Myotonia Fluctuans

Kenneth Ricker, MD; Frank Lehmann-Horn, MD; Richard T. Moxley III, MD

- Autosomal-dominantly inherited non-dystrophic myotonic disorders are an interesting group of muscle diseases that provide considerable opportunity for future molecular genetic studies to identify the genes responsible for specific membrane functions. A family with such a myotonic disorder is described with features that are distinctly different from myotonia congenita and paramyotonia congenita. Five members were affected in three generations. The myotonia fluctuated to an unusual degree. It did not worsen with cold but increased markedly with potassium loading. Muscle weakness never occurred. Analysis of the contraction force of the flexor digitorum muscle showed a unique type of myotonia, namely, exercise-induced delayed-onset myotonia. Microelectrode studies done on one muscle biopsy specimen revealed a normal chloride conductance of the muscle fiber membrane.

(ARCH NEUROL. 1990;47:268-272)

In 1977, Becker1 raised the possibility that there might be considerable heterogeneity for the autosomal-dominant nondystrophic myotonic disorders. The classic myotonic diseases of this type are myotonia congenita of Thomsen and paramyotonia congenita. It is now well established that both of these disorders are distinct diseases with specific clinical and electrophysiological abnormalities. The gene lesion responsible for each of these diseases has not yet been discovered. However, in myotonia congenita there is a decrease in chloride conductance of the muscle fiber membrane,2 while in paramyotonia congenita there is an increased conductance of sodium following exposure to cold.3 Another autosomal dominant disorder that in some families produces mild signs of myotonia is hyperkalemic periodic paralysis (adynamia episodica). The distinction between paramyotonia congenita and hyperkalemic periodic paralysis is less certain and there continues to be a discussion as to the best means to separate these two disorders.4 Regarding myotonia congenita and paramyotonia congenita, it has been suggested that there might be additional autosomal-dominant disorders with different clinical and electrophysiological characteristics.5 We describe a family with such a type of disorder. Characteristically, there was an unusual fluctuation in severity of the myotonia, and for this reason the disorder has been termed, "myotonia fluctuans." To identify the specific differences, patients with myotonia congenita and paramyotonia congenita have been included in the report for comparison.

REPORT OF CASES

Myotonia Fluctuans (Fig 1, Top Left)

Case III-2.—A 23-year-old man had occasionally experienced stiffness in his hands and legs that was unrelated to changes in temperature. Sometimes his eyes would be closed for a few minutes, and he had no difficulties while performing this amount of exercise. On one occasion he had run vigorously for some time while he was not able to open his eyes. He had similar episodes of stiffness in the sun to relax for about 20 minutes, and was then unable to arise due to generalized muscle stiffness. After some minutes while he struggled to get up, the stiffness gradually disappeared and he had no weakness.

Over a period of several months the patient would have 2 or 3 days during which he would experience the following symptoms. He would have momentary stiffness of the sternocleidomastoid muscle when he turned his head to the side. Muscle stiffness would occur following forceful biting or chewing, and for an instant he would be unable to open his mouth. If he wanted to turn his eyes rapidly to the side, he would have a momentary lag in the movement. He also observed transient stiffness in his legs and arms. During the intervening days he would remain free of symptoms.

The patient had well-developed muscularata without signs of hypotrophy or atrophy. He had a lid lag and had paradoxical eyelid myotonia after repeated forceful eye closure. He had slight nystagmus myotonia following percussion, but there was no grip myotonia. He could arise with normal speed from a squat and there was no evidence of myotonia in the legs. Results of routine blood studies including measurement of electrolytes were normal. The creatine kinase level was normal (<30 IU/L). Needle electromyographic (EMG) investigation was performed in the abductor pollicis brevis, flexor digitorum, and the right and left biceps muscles. All muscles demonstrated typical runs of myotonic discharges. Motor unit potentials appeared normal.

Cooling of the right hand and forearm (see "Special Investigations" section) did not produce clinical stiffness or weakness. Following ingestion of 120 mmol of potassium, severe generalized myotonic stiffness developed over a period of 20 minutes. The patient was unable to rise from the chair. There was no weakness. The serum potassium level was 5.4 mmol/L at the peak of the symptoms. Biopsy of the biceps muscle revealed no abnormalities on histochemical examination. Electron microscopic study showed a few subsarcolemmal vacuoles believed to represent a nonspecific enlargement of the tubular system.

