ELECTROPHYSIOLOGICAL STUDY IN SYNAPTIC CONGENITAL MYASTHENIC SYNDROME

End-plate acetylcholinesterase deficiency

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Congenital myasthenic syndromes (CMS) are a heterogeneous group of genetic diseases in which the safety margin of neuromuscular transmission is compromised by one or more mechanisms[1,2]. According to the site of the primary defect, the CMS can be classified as presynaptic, synaptic or postsynaptic[1,2]. In 1977, synaptic CMS was first described by Engel et al. as caused by absence of acetylcholinesterase (AChE) from synaptic space[3]. Although *ACHE* gene mutations are not able to cause end-plate AChE deficiency, recessive mutations in *COLQ* gene are responsible for this deficiency[1,2,4-6]. *COLQ* gene mutations are most described in synaptic CMS patients severely disabled from an early age with progressive involvement of the axial muscles which can cause severe scoliosis and restrictive ventilatory deficit[2]. Synaptic CMS can be confirmed by repetitive compound muscle action potential (CMAP) with decremental response on electrophysiological study and molecular analysis showing *COLQ* mutations; but, relatives with similar symptoms, scoliosis, slow pupillary light response, and no effect after administration of AChE inhibitors are considered as clinical clues pointing to the diagnosis[1-4].

We report a patient with synaptic CMS to describe the electrophysiological findings in end-plate AChE deficiency.

CASE

A 20-year-old man presented with progressive palpebral ptosis, limited eyes movements and facial weakness in first year of life. At 7 years of age weakness was more pronounced in the proximal limb muscles and worsening his walking with frequent falls and respiratory crisis episodes. He was born at term, but had delayed motor milestones. He denied dysphagia or neck weakness. He is a second child of consanguineous parents (first cousins).

Physical examination revealed abnormal teeth implantation and scoliosis. Neurological examination showed mild mental retardation; symmetrical ptosis; bilateral slow pupillary light response; bilateral ophthalmoplegia; bilateral facial weakness; scapular winging; proximal muscular atrophy in upper and lower limbs; muscle strength grade 4 (MRC scale) in upper limbs, grade 3 in proximal and grade 4 in distal lower limbs; axial muscle weakness; generalized hyporreflexia; and waddling gait.

The symptoms and signs were thought to be consistent with dysfunction of neuromuscular transmission, and the investigation showed the following results: (1) serum creatine kinase was normal; (2) absent anti-acetylcholine receptor antibody; (3) motor nerve conduction study with repetitive CMAP (second wave) in all nerves which disappear after a brief voluntary contraction (Fig 1); (4) decremental response greater than 10% on repetitive stimulation at 3 Hz of facial, spinal accessory, median and ulnar nerves (Figs 1 and 2); (5) rapid decremental response in repetitive CMAP (second wave) at repetitive stimulation at 3 Hz in studied nerves (Figs 1 and 2); (6) needle electromyography with myopathic potentials; (7) muscle biopsy was normal; and (8) molecular analysis revealed homozygous splice-site mutation IVS2+IG>C in *COLQ* gene.

The patient was diagnosed as having synaptic CMS by end-plate AChE deficiency due to *COLQ* gene mutation (molecular findings of this and others cases were previous reported[2]). Administration of pyridostigmine (240 mg/day) improved his walking (less dependency and falls), but did not improve ptosis, ophthalmoplegia or weakness. He never worsened the symptoms during 10 years of follow-up, but when pyridostigmine was withdrawn his gait became worse (increasing dependence and falls). Three years ago, fluoxetine was started (20 to 30mg/day) also

