Research Article

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Central nervous system dysfunction in primary biliary cirrhosis and its relationship to symptoms

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Background & Aims: Primary biliary cirrhosis (PBC) is associated with fatigue, memory impairment, and sleep disturbances. These symptoms suggest the possibility of underlying central nervous system (CNS) dysfunction. During exercise, fatigue develops due to muscular processes (peripheral fatigue) and decreased neurological activation of the muscle (central fatigue). In this study we objectively quantify central and peripheral fatigue in PBC and investigate the integrity of cortical inhibitory and excitatory circuits. Finally, we determine the relationship of these indices to the symptoms of PBC.

Methods: 16 early-stage PBC patients, 8 post-liver transplant PBC patients, and 12 age-matched controls were studied at the Specialist PBC clinic and neuroscience research unit. In these patients, twitch interpolation was used to measure peripheral and central fatigue. Paired-pulse trans-cranial magnetic stimulation was used to assess intra-cortical inhibition (ICI) and facilitation (ICF).

Results: PBC patients had a significantly lower central activation before fatiguing exercise (mean 86.6.8% (±12.75) vs. 95.2% (±7.4); p <0.05) and a greater response variability than controls. The decline in central activation during exercise and peripheral fatigue were normal. ICI was significantly reduced in PBC patients and daytime somnolence was greater in patients where net inhibition exceeded facilitation. Transplanted and non-transplanted patients had similar central activation, ICI, and ICF.

Conclusions: PBC patients have impaired central activation and abnormal ICI, suggesting CNS abnormalities beyond voluntary control. Transplanted and non-transplanted patients show similar abnormalities raising interesting questions about the mechanisms underpinning these changes and the permanence of neurological dysfunction in PBC. ICI and ICF and the balance between them are related to daytime somnolence (an important symptom in PBC).

Keywords: Muscle; Trans-cranial magnetic stimulation; Twitch interpolation; Cortical inhibition; Liver cirrhosis; Biliary.

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Abbreviations: TMS, trans-cranial magnetic stimulation; ICI, intra-cortical inhibition; ICF, intra-cortical facilitation; ESS, Epworth Sleepiness Scale; PBC, primary biliary cirrhosis; MVC, maximal voluntary contraction.

Introduction

Primary biliary cirrhosis (PBC) is a chronic, cholestatic, autoimmune liver disease. Management of PBC has traditionally focused on preventing advanced disease, liver failure, and cirrhosis. However, patients often experience profound fatigue, memory impairment, and excessive daytime somnolence which are seemingly unrelated in their degree to disease severity. Little is known regarding the processes which underpin these symptoms and there are currently no effective treatments [1–3]. The combination of fatigue, cognitive symptoms, and sleep disturbance points to central nervous system (CNS) dysfunction as a contributing factor. Despite these observations, there have been no objective studies exploring the extent to which fatigue and sleep disturbance in PBC reflect the presence of overt brain dysfunction. In particular, there have been no studies exploring CNS initiation of motor function, even though clinical observations suggest impaired motor function associating with fatigue in PBC [4,5]. The absence of such objective evidence has contributed to the widely held, but almost certainly incorrect, view that fatigue in these conditions is, if not a feature of encephalopathy, a manifestation of depressive illness [6].

In the current study, we applied twitch interpolation and paired-pulse trans-cranial magnetic stimulation to study CNS function in PBC and its relationship to the symptoms. During fatiguing exercise, fatigue results from processes in the muscle (termed peripheral fatigue) and decreased activation of the muscle by the CNS (termed central fatigue). The degree of central and peripheral fatigue can be assessed using twitch interpolation [7]. During a maximal voluntary contraction (MVC), in normal subjects, almost all motor units are recruited and firing at optimal rates. Electrical stimulation to the muscle recruits any motor units not recruited by the CNS or not firing at optimal rates, producing extra force (a twitch). In normal, well-motivated subjects the induced twitch is negligible, indicating that central activation is high (close to 100%). In central fatigue, where the muscle is not being maximally activated by the nervous system, electrical stimulation of the muscle recruits inactive motor units and induces a larger twitch, indicating impaired central activation [8]. Using the technique of twitch interpolation, we obtained objective quantification of central activation and the degree of central and peripheral fatigue during exercise.

