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Myoclonus in Adult Huntington's Disease

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Two brothers with clinically definite adult Huntington's disease developed disabling myoclonus years after the first signs of the disease. Their electroencephalograms were consistent with a primary generalized epilepsy, although neither man had seizures. The myoclonus was controlled with valproic acid therapy.

Vogel CM, Drury I, Terry LC, Young AB.
Myoclonus in adult Huntington's disease.
Ann Neurol 1991;29:213–215

Myoclonus is an uncommon clinical feature in Huntington's disease (HD). The prominent movement disorder in affected adults is chorea, whereas in juvenile patients, the clinical picture is one of parkinsonism [1, 2]. Only 3 patients with myoclonus complicating adult HD have been reported [2–4], although the prevalence of myoclonus may be greater in patients with juvenile onset [1, 5]. The patients described here illustrate that myoclonus can be a disabling but treatable feature in a subset of patients with adult HD.

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Received Mar 19, 1990, and in revised form Jul 31. Accepted for publication Aug 2, 1990.

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Patient Histories

T.T. was first evaluated at age 28 years, 2 years after the onset of cognitive decline and incoordination. The diagnosis of HD was supported by findings of dementia and choreiform movements, and a definite family history of adult onset dementia and chorea previously diagnosed as HD (Fig 1). Neuropsychometric testing revealed a full scale IQ (FSIQ) of 72, and positron emission tomography (PET) demonstrated hypometabolism in the caudate nuclei. Ceruloplasmin, serum and urine copper levels, electroencephalogram (EEG), head computed tomographic (CT) scan, and cerebrospinal fluid (CSF) analysis were normal. Serial examinations over the next 5 years demonstrated only a mild cognitive decline until he presented with a 1-month history of uncontrollable brief, rapid jerking movements. Examination revealed frequent generalized myoclonic jerks involving axial and appendicular muscle groups, exacerbated by any attempt at movement, and prominent rigidity. Benztropine mesylate and haloperidol had been started after the onset of the myoclonus. These drugs were discontinued without clinical change.

A head CT scan showed prominent caudate atrophy. An EEG demonstrated generalized bisynchronous polyspike waves, at times associated with myoclonic jerks, without loss of consciousness and enhanced by photic stimulation (Fig 2). The myoclonus, as recorded by surface electromyography over the right forearm, consisted of 40 to 80-msec bursts. The cortical component of short latency somatosensory evoked responses (SSERs) was not enlarged. An eccrine sweat gland biopsy for inclusion bodies, a periodic acid-Schiff stain for inclusion bodies in lymphocytes, an ophthalmological examination for a cherry red spot, and a lysosomal enzyme screen were negative. He did not cooperate with formal neuropsychometric testing.

Valproic acid was instituted daily with a pronounced reduction in myoclonus and a return to his previous level of function. Follow-up examination 5 months later revealed rare myoclonus and no polyspike-wave activity on EEG.

W.T., the older brother of T.T., was diagnosed with HD at age 30 years, 2 years after the onset of cognitive decline and involuntary movements. His initial evaluation was similar to his brother's except for caudate atrophy on head CT scan. Five years later, his caretakers reported a progressive decline in ambulation and recent onset of jerking movements that were worse on awakening. On neurological examination, any attempt to walk brought out myoclonic movements, which were otherwise infrequent. An EEG showed bisynchronous polyspike waves enhanced by photic stimulation. These appeared both independent of and concomitant with the myoclonus. The cortical component of the SSERs was not enlarged. Skin and rectal biopsies for inclusion bodies were negative by light and electron microscopy. Repeat neuropsychometric testing revealed a FSIQ of 64, with a pronounced decline in motor speed and dexterity. Five months after starting valproic acid therapy, he could walk unassisted; however, the remainder of his neurological examination, including the chorea, was unchanged. Follow-up EEG continued to show generalized polyspike waves. An EEG and SSERs were normal in a clinically unaffected brother.

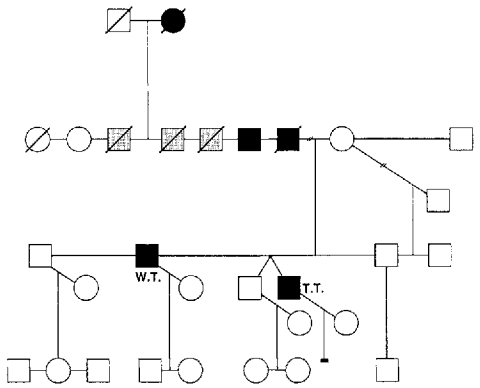

Fig 1. Family pedigree. Solid black squares = *definite Huntington's disease (HD);* shaded squares = *possible HD.*

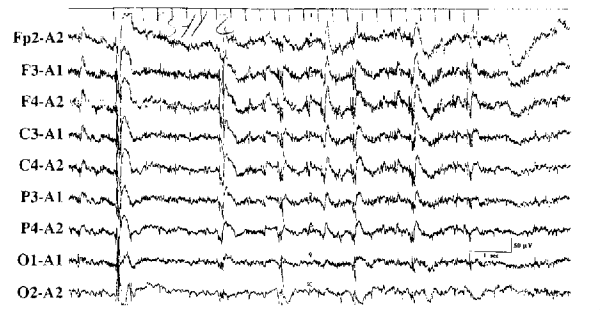

Fig 2. Generalized polyspike-wave discharges accentuated by photic stimulation in T.T. before treatment.

