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Case series of three Filipino siblings diagnosed with Thomsen disease with T310M missense mutation

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Abstract

Thomsen disease is an autosomal dominant, chloride channelopathy that presents with intermittent muscular stiffness, usually at rest, and generalized but mild muscular hypertrophy. This is a rare condition with a prevalence of 1:23,000 with only two unrelated individuals reported locally. Here we present a summary of clinical, EMG and laboratory findings of three Filipino siblings aged twenty-two, nineteen and seventeen, two of which were genetically confirmed to have T310M missense mutation, who came to our clinic for difficulty in ambulation, intermittent cramping and muscle hypertrophy.

Keywords: Congenita myotonia, Thomsen disease, T310M mutation.

INTRODUCTION

Thomsen Disease (TD) is an autosomal dominant, inherited, non-dystrophic myotonic disorder caused by reduced sarcolemmal conductance of chloride channel (CLC-1) due to mutations of the CLCN-1 gene[1-2] Due to delayed muscular relaxation, patients with this condition present with generalized myotonia, clumsiness, progressive muscular hypertrophy and stiffness upon initiation of movement especially after prolonged rest.[1,3]

TD begins during infancy or childhood, involves individual muscle groups and manifests with normal to supernormal strength. Mild muscle hypertrophy can be seen but most have normal muscle bulk. Life expectancy is the same as those with no similar condition.[1,3]

This condition is often caused by heterozygous missense mutations, the most common of which is the non-conservative substitution of glycine-230 with glutamic acid (G230E).[1] Other novel mutations were discovered in 88 unrelated patients: S132C, L238F, T310M, F428S, T550M and E193X and more are discovered each year.[4] Despite the numerous novel genotypes identified, the phenotypes almost always remain the same.

In the Philippines, only two case reports of clinically diagnosed unrelated congenita myotonia (CM) were reported.[5,6] To date, this is the first case series to report the clinical and electromyographic findings of patients with TD with T310M missense mutation in the country. While most CM patients are responsive to medications and live a normal life, one of our cases minimally responded to any drugs started and later on developed depressive symptoms which he attributed to the severity of the condition.

CASE REPORTS

The family of the Filipino kindred included 7 symptomatic individuals (5 men and 2 women) through three generations. As shown in Figure 2, clinico-myographic studies were performed on three symptomatic children of non-consanguineous parents from whom informed consents were obtained. Only two consented for genetic sequencing of CLCN-1 gene; Patient 1 and Patient 3. Table 1 summarizes the clinical findings of these three patients.

Patient 1 (III-3)

The proband is a 19 years old Filipino male who went to our hospital's Out-Patient Department (OPD) for intermittent muscle stiffness. At age 12, he started to have difficulty in climbing stairs because of intermittent and progressive stiffness of the thighs and legs associated with muscular hypertrophy, dysarthria, difficulty getting up from bed and intermittent extension and flexion of his first toe especially after prolonged rest. He also has difficulty opening his hands after continued grip and would need assistance to stand up from sitting

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Table 1: Summary of the cases

No	Gender	Age	Onset	Inheri-tance	Prox Weak-ness	Hyper-trophy	Intermittent Cramps	Dysarthria	Stiffness after Rest	Lid and Grip Myotonia	Gait Problem	Warm Up Pheno-menon	Herculean Built	Lockjaw	CKMM	NCS	Gene Sequence	Response to Treatment
1	M	19	12	AD	+	+	+	+	+	+	+	+	+	+	Normal	Myotonic Discharges	T310M Mutation	Mild
2	M	17	4	AD	-	+	+	–	+	+	-	+	+	-	Normal	Myotonic Discharges	Not done	No medications
3	F	22	20	AD	+	+	+	-	+	+	+	-	+	-	Normal	Myotonic Discharges	T310M mutation	No medications

position. Strenuous activities such as basketball would necessitate repetitive movement to be able to move smoothly. During childhood, he was called "macho-man" because of his well-defined and prominent muscles which he attributed to his paternal grandfather.

He has no other co-morbidities and has two siblings sharing some of his symptoms. He claims that his father, uncles and aunts in the paternal side have muscular built, But whether they share exactly the same condition and symptoms were unknown and undocumented.

