

*Short report*

## Absence of clinical or physiological changes during short-term cerebellar stimulation in a patient with Lafora body disease

G D S W R I G H T A N D D L M c L E L L A N

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**SUMMARY** A 17-year-old girl with Lafora body disease received short-term cerebellar stimulation but her epilepsy failed to improve and no changes were detected in her EEG. Neither visual nor somatosensory evoked potentials were changed by short bursts of cerebellar stimulation.

Lafora body disease is a form of progressive myoclonic epilepsy characterised by mucopolysaccharide inclusions in the brain and other tissues including the liver, the heart and muscles.<sup>1</sup> Cerebellar stimulation has been reported to suppress various forms of epilepsy<sup>2</sup> and to be effective in myoclonic seizures.<sup>3</sup> Immediate inhibitory effects of cerebellar stimulation on the EEG and somatosensory evoked potentials have been described in patients with various forms of epilepsy.<sup>4,5</sup> In a number of these patients, epileptic attacks virtually ceased from the onset of stimulation, while other patients showed a more gradual improvement building up over several weeks. This report describes an attempt to reproduce these acute changes in the EEG and clinical state in a patient undergoing diagnostic biopsy for progressive myoclonic epilepsy.

### Case report

The patient, a 17-year-old girl, had suffered with progressive myoclonic epilepsy and encephalopathy of undetermined cause since the age of 11. She was referred for a trial of cerebellar stimulation and at the time of her admission she was severely disabled by frequent grand mal seizures, absences and myo-

clonic jerks which were much worse in bright light. She could not walk unaided because of the combination of ataxia and frequent minor seizures. Her mental function was severely impaired; psychometric assessment was difficult but indicated a mental age of approximately 10 years. According to her parents, her condition fluctuated considerably and this greatly complicated her management at home. On some days she would be well enough to converse and enjoy family outings, but on others she appeared barely conscious. Her anti-convulsant treatment was primidone 1 g, sodium valproate 400 mg and ethosuximide 1 g, daily in divided doses. Previous trials of clonazepam, phenobarbitone, phenytoin and primidone had not been successful.

After discussion with the patient's family, it was decided to perform a brain biopsy in order to establish the precise diagnosis and define the prognosis; at the same time cerebellar stimulating electrodes would be implanted temporarily. The aim of treatment in this case was to prevent the severe and unpredictable fluctuations in her clinical state. It was accepted that the patient had a progressive encephalopathy that could not be reversed by stimulation, and therefore we considered that only a short trial of stimulation would be acceptable. The intention was to continue with long-term stimulation only if temporary stimulation produced the short-latency clinical and physiological effects previously reported in some successfully treated cases.

### Methods

Through enlarged occipital burr holes two pairs of

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eight button cerebellar electrodes with a total geometric surface area of 140 mm<sup>2</sup> were placed over the superior surface of the cerebellum on each side near to the midline (fig 1). The leads were brought

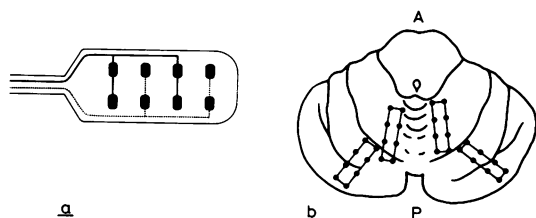


Fig 1 (a) Diagram of eight button electrode pad showing distribution of poles. (b) Estimated position of electrodes on anterior cerebellar surface.

subcutaneously down each side of the neck to exit sites over the supraspinati muscles. In order to confirm our clinical impression of Lafora body disease, a cerebellar biopsy was taken from the cortex lateral to the site of implantation and during the same anaesthetic the liver and right quadriceps femoris muscle were also biopsied. After the operation, strict asepsis was maintained around the exit sites of the leads and she was treated with penicillin, sulphadimidine and acetazolamide. Intermittent cerebellar stimulation was begun on the 3rd post-operative day and was continued for the next five days. The total stimulation time during this period was approximately 24 hours. Standard implantable radiofrequency receivers (Avery Labs Inc) were used to generate square-wave capacitatively coupled pulses (fig 2) lasting 0.5 ms with a repetition rate of 10 Hz.

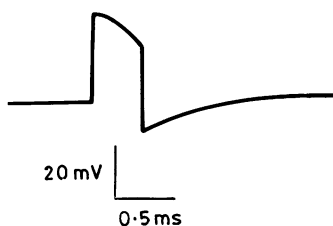


Fig 2 Waveform of pulses employed. This shows the shape of the voltage wave-form across a 10 ohm resistor in series with the electrode.

