

Letters to the Editor Related to New Topics

A Europe-Wide Assessment of Current Medication Choices in Huntington's Disease

Huntington's disease (HD) is a fatal neurodegenerative disorder, which usually manifests in middle age with motor, psychiatric and/or cognitive disturbances. In his recent review, Francis Walker stated that medical treatment of HD has made little progress in the past 20 years.¹ Despite a large number of reports on pharmacological interventions in HD, no treatment recommendation could be made in a recent evaluation of 20 randomized controlled clinical trials.² While symptomatic treatment of HD has been reviewed,³ a systematic evaluation of current prescription practices is missing. We have analyzed the use of symptomatic treatment for HD based on more than 7,000 entries in the European HD REGISTRY between 2004 and 2007. The REGISTRY collects data from centres across Europe with particular expertise in HD. As many as 1,796 of 2,128 registered HD patients (84%) received symptomatic treatment. About 1,058 patients (50%) were treated for depression and 596 (28%) received antichorea medication. Among the other common indications, 268 patients (13%) were treated for irritability and aggression, 188 (9%) for sleep disturbance, and 152 (7%) for psychosis. Fewer than 2% of patients received medication for rigidity (35), obsessive-compulsive behaviours (24), apathy (12), or mania (4). The most commonly prescribed drugs were neuroleptics and antidepressants. About 321 HD patients (15%) received citalopram, 283 (13%) tiapride, 249 (12%) olanzapine, 202 (9%) paroxetine, 181 (8%) tetrabenazine, 180 (8%) risperidone, 165 (8%) sertraline, 137 (6%) haloperidol, and 122 (6%) sulpiride. The choice of drug depended strongly on cultural influences. Thus, at least a quarter of the patients on neuroleptics received haloperidol in Germany (24%) and Italy (32%), but only 12% in the UK and 14% in Spain. In the UK, olanzapine was the neuroleptic of choice (55%), while this drug was rarely prescribed in Germany (5%). Tiapride was the most common HD medication in Germany (38%), but this drug was unavailable or not used in other European countries. Citalopram was the single most commonly prescribed antidepressant in the UK (41%). Interestingly, citalopram was used less often in Germany (18%) and not at all in Spain (0%). In Italy, paroxetine was the most commonly prescribed antidepressant (47%). Our findings suggest that in HD, and probably other orphan diseases, patients need to be aware of the lack of evidence-based criteria for medication choices and might want to look beyond the border of their country for additional symptomatic treatment options.

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Estimate of Point Prevalence of Parkinson's Disease Induced Psychosis in the United States

Neuropsychiatric symptoms in Parkinson's disease (PD) patients can be as high as 90%.¹ PD patients with psychosis have a poor prognosis, higher nursing home placement, and increased mortality.² Although prevalence rates for PD patients with psychosis (PDP) have been estimated as high as 40%, no common definition for PDP exists, and it can be difficult to distinguish from other primary causes of psychosis (DLB, Alzheimer's, primary psychiatric disorders, etc.) and therefore the true prevalence rate is unknown. An NIMH work group recently proposed specific diagnostic criteria for PDP to distinguish it from other causes of psychosis. A review of existent worldwide literature was completed to estimate the U.S. point prevalence of PDP as defined by this group.²

Primary worldwide literature published in English was screened using all available search engines from the University of Illinois Library, with primary and secondary refer-

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ces for the past 10 years checked. The diagnostic criteria from the NIMH working group served as the screening criteria for inclusion into the analysis.² Each reference was examined for its compatibility with these criteria. The total number of patients, weighted age of PD cohort, weighted age of PDP cohort, and weighted range of each was recorded. The mean weighted age of the group was then extrapolated to current U.S. prevalence rates, based on total number of patients, and age-specific subpopulations from projections to obtain estimates of prevalence of PDP in the United States.³

