Multiple sclerosis associated with defects in neuromuscular transmission

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SUMMARY Three patients with multiple sclerosis characterized by exacerbations and remissions of nervous system signs and symptoms disseminated in time and space also had the kind of easy fatiguability seen in myasthenia gravis. In each case abnormal decrements to repetitive stimulation were electromyographically demonstrated and treatment with ephedrine or anticholinesterase drugs increased the patient's functional capacity while improving the electromyographic abnormality. The suggestion is that these patients represent an overlap syndrome, analogous to the overlap syndrome existing between systemic lupus erythematosus and rheumatoid arthritis where clinical and laboratory features of two diseases coexist in the same patient at the same time. Presumably some patients with multiple sclerosis have deficient production of acetylcholine, just like patients with myasthenia, and treatment with agents useful in myasthenia is able partially to correct the symptoms caused by the deficiency. The cases illustrate how in neurology greater attention to the more immediate cause of clinical symptoms, in the absence of a known aetiology, may result in benefit to the patients.

Multiple sclerosis continues to be a disease of enigmas. Not only are we ignorant of its cause or cure, but also we can not adequately explain the exacerbations and remissions, or the lack of correlation between the patient's functional capacity and the number and severity of the demyelinated plaques (Namerow and Thompson, 1969). The significance of the peculiar epidemiology of the condition escapes us, as do the reasons for the reported association of multiple sclerosis with migraine (Watkins and Espir, 1969) and narcolepsy (Ekbom, 1966).

The existence of so much unexplained data has led some to postulate that multiple sclerosis is not a disease entity, but is merely a clinical syndrome which includes many disorders of different causation (Ekbom, 1966; Connor, 1970). An alternative explanation is that some diseases may use similar mechanisms of expression. To support this idea, we wish to report a class of multiple sclerosis patients who have signs and symptoms of both multiple sclerosis and myasthenia gravis analogous to the overlap syndrome existing between systemic lupus erythematosus and rheumatoid arthritis in which clinical and laboratory features of the two diseases coexist in the same patient. The recognition of the multiple sclerosis-myasthenia gravis overlap syndrome has both fundamental and practical significance in view of our ignorance of the cause of both conditions, as well as the possible diagnostic and therapeutic benefit that may be obtained for multiple sclerosis patients by drug induced improvement of neuromuscular transmission. In the absence of a known aetiology, our cases illustrate how an approach to therapy might be found in a better understanding of the causes of symptom formation.

CASE 1

O.R., a 26 year old Negro woman, was well until January 1968 when she noted episodes of marked weakness and easy fatiguability. By May 1968 she would wake up feeling normal but became quite fatigued on dressing, and at times was so weak she could not comb her hair. On lying down for 10 minutes the weakness remitted. She said she had occasional double vision and decreased vision which cleared spontaneously. Because of her fatiguability, she was unable to work at her job as a maid. In June of 1968, she presented to the Presbyterian Hospital complaining of double vision. On examination, she had mild weakness of both deltoid muscles. She could not walk on her toes or heels. No objective evidence for extraocular movement dysfunction was

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found. Intravenous saline gave no response but 10 mg edrophonium (Tensilon) made the patient feel strong, relieved the diplopia, and increased strength in the deltoid muscles. For the duration of the effect of Tensilon, she was able to walk on her toes and heels. She was admitted to the Neurological Institute for evaluation of possible myasthenia gravis.

WBC was 4150/cu mm with 47% lymphocytes. Lumbar puncture showed no RBC or WBC, sugar 67 mg and protein 15 mg/100 ml. on two determinations, with gamma globulin of 17%. The following tests were normal: sedimentation rate, fasting blood sugar, blood urea nitrogen, VDRL, two LE preparations, creatine phosphokinase, lactic dehydrogenase, SGOT, plasma electrophoretic pattern, sodium, potassium, CO₂, Cl, Ca+++, Mg+++, latex fixation, urinalysis, electrocardiogram, electroencephalogram, skull, and chest radiography.

Tensilon test in a double blind controlled manner again produced remarkable improvement, but the effect lasted over 20 minutes, so she was not considered to have typical myasthenia. The patient was discharged without a diagnosis and was further observed in clinic.

