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Original article

Postural rhythmic muscle bursting activity in Angelman syndrome

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Abstract

Postural impairment is one of the most consistent features of Angelman syndrome. Using multiple-channel electromyography, we studied a lower limb and an upper limb isometric postural task in 14 patients with Angelman syndrome and 18 unimpaired control subjects. Both tasks were associated with synchronous bursts of activity at frequencies of 6–8 s^{-1} in all recorded muscles in all patients with Angelman syndrome and none of the control subjects. This pattern was not altered by extra-loading. Electroencephalogram recorded during the upper limb task showed no change in relation to the task. Burst-locked back-averaging of the electroencephalogram showed no spiking before or during the bursts. Various physiological and pathological rhythmic muscle activities have been proposed to be a manifestation of oscillations in the central nervous system and it has been suggested that such oscillations may have a role in the processing of motor commands. The mechanism of the rhythmic muscle bursting activity associated with maintaining posture in patients with Angelman syndrome is not clear, although it could be consistent with cerebellar Purkinje cell dysfunction, either as a pathological feature or as an adaptive process to overcome deficits in motor coordination.
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Keywords: Angelman syndrome; Postural control; Electromyography; Electroencephalogram; Rhythmic EMG; Purkinje cells; Cerebellum

1. Introduction

Angelman syndrome (OMIM#105830) is a neurogenetic condition characterised by severe developmental delay, motor impairment, virtually absent speech and a peculiar behavioural phenotype [1] caused by *Ube3a* gene inactivation due to various abnormalities of chromosome 15q11-13 [2]. Postural impairment, which is included in the essential clinical diagnostic criteria [3], was recognised from the initial report by Angelman [1]. The so-called 'associated reactions' such as upper limb posturing during ambulation have been proposed to depend on different pathways than those implicated in voluntary movement [4]. Comparative analysis of motor competences in Angelman, Rett and Down syndromes characterised typical gait in Angelman syndrome as comprising balance-retaining strategies including extension and lateral rotation of the hips associated with lateral transfer of the body weight [5]. Non-selective lower limb intersegmental coordination in locomotion has been demonstrated [6]. In a previous study of postural control in leukomalacic spastic diplegia and Angelman syndrome, we found a tendency towards multiple-joint stiffening in both conditions with evidence supporting combined corticospinal and cerebellar dysfunction in the latter [7]. Multiple-channel electromyography (EMG) showed rhythmic bursts of activity in lower limb muscles only in patients with Angelman syndrome. Synchronous discharges of motor units in the same or different muscles are readily reflected in population recordings such as surface EMG [8]. This EMG activity is the only non-invasively accessible signal directly related to the final command of postural control [9]. In the present study, we aimed to qualify this phenomenon of rhythmic EMG bursting associated with postural control in Angelman syndrome.

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2. Material and methods

2.1. Study groups

2.1.1. Patients with Angelman syndrome

The study group was composed of 14 patients with Angelman syndrome aged between 7 and 13 years (9.4 ± 2.2 years). Nine patients had a microdeletion of chromosome 15q11-13, one had paternal uniparental disomy, two had an imprinting defect and two had *Ube3a* gene mutations. All the patients had normal magnetic resonance imaging of the brain. Motor milestones were recorded from the medical notes when available, or from the parents' retrospective account. They were attained late in all children. Independent sitting appeared from 10 to 25 months (15.6 ± 5.1 months) in the 11 patients in whom this time was reported. All the children started to walk independently from 22 to 48 months (35.7 ± 8.4 months). Seven patients received no medication. The others received only anti-epileptic drugs consisting of sodium valproate monotherapy in three, carbamazepine monotherapy in one and poly-therapy including lamotrigine, topiramate, clonazepam, nitrazepam and levetiracetam.

2.1.2. Control subjects

The control group consisted of 18 children aged 6–13 years (9.2 ± 2.2 years) with normal development and no disabilities.

2.2. Postural tasks

2.2.1. Lower limb task

Starting from the standing position, the subjects performed a forward bend of the trunk close to the horizontal and maintained the final flexed position for at least 5 s. Each subject performed three trials. Four patients (aged 10, 10, 11 and 13 years) and four controls (aged 10, 11, 11 and 13 years) performed an additional three trials while carrying a 2 kg load in a knapsack strapped ventrally over the chest.

2.2.2. Upper limb task

In the sitting position with flexion of the right shoulder and elbow extension, the subjects performed and maintained a maximal extension (dorsiflexion) of the right wrist.

