2] Early-onset dystonia represents the most severe form of primary dystonia and is transmitted as an autosomal dominant trait with reduced penetrance. The unique underlying mutation is a GAG deletion in the coding region of the DYT1 gene, located at chromosome 9q34, causing the expression of an abnormal protein named torsinA of unknown function.[3]

The more frequent presentation of DYT1 dystonia is early limb-onset generalised dystonia sparing the cranial muscles; however, the same mutation is also associated with different phenotypes, albeit less frequently.[3–5]

We report on a study of 30 patients affected by early-onset primary dystonia in order to evaluate the frequency of the DYT1 mutation and the clinical spectrum of the disease in Italy.

Methods

Thirty patients, 22 males and eight females, were screened for the DYT1 mutation. They were selected from the Dystonia

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Database of the Child Neurology Department of the National Neurological Institute C. Besta of Milan. None of the patients were of Jewish origin and all were sporadic cases. All patients fulfilled the diagnostic criteria for primary dystonia.[1] Patients with adult onset dystonia were not included in the study. Periodic evaluation of the patients included neurological examination, videotape recordings, and a standardised assessment of dystonia.[6] Clinical and family history was obtained from the medical records and the first-degree relatives were examined by a neurologist. The mean age at the time of the first evaluation was 13 years (range, 3.5–29 years), the mean follow-up was 7.3 years (range, 1–27 years).

Genetic Studies

After informed consent was given, genomic DNA was extracted from peripheral blood leukocytes using standard procedures. For rapid detection of the 3-bp GAG deletion in the DYT1 gene, a nonradioactive single-stranded conformation polymorphism (SSCP) analysis was performed. Polymerase chain reaction (PCR) conditions were those described previously.[3] Direct sequence analysis of the deleted fragment was performed by an automated sequencing system (373A; Applied Biosystems, Foster City, CA).

Results

Five patients (four males and one female) carried the DYT1 mutation. The mean age at onset of dystonia was 8 years (range, 8–11 years) and patients were last examined after a mean duration of the disease of 14.4 years (range, 8–21 years). Site of onset was the arm in three patients and the leg in the remaining two patients. At the end of the follow-up, two patients presented with a generalised dystonia sparing the cranial muscles, two had generalised dystonia with oromandibular involvement also, and the remaining one had a segmental dystonia affecting the neck and the upper limbs. We also tested for the GAG deletion the first-degree relatives of three out of the five DYT1-positive patients and in all cases the father was an asymptomatic carrier.

There were 25 mutation-negative patients (18 males, 7 females). The mean age at onset of dystonia was 7.7 years (range, 1.5–15 years); the mean duration of the disease at last examination was 20.2 years (range, 3–30 years). Site of onset was one upper limb in most cases (12 patients), followed by lower limb (nine patients), trunk (two patients), cranial muscles (one patient) and neck (one patient). Within 2–4 years from onset, dystonia spread to involve other body regions, becoming generalised in 22 and segmental in three patients. Cranial involvement represented by oromandibular or laryngeal dystonia was evident in 16 patients.

The impairment due to dystonia, as demonstrated by the scores obtained on the Disability and Severity Scales, was variable, from slight disability to completely dependent life, in particular among DYT1-negative patients.

Discussion

DYT1 mutation is an infrequent cause of early-onset primary dystonia among our patients (16%). The GAG deletion was found in patients with the characteristic phenotype of limb onset generalised dystonia sparing the cranial muscles, but also in those with oromandibular or laryngeal involvement and with segmental dystonia, confirming the broad clinical spectrum of the disease.[7]

Site of onset, distribution of dystonia, and functional impairment among DYT1-negative patients showed a greater variability. There were cases mimicking the DYT1 characteristic phenotype, but most of our noncarrier patients had generalised dystonia with prominent cranial involvement, as usually seen in mutation-negative patients.[4,7]

The frequency of DYT1 mutation in our series is similar to that observed in other studies of Caucasian population; however, the proportion of DYT1-positive patients among those with the typical phenotype is much lower.[4,8–10]

In conclusion, our study provides further evidence of the clinical and genetic heterogeneity of early-onset primary dystonia. The DYT1 gene is responsible for a small proportion of cases of early onset in Italy, even if the possibility of other mutations within the same gene cannot be excluded. Because of the broad clinical spectrum of DYT1 dystonia, it is important to screen for the GAG mutation in each patient with early onset for genetic counselling and to further characterise the genotypic-phenotypic correlation.

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Myoclonic Status Epilepticus: Video Presentation

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Abstract: A young woman with juvenile myoclonic epilepsy had recurrent attacks of myoclonic status epilepticus related to a long history of limited compliance and irregular sleep. The diagnosis of this clinical pattern is based mainly on clinical description. A home video captured an attack. © 2002 Movement Disorder Society

Juvenile myoclonic epilepsy (JME), a form of idiopathic generalized epilepsy, accounts for between 5% and 10% of all epilepsies.[1,2] Onset occurs around puberty and is characterized by seizures with bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms, clonic-tonic–clonic seizures, and typical absences. Myoclonic jerks, occurring preferentially after awakening, are the major diagnostic feature. Not necessarily a prelude to a major seizure, these can be of variable intensity, ranging from a tremor to severe jerks that can lead to falls, usually not accompanied by loss of consciousness. Why some patients do not develop generalized tonic–clonic attacks is unclear.

Myoclonic status, consisting of prolonged periods of recurrent myoclonus,[3] is a rare clinical pattern found in some patients with JME. There are massive bilateral jerks repeated at irregular intervals while the patient retains consciousness. Due to its unpredictability, however, myoclonic status epilepticus is difficult to document, and an ictal electroencephalogram (EEG) is rarely obtained. We present a patient with JME who had recurrent bouts of myoclonic status and demonstrate the clinical utility of home video review in diagnosis.

Case Report

This 24-year-old woman was the youngest of six children. She developed seizures at the age of 14 years. She had myoclonic jerks with objects falling from her hands, and rare generalized tonic–clonic seizures, but no absences. The patient and two of her siblings had attention deficit disorder. She had a history of maladjustment with peers in school and attempted suicide at age 18 years.

She developed episodes of myoclonic status at age 14 years, and continued to have these approximately every 2 weeks. They occurred when she was angry, disturbed, or frustrated, and particularly when she stayed up late. Episodes lasted for up to 2 hours. She thought that she was able to partially control less violent, isolated jerks. These were more frequent, occurring four to five times per week. A clonic–tonic–clonic seizure occurred when her medication was being changed.

She had been treated with phenytoin but was receiving carbamazepine when we first saw her. She was immature, had obvious difficulties in complying with her medication, and even more with sleep requirements. Social activities in her circle started late at night and continued until the small hours of the morning, and she was unwilling to forego participating in these. Her neurological and general physical examinations were normal, and she had no family history of epilepsy.

The mother videotaped several prolonged episodes of continuous myoclonic jerking occurring every 1 to 5 seconds (see Videotape). The jerks were intermittent, nonrhythmic, at times bilaterally synchronous, and at other times more pronounced in the left or right extremities. They predominated in the limbs and head, but shuddering and jerking of the entire body or bulbar myoclonus were present as well. She called, "Mummy, Mummy" repeatedly, remained fully conscious, and responded to simple questions. She had an overwhelming feeling of needing to void and touched her perineum. Afterward, she was tired and appeared confused. Review of the home videos made it clear that these attacks lasted 1 to 2 hours, frequently occurred in the morning, and clearly represented myoclonic status.

Prolonged daytime EEG video monitoring did not detect ictal events. Interictal discharge at rest consisted of single generalized, bilaterally synchronous spike and slow wave discharges at 2.5 to 3.5 Hz predominating over frontal regions. During sleep, slow spike-wave complexes at 1.5 to 2.0 Hz were recorded. She was not photosensitive. Background activity was poorly regulated, with alpha activity at 8 to 9 Hz. Magnetic resonance imaging (MRI) showed a slightly smaller right hippocampus, but this had no clear clinical significance.

Carbamazepine was replaced by lamotrigine. The effect of this change was difficult to assess because, for geographic reasons, psychotherapy was intermittent, and she did not adhere to a normal sleep pattern. Medication was then changed to valproate, and she had regular psychotherapy with great improvement.

Discussion

Gastaut recognized three forms of myoclonic status: Types 1 and 2, or "pure myoclonic status," indicative of idiopathic generalized epilepsy and secondary generalized epilepsy respec-

A videotape accompanies this article.

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tively; and Type 3 or "symptomatic myoclonic status," indicating acute or subacute encephalopathy of metabolic, toxic, viral, or degenerative origin. Gastaut did not consider Type 3 as status epilepticus in the strict sense of the term.[4]

Myoclonic status occurring in patients with primary generalized epilepsy is rare.[5–8] Jumao-as and Brenner described a patient with primary generalized epilepsy who developed myoclonic status due to low anticonvulsant levels. He was 1 of a cohort of 23 adult patients with myoclonic status. All but three had myoclonic status as a result of metabolic or anoxic encephalopathy and were recognized through EEGs recorded during their myoclonic state.[9]

Occasional patients with JME have recurrent type 1 myoclonic status but little tendency to generalized clonic-tonic-clonic attacks. They may have an unusual thalamocortical disturbance, which sets them apart from the majority of patients with JME.

