Journal of Clinical Neuroscience xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Opinion paper

Mechanism hypotheses for the electrophysiological manifestations of two cases of endplate acetylcholinesterase deficiency related congenital myasthenic syndrome

Qingyun Ding [a,1], Dongchao Shen [a,1], Yi Dai [a], Youfang Hu [a], Yuzhou Guan [a], Mingsheng Liu [a,b], Liying Cui [a,b,*]

[a] Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China
[b] Neuroscience Center, Chinese Academy of Medical Sciences, Beijing 100730, China

ARTICLE INFO

Article history:
Received 21 June 2017
Accepted 23 October 2017
Available online xxxx

Keywords:
Congenital myasthenic syndrome
Endplate acetylcholinesterase deficiency
Electromyography
Repetitive compound muscle action potential
COLQ

ABSTRACT

Objective: To summarize the electrophysiological characteristics of two cases of endplate acetylcholinesterase deficiency (EAD) related congenital myasthenic syndrome (CMS) caused by *COLQ* mutation and to discuss the possible mechanism of these electrophysiological phenomena.
Methods: Electrophysiological examinations were conducted including nerve conduction studies, routine electromyography (EMG), repetitive nerve stimulation (RNS) and single fiber EMG (SFEMG). The ulnar nerve was also stimulated at 50 Hz followed by 0.5 Hz to record the recovery process of compound muscle action potential (CMAP).
Results: Repetitive CMAP (R-CMAP) was found in motor nerve conduction in both cases. Needle EMG showed myogenic damages and SFEMG showed remarkably increased jitter values. Of note, the amplitude of CMAP and R-CMAP showed regular changing trends, and so did their time intervals in RNS studies.
Conclusions: The change patterns of CMAP and R-CMAP, in combination with other electrophysiological features are very useful for the diagnosis of EAD related CMS, especially in predicting the presence of correct gene mutations.

1. Introduction

The congenital myasthenic syndromes (CMS) are a group of heterogeneous genetic disorders caused by defects in proteins residing in the presynaptic, synaptic basal lamina or postsynaptic regions of the motor endplate, leading to abnormal signal transmission. To date, twenty-two CMS disease genes have been identified [1–3]. About half of CMS stem from defects in *CHRNE* which encodes the epsilon acetylcholine receptor (AChR) subunit; the second most common cause is mutations in *RAPSN* that encodes synapse-associated proteins, contributing to 15–20% of CMS; other frequently mutated genes include *DOK7* and *COLQ*, both accounting for 10–15% [4]. Here we present two cases with mutations in *COLQ* resulting in endplate acetylcholine esterase (AchE) deficiency (EAD) and report some special electrophysiological manifestations of the two patients, which might be useful for the diagnosis of EAD related CMS.

2. Patients and methods

Case 1. A 15-year-old girl presented with ptosis and fatigability for 15 years, and limited ocular motility and dyspnea for 2 years. She was born at full term with a normal delivery. In the first year of life, she was mildly hypotonic, had progressive bilateral ptosis and fatigued easily. She walked independently at 18 months and was unable to match her peers in athletic activities during school years. At the age of 13, she developed progressive limitation of eye movements in both horizontal and vertical directions, and was unable to sleep in the supine position due to worsening dyspnea. Her sister had similar symptoms, who died at the age of 1 because of pulmonary infection.

Neurologic examination revealed bilateral ptosis and fixed pupils, but no diplopia. There was no significant decrease in muscle

* Corresponding author at: Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, No. 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China.
E-mail addresses: dingqingyun12@sina.cn (Q. Ding), cherry_ef2002@126.com (D. Shen), 475852145@qq.com (Y. Dai), cmu2011@126.com (Y. Hu), tiantanwangxingao@163.com (Y. Guan), pumchals@163.com (M. Liu), pumchcuily@yahoo.com (L. Cui).
[1] These authors contributed equally to this paper.

https://doi.org/10.1016/j.jocn.2017.10.084
0967-5868/

volume. The neck muscles and proximal extremities were graded 3/5, and the distal limb muscles were graded 4/5 on the Medical Research Council scale. The sensory system was normal. Her deep tendon reflexes were absent and no pathologic reflex was elicited. She walked with a waddling gait and the Gower's sign was positive. She had lordoscoliosis and flat feet. The serum levels of creatine kinase, alpha-hydroxybutyrate and lactate dehydrogenase were all normal. The tests for anti-AChR, anti-MUSK, and anti-Titin antibodies were negative. Muscle biopsy showed fiber size variability under optical microscope, and a small amount of myofibrils degeneration was observed under electron microscope. The genetic tests revealed two compound heterozygous mutations in *COLQ*: c.1082delC (p.P361LfsX65) and c. G1190A (p.C397Y). The pathogenicity of the former mutation was first reported in two patients by Ohno et al. in 1998 [5]. While the latter missense mutation has not been reported in humans previously, there are several studies about its pathogenicity in cat models [6].

Case 2. A 13-year-old boy presented with ptosis and fatigability for 11 years. While his twin sisters had a normal full-term delivery, the patient was born with respiratory distress which then required mechanical ventilation. He walked independently at 20 months, later than his sisters, and he was unable to keep up with them physically during childhood. Symptoms of bilateral ptosis and fatigability appeared at the age of 2 and aggravated gradually thereafter. His twin sisters did not show similar symptoms.

