Hyperinsulinism and Neuromuscular Disorders

A Consideration of the Association of Pancreatic Adenoma with Wasting States

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• *Five cases, one reported herein, have been described in which progressive generalized muscle wasting, muscle fasciculations, increased myotatic irritability, and progressive motor disability were in evidence. In all of these cases, a pancreatic islet cell adenoma was present. In four of them arrest of the symptoms of muscular disease followed upon surgical removal of the islet cell adenoma. In the other case the tumor was not observed until postmortem examination, and in that case there was also histologic evidence of widespread and severe degeneration in the anterior horn cells of the spinal cord.*

The observations give rise to conjecture upon the possibility that endocrine dysfunction plays a part in the genesis of progressive muscular atrophy.

NEUROMUSCULAR DISORDERS belong to a clinical group in which the cardinal signs and symptoms are related to progressive wasting of muscles. As a group these disorders are etiologically vague and pathogenically unspecific. The broader classification of neuromuscular disorders includes those states characterized by some demonstrable alterations in the anterior horn cells, or in their peripheral processes, or by some alteration in structure in the muscle fibers, per se. The term *progressive muscular atrophy*, or the alternative term *progressive spinal (or nuclear) muscular atrophy*, is usually employed to designate that group of muscle-wasting states in which the anterior horn cells are the site of demonstrable alteration (amyotrophy). Phenomena in progressive muscular atrophy, therefore, are progressive wasting of muscles, muscle fasciculations, increased myotatic irritability, electromyographic evidence of fibrillation, and progressive motor weakness, involving chiefly the truncal and appendicular muscles. In the most classical form of this disorder there is an inevitable progression of the wasting of muscles to the point of almost complete motor disability, bedridden status, and death.

Since knowledge of this disorder, as of other progressive muscle-wasting states, is meager, every clue as to etiologic or pathogenic factors seems worthy of pursuit. No clue has as yet been obtained, for example, as to the character of any toxic, viral, chemical, genetic, metabolic, or deficiency factors which presumably might be causative. Recently, however, implication that disordered endocrine function plays a part in progressive muscle-wasting states has become increasingly impressive as more and more clinical observations have been recorded.[2-6]

There seems sufficient reason, therefore, for reporting here in brief the study of a case of progressive muscle wasting in which an endocrine factor seemed responsible. In this case, there was a generalized progressive wasting of muscle, muscle fasciculations, electromyographic evidence of muscle fibrillation, increased myotatic irritability, and progressive motor disability. Perhaps of greater importance is that this presumably inexorable progression of muscle atrophy was arrested following the surgical removal of a tumor of the pancreas, histologically confirmed as an islet cell adenoma.

It is noteworthy that the literature contains reports of four other cases of this kind, all published since 1946. In three of the previously reported cases, removal of a pancreatic adenoma brought about an arrest of the signs relating to progressive wasting of muscles; and in the fourth case, in which a pancreatic adenoma was not discovered until autopsy, there was microscopic evidence of an associated severe and widespread degeneration of anterior horn cells of the spinal cord (amyotrophy).

REVIEW OF LITERATURE

Silfverskiold in 1946[5] reported upon two male patients, one 17 years and the other 34 years of age, who had progressive generalized wasting of muscles, muscle fasciculation, electromyographic evidence of fibrillation, increased myotatic irritability, and progressive motor disability associated with a pancreatic adenoma. In each case the progression of clinical signs was arrested by surgical removal of

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the tumor, histologically verified as an adenoma of islet cell type.

Lidz and co-workers[2] in 1949 reported the case of a 23-year-old man in whom there was arrest in the signs and symptoms of progressive wasting of muscles, muscle fasciculations, increased myotatic irritability, and progressive motor disability after a pancreatic islet cell tumor was removed. There were no sensory abnormalities noted and no other neurologic abnormalities.

Tom and Richardson[7] reported a case in which at postmortem examination of a 33-year-old woman who had had progressive generalized muscle wasting, not only was an islet cell tumor found, but severe and widespread degeneration of the ventral horn cells of the spinal cord (amyotrophy) was observed histologically.

REPORT OF A CASE

A 42-year-old white man, a salesman, was first observed in November 1950 with complaint of progressive weakness and wasting of the muscles and of a "quivering" feeling in the muscles for about one month. During the preceding week the patient had noted especial difficulties in climbing stairs, in walking more than a short distance, and in buttoning a shirt, holding a pencil, using a knife and fork. In the previous few days he had begun to note that his feet tended to "slap" after he had walked any considerable distance.

Upon inquiry the patient said that for the previous year he had been noting increasingly frequent transient attacks of weakness, associated with tremulousness, mild disorientation and confusion, "blurring" of vision and diplopia, most often on awakening in the morning or just before breakfast. He had found that taking food relieved the attacks, and eventually he drank sweetened orange juice for amelioration of symptoms. Several months after the onset of these attacks he consulted a physician who made a diagnosis of hyperinsulinism. At that time the content of sugar in the blood, repeatedly determined, was subnormal (30 to 40 mg. per 100 cc.). Pancreatic adenoma was suspected and laparotomy was carried out. The suspicion was not confirmed but approximately two-thirds of the tail of the pancreas was resected. The previously described attacks continued and within a month after the operation the patient noted the signs and symptoms of progressive muscle wasting.

