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Myasthenia Gravis and Internal Secretion.

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Three cases of myasthenia gravis have come under my observation, one of which strongly resembles *Chvostek's* case hereinafter referred to. I should like to report the outcome of my studies on this case as a contribution to the study of the disease.

I. Literature.

Great as has been the increase in our knowledge of myasthenia gravis since the beginning of the present century, it is undeniable that the pathogenesis of the disease is still far from clear; the theories of this disease may be classified into (I) nervous, (II) muscular, and (III) secretory.

I) Nervous theory. The hypothesis of myasthenia gravis being a nervous disease has led many neurologists to the very careful study of a possible organic lesion in the nervous system; but the pathological examination of the nervous system has given a negative result in the vast majority of cases. In consequence the nervous theory now seems to have been generally abandoned.

II) Muscular theory. Recently in a large number of cases lymphoid infiltrations in voluntary muscles have been found, but as

it is not yet clear whether this muscular change is primary or secondary the muscular theory is not recognized as authoritative.

III) Secretory theory. In a number of cases which have occurred during recent years attention has been drawn to the existence of changes in endocrine organs. Let me here record the cases in the literature of the subject in which the autopsical or clinical findings indicate disorders of internal secretion: *Oppenheim* was the first to report a lesion of the thymus in this disease. Since then twenty-three cases have been reported in which some abnormality of the thymus was found at autopsy: Tumour of the thymus; *Oppenheim-Hansemann* 1899, *Laquer-Weigert* 1901, *Hun*, *Bloomer* and *Streeter* 1904. Persistence of the thymus; *Hödlmoser* 1902, *Link* 1902, *Burr* 1904, *Grüner* 1905, *Dupre* and *Paniez* 1905, *Buzzard* 1905 (2 cases), *Booth* 1908, *Wiener* 1908, *Laignel*, *Lavastine* and *Boudon* 1909, *Nazari* 1910, *Oderý Symes* 1911, *Acker* 1911, *Taylor* 1911, *Schumacher* and *Roth* 1912, *Hart* 1915 (2 cases), *K. Miura* 1918 (3 cases).

In myasthenia gravis marked change of endocrine organs is generally rare. Several cases have been reported in which lymphoid infiltration of the adrenal and thyroid glands have been found at autopsy, resembling in all respects that of the muscles, liver and other organs.

Clinically the combination of myasthenia gravis with symptoms of a lesion of the thyroid gland is not rare and may be classified as follows: A) Cases in which symptoms of Graves's disease supervened in the course of myasthenia gravis. (*Oppenheim* 1888, *Charcot* and *Marinesco* 1895, *Murri* 1895, *Finizio* 1898, *Remak* 1899, *Punton* 1899, *Brissaud* and *Bauer* 1904, *Loeser* 1904, *Rennie* 1908, *Meyerstein* 1911. B) Cases in which symptoms of myasthenia gravis supervened in the course of Graves's disease. (*Waraer* 1883, *Bristowe* 1885, *Jendrassik* 1886, *Ballet* 1888, *Seeligmüller* 1889, *Rothman* 1893, *Marina* 1896, *Bernhard* 1908, *Stern* 1914.) *Sattler*, *Salmon*, *Marina*, *Lorenzi* and others have reported many cases of Graves's disease with functional (myasthenic) ophthalmoplegia. C) Cases in which

symptoms of both diseases came alternately. (*Goldflam* 1893, *Kalischer* 1895, *Loeser* 1904, *Meyerstein* 1904, *Schumacher* and *Roth* 1912, *Tobias* 1912, *Csiký* 1914.) D) Cases in which symptoms of myxo-oedema appeared in the course of myasthenia gravis. (*Chvostek* 1908, *Markeloff* 1912.)

In myasthenia gravis the bronzing and pigmentation of the skin, symptoms of lesion of the adrenal gland, are described by *Raymond-Le-jonne* 1906, *Claud-Vincent* 1908, *Sitzen* 1909, *Stern* 1914, and *Bookman-Epstein* 1916.