**ELECTRODIAGNOSTIC STUDIES** Standard techniques were used as previously described (Lovelace and Horwitz, 1968). Conduction velocities in median, ulnar, peroneal, and posterior tibial nerves were normal. Repetitive stimulation of the median nerve at the wrist was performed, with the right arm, hand, and fingers rigidly controlled for movement. Recording of evoked potentials in the thenar muscles was made by firmly affixed surface electrodes. Repetitive stimulation of the right median/thenar system at 2/sec revealed decrements between 20 and 25% (Fig. 1); at 5/sec a decrement of 15% and less marked changes at 10/sec, with normal potentiation there and at 20 and 40/sec (Fig. 1). As shown (Fig. 2), well performed exercise of thenar muscles for one minute produced initial potentiation with disappearance of the decrement at 2/sec. The decrement progressively returned one minute after cessation of exercise. Similar changes were seen on repetitive stimulation of the ulnar/hypothenar system. Unipolar needle electromyography of right arm muscles was normal except for some excessive variation in amplitude of single firing motor unit potentials.

These findings indicated a defect in neuromuscular transmission suggestive of myasthenia gravis, since the greatest change was at 2/sec; but with demonstration of an atypical exercise study.

In July 1968, the patient was depressed over the apparent hopelessness of her condition. She asked

**FIG. 1. Repetitive stimulation of the right median-thenar system: case 1. Supramaximal stimulation showing decrements (A and B) and potentiation (C and D). A. 2/sec. B. 1/sec. C. 10/sec. D. 20/sec. Calibration = 1 mV.**
if she could take 'that medicine' (Tensilon) again, since she thought it was the only thing that had helped.

Examination showed nystagmus on vertical gaze. Repetitive hand gripping produced early fatigue. She had absent abdominal reflexes and a right sided hyper-reflexia.

Anticholinesterase therapy in the form of pyridostigmine (Mestinon) 60 mg three times daily was prescribed. The patient improved remarkably with this agent and she was able for the first time in nine months to return to work.

From September to December 1968, because of the side-effects of dry eyes and abdominal cramps, she stopped her medicine four times. Each time, her original weakness returned forcing her to restart the Mestinon in order to continue earning a living. Examination in December revealed only vertical and horizontal gaze nystagmus. The right sided hyper-reflexia had disappeared. Repeat electrical studies using the above techniques showed decrements at 2/sec (23%) and 5/sec (12%), but no abnormalities at 10 and 20/sec. This was still consistent with a defect in neuromuscular transmission under therapy.

In April 1969, in spite of her medicine, the patient developed ataxia, positive Romberg test, left internuclear ophthalmoplegia with failure to adduct the left eye, and coarse nystagmus in right eye (convergence was normal). The right hyper-reflexia had returned. By July 1969, her examination was normal except for downward drift of the right arm and some weakness of the left psoas muscle. In October 1969, she developed a numb sensation in the whole right lower extremity with decreased pain perception. In addition there was a Babinski sign on the right. By January 1970, the patient felt entirely normal. Her neurological examination revealed no evidence of cord or brain-stem pathology and she continued on Mestinon for relief of fatigue. She continued to work, but found the need for the medicine was gradually declining. By July 1970, she was able to do her job while taking only one tablet of Mestinon daily. Examination at that time showed nystagmus on left lateral gaze, bilateral Babinski signs, absent right knee and ankle jerks, and ptosis of the left eyelid. The Tensilon test was repeated in January 1971, after cessation of Mestinon therapy for 12 hours. Before injection, repetitive stimulation at 1 and 2/sec (Fig. 3) showed some decrement by approximately 15% which improved with continued stimulation. This was less marked at 5/sec with clear later potentiation. Ten milligrams of Tensilon was given intravenously, which produced complete clearing of the decrement.

