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Hyperexcitability of the asymptomatic motor cortex in a case of Mills' syndrome

Martin T. Conwill MRCP[a], James J.P. Alix PhD FRCP[a,b,c], Pamela J. Shaw MD FRCP[b,c]

[a] Department of Clinical Neurophysiology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK.

[b] Sheffield Institute for Translational Neuroscience, (SITraN) University of Sheffield, UK.

[C] NIHR Sheffield Biomedical Research Centre.

Correspondence

Dr James J.P Alix

Sheffield Institute for Translational Neuroscience, (SITraN) 385a Glossop Road, Sheffield, S10 1HQ, UK.

Email: j.alix@sheffield.ac.uk

Telephone 01142159100

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A slowly progressive spastic hemiparesis beginning in a single limb was first described by Mills in 1900[1] Case reports with similar clinical features have been documented and diagnostic criteria for a unique clinical entity have been proposed.[2] With results from short interval intracortical inhibition (SICI) transcranial magnetic stimulation (TMS) studies,[3] we present a case of Mills' syndrome with evidence of cortical hyperexcitability corresponding to the asymptomatic limb.

A 76-year-old male presented with a 4-year history of progressive left hemiparesis, starting in the left leg. There were no bulbar or sensory symptoms. Co-morbidities included hypertension, type II diabetes mellitus, psoriasis and chronic obstructive pulmonary disease.

Examination revealed left leg weakness in a pyramidal distribution and less prominent left upper limb weakness. Tone was increased on the left side. Left upper and lower limb reflexes were brisk, and the left plantar response extensor. No muscle atrophy or fasciculations were seen. Sensory examination was normal. The right upper and lower limb and cranial nerve examinations were normal.

MRI brain showed small vessel ischaemic disease within the supratentorial white matter and mild generalised cerebral and cerebellar atrophy. Cervical cord MRI showed mild multilevel degenerative changes but no evidence of spinal cord or nerve root compression. Cerebral spinal fluid (CSF) protein was slightly raised at 66mg/dl and the CSF white blood cell count was 6/mm³.

Motor nerve conduction studies of the left tibial, peroneal, median and ulnar nerves, demonstrated normal compound muscle action potential amplitudes.. Sensory nerve conduction studies of the left sural, superficial peroneal and median nerves were normal. Of note, the left ulnar nerve sensory nerve action potential was absent and motor conduction velocity slowing across the elbow in the fascicles to the first dorsal interosseous (FDI) and abductor digiti mini (ADM) was evident. On needle electromyography, only minor chronic neurogenic abnormalities were seen (very occasional long duration, polyphasic motor unit action potentials in three lumbar and two cervical segment muscles). No fasciculation potentials or other signs of active denervation were observed.

During TMS, no motor evoked potentials were elicited when stimulating the right motor cortex and recording from the left hand or foot ('cortical inexcitability'). Stimulating the left motor cortex and recording from right ADM demonstrated a slightly prolonged central motor conduction time (CMCT) (F wave method). CMCT to the right leg was normal.

Threshold tracking SICI (T-SICI) TMS studies of the left motor cortex were performed. We used both the T-SICI parallel (T-SICIp[3]) and T-SICI serial (T-SICIs[4]) protocols, recording from the right first FDI and abductor pollicis brevis (APB), respectively. The mean T-SICIp from inter-stimulus interval (ISI) 2-3ms was reduced (86.7, published cut-off 100.4[3]), as was the mean T-SICIs from ISI 1-7ms (-16.9%, published cut-off +5.5%[4]), thus cortical hyperexcitability was evident (Figure 1). In addition, intracortical facilitation (ICF) was also evident between 10-30ms.

The patient's progressive spastic hemiplegia is consistent with Mills' syndrome. Some authors view this as a rare phenotypic variant within the primary lateral sclerosis (PLS) spectrum, while others consider it a separate entity.[2,5] Past reports have documented pre-symptomatic upper motor neuron signs in the side contralateral to clinical onset and post-mortem histology has demonstrated bilateral degeneration of the corticospinal tracts.[2] In keeping with the PLS variant hypothesis, transition after many years to an ALS phenotype has also been reported.[2]

TMS studies in Mills' syndrome, though few, have consistently demonstrated prolonged CMCT on the symptomatic side (see references within[2]). One case manifested this finding on the clinically asymptomatic side, when tested at 14 years post-diagnosis.[2] In the present case, we found the symptomatic cortex to be inexcitable.

The findings of cortical inexcitability of the symptomatic cortex, possibly reflecting corticospinal tract degeneration,[6] together with cortical hyperexcitability of the clinically asymptomatic cortex, support this case of Mills' syndrome falling within the PLS spectrum. Cortical inexcitability is a well-documented finding in PLS (and late-stage ALS), while cortical hyperexcitability is found in both pre-

symptomatic and early symptomatic ALS, as well as in pure lower motor neurone variants.[7] We note the Newcastle group demonstrated coherence changes in the asymptomatic limb, also supporting subclinical motor cortex dysfunction in the clinically normal hemisphere.[2] Thus, we cannot exclude the possibility that our case, like others previously reported and more classic PLS, will eventually progress to ALS. Why this change occurs so slowly, or perhaps not at all in some cases, remains unclear.

Abbreviations

Short interval intracortical inhibition (SICI)

Transcranial magnetic stimulation (TMS)

First dorsal interosseous (FDI)

Abductor digiti mini (ADM)

Central motor conduction time (CMCT)

Threshold tracking SICI (T-SICI)

T-SICI parallel (T-SICIp)

T-SICIs serial (T-SICIs)

Abductor pollicis brevis (APB)

Inter-stimulus interval (ISI)

Intracortical facilitation (ICF)

Primary lateral sclerosis (PLS)

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Figure 1. Hyperexcitability in the asymptomatic left motor cortex.

A. Stimulation with a figure of eight coil, recording from first dorsal interosseous and using the T-SICIp protocol.

B. Stimulation with a circular coil, recording from abductor pollicis brevis and using the T-SICIs protocol.