

SHORT REPORT

Analysis of stimuli triggering attacks of paroxysmal dystonia induced by exertion

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Abstract

In a patient with a familial form of paroxysmal exertion induced dyskinesia (PED), the efficacy of different stimuli and manoeuvres in triggering dystonic attacks in the arm was studied. As a new approach, transcranial magnetic stimulation (TMS) of the motor cortex was used to trigger motor paroxysms and to monitor cortical excitability during attacks. Motor paroxysms could be provoked by muscle vibration, passive movements, TMS, magnetic stimulation of the brachial plexus, and electrical nerve stimulation. Sham stimulation over the motor cortex and thermal and tactile cutaneous stimuli were ineffective in triggering attacks. It is concluded that dystonic attacks are triggered by proprioceptive afferents rather than cutaneous stimuli or the descending motor command itself. Outside the attacks, motor cortical excitatory and inhibitory neuronal mechanisms as assessed by TMS (response threshold and amplitudes, duration of the contralateral and ipsilateral silent period, corticocortical inhibition, and facilitation) were normal, which underlines the paroxysmal character of the disorder.

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In paroxysmal exertion induced¹ or exercise induced dystonia (PED),^{2–4} which was formerly termed the intermediate form of paroxysmal dystonic choreoathetosis,^{5,6} dystonic attacks are precipitated by prolonged muscular exertion and last for 5 to 30 minutes. To investigate the pathophysiology of the paroxysmal motor phenomena, different stimuli and manoeuvres were studied in a patient with familial PED to investigate their efficacy in triggering dystonic attacks. Besides conventional ways to produce cutaneous and proprioceptive afferents such as touch, voluntary muscle contraction, passive limb movement, electrical nerve stimulation, and muscle vibration, also magnetic stimulation of the brachial plexus and motor cortex were performed as a new approach. Transcranial magnetic stimulation (TMS) was also used to monitor changes of cortical excitability dur-

ing PED. In intervals between paroxysms the function of intracortical inhibitory and excitatory mechanisms was also investigated with the paired pulse stimulation technique⁷ and by measuring the duration of the postexcitatory silent period and of the interhemispheric inhibition of tonic muscle contraction.⁸ Results of gait analysis and perfusion SPECT of the patient have been published separately.⁴

Case report

The 40 year old man and his son were the only members of a family with the same type of PED. PED of the legs and arms was present since the age of 7 and 14 respectively. In the legs, PED was elicited by walking about 1 km. In the arms, a dystonic contraction of the forearm muscles could be evoked by forceful manual work or prolonged writing. The attacks started with a feeling of stiffness in the hand and forearm, followed by abduction of the thumb, then of the fifth finger, and then by tonic cocontraction of the forearm flexors and extensors resulting in a slight wrist flexion. The attacks lasted between 5 and 45 minutes. Treatment with 3×200 mg carbamazepine subjectively reduced the frequency and severity of the attacks. Brain and skull MRI were normal. The patient was investigated off medication on four different days.

Methods and experimental procedure

Different stimuli and manoeuvres were analyzed for their efficacy to trigger PED (table). Thermal and tactile stimuli were applied to the palm of the hand by a cold pack and a toothbrush respectively. The median nerve was stimulated electrically at the level of the wrist (2 Hz, stimulus intensity 105% of the threshold twitches visible in the abductor pollicis brevis muscle, cathode positioned proximally) and by ring electrodes at the level of the middle and distal interphalangeal joint of the index finger (2 Hz; stimulus intensity 3 mA—that is, 110% of the threshold for subjective sensations; cathode positioned proximally). Muscle vibration was performed with the rubber surface of a programmable polisher (50 and 100 Hz; amplitude 2 mm) slightly pressed onto the forearm flexor muscles. Passive flexion and extension movements of the wrist (45 degrees in each direction) were performed with one hand of the examiner fixing the forearm while

