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Movement-activated cortical myoclonus in Dravet syndrome

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ABSTRACT

Purpose: we characterized multifocal myoclonus in Dravet syndrome (DS) that was never systematically typified before.
Methods: we studied EEG-EMG recordings of 19 consecutive patients, aged 2–29 years, with DS associated with *SCN1A* gene mutations to detect and evaluate myoclonus based on the spectrum of EMG activity on antagonist muscle pairs and cortico-muscular coherence (CMC).
Results: multifocal action myoclonus was detected in all patients corresponding to brief EMG bursts, which occurred synchronously on antagonist muscles at a frequency peaking in beta band. There was significant CMC in beta band, and a cortico-muscular transfer time consistent with a cortical origin of the jerks. The somatosensory evoked potentials (SSEPs) were giant in only one patient who also showed exaggerated long-loop reflexes (LLRs). The nine patients who had experienced myoclonic seizures showed greater CMC.
Conclusions: The cortical myoclonus consistently observed in patients with DS shows features that are similar to those characterizing progressive myoclonus epilepsy, but differs because it does not have a severely worsening course and is not commonly associated with increased SSEPs or enhanced LLRs. This kind of myoclonus is an intrinsic feature of DS associated with *SCN1A* mutations, and may be a cause of disability.
Significance: We hypothesize that myoclonus is generated in cortical motor areas by hyper-synchronous oscillations, which are possibly due to sodium channel dysfunction.

1. Introduction

Dravet syndrome (DS), previously called severe myoclonic epilepsy in infancy, is a rare, age-related epileptic encephalopathy that is usually associated with *SCN1A* gene mutations (Claes et al., 2001), although the DS phenotype may also arise from mutations in other genes (Marini et al., 2011). In the first year of life, DS presents with febrile and non-febrile, hemi-generalized and generalized tonic-clonic seizures, followed by polymorphic refractory seizures that often include myoclonic fits. Other signs appear during the progression of the disease, including developmental delay, cognitive impairment, behavioral changes, ataxia, pyramidal signs, and myoclonus (Dravet, 2000). The myoclonus has various presentations, including generalized jerks associated with spike-wave EEG discharges, and multifocal jerks that are usually not associated with obvious EEG changes (Guerrini and Aicardi, 2003). Previous observations indicate that between 38% (Oguni et al., 2001) and 100% (Dalla Bernardina et al., 1982) of cases had myoclonic seizures and multifocal myoclonus occurred in between 31% (Doose et al., 1998) and 90% (Dalla Bernardina et al., 1982) of cases. This variability may be due to the selection of patients included in the studies and to the uneven classification of the jerks, which may be a part of a seizure or be unrelated to epileptic EEG transients (Dravet et al., 2005). Moreover, in most of the published cases, multifocal myoclonus is not mentioned or there is no information about its EEG correlate (Caraballo and Fejerman, 2006). A recent study evaluating the long-term outcome of DS reported the common occurrence of movement disorders, including action tremor or fragmentary myoclonus (Genton et al., 2011). Movement disorders appear to persist also when epileptic seizures tend to become less frequent and less severe than in childhood, possibly contributing to

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the complex neurological impairment found in adult patients. Since this aspect is worthy of further investigation, we aimed our study at identifying and characterizing subtle, mostly action-activated myoclonus in DS patients aged from two to 29 years, diagnosed and followed at our Institute. To do this, we performed simultaneous EEG-EMG recordings, a simple and effective mean of detecting myoclonus, and we off-line analyzed the signals to characterize the EMG phenomena and their EEG correlates (Brown et al., 1999).

2. Methods

We included 19 patients observed at our Institute between 2009 and 2015, presenting clinical and electrophysiological picture of Dravet syndrome (Oguni et al., 2001; Commission report, 1989), and *SCN1A* mutations. Twelve patients had truncating mutations, five missense, while two had intronic mutations at a splicing site. All underwent neurological and neurophysiological evaluations, including polygraphic EEG-EMG recordings, somatosensory evoked potentials (SEPs) and long-loop reflexes (LLRs). During the EEG-EMG recordings, the seated patients were induced to move actively by a trained technician who encouraged them to reach forward for small toys moved in front of them. The patients who were capable of collaborating were also asked to maintain the hand extension for several seconds.

The EEGs were recorded using Ag/AgCl electrodes placed in accordance with the international 10–20 system; the EMGs were recorded using pairs of surface electrodes placed bilaterally over the wrist flexor and extensor muscles. The signals were digitized (Micromed SpA, Mogliano Veneto, Italy; sampling rate 512 Hz) using a montage with a common reference electrode allowing off-line mathematical data reformatting.