ESTUDO ELETROFISIOLÓGICO NA SÍNDROME MIASTÊNICA CONGÊNITA SINÁPTICA: DEFICIÊNCIA DA ACETILCOLINESTERASE DA PLACA MOTORA

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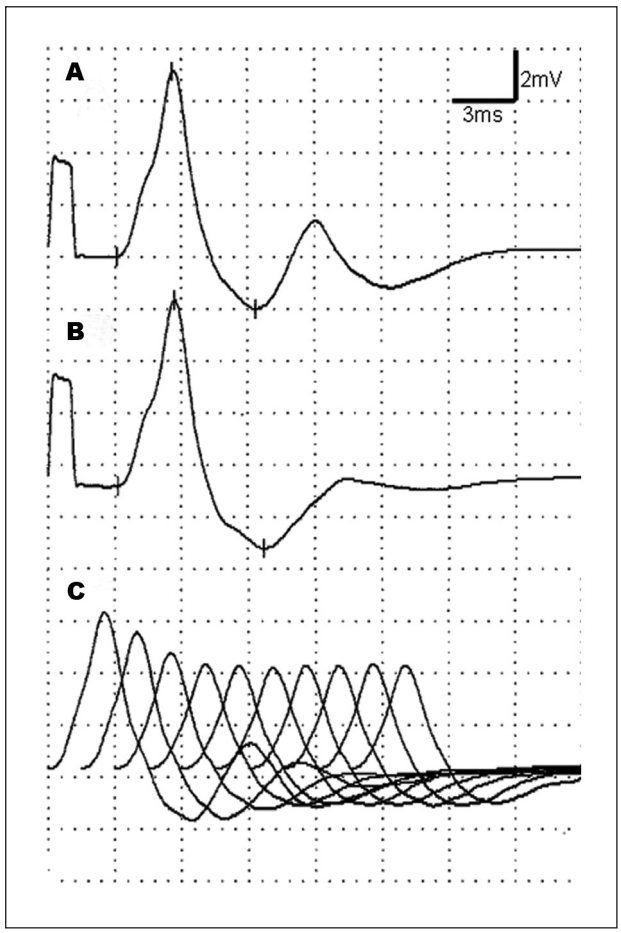

Fig 1. Classical electrophysiological features of end-plate AChE deficiency: [A] repetitive compound muscle action potential (CMAP) evoked by single stimulation applied to median nerve; [B] repetitive CMAP disappearing when single nerve stimulation was applied after a brief voluntary contraction of abductor pollicis brevis muscle; and [C] decremental response of main CMAP and its repetitive CMAP during 3 Hz stimulation of median nerve.

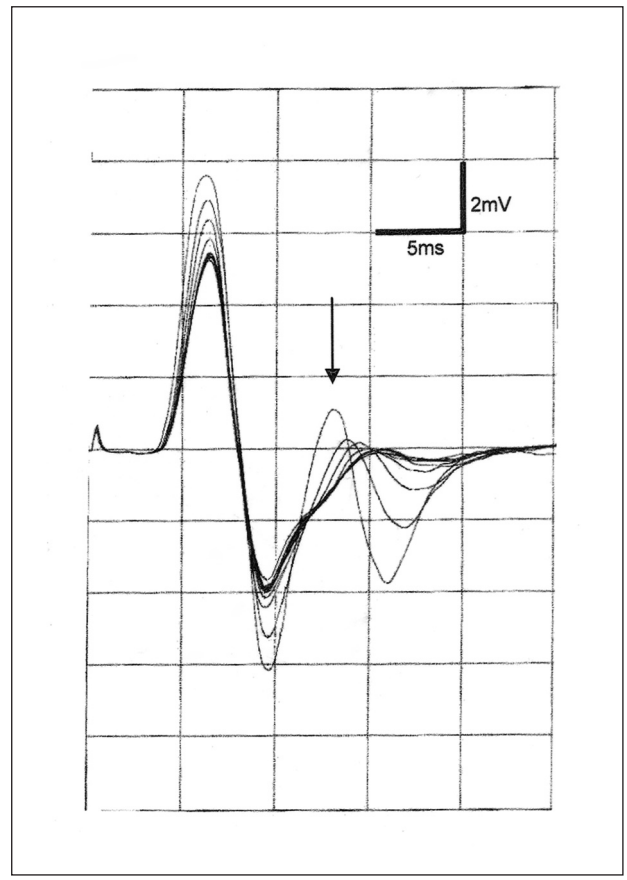

Fig 2. Compound muscle action potentials were superimposed in repetitive stimulation to highlight rapidly decremental potential response in secondary CMAP (arrow) than main CMAP in ulnar nerve.

with mild improvement in his gait (less falls) and respiratory crisis. However, these drugs management did not improve his electrophysiological features.