COMMENT This woman had a clinical syndrome characterized by a myasthenic defect in neuromuscular transmission associated with signs of

![Exercise Study of Right Thenar Muscles with Repetitive Stimulation: Case 1](image)

**Fig. 2.** Exercise study of right thenar muscles with repetitive stimulation: case 1. Evoked potentials are recorded at 2/sec stimulation and superimposed: amplitude when varying always decrements. Tracings are obtained before (first tracing) and at intervals after well-performed maximal exercise of thenar muscles. Reading from left to right intervals after well-performed maximal exercise of thenar muscles are: 10" = 10 sec, 30" = 30 sec, 1' = 1 min, 2' = 2 min, etc. Calibration = 1 mV.
CNS dysfunction that spontaneously exacerbated and remitted. Her complete remission in January 1970 was remarkable, but not unknown either in multiple sclerosis or myasthenia gravis.

According to Norris (1963), decrements in the supramaximally evoked potential at stimulus rates 10/second or below, as were seen in this patient, are diagnostic of myasthenia. Other criteria considered essential for the diagnosis of myasthenia gravis in our laboratories and by Simpson (1966a), such as an increment at stimulation rates of 10/sec and higher, together with the retention of post-tetanic facilitation were seen (Fig. 1). The elevated percentage of gamma globulin in the cerebrospinal fluid in the face of normal globulins in the peripheral blood is highly significant and characteristic of multiple sclerosis (Schneck and Claman, 1969). We therefore believe that the laboratory and clinical features of both myasthenia gravis and multiple sclerosis were present in this case, and that she has an overlap syndrome in which features of both conditions coexist in the same patient at the same time.

The remaining illustrative cases will be presented in less detail.

**CASE 2**

J. F., a 57 year old white man, was well until the age of 37 years when he developed attacks of weakness of both legs lasting several weeks and improving spontaneously. He also complained of day-long episodes of numbness and tingling of the legs. At age 41 years, the weakness became rapidly worse and he developed diplopia and numbness of the left side of his face and tongue. On examination there was hypalgesia of the left side of the face, nystagmus on horizontal gaze, bilateral Babinski signs, and cerebellar ataxia of the left arm. Routine laboratory evaluation similar to case 1 was normal. Lumbar puncture with CSF examination was normal except for a colloidal gold curve of 0013211000. Gamma globulin was not estimated. He was diagnosed as having multiple sclerosis and over the ensuing two weeks, spontaneous dramatic improvement occurred. He was then well except for mild episodic leg weakness until age 46 years when he developed numbness of the right leg, paraparesis, bilateral Babinski signs, and nystagmus. These gradually cleared, leaving only a mild paraparesis. At age 50 years, he had an episode of blurred vision which cleared spontaneously. After the attack, visual acuities were 20/30, but optic disks were pale and visual fields constricted to red test objects. His disease then stopped progressing, and he has remained with fixed neurological deficits. Because he complained of easy fatigability and had decreased strength with successive hand grips, electrical studies were performed.

**ELECTRODIAGNOSIS** Nerve conduction velocities were slightly slow with right median and ulnar motor
conduction velocity being 44 and 42 m/sec respectively. Median motor and sensory distal latencies were prolonged at 6.1 and 4.5 msec respectively. On needle electromyography, there were occasional spontaneous positive waves, but otherwise no abnormalities were seen. Repetitive stimulation showed decrements at 5, 10, 20, 30, and 50/sec. These decrements were less marked when the patient was treated by ephedrine and pyridostigmine (Fig. 4). Serial studies each week over the course of two months indicated unequivocal electrophysiological and clinical improvement while under therapy and there was a rapid relapse to the original state of disability when medicines were temporarily stopped.

COMMENT Whereas case 1 presented primarily with excessive fatiguability suggestive of myasthenia and only subsequently was found to have features of multiple sclerosis, case 2 presented in the reverse fashion: initially a picture of multiple sclerosis followed by the laboratory findings of myasthenia gravis. The use of ephedrine and Mestinon in this latter patient has enabled him to work again as a carpenter, something he had not been able to do for several years.

CASE 3

This 41 year old Negro woman was well until one year ago, when she noted episodic burning of the hands, and difficulty in buttoning her clothes. She also had attacks of unsteadiness with frequent falls. One episode of diplopia cleared spontaneously over the course of two weeks. Her main complaint was weakness of her hands, but questioning revealed that she suffered from easy fatiguability. Indeed, while doing housework she became so fatigued that she had to rest every few minutes to recover her strength. On examination, there were bilateral Babinski signs, decreased vibration and position sense in hands, nystagmus on lateral gaze, ataxic tandem gait, and bilaterally absent abdominal and triceps reflexes.