Lundborg, *Chvostek* and others attribute myasthenia gravis to the hyperfunction or dysfunction of the parathyroid glands, whereas they assume that the cause of tetany is to be found in the hypofunction of these glands. Against this hypothesis, atrophic findings of the glands (*Haberfeld* 1911) and tetany attacks (*Tobias* 1912, *Stern* 1914) in this disease have been described.

Reports of changes in the sexual glands (*Dreschfeld* 1893, *Oppenheim* 1897, *Curschmann* and *Hedinger* 1907), and of the pituitary body (*Tilney* 1907) in this disease are, even to date, few.

In the next place are to be mentioned experiments on the connection between internal secretion and the fatigue of voluntary muscles. *Mosso* (1898) administered thyroid material to two hospital patients who had been taught to use the ergograph, and believed that he secured evidence leading to the conclusion that their muscular power was increased. It is well known that in dogs, muscular weakness and increased skin pigmentation follow adrenal extirpation. *Rogers*, *Coombs* and *Rahe* (1918) report that the intravenous injection of the non-coagulable portion of alkaline saline extract of the thyroid, parathyroid and adrenal glands of the cat increased the vigor of contraction of fatigued voluntary muscles. In myasthenia gravis the glandular extracts (thyroid, adrenal and thymus) have been tried without appreciable results. However, in contrast to these reports, in *Chvostek's* case and in the case described below (both of which had symptoms of hypofunction of the sympathetic endocrine organs) the myasthenic symptoms were markedly diminished by the

administration of the thyroid material.

II. The Author's Case.

T. M., a Japanese woman of no occupation, aged 36, was admitted to the Second Medical Clinic of the University Hospital at Fukuoka on September 13, 1917, with the diagnosis of myasthenia gravis.

Family history. Grandparents died of old age. Father used to drink one go (ca one-fifth litre) of sake (Japanese alcoholic drink) every evening and died of pleurisy at 49 years of age. The mother was alive and in good health. Four sisters and two brothers were alive and well. No history was obtained of any hereditary or nervous disease in the family.

Previous history and habits. Although not robust, she was fairly well till 1899 when she was 18 years of age. Since then she had been troubled from time to time by epigastric pain and headache. Menstruation started at 18 and had since been irregular. She married at 18 but had never been pregnant. She was divorced at 22 and since then had remained single.

Present illness. In April, 1916, at 35 years of age, she noted a feeling of heaviness in the legs which gradually became habitual, and she frequently had to stop and rest for a few minutes during a walk. After July, 1916, both arms and hands frequently became fatigued, but she was able to regain use of them after a few minutes of rest. The condition of the limbs varied markedly: at times she could walk a few miles without resting; at times she was unable to walk more than a few yards without resting, and her arms were sometimes so weak and easily fatigued that she could not hold a plate in her hand for even a few minutes.

After December, 1916, it became difficult for her to read small print continuously. In August, 1917, she fell down a stairway about six feet in height and was struck on the loin and left shoulder so badly that the skin was abraded and slight bleeding ensued. A week later she noted the drooping of both eyelids and inability to raise them at will. This condition persisted. After September she

began to feel weakness in her lips and tongue and to speak through the nose. The voice would become feeble after a short conversation. She noted difficulty in masticating and swallowing which became more and more marked toward the end of the meal. From that time till admission to the clinic there had been no important change in the myasthenic condition.

Patient reported herself free from syphilis and gonorrhoea. She neither drank nor smoked. Her appetite was good. She slept rather lightly and was easily disturbed during the night. She had no aches nor complaints except headache.

Physical Examination. (September 13, 1917) Height 148 cm; weight 40.1 kg. Normally nourished. Muscles normally developed. Skin soft, elastic and of normal color except on the face where it appeared paler than normal. The face was somewhat expressionless owing to weakness of facial muscles. Pulse seventy-eight. Temperature 36.2°C. Intelligent and sensitive. No sign of degeneration.

Neurologic Examination.

Muscular System. All facial muscles feeble. Patient could close both eyes but could not screw them up tightly. Could not whistle. Persistent double ptosis. All muscular movements were fully performed at first, but the muscles soon became partially exhausted. No strabismus nor diplopia. There was sufficient power for opening and closing the jaws normally at first, but this became exhausted after eighteen repetitions. The palate moved well on phonation and in response to stimulation, both sides being raised equally. Movements of the tongue were good but power was easily exhausted. The swallowing muscles tired during the act of eating. Speech was normal at first, but after four minutes became laboured and indistinct, and the voice became nasal in character.

