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Abnormal intracortical facilitation in early-stage Huntington's disease

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Abstract

Objective: It is known from neuropathological and imaging studies that the neuronal degeneration in Huntington's disease (HD) is already quite severe when the first symptoms of the disease become clinically evident. This study was aimed at detecting neurophysiological changes, as assessed by means of transcranial magnetic stimulation (TMS), involved in the early pathogenesis of the neurodegeneration in HD.

Methods: Motor cortex excitability was examined in 12 patients with HD in the early clinical stage of the disease and in 15 age-matched control subjects, using a range of TMS protocols. Central motor conduction time, resting and active motor threshold, duration of the cortical silent period, the short-interval paired-pulse intracortical inhibition (SICI) and the paired-pulse intracortical facilitation (ICF) were examined.

Results: The early-stage HD patients showed a statistically significant reduction in ICF. The other measures did not differ significantly from the control subjects.

Conclusions: Our findings provide neurophysiological evidence that changes in motor function are present in the early HD. Since ICF is thought to depend upon the activity of intracortical glutamatergic excitatory circuits, the results of our study support the theory that altered NMDA receptor function plays an important role in the pathogenesis of HD.

Significance: These findings may provide clues to the underlying pathophysiology of the disease. A more complete understanding of the changes in motor cortex excitability that occur early in the course of HD will lead to a better definition of the disease process and may allow earlier diagnosis and intervention.

Keywords: Early-stage Huntington's disease; Transcranial magnetic stimulation; Intracortical facilitation; Glutamatergic transmission

1. Introduction

Huntington's disease (HD) is a neurodegenerative, autosomal dominant inherited disorder. Looking at the clinical course, different clinical types of HD can be distinguished; the classical type is characterized by a classical triad of symptoms, including involuntary movements (bizarre grimacing, respiratory irregularity, faulty articulation of speech, and irregular, arrythmic, unpatterned movements of the limbs), affective disturbances (erratic behaviour, emotional outbursts, irritability, and apathy) and cognitive impairment (deficits in attention and executive functions, visuospatial disturbances, memory dysfunction). The genetic basis of the disease is the expansion of an unstable CAG repeat chain, coding for polyglutamine, located within the IT15 gene of the 4th chromosome (The Huntington's disease Collaborative Research Group, 1993).

The pathophysiological mechanisms of HD are still not fully understood.

Transcranial magnetic stimulation (TMS) applications have an important place among the investigative tools to study patients with motor disorders and have demonstrated abnormal cortical excitability in many of these diseases, including HD (Roick et al., 1992; Priori et al., 1994; Tegenthoff et al., 1996; Abbruzzese et al., 1997; Hanajima et al., 1999; Modugno et al., 2001). Several authors have

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reported that the CSP had an abnormally long and variable duration (Roick et al., 1992; Priori et al., 1994; Tegenthoff et al., 1996; Modugno et al., 2001). However, studies using paired-pulse TMS technique have provided conflicting results. Abbruzzese et al. (1997) described a reduced intracortical inhibition and an enhanced intracortical facilitation; Tegenthoff et al. (1996) reported a motor cortical hypoexcitability; Hanajima et al. (1999) found normal intracortical inhibition. A recent study with repetitive TMS suggests that the excitability of facilitatory intracortical interneurones is decreased in HD patients (Lorenzano et al., 2006). The variability of the reported TMS abnormalities probably depends on the phenotypic heterogeneity, the various stages of disease in the patients examined, the different methods for data collecting, differences in patients selection, possible interference with involuntary muscle contraction (pre-activation because of involuntary movements).

In this study, we aimed to evaluate the sensitivity of TMS techniques in detecting early motor cortex excitability changes in HD patients in the earlier stage of the disease and at evaluating their relevance in the pathophysiological mechanisms of the disease. TMS can be used to measure objectively the disease progression and to monitor the effects of putative therapies in HD patients.

2. Methods

2.1. Subjects

The study included twelve patients (six men and six women, mean age 33.5 years, range 22–55 years) in the earlier clinical stage of HD, that is stage I according to Shoulson et al. (1979, 1989). All were recruited from family with a positive history of the disease.

Predictive testing was performed according to the guidelines given by the Committee of the IHA and the Working group on HD of the WFN (HA/WFN, 1994). The diagnosis was confirmed by molecular DNA analysis. Direct analysis of CAG triplets expansion in the HD gene was performed as described previously (Goldberg et al., 1993).

All subjects were assessed using the Unified Huntington's Disease Rating Scale (UHDRS). This assessment was performed blind to the TMS findings and to genetic status.

Table 1 shows the CAG repeat lengths, the clinical features, the motor and total functional capacity (TFC) scores of the UHDRS in all HD patients.

None of the early-stage HD patients suffered from any clinically relevant disorders, and none were on medication with neuroleptic drugs, dopamine depleters or memantine at the time of the study.

Table 1
Genetical and clinical characteristics of the early-stage HD (Huntington's disease) patients

Early-stage HD patients	G A	CAG repeat length	UHDRS motor score[a]	UHDRS TFC score[b]
1	F 22	42	0	13
2	M 40	41	13 Chorea oral = 1; bradykinesia during finger taps = 4, bradykinesia during pronation-supination = 3; vertical ocular pursuit = 2, saccade initiation = 1, saccade velocity = 2	8
3	F 36	44	0	13
4	M 35	48	6 Bradykinesia during finger taps = 2, bradykinesia during pronation-supination = 2; saccade initiation = 1, saccade velocity = 1	11
5	F 27	40	12 Bradykinesia during finger taps = 4, bradykinesia during pronation-supination = 2; horizontal ocular pursuit = 2, saccade initiation = 2, saccade velocity = 2	9
6	M 44	40	2 Bradykinesia during pronation-supination = 2	12
7	M 38	43	3 Bradykinesia during finger taps = 2, saccade initiation = 1	12
8	M 25	48	8 Chorea face = 1, chorea oral = 1; Bradykinesia during finger taps = 2, bradykinesia during pronation-supination = 2; saccade initiation = 2	10
9	F 22	47	4 Tone arms = 2; bradykinesia during finger taps = 2	11
10	F 27	41	0	13
11	M 55	40	10 Chorea face = 1; tone arms = 2; bradykinesia during finger taps = 2, bradykinesia during pronation-supination = 2; saccade initiation = 1, saccade velocity = 2	9
12	F 31	44	0	13

Legend: G, gender; A, age; UHDRS, unified Huntington's disease rating scale; TFC, total functional capacity. [a]Range 0–124. [b]Range 0–13.