Seminar

Myasthenia gravis

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Myasthenia gravis is an autoimmune disorder mainly caused by antibodies to the muscle acetylcholine receptors (AChRs) at the neuromuscular junction. Loss of these receptors leads to a defect in neuromuscular transmission with muscle weakness and fatigue. AChR antibody tests are widely available and overall incidence and prevalence of the disorder seem to be rising, especially in elderly people. The disease is heterogeneous with respect to age at onset, thymic changes and distribution of muscle weakness, but the roles of immunogenetic factors and thymic abnormalities in the causes of the different forms are unclear. Most patients are now effectively treated with cholinesterase inhibitors and immunosuppressive drugs, and in younger patients by thymectomy. In about 15% of patients with myasthenia gravis, AChR antibodies are absent, and many of these patients have antibodies to another neuromuscular junction protein, muscle specific kinase (MuSK). Myasthenia needs to be distinguished from other rarer but equally well characterised autoimmune, genetic, and toxic disorders of neuromuscular transmission by clinical and laboratory tests.

Myasthenia gravis (my: muscle, asthenia: weakness, gravis: severe) has been recognised as a disease since the Oxford physician Thomas Willis described a woman with dysarthria in 1672, and is a prototype for both synaptic and autoimmune disorders. In most patients, it is caused by autoantibodies specific for the human nicotinic acetylcholine receptor (AChR), which is concentrated at the post-synaptic region of the neuromuscular junction. These antibodies reduce the number of AChRs, causing impaired neuromuscular transmission and muscle weakness. Clinical[1] and experimental findings from the 1970s showing that myasthenia gravis was an autoimmune disease, established the ideas that have been applied to other autoimmune disorders of the neuromuscular junction.[2] Additionally, the subsequent identification of AChR mutations in a large proportion of patients presenting myasthenic signs at birth or neonatally has led to the definition of inherited or congenital myasthenic syndromes.[3] Thus, several myasthenic disorders are now recognised (figure 1). Here, we will focus mainly on myasthenia gravis, the most common disorder of neuromuscular transmission.

Epidemiology

Evidence suggests that frequency and recognition of myasthenia gravis is increasing. The annual incidence is between 0·25 and 2·00 people per 100 000, with no change in the number of patients aged younger than 40 years presenting, but a substantially increased age-related frequency in those over 60,[4] with a bias towards men.[5,6] Thus, the frequency is bimodal, with different male/female ratios in the two modes (figure 2). Future prevalence of the disease will be determined by the spontaneous remission rate (20%[7]) and the fact that without treatment a further 20–30% will die within 10 years.[7,8] Earlier point prevalence rates varied between 5 and 150 per million,[4,7,8] but a prevalence of 400 per million was reported in a recent prospective study.[9] Because of the improved survival of patients with myasthenia gravis, and the increasing longevity of the population, a life time risk of greater than 500 per million is probable (unpublished data).

Myasthenia gravis is a heterogeneous disorder. In about 90% of patients no specific cause can be identified, but there is strong evidence that the individual's genetic make-up is an important predisposing factor to development of the disorder, which might be precipitated by several, largely unidentified, environmental factors.

The strongest evidence for an immunogenetic predisposition to development of idiopathic myasthenia gravis is that patients with early-onset and late-onset myasthenia gravis have different HLA associations.[10] Additionally, those with early-onset disease have an increased frequency of other autoimmune diseases, monozygotic twins are at increased risk of concordancy, and more than one affected family member is not unknown.[7,8] Although there are no reported differences in overall worldwide frequency, the clinical expression and HLA associations can vary between populations, suggesting that precipitating factors might also differ. For instance, in Chinese and Japanese populations, up to 30% of patients present in early childhood, many with ocular myasthenia only.[11,12] Ocular myasthenia is associated with HLA-BW46 in Chinese patients,[13] suggesting that a particular environmental agent could be important. We do not know whether child patients are also seen in Chinese and Japanese people living in western countries.

