

Short communication

Cortical myoclonus in childhood and juvenile onset Huntington's disease

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ABSTRACT

Objective: Huntington's disease (HD) appearing before the age of 20 years gives rise to a distinct phenotype with respect to the classical adult-onset disease. Here we describe three patients with childhood or juvenile HD onset presenting with action myoclonus.

Methods: We performed jerk-locked back-averaging (JLBA), EEG-EMG coherence and phase analysis, long-loop reflexes (LLRs) and somatosensory evoked potentials (SSEPs). In one patient, we also performed transcranial magnetic stimulation (TMS) using single and paired pulses.

Results: In all patients, the EMG features revealed movement activated quasi-rhythmic repetitive jerks; the JLBA and EEG-EMG spectral and coherence profiles indicated a cortical generator of the myoclonus. All patients had enhanced LLRs during muscle contraction, while none showed giant SSEPs. The evaluation of intracortical inhibition by means of TMS revealed reduced inhibition at short and long inter-stimulus intervals.

Conclusions: The rhythmic course of the action myoclonus and the characteristics of the LLRs suggest that myoclonus is due to a reverberant circuit involving the motor cortex, possibly because of an imbalance between excitatory and inhibitory cortical neuronal systems.

Significance: Our findings suggest a similar cortical dysfunction in childhood and juvenile onset HD, which probably results from a specific circuitry impairment.

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1. Introduction

Huntington's disease (HD) is a rare hereditary neurological disorder presenting with chorea, ataxia, dystonia, behavioural disturbances and intellectual decay, due to the abnormal multiplication of CAG triplets in the *HTT* gene (4p16.3). In HD classical presentation, the symptoms appear at an age of 30–50 years, but they can occur earlier in a small percentage of patients with an especially high number of CAG repeats [1].

Myoclonus is unusual in adult-onset disease, but more frequent in juvenile HD (30–50% of subjects) [2,3] sometimes occurring as a dominant symptom, allowing the inclusion in the syndromic group of progressive myoclonus epilepsies (PMEs) [4]. According to the review of Caviness and Kurth [5], myoclonus in HD patients

could present with generalized or multifocal distribution, sometimes elicited by active movement or sensory stimuli; its generation has been attributed either to subcortical or to cortical circuitries, but few reports analysed in detail its neurophysiological characteristics.

The identification and precise definition of the myoclonus is important in the diagnostic workup because myoclonus needs specific treatments, whose choice partly depends from its physiopathological mechanisms [6]. We observed prominent action myoclonus in three HD patients, one with a childhood and two with a juvenile onset and we aimed our study at better defining clinical and neurophysiological characteristics of the jerks and at exploring the mechanisms of their generation.

2. Methods

We studied three patients with a positive genetic diagnosis of HD. All had a paternal disease inheritance and had a number of CAG repeats ranging from 60 to more than 100.

We recorded EEG signals by means of Ag/AgCl surface electrodes placed according to the 10–20 International System using linked ear lobe electrodes as

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reference and the EMG signals using pairs of surface electrodes with belly-tendon placement. The signals were digitally acquired (sampling frequency 512 Hz; band pass filters 1.6–120 Hz; Micromed Brain Quick System, Mogliano Veneto, TV, Italy). The relationship between the EEG and EMG-bursts recorded on the wrist extensor was analysed using jerk-locked back-averaging (JLBA) and by estimating the coherence and phase functions using a bivariate parametric (AR) model, as previously described [7], while the patients maintained a mild hand extension; the measures were compared with those obtained in a group of eight healthy controls (age: 30.3 ± 4.8 years).

Short- and long-loop reflexes (SLRs and LLRs) were recorded in the thenar muscle by stimulating the median nerve at the wrist just above the motor threshold (0.7 ms, 0.5 Hz). The SLR/LLR amplitude ratio was measured during tonic EMG activity at 30–40% of the maximum. We applied the same procedure in 12 healthy subjects (age: 30.9 ± 4.7 years).