Sheth and Gidel[10] recently described a 28-year-old patient with a 6-month history of four episodes of myoclonic jerks which occurred every 10 to 15 seconds and lasted a few to 24 hours, with confusion and automatic behavior. Another 15-year-old girl had a 72-hour-long episode with confusion, staring spells, and whole body jerks.[10]

Janz has described patients with JME as being impulsive, nonchalant, with brief attention span, and a tendency to psychopathology and depression.[6] Three of his 280 patients committed suicide. Although JME patients are usually of average intelligence, they often do not use their full potential and perform below their expected level. According to Janz, patients with JME need a regular sleep waking routine and an orderly life. However, they have difficulty waking in the morning and feel best in the evening. This aggravates sleep deprivation and provokes seizures. Regular sleep habits with at least 8 to 9 hours of night-time sleep are essential. Alcohol should be avoided totally unless small quantities are shown to be well tolerated. Emotional and physical stress can provoke seizures, but these conditions are difficult to avoid in everyday life.[6]

Sodium valproate, an excellent antimyoclonic agent, is usually the drug of choice for most patients with JME.[11] Some patients with persistent myoclonic jerks have been treated with a combination of valproate and clonazepam.[2] Due to side effects such as weight increase, hair loss, tremor, and hormonal dysfunction in women, as well as teratogenic effects, valproate has sometimes been replaced by lamotrigine with good results.[12] However, lamotrigine may not be an effective antimyoclonic agent and may even precipitate myoclonic status.[13] In some patients, combination therapy with lamotrigine and valproate is required.[14]

Piracetam in high doses has been shown to be an antimyoclonic agent in progressive myoclonic epilepsy.[15,16] Two patients with myoclonic jerks had clear reduction of their myoclonus in a study investigating the utilization of levetiracetam in patients with photosensitive epilepsy.[17] Zonisamide has been used in progressive myoclonus epilepsy with some success, and some patients with idiopathic generalized epilepsy were also completely controlled by zonisamide.[18]

Intravenous valproic acid was used in two patients with myoclonic status who had continuous EEG recording. Polyspike and spike-wave discharges and myoclonic jerks disappeared within 30 minutes after valproate infusion, and the mental state returned to normal.[10] Among the benzodiazepines, clonazepam and nitrazepam are more effective antimyoclonic agents than clobazam. Clonazepam can occasionally precipitate generalized tonic clonic seizures.[2] Carbamazepine and vigabatrin may both activate myoclonus and trigger myoclonic status.[14]

Without a home video recording, diagnosis of our patient would have been difficult. We encourage family members to use home videos for patients who have rare seizures, especially if video-EEG monitoring in the hospital did not record attacks. For patients who have less frequent seizures when monitored in hospital, a home video can be particularly helpful.

Our patient had obvious difficulty complying with her medication regimen and sleep requirements. It is possible that now, with the administration of valproate and regular psychiatric intervention, her epileptic manifestations may be fully controlled.

Legends to the Videotape

Segment 1: Myoclonus involves the bulbar musculature, limbs, and trunk. The patient remains fully conscious and communicates with her mother who videotaped the attack.

Segment 2: Frequent, violent, and repetitive myoclonic jerks, involving the face, neck, and upper extremities.

Segment 3: Bulbar myoclonus is at times accompanied by vocalization and wide opening of the eyes.

Segment 4: Late in the attack, the myoclonus is of lower amplitude and is less frequent.

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Suppression of Cortical Myoclonus by Levetiracetam

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Abstract: A 16-year-old boy suffered severely disabling post-hypoxic myoclonus. Neurophysiological investigation showed cortical but not reticular reflex myoclonus. Add-on therapy with levetiracetam significantly improved the patient's clinical condition, suppressed cortical myoclonus-associated spikes, and enabled further neurorehabilitation. © 2002 Movement Disorder Society

Myoclonus refers to rapid involuntary muscle jerking, which may occur spontaneously or in response to various stimuli.[1] Stimulus-sensitive reflex myoclonus is a frequent sequel to hypoxic encephalopathy,[2,3] and may either be of cortical origin,[4] or due to a hyperactive reflex mediated in the brainstem.[5] Both types may be present in the same patient[1] but clinical differentiation is often difficult. Neurophysiological investigation comprising polygraphic electromyography (EMG), somatosensory evoked potentials (SEP), long loop reflexes (LLR), and jerked-locked back-averaging (JLBA) of electroencephalography (EEG) may aid to locate the origin of the myoclonus.[1] We describe a patient with neurophysiologically characterized, medication-resistant, cortical reflex myoclonus who responded well to levetiracetam, a novel anti-epileptic drug.

Case report

A 16-year-old boy sustained a severe thoracic trauma with cardiocirculatory arrest and ensuing cerebral anoxia of unknown duration. Initial Glasgow Coma Score was 3. On day 6, T2 weighted magnetic resonance imaging (MRI) was consistent with diffuse brain edema and bilateral hypoxic lesions in the thalamus and basal ganglia. Intended weaning from the respirator resulted in appearance of stimulus-sensitive myoclonic jerks predominately in both upper extremities. Routine EEG showed diffuse θ–δ activity but failed to demonstrate muscle jerk-associated cortical activity. On clinical examination after successful weaning, the patient presented with an apallic syndrome.[6]

During the ensuing 8 months of neurorehabilitation, the patient experienced a remarkable improvement of his severe attention and short-term memory impairment. Further recovery of motor function, however, was impeded by his permanent myoclonus, which was resistant to an armamentarium of various medications. On day 6, anticonvulsant treatment was initiated comprising intravenous clonazepam (8 mg/day) and piracetam (36 g/day). Five days later, valproate was added (1,800 mg/day per gastric tube). Four weeks postinjury, oral antiepileptic formulas (per gastric tube) were substituted for intravenous medication, and clonazepam was increased to 10 mg/day. Tetracosactid was continuously infused for 10 days (1 mg/day intravenously) resulting in mild transient suppression of involuntary muscle jerks. Six weeks postinjury, the patient experienced a first focal grand mal seizure. Repeat EEG again revealed diffuse θ–δ slowing without spikes or myoclonus-associated cortical activity. Carbamazepine (400 mg/day) was added to clonazepam, piracetam, and valproate, and this regime was maintained for 8 months. The patient did not experience any more grand mal seizures; however, his myoclonias remained insufficiently controlled. In the search for alternative therapeutic options, to better understand the pathophysiological mechanism, and to locate the origin of the myoclonus, the patient underwent detailed neurophysiological investigation based on previously reported methods.[7–9]

Three months postinjury, cortical median nerve SEP,[7] which had been reduced bilaterally 5 days after injury (N20–P25: 0.4 μV following right-side stimulation; 1.0 μV following left-side stimulation; normal range, 1.5–7.5 μV), increased to 11.4 μV following right-side and 6.9 μV following left-side stimulation (Fig. 1). Absolute and interpeak latencies remained within normal limits. Right median nerve stimulation also elicited an exaggerated transcortical LLR recorded at rest over the brachial plexus. Its onset latency of 32 msec was compatible with a response from neck or proximal upper extremity muscles (Fig. 1). Transcranial magnetic stimulation[8] elicited recurrent responses with normal latencies from the abductor digiti minimi muscle bilaterally, even when using intensities as low as 40% stimulator output (Fig. 2). Brainstem auditory evoked potentials[8] were normal bilaterally, and auditory startle responses[9] had normal onset latencies and normal habituation. Eleven months postinjury, JLBA of EEG during action-induced myoclonus revealed a time-locked cortical discharge preceding muscle jerks in both upper extremities. When triggering with activity in the right biceps brachii muscle, associated cortical activity was recorded predominantly over the left hemisphere, while bilateral predominantly right-side activity was present with left biceps brachii triggering (Fig. 3).

These findings were consistent with cortical involvement in myoclonus generation, which prompted us to add levetiracetam (1,000 mg/day) to the existing therapeutic regime, as recent

A videotape accompanies this article.