During the interview, intermittent locking of the jaw and episodes of dysarthria were noted. He has prominent temporalis and masseter muscles but the rest of cranial nerves were intact. On inspection, he has herculean built with good muscle tone (Figure 3). Lid and grip myotonia were present. Percussion myotonia of the thenar and calf muscles was also seen. The manual muscle testing was 5/5 in all extremities. He had normal reflexes and no sensory deficits. He has difficulty standing up after sustained sitting and would use a quad cane for few minutes before walking normally. The rest of the neurological examination was normal.

Creatine kinase total and muscle creatine kinase (CK-MM) were normal. Nerve conduction studies were also normal. Electromyography (EMG) showed increased insertional activities in all muscles tested with waxing and waning compound muscle action potential (CMAP) amplitude and frequency. Dive bomber or chainsaw motor sound, characteristic of myotonic discharges, was noted during EMG (Figure 1A). Repetitive nerve stimulation was not done.

Gene sequence of CLCN-1 showed T310M mutation (Figure 5A).

Patient was started on acetazolamide 250 mg/tab twice a day with minimal improvement of symptoms. He was also tried on levetiracetam 250 mg/day twice a day, carbamazepine 200 mg/day twice a day and phenytoin 100 mg/tab twice a day with no or minimal relief of symptoms. He was later on referred to Psychiatry department for depressive symptoms. Mexiletine was initially offered but was not available in the Philippines.

Patient 2 (III-4).

Patient 2 is a 17 years old male, who started to have intermittent muscle stiffness at 4 years old. He described this as progressive recurrent locking of left knee lasting for 30 to 60 seconds, more prominent after a lengthy rest. To relieve the locking, he would flex his left knee repeatedly

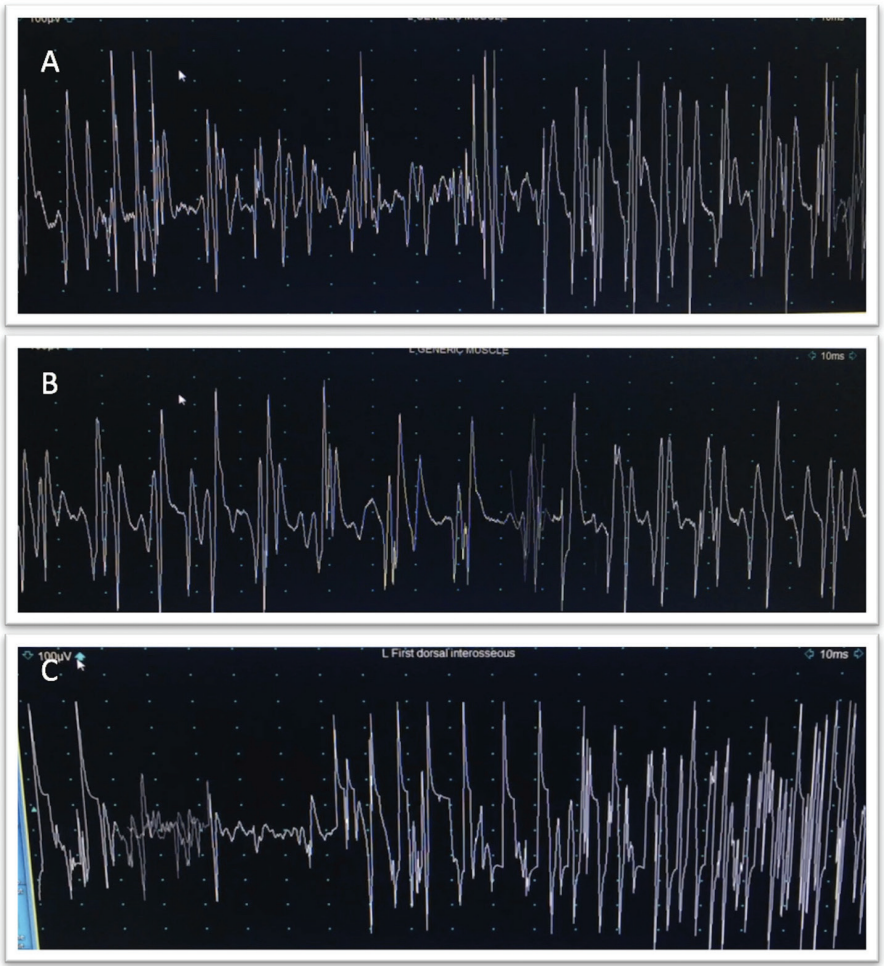

Figure 1 A, B, C: Needle electromyography of patients 1, 2 and 3 respectively showing myotonic discharges.