Different patterns of electrode activation were tested. In the alternating mode, the polarity of alternate pulses was reversed, so that each set of four buttons on each electrode pad would be alternately anode and cathode. Using this mode, each electrode was first tried singly, then in pairs in parallel and then all four were activated together in parallel. Using the same mode, all eight buttons on each electrode pad were then connected together and the effects of activating the medial and lateral electrode pads on the

right cerebellar hemisphere were assessed. The two electrodes on the left cerebellar hemisphere were tested in the same way. Finally, the two electrode pads on the right cerebellar hemisphere were connected together as one pole, and the pads on the other hemisphere as the other pole. The whole sequence was then repeated using monophasic or constant-polarity pulses. Stimulation at a range of currents from 0.5 mA was examined but the current through each electrode pad did not exceed 5 mA because of the patient's pain threshold. For the periods of prolonged stimulation both electrode pads on one side were connected in parallel and stimulated with biphasic alternating pulses; the contralateral electrodes were also connected in parallel but stimulated with monophasic pulses.

Changes in the patient's clinical state were monitored carefully throughout. The effect of 1 min bursts of cerebellar stimulation on the EEG, the visual evoked responses and the somatosensory evoked response were carefully examined. The evoked response recordings were begun only after a 30 min rest from previous episodes of stimulation. The EEG was recorded continuously; it was quantified by counting page by page the percentage of time occupied by spike and wave activity. Cerebral somatosensory potentials evoked by electrical stimulation of the median nerve at the wrist were recorded immediately after the 1 min bursts of cerebellar stimulation had ceased. The median nerve stimulus strength was the smallest that would cause a visible twitch in the thenar muscles and the averaged response to 256 stimuli delivered at 1 s intervals was recorded by standard techniques. Cerebellar stimulation was repeated at 4 min intervals using the different electrode currents or patterns of activation. Standard techniques were used for all the recordings.

## Results

A cerebellar biopsy confirmed the diagnosis of Lafora body disease. Lafora bodies were seen in the white matter but more especially in the granule cell layer and molecular layer. Very much smaller PAS-positive granules were seen in some of the Purkinje cells. Purkinje cells were reduced in number but there was little proliferation of Bergmann glia.

### Clinical effects

Immediately after recovery from the anaesthetic, but before any stimulation had begun, there was marked improvement in the patient's condition. She was more alert and had no seizures for 48 hours. Gradually her condition relapsed. The periods of therapeutic stimulation had no effect clinically upon her or upon her epilepsy and she had reverted to her previous state by the eighth day after operation. Her photosensitivity was the last

manifestation to reappear. The electrodes were removed on the following day.

#### *Electroencephalography*

Resting EEG recordings before and after operation were grossly abnormal with generalised slow waves and frequent bilateral paroxysmal discharges. The posterior regions were most severely affected. A pronounced photic following response was seen which at certain frequencies was associated with myoclonic jerks. Despite the obvious clinical improvement brought about by wearing dark glasses, there were no demonstrable differences in the EEG between recordings done with the patient's eyes open in daylight, wearing dark glasses, wearing a patch over either eye, or with the eyes shut in a dimly lit room. Cerebellar stimulation produced no change in the EEG.

#### *Evoked responses*

The visual evoked responses were of pathologically increased amplitude but of normal latency and duration. None of these factors was changed by cerebellar stimulation. The electroretinogram was normal. The somatosensory evoked potentials were of pathologically increased amplitude. Cerebellar stimulation did not alter the amplitude, waveform or latency of these potentials.

#### **Discussion**

It was disappointing that this short trial of cerebellar stimulation had no measurable effect since Cooper *et al*<sup>3</sup> reported that myoclonic epilepsy is responsive to cerebellar stimulation. We were unable to demonstrate any of the effects of acute cerebellar stimulation on the EEG and the somatosensory evoked responses reported in this and other forms of epilepsy.<sup>4 5</sup>

Cooper *et al*<sup>3</sup> reported total suppression of generalised seizures in various forms of epilepsy within hours and in some cases minutes of starting the stimulation. In some patients, however, the effect of stimulation became more pronounced during the first few months of chronic stimulation. One patient suffering from post-anoxic action myoclonus with only nocturnal seizures showed no effect for the first few weeks of stimulation, thereafter showing gradual and progressive improvement. Two further patients with myoclonic epilepsy also improved clinically but the time course of their response was not stated. Some of these patients were said to show immediate changes in the amplitude of somatosensory evoked potential after one minute of stimulation and immediate

suppression of paroxysmal discharges in the EEG with post-stimulation rebound.<sup>4</sup>

Our patient's failure to respond to short-term cerebellar stimulation could indicate a physiological difference between the myoclonic epilepsy seen in Lafora body disease and other forms of myoclonic epilepsy. Alternatively, her epilepsy may have been too severe to be modified by cerebellar stimulation. Our findings suggest that future studies of the effects of stimulation in degenerative disease should not rely upon the demonstration of acute physiological effects. For the reasons given above we considered that only a brief exploratory trial could be justified in our patient, and because of this we were not able to test the effects of chronic stimulation, that might have had a greater chance of clinical success.

It is difficult to justify the discomfort and expense of cerebellar stimulation for patients with progressive disease unless marked clinical benefits can be expected. We are therefore restricting our present studies in this field to a double-blind evaluation of the results of long-term cerebellar stimulation in non-progressive disease.

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