The most important known cause is thymic tumour. 30–60% of thymomas are associated with myasthenia gravis,[14] and about 10% of patients with the disease have a thymoma.[7,8] A rare subgroup (1–2%) of patients develop myasthenia gravis, or have low concentrations of antibodies to the AChR, during penicillamine treatment, usually for rheumatoid arthritis although also occasionally for Wilson's disease. These patients generally have HLA-DR1,[15] which is not usually associated with either myasthenia gravis or rheumatoid arthritis. Penicillamine-induced myasthenia gravis is

Lancet 2001; **357:** 2122–28

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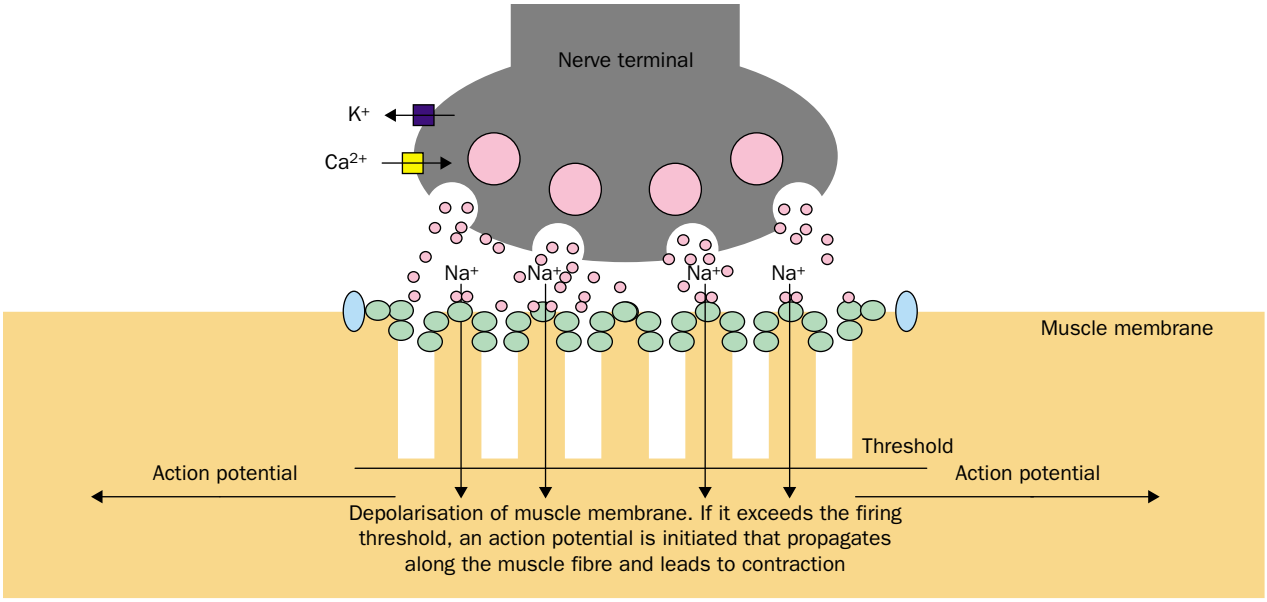

Target	Autoimmunune disease of neuromuscular junction	Genetic disease of neuromuscular junction
Acetylcholine receptors	Myasthenia gravis	Acetycholine receptor deficiency Slow-channel syndrome Fast-channel syndrome
Muscle specific kinase, MuSK	Generalised myasthenia gravis without AChR antibody	Not known
Voltage-gated calcium channels	Lambert-Eaton myasthenic syndrome	Not known
Voltage-gated potassium channels	Acquired neuromyotonia	Episodic ataxia with myotonia

Figure 1: **The neuromuscular junction, the ion channels involved in neuromuscular transmission, and the disorders that affect it**
The receptor muscle-specific kinase, MuSK, that now seems to be a major target in AChR seronegative myasthenia gravis is also shown.

indistinguishable from other forms of the disease, but typically remits on withdrawal of the drug.

