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Upper motor neuron involvement in X-linked recessive bulbospinal muscular atrophy

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Abstract

Objective: Clinicopathological findings of X-linked recessive bulbospinal muscular atrophy (SBMA) are indicative of lower motor neuron and primary sensory neuron involvement. The aim of our study was to investigate the presence of subclinical upper motor neuron (UMN) dysfunction in this disease.
Methods: Two siblings with clinical presentation, routine electrophysiological tests, histopathological features of muscle and nerve biopsies and genetic testing consistent with diagnosis of SBMA underwent transcranial magnetic stimulation (TMS). The analysed parameters were motor evoked potential (MEP) threshold, silent period (SP) and central motor conduction time. Intracortical inhibition with paired pulses from 1 to 6 ms interstimulus intervals (ISIs) was evaluated in the older brother.
Results: MEP parameters were significantly altered in limb and cranial muscles and MEP suppression after paired stimulation significantly reduced in the older brother. MEP abnormalities were present in one lower limb, but SP abolished in all limbs, in the younger brother.
Conclusions: Subclinical involvement of UMNs may be present in patients affected by SBMA. This finding suggests that the array of neuronal systems whose function may be affected by the pathogenic process of SBMA is larger than it was considered so far.
Significance: TMS is a sensitive diagnostic tool for the identification of UMN dysfunction and should be included in the diagnostic evaluation of patients with SBMA.

Keywords: X-linked recessive bulbospinal muscular atrophy; Kennedy's disease; Upper motor neuron; Transcranial magnetic stimulation; Muscle biopsy; Nerve biopsy.

1. Introduction

X-linked recessive bulbospinal muscular atrophy (SBMA), or Kennedy's disease, is a slowly progressive neuronopathy characterized by an adult onset weakness and atrophy of proximal limb and bulbar muscles with prominent muscle cramping and fasciculations (Kennedy and Alter, 1968). Signs of androgen insufficiency such as gynecomastia, testicular atrophy and feminized skin may be present. Electromyography shows acute and chronic neurogenic damage. Sensory nerve action potentials (SNAPs) are often absent or reduced in amplitude, and sensory evoked potentials (SEPs) show abnormal central conduction time (Harding et al., 1982; Kachi et al., 1992; Ferrante and Wilbourn, 1997). Pathological studies have revealed degeneration of anterior horn cells and dorsal root ganglia (DRG) cells, together with demyelinating sensory neuropathy (Harding et al., 1982; Li et al., 1995).

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The disease is genetically determined by the expansion of an unstable CAG repeat within the first exon of the androgen receptor (AR) gene, in the X-chromosome (Fischbeck et al., 1986, 1991; La Spada et al., 1991). The pathological mechanism that leads to neuronal loss in SBMA is thought to involve a toxic gain of function of the mutant gene product that accumulates intracellularly, particularly within motor neurons of the pons, medulla and anterior horns and in primary sensory neurons (PSN) (Adachi et al., 2005). However, it remains to be elucidated whether these inclusions are truly pathogenic or merely disease markers (Tarlac and Storey, 2003).

Although upper motor neurons (UMN) are not clinically affected in this disease, sporadic descriptions suggest their subclinical involvement (Shaw et al., 1998; Karitzky et al., 1999; Sperfeld et al., 2002). We report on two siblings with SBMA in which transcranial magnetic stimulation (TMS) revealed a dysfunction of corticospinal tracts (CST).

2. Case report

A 72-year-old man (subject 1) presented with a 19-year history of slowly progressive muscle weakness and wasting, initially affecting proximal districts of lower limbs and leading to difficulty in climbing stairs and restriction of gait autonomy. Subsequently, he manifested muscle weakness in the proximal districts of upper limbs and mild dysphagia. Diffuse fasciculations, localized on limbs, trunk, facial districts and tongue, appeared later on. Family history revealed similar symptoms in the patient's younger brother (subject 2) aged 64 years, who underwent diagnostic evaluation in another neurological center and was diagnosed with lower motor neuron (LMN) disease.

Neurological examination of our proband showed atrophy of facial muscles, primarily of muscles of mastication and tongue; diffuse muscle atrophy of shoulder and hip girdle and thighs was also prominent. Continuous fasciculations were evident in face, tongue and limb muscles. The patient had hypophonic voice, bilateral gynecomastia and a broad ataxic gait. Testing of muscle strength revealed symmetrical motor deficit of proximal districts of the four limbs. Medical Research Council (MRC) scale (0–5) values were 4− in deltoid, triceps and biceps brachii muscles and 4+ in the remaining districts of upper limbs, 4− in iliopsoas and quadriceps and 4+ in the remaining muscles of lower limbs. Facial and pharyngeal musculature showed diffuse weakness. No sensory deficit was detectable. Deep tendon reflexes were absent in the four limbs, and Babinski sign was absent bilaterally. Laboratory analyses revealed elevated CK level (706 U/L). Magnetic resonance imaging of the brain was unremarkable.

Nerve conduction studies were performed with surface recordings, using standardized techniques (Stalberg and Falck, 1993; Falck et al., 1994). Motor nerve conduction studies showed compound muscle action potentials (cMAPs) of normal amplitude, latency and duration; motor conduction velocities and F-waves latencies were in the normal range. Sensory nerve conduction studies were performed antidromically in sural and radial nerves and orthodromically in median and ulnar nerves and documented SNAPs of markedly reduced amplitude but normal latency. Sensory conduction velocities were normal. Electromyography performed in distal and proximal limb muscles and facial districts such as masseter and genioglossus evidenced neurogenic damage in all examined muscles with features of active denervation including increased insertional activity, abundant fasciculations, fibrillation potentials and positive sharp waves and features of chronic denervation consisting of motor unit potentials (MUPs) of markedly elevated amplitude and duration and polyphasic morphology. Moment-to-moment MUP amplitude variation was revealed, representing motor unit instability. Reduced recruitment was prominent in all muscle districts at voluntary maximal contraction. SEPs were not reproducible at the cauda equina, stimulating both tibial nerves at the ankle; cortical responses were absent when stimulating the right side and of prolonged latency when stimulating the left side, suggesting damage of peripheral and central somatosensory pathways. Upper limb SEPs to median nerve stimulation at wrist were normal.

A quadriceps muscle biopsy showed signs of chronic partial denervation (Fig. 1A). In addition, sporadic myopathic changes, including mild fibrosis and necrosis were detected. A type-grouping pattern was observed with the ATP-ase reaction. A sural nerve biopsy showed a severe neuropathy, characterized by a reduced thickness of myelin sheaths in many nerve fibers and a marked loss of myelinated fibers (Figs. 1B and C).

Analysis of CAG repeat length in the AR gene was performed in both subjects as previously described (Greenland et al., 2004). A pathologically expanded CAG sequence was detected in both patients, the size of the expansions being 45 and 49, respectively, while in normal subjects a range of 10–36 repeats has been reported (La Spada et al., 1994).

3. Transcranial magnetic stimulation (TMS)

The TMS was performed in order to explore the extent of the UMN involvement. The evaluation included single TMS, conducted in subjects 1 and 2, and paired TMS (Kujirai et al., 1993), performed only in subject 1. A Magstim 200 stimulator (2.0 Tesla) was employed. Motor evoked potentials (MEPs) were recorded from opponens pollicis and flexor hallucis brevis muscles of both sides via surface electrodes in a belly-tendon montage. MEPs from cranial districts, obtained only in subject 1, were recorded from orbicularis oris and masseter muscles of both sides. A regular coil was applied on the scalp region overlying the right or left central sulcus for stimulation of hand and face motor areas and on the