Somatosensory evoked potentials (SSEPs) were recorded using standard procedures. The amplitude of N20–P25 cortical components was compared with the normative laboratory data (5.2 ± 2.4 μ V), assuming as “giant” the components exceeding the mean value + 3 standard deviation (SD) of healthy subjects.

In patient #1 only, motor evoked potentials (MEPs) were measured (Keypoint; Medtronic, Solvunde, Denmark; band pass filters: 20 Hz–10 kHz) by applying transcranial magnetic stimulation (TMS) (MagPro $\times$ 100, Medtronic, Denmark) through a circular coil placed on the vertex. The cortical relay time was measured by subtracting SSEP N20 latency and total motor conduction time from LLR latency. For paired-pulse TMS, we evoked MEPs on resting thenar muscle using an eight-shaped coil (biphasic stimulus waveform) over the site at which a supra-threshold magnetic pulse led to the largest potential. To explore short interval cortical inhibition (SICI), the conditioning stimulus was set at 90% active motor threshold (AMT), and the test stimulus at 120% resting motor threshold (RMT); individual or paired stimuli were randomly delivered at interstimulus intervals (ISIs) of 1, 2, 3, 4, 5, 6, 10 and 15 ms (five trials for each ISI). For long-term intracortical inhibition (LICI), the conditioning and test stimuli were both set at an intensity of 120% RMT and randomly given at ISIs of 30, 40, 60, 80 and 100 ms (five trials for each ISI). We calculated the size ratio between the mean amplitude of the conditioned and basal MEPs for each ISI and we compared the values with those obtained in a group of 18 healthy subjects (age: 30.3 ± 4.8 years); Grubbs' test for outliers was applied to compare the values obtained in the patient with those obtained in the healthy controls.

All procedures were carried out with the adequate understanding and written consent of the subjects involved or of their parents, in accordance with the Declaration of Helsinki.

3. Results

At the time of our observation (Table 1), all patients had severe neurological and psychiatric symptoms including hypokinesia, ataxia and moderate-severe cognitive impairment. In all, myoclonus was the most severe motor sign. Patient #1 was treated with a low dose (125 mg) of topiramate, patient 2 was untreated and patient #3 was fully treated with clonazepam and valproate.

In all patients, voluntary movements consistently activated jerky movements with a quasi-rhythmic course, appearing as a tremor-like disorder that disturbed posture maintenance and motor performances. Sporadic spontaneous jerks occurred at rest in patient #3.

MRI showed atrophic changes and increased signal intensity of the caudate nucleus and putamen in all of the patients.

3.1. Neurophysiological evaluation

3.1.1. EEG-EMG polygraphy

Patients #1 and #2 showed low-voltage (about 20 μ V) EEG signal with preserved fragmentary posterior alpha activity (Fig. 1A and B). Patient #3 showed diffusely slow (5–6 Hz) EEG background (Fig. 1C), while multifocal spikes occurred only when she kept her eyes closed. In all patients, voluntary movements elicited brief (<50 ms) EMG-bursts that synchronously involved antagonist muscle couples occurring with repetitive quasi-rhythmic course (Fig. 1A, B and C). JLBA revealed the presence of an EEG correlate of the action-activated jerks on the central derivations that had a complex shape (Fig. 1D) because the rhythmic recurrence of both jerks and EEG waves, including a main positive peak preceding the onset of the jerks on the contralateral wrist flexor-extensor by 12–14 ms (Table 1).

The EEG-EMG coherence spectra in all patients revealed significant peaks in the beta band (Fig. 1E upper panel). The frequency of the coherent peak was similar in patients and controls (20.9 ± 2.3 and 21.0 ± 2.3 Hz Fig. 1F, upper panels), whereas the peak coherence values were larger in patients than in controls (0.34 ± 0.12 and 0.11 ± 0.02), all exceeding the limit of 3 SD of control data (Fig. 1F, lower panels). The EEG-EMG time lag, estimated on the slope of the linear tract of the phase function around the beta coherence peak, indicated that EEG (C3) preceded the EMG activity recorded on the right wrist flexor by 14.3 ± 0.9 ms on average (Fig. 1E, lower panel).