The disorder can first present during pregnancy, or postnatally. Because patients with myasthenia gravis are particularly susceptible to muscle relaxants, weakness can be first, or only, noticed after general anaesthesia. Other drugs that could exacerbate poorly controlled myasthenia gravis are some antimalarials, β blockers, verapamil, and aminoglycosides. In some patients, myasthenia gravis (as in other immunologically mediated diseases) seems to be precipitated by infection.

Clinical features

The clinical presentation has been reviewed by Oosterhuis,[7,16] and by Grob,[8] who have undertaken studies of the natural history of the disease. The most characteristic presenting feature of myasthenia gravis is painless, fatiguable weakness—ie, weakness either developing or becoming more evident with exertion. However, fatigue is not always evident, or might easily be overlooked. The pattern of muscle involvement varies between individuals. The disease frequently presents with ptosis and diplopia, caused by involvement of the extraocular and levator palpebrae muscles. Bulbar and facial muscle weakness causes reduced facial expression (eg, a snarling appearance when attempting to smile), and speech, chewing, and swallowing difficulties. Neck weakness leads to head droop. Limb weakness is most pronounced proximally, although often with specific weakness of the small muscles of the hand. Respiratory muscle weakness can be life-threatening and is best monitored by measurement of forced vital capacity, rather than peak flow. Weakness can remain localised to one group of muscles for many years (commonly in the eye muscles—termed ocular myasthenia) or spread to affect other skeletal muscles (generalised myasthenia gravis).

The onset of symptoms can be acute, or subacute, and relapses and remissions can occur. The weakness is usually detectable on examination, but in mild cases

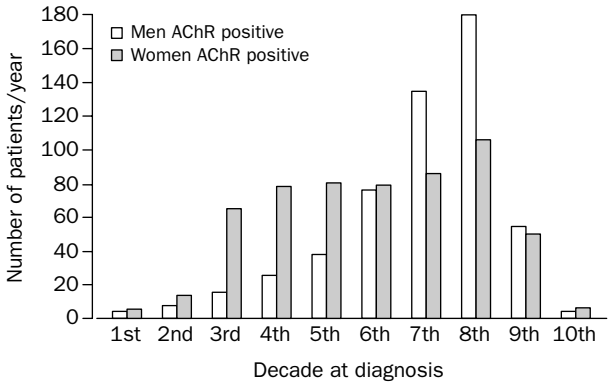

Figure 2: **Number, age, and sex distribution of patients presenting with AChR antibody positive myasthenia gravis in a typical year in the UK**
Data are averaged from 1997–99.

might only be obvious with tests of fatigue—eg, repetitive shoulder abduction or up-gaze (which might need to be sustained for 1 min, to precipitate ptosis). Tendon reflexes are normal and sensory involvement is absent. Myasthenic crises are life-threatening episodes of respiratory or bulbar paralysis. Cholinergic crises are caused by excessive anticholinesterase medication, leading to a depolarisation block of neuromuscular transmission that exacerbates weakness. Cholinergic crises are characterised by the associated cholinergic symptoms of hypersalivation, lacrimation, sweating, vomiting, and miosis.

Heterogeneity of myasthenia gravis

Although myasthenia gravis is generally caused by autoantibodies to the AChR, or, to a smaller extent, by antibodies to other neuromuscular junction protein(s), the management and prognosis differs depending on several associated factors. Figure 2 shows the incidence rates and age at onset in patients with generalised disease.

Childhood myasthenia gravis is rare in caucasians, but common in oriental populations.[11,12] A high proportion of caucasian, but not oriental,[12] childhood patients are seronegative for antibodies to AChR, making diagnosis difficult.