Lumbar puncture and CSF examination was normal except for a protein of 38 mg/100 ml., 21% of which was gamma globulin. Colloidal gold curve was 222330000. ESR was 40 mm in the first hour and EEG was mildly and non-specifically abnormal due to bilateral slow waves. The rest of the routine laboratory tests were normal.

ELECTRODIAGNOSIS Conduction velocities and needle electromyography were normal. Repetitive stimulation showed decrements especially at 10, 20, and 50/sec (Fig. 5). During the two minutes after intravenous edrophonium (Tensilon), there was clear improvement in the weakness and fatiguability together with a less marked decrement on repetitive stimulation.

One month later, she had an ataxic gait, a right medial longitudinal fasciculus lesion with failure to adduct the right eye and coarse nystagmus in the left eye on attempted left lateral gaze. In addition, there was rotatory nystagmus on upward gaze with the quick component clockwise. Decreased position sense in the right hand was still present, but position sense in the left was normal. Babinski's sign, previously
FIG. 5. Decrements in patient 3. A. Supramaximal stimulation of median-thenar system at 10/sec for 15 sec produced a 20% decrease in the amplitude of the evoked muscle action potential. B. At the rate of 20/sec for 15 sec the decrement was again 20%. C. At 50/sec for 15 sec the decrement was 35%. Tensilon test in patient 3: D. Control trace: in spite of recovery of the amplitude of the single action potential, supramaximal stimulation at 10/sec for 15 sec shows 40% decrease in amplitude. This decrement is greater than previously seen in this patient at this rate (see A above) and probably indicated residual fatigue from the 50/sec stimulation which had taken place, 10 min before. E. Tensilon trace: one minute after the injection of Tensilon intravenously a repeat tracing was made for 15 sec. The amplitude of the first potential is the same as in the control (D). However, subsequent potentials in the Tensilon trace are 10% greater than the control for the first 10 sec. However, the ultimate decrement at 15 sec is the same as in D (40%). Time line (0-1 sec) is seen in all tracings below lower horizontal line; at lower edge of potentials in A, B, and C, but superimposed on D and E.

bilateral, was now present only on the right. One month after that, she felt less fatigued and had no trouble in buttoning her clothes. Her Romberg test was negative, the medial longitudinal fasciculus lesion had disappeared, and sensation was normal. The Babinski sign was also gone. Repetitive hand grips produced no decrements in strength.

COMMENT The clinical presentation of this patient's disease was puzzling. Her initial disability could have been explained by a cervical syrinx, but the elevated gamma globulin and abnormal colloidal gold curve of the CSF suggested multiple sclerosis. The subsequent carefully documented exacerbation and remissions of CNS signs support the diagnosis of demyelinating disease. Myasthenia gravis was not considered at all. Yet without invoking that diagnosis the decrements to repetitive hand grip, electrical findings, and positive Tensilon test cannot be explained. In retrospect, her easy fatiguability takes on a greater meaning and was the first clue to the presence of a defect in neuromuscular transmission.

DISCUSSION Stimulation for 15 seconds of the median-thenar system in normal controls in our laboratory at frequencies including 50/sec produces a slight potentiation but no decrements in the amplitude of the evoked muscle action potential (Fig. 6).
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We, therefore, believe that normal human muscle action potential evoked by supramaximal stimulation in these circumstances maintains its amplitude and does not decrement. By contrast, the fatiguability demonstrated electrically and clinically in our cases occurred within one to two seconds at low stimulus frequencies and resembles the fatigue seen in myasthenia gravis.

