Impaired P50 sensory gating in Machado-Joseph disease

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Abstract

Objective: Machado-Joseph disease (MJD), an autosomal dominant spinocerebellar degeneration caused by an expanded CAG repeat on chromosome 14q32.1, is a disorder with wide range of neurological findings and brain regions involved. Studies evaluating neurophysiological parameters related to sensory gating in MJD are lacking.

Methods: This study intends to investigate P50 suppression, an auditory mid-latency evoked potential in a test-conditioning paradigm, considered as an index of sensory gating function. Twelve patients with MJD, 24 normal subjects and 12 schizophrenic patients were evaluated.

Results: MJD subjects had higher P50 ratios as compared to normal subjects (76.2 vs. 42.1%, P = 0.001), but similar to the group of schizophrenic patients. The difference from controls was due to greater test amplitudes (3.4 vs. 2.0 μV, P = 0.002), rather than to conditioning amplitudes. Latencies were higher for the MJD subjects than for controls (60.4 vs. 56.1 ms, P = 0.016).

Conclusions: MJD may present sensory gating dysfunction. However, the pattern of this dysfunction seems to slightly differ from that classically found in schizophrenia, were both test and conditioning amplitudes seem to be implicated.

Significance: These results point out the P50 paradigm as a potential tool for further neurophysiological surveying in MJD.

Keywords: Machado-Joseph Disease; Sensory gating; Event related potentials; P50; Spinocerebellar ataxias; Polyglutamine diseases

1. Introduction

Machado-Joseph disease (MJD) is an autosomal dominant multisystem degeneration manifested as a form of spinocerebellar ataxia (Nakano et al., 1972; Rosenberg et al., 1976; Woods and Schaumburg, 1972), caused by an expanded CAG repeat on chromosome 14q32.1 (Kawagushi et al., 1994; Takiyama et al., 1993).

This disorder has a wide range of neurological findings, which evolve in a chronic and progressive pattern. Clinical manifestations include cerebellar ataxia, pyramidal syndrome, a supranuclear, progressive external ophthalmoplegia, extrapyramidal signs (dystonia, rigidity and/or bradykinesia), a lower motor neuron disease, sensation loss, abnormal tendon reflexes, eyelid retraction, contraction fasciculations, weight loss and a sleep disorder (Durr et al., 1996; Fukutake et al., 2002; Jardim et al., 2001). Less frequently, deficient emotional control with laughter and crying, similar to those found in pseudobulbar palsy, can be seen later in the course of the disease. Cognitive functions are spared (Radvany et al., 1993).

Some electrophysiological studies have been performed in MJD showing considerable degree of dysfunction.
However, proper works evaluating sensory gating in MJD are lacking. Previous studies have mostly focused their attention on routine neurophysiological tests. Kondo et al. (1990) have found alterations of the auditory brain-stem response and somatosensory central pathways in clinically diagnosed patients with MJD in Japanese families. Yamamoto et al. (1997) have found abnormalities of somatosensory pathways in MJD, specifically accessing pain and electric SEP that were not related to the clinical severity of sensory impairment, but suggest that MJD presents a subclinical abnormality for the ascending somatosensory pathways not only for vibratory sense but also for pain sense. Other evoked potential studies have confirmed multimodal abnormalities in MJD (Arpa et al., 2000; Colding-Jorgensen et al., 1996; Takegoshi and Murofushi, 2000).

The suppression of the P50 component of the auditory event-related potential has been used as an index of sensory gating in neuropsychiatric research. (Adler et al., 1998; Freedman et al., 1983). The P50 wave is a small amplitude, positive wave occurring about 50 ms after an auditory stimulus. In the P50 suppression paradigm, when two stimuli are presented 500 ms apart, the amplitude of the second peak (S2), compared to the first (S1), is usually attenuated in healthy subjects, whereas in patients with schizophrenia or acute mania this suppression is impaired (Adler et al., 1998). The hippocampus as well as structures of brain-stem and temporal cortex have been suggested to mediate P50 suppression and it is generally assumed that impaired suppression in schizophrenia is due to an inhibitory deficit, which leads to an overflow of information and diminished capacity to filter out irrelevant stimuli (Adler et al., 1998). The neurochemical basis of the P50 suppression is not yet completely understood, but cholinergic, GABAergic and monoaminergic systems have been proposed to modulate this phenomenon (Adler et al., 1998; Hershman et al., 1995; Light et al., 1999) and more recently adenosine has been implicated in P50 dysfunction (Ghisolfi et al., 2002).

The main purpose of this study is to perform a sensory gating evaluation through a double-click paradigm of P50 evoked potential in patients with MJD comparing to healthy and schizophrenic subjects.

2. Methods

2.1. Subjects

This study was approved by our local ethical committee and all the participants have signed an informed consent form after complete explanation about the protocol, the purpose of this study and potential risks involved in lay terms.

