Mary Broadfoot Walker (1888–1974): A Historic Discovery in Myasthenia gravis

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Abstract

As a clinical entity, myasthenia gravis was not recognized until Samuel Wilks in 1877 described bulbar and peripheral muscular weakness. In the *Lancet* of June 2, 1934, the remarkable discovery of physostigmine treatment by Dr. Mary Walker was published, which was to become the mainstay of symptomatic treatment. A quiet and modest physician, she laboured with considerable success under many obstacles in her work and career.

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As a clinical entity, myasthenia gravis was not recognized until Samuel Wilks in 1877 described bulbar and peripheral muscular weakness and was struck by the absence of pathology in the central nervous system [1]. However, the earlier, controversial description by Thomas Willis [2] (ignored by Osler) is a convincing clinical account [3].

The German physicians Erb in 1879 and Goldflam in 1893 later reported new and detailed expositions, though Erb, a pioneer of electrodiagnosis, failed to record the myasthenic decrement in response to faradic stimulation. Jolly, in 1895, wrote:

‘When muscles are stimulated repeatedly by Faradism a reaction of asthenia is demonstrated, yet when the muscle no longer responds, it will respond immedi-

ately to Galvanic direct current ... the myasthenic reaction [4].’

The association with thymic tumours and hyperplasia was not recognised in any of these early works. In 1901, Carl Weigert, a German pathologist (1845–1904), first described a myasthenic patient with a thymic mass [5].

In the *Lancet* of June 2, 1934 and in the local paper *The Kentish Mercury* on March 15, 1935, the remarkable discovery of a doctor was published, which was to become the mainstay of symptomatic treatment of myasthenia gravis [6].

‘Mrs. M. aged 56 had previous attack of myasthenia gravis lasting about six months ago, 14 years ago ... Towards the end of last February she found that she was unable to hold her shopping bag, and that her head used to fall forwards when she knelt to do the hearth. She had to remain in bed after March 18th, and had difficulty sitting up. Her jaw then began to droop, she had to hold it up with her hand and the left eyelid began to droop. Speech became indistinct ... swallowing was difficult and fluids sometimes regurgitated through her nose ...

On April 11th treatment with hypodermic injections of physostigmine salicylate, gr. 1/60 once a day was begun. In from half an hour to an hour after the injection the left eyelid “goes up” (see figure), arm movements are much stronger, the jaw drops rather less, swallowing is improved, and the patient feels “less heavy”. The effect wears off gradually in from 2–4 hours. With injections of gr. 1/50 the improvement is greater, and it lasts for 4–5 hours ... Given by mouth physostigmine salicylate

Fig. 1. Dr. Mary Walker.

gr. 1/60 produced no obvious effect, but an hour after gr. 1/30 slight improvement occurred.'

No improvement followed control injections of water, pilocarpine, strychnine, adrenaline, ephedrine or acetylcholine.

'I think that this effect of physostigmine on myasthenia gravis is important, though it is only temporary, for it improves swallowing and might tide the patient over a respiratory crisis. It supports the opinion that fatigability is due to poisoning of the motor end-organs, or "myoneural junctions" ...

I am, Sir, yours faithfully, M.B. Walker.

St. Alfege's Hospital Greenwich, May 12th [1935].'

Physostigmine had to be given by injection and had unpleasant side-effects and so Walker tried oral prostigmine (Roche). In 1935, a 'Miss C.' became the first person given oral prostigmine (neostigmine) for myasthenia gravis. A myasthenic since February 1928, she had failed to benefit from several hospital admissions. She was transferred to St. Alfege's Hospital on October 24, 1934 and given hypodermic prostigmine 2.5 mg and atropine 1/100 g three times daily with an excellent response.

However, the report of the beneficial effect was greeted with general skepticism because the relief of myasthenic weakness was brief. In 1938 when her discovery was formally demonstrated to the Royal Society of Medicine and others had confirmed the benefits, general acceptance supervened. She described her detailed observations and experiments in her MD thesis (Edinburgh Uni-

versity in 1935) for which she was rewarded with a gold medal. Mary Walker had made one of those few therapeutic discoveries for a specific disorder, like finding the key for a locked gate.

