Short Notes and Clinical Cases.

A CASE OF MYASTHENIA GRAVIS.

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THE comparative rarity and etiological obscurity of myasthenia gravis must be my excuse for reporting the following case, which presented certain unusual features, though circumstances prevented a complete examination being made.

The general aspects of the disease as originally described by Sir Samuel Wilks in 1877¹ are too well known to require detailed reference here, and a very complete summary of cases (up to 1908) will be found in the Guy's Hospital Reports for that year by Morton Palmer,² but reference may be made to certain clinical and pathological features which from time to time have been added to Wilks' original description. The most important of these is that of Buzzard,³ who first described the peculiar collections of lymphocytes which are found in the skeletal muscles, as well as in the internal organs, liver, lungs, spleen and kidneys, and to which he gave the name 'lymphorrhages.' Oppenheim next reported an enlargement of the thymus gland in this disease, and since his communication a large number of other observers have corroborated this. Mandelbaum and Celler⁴ consider that new growth of the thymus is a probable pathogenic factor at any rate in a large number of cases, and Symonds⁵ has recently reported a case with an "enormously enlarged thymus which lay upon the pericardium and looked much the same size and shape as the heart." On section this was found to be largely a solid growth with enclosed cysts, and histologically "to consist of densely packed lymphoid tissue."

This enlargement of the thymus, however, only occurs in some 25 per cent. of cases, and therefore cannot be of fundamental etiological significance, though any theory as to the nature of the disease must explain this pathological fact.

Certain changes in tissue metabolism have still more recently been described in connection with myasthenia gravis, notably the diminution in creatinin excretion which is found to occur. Spriggs⁶ and Pemberton⁷ both give analyses of the urine with low creatinin values, and the latter also states that the calcium output is likewise diminished. Bookman

and Epstein⁸ investigated a case from the metabolic point of view, and found that except for creatinin "there was no striking variation from the normal in any of the constituents studied during the experiments."

The association of myasthenia gravis with Graves' disease has been noted by several observers, and Stern⁹ cites a number of cases collected from the literature, together with one of his own, in which there were also bronzing of the skin and tetanoid convulsions of the fingers. Chvostek¹⁰ has suggested that myasthenia gravis may be due to altered parathyroid function, but there seems little evidence to support this, and the occurrence of bronzing, suggesting a possible adrenal lesion, offers a more likely field for investigation, since the loss of adrenal secretion is certainly intimately connected with asthenia.

However, the underlying cause of this condition is still undetermined, though there seems to be a moderate consensus of opinion that in all probability it is due to some kind of chronic infection or intoxication, and it may be that such toxin at times throws out of gear one or other of the endocrine glands, thus producing a varying clinical picture.

Case.—Seen in Ophthalmic wards, Sheffield Royal Hospital, February 26, 1923, with the following notes :—

A. H., aged sixty, married. Left eye operated on in London before the war (condition unspecified). Summer, 1922, noticed that strong light hurt the right eye. November, 1922, right eye became inflamed, and has been 'operated on' three times since then. Admitted January 12, 1923, complaining of severe pain in right side of head and face and right eye. There is deep conjunctival and ciliary injection of right eye, but cornea is clear.

Local and general treatment failed to improve the condition, and an examination of the nasal and accessory sinuses was carried out with a view to ascertaining whether any septic focus lay therein, but nothing abnormal was detected.

February 13. Local inflammation has subsided; there is no injection, but patient complains of pain in the right side of the neck where there is now a large glandular swelling.

There is no pyrexia, and no evidence of inflammation in mouth or throat.

February 26. 'Nct improving.'

February 28. She was admitted to the general medical wards, and the following is an abstract of her case sheets :—

Thin elderly patient, lies in bed with her eyes shut and her head wrapped in a large woollen muffler on account of 'neuralgia'; she keeps up an intermittent querulous complaint in a low whining monotone which is difficult to understand owing to her defective articulation; the lips hardly move at all.