All studies were carried out following informed consent.

DISCUSSION

The end-plates species of AChE is an enzyme composed of tetramers of the globular and asymmetric catalytic subunits that is attached to a triple-stranded collagen tail[4-6]. Asymmetric AChE is specifically localized to basal lamina at the neuromuscular junction[5,6]. The collagen tail anchors the AChE to the basal lamina and is composed of three subunits: N-terminal region, collagen domain and C-terminal region[4-6]. Thus, mutations in *COLQ* gene could cause a defect that binding of collagen tail subunits to AChE or the anchor of collagen tail subunits in basal lamina[4-6].

Synaptic CMS demonstrated absence of AChE from end-plate by histochemical, immunocytochemical, and electron cytochemical criteria[4]. AChE is the enzyme responsible for rapid hydrolysis of acetylcholine (ACh) release at cholinergic synapses[4,5]. At the normal end-plate, AChE limits the number of collisions between ACh and its receptor (AChR) determining the duration of the synaptic response[5]. Therefore, AChE inhibition results in prolonged exposure of AChR to ACh because more ACh remains in the synaptic cleft for a longer period before diffusing away[4,5,7,8]. Normally, activation of AChR by ACh evokes an end-plate potential (EPP) to propagate an action potential[5]. In vitro microelectrode studies in synaptic CMS revealed prolonged miniature end-plate potential and EPP outlast the muscle's refractory period[7,8]. Thus, EPP remains above threshold beyond the refractory period and produces one or more additional action potentials[7,8].

Electron microscopy studies of the end-plate reveal abnormally small nerve terminals, often by Schwann cell processes, which extend into the synaptic cleft, partially or totally isolating the postsynaptic region[3-5]. This occurs

to restrict the number of ACh quanta that can be released by a nerve impulse[4]. Despite this protective mechanism, many end-plates display focal degeneration of the junctional folds with loss of AChR[4,5]. AChE inhibition also produces desensitization of AChR and depolarization block at physiological rates of stimulation[4].

Repetitive stimulation reveals decremental response at low rates (2–3 Hz) in clinically affected muscles[7,8]. Therefore, single nerve stimulation evoke repetitive CMAP, with two or more small waves separated by 6–10 ms which also decrements at repetitive stimulation[7,8]. Repetitive CMAP are smaller than the preceding one, and disappear more rapidly than the main CMAP after a brief voluntary contraction or repetitive stimulation at rates between 0.2 and 2 Hz, similar our case[7-9]. However, repetitive CMAP also can occur in slow-channel syndrome, pharmacological inhibition of AChE and rarely in normal people[8-10]. The repetitive CMAP with single stimulation may be absent in young infants and in severely affected patients with congenital AChE deficiency, but can be easily observed after administration of AChE inhibitors[2,8]. This may be result of severe restriction in the ACh quantal content to form EPP, which could overshadow the effect of the prolonged EPP duration[8].

Electromyographic findings vary according to the time when the study is performed and the severity of the disease[8]. In early cases electromyography can be normal, whereas in those patients in late stages of the disease an electromyography study can show abnormalities suggestive of myopathic pattern[8]. This finding can be found when this CMS is associated with end-plate myopathy, with abnormal motor unit potentials with reduced amplitude and duration, an increase in the density of short polyphasic potentials and increased motor unit recruitment[7,8]. AChE inhibition cause an endplate myopathy with loss of AChR owing to cationic overloading of the postsynaptic region, by toxic effects of calcium, which enters the end-plate region in excess due to prolonged duration of the miniature end-plate current[4,8].

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