Rippling Muscle Disease with Irregular Toe Jerks and Anti-acetylcholine Receptor Antibodies: Remission after Extended Thymectomy

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Abstract:
We herein report a 63-year-old rippling muscle disease (RMD) patient who presented with painless stiffness, muscle hypertrophy and muscle contractions elicited by mechanical stimulation. He also showed irregular toe jerks and a slightly elevated level of anti-acetylcholine receptor antibody (AChR-Ab). Since he had a mediastinal mass mimicking thymoma, which was later revealed to be a bronchial cyst, he underwent extended thymectomy. The irregular toe jerks disappeared within a week after the operation. The other muscle symptoms completely remitted 27 months after the onset. This is the first report of a sporadic case of RMD with irregular toe jerks that resolved after extended thymectomy.

Key words: anti-acetylcholine receptor antibody, thymectomy, muscle biopsy, caveolin-3, muscle jerk

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Introduction
Rippling muscle disease (RMD) is a rare disorder characterized by muscle stiffness, muscle hypertrophy and rippling muscle induced by stretching or percussion that occurs in both familial and sporadic forms (1, 2). Most cases with non-familial RMD cases have been reported to be associated with autoimmune diseases or cancers and responded to immunosuppressive therapy (2-9). However, sporadic RMD cases initially unassociated with autoimmune or malignant disorders rarely undergo treatments and sometimes later develop myasthenia gravis (MG) (4, 10, 11).

We herein report a man with sporadic RMD without co-existing autoimmune disorders or malignancy who uniquely showed irregular toe jerks. Since he had a slightly elevated serum anti-acetylcholine receptor antibody (AChR-Ab) level and a mediastinal mass mimicking thymoma, he underwent extended thymectomy. His frequent irregular toe jerks disappeared within a week after the operation, and his muscle rippling and stiffness gradually improved over two years after the operation without further therapies. He did not show any signs and symptoms of autoimmune disorders, including MG, at 39 months after the operation. Our case may illustrate a wide spectrum of neurological manifestations associated with sporadic RMD.

Case Report
A 63-year-old man was admitted to our outpatient clinic with muscle stiffness after exercise for 8 months. He first noticed muscle stiffness in his lower leg muscles after exercise, which spread to his arms and pectoralis muscles eight months later. Since a blood test revealed an elevated level of creatine kinase (CK; 883 U/L) 4 months after the onset of the stiffness, he stopped atorvastatin used for 14 months.

Despite cessation of the atorvastatin, he felt difficulty moving his legs in daily activities due to painless stiffness and

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was admitted to our hospital. He had no easy fatigability. He had proximal limb muscle hypertrophy, a wave of muscle contractions and focal mounding elicited by mechanical stimulation on the biceps brachii, rectus femori, and soleus muscle.

A neurological examination revealed no other abnormal findings. Needle electromyography (nEMG) showed that the muscular contraction and focal mounding were electrically silent, suggesting that the abnormal movements were muscle rippling. He also had irregular toe jerks at frequencies of 1-2 Hz with dystonic posture (in dorsiflexion), and he was able to voluntarily suppress the movements for a few seconds. Unfortunately, we performed neither electromyography (EMG) nor surface EMG recordings of the jerks.

The serum CK level was mildly elevated (629 U/L, normal range 50-230 U/L), with normal levels of free T4 and TSH and negative thyroid peroxidase autoantibodies. Autoantibodies screening showed a slightly elevated AChR-Ab (0.5 nmol/L, normal <0.3 nmol/L) with negative anti-GAD, MuSK, LGII/CASPR2, VGCC antibodies and paraneoplastic neurological antibodies (AMPH, CV2, PNMA2, Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65, Tr). A cerebrospinal fluid (CSF) analysis showed a slight increase in protein level (82 mg/dL, normal range 10-40 mg/dL) with a normal cell count.

On a physiological examination, repetitive nerve stimulation showed no waning, and nerve conduction studies were normal. Chest computed tomography (CT) showed a mediastinal mass. Although neither signs nor symptoms of MG were observed, we suspected that the positive AChR-Ab findings suggested thymoma.

He underwent extended thymectomy on the 23rd hospital day. The pathological studies of the resected specimen revealed a bronchogenic cyst with atrophic thymus tissues. Although neither signs nor symptoms of MG were observed, we suspected that the positive AChR-Ab findings suggested thymoma.

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RMD is a rare disorder characterized by muscle stiffness and electrically silent wave-like contractions of the skeletal muscle, percussion-induced mounding and percussion-induced rapid muscle contractions (PIRCs) (1). Some cases have a genetic disorder causing RMD, while others may have an immune-mediated disorder inducing RMD (iRMD). The present patient had clinical features of RMD, no family history of RMD and no pathogenic mutations in the CAV3 gene, supporting the diagnosis of sporadic RMD. A mosaic pattern of reduced sarcolemmal caveolin-3 in the biopsied muscle is compatible with iRMD (3, 10, 12).

Importantly, all of the muscular symptoms of our AChR-Ab-positive RMD patient had disappeared at one and a half years after extended thymectomy without intensive immunosuppressive therapies, such as steroid administration or plasmapheresis. There have been no AChR-Ab-positive RMD cases without associated cancers or MG reported in the literature. Indeed, thus far, all 21 reported cases with AChR-Ab-positive RMD were associated with MG or cancers and consistently responded to immunosuppressive treatments (2-4, 6, 8, 10, 11, 13-17).

However, RMD patients with neither autoimmune disorders nor cancers at the first presentation are not usually treated with intensive immunosuppressive therapies. Some of those patients develop MG with persistent rippling phenomena several months to years after the onset of RMD. Furthermore, all of the patients with AChR-Ab-positive RMD required immunosuppressive agents to achieve remission of muscle rippling (4, 10, 11). Although our patient had no MG symptoms, we suspected that persistently elevated levels of AChR-Ab might be a risk factor for the development of autoimmune dysfunction. We have followed up this patient for about three years after since thymectomy without recurrence of RMD or development of MG, suggesting that extended thymectomy might exert a beneficial effect on the natural course of this patient. More detailed studies will be required to establish therapies for sporadic RMD patients, especially in AChR-Ab-positive cases without obvious autoimmune diseases or cancers.

Notably, our patient presented with irregular toe jerks, which have never been reported previously in patients with RMD. The jerks were irregular extensions and flexions of the toes observed at rest without apparent triggers. Although neither EMG nor surface EMG were recorded to identify the electrical properties of the jerks, we suspect that the jerks and rippling phenomena might share some common mechanisms, as both symptoms presented at the same period and might have been caused by the increased sensitivity to stretching due to the absence of caveolin-3 (18). More detailed studies are needed to clarify the mechanisms producing the jerks, which might have led to the biphasic symptomatic remissions in this case.

In conclusion, we encountered a man with AChR-Ab-positive RMD who achieved complete remission one and a half years after extended thymectomy. Since symptomatic remission has not been seen in previously reported AChR-Ab-positive RMD cases without using immunosuppressive agents, we believe that these findings will prove useful for considering extended thymectomy as a therapeutic option in AChR-Ab-positive RMD patients.

The authors state that they have no Conflict of Interest (COI).

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