She complains of severe pains in the head on the right side, and also of pain in the right eye and over the right side of the face.

She lies flat in bed with the limbs extended, and her musculature is wasted and flabby. She cannot turn in bed or move a limb except slowly and with great difficulty. There is no paralysis and no tremor.

Both eyes are closed though she can open them to command, but the lids almost immediately again begin to drop.

Her mental state appears to be a kind of semi-somnolence; she will answer questions in a sleepy, monotonous voice, but has apparent difficulty in recalling events. There is no delayed cerebration, e.g., if asked to put out the tongue the act will be begun in normal time, but its completion is extremely delayed. There is a slight facial asymmetry, the right side appearing 'drawn,' suggesting slight spasm of this side or paresis of the other. Besides this asymmetry there is a complete absence of expression, and no emotional change can be evoked; the pain of a sudden pin-prick merely accentuates the querulous moaning without the participation of any facial muscle.

Eyes.—The eyes present the result of previous inflammation, old and recent. There is an arcus senilis present in each eye but not complete. The pupils are inactive to light and unequal, the right being smaller than the left. Accommodation cannot be compassed. Conjunctivitis is present in the right eye.

Neck.—Multiple scars of old operations for removal of glands. Cervical glands on both sides are swollen and tender.

Limbs.—The upper limbs are thin and wasted, but the skin appears healthy. Motor power is fair, but the actions are carried out slowly. Sensation is quite normal.

Tendon jerks are all elicited in what appears normal time, and, if anything, they seem rather increased.

The lower limbs present a similar wasted appearance, but the motor power is not so good as in the upper, slight resistance sufficing to prevent any voluntary movement, though sensation is unimpaired and the tendon reflexes are all present, and, as in the upper limbs, seem to be rather brisker than normal.

The plantar reflex is flexor in type. (On the inner side of the right knee there is a hard swelling which is apparently due to enlargement of the internal condyle.)

Abdomen.—The movements of the anterior abdominal wall during respiration are normal, motor power is fair, and sensation unaffected. Abdominal superficial reflexes cannot be elicited. There is no palpable abnormality.

Chest.—The chest is pigeon-breasted, and there are several pigmented warts present. There is very marked wasting of muscles of the left shoulder (deltoid, supra- and infra-spinatus).

On percussion there is a very definite area of dulness over the front of the chest from the level of the third rib above to the lower border of the fifth rib below, on the right side, and extending about 3 in. to the right of the mid-sternal line. Behind, the percussion note is impaired over the right scapular spine. Breath sounds are feebly heard over the whole chest but are harsher on the right side than on the left, and over the area of impaired resonance there is heard bronchial breathing and marked increase of vocal resonance.

Heart.—The cardiac impulse is palpable 2 in. from the mid-line in the fourth left intercostal space; a faint systolic murmur is audible at the level of the second right costal cartilage, but otherwise the heart appears normal.

There are multiple scars of operation incisions in both breasts and both axillæ.

The clinical examination was carried out with great difficulty, owing to the extreme lassitude of the patient, and three or four days were consumed in eliciting the facts embodied in the above notes. The diagnosis was at first by no means clear, and in view of her long illness and general demeanour it was thought she might be suffering from hysteria, but by the time the examination was completed it was realized that such was not the case, and that she was in all probability the subject of myasthenia gravis, now rapidly progressing.

In an interview with her husband, the following additional facts in her past history were obtained.

She married in 1887, and had two children, a boy and a girl, both of whom are now living and quite well. Soon after marriage, the interval, however, being uncertain, she developed a 'black wart' under the left arm, which for a short time 'discharged matter.' From this time until 1911 she remained quite healthy and led a very active life. She was always an unusually unselfish and sensible woman, with a large circle of friends and extremely happy in her family life.

In 1911 there developed at the 'navel' a small growth which 'discharged' and was cured.

In 1912 she began to have attacks of nocturnal choking and in consequence was medically examined, but nothing was found.