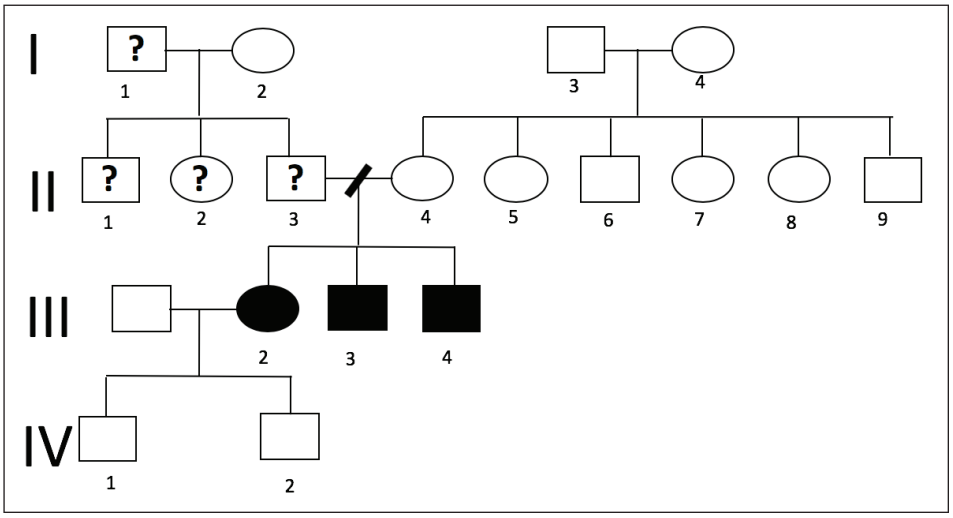

Figure 2. Family Pedigree. The affected individuals are designated with filled symbols, and the unaffected with open symbols. Individuals with question marks are suspected to have the condition but were not examined clinically. Only patients III-2 and III-3 consented for gene sequencing of CLCN-1. The parents of the patients are not related to each other. They separated already as indicated by a single bold slash mark.

before doing an activity. In the interim, his bilateral upper extremities became affected which he described as intermittent extension of the elbows.

On physical examination, he also has herculean built but not as severe as his brother (Figure 4). He has grip and percussion myotonia of the thenar and calf muscles. The strength was normal for all extremities and the patient denies any sensory deficit. He was able to sit and stand with no difficulty. The rest of the neurological examination was normal.

EMG done also revealed myotonic discharges (Figure 1B). He did not consent for CLCN-1 gene sequencing. He was not started on any medications.

Patient 3 (III-2).

Patient 3 is the eldest of the siblings but with the mildest of symptoms. She is a 22 years old female who suffered from two-year history of gradual sporadic bilateral calves' cramping associated with difficulty in getting up from extended sitting, grip myotonia and clumsiness resulting into frequent falls. She also has difficulty in climbing up stairs due to recurrent extension of her bilateral knees. All of her symptoms started after giving birth to her second son. Her sons, one and five years old have no signs of myotonia.

Prominent temporalis and masseter muscles were also present. She also has herculean built but not as severe as her younger siblings. Percussion and grip myotonia were seen in the thenar and hand muscles respectively. The rest of her neurologic examination was normal.

Myotonic discharges were also seen on the EMG of patient 3 (Figure 1C). Medication was not started since her symptoms were not as disabling as her younger brothers. She also has T310M mutation on CLCN-1 gene (Figure 5B).

Genetic Testing

Ten ml of blood was collected from the patients and were placed in EDTA tubes. These samples were sent to the Department of Clinical Laboratory in Mie University in Japan. High molecular weight genomic DNA was extracted according to standard procedures from the peripheral blood leukocytes and the purified fragments were sequenced by the deoxynucleotide chain termination method using automated DNA sequencer ABI 310 (Perkin-Elmer, Foster City, California).