The Neck. When sitting up the head gradually fell forward.

Upper Extremities. All movements of both upper extremities were feeble, right and left being nearly equal, dynamometer grasp both 5 (average Japanese adult male, right 35, left 30). She could raise her arms above her head but could not maintain them in that

position for more than forty seconds. They fell gradually as though heavy weights were attached to them. After three minutes of rest she was able to repeat the movement.

Trunk. She could rise without the use of the hands, but could not do so after ten repetitions. The abdominal muscle could be felt to contract firmly. The chest expanded less and less with each successive forced breathing.

Lower Extremities. All movements of the lower extremities were well performed, and their power was in general higher than that of the muscles of the upper extremities; right and left nearly equal. The gait was natural at first, but after walking a little distance it became slower and waddling in character. After walking twenty yards she could walk no more.

Muscular tone normal; no muscular atrophy. No fibrillary twitchings. Coordination of the upper and lower extremities normal. Romberg's sign absent.

Electrical reaction. (September 14, 1917) Myasthenic reaction was more or less markedly present in many muscles. Faradic and galvanic irritability of nerves and muscles almost normal; electrical reaction of degeneration absent.

Sensory system. Vision good and the optic discs and fundi normal. Smell, taste and hearing perfect. Skin sensitivity normal.

Reflexes. Pupils equal and reacted briskly to light and accommodation. All tendon reflexes slightly increased. Skin reflexes nearly normal. Babinsky reflex and ankle clonus absent.

Vasomotor and trophic system. No vasomotric or trophic changes discovered.

Sphincters. Sphincters functioned normally.

Cranium and spinal column. No abnormality.

Circulatory, Respiratory, Digestive and Urinary Systems. Examination of these organs revealed nothing pathological. No evidence of glandular enlargement in the neck or elsewhere. Examination of urine and stool negative.

Cerebrospinal fluid. (September 15, 1917) Examination gave

negative results. Wassermann test of fluid negative.

Blood. (September 16, 1917) Wasserman blood test negative. Haemoglobin 43 % (Sahli); leucocytes 9600; red blood corpuscles 4,600,000; polymorphonuclears 75 %; small lymphocytes 18.2 %; basophils 0.6 %; eosinophils 1.6 %; large mononuclears 3 %; transitionals 1.6 %.

Gastric juice. (September 17, 1917) Acid. Günzburg's test positive. No other pathological change.

Sugar tolerance. (September 22, 1917) 100 g was given; after two hours a trace of sugar appeared in the urine.

Roentgen-ray examination. (October 9, 1917) Roentgen-ray examination of chest and stomach revealed no abnormalities.

Roentgenographic examination of the cranium. (October 9, 1917) No abnormalities.

Clinical course. Throughout the course there were many variations in the myasthenic condition: (1) as a monthly routine, becoming worse at the premenstrual and menstrual periods (beginning July, 1917) and improving after the periods: (2) as a daily routine, becoming worse towards evening, and improving after a night's sleep; (3) as incidental variations, improving transiently, for a few hours or for a few days.

September 13, 1919. Patient's condition somewhat worse than when admitted. During the past two years myasthenic reaction has been present, more or less markedly, in many muscles; all reflexes have remained unchanged; weight has varied between 38.2 and 45 kg; temperature has risen daily to 37.2°C or higher, and the patient has been troubled from time to time by headache or epigastric pain. Medically, bromide, arsenic and calcium preparations have been given for a long time without benefit.

