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Intrafamily phenotypic heterogeneity in a large Thai slow-channel-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 generation of a large Thai kinship suffering from a 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 families but not in Asian patients. The clinical features include ptosis, ophthalmoparesis, and weakness of the cervical and finger extensor muscles as well as marked intrafamily phenotypic heterogeneity.

Keywords

congenital myasthenic syndrome; slow channel syndrome; alpha subunit; acetylcholine receptor; mutation

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 cases presenting in adults to severe cases presenting in the neonatal period. Selectively 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.

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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 Buriram in the northeastern province of Thailand. The family members were interviewed and examined and blood samples were taken for genetic analysis. All participants gave both verbal and written informed consent. The study was approved by the Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects, Rhamathibodi 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 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 10-s postexercise recording were obtained from the abductor digiti minimi muscle (ADM). 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) of 20 potential pairs. The test was considered abnormal when more than 2 potential pairs had increased jitter and when MCD and mean of MCDs were 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 (Figure 1) and were able to interview and examine 10 clinically affected and 10 clinically unaffected family members. Among the 10 affected patients 6 were women and 4 were men. Their ages ranged from 4 to 70 years and the age at onset of symptoms ranged from 1 to 32 years.

The clinical symptoms included drooping of the eyelids (3), double vision (1), difficulty swallowing (3), difficulty chewing (1), neck pain (5) weakness of the extremities (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. The ptosis was asymmetric in with the right side worse than the left except in 2 of 3 patients with moderately severe ptosis it was worse on the left side. (Patients I.1, II.30 and III.21). A few subjects had wasting of neck extensors, finger flexors and extensors and small muscles of the hands. Asymmetric involvement of the finger 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. Figure 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 (an older sister of patient II.15 and a cousin of patient II.30), 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 but worsened slowly over the years. Her developmental motor milestones were normal and she had no episodes of respiratory insufficiency. She was not disabled and walked normally. Her mother, a few of her mother's siblings, her 2 younger sisters, her younger brother and her cousin (boy) were also affected. Her maternal grandparents were not related. On examination, she had mild bilateral ptosis, slight limitation of upward and lateral eye movements, and mild weakness of both orbicularis oculi muscles. There was moderately severe weakness of the neck flexor and mild weakness of the neck extensor muscles. In the extremities, there was mild weakness of both deltoid, biceps, finger extensor, abductor pollicis brevis and abductor digiti minimi and of the hip flexor muscles. Anti-AChR antibodies were absent. The symptoms were refractory to pyridostigmine bromide.

Patient II.15

A 28-year-old woman (a younger sister of patient II.11 and a cousin of patient II.30), presented with a history of weakness of arms and legs since the age of 23 years. Her other symptoms and physical signs were similar to Patient II.11 except for the presence of weakness of first dorsal interosseous and quadriceps muscles. The symptoms were refractory to pyridostigmine bromide.

Patient II.30

A 26-year-old male (a cousin of patients II.11 and II.15), presented with a history of neck pain and weakness and difficulty swallowing since the age of 19 years. He occasionally choked on swallowing and regurgitated water through his nose. He had difficulty holding his head upright, and had to support it with both hands when lying down to prevent it from hitting the floor. He also had difficulty using his hands but his legs were strong and he walked normally. His developmental milestones were normal and he learned to walk at the age 1.5 years. The examination showed limitation of eye movement in all directions, moderate bilateral ptosis, mild weakness of both orbicularis oculi muscles, and a hypernasal voice. There was marked weakness of neck flexor and moderate weakness and atrophy of neck extensor muscles, moderate weakness of right finger flexor and extensor muscles, and mild weakness of right abductor pollicis brevis and first dorsal interosseous muscles. Anti-AChR antibodies were absent. The symptoms did not respond to pyridostigmine bromide.

EMG studies were performed in patients II.11 and II.30. The motor and sensory nerve conduction study were normal in all extremities of both patients. In both patients, stimulating the ulnar nerve evoked a repetitive compound muscle action potentials (CMAP) in the hypothenar muscles. RNS showed mild decremental response only in orbicularis oculi (−21%) of patient II.11 and in the nasalis (−13%) and trapezius (−16%) muscles of patient II.30. SFEMG was also abnormal showing increased jitter in 15 and 12 out of 20 potential pairs and a mean MCD of 67 μs and 69 μs in patients II.11 and II.30 respectively.

Blood samples were obtained from 20 members of the family. All the affected members had a heterozygous c.457G->A transition in the *CHRNA1* resulting in a glycine to serine substitution at codon 153 (p. Gly153Ser). The 10 unaffected members tested negatively for the mutation.

3. Discussion

The clinical features of the SCCMS are those of weakness and abnormal fatigability of the ocular, bulbar, neck, limb and respiratory muscles. These symptoms can also appear in autoimmune myasthenia gravis (MG) which makes it difficult to differentiate the two entities clinically. However, involvement of the finger extensors is seldom conspicuous in MG but is a common feature in the SCCMS. This clinical feature, together with the repetitive CMAP, refractoriness to pyridostigmine, and a family history consistent with

autosomal dominant inheritance are strong phenotypic clues for the diagnosis of the SCCMS [6–9]. A few instances of AChR-antibody positive MG mimicking the phenotypic features of the SCCMS have also been reported [10, 11].