Case III-3.—A 22-year-old man had occasionally experienced stiffness in his hands during prolonged jogging during the previous several years. On a few occasions the stiffness had caused him to stumble and fall. Most of the time he had no difficulty performing this amount of exercise. On one occasion he had run vigorously for some while and had no symptoms. He laid in the sun to relax for about 20 minutes, and was then unable to arise due to generalized muscle stiffness. After some minutes while he struggled to get up, the stiffness gradually disappeared and he had no weakness.

Over a period of several months the patient would have 2 or 3 days during which he would experience the following symptoms. He would have momentary stiffness of the sternocleidomastoid muscle when he turned his head to the side. Muscle stiffness would occur following forceful biting or chewing, and for an instant he would be unable to open his mouth. If he wanted to turn his eyes rapidly to the side, he would have a momentary lag in the movement. He also observed transient stiffness in his legs and arms. During the intervening days he would remain free of symptoms.

The patient had well-developed musculature without signs of hypotrophy or atrophy. He had a lid lag and had paradoxical eyelid myotonia after repeated forceful eye closure. He had slight nystagmus myotonia following percussion, but there was no grip myotonia. He could arise with normal speed from a squat and there was no evidence of myotonia in the legs. Results of routine blood studies including measurement of electrolytes were normal. The creatine kinase level was normal (<30 IU/L). Needle electromyographic (EMG) investigation was performed in the abductor pollicis brevis, flexor digitorum, and the right and left biceps muscles. All muscles demonstrated typical runs of myotonic discharges. Motor unit potentials appeared normal.
null
Fig 3.—Recording of electromyography (top) and contraction force (bottom) of the flexor digitorum muscle in patient III-2 with myotonia fluctuans. Time scale in seconds. Left, Completion of exercise; middle, 2 minutes later, and right, 10 minutes later. There is delayed onset of electrical and mechanical myotonia after exercise.

Fig 4.—Maximum contraction force (top) and relaxation time (bottom) of the flexor digitorum muscle in patient III-2 with myotonia fluctuans. A indicates two contractions at a 15-second interval at baseline conditions; B, completion of exercise and 15 seconds later; C, 2 minutes later; D, 7 minutes later; E, 14 minutes later; and F, 20 minutes later.

Fig 5.—Diagram according to Fig 4 showing local muscle cooling of the forearm. Arrows indicate completion of exercise of the cooled muscle. For myotonia congenita (MC; patient VIII-1), A indicates two contractions at room temperature; B, after 30 minutes of cooling; C, completion of exercise and 1 minute later; and D, after 10 minutes. For paramyotonia congenita (PC; patient VI-11a), A indicates room temperature; B, after 15 and after 30 minutes of cooling; C, completion of exercise; D, after 10 minutes; and E, 2 hours later. For myotonia fluctuans (MF), at left (patient III-2), A indicates room temperature; B, after 30 minutes of cooling; C, completion of exercise; D, 2 minutes later; and E, 10 minutes later. At right (patient III-3), A indicates room temperature; B, after 30 minutes of cooling; C, completion of exercise; D, After 1 minute, 4 minutes, and 5 minutes; and E, after 10 minutes.
muscles were cooled with water at 14°C to 15°C for 30 minutes.

**Quantitation of Mechanical Myotonia**

The recordings of muscle contraction were analyzed by a computerized technique. Relaxation time (which equals mechanical myotonia) was measured as the time required for the force to decline from 90% to 10% of the average maximum force of a contraction (Fig 2).

**In Vitro Investigations**

Patient III-3 gave informed consent to a muscle biopsy. A specimen of the biceps brachii was excised under local anesthesia and kept at 37°C in gassed solution. The solution contained 1 μmol of tetrodotoxin (TTX) to suppress spontaneous activity. The specimen was dissected into bundles of about 2 mm in diameter. Resting and action potentials were recorded by means of capacity-compensated microelectrodes from resealed fiber segments. Voltage-clamp experiments were performed with three microelectrodes.

---

**RESULTS**

**Mechanical and Electrical Myotonia**

Patients III-2 and III-3 with myotonia fluctuans displayed no abnormality in relaxation time in their baseline studies. Under certain conditions, electrical myotonic after-activity and mechanical myotonia (which equals prolonged relaxation time) became prominent (Figs 3 and 4); a short contraction performed 20 seconds after completion of exercise had a normal relaxation time. Two minutes later, when the contraction was repeated, there was a marked prolongation of the relaxation time. With further rest followed by another contraction, the relaxation time increased even more. This pattern of increasing prolongation of relaxation time was termed "exercise-induced delayed-onset myotonia."