DISCUSSION

TD can be mimicked by dystrophica myotonia (DM) Types 1 and 2, sodium channel myotonias like paramyotonia congenita, potassium aggravated myotonia and drug-induced. The generalized muscular hypertrophy in the three siblings rules out the possibility of a DM which is characterized by myotonia associated with atrophy and weakness. Sodium channelopathy is also unlikely because our patients did not present with worsening after exercise and potassium ingestion. The absence of intake of drugs like fenofibrates completely rules out drug induced myotonia.[1]

Two clinically diagnosed cases of congenita myotonia were reported in the Philippines. One of them was a 16 years old female who presented with chronic muscle cramps, grip and percussion myotonia, proximal muscle hypertrophy and myotonic discharges in EMG. Although the signs and symptoms were similar to our patients, the family members of previously reported case were not affected. No genetic testing was done to confirm their diagnosis of Becker's disease.[5] The other report was that of a 40-year old male presenting with myotonia, herculean built, elevated serum creatine kinase total and myotonic burst in needle EMG. He was prescribed with carbamazepine and quinine and was subjected to inpatient rehabilitation. This led to reduction of myotonia and improvement in the performance of activities of daily living (ADL) and instrumental ADL (i-ADL). Patient 1 also underwent rigorous rehabilitation with little improvement. He was later started on acetazolamide, levetiracetam, phenytoin and carbamazepine with mild reduction of myotonic attacks. No medication was started on other siblings for paucity of severe myotonia. The previously reported case was older compared to our patients.[5] Mexiletine was not available in the Philippines.

Family members who suffer the same condition may have variable severity of manifestation. Symptoms may be more prominent in one family member and less in another. This was particularly true in our case as Patient 1 displayed worst symptoms while the eldest and female sibling, exhibited the mildest. Neither TD nor Becker Disease (the autosomal recessive CM) found that men are more frequently affected than women, although recent studies conclude that at least in recessive myotonia congenita, the severity of myotonia (and possibly of transient weakness) may be somewhat more pronounced in men than women.[7]

For myotonia in general, there were no systematic comparisons of myotonic stiffness in the pregnant and non-pregnant states. There were also no studies of electrolyte changes in pregnant

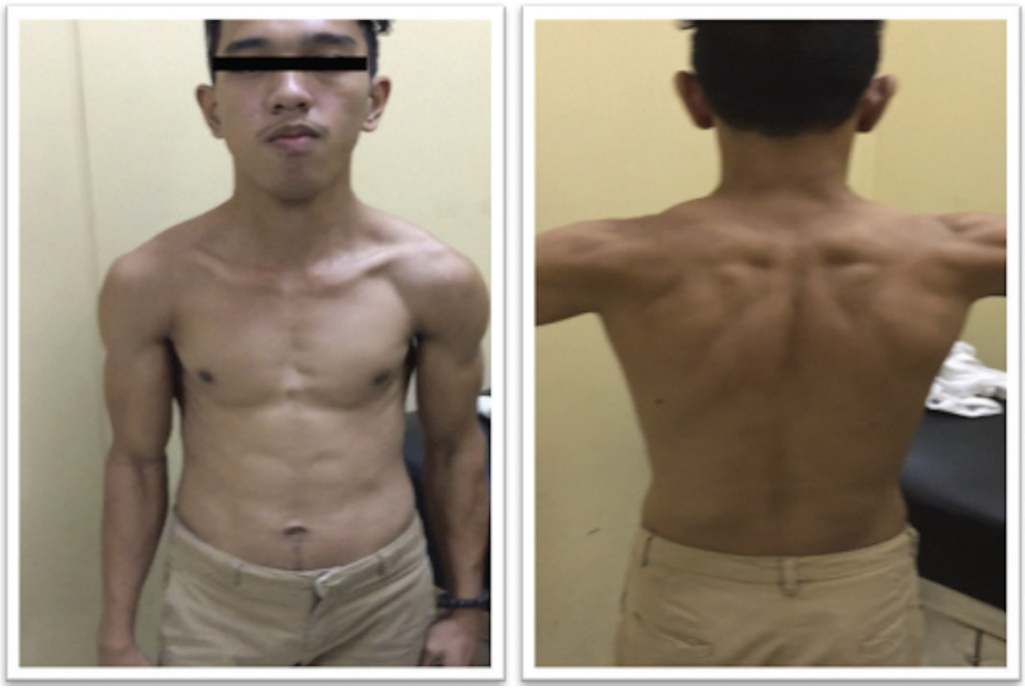

Figure 3. A. the proband showing his herculean built. B. Generalized muscular hypertrophy of the back.