3.1.2. LLRs

An EMG reflex response consistently occurred at rest (latency: 63 ms) only in patient #2, but was present in all during muscle contraction, including a single component with a latency of 38 ms in patient #3, and two components (LLR1 and LLR2) in patients #1 and #2 with latencies of about 42 ms and 62 ms. All patients had enhanced LLRs, reflecting in low SLR/LLR ratio (0.83 ± 0.45) that exceeded the limit of 3-SD of the control mean (5.3 ± 1.5) in patients #1 and #2, and 2-SD in patient #3 (Table 1).

3.1.3. SSEPs, cortical relay time and SICI-LICI

SSEPs had a normal shape and latencies of the N20 component that was normal in patients #1 and #2 and minimally prolonged in patient #3 (22 ms); the N20–P25 amplitude was slightly enlarged, but not giant, in patients #1 and #2 (Table 1).

In patient #1, the cortical relay time measured on the earliest LLR component was 1.4 ms, based on the following calculation: $42 - (20.3 + 20.3)$ ms. In the same patient, the measure of conditioned/basal MEPs revealed a different profile of intracortical excitability with respect to that observed in the healthy subjects (Fig. 1G) including outlier values at ISIs 3 and 100 ms, which indicated a reduced inhibition.

Table 1
Genetic and clinical features of the patients.

	Triplet repeats	Age at onset/age at last observation	Symptoms at onset	Neurological symptoms ^a	Psychiatric symptoms	Global motor impairment	LLR/SLR amplitude	SSEP N20/P25 amplitude	JLBA latency
Patient 1	60	12/33 ys	Attention deficit	Myoclonus (29 ys); rigidity; hypokinesia; ataxia;	Depression; severe cognitive impairment	Wheelchair bound (30 ys)	0.8	8 μ V	12 ms
Patient 2	85	10/27 ys	Attention deficit; clumsiness	Myoclonus (25 ys); rigidity; hypokinesia; ataxia; dysphagia; abnormal pursuit	Depression; delirium; severe cognitive impairment	Wheelchair bound (27 ys)	0.4	7.3 μ V	14 ms
Patient 3	>100	7/10 ys	Sleep disorder; seizures	Myoclonus (8 ys); hypotonia; hypokinesia; ataxia; dysphagia;	Obsessive-compulsive behaviour, delirium; moderate cognitive impairment	Autonomous gait (10 ys)	1.3	2 μ V	12 ms

^a Age at onset of symptoms in parentheses.