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Efficacy of different stimuli and manoeuvres in triggering PED attacks

| Type of stimulus | Onset of PED after begin of stimulation (s) | Overlasting of PED after end of stimulation (s) | Severity of PED* |
|---|---|---|------------------|
| Thermal stimulus to palm of the hand (-5°C) | | | No reaction |
| Brushing of palm of the hand | | | No reaction |
| Voluntary contraction of forearm muscles | 300 | 300 | +++ |
| Passive movement: | | | |
| Distal interphalangeal joint | 260 | 80 | + |
| Wrist | 80 | 420 | ++ |
| Electrical stimulation: | | | |
| Finger (ring electrode) | 60 | 120 | + |
| Wrist | 230 | 180 | ++ |
| Magnetic stimulation: | | | |
| Motor cortex | 135 | 240 | ++ |
| Brachial plexus | 135 | - | ++ |
| Sham magnetic stimulation over the motor cortex | | | No reaction |
| Vibration of forearm flexors: | | | |
| 100 Hz | 55 | 400 | +++ |
| 50 Hz | 15 | 320 | +++ |

*Mild (+), medium (++), maximal (+++).

†Not measured.

the other hand moved the hand by holding it at the metacarpalia II and V with a frequency of 1 Hz. For producing active contractions of the forearm muscles a soft ball was kneaded with a frequency of 0.5 Hz.

Low frequency (0.33 Hz) TMS was used for both, as a stimulus for eliciting PED but also to monitor cortical excitability during PED. For cortex stimulation the centre of a large eight shaped coil was placed 4.5 cm right of the vertex on the interaural line (anteroposterior coil currents; Magstim 200 stimulator, 2-Tesla version; Magstim Company, Dyfed, UK). Sham stimulation was performed at the same point. Stimulation of the brachial plexus was performed with a circular coil placed over the supraclavicular fossa.

To monitor motor cortical excitability, transcranially elicited EMG responses were recorded from forearm flexor and extensor muscles (stimulus intensity 130% of threshold at rest). To assess intracortical excitability, EMG responses evoked by TMS were analyzed in a paired conditioning test stimulus paradigm⁷ in which a subthreshold conditioning stimulus (95% of active threshold) was followed by a suprathreshold test stimulus (110% of threshold at rest) at randomly intermixed interstimulus intervals of 3, 5, and 10 ms. The duration

of inhibition of tonic voluntary muscle contraction in hand muscles ipsilateral or contralateral to cortex stimulation (interhemispheric and postexcitatory inhibition) was investigated with stimulus intensities of 170% of threshold at rest (80% of maximum stimulator output).⁸

Surface EMG signals were analyzed with a computer using a CED 1401 interface and a data collection program (Sigavg, sampling frequency of 5.000/s/channel). Baseline to peak amplitudes and onset latencies of excitatory responses were determined in non-rectified signals. Other parameters were measured in averaged (n=20) and rectified EMG signals. The duration of postexcitatory inhibition was measured from the onset of the response to the end of the inhibition. The onset latency of interhemispheric stimulation was measured from the stimulation artefact to a point where the signal of the averaged tonic EMG activity in the hand ipsilateral to stimulation clearly fell under the mean amplitude of the EMG activity before the stimulus. Its duration was measured from its onset to a point where the EMG activity again reached the baseline EMG activity before the stimulus.