Early-onset myasthenia gravis is defined as presenting before age 40 years and is more common in women. Many patients present during adolescence or early adult life. Most are positive for AChR antibodies, and the thymus gland is enlarged. These patients seldom have antibodies to other muscle antigens, but might have other organ-specific autoantibodies.[7,8,10] About 60% of early-onset patients are HLA-B8 and DR3 positive.[12]

Late-onset myasthenia gravis is usually defined as first presenting in people older than 40 years, with a small bias to men. The thymus gland is not enlarged, but there is an HLA association with B7 and DR2.[10] Perhaps because of the increasing age of the population, and the ability to diagnose myasthenia gravis by a serum antibody test that is widely available, the recognition of this form of the disease is increasing, and patients with late-onset disease now represent more than 60% of all those diagnosed every year (figure 2).

Thymoma-associated myasthenia gravis presents at any age, but the peak onset is during the fourth to sixth decades. There are no clear HLA associations. The patients usually have antibodies to other muscle antigens such as titin and ryanodine receptor.[17,18] In about 10% of patients, the thymic tumour recurs as mediastinal or pleural metastases, and therefore, long-term follow-up, including chest scans (computed tomography or magnetic resonance imaging), is required.

Ocular myasthenia gravis is restricted to the eye muscles. However, electromyography and in-vitro studies on muscle biopsy samples indicate that the disease is probably present subclinically in other muscles.[19,20] The titres of antibodies to AChR are lowest in this subgroup, and undetectable in 40–60% of patients. If symptoms and signs remain confined to the eyes for longer than 2 years, the risk of subsequent development to generalised myasthenia gravis is low, but if the disease does progress, the acetylcholine receptor antibody assay might become positive.

AChR antibody negative generalised myasthenia gravis is not distinguishable clinically from AChR antibody positive cases. The development of neonatal disease in babies born to seronegative mothers with myasthenia gravis,[21] the success of plasma exchange in patients with seronegative myasthenia gravis, and other experimental evidence,[22] indicates that this form of the disease is also antibody mediated. Hoch and colleagues'[23] findings, indicate that a high proportion of patients with seronegative myasthenia gravis have antibodies to a muscle-specific receptor tyrosine kinase, MuSK. Further information about the frequency and clinical relevance of this antibody is awaited.

Maternally-mediated forms

Neonatal myasthenia gravis occurs in about 10% of babies born to women with the disease,[7,8,16] and can occasionally occur when the mother is symptomfree.[24] It is caused by placental transfer of maternal IgG AChR antibodies. Babies present with feeble cry and feeding difficulties. Symptomatic improvement can be obtained from anticholinesterase medication, and spontaneous resolution usually occurs within a few weeks.

The syndrome of antibody mediated arthrogryposis multiplex congenita describes the presence of multiple joint contractures at birth and results from absence of fetal movement, whatever the cause. Occasionally, arthrogryposis occurs in babies of mothers with myasthenia gravis,[25] and two cases have been reported in offspring of women without evidence of the disease, who had AChR antibodies[26] (A Vincent, unpublished observations). The mothers had very high titres of antibodies specific for the fetal isoform of the AChR, and low concentrations of antibodies directed towards the adult isoform of the AChR.[26] Although only a rare cause of arthrogryposis, the presence of AChR antibodies should be looked for in women with affected babies, since thymectomy, plasma exchange, and immunosuppression could result in further successful pregnancies (S Huson, J Newsom-Davis, A Vincent unpublished observations).

Pathophysiology

In most patients, myasthenia gravis is caused by pathogenic antibodies to the muscle form of the nicotinic AChR. The antibodies bind to the extracellular domains of the native molecule. They can be detected by immunoprecipitation of iodine-125 α-bungarotoxin-labelled AChRs extracted from human muscle,[27] or from human muscle-like cell lines.[28] α-Bungarotoxin is a snake toxin that binds specifically and irreversibly to the AChRs (this, and similar neurotoxins are common causes of neuromuscular failure in countries where envenoming is common).