December 16, 1919. Since October she has become gradually weaker. She has marked ptosis which becomes worse in the evening than in the morning. There are practically no vertical or outward movements of the eyeballs, and inward movements are very limited. Pupils react well. Chewing food causes rapid exhaustion of the jaw

muscles. All facial movements are very feeble. She can not fully close the eyes, nor whistle. The face is expressionless. In smiling the mouth is merely elongated and its angles slightly raised. The muscles are not wasted. Fluids tend to run down from the corners of the mouth and solid food collects between the teeth and cheeks. Flowing out of fluid through the nostrils takes place occasionally. Swallowing of solids is at times very difficult. Power of articulation and phonation easily exhausted. Repeated movements of the tongue quickly cause tongue-tire. She can not extend the upper extremities in front of her more than twenty seconds. Dynamometer grasp, right 4, left 3. Respiration chiefly diaphragmatic; thoracic movements feeble. No special weakness of abdominal or spinal muscles observed. All movements of lower extremities very feeble. She can not walk more than three yards without assistance. Myasthenic reaction is markedly present in many muscles.

February 27, 1920. Since the beginning of January she has become gradually weaker. Marked ptosis of both eyelids and inability to raise them, even immediately after a night's sleep. There are practically no movements of the eyeballs. The face is very expressionless. The lower jaw sags. Phonation is very feeble with a marked nasal quality. Masticating and swallowing have become very difficult. Since the end of last year she has been fed only by a stomach tube. She can not extend the upper extremities in front of her for more than a few seconds. Dynamometer grasp, right 2, left 2. For the last forty days she has had to remain in bed and is hardly able to raise herself. She can walk no longer even with assistance.

March 1, 1920. She is lying on her back with jaw sagged. Since the myasthenic condition has become markedly worse she has become vagotonic, accompanied by hypoglycemia. (Cf. "Examinations" I and II.)

March 5, 1920. To-day the administration of thyroid tablet is started. The myasthenic condition has remained the same although she has lost much of her weight.

March 15, 1920. Since the beginning of the thyroid treatment the myasthenic condition has remained unchanged, but it is much improved to-day. Moderate ptosis, upward movement of eyeballs defective, both external recti weak, both internal recti moving well, jaw muscles easily tired, facial weakness markedly present, tongue moving freely but easily exhausted. Arms and legs weak. Dynamometer grasp, right 9, left 8. She can stand up and walk, but cannot walk more than twenty yards without resting. She has much difficulty in dressing herself.

March 17, 1920. Ptosis is present only slightly and even in the evening not so marked.

March 18, 1920. To-day, as she has become able to eat food with ease, feeding by the stomachtube is given up.

March 26, 1920. It is especially noticeable that there has been no change in the myasthenic condition at the premenstrual and menstrual periods this month.

March 27, 1920. She can walk very well and can dress herself easily. The vagotonic symptoms have disappeared.

April 10, 1920. The myasthenic condition has gradually become improved. Ptosis very slight. External movement of eyeballs weak, other movements good. She can close the jaws firmly. Speech is distinct, but somewhat nasal. Movements of facial muscles can be made at command but power to continue easily exhausted. The tongue can be protruded through the lips but not many times in succession. All movements of arms and legs are carried out vigorously. Dynamometer grasp, right 14, left 13. She can walk a mile without resting. The gait is natural but slow.

April 28, 1920. Patient's condition has remained much the same. Under thyroid tablet so much improvement was made that in five weeks she felt almost well. Improvement began ten days after the thyroid treatment began and continued for at least seven weeks.

April 29, 1920. She catches cold.

May 5, 1920. Stomach washed out by means of a stomachtube.

May 7, 1920. Since using the stomachtube swallowing has become very difficult and phonation feeble; myasthenic symptoms have somewhat increased.

May 23, 1920. Symptoms of pneumonia appeared to-day.

May 25, 1920. Respiration very short and stertorous. She died of pneumonia at 10 a. m.

Examinations.

(I) while the case was under clinical treatment pharmacodynamic and physical examinations of the nervous system were repeatedly made. The results are summarized in Table I.

Table I. Pharmacodynamic and Physical Examinations of the Vegetative Nervous System.