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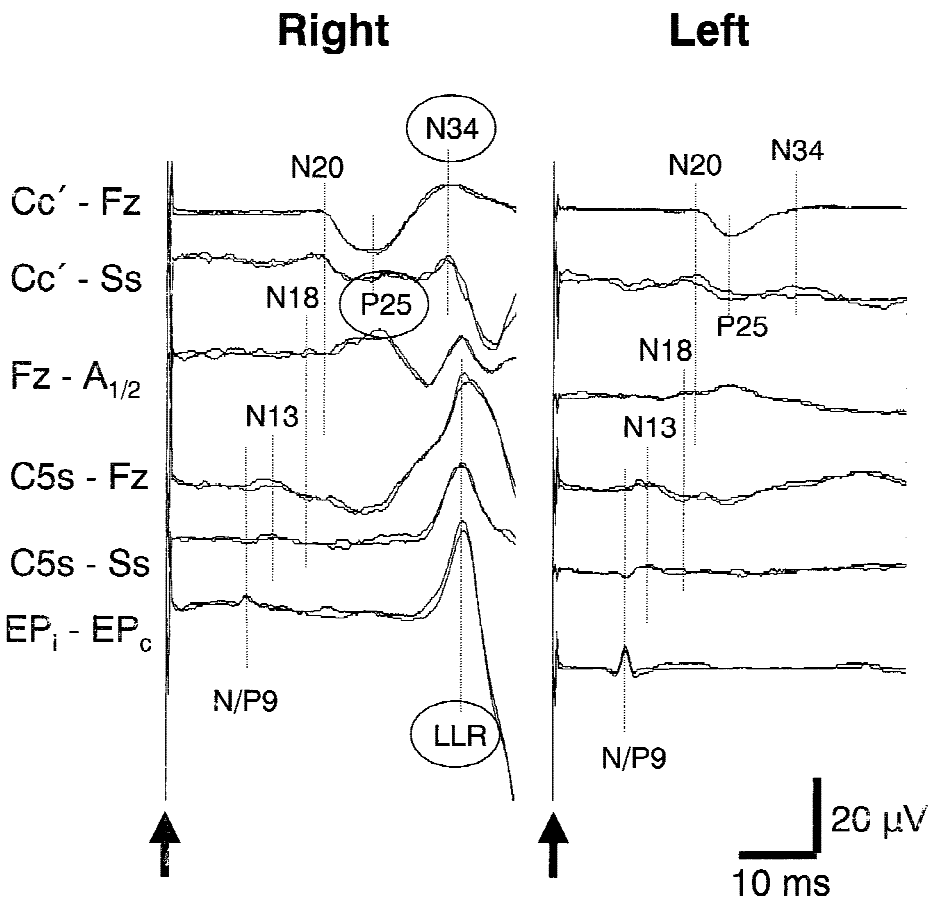

FIG. 1. Somatosensory evoked potentials (SEPs) following right median nerve (left column) and left median nerve stimulation (right column) at the wrist. Traces from below to above represent recordings over the brachial plexus (N/P9; EP2–EP1; EP1–EP2), fifth cervical vertebra with a suprasternal and a frontal reference (N13; C5s–Ss; C5s–Fz), frontal cortex with a linked ear reference (N18; Fz–$A_{1/2}$), and the hand area of the contralateral sensory cortex with a noncephalic (suprasternal) and a frontal reference (N20, P25, N34; C3'–Ss; C4'–Ss; C3'–Fz; C4'–Fz). Electrodes were placed according to the International 10–20 System. Two series of 250 responses are superimposed. The arrows indicate stimulus onset. Note the enlarged cortical responses in the upper three traces, and the long-loop reflex (LLR) in the lower three traces following right median nerve stimulation.

studies suggest a beneficial effect of this piracetam analogue in epilepsy.[10] Within 1 day, myoclonus subsided almost completely. Some myoclonic jerks reappeared by the third day, albeit at a much lower rate and intensity. Repeat JLBA of EEG 1 week later revealed a marked reduction of cortical spike activity (Fig. 3). An increase of levetiracetam up to 3000 mg/day yielded no further clinical improvement, while drug holidays for 5 days caused an immediate deterioration to the previous condition. Administration of levetiracetam (1,000 mg/day) for 8 months resulted in a lasting improvement of myoclonus, enabling the patient to develop head and trunk control, and to sit without support. He gained the ability to feed himself using a "neater eater" (Michaelis Engineering and Neater Solutions, Buxton, Derbyshire, U.K.), steer a wheelchair, communicate verbally, write, operate a personal computer using a special keyboard with large keys, and participate in formal education provided by a private teacher.

Discussion

In our patient, neurophysiological examination was consistent with cortical reflex myoclonus.[4] This is supported by the presence of giant cortical SEP,[1] an exaggerated transcortical LLR,[1,11] repetitive discharges following single pulse transcranial magnetic stimulation,[12] and cortical spike activity with JLBA of EEG.[1] Furthermore, there was no brainstem dysfunction on clinical examination, no evidence of a structural brainstem lesion on MRI, no abnormality of repeat auditory evoked potential examinations, and an intact auditory startle response. Thus, our findings did not support the presence of reticular reflex myoclonus.[5]

Established treatment options including a combination of high-dose clonazepam, valproate, and carbamazepine[3,13] did not sufficiently control cortical myoclonus in our patient. Tetracosactid[14] exerted only a mild effect, and even high-dose piracetam[15] failed to suppress the disabling myoclonic jerks. Only the addition of levetiracetam brought about significant relief to the patient and enabled further neurorehabilitation.

The piracetam analogue levetiracetam ([S]-α-ethyl-2-oxo-1-pyrrolidine acetamide, UCB S.A. Pharma Sector, Braine-l'Alleud, Belgium) is a novel and potent anti-epileptic drug. Its efficacy and safety have recently been demonstrated in patients with partial seizures as add-on medication[10,16] or monotherapy.[17] Its mechanism of action has not yet been exactly defined, but seems to be different from established mechanisms of other anti-epileptic drugs. Changes in γ-aminobutyric acid metabolism and turnover, inhibition of depolarizing ion currents, calcium channel-dependent effects, and dopaminergic

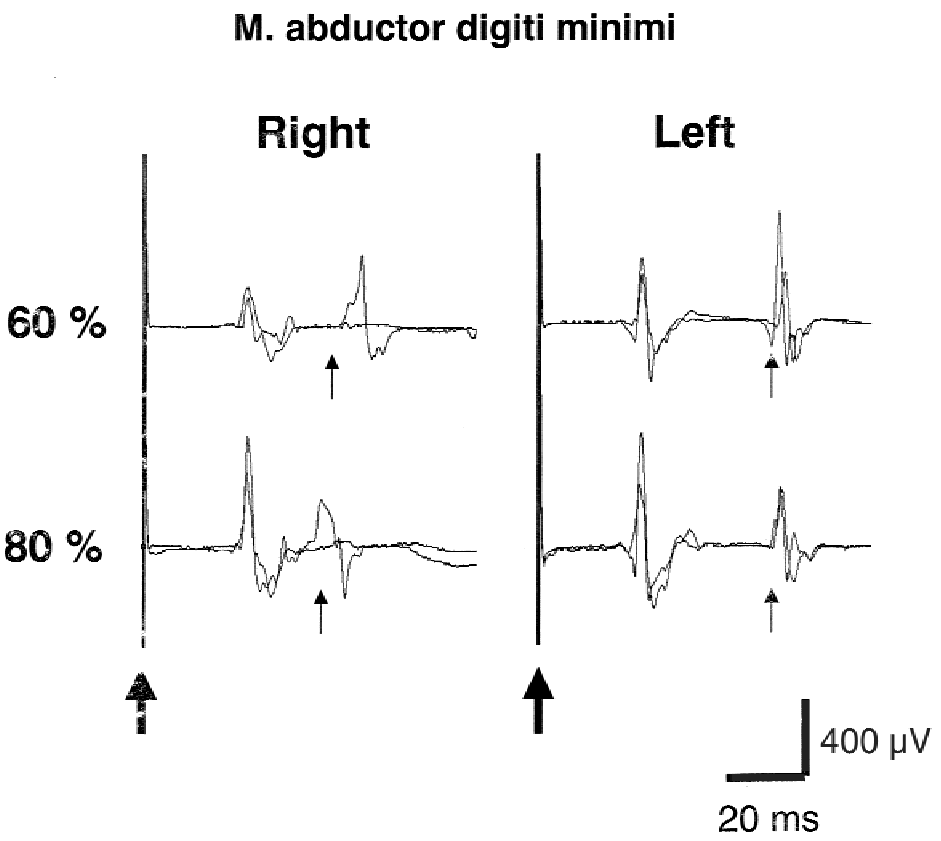

FIG. 2. Motor evoked potentials recorded from right and left abductor digiti minimi muscles following single pulse transcranial magnetic stimulation over the contralateral hand area with 60% and 80% stimulator output. Two traces are superimposed. Thick arrows indicate stimulus onset. Note the repetitive discharges on either side (thin arrows).

activation have been proposed. Despite similar chemical structures, levetiracetam and piracetam have distinct pharmacological profiles and clinical effects.[18] Piracetam shows efficacy in the treatment of impaired cognition and post-stroke aphasia. It is also effective against cortical myoclonus, but at very high dosages.[19] In contrast, levetiracetam exhibits fewer nootropic effects but potent protection against seizures even at low doses.[10,16,17] Meanwhile, supporting studies have emerged promoting levetiracetam in posthypoxic and postencephalitic myoclonus.[20]

Chronic posthypoxic myoclonus may improve several years after the anoxic event, and few patients may be able to stop taking antimyoclonic medication.[21] This natural beneficial development seems unlikely to be the cause of improvement seen in our patient. The efficacy of levetiracetam in our patient was unequivocally confirmed by: (1) clinical improvement during medication; (2) accompanied by a distinct suppression of cortical spike activity demonstrated by JLBA of EEG; and (3) clinical deterioration during drug withdrawal.