The role of the antibodies in causing myasthenia gravis was clearly established in the 1970s. Plasma exchange, which removes circulating antibodies, leads to a substantial but transient improvement in muscle function lasting up to 2 months.[29] Injection of patients' IgG antibodies into laboratory animals, usually mice, led to loss of AChRs, and variable muscle weakness in the recipients.[30] Confirmation that antibodies to AChR alone could cause myasthenia gravis, came from immunisation against purified AChRs,[31] and the fact that monoclonal antibodies to AChR can produce similar effects in laboratory animals.[32] The antibodies in patients with the disease are IgG but heterogenous in light chain, subclass, and in their reactivity with different regions on the AChR.[33] A variable proportion in each patient binds to a region on each of the two α subunits, called the main immunogenic region.[34]

The neuromuscular junction can be seen by staining muscle fibres for acetylcholinesterase (AChE). In

myasthenis gravis, it is typically elongated, and electronmicroscopy shows a reduction in the length of the postsynaptic membrane that contains the AChRs.[35] There are deposits of immunoglobulins, complement components, and the final lytic membrane-attack complex in the synaptic cleft.[36] These changes show the damage that occurs when antibodies bind to the AChRs and initiate pathogenic mechanisms. The muscle fibres are not usually abnormal in myasthenia gravis.

Antibodies in myasthenia gravis are thought to lead to a loss of functional AChRs at the neuromuscular junction by three mechanisms. First, the antibodies cause complement-dependent lysis of the postsynaptic membrane.[35,36] Second, the antibodies, because they are divalent, are able to cross-link AChRs on the surface of the membrane, which leads to an increase in the rate of internalisation and degradation of the AChRs.[37] Third, in some patients, antibodies inhibit AChR function directly.[38] The importance of these mechanisms in individual patients is unclear; for instance, there is a compensatory increase in AChR synthesis that may offset the increased degradation.[39] Thus, complement-mediated damage to the whole postsynaptic membrane may be the most important determinant of loss of functional AChR.

Despite the absence of antibodies to the AChR, seronegative myasthenia gravis is clearly an antibody-mediated disease.[21,22] Although the presence of MuSK antibodies in patients with seronegative disease has only been reported recently, these antibodies seem to be able to inhibit the function of MuSK in cultured cells.[23] MuSK is a receptor tyrosine kinase that is an essential component of the developing neuromuscular junction; its role in adult life is unclear, but it might be involved in the maintenance of the high density of AChRs at the neuromuscular junction. Interference with this function could be occurring in patients with MuSK antibodies, and MuSK antibodies might cause complement-mediated damage to the neuromuscular junction.

The thymus gland is thought to be necessary for the deletion of auto-reactive T cells, and seems to have an important role in the pathogenesis of myasthenia gravis. In early-onset patients, the thymus is typically enlarged, and contains many germinal centres with T and B cell areas very similar to those seen in lymph nodes.[40] B cells obtained from the thymus spontaneously synthesise anti-AChR,[41] and thymic T cells are clonally restricted.[42] A few T cells cloned from the thymus have proved specific for AChR epitopes.[43] AChR is expressed both in the thymus of patients with myasthenia gravis, and in healthy controls, on muscle-like myoid cells that are embedded in the thymic medullary epithelium.[44] In late-onset disease patients, the thymus is usually atrophic. The relation between thymomas and myasthenia gravis has not been explained.[17] The tumour in thymoma-associated disease is typically epithelial in nature, but usually contains many lymphocytes (unless the patient has been given steroids). AChR epitopes may be expressed by the neoplastic epithelium. It seems probable that the thymoma epithelium sensitises T cells to these AChR epitopes, and that the T cells leave the thymus and initiate antibodies against AChR, and other muscle antigens, in the periphery.[18] Buckley and colleagues[45] showed that mature T cells generated by the thymoma can persist in the periphery for several years after removal of the tumour. The number of these T cells increases substantially if the tumour recurs, potentially providing a new technique for identifying tumour recurrence.

