Clinical Studies on Muscle Diseases*

Eijiro Satoyoshi**, MD

An outline of the recent progress of clinical myology based on our own materials and clinical studies. Four new diseases or syndrome were summerized briefly. These are many unknown diseases in neuro-muscular disorders which would be found and classified in the forthcoming few decades.

In the latter half of the last century, a number of well-known muscle diseases such as polymyositis, dermatomyositis, progressive muscular dystrophy, myasthenia gravis, myotonia and others, were established by an effort of the great historical neurologists, while a brilliant progress took place in the field of clinical neurology. Since 1950 in this century, again, tremendous advance of clinical research on neuro-muscular disorders has been going on and a number of new diseases or syndromes were reported by an assistance of new biochemical, histochemical, electronmicroscopical, electrophysiological and immunological technologies. In this paper, an outline of recent advance on clinical myology would be described in regards to the new diseases, found in our laboratory in the last twenty years.

OCULOPHARYNGODISTAL MYOPATHY

Muscular dystrophy may be defined as genetically-determined primary degenerative muscle disorders. Besides the classical Duchenne type, limb-girdle or fascioscapulohumeral dystrophy, there were several varieties of distal myopathy, ocular myopathy, oculopharyngeal dystrophy and benign Duchenne type. A new variety of "Oculopharyngodistal myopathy" was first introduced by us in 1958** and established in 1977 as a clinical entity. This disease is transmitted as an autosomal dominant inheritance. Seventeen cases in four families were studied. The onset was later than 40 years with a mean mean of 48. Initial symptoms are ptosis, weakness and atrophy of distal muscles of the extremities. Slowly progressive external ophthalmoplegia, weakness and atrophy of the masseter and facial muscles, particularly in the lower half, bulbar muscle as well as distal involvement of the limbs over 20 or 30 years are the clinical feature of this disease. Prognosis is benign and the patient can live as long as 85 years of age. Serum CPK is either normal or slightly elevated. Muscle biopsy revealed degenerative changes of muscle fibers accompanying fibrosis. Mitochondrial accumulation was absent. In one case, autopsy disclosed no remarkable changes in the central and peripheral nervous system. The distribution of muscle

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**Professor of the Fourth Department of Medicine, Toho University School of Medicine Present: Director of the National Neurological Center, Kodaira.
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Table 2. Disorders with Similar Distribution of Muscular involvement.

<table>
<thead>
<tr>
<th>Present Illness</th>
<th>Oculopharyngeal Dystrophy</th>
<th>Myotonic Dystrophy</th>
<th>Kearns-Shy Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>&gt; 40</td>
<td>20-40</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Muscular involve ment*</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ptosis</td>
<td>+</td>
<td>+</td>
<td>- or +</td>
</tr>
<tr>
<td>Extracocular</td>
<td>+</td>
<td>- or +</td>
<td>- or +</td>
</tr>
<tr>
<td>Masseter</td>
<td>+</td>
<td>- or +</td>
<td>- or +</td>
</tr>
<tr>
<td>Facial</td>
<td>+ or +</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bulbar</td>
<td>+</td>
<td>+</td>
<td>- or +</td>
</tr>
<tr>
<td>Dystonia</td>
<td></td>
<td>+ or +</td>
<td>- or +</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td>+</td>
<td>+ or +</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td></td>
<td>+</td>
<td>+ or +</td>
</tr>
<tr>
<td>Retinitis pigmentosa</td>
<td>-</td>
<td>-</td>
<td>- or +</td>
</tr>
<tr>
<td>Endocrine disorder</td>
<td>-</td>
<td>-</td>
<td>- or +</td>
</tr>
</tbody>
</table>

*--Indicates absent; +, present; + +, markedly present.

involvement, course and laboratory studies could be easily differentiated from the similar disorders such as myotonic dystrophy, oculopharyngeal dystrophy or Kearns-Shy syndrome. (Table 1)