At the time of examination by the author, approximately one month later, there was diffuse atrophy of moderate degree of the appendicular and truncal musculature, generalized muscle fasciculation, increased myotatic irritability, and electromyographic evidence of fibrillation. Walking was difficult and of the "steppage" type. Hand grasps were weak. Rising to a sitting or standing position was difficult. All deep reflexes were intact and hyperactive, except the Achilles reflexes, which were diminished. No sensory abnormalities were noted. All other neurologic findings were within normal limits.

During the next few weeks the patient continued to have transient early morning attacks associated with hypoglycemia (the sugar content of the blood was 6 mg., 15 mg. and 18 mg. per 100 cc. on three occasions). Muscle wasting and muscle fasciculation continued and motor disability increased. Surgical consultants concurred in a diagnosis of hyperinsulinism and recommended reexploration for possible pancreatic adenoma. In February 1951, four months after the onset of progressive muscle wasting, a pancreatic adenoma 2 cm. in diameter was removed from the inferoposterior surface of the head of the pancreas. It was histologically identified as an islet cell tumor.

No further early morning attacks or hypoglycemia were noted, and muscle wasting and motor disability were arrested. In the course of several weeks, with the aid of physiotherapy, the patient regained considerable motor capacity. Seven months after removal of the pancreatic adenoma, he was able to grasp a pencil, to write, to button his shirt, and to walk approximately a mile without tiring. He had regained nine pounds of weight lost during the illness.

DISCUSSION

The pathogenesis of the clinical entity commonly referred to as "progressive muscular atrophy" remains obscure. Duchenne (in 1848) and Aran (in 1850) expressed belief that the disease is of muscular (myogenic) rather than of neural (neurogenic) origin. In 1853 Cruveilhier reported that in such cases he had noted a slimness of the anterior roots of the spinal cord, and thus attention was focused on the possibility that progressive muscular atrophy was neurogenic; and in 1860 Luys reported that degenerative changes were observed in the anterior horns of the spinal cord at postmortem study of patients who had the disease. Within the next decade or two the work of Leyden (1876), Landouzy (1885), Dejerine (1885), and Erb (1891), served to bring about a clear distinction between progressive muscle atrophy related to anterior horn cell alteration (neurogenic) and muscle dystrophy associated with alterations in the muscle fibers, per se (myogenic). Since that time, although anterior horn cell alteration is a sine qua non of progressive muscular atrophy, the cause of anterior horn cell dissolution remains obscure.

It is well to consider, therefore, the possibility that disordered endocrine function plays a part in the disease clinically characterized by progressive wasting of muscles, muscle fasciculations, electromyographic evidence of fibrillation, increased myotatic irritability, and progressive motor disability.

The clinical features in all of the five cases reviewed herein were identical. In all of them the symptoms were associated with the existence of a pancreatic islet cell tumor.

The evidence is strong in support of a hypothesis that at least in some cases of progressive muscular atrophy, abnormality of endocrine function may bring about the sine qua non of this disorder—anterior horn cell dissolution (amyotrophy). And it gives rise to conjecture that either in the islet cells or in some remote endocrine gland (such as anterior pituitary, thyroid or adrenals) there might be sufficient hormonal imbalance or altered hormonal function to result ultimately in anterior horn cell dissolution. The well known hormonal antagonisms which exist between the islet cell hormone (or hormones) and those of the anterior pituitary (Houssay[1]) and

the physiologic interdependence of these and other hormone-producing organs needs no emphasis. As to the five cases reviewed here, there can be little doubt of endocrinic pathogenesis; in all of them the clinical features conformed to those of "progressive muscular atrophy" except that the progress was arrested by removal of an islet cell tumor. Further study is needed to determine to what extent pituitary-islet cell, pituitary-adrenal-gonadal, or pituitary-thyroidal, or other endocrine system dysfunctioning is of etiologic significance in progressive muscle-wasting states (amyotrophy).

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REFERENCES

1. Houssay, B. A., Biasotti, A., et al.: The hypophysis, carbohydrate metabolism, and diabetes, Endocrin., 15:511, 1931.

2. Lidz, T., Miller, J. M., Padger, P., and Stedem, A. F. A.: Muscular atrophy and pseudologica fantastica associated with islet adenoma of the pancreas, Arch. Neur. and Psych., 62:304-313, 1949.

3. Moersch, F. P., and Kernahan, J. W.: Hypoglycemia, neurologic and neuropathologic studies, Arch. Neur. and Psych., 39:242-257, 1938.

4. Shy, G. M., and McEachern, D.: Clinical features and response to cortisone of menopausal muscular dystrophy, J. Neurol., Neurosurg., and Psychiat., 14:101, 1951.

5. Silfverskiold, B. P.: Polyneuritis hypoglycemica; late peripheral paresis after hypoglycemic attacks in two insuloma patients, Acta Medica Scandinavica, 125, fasc. V, 1946.

6. Thorn, G. W., and Eder, H. A.: Studies on chronic thyrotoxic myopathy, Amer. J. of Med., 1:583-601, Dec. 1946.

7. Tom, M. I., and Richardson, J. C.: Hypoglycemia from islet cell tumor of pancreas with amyotrophy and cerebrospinal nerve cell changes, J. of Neuropath. and Exp. Neurol., 10:57-66, Jan. 1951.