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Phenotypic heterogeneity in a large Thai slow-channel congenital myasthenic syndrome kinship

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Abstract

The slow-channel congenital myasthenic syndrome (SCCMS) is an autosomal dominant neuromuscular disorder caused by mutations in different subunits of the acetylcholine receptor (AChR). We here report our clinical findings in three generations of a large Thai kinship suffering from SCCMS and trace the disease to the p.Gly153Ser mutation in the AChR α subunit. The same mutation had previously been reported only in Caucasian but not in Asian patients. The clinical features include ptosis, ophthalmoparesis, and weakness of the cervical and finger extensor muscles as well as marked phenotypic heterogeneity.

Keywords: Slow-channel congenital myasthenic syndrome; Alpha subunit; Acetylcholine receptor; Phenotypic heterogeneity

1. Introduction

Congenital myasthenic syndromes (CMS) are a group of heterogeneous diseases caused by genetic defects that affect the safety margin of neuromuscular transmission. Depending on the site of the defect, they can be classified presynaptic, synaptic and postsynaptic CMS, with the last group the most common [1,2]. The slow-channel CMS (SCCMS) is caused by mutations in different subunits of the acetylcholine receptor (AChR). Clinical features can vary from mild presenting in adult life to severe presenting in the neonatal period. Selective involvement of dorsal forearm muscles is a common clinical feature. Unlike the other CMS identified thus far, the SCCMS is typically transmitted by autosomal dominant inheritance owing to the pathologic gain of function arising from the markedly prolonged opening events of the AChR channel [3]. We here describe the clinical features of the SCCMS caused by the p.Gly153Ser mutation in the AChR α subunit in three generations of a large Thai kindred.

2. Family studies

Two siblings and a cousin originally presented at our neurological clinic with bilateral ptosis. This presentation prompted us to investigate other family members in a village in Burirum, a northeastern province of Thailand. The study was approved by the Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects, Ramathibodi Hospital, Mahidol University (ID 03-53-22) and was in accord with guidelines of the Institutional Review Board of the Mayo Clinic. Each available family

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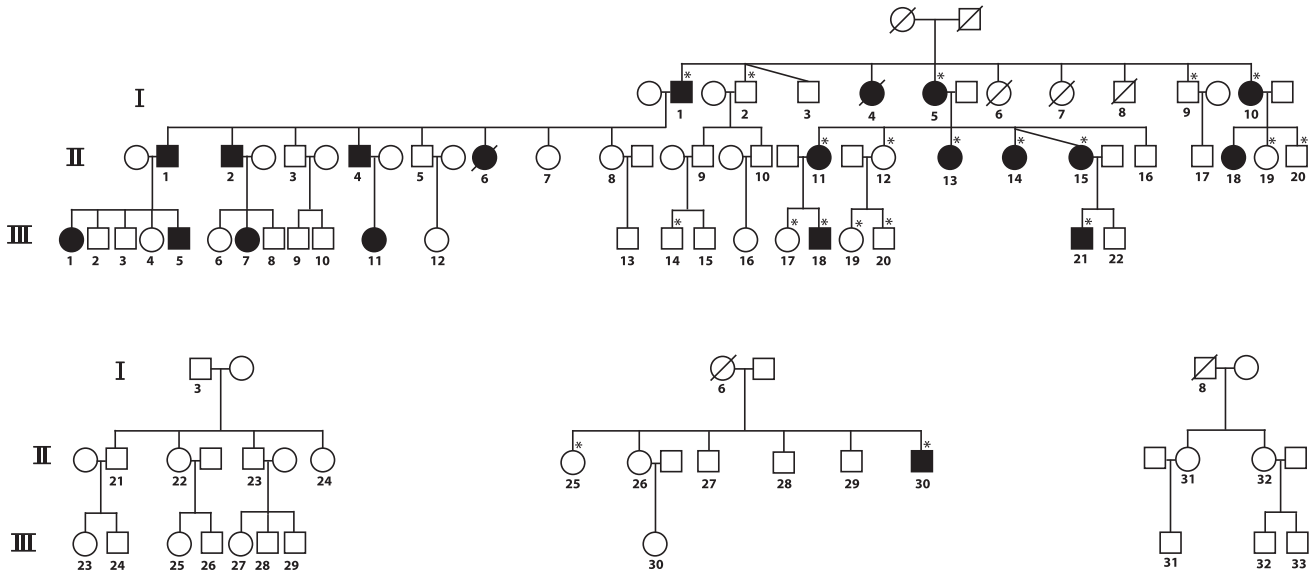