CONGENITAL MYOPATHIES

This group of muscle disorders may be defined as congenital, non-progressive muscle disease based on structural abnormalities such as core in the center of fibers, Z-band degeneration with abnormal rod body, abnormal distribution of muscle fibers, mitochondrial accumulation and so forth. Central core disease, multicore disease, myotubular myopathy, nemaline myopathy, fibre type disproportion, and type 1 fiber atrophy belong to this group. Clinically these patients are characterized by hypoplasia of muscles, hypotonia and generalized muscular weakness since birth or childhood. The diagnosis of these condition was done by histopathologic and histochemical examinations of the biopsied muscle. In the majority of these diseases, type 1 fiber atrophy was common which suggested that pathogenesis of this group of diseases may be related to neurogenic factors, occurred during fetal life. In fact, some of these congenital myopathies are accompanied with skeletal abnormalities as Marfan's syndrome, mental reardation or abnormal EEG findings. Accordingly, this group of disorders may be a congenital developmental anomalies and not a simple muscle disease.

SEGMENTAL MYOPATHY

Some unknown muscular disorders are classified frequently on the basis of pathognomonic morphological abnormalities. This is an example of this kind. A 23-year-old female died of respiratory distress. She had a history of slowly progressive contracture of the calf muscles since age of 16. Later she developed to marked weaness of glossoharyngeal and neck muscles as well as proximal muscle weakness which progressed and resulted in respiratory insufficiency. Autopsy revealed a unique muscle abnormality of segmental degeneration of individual muscle fibers with peculiar inclusions. Electronmicroscopically, these inclusions resembled cytoplasmic bodies, being formed of two concentric zones of filamentosous materials. They seemed to arise from filaments of myofibriles that were fragmented and highly disorganized in affected areas. In spite of these remarkable changes, serum CPK activity remained in normal range. This fact suggested that cell membrane was intact in affected fibers. This myopathy is a new one which was not described previously.

KEARNS-SHY SYNDROME

In the literature, there have been many cases of chronic progressive external ophthalmoplegia some of which were accompanied with various neurological complications. In 1958 Kearns proposed a specific combination of ophthalmoplegia, heart-block and retinal pigmentation as a clinical entity and later Shy et al described pathologic characteristics. Clinically this syndrome is characterized by external ophthalmoplegia, optic atrophy, pig mental degeneration of the retion, hearing loss, dysphonia, dysphagia, facial weakness, abnormal CSF protein, myasthenic phenomenon, peripheral, neuropathy cerebellar ataxia, low intelligence, cardiac abnormalities and/or short stature. Histochemical and electronmicroscopic examinations of biopsied
muscles demonstrated mitochondrial abnormalities and accumulation of lipid droplets. This syndrome, therefore, a generalized disorder of unknown etiology, probably metabolic origin.

**METABOLIC MYOPATHIES**

The most prominent progress in recent studies on clinical myology is a discovery of metabolic myopathy. These myopathies would be classified into four categories. 1. myopathy due to carbohydrate metabolism disturbances 2. those due to lipid metabolism disturbances 3. those of other energy pathway disturbances 4. those of electrolytes or membrane abnormalities.

Myopathies due to defects in glycogenesis and glycolysis were discovered almost completely. Generally speaking, myopathies due to glycogenesis defects are characterized by generalized weakness and atrophy and hypotonia of muscles. Those due to glycogen breakdown are by stiffness, contracture, muscle atrophy and myoglobinuria during exercise. In the latter cases, lack of lactate formation under ischemic exercise is a characteristic laboratory finding which was recognized uniformly. A new myopathy due to a block at the level of phosphohexoisomerase was reported first in 1967 by us and administration of fructose showed relief of this symptom over 15 years until present.

Lipid is an important energy source of the skeletal muscle. In 1972 Engel and other reported first lipid storage myopathy due to generalized carnitine deficiency. Later myopathy due to carnitine palmityltransferase deficiency, without accompanying lipid storage, was found. In the former, lipid was stored in type I fibers.

A case of similar lipid storage myopathy was seen in our clinic. A 23-year-old male had a history of muscle weakness and atrophy for the last 8 years, in particular on the lower limbs. Laboratory studies disclosed hypercholesteremia of type II a-b. Muscle biopsy study revealed accumulation of lipid in type I fibers. Carnitine content of biopsied muscle showed decrease by 50% of normal control and triglyceride increased to about 5 times higher than that of control. However, urinary excretion of carnitine and its response to fasting, loading of fatty acid or of ACTH was normal and carnitine deficiency was not proved. Serum analysis of his family disclosed familial hypercholesteremia. The cause of this myopathy and familiar hypercholesteremia relating to this myopathy was unknown.