Paired-pulse trans-cranial magnetic stimulation (TMS) [9] non-invasively assesses the function of inhibitory and excitatory

neural circuits in the motor cortex; abnormalities of which suggest neurological dysfunction beyond volitional control. Intra-cortical inhibition and intra-cortical facilitation were therefore assessed in patients and controls. A group of PBC patients who had undergone liver transplantation was included to establish if neurological dysfunction is present post-transplantation.

Methods

Subjects

Neurophysiological function was studied in 16 PBC patients, 8 post-transplant PBC patients, and 12 healthy controls. Patients were recruited from a specialist PBC clinic. Diagnosis was confirmed in each case using established diagnostic criteria [10]. The PBC patients all had clinically early disease with normal synthetic function and no history of encephalopathy, decompensation, or features suggestive of portal hypertension. All had normal nutritional status. The post-transplant group consisted of PBC patients who had undergone liver transplantation, none of whom had clinical features suggestive of recurrent PBC. All had been transplanted for prognostic reasons, rather than for the management of PBC-specific symptoms. The healthy controls were matched as a group for age with the PBC patients. All subjects were female. Subjects with a history of seizures, metal implants in the head or neck, a pacemaker, or a disabled right arm were excluded from the study. All procedures were approved by the local ethics committees, and subjects provided written informed consent.

Symptom assessment tools

Subjects completed symptom assessment tools immediately prior to neurophysiological assessment. These tools were:

Fatigue Impact Scale (*FIS*): a well-validated instrument that has been extensively used in chronic diseases (including validation for use in liver disease). Higher scores reflect increasing fatigue (range 0–160) [11].

Epworth Sleepiness Scale (*ESS*): a fully validated tool assessing daytime sleepiness (range 0–25). An ESS score of 10 or more indicates significant daytime hyper-somnolence [12].

General experimental arrangement

Subjects were seated in a rigid chair. The right upper arm was on a horizontal rest at shoulder height. The forearm was held vertically in supination against a strain gauge which measured isometric torque about the elbow, which was flexed to 90° angle. Straps held the wrist to the strain gauge and the upper arm against the rest. A belt around the subject's lap prevented movement in the chair, and the subject's legs were supported on a footstool. These measures ensured that the strain gauge sensed only torque around the elbow joint. The head rested between padded cushions, attached to the chair, and straps across the forehead held the head firmly. The TMS coil was clamped to the chair. This arrangement minimized relative movements between the coil and the head.

During paired-pulse TMS and assessment of the neuromuscular junction (see below) electromyogram (EMG) was recorded using adhesive surface electrodes (Biotrace 0713C, MSB Ltd., Marlbrough, UK; amplification gain 500–5 K, band pass 30–2 kHz) placed over the muscle belly and a nearby tendon. The output of the strain gauge, EMG, and markers indicating the time of stimulus delivery were sampled to a computer using a 1401 laboratory interface running Spike2 software (both Cambridge Electronic Design Ltd., Cambridge, UK). Analysis was performed off-line using the MATLAB programming environment (Mathworks, Natick, MA). The significance of population differences was assessed by Mann–Whitney *U* test.