Using an arbitrary scale based on the visual assessment of the EMG traces and concurrent video-EEG, the movement-activated myoclonus was classified as dominant (when runs of EMG bursts represented more than 50% of the whole muscle contraction), subdominant (less than 50%) or rare (occurring in short runs).

The SEPs were obtained by means of the 1 Hz electrical stimulation of the median nerve; N20-P25 and P25-N33 were considered increased when they exceeded the mean value + 2SD of the normative values (N20-P25: $7.0 \pm 3.6\ \mu V$; P25-N33: $2.8 \pm 2.5\ \mu V$). The LLRs were estimated using 0.5 Hz electrical stimulation of the median nerve at the wrist immediately over the motor threshold, and recorded on the thenar muscle at rest.

This study was evaluated and approved by the local institutional Ethics Committee. Written informed consent to all of the diagnostic procedures was obtained from the patients' legal representatives.

2.1. EMG analysis

The power and coherence spectra of the EMG signals were estimated using block-wise bivariate autoregressive (AR) models (see Panzica et al., 2003), with the model order being determined on the basis of Akaike's information criterion (AIC). The goodness of fit was verified using portmanteau chi-squared and Anderson's tests (Lopes da Silva and Mars, 1987; Box and Jenkins, 1970). The auto-spectra were divided into the sum of spectral components using the decomposition method based on residual integration, (Lopes da Silva and Mars, 1987) and the frequency, bandwidth (BW) and power of the peak were evaluated for each component, together with the relative power (RPW). At least 90 consecutive one-second epochs of muscle contraction (with or without myoclonic bursts) were analyzed. Coherence analysis was applied to antagonist muscles in order to demonstrate the consistency of the jerks synchronously involving the paired muscles.

2.2. EEG-EMG analysis

The EEG-EMG relationship was evaluated using jerk-locked-back-averaging (JLBA) with the onset of the EMG bursts as the trigger point, and cortico-muscular coherence (CMC) and phase analysis of the EMG signals and contralateral fronto-central or centro-parietal EEG derivations in selected 500 millisecond epochs free of EMG artifacts. The EEG-EMG transfer time was computed using the slope of the phase spectrum over the frequency range at which the coherence values were significantly different from zero and a linear relationship between phase and frequency could be determined. The data analyses were made using custom-written routines in the Matlab environment (R2014a; Mathworks Inc., Natick, MA, USA).

The statistical analysis was made using SPSS software (SPSS software, version 14, SPSS Inc. Chicago, IL, USA), with analysis of variance (ANOVA) being used to compare the continuous variables and Pearson's chi-squared test for ordinal values. As the coherence values did not fit a Gaussian distribution, the data were normalized using Fisher's transformation before being statistically analyses; however, the results are reported using non-normalized data for the sake of clarity.

3. Results

At the time of the analysis, the patients' mean age was 8.5 years (range 2.5–29) years. Although all of the patients were receiving multiple drug therapy, they still experienced recurrent seizures; all of them also had neurological defects and showed cognitive impairments of different severity. Seizure onset occurred in the first year of life. All of the patients had polymorphic seizures including myoclonic fits in nine patients (Table 1). Brain magnetic resonance imaging was normal in sixteen and revealed mild cortical or subcortical atrophy in three (#14, 17 and 19).

The visual inspection of EEG traces showed markedly slow background activity (theta-delta) in 13 patients (asymmetrical with prominent delta activity in the right hemisphere in one, #8), or moderately slow activity with prominent slow alpha (about 8 Hz) mixed with beta activity in six. Interictal epileptic activity was diffuse in three patients, diffuse and focal in two, and focal in four; ten patients showed no epileptic transients in awake EEG recording. A photoparoxysmal response to light stimulation occurred in only one patient (#18).

Spontaneous isolated myoclonic jerks with a multifocal and asynchronous presentation occurred sporadically in nine patients (#7, 8, 10, 12–14, 16–18), but all of the patients showed repeated EMG bursts in beta frequency during active movements. Based on polygraphic recordings, the action myoclonus was judged to be dominant in five, subdominant in 12, and rare in two. Individual EMG bursts were consistently brief in 17 patients (range 24–48 ms), and slightly longer in two (#5 and 8, range 37–85 ms). The EMG bursts were grouped in quasi-rhythmic sequences in the beta band. Fig. 1A and B shows example EEG-EMG recordings of a representative patient (#18).

3.1. SSEPs and LLRs

The SEPs showed increased central conduction time in three patients, decreased amplitude of the cortical components in two, and increased amplitude in one (# 18, see Fig. 1D); the findings in the remaining ten patients were normal. The LLRs were investigated in 15 patients, only one of whom showed enhancement (#18, see Fig. 1E and Table 1).