Routine EEG failed repeatedly to demonstrate cortical activity associated with myoclonus. In contrast, JLBA of EEG demonstrated spike activity preceding the myoclonic jerks, and proved a cortical generation of myoclonus,[1] as reticular reflex myoclonus lacks associated cortical EEG activity.[5] Thus, advanced neurophysiological techniques should be implemented in selected patients, in whom cortical myoclonus is suspected but cannot be documented by routine EEG.

In our patient, add-on therapy with levetiracetam suppressed cortical reflex myoclonus to a large extent and was long-lasting, enabling further progress in neurorehabilitation which would have been otherwise impossible.

Acknowledgments: We thank Maria Hoch for expert technical assistance, and Andreas Mayr for preparation of the videotape.

Legends to the Videotape

Patient with posthypoxic cortical reflex myoclonus: nine brief segments, five without and four with levetiracetam treatment.

Segment 1. Three months posthypoxia, without levetiracetam, shows the patient sitting, trying to assume an upright position. There are frequent, irregular, bilateral action-induced myoclonias, with a predominant flexion pattern in both upper extremities, and a predominant extension pattern in the lower extremities and in the neck. Two therapists are intensely involved in supporting the patient.

Segment 2. Three months posthypoxia, without levetiracetam, shows the patient leaning against a therapy stretcher, his feet and legs supported by one therapist, while a second therapist behind the patient tries to prevent him from falling forward. The patient's attempts to assume an upright position result in frequent irregular myoclonias predominantly in the left upper extremity, accompanied by jerky neck extensions. The patient is barely able to gain his posture.

Segment 3. Three months posthypoxia, without levetiracetam, shows the patient at the standing, supported with belts,

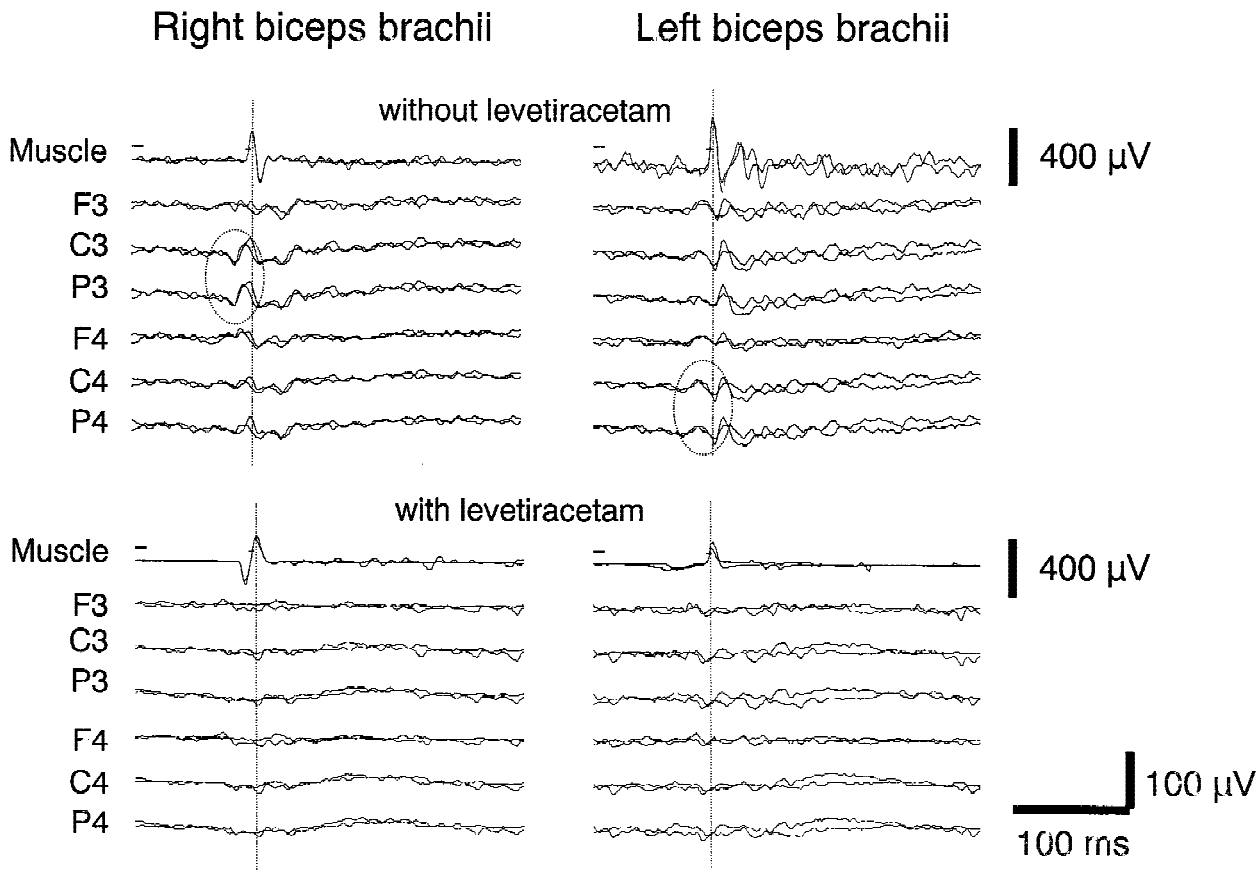

FIG. 3. Jerk-locked back-averaged electroencephalographic recordings with frontal (F3, F4), central (C3, C4), and parietal (P3, P4) electrodes and a linked ear reference ($A_{1/2}$), placed according to the International 10–20 System. Muscle activity above trigger level (horizontal line in the top trace of each panel) recorded from the right (left column) or left biceps brachii muscle (right column) triggered the sweep. The upper panels show recordings before application of levetiracetam (two series of 50 responses superimposed). Note the predominantly contralateral muscle jerk-associated cortical activity (circles). The lower panels show recordings during application of levetiracetam 1,000 mg/day (two series of 15 responses superimposed). Note the striking suppression of jerk-locked responses.

straps and cushions at hip, knees, and heels. Again, there are severe myoclonias predominantly in the left upper extremity and the neck.

Segment 4. Six months posthypoxia, without levetiracetam, shows the patient sitting in a wheelchair with his right arm supported by a pillow. Despite good intentional movements, his attempts to switch on a personal computer are to no avail due to incapacitating action-induced myoclonias, causing irregular upper trunk and neck extension, and jerky arm movements.

Segment 5. Six months posthypoxia, without levetiracetam, shows the patient sitting in the same wheelchair, while he attempts to operate the personal computer by punching big buttons with his left arm, but involuntary jerky elbow flexions cause frequent error trials.

Segment 6. Eleven months posthypoxia, with levetiracetam, 1,000 mg/day, shows the patient sitting in a wheelchair. He is operating the personal computer by successfully punching the buttons with his left arm with adequate speed and pressure, and without error trials. There are no myoclonias.

Segment 7. Eleven months posthypoxia, with levetiracetam, 1,000 mg/day, shows the patient sitting in a wheelchair, using a "neater eater" (modified for left-handed operation). There are almost no involuntary muscle jerks, only mildly affecting intentional movements of the head when tending to the spoon. There is good head, neck, and trunk control, and good arm-head coordination. A therapist is observing, but not aiding.

Segment 8. Eleven months posthypoxia, with levetiracetam, 1,000 mg/day, shows the patient sitting unsupported on a therapy stretcher, displaying good head, neck, and trunk control. There are only few and barely disturbing stimulus-sensitive tactile myoclonias. For safety reasons, two therapists offer some resistance against the patient's knees, but do not hold him firmly.

Segment 9. Eleven months posthypoxia, with levetiracetam, 1,000 mg/day, shows the patient standing upright leaning against a therapy stretcher. Two therapists offer knee support without holding the patient firmly, who requires only a little intermittent support on shoulder and trunk for upright positioning. There are few jerks in the proximal upper extremities predominantly on the right side, when the patient tries to push himself up and moves his shoulders backwards. Finally, he is waving at the camera with his left hand without action-induced myoclonias, no concomitant trunk sway, and no disequilibrium.