Twelve MJD outpatients with a previously detected CAG expansion in the MJD1 gene were included (two men and 10 women, mean age of 43.1 ± 7.8 years). The MJD patients were all Brazilian with Azorean-Portuguese ascendance, with a mean disease duration of 9.5 ± 2.6 years. The expanded CAG lengths varied between 71 and 77 repeats. Regarding clinical presentation, 7 patients were classified as type II and two patients as type III. The disease in the other 3 patients had such a long duration that it was impossible to classify them. Twenty-four healthy volunteers were recruited for this study among university students and local hospital employees (4 men and 20 women, mean age of 38.5 ± 5.8 years). Twelve DSM-IV schizophrenic outpatients were included as an additional comparison group (two men and 10 women, mean age of 38.1 ± 8.4 years). All groups were balanced regarding age and gender. Healthy volunteers were interviewed by medical doctors with psychiatric training and submitted to a structured interview. Exclusion criteria were a DSM-IV in axis I diagnosis of any disorder, clinical illness and any current pharmacotherapy, current use of alcohol and drugs of abuse, except for nicotine and oral contraceptives. None of MJD and control subjects were currently taking psychotropic medication, but all schizophrenic patients were on stable treatment with typical antipsychotics. Subjects with familiar history of schizophrenia or other psychotic disorders in first or second degree were also excluded. Subjects could not use tobacco in the preceding 2 h neither used caffeine or any beverages containing methyl-xanthines over the 4 h preceding the recordings.

2.2. Electrophysiological recordings

The method for electrophysiological recordings has been previously described (Ghisolfi et al., 2002). In brief, subjects were recorded seated, relaxed, and awake with eyes open and fixed on a distant target to decrease drowsiness during the recording. Electroencephalographic activity was recorded from a disk electrode affixed to the vertex (Cz) and referenced to both ears. Electroencephalogram (EEG) was provided using a Nihon-Kohden MEM-4104K system in 4 channels for recording of evoked responses integrated with auditory stimulator. The mean signal was registered in two channels, one for each side of the cranium, and amplified 20,000 times with a bandpass filter between 10 Hz and 10 kHz. EEG was collected for 1000 ms for each paired stimulus presented. Additional channels were used to record the electro-oculogram (EOG) between the superior orbita and lateral canthus. Trials were rejected if they contained artefacts indicated by an EEG tension of ± 100 μV over the area of P50 for evoked potentials or the EOG recordings. Auditory stimuli were presented in a conditioning training paradigm with an interpair interval of 500 ms and intertrial interval of 10 s. A 0.1 ms square wave pulse was amplified in the auditory frequencies (20–12,000 Hz) and delivered through earphones that produce 1 ms sound with an intensity of 60 dB sound.
pressure level over the auditory acuity threshold. The auditory acuity threshold of each subject was measured 15 min before the recordings. Thirty non-rejected waves were added together to give a grand average signal, which was used for analysis. Two grand average waves were collected in sequence and the mean of both was considered for analysis. The most positive peak between 40 and 90 ms after the conditioning stimulus was selected as the P50 final latency and the wave amplitude (S₁) was measured relative to the previous negativity, determining the initial latency and the first P50 wave. The second wave (test) was determined using the corresponding peak almost always between 500 ± 10 ms away from latency of the first wave form (conditioning) and its amplitude (S₂) also measured relative to the previous negative peak. Tracings were analysed by a blind rater, so that the test peaks that were away from the predicted interval (approximately 5%) were not overlooked. Averages with no discernible conditioning P50 waves were excluded from analysis. Test/conditioning ratios were calculated by dividing the test P50 amplitude (S₂) by the conditioning P50 amplitude (S₁). This ratio was multiplied by 100, thus representing a percentage. The data were collected by an unblinded researcher and analysed by an independent ratter blinded to the diagnosis.

2.3. Statistical analysis

P50 variables of both groups were compared comprising P50 ratio (i.e. S₂/S₁), P50 amplitudes (S₁ and S₂) and latencies, which were considered apart as dependent variables, and the characteristic of the group (MJD or controls) as the independent variable. Comparisons between groups were performed using Student’s t test for means, preceded by Levene’s Test for Equality of Variances. The effect of the length of CAG repeats and of the disease duration on P50 variables were assessed by the Spearman correlation coefficient. Statistical significance was considered to be P < 0.05. All analyses were implemented with the SPSS 10.0 for Windows.

3. Results

Patients with MJD showed lower suppression, evidenced by greater P50 ratios when compared to normal subjects (Table 1, Fig. 1). Conditioning amplitudes (S₁) did not differ, whereas test (S₂) amplitudes were significantly greater for MJD and schizophrenic patients than for controls (Table 1, Figs. 2 and 3). Latencies of the conditioning (S₁) P50 component of auditory evoked potentials were longer for MJD subjects than for controls and schizophrenic patients (Table 1, Fig. 4). The results of both grand average signals (blocks) collected in sequence were very similar.

