Myotonia Fluctuans

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- 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, Becker 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 electrophysiologic 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, while in paramyotonia congenita there is an increased conductance of sodium following exposure to cold. 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. Regarding myotonia congenita and paramyotonia congenita, it has been suggested that there might be additional autosomal-dominant disorders with different clinical and electrophysiologic characteristics. 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 disease 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-3.—A 22-year-old man had occasionally experienced stiffness in his legs 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 swum 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 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 or arms. During the intervening time he would remain free of symptoms.

The patient had well-developed muscularity without signs of hypertrophy or atrophy. He had a lid lag and had paradoxical eyelid myotonia after repeated forceful eye closure. He had slight thenar 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 U/L). Needlet 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-2.—A 23-year-old man had, for 4 to 5 years, noticed on several occasions stiffness in his hands and legs that was unrelated to changes in temperature. Sometimes his eyes would not open. Once during a track meet he had attempted to run a 50-m dash, and, after taking some steps, became too stiff to complete the race. He had spent most of one summer day working to repair a tread on a tank. In the afternoon he developed marked flexion of his fingers due to stiffness of the thenar eminence. He could not release the heavy hammer that he was using. His trunk and legs were also stiff. Usually, the patient made long trips by bicycle and had no muscle stiffness.

He had no hypertrophy or atrophy of his muscles. On the initial assessment there was a mild lid lag or a mild paradoxical myotonia developed with forceful eye closure. On a subsequent examination 5 months later there was pronounced lid lag and a definite grip myotonia.

Results of routine blood studies were normal. The creatine kinase level was 258 U/L and 266 U/L on repeated measurement. An EMG of the hypothenar and flexor digitorum muscles revealed myotonic runs.

The patient did not develop stiffness and weakness after local cooling. After ingestion of 90 mmol of potassium he developed generalized myotonic stiffness and required 12 seconds to climb nine steps. Before potassium ingestion he needed 3 seconds, which is normal.

Case III-1.—A 26-year-old man could not recall having any neuromuscular symptoms. His muscles had a normal appearance. There was a lid lag. There was no paradoxical myotonia following forceful eye closure, and no grip myotonia. The EMG of the hypothenar muscles revealed myotonic runs.

Case II-1.—A 58-year-old woman recalled that on several occasions while loading hay on a wagon with a pitchfork, she developed stiffness in her fingers, arms, and sometimes in her legs. During one of her pregnancies she stumbled and fell, and subsequently for several minutes was unable to arise because of generalized muscle stiffness.

She had normal muscle strength and development. There was no lid lag or grip myotonia. After forcefully closing her eyes.
three times she could open them only slowly. The EMG of the hypothenar muscles showed myotonic runs.

CASE I-1.—An 86-year-old woman was in good general health except for a memory disturbance. Other family members could not recall her complaining of any neuromuscular symptoms. She had no muscle weakness or myotonic signs. However, the EMG of the hypothenar muscles showed typical myotonic discharges. The husband and the sister (II-2) of patient II-1 had electromyographic studies of the hypothenar muscles and there were no myotonic discharges. There was no history of cataracts in any of the members of the family.

Myotonia Congenita
(Thomsen's Disease)

CASE VIII-1.—A 43-year-old man was a member of the original Thomsen’s disease kindred (Fig 1, bottom). The pedigree has been discussed previously.1 He had a history of generalized myotonia, the degree of which had remained constant throughout his life. For example, after sitting at his desk, it took a few moments of effort for him to rise. He was then able to move normally. The severity of his myotonia had not varied with temperature. He had participated in sports, such as soccer.

He had well-developed muscles, a lid lag, and grip myotonia, which disappeared after two repeated contractions. His creatine kinase level was 60 U/L. The EMG of the flexor digitorum showed myotonic runs. The history and findings were similar for the patient’s sister (VIII-2). However, his 9-year-old son (IX-1) had much more severe myotonia. After resting for 15 minutes, the son required 16 seconds to climb nine steps, whereas his father (VIII-1) needed 5.5 seconds.

Paramyotonia Congenita

CASE VI-11a (Fig 1, Top Right).—A 20-year-old man had the classic form of the disease, and his family has been described in detail by Becker. Since early childhood he had developed stiffness of the face or fingers following exposure to the cold. If he exercised his forearm muscles when they were stiff due to exposure to the cold, they would become very weak. It would take several hours to recover strength. In a warm environment he was free of symptoms. He never had any weakness in the absence of exposure to the cold.

The patient had well-developed muscles. There was mild lid lag and paradoxical myotonia following several forceful eye closures but no grip myotonia. He required 3.2 seconds to climb nine steps. His creatine kinase level was 110 U/L. The EMG of the flexor digitorum showed myotonic runs.

SPECIAL INVESTIGATIONS
Recording Isometric Muscle Strength and Electromyographic Activity From the Flexor Digitorum Profundus Muscle

The forearm and hand of the patient were placed in supination with the fingers flexed so that the distal phalanges were in touch with the force transducer. The forearm and hand were fixed in such a way to allow muscle contraction under isometric conditions. Two wire electrodes were placed in the flexor digitorum muscle 10 mm apart to record EMG activity. Each patient was instructed to make a maximum voluntary contraction and to maintain this effort for 2 seconds. The protocol for “exercise” consisted of maximum contraction for 60 seconds, interrupted by two 10-second rests. The equipment allowed the recording to be carried out in a water bath. The forearm...
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.
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The solution contained 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.

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. This abnormal activity, as expected, was observed in the patient with paramyotonia congenita, but also in the two patients with myotonia fluctuans.

Effect of Potassium (Fig 6)

A severe increase in myotonia 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 ± 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 muscle.
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 hyperkalemia, and this decrease in intracellular pH is known to exert a stabilizing effect on the muscle membrane.14,15 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 fenotol, an α-adrenergic drug, is capable of severely increasing myotonia in some myotonic patients.16 Future electromyographic muscle fiber studies and DNA analysis should clarify the mechanisms in myotonia fluctuans in terms of the molecular membrane defect and the gene lesion.

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References