One hundred twenty publications were identified for review, with 24 being primary literature surveys or studies with data on psychosis in PD patients. Of these 24, nine studies matched the criteria identified by the NIMH working group. In the nine studies, 468/2,041 PD patients (23%) matched the PDP definition.⁴⁻¹² Two studies did not report overall PD population age and one study did not report PDP ages. There were seven ex-U.S. studies^{4-6,9-12} and two U.S. studies.^{7,8} The percentage of PDP patients in the U.S. studies did not differ from the overall population analyzed (24% vs. 23%, $P = 0.99$). The weighted age of the PD population was 69 years (52–83) and differed from the general PDP and U.S. PDP population (both 71 years, $P < 0.05$). The weighted-age range for PDP patients was 56 to 82 years. The weighted mean age of onset of PD symptoms was 59 (43–78) years in six studies where age was reported, which was significantly different than the age of onset of PDP reported in three studies (69 years, $P < 0.0001$). Using the mean age of PD onset of 59 years and the recent census data³ indicating that there are 538,293 PD prevalent patients greater than 60 years and 340,000 PD prevalent patients greater than 50 years in the United States today, an estimate of point prevalence was determined to be between 129,190 and 81,000 patients with PDP in the United States in 2008.

A review of studies that allows for analysis and application of a consensus definition of PDP indicates that even when eliminating common causes of psychosis, there is still a substantial subpopulation that has a specific PD-associated psychosis. It occurs significantly after the onset of PD and generally does not occur before age 50. Although most of the studies reviewed were European studies, there were no demographic differences noted between the cohorts, suggesting confidence in the extrapolation to the U.S. population. Because it has been postulated that neuropsychiatric symptoms occur in clusters representing specific neurobiological deficits in PD patients, these patients, once diagnosed with a specifically associated PDP, may require targeted therapy, yet to be identified. Further research should be aimed at validating the proposed definition and the best treatment options for PDP patients.

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Ataxia Due to Isolated Infarction of the Precentral Knob

Video 

The precentral knob is a radiologically easily recognized landmark for the identification of the primary motor cortex concerned with the control of hand movements. Functional MRI has demonstrated motor hand activation in the precentral gyrus and the anterior wall of the postcentral gyrus in the area of the precentral knob.¹ Lesions at this site are known to cause isolated hand weakness.² To date, there have been four reported cases of cerebral infarction of the precen-

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tral knob presenting with isolated ataxia, although a clear mechanism for this is yet to be described.^{3,4}

We present two further patients with infarctions of the precentral knob showing typical cerebellar ataxia in the absence of significant other motor or sensory deficit.

Patient 1.

A 43-year-old man was admitted with the abrupt onset of clumsiness in both hands. He had a history of poorly controlled diabetes mellitus and was a heavy smoker. Examination revealed normal tone, power and reflexes, and sensation in both upper limbs. Bilateral upper limb ataxia was evident with intention tremor, past pointing, and dysdiadochokinesis (Segment 1). There was no gait ataxia or heel-knee-shin ataxia. The neurological examination was otherwise normal.

MRI of the brain showed small areas of T2 hyperintensity and corresponding reduced diffusion consistent with infarction in the posterior portions of the precentral knobs bilaterally, and the anterior portion of the postcentral gyrus on the left (Fig. 1). There was also a small area of prior infarction and gliosis in the left inferior parietal region. The scan was otherwise normal. Over a period of 6 weeks, the upper limb ataxia almost entirely resolved.

Patient 2.

An 85-year-old man was admitted with a sudden onset of difficulty using his right hand. He had a history of hypertension and hypercholesterolaemia. Examination revealed normal tone, power, reflexes, and sensation bilaterally. There was ataxia of the right upper limb with intention tremor on finger nose testing and dysdiadochokinesis (Segment 2). Cerebellar testing of the left upper limb was normal. There was no gait ataxia or heel-knee-shin ataxia. MRI of the brain showed T2 hyperintensity and reduced diffusion of the left precentral knob and in the anterior part of the postcentral gyrus opposite the knob (Fig. 2). It also showed an old left cerebellar infarction. The patient's ataxia resolved entirely over a 2-month period.

Both of our patients had signs suggestive of upper limb cerebellar ataxia in the absence of other motor or sensory deficits. MRI scans confirmed recent infarction of the precentral knobs bilaterally in Patient 1, and on the contralateral side to the ataxia in Patient 2. There were no other lesions visible on scanning to explain the ataxia.