Furthermore a standard EEG recording including flicker light stimulation was

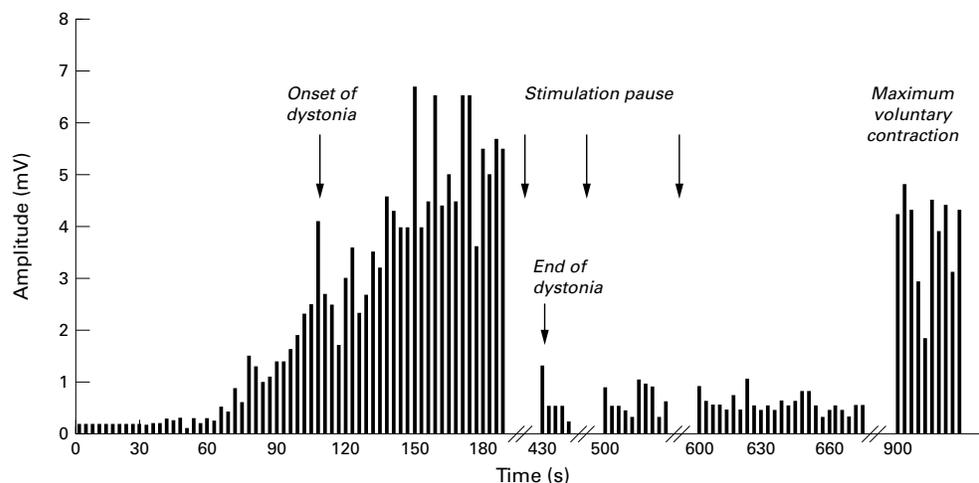


Figure 1 Dystonic attack evoked by TMS of the motor cortex as reflected by changes of EMG responses elicited in the forearm flexors. Each vertical column represents the amplitude of one response.

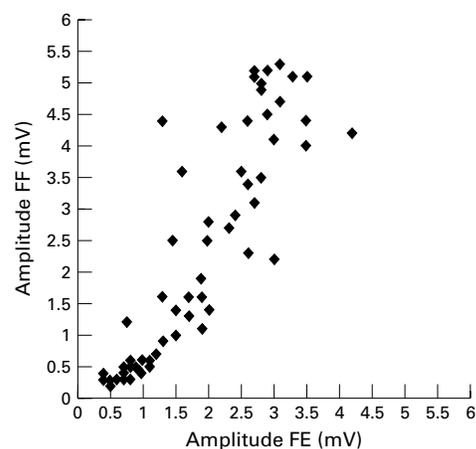
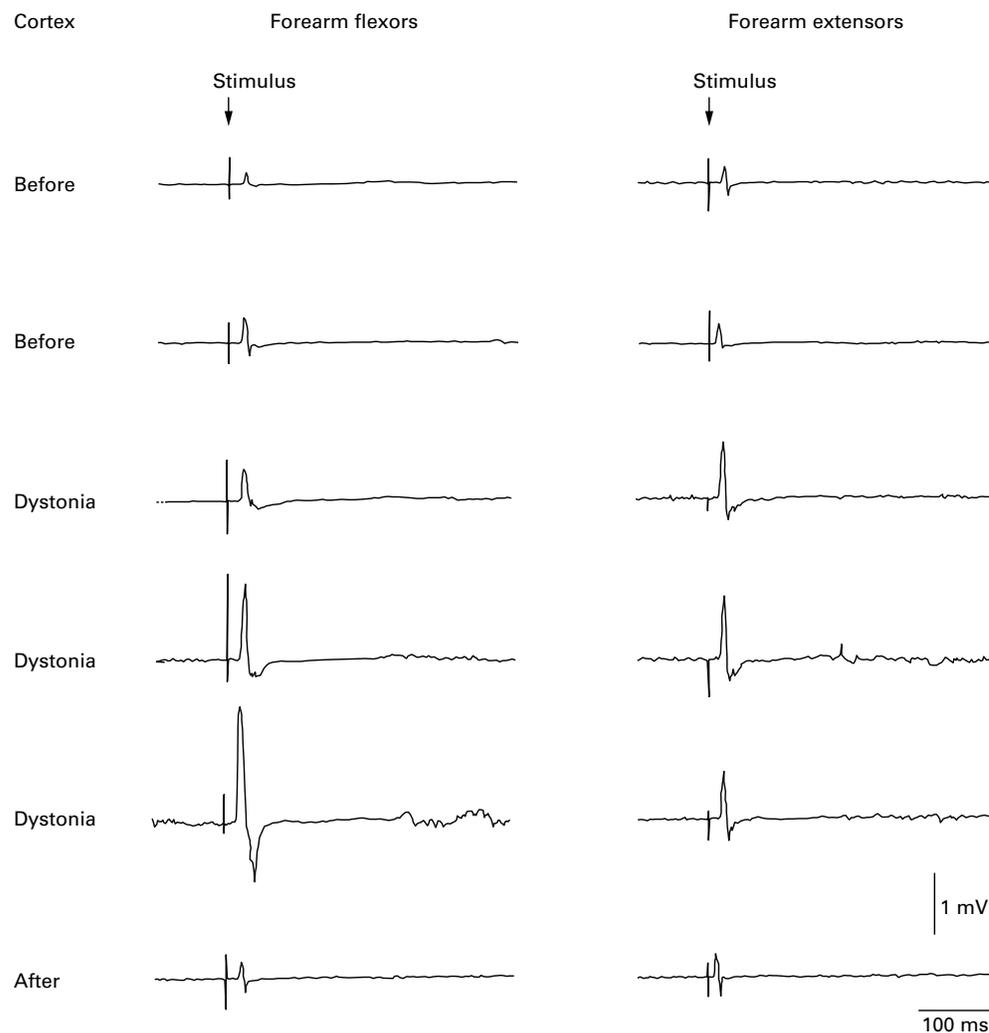