Figure 4. Patient 2 at 6 years old. Notice his well-developed deltoids and biceps at such a young age.

patients with CM. Because resting potentials are generally similar in myotonic patients and controls, it is speculated that muscle membranes are hyperpolarized in pregnant women, decreasing the threshold for muscular contraction. This in turn may lead to worsening of symptoms during pregnancy and may explain the appearance of symptoms in Patient 3 after giving birth to her second child.[7,8] Another possible explanation is the presence of chloride-sensitive mutations affected by pregnancy induced lowering of internal chloride although studies with more patients may be needed to confirm these.[7]

Although a good history, pedigree and physical examination are enough to clinically diagnosed CM, a gene sequencing of CLCN-1 gene is still necessary to definitively diagnose this condition. Six novel mutations were discovered in 88 unrelated patients with myotonia: S132C, L238F, T310M, F428S, T550M and E193X. Patients with F428S mutation exhibited symptoms characteristic of paramyotonia congenita by reducing the expression level of hClC-1 channels. Other mutations were theorized to cause myotonia by affecting the hClC-1 differently: S132C and T550M conferred novel hyperpolarization-induced gating steps while L283F and T310M caused a shift of the activation curve to a more positive potential.[4] Despite the number of novel mutations identified, only few studies report the

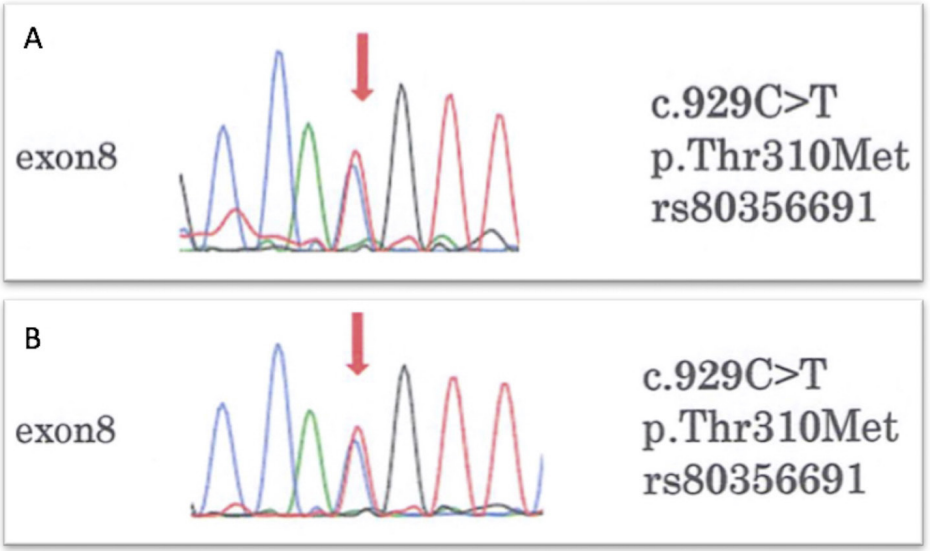

Figure 5 A and B. Gene sequence of CLCN-1 of patient 1 and 3 respectively, revealing a C to T transition in 929th nucleotide, predicting the replacement of the 310th amino acid, threonine residue, by methionine.

genotype : phenotype correlations of TD. In these few studies, clinical presentation is almost similar in all genotypes. Two of our patients have T310M mutation, the severity of which are quite variable.

In Singapore, a case series of 3 cases of a Chinese family with suspected autosomal recessive myotonia was reported. Two of the unaffected brothers have elevated serum creatine phosphokinase and were suspected to be carriers of the disease.[9] In Taiwan, 3 cases of non-dystrophic myotonias were reported. Two were noted to be responsive to mexiletine.[10] There were also clusters of families of CM in other East Asian countries.[2]

In conclusion, we report 3 Filipino siblings diagnosed clinically and genetically with TD with T310M missense mutation and suggest that their clinical features are quite variable even between patients sharing a same mutation.

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DISCLOSURE

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Conflict of interest: None.

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