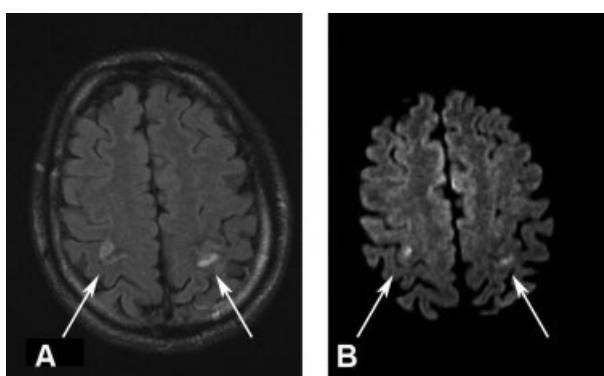


FIG. 1. MRI FLAIR (A) sequence and diffusion weighted and (B) images showing recent infarction of the precentral knob bilaterally.

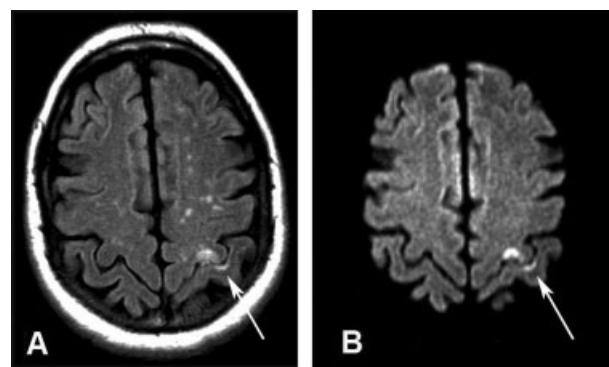


FIG. 2. MRI FLAIR (A) sequence and diffusion weighted and (B) images showing recent infarction of the left precentral knob.

Similar isolated upper limb ataxia has been reported previously in two cases with infarction of the precentral knob.⁴ Two further cases had isolated proximal upper limb ataxia.³ The demonstration of ataxia in the absence of hemiparesis is unexpected as most lesions in this region have been associated with isolated hand weakness.

Cortical infarction has been reported as causing the ataxic hemiparesis syndrome, typically with leg weakness and brachial ataxia. The weakness in the ataxic hemiparesis syndrome may be transient and it is possible that our patients did demonstrate weakness prior to our examining them, although this would have been very transient.

Presumably, interruption of cortico-pontocerebellar or dentato-rubro-thalamocortical pathways is involved in the development of the isolated ataxia. The scattered white matter lesions seen in the centrum semiovale in both cases could possibly have contributed to the ataxia by interrupting these pathways. None of these lesions, however, demonstrated restricted diffusion on MRI scanning. Therefore these lesions are not acute and would not have been responsible for the acute ataxia seen in these two patients.

Our two cases provide further evidence that cerebellar ataxia can occur with lesions distant to the cerebellum in the absence of weakness or sensory loss. They implicate the region of the precentral knob as integral to the complex cortico-cerebellar connections which coordinate hand movements.

Legends to the Video

Segment 1. The video segment demonstrates an intention tremor, past pointing and dysdiadochokinesis bilaterally.

Segment 2. The video segment shows an intention tremor, past pointing and dysdiadochokinesis of the right upper limb. The left upper limb examination is normal.

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Orolingual Tremor as Unusual Presentation of Anti-Hu Paraneoplastic Syndrome

Video 

We report a case of an anti-Hu positive patient who presented with clinical and electromyographic features of orolingual tremor. Anti-Hu syndrome is the most commonly recognized form of paraneoplastic syndrome (PNS) that often antedates the diagnosis of an underlying not evident cancer that is usually small in size and stage limited.^{1,2} However, cases of PNSs are rare and occur in less than 1% of patients with cancer. Some cases of PNSs are associated with serum and cerebrospinal fluid (CSF) antibodies against neural antigens expressed by the tumor such as anti-Hu antibodies. Various forms of neurological dysfunction can occur from PNSs, including cerebellar degeneration, sensory neuronopathy, brainstem encephalopathy, limbic encephalitis, and motor-neuron dysfunction.^{1,2}