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Orofacial Dyskinesias in a Patient with Primary Biliary Cirrhosis: A Clinicopathological Case Report and Review

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Abstract: We describe the pathological and clinical aspects, including video and radiological magnetic resonance imaging, of a case of chronic acquired hepatocerebral degeneration with orofacial dyskinesias in relation to a primary biliary cirrhosis. We provide a review of the literature on this subject. © 2002 Movement Disorder Society

Neurological complications of chronic hepatic failure or portal–systemic anastomotic shunt are usually associated with hepatic encephalopathy and denominated as chronic acquired hepatocerebral degeneration (CAHD). Two forms of CAHD are described: the familial Wilsonian form and the nonfamilial form of CAHD.[1,2] Several diseases can lead to a non-Wilsonian CAHD. These conditions include primary or secondary biliary cirrhosis, portal-systemic anastomotic shunt, active chronic hepatitis, alcoholic cirrhosis, and hemochromatosis.[3,4] Neurological manifestations may combine somnolence, abnormal movements, dysarthria, and, rarely, myelopathy.[3]

Primary biliary cirrhosis is a chronic liver disease affecting middle-aged subjects, more women than men, and characterized by fatigue, itching, hepatomegaly, and, at late stages, cirrhosis, portal hypertension signs, and ascites.[5] Biological tests usually reveal a cholestatic pattern and the presence of antimitochondrial antibodies.[5] To our knowledge, only four cases of CAHD during primary or secondary biliary cirrhosis have been histopathologically studied.[3,6,7] However, these are rather old reports that did not benefit from the contribution of MR imag-

A videotape accompanies this article.

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ing, contrary to more recent reported cases that were not, except for the case described by Lee and colleagues (1998), studied histologically.[8–13] We describe the pathological and clinical, including video and radiological magnetic resonance imaging (MRI), aspects of a case of CAHD with orofacial dyskinesias in relation with a primary biliary cirrhosis. We provide a review of the literature on this subject.

Case Report

A 59-year-old man was referred to the Department of Gastroenterology because of an asymptomatic cholestasis (serum alkaline phosphatase: 515 U/L [normal < 117 U/L] and γ-glutamyltransferase: 527 U/L [normal < 49 U/L]). Liver biopsy showed a nonspecific inflammatory reaction but no copper deposit. The diagnosis of primary biliary cirrhosis was based on positivity of antimitochondrial antibodies, the lack of excessive accumulation of serum copper, the negativity of hepatitis screening, and normal abdominal echography. Five years later, the patient presented with pruritus and hepatomegaly, suggesting cirrhosis. Biology was unchanged. At age 67 years, the patient developed ascites and edema of the lower limbs. The blood ammonium level was elevated (150 μmol/L; normal <40 μmol/L). Abdominal echography revealed a splenomegaly, whereas the gastroscopy showed esophageal varices. During the following years, this patient suffered from four episodes of acute hepatic encephalopathy, which were successfully treated with ornithine and lactulose. The patient subsequently developed, at age 73 years, progressive neurological symptoms that were different from the acute episodes of hepatic encephalopathy. These episodes consisted of unsteadiness with frequent falls, severe dysarthria, and tremor. The patient was alternately apathetic or aggressive and had inappropriate behavior, but was not confused or disoriented. Neurological examination revealed orofacial, cervical, and lingual choreic dyskinesias, ataxia and bilateral action and postural tremor, but no other cerebellar or parkinsonian signs. The lumbar puncture was normal. The electroencephalogram showed diffuse theta activity. A cerebral MRI (1 T) disclosed increased T_1 signal within the striatum and pallidum, bilaterally (Fig. 1A). Gadolinium injection enhanced this hypersignal (Fig. 1B). No abnormality on the T_2-weighted images was disclosed in the pallidum and striatum, whereas small lacunar infarcts were noted in the periventricular white matter (Fig. 1C). A few months later, the patient suddenly became comatose. Liver function test showed a cholestatic and cytolytic pattern: alkaline phosphatase, 320 U/L (normal < 117 U/L); ASAT, 230 U/L (normal < 40 U/L); ALAT, 150 UI/L (normal < 45 U/L). Prothrombin time was 45%. The blood ammonium level was 110 μmol/L (normal < 40 μmol/L) and a thrombocythemia was noted (85 G/L). The manganese blood level was 0.4 μg/L (normal range, 0.5–1.1 μg/l). The patient died a few months later, 14 years after the diagnosis of primary biliary cirrhosis was made. At autopsy, hepatic histology confirmed the diagnosis of stage IV primary biliary cirrhosis. On macroscopic examination of the brain, a moderate atrophy was disclosed. Histopathologically, a microcavitation was found between cortical layers 6 and 4, predominantly in the frontal and temporal cortex and in the striatum (Fig. 2A,B). There was a definite neuronal loss in these regions. In addition, most astrocyte nuclei were enlarged in the cortex and the basal ganglia, corresponding to Alzheimer type II astrocytes. No abnormality was seen in the brainstem. In the cerebellum, a Bergmann gliosis was noted in the Purkinje layer. In addition, no proteinase K–resistant prion protein was disclosed in the frontal cortex and the striatum by using anti-PrP 3F4 antibody.

Discussion

This report is a well-documented clinical and pathological case of CAHD secondary to primary biliary cirrhosis, which includes video recordings of orofacial dyskinetic movements and brain MRI findings not previously reported. The first nonfamilial case of CAHD was described in 1914 by van Woerkom[2] and was characterized by tremor, rigidity, and emotional instability. The occurrence of CAHD after portal-

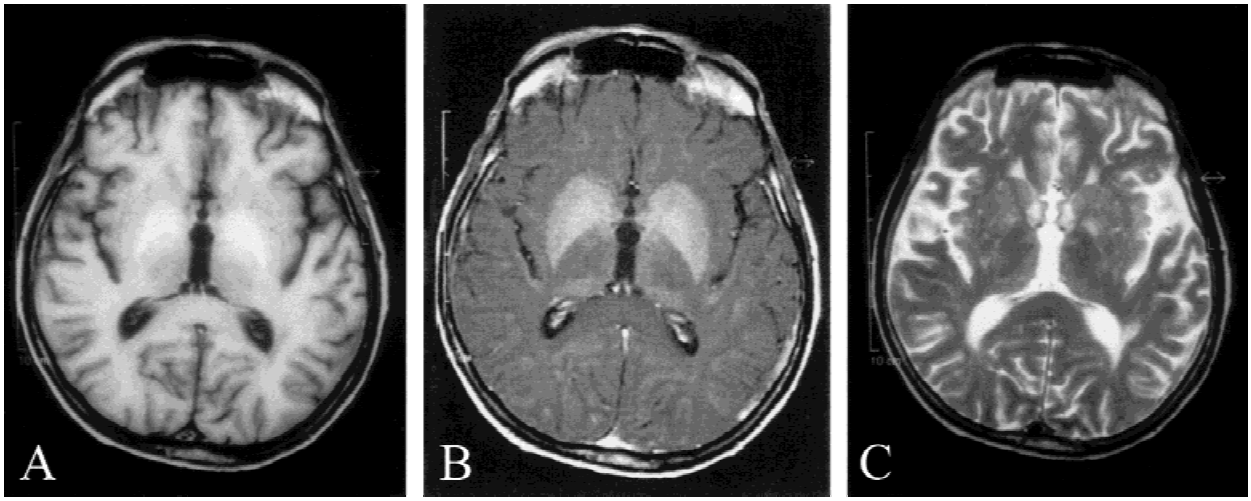

FIG. 1. A: T_1-weighted magnetic resonance imaging (MRI) sequences (echo time [TE], 20 msec; repetition time [TR], 550 msec) showing a bilateral spontaneous hyperintensity in the internal pallidum. **B:** T_1-weighted MRI sequences (TE, 15 msec; TR, 900 msec) after gadolinium injection showing a bilateral enhancement of the hypersignal in the internal pallidum and striatum. **C**: T_2-weighted MRI sequences (TE, 20 msec; TR, 2,200 msec) showing no signal abnormality in the pallidum and striatum.

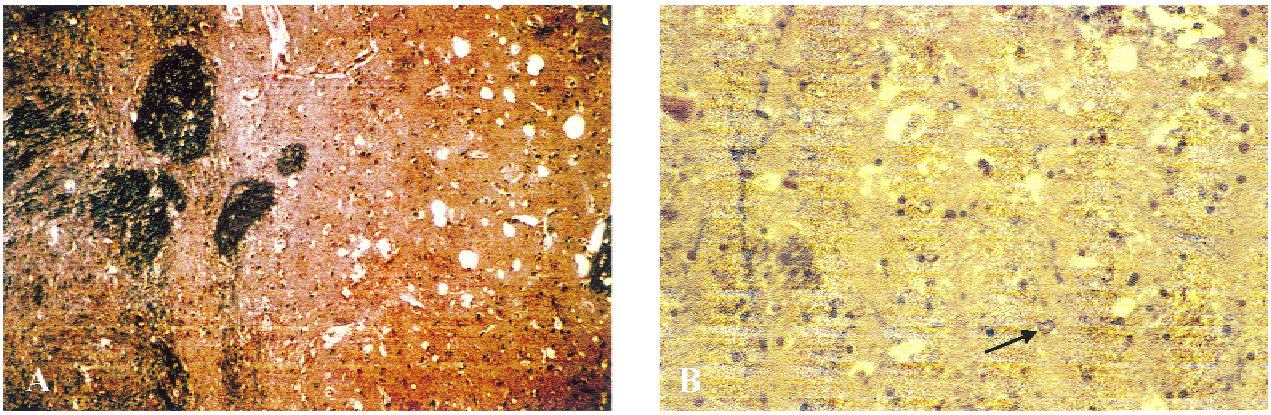

FIG. 2. A: Photomicrograph of striatum showing a spongy degeneration (×100). Phosphotungstic hematoxylin stain. **B:** Photomicrograph of striatum showing the presence of Alzheimer type II astrocytes with enlarged nuclei (arrow; ×200). Phosphotungstic hematoxylin stain.

systemic anastomotic shunt was first reported in 1957.[14] Victor and colleagues[3] clinically and pathologically described 27 cases of CAHD.