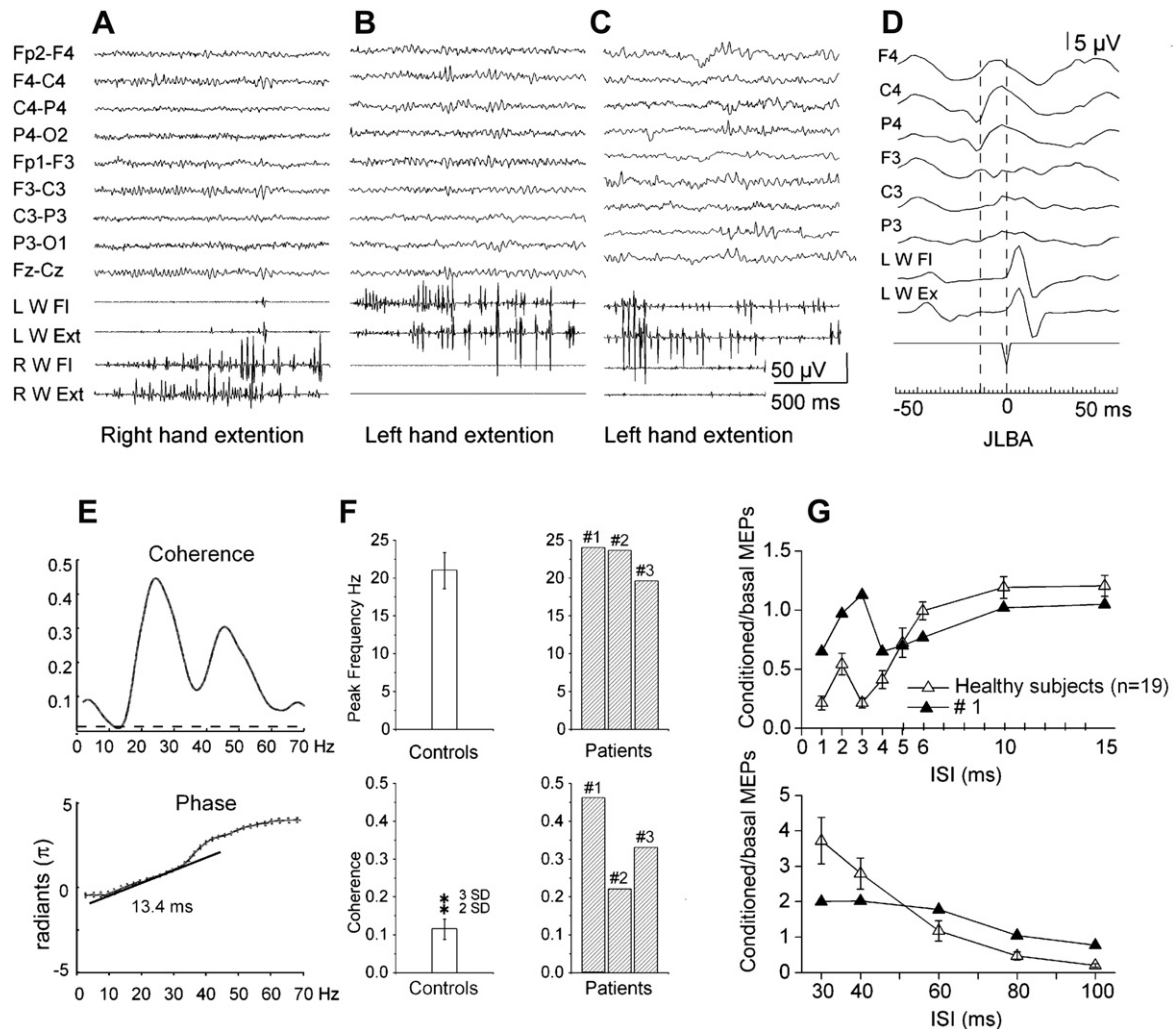


Fig. 1. A, B and C: EEG-EMG recordings in patients #1 (A), #2 (B) and #3 (C) showing action myoclonus induced by mild hand extension; D: Jerk-locked back-averaging in patient #1 performed on 81 epochs; E: Coherence and phase spectra evaluated on C3 and right wrist extensor in patient #1 in the presence of action myoclonus. The dashed line in the coherence spectrum indicates the 95% significance level and the dotted lines on the phase graph the 95% confidence interval; F: graphic representation of the coherence peak frequency (upper panel) and coherence values (lower panel) in controls (mean + SD) and in patients (individual values) obtained during mild hand extension. Asterisks indicate the limits of 2- and 3-SD of the control values; G: Short intracortical inhibition (SICI) and facilitation (ICF) (upper panel) in control subjects (white triangles) and in the patient #1 (black triangles). Long intracortical inhibition (LICI) (lower panel) in control subjects (white triangles) and in the patient #1 (black triangles). The error bars indicate the 95% confidence interval.