Harvey and Masland, in their original studies of repetitive stimulation, noted that patients with myasthenia gravis showed initial fatigue, then some recovery, and finally more fatigue (Harvey and Masland, 1941). The cause of the temporary recovery is unknown, but initial decrement, followed by potentiation, followed by decrement was not characteristic of our patients with multiple sclerosis (Fig. 6). Harvey and Masland thought that some apparently normal individuals had unusually rapid fatigue, but they did not identify these controls or specify how many were studied, and what stimulus frequencies produced what degrees of decrement. They did say that none of these allegedly normal people had any significant change in either strength or evoked potential during Tensilon testing, and, therefore, concluded that the favourable response to Tensilon was a more reliable sign of myasthenia gravis than repetitive stimulation alone. In this regard, all of our cases showed definite, and at times dramatic, improvement in amplitude of evoked muscle potential with Tensilon confirming that repetitive stimulation studies during the maximal effect of this short-tracing anticholinesterase drug are quite useful and provide a quantitative, objective assessment of the patient’s response.

The suggestion is that acetylcholine is deficient in our patients, just as it is in myasthenia gravis (Roberts and Wilson, 1968), and that the decrements reflect the easy fatiguability of metabolically deficient neurones. The clinical and electrical improvement with Tensilon, ephedrine, and Mestinon, drugs effective in myasthenia gravis, indicates that the defect in neuromuscular transmission is in part correctable. In this connection, it must be remembered that the patients reported here are a highly selected group in which myasthenic features were easily detected clinically, and were superimposed on an underlying substrate of multiple sclerosis. Anticholinesterase drug therapy, because of possible toxic side effects, is not needed in all cases of multiple sclerosis. Certainly, only those patients with unequivocal clinical and electrodiagnostic

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**FIG. 6.** Comparison of normal, myasthenic, and multiple sclerosis neuromuscular response to repetitive stimulation. A. Normal (BP): supramaximal stimulation of median-thenar system at 50/sec for 15 sec produces a slight increase in the amplitude of the evoked muscle action potential. B. Myasthenic: stimulation under the same conditions produces an initial decrement, followed by potentiation, followed by decrement. C. Multiple sclerosis: stimulation of case 2 under same conditions produces a 70%, decrease in the amplitude of the evoked action potential. The potentiation seen in normals and in myasthenics is not present. A and C include lower time line as in Figs 4 and 5.
responses to these agents are suitable candidates for long-term treatment.

Milder defects in neuromuscular transmission than reported here may be more common than generally realized, as studies indicate some fatiguability to repetitive stimulation in amyotrophic lateral sclerosis (Simpson and Lenman, 1959; Mulder, Lambert and Eaton, 1959), chronic polyneuritis (Baginsky, 1968), and poliomyelitis (Hodes, 1948). Of course, myasthenic features have been noted with carcinoma of the lung, botulinus intoxication, magnesium intoxication (Lambert, 1966), thyroid disease (Norris, 1966), trimethadione therapy (Peterson, 1966), and with the use of various antibiotics (McQuillen, Cantor, and O'Rourke, 1968). None of these known causes of a myasthenic syndrome was present in our cases. One case of multiple sclerosis-myasthenia gravis overlap syndrome has been previously identified (Margolis and Graves, 1945), and Keane's patient (Keane and Hoyt, 1970) with tingling in the hands and feet, unsteady gait, blurred vision in the evenings, 'dubious' Babinski sign on the right, pale optic disks, vertical gaze nystagmus with a rotatory component who had a positive Tensilon test, reported as a puzzling case of myasthenia gravis, seems to more closely fit the overlap syndrome reported here.