In 1913 a 'growth' appeared in the left shoulder and an operation was performed, and two 'lumps' were removed which were 'non-malignant.' She still suffered from occasional choking at night.

In 1914 more 'lumps' were removed from the left axilla, and during this year she began to have ulcers in the right eye, which were treated for some time, and finally an iridectomy was done on this eye.

From 1914 to 1922 she had various glands removed from her breasts, chest-wall, and axillæ. In the summer of 1922 she began to get very tired after the least exertion, which fatigue gradually increased until her

admission to hospital in January, 1923, at which time she could walk only with assistance.

There was a history of some slight injury to the right knee, but particulars could not be ascertained.

The photograph (*Fig. 1*) shows, howbeit poorly, the general facies, and so long as I had her under observation I never saw her eyes open

FIG. 1.—Facies.

spontaneously, nor did she ever make any voluntary movement of any kind, being hand-fed with extreme difficulty, owing to asthenia of her tongue, masseters, buccinators and muscles of deglutition, though there was never any regurgitation of food.

An electrical examination was carried out, and the following is a copy of the report from the electro-therapeutic department:—

“**Faradism.**—Muscle groups react strongly at first, but on continued stimulation the response appears to diminish gradually until it

FIG. 2.

is practically *nil*. After two or three minutes' rest, restimulation evokes a brisk response, which, however, rapidly diminishes as the current is repeatedly sent in. Strength of current used, sufficient to produce a brisk contraction in normal arm.

“**Galvanism.**—Muscles twitch sharply and the twitch remains constant on repeated stimulation. K.C.C. greater than A.C.C. Strength of current, 10 m.a.”

The accompanying tracing (*Fig. 2*) is a myogram of the contraction of the finger flexors on stimulating with a faradic current sent in at

intervals of a second, the current being switched off when the waves were seen to be minimal and restarted in about twenty seconds.

The tracing shows a gradual diminution in the response, up to complete absence, followed by a quick return after the muscle has rested (the excursion of the point is small, as the muscle was contracting against a spring resistance to produce fatigue quickly).

A complete basal metabolic examination could not be undertaken, but Dr. C. G. Imrie kindly carried out a urinalysis with the following results :—

Total quantity in 24 hours	305 c.c.
Creatinin	0.602 grm.
Creatinin after hydrolysis	0.658 „
Creatin	0.056 „

After hydrolysis the urine was very dark in colour, making accurate reading extremely difficult, and it is not certain that all the urine was obtained, so that the result of this examination is not of great weight, particularly as it could only be done on one occasion. Such as it is, the figures show a slight diminution in the excretion of creatinin.

A blood count gave the following figures :—

Red cells	4,353,000 per c.mm.
Hæmoglobin	58 per cent.
Colour index	0.67
White cells	6,133 per c.mm.

Beyond a slight anæmia of secondary type and a rather more pronounced leukopenia the blood count presents nothing abnormal. A differential count of leucocytes was not recorded, but there were no abnormal cells of any kind.

A skiagram of the chest was taken (*Fig. 3*). It will be noticed that there is a well-marked band of shadow on the right side, in the same situation as the area of impaired resonance elicited in the clinical examination of the chest. The radiologist's report is as follows :—

“On account of the mental and physical condition of the patient, it was not possible to make a complete examination, particularly as regards the posterior mediastinal space. The film shows a broad band-like opacity on the right side, springing from the right hilar region and running transversely across the lung. This is possibly due to peribronchial infiltration. There is also some flocculent opacity on the left side extending from the hilar region to the left apex.”

The Wassermann reaction was negative in the blood.

The above examinations were made between February 28 and March 7, on which day the patient's husband asked permission to take her home, as it was clear that her death was a matter of a short time only. After her return home no further observations were possible, but she lived for ten days in a state of gradually increasing asthenia.