2.3. Electrophysiological recording

Surface EMG activity was recorded with a TELEMG multi-channel electromyograph (BTS), using standard clip-type adhesive pre-gelled disposable silver–silver chloride electrodes. The EMG signals were recorded at a sampling rate of 1000 Hz. They were pre-amplified and transmitted to the main unit with the telemetry system. For the lower limb task, the electrodes were positioned over the belly of the rectus femoris, biceps femoris, tibialis anterior and lateral gastrocnemius muscles of both lower limbs. For the upper limb task, two electrodes were placed over the extensor carpi radialis longus muscle. For two patients and two controls, the upper limb task was recorded using the Brainnet system (Medatec), so that EMG and electro-encephalogram (using conventional 10–20 electrode placement) could be recorded at the same time.

2.4. Data analysis

The EMG signals were rectified and integrated using the Myolab 0.1 software (BTS). Fast Fourier transform and cross-correlation function analyses were performed using Statistica 5.1 (Softcom). Burst-locked back-averaging of electroencephalogram was performed using Brainnet-Morpheus 3.0 (Medatec).

2.5. Ethical aspects

This project has been approved by the local Ethics Committee. Informed consent was obtained from the parents.

3. Results

3.1. Lower limb postural task

During the lower limb task, surface EMG recordings disclosed bursts of activity at frequencies of 6–8 s^{-1} in agonist–antagonist muscle pairs seen superimposed over persistent background tonic activity in patients with Angelman syndrome (Fig. 1). The amplitude of the bursts was stable throughout the task. These frequencies were confirmed by fast Fourier transform analysis. The bursts of activity were brief (15–25 ms) in duration. The amplitude of the bursts was more prominent in the distal muscles (tibialis anterior and gastrocnemius) in nine patients and in the proximal muscles (rectus femoris and biceps femoris) in the other six patients. This pattern was not related to age or genotype. They appeared synchronous in homologous muscles of the right and left leg, as well as in antagonistic muscles. Synchrony was confirmed by cross-correlation function analysis (significant $P > 0.5$ maximal peak of cross-correlation coefficient at 0 ms lag). When extra-mass was added, no significant change ($P > 0.1$) in the occurrence of the rhythmic bursts, their duration, frequency, synchrony or distribution was noted in the four patients in whom this was tested.

No rhythmic bursting activity was seen in any of the control subjects. Minimal tonic EMG activity was present in all recorded muscles. Occasional phasic activity was synchronously recorded in agonist–antagonist pairs, but these eventual bursts were longer in duration (100–500 ms) than the rhythmic bursts recorded in patients with Angelman syndrome, and they were mostly isolated and never showed

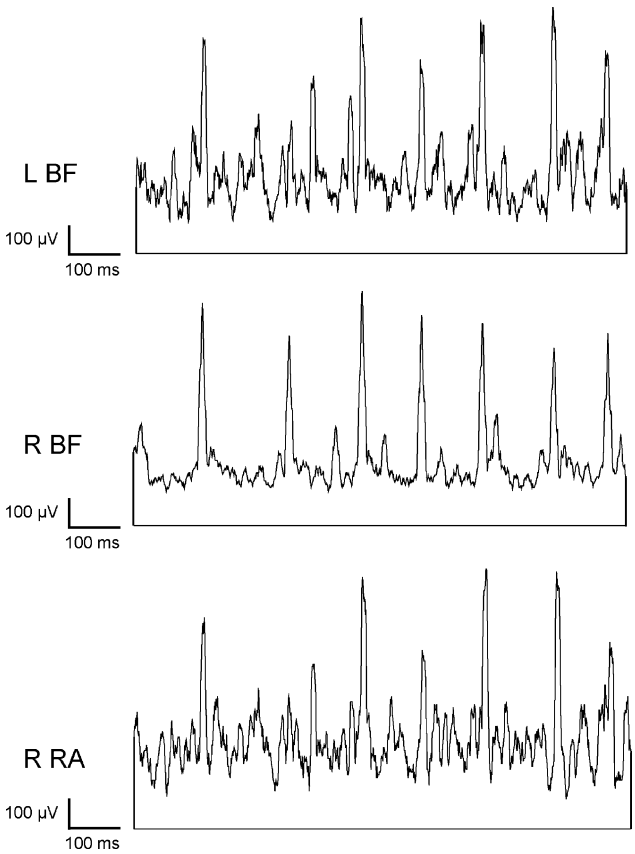

Fig. 1. Rectified integrated electromyographic activity of the left biceps femoris (L BF), right biceps femoris (R BF) and right rectus femoris (R RA) muscles during the lower limb task in a patient with Angelman syndrome. The right biceps femoris muscle has a periodogram peak at 2.09 for 7 Hz, with a spectral density of 1.31, and cross-correlation coefficient peaks at 0.68 and 0.66 at 0 ms with the L BF and R RA muscles, respectively.

rhythmicity. With loading, the subjects tended to show tonic activity in the proximal muscles. No phasic activity was observed. In particular, no rhythmic EMG bursting appeared.