She also described a clinical sign in myasthenia known as 'the Mary Walker effect': the myasthenic patient vigorously exercises the forearm with a tourniquet applied at the elbow inflated to 200 mm Hg; the tourniquet is released when the patient tires and partial ptosis develops a few minutes later. The humoral mechanism responsible remains open to speculation [7].

Mary Broadfoot Walker (fig. 1) was born at Croft-an-Righ, Wigtown, Scotland. After school, she entered the medical school with all the customary difficulties then imposed on women. In 1913, she graduated MB, ChB from Glasgow and Edinburgh Medical College for Women. In World War I, she joined the Royal Army Medical Corps and served at the 63rd General Hospital, Malta. After the war, in 1920, she became Assistant Medical Officer in 'Poor Law Service' at St. Alfege's Hospital, Greenwich. Against formidable competition at the time in 1932, she passed the London Membership of the Royal College of Physicians. It was 2 years later that she revealed her findings in myasthenia gravis in the work which formed the substance of her 1935 MD thesis.

It is hard to imagine now the difficulties faced by women doctors in Britain during the early 20th century. Dr. Walker was offered a senior post at the Elizabeth Garrett Anderson Hospital but financial constraints limited her to a salaried post. She moved from St. Alfege's Hospital in 1936 to St. Leonard's Hospital, Shoreditch, as a Medical Assistant, then moved to St. Francis' Hospital, Dulwich and later to St. Benedict's Hospital, Tooting. Many contemporaries commented on her quiet and reserved manner; to what extent this too limited her professional advancement remains speculative.

Treatment of myasthenia was not her only discovery, for with few resources, she was possibly the first to demonstrate that familial periodic paralysis was associated with hypokalaemia [8, 9]. The title of this 1935 paper is misleading and probably reflects the confusion at that time about the nosology of myasthenia gravis, periodic paralysis and the role of defects in potassium metabolism.

In 1954, she retired to Croft-an-Righ, her father's home, originally built as a hunting lodge for Scottish Kings. 'Local people remember her tenure of the house as one filled with laughter and cats and stories about the walnut tree in her garden.' But ever zealous, she also continued to work at Glasgow Royal Maternity and Women's Hospital. Her interest in myasthenia continued as shown by the letter

written to a Miss Sylvia Bates in 1961 wherein Dr. Walker advocates a controlled trial of thymectomy to ascertain its role in the management of myasthenia gravis

Though never made a Fellow of the Royal College of Physicians, she was awarded their Jean Hunter Prize on Thursday, November 29, 1962, *for the advancement of research into the treatment of nervous exhaustion and for her original contribution to the fundamental knowledge of the nature of myasthenia gravis, made while carrying out the routine duties of a medical officer at a large metropolitan hospital.*

She died [10] in September 1974 aged 86.

Keesey's [11] conclusion is that

'Mary Walker, with her brief case reports and her frequent demonstrations, ... stood the test of time, but also provided the most convincing evidence at the time that the neuromuscular junction was the focus of the disease.'

In 1997, A.H. Keeney and V. T. Keeney remarked [12]:

'In an era when women were not admitted to the University of Edinburgh and when England's first female physician (Elizabeth Garrett Anderson, 1836–1917) had to venture to Paris, France, to earn her MD in 1870, the career of Mary Broadfoot Walker (1888–1974) stands out for truly remarkable achievement.'

Later Developments

Sir Henry Dale's Nobel-Prize-winning work (1934) showed acetylcholine as a neurotransmitter at the myoneural junction. Research later showed that 3/4 of patients with generalized myasthenia and half with ocular

myasthenia had serum acetylcholine receptor antibodies and in cases with thymomas, CD4+ and CD8+ T cells were generated [13].

In 1960, J. A. Simpson suggested that myasthenia gravis 'is an "auto-immune" response of muscle in which an antibody to end-plate protein may be formed' [14]. Osserman and Genkins [15] confirmed the role of an auto-immune genesis and established a classification. Current immunosuppressive treatments are based on these investigations.

Appendix: Bibliography of Mary Walker

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