No autopsy was obtainable, but permission was given to excise a small piece of muscle from the calf, and this was done with great difficulty through a small linear incision. It is regretted that no other pathological findings are available, as the tissues underlying the scars might have been of much interest, and the nature of the cervical swellings, as well as the cause of the 'thoracic shadow' and impaired chest resonance, might have been disclosed. It was hoped that permission might have been obtained to take the muscle for examination from the group of atrophied shoulder muscles, but unfortunately the calf muscle was specified. This is the more regrettable, as the small fragment obtained from an area free from any gross clinical changes is of considerable interest and shows marked departure from the normal (*Figs. 4 and 5*). The striation of the muscle fibres seems to be irregular, some fibres being well, others rather poorly, striated, and there is a very marked increase in the number of the sarcolemma nuclei. These nuclei are seen between the muscle fibres in much greater profusion than normal, and in several places they are so numerous as to be contiguous, giving the appearance of a thread of jointed mycelium. Besides the increase in nuclei, there are also some deep-staining granular masses between the muscle fibres.

DISCUSSION.

The case presents several features of clinical and pathological interest. In the first place, the illness began by the appearance of glandular enlargements of indeterminate type, and that this was an integral feature of the condition is supported by their almost continuous appearances up to the date of death. It seems reasonable to assume that the percussion dulness and the *x*-ray shadow in the chest were in all probability due to glandular swellings in the mediastinal space and along the interlobar plane of the right lung.

Again, the condition of the eyes is of great interest, since it was of such chronicity that it was present from 1914 to 1923, and though not cataractous, yet was of such a nature as to necessitate an iridectomy on account of 'opacity.' It is to be further noted that during the last stages of the illness, together with an exacerbation of the conjunctival inflammation, there appeared simultaneously a swelling of cervical glands, a combination of symptoms which had occurred more than once before, suggesting that both were due to a common cause and seemingly pointing in the direction of a possible infection.

The most interesting pathological feature is the histological appearance of the muscle fibres. Though none of the typical lymphorrhages were found in the small fragment examined, there was noted a very marked increase in the nuclei of the sarcolemma. These were arranged in chains and were sometimes contiguous, closely resembling the picture recently described by Adie and Greenfield¹¹ in cases of myotonia

FIG. 3. – Skiagram of Chest.

FIG. 4.

FIG. 5.

atrophica, though there were none of the intrafibrillar rods which these authors look upon as the essential histological feature in this disease. It will be recalled that both in myotonia atrophica and myasthenia gravis cataract forms a common extra-muscular accompaniment.

Though it cannot be claimed that the case recorded here warrants any definite conclusion, nevertheless it lends some support to the view of a toxi-infective process as the possible cause of the disease: the recurring glandular swellings which at times underwent rapid changes, as in the case of the cervical glands during the last month of life, strongly suggest a reaction to some infection, and the fact that this occurred with a flaring up of a frank conjunctival infection is some corroboration of such a hypothesis. The previous history of the illness further points to the probability that such glandular swellings had been periodic, which at once suggests a dim possibility of relationship to Hodgkin's disease.

I should like to record my thanks to Professor A. J. Hall, to whose kindness I am indebted for permission to observe and record the case.

SUMMARY.

1. The first sign of any ill-health was in 1911, with the appearance of pigmented warts.

2. In the following year (1912) occurred periodic attacks of nocturnal choking, which, in view of later events, suggest the probability of swelling of thymus or other glandular tissues.

3. In 1914 multiple lymphoid growths appeared from time to time, together with chronic inflammation of the eyes.

4. The last six months of life were characterised by rapidly progressing muscle fatigue with some atrophy.

5. The clinical diagnosis of myasthenia gravis seems fairly established.

6. The histology suggests some resemblance to that of the muscles in myotonia atrophica.*

7. The eye symptoms may also be considered as indicating a possible connection with the latter condition.

8. The periodic glandular swellings also recall the similar condition in some cases of lymphadenoma.

* Buzzard, in his article on myasthenia gravis in Clifford Allbutt's *System of Medicine* (vii, 57), suggests its possible relationship with Thomsen's disease.

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