Neurological manifestations of non-Wilsonian CAHD include cognitive deterioration, dysarthria, movement disorders, and, rarely, myelopathy. The cognitive symptoms may be severe, with dementia, or mild, consisting of apathy and behavioral abnormalities.[3,7,15] Dysarthria is observed in almost all the CAHD cases and is often mixed, of parkinsonian and cerebellar types.[3,6,7,14–17] Movement disorders are heterogeneous. Intentional and postural tremor is the most frequent movement disorder observed.[3,6,15–18] Resting tremor is rare and usually associated with parkinsonism.[3,15] Flapping tremor is noted in cases of hepatic encephalopathy.[3,7] Choreic movements are the second most common manifestation and typically present as prominent orofacial-buccal and lingual chorea but may be generalized.[3,7,15,17] Dystonia is less frequent.[3,7] Myelopathy is very unusual and can present as a transverse myelitis.[3,13] These neurological manifestations may, in some cases, precede the hepatic symptoms, are not correlated with the stage of the disease, and appear independent from the hepatic encephalopathy episodes, which was the case for our patient.[3] In the few reported cases of CAHD related to a biliary cirrhosis, the hepatic signs usually precede the neurological manifestations for years, as in our observation.[3,6,7] The importance of the hepatic symptoms were variable: (1) no hepatic sign[7]; (2) isolated hepatomegaly[3]; or (3) hepatomegaly and portal hypertension signs, as in our patient.[3,6] Neurological features are similar in the biliary cirrhosis type of CAHD and in the other forms of CAHD. In the four patients described to date, as in ours, there was a combination of ataxia, cognitive changes, attention impairment, and apathy with aggressiveness.[3,6,7] Only one patient presented isolated asterixis.[3] Concerning the movement disorders, tremor was also observed by Victor and associates[3] in their two biliary cirrhosis patients, but lingual chorea was only noted in one patient.[7] It is interesting to note that the choreic movements of this latter case tended to spread to the superior and inferior limbs.

CAHD, whatever the cause, share common neuropathological characteristics. The first reported observation is a global cerebral atrophy.[3] Microscopically, the lesions consist of (1) the presence of Alzheimer type II cells, which correspond to astrocytes with considerably enlarged nucleus found in the cortex, basal ganglia, and cerebellum[3,15]; (2) the existence of periodic acid–Schiff-positive intranuclear inclusions in these cells[15]; (3) a spongy degeneration affecting predominantly the cerebral cortex, underlying white matter, basal ganglia, cerebellar cortex, and dentate nucleus [3,7,15]; (4) a diffuse loss of Purkinje cells and increased number of Bergmann glial cells in the cerebellum[3,6,7]; and (5) a degeneration of the posterior and lateral tracts of the spinal cord.[3,15] In the rare cases of CAHD associated with a biliary cirrhosis, Alzheimer type II astrocytes were found in the putamen and the cerebral cortex (especially layers V and VI). In three patients, these lesions were also noted in the caudate nucleus, pallidum, and subthalamic nucleus.[3,6] In our observation, the Alzheimer type II astrocytes predominated in the striatum. The microcavitation was observed in the basal ganglia and cerebral cortex, predominantly in temporal and frontal regions, in our observation as in two previously reported cases.[3,7] In conclusion, no histopathological distinction exists whatever the etiology of the CAHD.

Brain MRI abnormalities were first reported in 1991 in patients with portal–systemic encephalopathy and are now well documented.[19] The abnormalities consist of a hyperintense signal in the T_1-weighted sequences located mostly in the internal pallidum, but also in the putamen, mesencephalon, caudate nucleus, and sometimes in the internal capsule, brainstem, and subcortical white matter.[8,11,12,15,19–21] This hypersignal is independent from age, sex, or etiology of the underlying liver disease but appears reversible after treatment of the hepatic disease.[22] Contrast enhancement studies have rarely been performed. No reinforcement of this T_1 hypersignal is found after gadolinium injection in one report.[12] Interestingly, however, a marked enhancement of the T_1 hypersignal after gadolinium injection was noted in our patient, which may correspond to a disruption of the blood–brain barrier. A brain atrophy is also reported in approximately half of the patients.[8] Inoue and coworkers[19] found a relationship between the existence of a portosystemic shunt and the T_1 MRI hypersignal. No correlation was established between these MRI abnormalities and the level of alkaline phosphatase, bilirubin, transaminase, or prothrombin time.[9,20] However, a correlation was made between the T_1 abnormalities and the severity of the hepatic disease according to the Child Pugh scale.[9] An eventual correlation with the ammonium level is still discussed.[8,21,23] At least, however, these T_1 abnormalities are more important in the case of cog-

nitive changes but are not related to EEG abnormalities.[8,9,22] In addition, movement disorders are usually associated with T_1 hyperintense signal in the basal ganglia.[22,23] In most cases, no abnormalities are detected in the T_2-weighted sequences, although some authors described T_2 hyperintensities in the pallidum and pons.[8,20] Our observation presented similar MRI findings as previously described, which confirms that MR abnormalities are independent from the cause of CAHD. The pathophysiology of the MRI lesions is still debated. The two major hypotheses are a modification of astrocyte metabolism leading to the development of Alzheimer type II cells or the accumulation of manganese in the basal ganglia, as described in professional manganese intoxication.[21] A regression of the MRI abnormalities after a liver transplant for Alagille's syndrome was reported in association with a normalization of the manganese blood level and a disappearance of the movement disorders.[24] The role of manganese accumulation in the occurrence of these MRI hyperintense signals on T_1 sequences is also documented by histological studies showing manganese deposit in the pallidum and cortex in cirrhosis patients.[25] The lack of biliary excretion of manganese may be the cause of this accumulation. Conversely, a correlation between the blood manganese level and the existence of MRI abnormalities is reported in cirrhosis patients.[10] However, the manganese blood level does not necessarily correlate with intracerebral accumulation of manganese.[26] In our observation, the manganese blood level remained normal throughout. However, it must be noted that the manganese accumulation probably does not explain all the pathophysiological aspects of CAHD. Other pathogenic hypotheses may be the accumulation of toxic substances for astrocytes like ammonium; dysfunctions of the serotoninergic, glutamatergic, adrenergic, and dopaminergic pathways; or increased production of free radicals.[27,28]

This detailed clinical, radiological, and histological case report illustrates one of the rare observations of CAHD in relation to a biliary cirrhosis. It also underlines the occurrence of choreic type orofacial movements at a late stage of the disease. A review of the literature confirms that this neurological syndrome may be encountered in all types of liver disease and has a characteristic clinical, pathological, and radiological presentation.

Legend to the Videotape

The patient at the age of 73 years shows marked oral and lingual dyskinesias. Less pronounced dyskinesias are seen in the upper face. A severe dysarthria is also noted. In addition, a dropped-head syndrome related to hypotonia is present.