Myopathies due to disturbance of other energy production were also reported infrequently. The first confirmed was “Hypermetabolic myopathy” or “Luft disease” caused by a block of interconnection between respiration and oxidative phosphorylation in the mitochondria. This metabolic disturbance results in striking hypermetabolism, hyperhidrosis, marked weight loss and muscular weakness. Electronmicroscopic study disclosed an accumulation of abnormal and giant mitochondria in biopsied muscle specimens.

Leigh syndrome is the other variety of metabolic disease due to a block of energy production in brain, muscle and other organs as well. A case of this syndrome, studied in our laboratory, demonstrated marked increase of blood lactate due to a block at pyruvate break down and in pathway of Krebs cycle. Histochemical and electronmicroscopic studies showed remarkable mitochondria accumulation in muscles.

Abnormal accumulation of normal or abnormal mitochondria was occasionally observed in various muscle disorders. Those are megalonconial myopathy, pleoconial myopathy, Kearns-Shy syndrome, periodic paralysis or unclassified myopathies. In most of these cases, the real cause of metabolic disturbances was not clarified.

**STEROID RESPONSIVE, MYASTHENIC NEUROMYOPATHY**

Periodic paralysis, myasthenia gravis or Eaton-Lambert syndrome are functional...
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disorders of muscles. Recent studies brought up the facts that myasthenia gravis is a disease caused by autoimmune reaction by acetylcholine receptor protein at the neuro muscular junction.

Steroid responsive myasthenic neuro-myopathy, a new myosthenia variety, was proposed from our department. Clinical features are easy fatiguability, slowly progressive muscle weakness and atrophy accompanying fasciculation. EMG study showed decrement response to repetitive stimulation to the nerve similar to myasthenia. Serum CPK activity increased to several hundreds units. Histology of biopsied muscle showed both neurogenic and myogenic changes. Administration of anticholineesterase drug improved myasthenic symptoms, and steroid therapy normalized serum CPK level with clinical improvement. These symptoms did not fit to the previous disease entity and this was considered to be a new variety of muscle disorders.

A SYNDROME OF PROGRESSIVE MUSCLE SPASM, ALOPECIA, AND DIARRHEA

This new disease was first reported in 1963 by us and described in 1967 in Archives of Neurology. For the last twenty years, 17 identical cases were collected from various parts of Japan and abroad and a complete paper including clinical, pathological and electrophysiological studies was published recently.

The disease is characterized by painful intermittent muscle spasms of a slowly progressive nature with early onset, endocrine disorders, diarrhea, disturbed carbohydrate metabolism, and occasional association with bony abnormalities with epiphyseal destruction and retardation of growth. Age of onset ranged from 6 to 15 years with a mean of 10. Female was predominant and the ratio of male to female was 1 to 3. In 17 patients, 5 died and the duration of illness was, at present, 9 to 33 years.

Initial symptoms are severe painful muscle cramps of limbs and alopecia. Alopecia totalis was seen by 70% and diarrhea by 30%. Amenorrhea occurred in all female cases and joint deformities associated with growth retardation were seen by 60%. Intermittent muscle cramps usually localized in lower limbs, particularly in the calf and progressed slowly in severity and frequency and spread up to abdomen, and upper limbs. Several years after onset, neck and masseter muscles were affected frequently which may show some difficulty of speaking and chewing. The first two cases died of cerebral sinus thrombosis or iliac vein thrombosis. Autopsy disclosed generalized polypoid elevation of the mucosa throughout the gastrointestinal tract. Pathologic diagnosis was “gastroenterocolitis cystica polyposa” which was not described in the past. Endocrine glands showed simple atrophy. EMG studies during state of this illness suggested that the spasm is originated from the functional disturbance of interneurone such as Renshow cell in the spinal cord and brain stem.

In the early period of observation, this new disease is a specific muscle disorder. However, after follow up over 20 years, autopsy confirmed that this disease is a new variety of malabsorption syndrome, which was not described previously.

REFERENCES