Figure 2 EMG responses in forearm flexor and extensor muscles before, during, and after a dystonic attack evoked by TMS of the contralateral motor cortex. Each recording represents the average of five consecutive responses. During the attack, the excitability of the corticospinal system supplying the forearm flexor and extensor muscle increased in parallel (coactivation) as it is reflected by the amplitudes of the motor responses elicited simultaneously by single cortex stimuli in both muscle groups (x-y plot).

performed. During EEG recording electrical stimulation of the median nerve was performed consecutively on both sides to investigate cortical somatosensory evoked potentials.

Results

Different types of stimuli and manoeuvres were differently effective in provoking motor paroxysms (table) that resembled those induced by

exercise. The different stimuli were applied twice or thrice (series of magnetic stimuli applied to the cortex) and proved to be fully reliable in eliciting dystonic attacks. Although cutaneous stimuli such as cold and touch did not elicit PED, muscle vibration was very effective in quickly provoking a long lasting and severe attack of PED. For example, vibrating the forearm flexors with 50 Hz led to a strong

PED after only 15 seconds which outlasted vibration by 5 minutes.

MONITORING OF CORTICAL EXCITABILITY DURING THE ATTACK

Serial 0.33 Hz TMS of the right motor cortex provoked a dystonic attack after 35 cortex stimuli (fig 1). At that time the response amplitudes started to increase from a baseline value of 0.4 (SD 0.05) mV (n=35) and after 10 more stimuli the dystonic attack became also clinically visible. During the 17 subsequent cortex stimuli the amplitudes of the responses gradually increased and reached maximal values of 5.4 (SD 1.0) mV (n=15) and by this time were larger than those elicited during maximal voluntary contraction (3.8 (SD 0.9) mV) (fig 1). The dystonic cocontraction of forearm flexors and extensors during the attack was paralleled by an increase in the amplitudes of the cortically elicited responses in both muscles (fig 2). Increased corticospinal excitability outlasted the end of stimulation by 4 minutes (fig 1).

CORTICAL EXCITABILITY BETWEEN ATTACKS

At rest, thresholds for eliciting motor responses by TMS were normal (*M* interosseus dorsalis I 45%, normal subjects mean 43 (SD 6), n=26 hands; forearm flexor, and extensor muscles 47% and 48%, normal subjects mean for both muscles 48 (SD 6), n=20 arms). Using the paired pulse technique and referring to our own normative data, corticocortical inhibition was normal for interstimulus intervals of 3 ms and 5 ms. The amplitude of the conditioned response amounted to 33% and 78% of the non-conditioned test response. Corticocortical facilitation tested for an interstimulus interval of 10 ms was also normal (123% of the unconditioned test response).

Postexcitatory and transcallosal inhibition of tonic hand muscle EMG activity had normal duration and lasted 243 ms (normal 176 (SD 38) ms) and 32 ms (normal 25 (SD 4) ms, n=26 hands).