4. Discussion

Action myoclonus was a prominent symptom in our three HD patients, although it was associated with uneven neurological signs. Indeed, in the two patients with a juvenile disease onset, the movement disorder combined with extrapyramidal signs; in the patient with childhood disease onset, action myoclonus was conversely associated with recurrent seizures and ataxia, giving rise to a PME phenotype similar to that described by Gambardella [4].

Our observation suggests that, in spite of uneven neurological conditions, myoclonus shares homogenous features in childhood and juvenile HD, predominantly presenting with high frequency repetitive jerks induced by voluntary movements. JLBA indicated a cortical origin of the jerks; moreover, coherence and phase analyses, which can better describe the relationships between EEG and EMG in the case of high frequency rhythmic myoclonus [7], revealed the presence of central fast EEG activity related to the rhythmic jerks, allowing us to measure an EEG-EMG time lag that fitted a cortical generation. These observations suggest the cortical

origin of myoclonus in our patients, even if the assumption of cortical origin can not be applied to all HD patients; a cortical origin is in line with previous observations [2,5], but the rarity of patients with juvenile HD [1], the scarcity of detailed neurophysiological studies and the different applied methods prevent a reliable comparison.

Enhanced LLR also suggested the involvement of a cortical circuitry. The presence of two components in the two patients with a juvenile HD probably indicates additional involvement of the motor cortex through a reverberant circuit, possibly implicated in the generation of repetitive myoclonic jerks during action. Patient #3, with a childhood onset and a phenotype more obviously reminiscent that of a severe PME, showed only slightly enhanced LLR. A similar condition occurs also in other severe PMEs, such as Lafora body disease [8]. We can hypothesize that the current neurophysiological tests fail to detect circuitry hyperexcitability in the presence of disrupted cortical functioning or antiepileptic drug therapy (fully ongoing in patient #3 at the time of evaluation).

Our patients did not show giant SSEPs, differently from one patient reported by Caviness and Kurth [5], but in line with findings

obtained in other myoclonic HD patients [2]. Giant SSEPs often, but not necessarily, characterise the neurophysiological presentation of cortical reflex myoclonus, indicating the involvement of both the sensory and motor cortex [8]. In the specific case of the myoclonic presentation of juvenile and childhood HD, we can hypothesize that the circuitry generating the enhanced early LLR component mainly involves the motor cortex, may be through a direct thalamo-motor cortical pathway. This condition is similar to that occurring in corticobasal degeneration and in a subset of patients with PMEs, including Unverricht-Lundborg disease [8], and could explain the short cortical relay time observed by Thompson [2] and confirmed by us in patient #1.

Though the pathogenesis of the myoclonus in HD patients is unknown, some evidences obtained by neuroimaging [9] point to high glutamate levels. Moreover, evidences obtained in the R6/2 mouse model of juvenile HD indicate that enhanced glutamate release induce excitotoxicity and neuronal loss. Concurrently, a reduced inhibitory power of interneurons may add to glutamate dysfunction in the pathophysiology of myoclonus and seizures [10].

An imbalance of excitatory and inhibitory neurotransmission involving neocortex may well account for sustained action myoclonus found in our HD patients. As well, it can account for enhanced LLR and is in line with reduced intracortical inhibition found by means of paired TMS stimuli. It is unlike that the change in response to TMS may result from pharmacological treatment with a low topiramate dose, since previous data indicate that cortical inhibition is rather enhanced than reduced by this drug [11]. Our finding of a reduced inhibition at short and long intervals (even if limited to a single patient) may thus support that, in the myoclonic form of the early-onset HD, the impairment of cortical circuitries is similar to that observed in other neurodegenerative disorders presenting with prominent cortical myoclonus [12] and possibly implies defective GABAergic circuitries. This can also sustain the

rational use of drugs suitable for potentiating GABAergic transmission and/or reducing glutamate excitotoxicity.

Conflicts of interest

None.

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