Neurologic examination revealed much the same as that in Case 1 except that he did not have flat feet. The test for anti-AChR antibodies was negative. No obvious abnormality was noted for myofibrils under electron microscope. The genetic tests revealed a homozygous mutation in *COLQ*: c.G444A (p.W148X), which has been described previously [7].

Both patients showed no response to pyridostigmine bromide 60 mg tid. The girl patient had partial response to ephedrine 15 mg bid with a slightly improved exercise tolerance and a longer sleep time in the supine position. The boy patient did not take ephedrine.

3. Electrophysiological examination

Written informed consent was obtained from the patients' guardians, as set forth by the Declaration of Helsinki. Both patients were tested using the same methods. All the electrophysiological studies were performed on a Viking IV electromyography (EMG) machine (Keypoint, Alpine bioMed ApS, Skovlunde, Denmark). Nerve conduction studies (NCS) were performed using conventional procedures. The ulnar, median, tibial, peroneal, facial, and accessory nerves were stimulated, and the peak-to-peak compound muscle action potential (CMAP) of the abductor digiti minimi (ADM), abductor pollicis brevis (APB), abductor hallucis (AH), extensor digitorum brevis (EDB), orbicularis oculi, and trapezius muscles were recorded. Needle EMG and single fiber EMG (SFEMG) were performed using the monopolar needle electrode. Conventional needle EMG was performed in the deltoid, extensor digitorum, and vastus medialis muscle. SFEMG was performed in the extensor digitorum communis muscle under voluntary contraction, and the jitter values (mean consecutive difference, MCD) were recorded. In the repetitive nerve stimulation (RNS) studies, the facial, accessory, ulnar and tibial nerves were stimulated for 10 times with a duration of 0.1 ms at low frequencies of 3 Hz and 5 Hz. High frequencies (10 Hz, 20 Hz, 30 Hz and 50 Hz) stimuli were performed in the ulnar nerve for 75–100 times. We also compared our RNS results with previously reported human patient cases and experiments on animal models. In order to investigate the recovery procedure of the CMAP after high frequency RNS, the ulnar nerve was additionally stimulated for 20 times at 0.5 Hz (minimum stimulus without disturbing the recovery procedure) following the high frequencies stimulation (50 Hz) to record its change pattern.

4. Results

1. Motor nerve studies showed a small but distinct repetitive CMAP (R-CMAP or M2) after the normal CMAP (M1) being recorded at the ADM (Fig. 1A), APB, AH, EDB and orbicularis oculi muscles. The peak-to-peak time interval from M1 to M2 was 5.8–8.5 ms in Case 1 and 4.0–7.3 ms in Case 2. In Case 1, two major peaks (M1) were found when the facial nerve was stimulated at orbicularis oculi (Fig. 1B), but were not observed in Case 2.
2. In the routine EMG tests, early recruitment of the extensor digitorum communis was noted in Case 1; while in Case 2, all tested muscles showed such abnormalities. EMG results of both patients suggested myogenic damages.
3. SFEMG studies showed a remarkable increase of the mean jitter value in each case, with MCD being 107 μs and 173 μs, respectively (normal value <34.9 μs) [8]. Case 2 showed evidence of blocking, while Case 1 did not manifest such alterations.
4. RNS studies showed: 1) when stimulated at 3 Hz and 5 Hz, an obvious decrease of M1 amplitude in ADM, AH and trapezius muscle was noted in both patients; but for the orbicularis oculi muscles, Case 1 did not show such changes while Case 2 did. Meanwhile, it was found at all nerves that the amplitude of M2 gradually decreased and eventually disappeared with prolonged time intervals between M1 and M2 (Fig. 1A). The same change pattern was also found in the two major peaks of orbicularis oculi in Case 1 (Fig. 1B); 2) A regular varying pattern (rapid decrease-slow increase-slow decrease-stabilization) of M1 amplitude in ADM was observed at the stimuli of 10 Hz, 20 Hz, 30 Hz and 50 Hz; furthermore, the change curve was much steeper when stimulated at 50 Hz than the other frequencies (Fig. 2).
5. When the ulnar nerve was stimulated sequentially at 50 Hz and 0.5 Hz, the time interval between M1 and M2 became increasingly shorter (Fig. 3A). At the same time, the amplitude of M1 and M2 increased at first and then dropped gradually (Fig. 3B).

Since the electrophysiological manifestations of the two patients were similar, we only presented the result pictures of Case 1. Result pictures of Case 2 can be found in the supplementary material.

5. Discussion

This study demonstrated two CMS cases, with mutations in *COLQ* as the underlying cause. Their diagnoses are based on positive family history (not in Case 2), clinical findings during neonatal period, negative test results for anti-AChR antibodies in the serum, and molecular genetic analysis. Our study focused on their characteristic electrophysiological manifestations.

The presence of M2 is a characteristic feature of EAD. It is usually explained by that the extended residence of acetylcholine in the synaptic space results in prolonged synaptic currents and action potentials [9–12]. M2 can be seen not only in EAD but also in other entities with different mechanism, including slow-channel syndrome, organophosphate poisoning, and application of anti-acetylcholinesterase.

The needle EMG results suggested myogenic damages and no spontaneous potential was recorded, which is similar to slow-channel syndrome. The phenomena are commonly thought to be related with abnormal neuromuscular transmission and endplate myopathy.

Please cite this article in press as: Ding Q et al. Mechanism hypotheses for the electrophysiological manifestations of two cases of endplate acetylcholinesterase deficiency related congenital myasthenic syndrome. J Clin Neurosci (2017), https://doi.org/10.1016/j.jocn.2017.10.084