Twitch interpolation to assess central and peripheral fatigue

The protocol used to assess central and peripheral fatigue is illustrated using data from a single subject (Fig. 1). Electrical stimulation of the muscle was carried out with a Digitimer DS7AH isolated stimulator (Digitimer, Welwyn Garden City, UK; 0.2 ms pulse width). Direct stimulation of the biceps used electrodes made from stainless steel plates (30 × 15 mm), covered in saline-soaked gauze, and positioned over the muscle belly (cathode) and distal tendon (anode). The subject-specific supra-maximal stimulus level was set by slowly increasing the current until further increases failed to produce any increment in twitch tension;

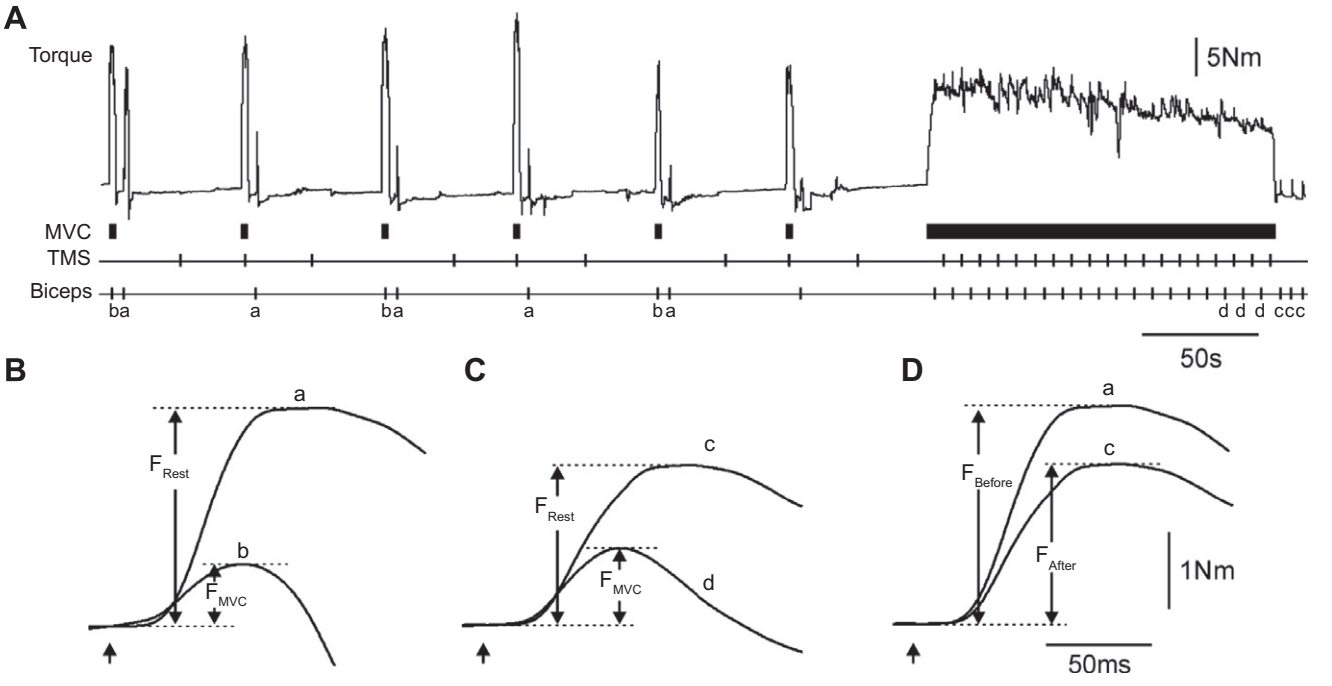

Fig. 1. Recordings from a single non-transplanted PBC patient illustrating the twitch interpolation method. (A) Torque record and markers indicating when the patient was required to produce an MVC and when TMS or electrical stimulation of the biceps was delivered. (B–D) Average twitch tensions evoked by the electrical stimuli to the biceps muscle identified by lower case letters in panel (A), on an expanded time scale. (B) Comparison of twitch amplitude at rest (F_{Rest}) with that during MVC (F_{MVC}) allows estimation of central activation at the start of the recording, prior to fatigue (see formula in text). (C) The same comparison after a long fatiguing contraction provides an estimate of central activation after fatigue. A decline in central activation will show a central contribution to the decline in force during fatigue. (D) Comparison of twitch amplitude when stimuli are given at rest before (F_{Before}) and after (F_{After}) the fatiguing contraction allows assessment of peripheral fatigue (see formula in text).