**Effect of Cooling (Fig 5)**

In the two patients with myotonia fluctuans, the relaxation time showed no abnormality after cooling. After the completion of exercise the delayed-onset myotonia appeared in a similar pattern to normal temperature.

The patient with myotonia congenita had no abnormality of his relaxation time during cooling. In the patient with paramyotonia congenita, the relaxation time became highly prolonged. After cooling and exercise the paramyotonic muscle showed a severe and long-lasting weakness. Contraction force decreased to approximately 10%, compared with 100% force with normal muscle temperature.

A peculiar form of abnormal spontaneous EMG activity has been observed recently in paramyotonia congenita during cooling. This spontaneous muscle fiber activity resembles the pattern of dense fibrillation activity.

**Effect of Potassium (Fig 6)**

A severe increase in potassium developed in the two patients with myotonia fluctuans following the ingestion of potassium (see case reports). There was a pronounced prolongation of muscle relaxation time. Exercise of the flexor digitorum muscle normalized the relaxation time (Fig 6, right). However, after 15 seconds of rest, the relaxation time increased again. The abnormality in the relaxation time persisted until the serum potassium concentration returned to baseline. There was no weakness of contraction force.

**In Vitro Investigations**

The mean resting membrane potential of the resealed fiber segments was normal, measuring $-80.0 \pm 6.0$ mV ($n = 20$). Similar values have been measured in both intact intercostal muscle fibers and resealed fiber segments from normal subjects. When TTX was removed from the bathing solution, some fibers showed repetitive (myotonic) activity.

The steady-state current-voltage relationships were similar to those of normal fibers. The mean membrane conductance value of the fibers was 280 microsiemens/cm², which is within the range for normal fibers. To determine the component conductances, the current-voltage relationships were recorded in a chloride-free solution containing TTX. The remaining membrane conductance represents the potassium conductance, which in these fibers was 66 microsiemens/cm². This value is within the range of a normal
This grip myotonia decreases following repeated muscle contractions, and gradually returns after 5 to 15 minutes of rest. The delayed-onset myotonia, however, is only brought about by exercise. It does not appear immediately, but only with a certain delay after exercise. During a variable period of time, after exercise, the muscle is in a state capable of producing myotonia.

Exercise-induced delayed-onset myotonia should not be confused with paradoxical myotonia. Paradoxical myotonia is frequently observed in patients with paramyotonia congenita when the muscle has been cooled slightly. With repeated contractions at short intervals, the myotonia increases with each contraction (the muscle relaxation time is increasing). In the patient with myotonia fluctuans the muscle relaxation time at the completion of exercise is normal, but after a delay of sometimes several minutes a single contraction might produce severe myotonia.

As with other myotonic disorders, there is likely to be a defect in the muscle membrane that accounts for the symptoms in myotonia fluctuans. In myotonia congenita and in autosomal recessive myotonia, there is a decrease in the conductance of chloride. In the one patient with myotonia fluctuans studied so far, the chloride conductance was normal, and the specific type of membrane defect is unknown.

For unknown reasons, the patients with myotonia fluctuans have a marked sensitivity to potassium. With exercise there is a physiologic local rise in the extracellular concentration of potassium around the muscle fibers. However, exercise also causes a transient increase in intracellular potassium concentration, and this decrease in intracellular pH is known to exert a stabilizing effect on the muscle membrane. This might explain why these patients with myotonia fluctuans do not develop myotonia during exercise. Maybe some time after exercise the increase in extracellular potassium cannot be effectively counterbalanced by the intracellular pH, and a period of myotonia occurs. Furthermore, exercise stimulates the release of hormones locally in the tissue bed as well as provoking the release of adrenergic hormones into the systemic circulation. The effects of these hormones may contribute in some unknown way to the phenomenon of exercise-induced delayed-onset myotonia. It should be mentioned in this connection that fenoterol, an α-adrenergic drug, is capable of severely increasing myotonia in some myotonic patients. Future electrophysiologic muscle fiber studies and DNA analysis should clarify the mechanisms in myotonia fluctuans in terms of the molecular membrane defect and the gene lesion.

This research was supported by the NP Gesellschaft, Deutsche Gesellschaft für Kardiologie, and National Institutes of Health Grants DK-32884, AM-33193, and AR-89694.

We wish to thank Manuela Koch, MD, for providing us with an update of the Thomsen kindred, and Wilhelm Schulte-Matthier for designing the computer program used to analyze the muscle contraction recordings. We would also like to thank Jean Ellinwood for typing the manuscript.

References