Differential diagnosis of myasthenia gravis

Generalised myasthenia
Other neuromuscular junction disorders:
- Lambert-Eaton myasthenic syndrome
- Congenital myasthenic syndromes
- Neurotoxins
  - Botulism
  - Venoms (snakes, scorpions, spiders)

Idiopathic inflammatory demyelinating polyradiculoneuropathies
- Acute (Guillain-Barré)-motor type
- Miller Fisher syndrome
- Chronic

Many myopathies (idiopathic inflammatory, metabolic, dystrophies [rarely])

Bulbar myasthenia
Brain stem stroke
Motor-neurone disease (pseudobulbar palsy)

Ocular myasthenia
Mitochondrial cytopathy (chronic progressive external ophthalmoplegia)
Oculopharyngeal muscular dystrophy
Thyroid ophthalmopathy
Other causes of ptosis eg, contact-lens syndrome
Brain-stem lesions

Diagnosis

AChR antibodies are positive in about 85% of patients with generalised disease, and when identified, are diagnostic for myasthenia gravis. The classic neurophysiological finding is an increased decrement (>10%) of the evoked compound muscle action potential in response to repetitive supramaximum nerve stimulation at 3 Hz.[46] More sensitive, but less widely available, is single fibre electromyography. This test measures the firing time of two muscle fibres within the same motor unit. In neuromuscular junction disorders, and in denervation, there is increased variability (jitter), and occasional blocking of impulses.[46] In the edrophonium (Cambridge Laboratories, Newcastle-upon-Tyne, England) (tensilon or camsilon) test, a shortacting anticholinesterase is given intravenously. There is rapid (within 2 min) but short-lived (less than 5 min) improvement in strength in most patients with myasthenia gravis. However, false-positive and false-negative results can occur, and there is a small risk of cardiorespiratory collapse. Once the diagnosis has been made, computed tomography or magnetic resonance imaging of the chest should be done to exclude an associated thymoma. Thyroid function and thyroid antibodies should be measured, because of the increased frequency of thyroid disease.

The differential diagnosis of myasthenia gravis is wide (panel), although in practice, most patients do not present major diagnostic difficulties. As noted, a positive AChR antibody test is diagnostic of the disease, since false positives are very rare. A particularly common difficulty is the differentiation of ocular myasthenia gravis (of whom about 50% are AChR antibody-negative), and mitochondrial cytopathy. Another major practical problem is patients with generalised weakness, who are negative for AChR antibodies—their differential diagnosis includes neuropathies and myopathies (panel), and other disorders of the neuromuscular junction (in which neurophysiological studies might show changes similar to those of myasthenia gravis).

Treatment

Oral anticholinesterase treatment, such as pyridostigmine, is the first-line treatment in patients with mild myasthenia gravis. High concentrations of these drugs can precipitate a cholinergic crisis, and the daily dose of pyridostigmine should only very rarely exceed 450 mg. Muscarinic anticholinergic agents such as propantheline may be used to counteract occasionally troublesome gastrointestinal side-effects, such as abdominal cramping, and diarrhoea.[47,48]