Discussion

These brothers are similar to the 3 previously reported patients with adult HD with myoclonus [2–4]. In all these patients, myoclonus was precipitated by the initiation of voluntary movement and often appeared as massive sudden jerks involving axial and appendicular muscle groups, and was easily controlled by either valproic acid or clonazepam. Each patient inherited HD from his father, and the onset of symptoms appeared in the third or early fourth decade.

Hereditary syndromes of myoclonus, dementia, and chorea comprise a rare and heterogenous group of disorders. In addition to HD, the differential diagnosis includes storage disorders (e.g., Lafora body disease, and neuronal ceroid lipofuscinosis and sialidosis), mitochondrial encephalomyopathies (e.g., myoclonic epilepsy and ragged red fibers, and "Tweed Ball" mitochondropathy), inborn errors of metabolism (e.g., glutaric acidemia, sulfite oxidase deficiency, and Lesch-Nyham syndrome), Wilson's disease, chorea-acanthocytosis, and a few clinically or pathologically defined progressive myoclonic epilepsies (Unverricht-Lundborg disease, May-White syndrome, Hallervorden-Spatz disease, dentatorubralpallidoluysian atrophy, neuronal axonal dystrophy, action myoclonus–renal failure syndrome [5–8]). These brothers, however, lacked the inheritance pattern and clinical, laboratory, or pathological findings specific to these disorders. The autosomal dominant transmission, adult onset of chorea and dementia, and highly characteristic PET and CT findings strongly support HD as the clinical diagnosis in this family and the previously reported patients.

The electrophysiological features present in these patients are most consistent with reticular reflex myoclonus, which has been characterized as a fragment of generalized epilepsy [9]. There was an identifiable EEG correlate in the form of generalized polyspike waves that was not time-locked to the myoclonus. The cortical component of the SSERs was normal. Although these brothers did not have generalized seizures, their EEGs were similar to those seen in patients with a primary generalized seizure disorder, and 2 of the 3 previously reported patients with adult HD with myoclonus had documented seizures. Seizures occur rarely in patients with adult HD, compared with two-thirds of the patients with juvenile HD [1].

Deficiencies in gamma-aminobutyric acid (GABA) activity may play a role in the pathogenesis of some types of myoclonus. Reduced levels of GABA are present in the CSF of patients with postanoxic myoclonus and progressive myoclonic epilepsies compared with controls consisting of patients suffering from other neurological disorders [10, 11]. The photosensitive myoclonus in the Senegalese baboon *Papio papio* can be blocked by gamma-acetylenic GABA and gamma-vinyl GABA, irreversible inhibitors of the degrading enzyme, GABA-transaminase [12]. The manipulation of GABA activity in the contralateral striatum of rats results in sustained focal myoclonic jerks [13]. Clonazepam and valproic acid, effective treatments of myoclonus due to diverse pathologies, exert their therapeutic effects at least in part by influencing the GABA system [14].

In patients with rigid or juvenile onset HD, the denervation in the substantia nigra pars reticulata is profound [15]. Bilateral lesions of the reticulata or inhibition of the reticulata neurons by GABA agonists attenuate kindled seizures in rats [16]. Stimulation of the substantia nigra pars reticulata neurons or injection of GABA antagonists lower the seizure threshold in a similar animal model [17]. This loss of nigral inhibition from the striatum may play a role in the susceptibility to myoclonus or seizures of some patients with HD.

If deficiencies in GABA are central to the pathogenesis of both HD and some forms of myoclonus, it is unclear why myoclonus is so infrequent in adult HD. HD is genetically homogeneous, with the gene localized to the short arm of chromosome 4 [18]. Further studies will be necessary to elucidate why this population of patients with HD manifests a different expression of the same gene. Myoclonus should be

recognized as a treatable feature in some patients with adult HD.

C.M.V. is a recipient of National Institutes of Health Training Grant 5-732 NS-07222.

Presented in part at the 114th Annual Meeting of the American Neurological Association, New Orleans, LA, September 1989.

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Continuous Muscle Fiber Activity, Peripheral Neuropathy, and Thymoma

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Two patients, one of them with myasthenia gravis, presented symptoms of continuous muscle fiber activity syndrome before discovery of a thymoma. Peripheral neuropathy was present in both patients, with axonal and demyelinating lesions in sural nerve biopsy. The syndrome remained unchanged or worse after thymectomy. Both patients died of associated complications.

García-Merino A, Cabello A, Mora JS, Liaño H. Continuous muscle fiber activity, peripheral neuropathy, and thymoma. Ann Neurol 1991;29:215–218

The syndrome of continuous muscle fiber activity at rest (CMFAS) [1] associates a wide spectrum of clinical manifestations with spontaneous electromyographic (EMG) discharges. The condition is a polymorphous entity described under various names such as neuromyotonia, pseudomyotonia, Isaacs' syndrome, and CMFAS [2]. We report here two patients with CMFAS, thymoma, and peripheral neuropathy, an association previously not recognized. The purpose of this report is to draw attention to the possible relevance of thymoma in the pathogenesis of the syndrome.

Patient Reports

Patient 1

A 56-year-old, previously healthy woman began to note facial twitching, blurred vision, occasional trismus, and soon after, vague thoracic discomfort. Six months after onset of symptoms, a large lymphoepithelial thymoma was found and resected. A few days after surgery, she developed profuse sweating, widespread muscle twitching, dyspnea, and carpal spasms. Serum calcium and magnesium were normal and intravenous calcium did not modify the spasms, which were only relieved by diazepam. Her condition deteriorated progressively. Her dyspnea became present on minimal effort and she developed laryngeal stridor. Extensor spasms of the

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Received Jul 27, 1989, and in revised form Apr 2, Jul 24, and Aug 27, 1990. Accepted for publication Aug 30, 1990.

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