The interrelationships between peripheral and central nervous system are only recently coming to light. Antineuronal antibodies have now been reported in myasthenia gravis (Kornguth, Hanson, and Chun, 1970) and muscle biopsies in myasthenia gravis are said to show neurogenic atrophy (Engel and McFarlin, 1966). Sensory loss, psychosis, epilepsy, face numbness, loss of taste and smell were well recognized in myasthenia gravis, especially in early studies (Simpson, 1966b). In fact, Simpson at the Erb Muscle Symposium in Heidelberg in 1966 commented on 10 cases of myasthenia gravis with raised protein in the cerebrospinal fluid, one of which had increased gamma globulin level (an abnormal Lange curve), probably due to multiple sclerosis associated with myasthenia gravis (Simpson, 1966c). Indeed, some of the older necropsy reports of myasthenia gravis concentrated on cerebral and spinal pathology exclusively with no mention of peripheral disease (McAlpine, 1929; Mott and Barrada, 1923). These observations, our own data, and Desmedt's electrophysiological evidence that the presynaptic region of the neuromuscular junction is the site of primary involvement in myasthenia gravis (Desmedt, 1966) should lead us to consider whether myasthenia gravis is a primary neurogenic disorder. Other muscle conditions such as muscular dystrophy and myotonic dystrophy have been associated with intellectual defects and central nervous system pathology (Worden and Vignos, 1962; Rosman and Rebeiz, 1967), and Engel has recently reported abnormal muscle enzymes and muscle biopsies in patients with acute psychoses (Engel and Meltzer, 1970). The cases reported here indicate that multiple sclerosis is another condition in which association between central and peripheral nervous system may be found. Even though nerve histopathology (Ward, Cannon, and Lindsay, 1965), conduction velocity, and needle electromyography are normal in multiple sclerosis (Rinne and Tuovinen, 1968), the demonstration of a defect in neuromuscular transmission in some patients with this condition indicates that further study of the peripheral nervous system should be undertaken.

It is difficult at present to draw any firm conclusions about the significance of the multiple sclerosis-myasthenia gravis association. Simpson points out that the factors which may be associated with the first attack or later relapses of myasthenia gravis are emotional disturbances, infection, and trauma (Simpson 1966b). In this respect, and also in sex incidence, age of onset, and remittent course, there are striking resemblances with the collagen vascular diseases and multiple sclerosis. The occurrence of myasthenia gravis with other diseases of supposed autoimmune origin including pemphigus (Beutner, Chorzelski, Hale, and Hausmanowa-Petrusewicz, 1968), haemolytic anaemia (Halperin, Minogue, and Komninos, 1966), ulcerative colitis (Engel and Meltzer, 1970), polymyositis (Halperin et al., 1966), and thyroiditis, systemic lupus, and pernicious anaemia (New England Journal of Medicine, 1966) could not have been an accident. Thymic germinal centres, identical to those seen in myasthenia gravis, have been reported in lupus erythematosus, rheumatoid arthritis, colitis, and thyroiditis (New England Journal of Medicine, 1966), and should increase our consideration of the possible relation of myasthenia gravis to these diseases and to the autoimmune diseases in general. In myasthenia gravis the most significant observation has been the finding of muscle antibodies directed against thymic epithelial cells, that cross-react with the A band of striated muscle.
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(New England Journal of Medicine, 1966). These anti-A band antibodies are not useful to explain myasthenic phenomena when all available information indicates a disorder of neuromuscular transmission and normal A band function. Nevertheless, the thymic pathology, chronic lymphocytic infiltration of muscles, autoantibodies, and the beneficial response to ACTH (Grob and Namba, 1966) and immunosuppressive agents (Mertens, Balzereit, and Leipert, 1969) indicate that immune mechanisms are playing an important role in the genesis of symptoms.

The relationship of multiple sclerosis to autoimmunity is not clear, but the demonstration of a multiple sclerosis-myasthenia gravis overlap syndrome tends to strengthen the association. The discovery of a serological factor in both experimental allergic encephalomyelitis, a demyelinating disease of susceptible animals, and multiple sclerosis, which actively demyelinates cultures of rat cerebellum, raises the question of the role of circulating antibody in the pathogenesis of demyelinating disease (Dowling and Cook, 1968). The report of systemic lupus erythematosus and multiple sclerosis in identical twins suggests that these two diseases are related but clinically distinct separate manifestations of a basic disease process (Holmes, Stubbs, and Larsen, 1967). Further study of the inter-relationship of multiple sclerosis, myasthenia gravis, and the autoimmune diseases is clearly needed. The clinician must avoid too rigid thinking about classifying these conditions, so that a fundamental relationship or a new overlap syndrome that could be quite important is not obscured or missed. The association of the signs and symptoms of one disease with another is more than fortuitous and indicates the possibility of different diseases using like mechanisms of clinical expression. In neurology the attention to the correction of the immediate cause of symptoms may, in the absence of a known aetiology, be of benefit to the patient.

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