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Association of Chorea and Motor Neuron Disease

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Abstract: Amyotrophic lateral sclerosis (ALS) is classically characterized by the presence of symptoms or signs of upper and lower motor neuron impairment and sparing of other neuronal systems.[1] We report on a patient who was primarily diagnosed as typical ALS and developed chorea 10 years after the onset of motor neuron signs. © 2002 Movement Disorder Society

Case Report

A 40-year-old man developed progressive weakness of the lower limbs in 1989. He had no personal or family history of neurological diseases. He had two brothers (30 and 34 years old) and two sisters (36 and 41 years old). His mother and father were 68 and 72 years old, respectively. At that time, neurological examination showed signs of upper motor neuron (spasticity, symmetric brisk deep tendon reflexes, bilateral Babinski, and Hoffman signs) and lower motor neuron (fasciculations, muscle atrophy) involvement. Muscle testing was abnormal in the lower (MRC scores ranging from 4–5) as well as upper limbs (MRC scores ranging from 3–5). The examination was otherwise unremarkable. Electromyography showed diffuse denervation with giant potentials. The patient was diagnosed with ALS and treated with riluzole from 1992 on. He did not take any other drug and riluzole was continued during the entire course of the disease. During the following years he experienced a slow progression of the motor weakness of the four limbs and bulbar signs appeared (dysarthria and dysphagia), followed by respiratory dysfunction. In 1998, at age 49 years, he progressively developed hyperkinetic movements. In 1999, neurological examination showed considerable choreic movements affecting the four limbs and the face (see Video, Segment 1). Motor deficit and muscle atrophy had worsened (see Video, Segment 2). Muscle testing showed MRC scores between 2 and 4 in the upper limbs and between 0 and 4 in the lower limbs. He was dysarthric, dysphagic, and exhibited slow ocular saccades. His forced vital capacity was 43% of predicted value. Neuropsychological testing showed impairment of executive functions on verbal and nonverbal frontal lobe tests with deficit on the 64-item Wisconsin Card Sorting Test. Brain magnetic resonance imaging (MRI) demonstrated a severe widespread cerebral atrophy (Fig. 1). Single photon emission computed tomography (SPECT) study showed cortical hypoperfusion predominating in the frontal lobes. [^{8}F]fluoro-2-deoxy-D-glucose positron emission tomography also demonstrated bilateral hypometabolism with anterior predominance. Striatal metabolism normalized to global cerebral metabolism

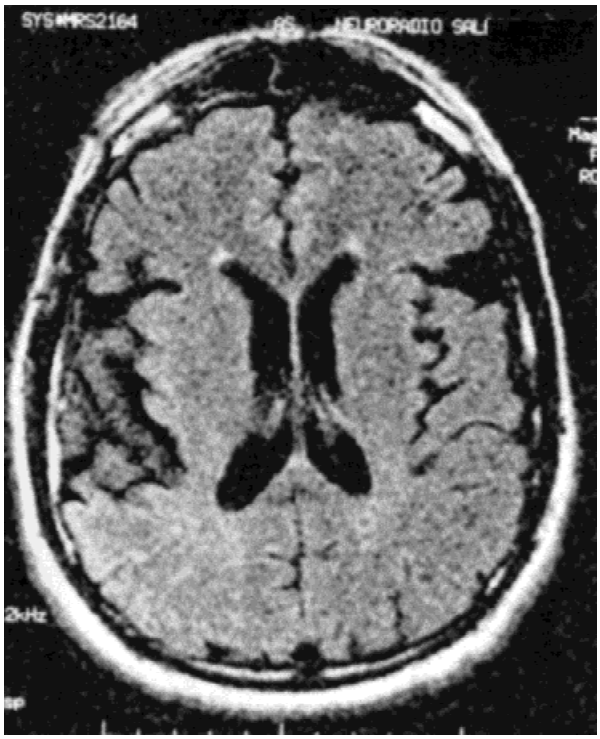

FIG. 1. Cranial magnetic resonance imaging (FLAIR) showing diffuse cortical atrophy.

A videotape accompanies this article.

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was normal. Tests for Huntington's disease (genetic testing for the IT15 expansion), autosomal dominant spinal cerebellar ataxia (genetic test for SCA1, 2, 3, 6, and 7), dentato-rubro-pallido-luysian atrophy (genetic test), chorea-acanthocytosis (peripheral smear), GM2 gangliosidosis (serum and leucocyte hexosaminidase levels), Wilson's disease (ceruloplasmin dosage), lupus (antinuclear factor dosage), endocrinopathy (thyroid and parathyroid hormones dosages), and mitochondrial disorders (muscle biopsy with specific search for mitochondrial alterations) were negative.

Discussion

Published data concerning the association of motor neuron disease and chorea are sparse and essentially refer to Huntington's disease (HD). Nine cases of coexistence of ALS and Huntington's disease (HD) have been reported.[2–8] In our case, the disease was sporadic and the patient was negative for HD as well as for other classic causes of chorea. Our patient was initially diagnosed as having "definite ALS" according to the El Escorial criteria,[1] until he developed chorea 10 years after the onset of motor neuron signs. To our knowledge, the onset of hyperkinetic movements in a patient diagnosed with ALS without a personal or familial context of HD has been reported in a single previous report.[9] In this case, hemiballism and choreoathetosis appeared more than 2.5 years after the onset of motoneuron signs. The patient also exhibited gaze palsy. Postmortem examination revealed major motor neuron loss in the brainstem and the medulla, but also in the pallidum, the substantia nigra, and in the supranuclear centers for eye movement. There was no evidence of multiple system atrophy or progressive supranuclear palsy. Immunohistochemistry showed the presence of intranuclear ubiquitin-positive inclusions in motor neurons, a feature now considered a hallmark of ALS (for review, see Ince et al.[10]).

It is now clear that degenerative lesions are not restricted to the upper and lower motor neuron systems in ALS patients. Cortical degeneration with neuropathological markers of ALS, ie, neuronal ubiquinated inclusions, may extend outside the primary motor cortex.[10] Evidence of extrapyramidal system involvement in ALS patients is also accumulating. Degeneration in the globus pallidus, thalamus, and substantia nigra has been demonstrated in necropsy studies[11,12] and dysfunction of the dopaminergic nigrostriatal pathways has been shown in vivo by positron emission tomography[13–15] and SPECT[16] studies.

We may hypothesize that the long course of the disease in our patient favored the degeneration of extrapyramidal structures, leading to the onset of hyperkinetic movements and the extension of cortical degeneration, leading to a severe diffuse cerebral atrophy. As well, long-surviving patients developed dysfunction of areas not classically involved in ALS, such as oculomotor palsies, related to degeneration of supranuclear systems.[17] This hypothesis is in accordance with the emerging concept, based on neuropathological findings, that ALS may be considered a multiple system degeneration.[10] However, we are aware that the place of ALS variants in the nosology of degenerative diseases will not be solved until the pathogenesis of neurodegeneration in ALS has been established.

Legend to the Videotape

Segment 1: The patient exhibits choreic movements.
Segment 2: Muscle testing showing diffuse weakness and amyotrophy (the skin lesions correspond to burning sequelae).

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Entacapone in Restless Legs Syndrome

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Abstract: Entacapone increased the duration of action of carbidopa–levodopa and resulted in longer periods of symptomatic relief in a patient with restless legs syndrome. The only side effect was nausea. ©2002 Movement Disorder Society

Restless legs syndrome (RLS) is characterized by an intense, irresistible urge to move the legs when sitting or lying still or, rarely, on standing. It is a common disorder in the elderly.[1] A case is presented in which entacapone increased the duration of action of carbidopa–levodopa and resulted in longer periods of symptomatic relief in a patient with RLS.

Case Report

A 62-year-old woman presented with symptoms of RLS. The patient had chronic renal failure due to polycystic kidney disease. She was on hemodialysis. The patient was experiencing an intense and irresistible urge to move the legs when sitting or lying still. The symptoms were usually worse in the evenings and at night. The patient was also experiencing the symptoms of RLS during the day (during hemodialysis). The symptoms of RLS during the day were not due to a rebound effect (as a result of treatment with carbidopa–levodopa). The symptoms had been gradually worsening for 1 year. Other comorbidities included hypertension, hypercholesterolemia, and iron deficiency anemia. The patient was taking amlodipine, pravastatin, iron supplement, and vitamins. There was no history of alcohol, tobacco, or illicit drug abuse. The neurological examination was unremarkable except for absent ankle reflexes. Prior to the referral to our clinic the patient had been tried on quinine, clonazepam, pramipexol, and gabapentin with either no relief in the symptoms of RLS or intolerable side effects.

Clinical Course

The patient was prescribed carbidopa-levodopa 25–100 mg three times daily. This initially provided satisfactory symptom relief. However, on the next follow-up visit after 3 months, the patient reported only 2–3 hours of symptom relief following each dose of carbidopa–levodopa. The formulation was then changed to the sustained release carbidopa–levodopa 50–200 mg three times daily. On the next follow-up visit, the patient reported that the latency to the onset of action had changed from 1 hour after taking the regular carbidopa–levodopa to 90 minutes after taking the sustained release carbidopa-levodopa. The duration of relief of symptoms of RLS had also changed form 2–3 hours after taking the regular carbidopa–levodopa to up to 4 hours after taking the sustained release carbidopa–levodopa. The patient was still not satisfied with the control of her symptoms during the day (during the hemodialysis) and during the night.

Entacapone was then added to the regimen. The patient was instructed to take one tablet of entacapone (200 mg) along with each tablet of sustained release carbidopa–levodopa three times a day. After adding entacapone to the sustained release carbidopa–levodopa, the duration of relief of symptoms increased to up to 5 hours. This accomplished the goal of alleviating the symptoms of RLS during most of the day and night. Unfortunately, the patient started experiencing nausea, which she attributed to entacapone. However, the reason for discontinuation of entacapone was the patient's insurance provider declining to cover entacapone. The benefit of entacapone lasted during the entire 1 month of its use.