A 58-year-old man presented with a 3-month history of involuntary oscillatory movements of the tongue and perioral twitching that often interfered with his speech and deglutition, causing mild dysarthria and dysphagia. The movements were almost continuous. This tremor occurred either at rest or with the activation of the orolingual structures, such as with the tongue protruded and performing actions (see video). By the time this man was admitted to our neurology department 6 months after the onset, his neurological examination showed spontaneous, oscillatory twitching of the tongue, rhythmic clonic jerks of the left side perioral muscles, and unbalanced gait. He demonstrated mild axial ataxia and mild weakness at distal muscles of all limbs. At the lower limbs, tendon reflexes were absent, and there was a sensory deficit with decreased pallesthesia. He used to smoke about 20 cigarettes per day. He had no family history of lung cancer nor past history of electrical injury, Wilson's disease, brainstem astrocytoma, neurosyphilis, or exposure to neuroleptic drugs. The electromyographic examination (see Fig. 1) was normal except for a rhythmic activity, with a 10-Hz frequency

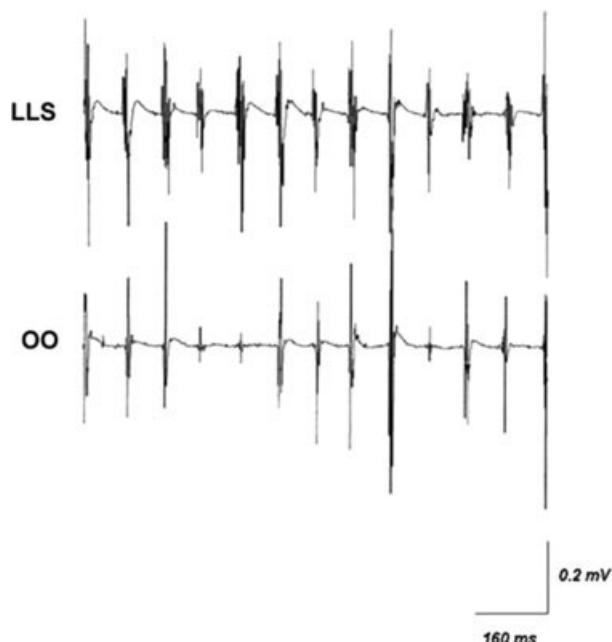


FIG. 1. Electromyogram (EMG) traces. At rest, rhythmic 10-Hz EMG activity involving simultaneously perioral muscles. LLS, levator labii superioris muscle; OO, orbicularis oris muscle.

frequency simultaneously recorded from orbicularis oris and levator labii superioris muscles (orolingual tremor at high frequency).³ He was treated with 2 mg of clonazepam, obtaining a marked attenuation of the tremor and improvement of his speech and deglutition; however, there was no effect on his ataxia (see video). He had no awake, sleep-deprived, or polygraphic EEG abnormalities. Routine laboratory analysis were normal, whereas CSF examination revealed a marked increased protein level (1,790 mg/L, n.v. 180–430 mg/L) including oligoclonal IgG bands without any cells. Serum and CSF anti-Hu antibodies were found positive and remained positive at serum dilutions greater than 1:100,000. To localize the suspected malignancy, the patient underwent chest X-ray, brain, and spinal MRI, including FLAIR and postgadolinium sequences and upper and lower gastrointestinal endoscopy, which were all normal. Conversely, a whole-body PET/CT scan demonstrated an intense focal hot spot of increased uptake of 18-F-FDG with a SUV maximum of 5.9 in the mediastinum (see Fig. 2). Given the patient's smoking history, the whole body PET scan finding, the presence of anti-Hu antibodies, and their strong association with small cell lung cancer,⁴ we believed that the most likely diagnosis was anti-Hu syndrome associated with bronchogenic carcinoma. Interestingly, the biopsy of the mediastinic lymph node diagnosed an underlined and unsuspected nonsmall cell lung cancer (poorly differentiated non-small cell lung carcinoma).

To our knowledge, this is the first report of a patient whose orolingual tremor was the unique manifestation of anti-Hu associated PNS preceding a nonsmall cell lung cancer. This case extends the clinical spectrum of neurological manifestations of anti-Hu associated PNS.

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FIG. 2. Coronal slices of $[^{18}\text{F}]\text{-FDG PET/CT}$. Intense focal increase of metabolism in a right paratracheal lymph node is evident on PET (A), CT (B), and fused images (C). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Legend to the Video

The first part of the video shows at rest involuntary perioral twitching and movements of the tongue at either rest or with the tongue protruded. The second part of the video shows a complete resolution of the tremor after 2 mg of oral clonazepam.

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