3.2. Upper limb postural task

During the upper limb task, surface EMG of the extensor carpi radialis longus muscle showed similar 6–8 s^{-1} bursting as recorded in lower limb muscles during the lower limb postural task. It appeared over background tonic EMG. The frequencies were confirmed by fast Fourier transform analysis. This activity was not present at rest, during which virtually no EMG activity was seen. In the patients who had an electroencephalogram during the task, the typical patterns of Angelman syndrome [10] were observed, but no electroencephalographic change was seen during the task (Fig. 2). In particular, no changes were observed in correlation with the EMG bursting activity. Burst-locked back-averaging of the electroencephalogram disclosed no spike or other grapho-element before or during the bursts.

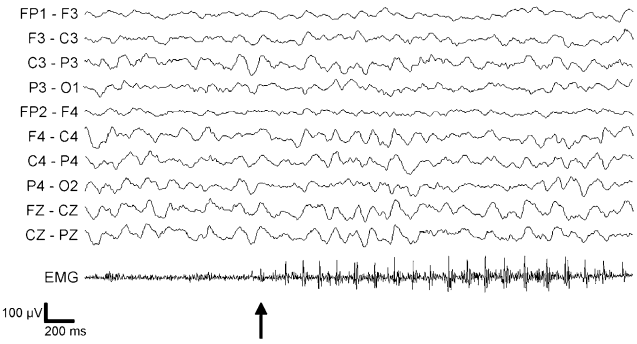

Fig. 2. Electroencephalogram and extensor carpi radialis longus muscle raw electromyogram (EMG) before and during the upper limb task in a patient with Angelman syndrome. Amplitude scale refers to electroencephalogram. The arrow indexes the beginning of the upper limb task. Note the typical diffuse theta activity ('pattern II' according to Boyd [10]), the absence of electroencephalographic change associated with the task and the rhythmic electromyographic bursting.

In the control subjects, the task was associated with tonic activity of the extensor carpi radialis longus muscle. No bursts appeared. In particular, no rhythmic EMG activity was observed. The subjects who had an electroencephalogram recorded during the task showed no change in this investigation.

4. Discussion

We found 6–8 s^{-1} rhythmic bursts of EMG activity in muscles of the upper and lower limbs in patients with Angelman syndrome while maintaining a certain posture.

This activity appeared superimposed over tonic activities that was distributed widely over most recorded muscle groups. The latter have been described in other populations while assuming a weight-bearing position [11]. This type of agonist–antagonist muscle co-activation could a manifestation of upper motor neurone syndrome which is suggested by other features of corticospinal impairment in Angelman syndrome, such as hyperreflexia [3] and multi-joint control synergies [7]. Tonic muscle co-activation increases joint stiffness and therefore attenuates the effects of eventual perturbations. The stabilising effect of co-activation is independent of the timing, direction and intensity of perturbations [12].

The rhythmic muscle bursting appeared with a temporal association in agonist–antagonist muscle pairs that reflects a co-activation command. However, the role of this activity is not clear. The occurrence of the EMG activity in isometric conditions may imply a role of Golgi tendon organs. These have Ib afferent axons projecting to spinal interneurones that project to motor neurones and neurones in Clark's column and the spinocerebellar tracts. The rhythmicity of the activity might then reflect the necessary time for the peripheral receptors to react to a perturbation induced by a preceding burst. Alternatively, an epileptic phenomenon may be hypothesised as the cause of the rhythmic activity.

However, the absence of correlated electroencephalographic activity suggests that it is not. In particular, the absence of electroencephalographic spike activity preceding the EMG bursts revealed by burst-locked back-averaging show the bursts to be different from cortical myoclonus previously described in Angelman syndrome [13]. The cortical myoclonus reported in this syndrome appears to be different from other forms of cortical myoclonus as it is not associated with giant somatosensory evoked potentials or C-reflex. Therefore, it seems to reflect a distinct neuropathophysiological characteristic of Angelman syndrome.