Thymectomy is currently done early in young-onset, AChR antibody-positive patients with generalised myasthenia gravis as a therapeutic option. Evidence from retrospective uncontrolled studies suggests benefits, but is not conclusive.[49] Surgery alone, or with radiotherapy and chemotherapy, is indicated for the treatment of thymoma, but does not usually improve myasthenia.[14] Thymectomy is not usually beneficial in late-onset patients, and is seldom done in ocular disease. It is also not undertaken in AChR antibody-negative patients at some centres, because such patients rarely show thymic abnormalities. If symptoms are not well controlled on such treatments then immunosuppression treatment is indicated.[47,48] Prednisolone is the mainstay of treatment. An alternate day regimen is used to keep side-effects to a minimum (and osteoporosis prophylaxis is mandatory). Treatment is best started at a low dose and gradually increased, because high doses might exacerbate myasthenic weakness. On remission, the dose is gradually reduced, and the minimum dose needed to maintain remission established. Azathioprine can be added, either initially, or later, as an effective steroid-sparing agent, although it might take over 1 year to achieve maximum benefit.[50] Prednisolone with azathioprine is more effective, and better tolerated, than prednisolone alone.[50] Ciclosporin, methotrexate, and cyclophosphamide can be useful in poor responders, or in those who are not able to tolerate azathioprine. In severely affected patients, plasma exchange,[29] or intravenous immunoglobulins can produce a striking, albeit temporary improvement, and can also be useful in the reduction of severe weakness that poses an anaesthetic risk before thymectomy.[51] Myasthenia gravis is one of the best examples of a disease caused by autoimmunity to a specific antigen; there are many possibilities for more antigen-specific therapies that have, so far, only been tested in animals.

Other neuromuscular junction disorders

Although other neuromuscular junction disorders are much less common, they might be misdiagnosed as seronegative myasthenia. The Lambert–Eaton myasthenic syndrome is caused by antibodies to voltage-gated calcium channels on the presynaptic nerve terminal of the motor nerve. Electromyographic findings can be distinguished from those of myasthenia gravis by the presence of a small compound muscle action potential at rest, and an increase in the amplitude of the action potential after maximum voluntary contraction.[3,52] Diagnosis can be confirmed in most patients by detection of antibodies to voltage-gated calcium channels. In about 50% of patients there is an associated small-cell lung cancer that can postdate the onset of this paraneoplastic syndrome by up to several years. In these patients, neurological signs frequently improve after removal of the tumour. Small-cell lung carcinoma can also be associated with cerebellar ataxia. Antibodies to a neuronal nuclear protein called Hu, or calcium-channel antibodies, or both, can be seen in such patients.[53] 3,4-diaminopyridine prolongs the motor-nerve action potential, thereby increasing neurotransmitter release, and is frequently a highly effective treatment for the Lambert-Eaton myasthenic syndrome. It can be used in combination with anticholinesterases. In the UK, 3,4-diaminopyridine is restricted to specialist pharmacies, on a named patient basis only. In patients who do not respond to 3,4-diaminopyridine, prednisolone combined with azathioprine or ciclosporin can be effective in those without cancer, whereas prednisolone alone is usually used in patients with cancer.

Acquired neuromyotonia is another autoimmune disorder, frequently caused by antibodies to the voltage-gated potassium channels being present at motor-nerve terminals. Most patients present with muscle twitches (fasciculations and myokymia) and cramps. However, the disorder can co-exist with neuropathies or with myasthenia gravis (particularly if a thymoma is present), and muscle weakness can be the major complaint. Antibodies to potassium channels can be measured in specialist centres, but the diagnosis rests on characteristic electromyographic findings. Membrane stabilisers such as carbamazepine and phenytoin are sometimes sufficient to control the hyperactivity. Immunomodulatory treatments are occasionally necessary.[2,54]

Congenital myasthenic syndromes are rare, but need to be distinguished from myasthenia gravis because, although patients might respond to anticholinesterases, and/or 3,4–diaminopyridine, they should not receive immunosuppressive treatments or thymectomy. The syndromes are a heterogeneous group of disorders, many already with identified genetic mutations.[3,55,56] Presynaptic, synaptic, and postsynaptic forms exist. Most are autosomally recessively inherited. They typically present before the age of 2 years with similar symptoms to myasthenia gravis. The disorder might be difficult to distinguish from rare cases of very early-onset disease without AChR antibodies, and from mitochondrial myopathies.