	Atropin- test	Pilo- carpin- test	Adren- alin- test	Thyroid- tablet- test	Oculo- cardial Reflex	Respira- tory Arrhy- thmia	Dermo- graphia
Sept.-Dec. 1917	Non- sensitive	Very Sensitive	Non- sensitive	Non- sensitive	(++)	(-)	(-)
During 1918	"	"	"	"	(++)	(-)	(-)
During 1919	"	"	"	"	(++)	(-)	(-)
Jan.-Feb. 1920	"	"	"	"	(++)	(+)	(-)

As will be seen, a state of so-called "vagotonia" took place gradually and continued unmistakably after the myasthenic condition had become very much worse. Such a severe vagotonia is reported to take place usually in sympathetic endocrine diseases like myxoedema and Addison's disease. (Higier 1919, and others.)

(II) Quantitative determination of the blood sugar was made repeatedly by Bang's method.

Table II. Blood Sugar Percentage.

17/ 9/1919	0.078 %
29/ 9/1919	0.052 %
6/10/1919	0.052 %
6/12/1919	0.056 %
25/ 1/1920	0.052 %

It was found that a moderate hypoglycemia was present in this case. Hypoglycemia has been observed in connection with the following: Addison's disease (Porges 1909—1910, Bernstein 1911 and others), adrenalectomy (Bierry and Malloizal 1908, Mayer 1908), dyspituitarism (Cushing 1910), thyroidectomy and parathyroidectomy (Janney 1907 and others). Besides the above, heavy muscular activity, diphtheria toxin (Rosenthal 1914) and phosphorus poisoning (Frank and Isaacs 1910—1911) produced a temporary hypoglycemia, accompanied by profound asthenia. In phosphorus poisoning and diphtheria toxemia the parallel, between severity of muscular weakness and decrease in blood sugar was very marked. In addition to this in a successfully treated case of Addison's disease a parallel between increase in strength and rise in blood sugar was observed. (Grote 1914)

(III) During the thyroid treatment the myasthenic reaction was repeatedly proved. The results are as follows:

Table III. Myasthenic Reaction of Muscles during the Thyroid Treatment.

Administration of thyroid tablet through the mouth.		L. Sternomastoid	L. Trapezius	L. Deltoideus	L. Biceps brach.	L. Triceps brach.	L. Quadriceps fem.	L. Gastrocnemius
5/3/1920	Treatment started	30	14	15	15	20	11	13
15/3/1920		50	32	70	42	46	43	52
18/3/1920	daily 0.13 g	58	46	48	38	44	46	29
25/3/1920		/	/	/	/	/	/	/
26/3/1920		120	110	110	96	98	48	72
10/4/1920	daily 0.065 g	115	120	114	92	98	72	59
24/4/1920		98	72	68	90	48	77	60
25/4/1920	daily 0.088 g	77	62	59	72	70	60	52
30/4/1920		82	93	79	48	49	67	68
1/5/1920	daily 0.065 g	/	/	/	/	/	/	/
17/5/1920	Treatment ended	/	/	/	/	/	/	/

Autopsy. The autopsy was performed in the pathological Institute, twenty-seven hours after death by K. Ono, M. D. The main

pathological diagnoses were :

- 1) Tracheobronchitis catarrhalis acuta.
- 2) Persistentia thymi.
- 3) Intumescencia lymphoglandularum gradis levioris.
- 4) Hyperaemia venosa organorum.
- 5) Pleuritis fibrosa dextra.

The description was briefly as follows: Rigor mortis is present. The body is normally nourished. Neither the brain nor the spinal cord shows any change to the naked eye. The pituitary body and pineal gland seem normal. Behind the manubrium lies a large thymus. The weight of the thymus is 20 g and its consistency is firm throughout. The thyroid gland appears to be natural in size, shape and consistency; the left lobe weighs 11g and the right 10 g. Pancreas, spleen, liver and kidney seem healthy, except for the presence of the venous hyperemia. The heart is natural. The left pleural cavity is free from adhesions, but there are fibrous adhesions at the posterior portion of the right lung. The lungs are hyperemic throughout and the bronchial mucous membrane is covered with mucous substance and is hyperemic. The right ovary is cystic. The bronchial and mesenterial lymph nodes are moderately enlarged. The size of each endocrine organ is as follows:

Table IV

(Organ)	(Length)	(Breadth)	(Thickness)
Pituitary body	14.0 mm	6.5 mm	4.0 mm
Pineal gland	7.5 "	4.0 "	1.5 "
Thymus	160.0 "	42.0 "	7.0 "
Thyroid gland, left	39.0 "	18.0 "	12.0 "
Thyroid gland, right	40.0 "	22.0 "	17.0 "
Upper parathyroid, left	9.5 "	3.4 "	2.0 "
Upper parathyroid, right	7.5 "	4.0 "	2.0 "
Lower parathyroid, left	5.0 "	2.5 "	1.5 "
Lower parathyroid, right	6.0 "	3.0 "	2.2 "
Adrenal gland, left	65.0 "	38.0 "	5.0 "
Adrenal gland, right	55.0 "	34.0 "	5.0 "

Microscopical.

Central nervous system. The Weigert, Mallory, Marchi and haematoxylin-eosin methods were employed for the purpose of examining sections from the motor cortex, pons, medulla and spinal cord, but the results in all cases were negative so far as the discovery of any pathological changes is concerned.

Peripheral nerves. Sections from ulnar and sciatic nerves were stained by the Weigert method, but these presented no evidence of pathological change.

Voluntary muscles. Portions of the internal rectus, levator palpebrae superior, deltoid, biceps brachii, brachioradialis, biceps femoris, vastus internus and triceps muscles were examined microscopically after embedding in celloidin. Most of the sections were stained by haematoxylin and eosin, but a few were stained by the van Gieson method. In the sections of these muscles only a very few lymphoid infiltrations were found and these were all of small size. There was no marked increase of nuclei nor proliferation of connective tissues.

Liver. Sections of this organ showed a few lymphoid infiltrations. In other respects the sections appeared healthy.

Adrenal glands. Histologically the organs were healthy looking, except for the presence of lymphoid infiltrations, which were numerous. They were found in the medullary part, in the cortex and in the loose connective tissue of the capsule.

Parathyroid glands. Besides the ordinary cells there were one or two groups of larger eosinophil cells (Welch) in the sections of each parathyroid gland. In other respects the sections appeared healthy.

Thymus. The gland presented a normal appearance under a low power, and there was no evidence of fibrosis. The cortex and medulla were clearly differentiated, and the cellular constituents were of normal structure.

Pancreas, kidneys, spleen, thyroid gland and pituitary body were all healthy as regards their histological appearance, except for the

presence of venous hyperemia.

Pineal gland. Microscopic examination of this organ revealed no abnormal features.

The points of interest in this case may be briefly summarized as follows:

Clinical.

- 1) A characteristic case of myasthenia gravis.
- 2) A condition of vagstonia accompanied by hypoglycemia after the myasthenic symptoms had become manifest.
- 3) Thyroid treatment given because of the probability of a sympathetic endocrine disorder. This probability was indicated by the two facts: 1. Vagatonia and hypoglycemia usually occur in sympathetic endocrine disorders; 2. Experiments by Frank and Grote indicate that hypoglycemia has a close connection with muscular weakness.
- 4) Myasthenic symptoms markedly diminished under the thyroid treatment.

Pathological.

- 1) Lymphoid infiltration present in muscles, liver and especially in the adrenal glands. These findings are similar to those of Buzzard (five cases, 1905), and of Vieuderowitch (1909).
- 2) A few groups of larger eosinophil cells present in the parathyroid glands.
- 3) Persistence of the thymus.

III Conclusions.

The conclusions to be drawn from the literature of the subject and from the author's investigations may be briefly summarized as follows:

- 1) In myasthenia gravis clinical and pathological findings (though these are neither regular nor constant), which are the result of endocrine disorders, have often been obtained during the last twenty years; and in the case under review also these findings were obtained.

2) It was established experimentally that certain preparations of the thyroid, parathyroid and adrenal glands increase the vigor of contraction of fatigued voluntary muscles. Clinically, by the administration of thyroid preparation the characteristic symptoms of myasthenia gravis were markedly diminished in *Chvostek's* case and in that under review.

3) The characteristic symptoms of myasthenia gravis have, therefore, a close connection with some endocrine disorder.

In closing, I desire to express my hearty thanks to Prof. *Hiroshi Takeya*, for his permission to undertake the study of this case, and for his very helpful interest in it.

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