Standard EEG recordings including flicker light stimulation disclosed a normal alpha rhythm but no epileptic activity. Electrical stimulation of the median nerve triggered a PED after 230 seconds. Because of myogenic artifacts no somatosensory evoked potential (SEP) could be recorded.

Discussion

Fifteen sporadic cases of PED^{1 3 9 10} and 11 cases in four families with autosomal dominant transmission^{2 4 6 11} have been described. As voluntary motor activity provokes PED, TMS of the sensorimotor cortex was applied in a patient with hereditary PED to test the hypothesis that corticospinal outputs during voluntary movement might trigger dystonic attacks. If cortical stimulation alone but not magnetic plexus stimulation had evoked an attack, corticospinal output to α -motor neurones or fusimotor neurones,¹² a copy of the output to other subcortical sites, or intrahemispheric corticocortical outputs from the sensorimotor cortex¹³ might have triggered the

attack. However, the fact that cortex and magnetic nerve stimulation, which both elicited painless muscle twitches in one arm, evoked motor paroxysms in the appropriate arm, brings proprioceptive afferents from muscle spindles or tendon organs to a focus as a trigger for the attacks. This view is supported by the finding that muscle vibration and muscle stretch during passive movements—both leading to spindle afferents—were very effective in provoking PED in our patient. Muscle vibration easily activates muscle spindles and reflexively excites via Ia afferent α -motor neurons resulting in the tonic vibration reflex. A possible role of muscle afferents in producing or reinforcing dystonia has also been suggested by abnormalities of the perception of the tonic vibration reflex in patients with focal dystonia¹⁴ and by findings in patients with writer's cramp in whom blockade of muscle afferents by intramuscular injection of local anaesthetic¹⁵ reduced action induced dystonia. Furthermore, intramuscular injection of botulinum toxin modified reciprocal inhibition between flexor and extensor muscles of the forearm.¹⁶ This was explained by a paralysis of intrafusal fibres and consequent changes in muscle spindle afferents to the spinal circuits mediating reciprocal inhibition. A significant contribution of cutaneous afferents in triggering PED is unlikely in our case as twitches elicited by motor cortex stimulation led to dystonic attacks without eliciting cutaneous afferents. Furthermore, PEDs were not provoked by tactile or thermal stimuli. That electrical stimulation of the index finger with ring electrodes also elicited a PED in our patient might be explained by the position of the electrode, which might have excited nerve fibres originating from tendon organs and joint receptors.

Despite the fact that the exact pathomechanism of PED was beyond the scope of our investigation, the study enabled us to further characterise the disorder:

Paroxysms were not related to the execution of motor programmes as they could be elicited by brief "myoclonic" jerks. During the paroxysms, the excitability of the corticospinal system (including that of the spinal α -motor neurones) as assessed by TMS of the motor cortex gradually increased and finally reached a maximal level.

The paroxysms had electromyographic features of dystonia. The parallel facilitation of cortically elicited responses in forearm flexors and extensors during the paroxysm suggests an abnormally increased common corticospinal drive to the motor neuron pools of antagonistic muscles as has recently been suggested by a cross correlation study of EMG activity in upper limb dystonia.¹⁷

Normal excitability of the motor cortex in the interval between dystonic attacks emphasises the paroxysmal character of the disorder and distinguishes PED from task dependent dystonias in which abnormal motor cortex inhibition was also detected during isometric muscle contraction.¹⁸ Stimulation of the motor cortex by TMS and analysis of different electrophysiological parameters disclosed normal neuronal

membrane excitability and normal function of inhibitory and excitatory interneurons within the motor cortex.¹⁹ This can be derived from normal cortical thresholds for motor responses, normal corticocortical inhibition and facilitation as studied by the paired pulse stimulation technique, and normal duration of the inhibition of tonic EMG activity after stimulation of the contralateral and ipsilateral motor cortex. Normal stimulation effects of TMS of the motor cortex also make it very unlikely that cortical areas projecting to the primary motor cortex were lesioned in the patient.²⁰ Finally, a normal EEG, intact consciousness during PED, and absence of any seizures in the history also make reflex epilepsy as the cause of PED in the studied patient very unlikely.

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