A wealth of studies have indicated that various physiological and pathological rhythmic activities such as patterns of rhythmic muscle activities may be a manifestation of oscillations in the central nervous system and it has been suggested that such oscillations may have a role in motor control [14]. In particular, it has been proposed that linking of oscillations plays a part in the processing of motor commands.

The findings of bursting EMG activities being time-locked in the right and left lower limbs and unaffected by loading, suggest that they are driven centrally, i.e. by a central pattern generator. Although the concept of such generators is usually postulated to describe the neural organisation of rhythmical movements such as locomotion and respiration, it can be relevant to the description of postural control [15]. According to this concept, specific coordination of the activity of many muscles can be generated by a defined organisation of neurones which interact with each other [16].

Faster rhythmic activities than the ones we recorded in Angelman syndrome have been reported to occur in normal adults performing various motor tasks, notably including isometric muscle contraction. Neurophysiological study of this phenomenon showed that oscillatory activity in the primary motor cortex is coherent, or phase-locked, to activity in the 15–30 Hz range in contralateral muscles involved in a voluntary motor task [17]. However, lower levels of coherence were found during isometric contractions than in compliant conditions [17].

Rhythmic isometric muscle contractions in the 12–18 Hz during postural activity range also occur in primary orthostatic tremor, a rare and poorly understood condition described in adults [18,19]. In this condition, the tremor appears predominantly in weight-bearing muscles and in muscles that are active in sustained isometric contraction, and it is facilitated when the contracted muscles are loaded. The EMG discharges are synchronous between homologous muscles. This condition is thought to be of cerebellar origin.

Oscillation caused by dysfunction of the cerebellum is usually manifested clinically through the ascending pathways to the thalamus, mostly to the ventrolateral thalamus and in particular, the nucleus ventralis intermedius thalami [20]. These thalamic pathways have been shown to play an important role in motor adaptation [20]. As these pathways continue to mature throughout childhood, such oscillation may not be apparent clinically in children. However, several lines of evidences also point to thalamic dysfunction in Angelman syndrome with particular respect to rhythmic activities [10]. We found no significant differences between the younger (aged 7) and older children (aged 13) in the study group. This may suggest alternative organisation of functional connections between the cerebellum and other neuronal systems involved in postural regulation, similar to the cortical reorganisation previously proposed to account for acquired automatico-voluntary dissociation in this condition [4].

On the basis of multiple-electrode recordings of Purkinje cells in rats, Welsh and Llinás [14] have postulated that phase-locking of 6–10 Hz oscillations arising from the inferior olive may enable dynamic linking of certain groups of olivary outputs to the cerebellum. In Angelman syndrome, cerebellar dysfunction contributes to the motor impairment [7], as already suspected by Angelman [1]. Neuroradiological and neuropathological studies of this syndrome have shown no abnormalities except for some reports of mild to moderate non-specific cerebral atrophy and one documented case of cerebellar atrophy that may be secondary to anticonvulsant therapy [21]. However, isotopic imaging using ligands binding onto the benzodiazepine site of the γ-aminobutyric acid type A ($GABA_A$) receptor complex showed decreased binding in several regions including the cerebellum [22]. The recent development of animal models of the syndrome has opened the way to more specific studies. In situ hybridisation studies showed lack of *Ube3a* expression in Purkinje cells of a mouse model of Angelman syndrome with partial uniparental disomy [23]. The phenotype of deficient mice resembles human Angelman syndrome [24]. Another mouse model with targeted inactivation of maternally inherited *Ube3a* showed increased levels of cytoplasmic p53, a substrate of Ube3a, in Purkinje cells and motor impairment [25]. More recently, succedaneous activity to *Ube3a* was found in the Purkinje cell layer in genotypically and phenotypically similar mice in which a *lac-z* cassette was inserted in the maternally inherited *Ube3a* gene [26]. These converging evidences suggest cerebellar dysfunction involving Purkinje cells. Purkinje cells occupy a final integrating position in the cortical cerebellar network. Recent findings of oscillatory local field potentials generated by Purkinje cells in mice with maternal inactivation of the *Ube3a* gene, with high levels of synchrony of Purkinje cell activity along the parallel fibre beam [27] may link to the present observation.

However, it remains unclear whether the rhythmic EMG bursting associated with maintenance of posture is a pathological feature, perhaps of cerebellar dysfunction, or represents an adaptive process to overcome deficits in motor coordination.

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