Considering clinical subtypes, no difference between subgroups was found, except for latencies in subtype III, which was significantly longer than any other subgroups of MJD and controls (healthy and schizophrenic subjects). However, in face of the small number of subjects in this stratified analysis, this finding should be considered preliminary.

No correlation was found between disease duration and P50 variables. The CAG lengths at the MJD1 gene were also not associated with P50 ratios, conditioning and test amplitudes, or with latencies.

4. Discussion

In the present study MJD patients showed diminished sensory gating expressed by a deficit in P50 suppression compared to healthy subjects. MJD subjects presented higher P50 ratios between conditioning and test amplitudes, which was mostly due to a failure to suppress S₂ response. The pattern of this dysfunction was mostly indistinguishable from the findings in our schizophrenic patients, which replicated previous results from the literature in this disorder (Adler et al., 1998). Although schizophrenic patients might also have diminished S₁ response, especially when off treatment with antipsychotics, normal S₁ response was found in MJD. Nevertheless, in our sample there was a trend towards smaller S₁ amplitude in schizophrenic patients, so their treatment with typical antipsychotics could be regarded as a conservative bias.

Table 1
Amplitudes (test, conditioning, their ratio) and latencies of the P50 evoked potential

<table>
<thead>
<tr>
<th>Group</th>
<th>Ratio (S₂/S₁), %</th>
<th>Conditioning (S₁), µV</th>
<th>Test (S₂), µV</th>
<th>Latency (conditioning), ms</th>
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<tbody>
<tr>
<td>Control (n = 24)</td>
<td>42.1 ± 4.4</td>
<td>5.5 ± 0.6</td>
<td>2.0 ± 0.2</td>
<td>56.1 ± 1.1</td>
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<tr>
<td>MJD (n = 12)</td>
<td>76.2 ± 7.3</td>
<td>5.6 ± 0.7</td>
<td>3.4 ± 0.3</td>
<td>60.4 ± 1.3</td>
</tr>
<tr>
<td>Schizophrenia (n = 12)</td>
<td>87.2 ± 12.8</td>
<td>4.2 ± 0.5</td>
<td>3.2 ± 0.3</td>
<td>56.8 ± 1.7</td>
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<tr>
<th>Significance (P)</th>
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<tr>
<td>MJD × cont</td>
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<td>MJD × SCH</td>
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*Significant between-group difference. Data presented as mean ± SEM.
The result that most clearly distinguished MJD patients from both healthy and schizophrenic controls was increased latency for the $S_1$ response. This result using the P50 wave seems to be in accordance with previous findings showing delayed transmission of sensory stimuli (Colding-Jorgensen et al., 1996) using classical neurophysiological parameters in patients with MJD. Diversely from several other neurological findings, the increased latency and ratio of P50 potentials were not associated with CAG length or with disease duration. The finding of the longer latencies in the two type III patients should be interpreted with caution, due to the small number of the sample.

The deficit in suppressing the response to test stimulus is classically regarded to reflect an impaired central inhibitory activity. This inhibitory deficit can affect sensory gating, but could also influence other domains such as timing or pain response. The present results may also indicate a dysfunction in brain regions responsible for P50 suppression, among which the CA3 region of the hippocampus has been considered (Adler et al., 1998). Interestingly, hippocampus seemed to be spared in the majority of neuropathological studies of MJD (Sequeiros and Coutinho, 1993). However, structural and functional MRI studies have shown abnormal perfusion and atrophy of the frontal and temporal lobes (Etchebehere et al., 2001; Murata et al., 1998), which are brain regions implicated in P50 sensory gating (Adler et al., 1998).

A putative candidate molecule to mediate this inhibitory deficit is adenosine, an inhibitory neuromodulator released upon neuronal activity. Besides this rationale, we recently showed that the adenosine receptor antagonist
theophylline administered to healthy subjects disrupted P50 sensory gating to the level found in schizophrenia. However, other mediators possibly implicated in this deficit include the cholinergic system through alpha-7 receptors and GABAergic system through GABA-B receptors (Adler et al., 1998). In terms of treatment, there is evidence that atypical, but not typical antipsychotics, are capable of correcting P50 deficit as well as improving a wider range of symptoms in schizophrenia (Light et al., 2000). Further studies could address if this class of medication would provide symptomatic benefit and improve P50 alterations in MJD.

This study extends previous neurophysiological findings in MJD, showing for the first time a sensory gating deficit. Further studies are necessary to better understand the etiopathology of this neurophysiological dysfunction and its nature as a trait or state marker, as well as its possible utility for studying neurochemical alterations or effects of pharmacological treatments in MJD.

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References