Discussion

RLS is a common disorder in the elderly, occurring in about 5% of the population.[2] RLS is classified as primary or secondary. In at least 60% of primary RLS cases, a family history is reported by the patient. One study of 133 patients with typical RLS found the mean age at onset to be 27.2 years.[3] Secondary RLS is associated with neuropathy, renal failure, iron deficiency, vascular disease, pregnancy, and rheumatoid arthritis. The severity of the symptoms increases with age, sleep deprivation, and mental stress. The conventional treatments include benzodiazepines, dopamine agonists, opiates and levodopa. Catechol-*O*-methyl transferase (COMT) inhibitors block the peripheral metabolism of levodopa, increase its half-life, and enhance its brain availabililty. Two COMT inhibitors, tolcapone and entacapone, have been made available as adjunctive agents to levodopa. In Parkinson's disease with motor fluctuations, they have been shown to increase *on* time and reduce *off* time.[4] We are not aware of any reports of patients with RLS who were initially treated with carbidopa–levodopa with subsequent addition of tolcapone or entacapone to increase the duration of symptom relief. Our patient reported significant increase in the duration of symptom relief after entacapone was added to the regimen and the therapeutic goals were met. The regimen was continued for 1 month. Although the patient experienced nausea, which she attributed to entacapone, the cost of entacapone and the refusal by the insurance provider to cover entacapone were the primary reasons for its discontinuation. Whether entacapone's action to increase the therapeutic relief provided by carbidopa–levodopa in RLS can be sustained long-term in not known. A clinical trial of entacapone combined with carbidopa–levodopa to increase the duration of symptom relief in patients with RLS seems warranted.

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Woman with Facial Spasm Induced Exclusively by Sound

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Abstract: A woman is described in whom facial spasm occurs solely and predictably in the presence of certain noises. The symptoms resolve promptly as soon as the auditory stimulus stops. © 2002 Movement Disorder Society

Dystonia is a symptom characterised by prolonged, involuntary muscle spasms producing abnormal, often twisting postures. Muscle spasms vary in severity with the context in which they occur and sometimes a single specific activity can induce symptoms of dystonia. Blepherospasm that occurs only while talking is one example of this context dependency. Other specific activities, usually by means of sensory input and sometimes called "sensory tricks," may produce substantial reduction in dystonia.[1] The task-specific nature of some dystonic symptoms has led to the concept that dystonia could result from inappropriate performance of complex motor programs, possibly from a disturbance in the basal ganglia and supplementary motor area.[2] The fundamental cause or causes as well as the pathophysiology of dystonia still remain unknown. The particular form of input necessary to induce muscle spasms in task-specific dystonia varies but has been proposed to involve sensory or proprioceptive feedback from a part of the body used for a specific task, i.e., the hand in writers, or the mouth in trumpet players.[3] Although input from the special senses such as visual and auditory input can influence the perception of dystonia, there is no evidence that this type of input actually induces dystonic symptoms

This study is, to the best of our knowledge, the first to present a patient with acquired facial spasm occurring exclusively in the presence of certain noises.

Case Report

The patient is a Caucasian woman without any family history of dystonia or other neurological diseases. There is no history of any significant previous illnesses apart from lower back pain following surgical treatment of a lumbar discus prolapse at the age of 40 years. She had never been treated with neuroleptics.

At 52 years of age, she suddenly developed a constant high frequency tinnitus of the right ear. A few months later, she noticed mild involuntary contractions of the lower facial muscles on the right side when in the presence of certain noises such as the squeaking of a chair or the sound of a washing machine spinning. Over the next few months, the condition progressed to severe but transient right-sided facial spasms when hearing these certain noises. The spasms diminish but do not completely disappear when putting cotton wool or a masking hearing aid in the right ear but not in the left ear. The symptoms are not induced by all noises, but they have never occurred in the absence of sound and have never been provoked by any other stimulus.

Neurological workout was completely normal and there was no evidence of any psychiatric morbidity. However, when a tape with the noise of a washing machine was played, there was prompt initiation of sustained contraction of facial muscles on the right side without involvement of the eyelids, tongue, lips, or platysma, which completely vanished when the noise was stopped.

Extensive investigations showed no abnormal findings. Magnetic resonance imaging (MRI) of the brain including MR-angiography, brainstem-evoked potentials, and extensive blood tests were all completely normal. A lumbar puncture looking for borrelia and oligoclonal bands was also normal and there was no evidence of Whipple's disease. Ear, nose, and throat examination was performed several times, finding largely normal audiometry apart from a slight bilateral hearing loss for high frequencies, negative Tullio phenomenon, and no exaggeration of the startle response. Electroencephalogram performed during one of the incidences of facial spasm was normal, as were electromygraphic (EMG) and nerve conduction studies of the right facial nerve and its branches, which showed no signs of ephaptic impulse transmission. There was no evidence of EMG activity in the facial muscles on the left side. Single-photon emission computed tomography of the brain using TC99m-labelled ceretec performed during a bout of facial spasm showed a small area of hyperperfusion in the right temporal lobe, which was considered insignificant. A tape recording of some of the noises that evoke the patient's symptoms was analysed by an experienced electronic engineer who characterised the different sounds as "noise" with a wide range of different frequencies with a completely unsystematic distribution.

There was a slight remission of the patient's tinnitus, but otherwise the condition remained fairly stable during the last few years without any development of other symptoms or dystonia in other parts of the body. Treatment with carbamazepine seemed to have a modestly positive effect on the symptoms as did a masking hearing aid.

Discussion

To our knowledge, this is the first case report of a patient with facial spasms exclusively evoked by auditory stimuli. There has been, however, a Japanese report of a woman with hemifacial spasm induced synchronously by stimulation with sound, but the spasm also occurred voluntarily and the condition completely resolved after microvascular decompression of the facial nerve.[4] Scolding and colleagues[5] reported focal dystonia of the jaw in an auctioneer, and Lagueney and associates[6] described a patient with jaw dystonia triggered by biting into hard food. Both these cases occurred predictably in task-specific situations and although the facial spasm described here

A videotape accompanies this article.

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was likewise predictable and resolved when the stimulus stopped, it cannot be called task-specific or occupational and is thus quite different from previous reports. Focal dystonia can also be induced by peripheral trauma[7] and by exposure to toxic substances[8] but this was not the case in our patient. One report described an oculomasticatory syndrome related to systemic Whipple's disease[9] but there was no evidence of this condition or any other systemic illness in the present case.

A psychogenic explanation cannot be completely ruled out. The sustained chronic contraction without involvement of eyelids, tongue and lips; the prompt initiation and termination of the condition when the tape is turned off; and the fact that the symptoms are provoked only by some sounds with an unsystematic distribution of different frequencies would seem to favour a psychogenic origin. Walters and Hening[10] described a case with noise-induced psychogenic tremor associated with post-traumatic stress disorder, but in this case the tremor could disappear on distraction and continue long after the offending stimulus had stopped, and there was a markedly exaggerated startle response. In the present case, there were no precipitating stressful events, and several psychiatric assessments over a long period of time were all normal without any evidence of affective symptoms, personality disorder, or secondary gain. These points, together with the predictability and the consistency of the symptoms over several years as a normal startle response, and lack of EMG activity in the facial muscles on the nonsymptomatic side, favour organicity. Certainly, no psychiatric diagnostic label according to neither DSM-IV nor ICD 10 can be attached to the patient, and the condition has been designated as "idiopathic."

Thus, the mechanism responsible for the symptoms in the present case is unknown, although it might be that certain types of auditory input, possibly via connections with the basal ganglia, are able to disrupt the normal inhibiting action of central nervous pathways connecting with the peripheral nerve, thus causing an overactivity of the nerve. It has been suggested that altered proprioceptive input could play an enhancing or partially causative role in orofacial dystonia,[11] and it is not an entirely uncommon clinical observation that tactile stimuli sometimes can provoke or worsen dystonia, especially in occupational dystonia such as writers cramp. There is evidence that deficiencies in spinal reciprocal inhibition and abnormalities of central sensory processing and motor input may be related to reduced cortical inhibition; and in primates, repetitive motions can induce plasticity changes in the sensory cortex leading to degradation of topographic representations of the hand.[12] Finally, Munchau and colleagues[13] found an abnormal interaction between vestibular and voluntary head control in patients with spasmodic torticollis, showing that there is an abnormal use of vestibular signals at the highest levels of the motor system. It is possible that abnormal voluntary interaction with short latency reflex responses could be a more widespread neurophysiological deficit in dystonia and might also be applicable to the cochlear system.

As long as the etiology of dystonia in general has not been established, there probably will be no completely feasible explanation for our case. Future case reports like this one might be able to provide insight that can lead researchers in the right direction.

Legend to Videotape

Fifty-five-year-old woman with severe facial spasm that develops when a pre-recorded sound of a washing machine is played, and stops when the tape recorder is turned off.

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