Intrafamily phenotypic heterogeneity in this family is evidenced by variation of the age at onset (1 to 32 years), the rate of progression, and the severity of the disease, as seen in Patients II.11 and II.15 versus II.30, and in Patients I.1 and I.5 who had little disability at age 70 and 60 years although their disease presented in the first year of life; and that 2 other members (Patients III.21 and I.10) were moderately severely affected in the first and fifth decade of life.

On the whole, the progression of the disease in this family was slow resulting in little disability.. The p. Gly153Ser mutation in the AChR α subunit is positioned close to α -Trp159 at the center of the AChR binding site. The proposed effect of this mutation is to increase ACh affinity for AChR causing repeated channel openings during the prolonged sojourn of ACh at its binding site [5]. Different mutations have been discovered in different AChR subunits and in different functional domains of the subunits [5, 12–20]. A review of these reports is consistent with the notion that mutations in the extracellular domain of the receptor have milder consequences than those involving the ion channel.

To the best of our knowledge, this is the first report of an East Asian family that harbors a SCCMS mutation. A previous report described a patient with consanguineous parents from Bangladesh who carried a recessive S278del (c.833_835delCTC) slow channel mutation on one allele and a low-expressor of c. R217L mutation on the second allele of the AChR epsilon subunit [21, 22]. These data suggests that slow-channel syndrome seldom occurs in Asians or, more likely, that it is seldom recognized.

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Fig. 1.
Pedigree of Thai family with slow-channel congenital myasthenic syndrome. * indicates number of family members 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.

Figure 2.

(A) A representative case, Patient II.30. (B) Patient II.30's eyes showing asymmetric ptosis which is slightly worse on the left. (c) Patient I.10's fingers showing weakness of the finger extensor muscles. (D). Patient II.30's forearms showing atrophy of the right forearm muscles.

Table 1

Clinical characteristics and distribution of weakness in affected members of the Thai family with slow-channel myasthenic syndrome.

Characteristics	Case	I.1	I.5	I.10	II.11	II.13	II.14	II.15	II.30	III.18	III.21	Total
Age, year	70	60	44	39	31	28	28	24	6	4		
Sex	M	F	F	F	F	F	F	M	M	M		
Age at onset, year	1	1	25	32	25	23	24	19	4	1		
Symptoms												
Drooping of eyelids	-	-	+	-	-	-	-	+	-	+	+	3
Double vision	-	-	+	-	-	-	-	-	-	-	-	1
Difficulty swallowing	-	+	-	+	-	-	-	+	-	-	-	3
Difficulty chewing	-	-	+	-	-	-	-	-	-	-	-	1
Neck pain	+	-	-	+	+	+	+	+	-	-	-	5
Weakness of the arm	-	-	+	+	+	+	+	-	+	+	+	7
Weakness of the hand	-	-	-	+	-	-	-	-	-	-	-	1
Weakness of the leg	-	-	+	-	-	-	+	-	-	+	+	3
Intermittent worsenings	-	-	+	+	+	+	+	-	-	+	+	6
Distribution of weakness												
Nasal voice	-	-	+	-	-	-	-	+	-	+	+	3
Ptosis	+	+	++	+	-	+	+	++	+	++	++	9
Ophthalmoparesis	+	+	+	+	-	+	+	+	+	+	+	9
Weak orbicularis oculi	+	-	+	+	+	+	+	-	+	+	+	8
Weak neck flexor	+	++	++	++	+	+	+	++	+	++	++	10
Weak neck extensor	-	+	++	+	-	-	-	++	+	++	++	6
Weak wrist flexor	-	-	+	-	-	-	-	-	-	-	+	2
Weak wrist extensor	-	-	++	-	+	-	-	-	-	+	+	3
Weak finger flexor	-	-	+	-	-	-	-	+	+	+	+	3
Weak finger extensor	-	+	++	+	+	-	+	+	+	+	+	8
Weak small hand muscles	+	+	+	+	-	-	+	+	+	-	-	6
Weak proximal arm muscles	-	+	+	+	+	+	+	-	-	-	-	6
Weak distal leg muscles	-	-	-	-	-	-	-	-	-	-	-	0

Characteristics	Case	L1	L5	L10	IL11	IL13	IL14	IL15	IL30	IL18	IL21	Total
Weak proximal leg muscles	+	+	+	+	+	-	-	+	-	-	-	5
Atrophic neck extensor	-	-	-	+	-	-	-	-	+	-	+	3
Atrophic finger flexor	-	-	-	+	-	-	-	-	+	-	-	2
Atrophic finger extensor	-	-	-	+	-	-	-	-	+	-	-	2
Atrophic small hand muscles	-	-	-	+	-	-	-	-	+r	-	-	2
Atrophic proximal arm muscles	-	-	-	+	-	-	-	-	-	-	-	1
Atrophic distal leg muscles	-	-	-	+	-	-	-	-	-	-	-	1
Atrophic proximal leg muscles	-	-	-	+	-	-	-	-	-	-	-	1

- = no, + = mild, ++ = moderate, r = right side only