Fig. 1. Pedigree of the Thai family with slow-channel congenital myasthenia syndrome. * indicates member of the family who was studied. The lower panel represents branches of the pedigree depicted in the upper panel and only married members of the family whose own family are not in the upper panel are shown here.

member was interviewed and examined and blood samples were obtained for genetic analysis with verbal and written informed consent. Routine motor and sensory nerve conduction studies as well as repetitive nerve stimulation (RNS) at 3 Hz of the orbicularis oculi, anconeus, extensor digitorum communis (EDC), nasalis, and trapezius muscles were performed. Pre- and post-10-s exercise recordings were obtained from the abductor digiti minimi muscle (ADM) on stimulating the ulnar nerve. Single-fiber electromyography (SFEMG) was performed on the EDC muscle during voluntary muscle activation by measuring the mean consecutive difference of successive interpotential intervals (MCD or jitter) of 20 potential pairs. The test was considered abnormal when more than two potential pairs had increased jitter and when mean of MCDs was abnormal for patient age and tested muscle according to published reference values [4]. DNA was extracted from peripheral blood samples by standard techniques. The c.457G->A mutation was analyzed by direct sequencing of DNA, as previously described [5].

We were able to trace 75 members in 3 generations of the family (Fig. 1) and were able to interview and examine 10 clinically affected and 10 clinically unaffected family members. Among the affected patients, 6 were women and 4 were men. The disease onset ranged from 1 to 32 years and the patients were 4–70 years of age when examined. The clinical symptoms included drooping of the eyelids (3), double vision (1), difficulty swallowing (3), difficulty chewing (1), neck pain (5) and limb weakness (7). Six out of 10 patients had experienced intermittent worsenings. The clinical signs consisted of nasal voice (3), ptosis (9), ophthalmoparesis (9), weakness of orbicularis oculi (8), and weakness of neck flexor (10) and extensor muscles (6). There was also weakness of the limb muscles including wrist flexor (2) and extensor (3), finger flexor (3) and extensor (8) muscles as well as of the proximal arm (6) and leg (5) and small hand (6) muscles. The tendon reflexes were normally active. Table 1 shows that the most consistent features were ptosis, ophthalmoparesis and weakness of orbicularis oculi, neck flexor, neck extensor and finger extensor muscles. The ptosis was mild in most patients but more marked in a few severely affected patients. Interestingly, ptosis was observed in most patients examined (9/10) but only noted by 3 patients, confirming it was very mild. The ptosis was asymmetric in most patients with the right side slightly worse than the left except in 2 of 3 patients with moderately severe ptosis in whom it was slightly worse on the left side (Patients II.30 and III.21). In addition, ophthalmoparesis was detected in most of the patients (9/10) but was generally asymptomatic, diplopia being reported by only one patient, indicating the ophthalmoparesis was of long-standing. A few subjects had wasting of neck extensors, finger flexors and extensors and small muscles of the hands. Asymmetric involvement of the finger flexors and extensors, and small muscles of the hand was observed in Patient II.30, and of the deltoid, wrist extensor and finger extensor muscles in Patient II.13 with only muscles on the right side being affected. Fig. 1 shows that the disease was transmitted by autosomal dominant inheritance consistent with SCCMS.

3. Representative case histories

Patient II.11. A 39-year-old woman presented with a history of aching of the neck, difficulty swallowing and weakness of the arms since the age of 32 years. The symptoms were worse in the evening and improved by rest and worsened slowly over the years. Her developmental motor milestones were normal and she had no episodes of