The most common congenital disorder of the neuromuscular junction is a postsynaptic reduction in the number of AChRs caused by mutations in the ϵ subunit (specific to the adult isoform) of the AChR. The non-lethal nature of the mutation is probably accounted for by persistence of the fetal form of the AChR receptor, which uses a γ instead of an ϵ subunit. Other rarer postsynaptic syndromes involve abnormal AChR channel opening kinetics, such as the slow channel syndrome. This syndrome can present in infancy, or in adult life, and characteristically involves the scapular and forearm muscles. It differs from other congenital myasthenic syndromes in that it is dominantly inherited, has additional electromyographic and pathological findings, and might be worsened by anticholinesterases and 3,4–diaminopyridine. Acetylcholinesterase deficiency is caused by a mutation in the collagen-like molecule that anchors AChE in the synaptic cleft. There is severe weakness and wasting, and characteristically, a slow pupillary response to light. Patients with this deficiency do not respond to anticholinesterase drugs. Finally, mutations in the enzyme that synthesises acetylcholine have been demonstrated in a presynaptic form of congenital myasthenic syndrome with episodic apnoea.[57]

We thank Prof John Newsom-Davis for his helpful comments.

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The uses of error: Sharing with colleagues

Let's call him John—a calm and lithe 15-year-old who came to see me with his father in 1980 because of epileptic fits. The eldest of three children, he wanted to follow his father's footsteps and become an accountant. When not at school, he spent most of his time with sports, especially competitive swimming, speed skating, and volleyball.

The problem was not the diagnosis, which was offered to me on a silver tray. John had had four fits in five years' time: on each occasion it had been provoked by flickering lights. With the first two attacks he had been found on the floor, in front of the television set. The last two fits occurred in the car, with the glare of a low winter sun ahead, rhythmically interrupted by trees or buildings.

I had qualified as a neurologist only a few years previously, and my experience with managing epilepsy was limited. Yet for some reason their general practitioner must have advised them to see me. The outpatient facilities in the institution where I then worked were so cramped that consultants had to see the occasional outpatient in their personal office. Despite the usually open atmosphere in the department, such encounters were thus shielded by an air of privacy. Everything else was discussed extensively, but not one's "own" patients. I should point out there was not the slightest financial incentive in this system.

As it did not occur to me to discuss this case with my colleagues, I bought a monograph on photosensitive epilepsy. The intricacies of the EEG were explained much better than a course of action, but I had worked out some practical measures by the time John and his father came back to hear about the results of the CT scan (predictably normal) and the EEG (predictably abnormal—ie, photosensitivity).

My advice was to wear sunglasses when appropriate, to watch television only at a distance and with sidelight, and not to swim or cycle unaccompanied.

Textbooks now advise sodium valproate when conservative methods fail, and it may have even been available here at that time. I should have conferred with more senior colleagues when John and his father came back six months later. His friends had suddenly spotted him on the bottom of the swimming pool; he was brought up and had a brief spell in an intensive care unit. He had slept very little the night before, and there had been bright sunshine with strong reflections on the water.

I prescribed increased wearing of sunglasses. Another six months later his father came to see me—alone. John had been fishing and was found drowned in a ditch that was only two feet deep. It had been a sunny day.

There was not even a hint of reproach in the father's account. He only wanted to share his grief with me. That is one reason why John haunts me most of all whenever I pay a visit to my secret churchyard—as so many colleagues must do.

I have made worse blunders, but with somewhat better excuses: missing infective endocarditis in a young man with hemiplegia, fever and a bruit (Osler's triad, but the cardiologist maintained it was a functional bruit), diagnosing bacterial meningitis only at autopsy (steroids had suppressed fever and inflammatory response), and repeating this experience with a brain abscess (the radiologist and the neurosurgeon had agreed it was a tumour).

What error did I make in John's case? Undue reluctance to give drugs to such a healthy child? Perhaps. The main error was not to share the problem with a more experienced colleague. I remember whispering a few words to someone, but I wasted the opportunity to exploit the full potential of an academic department. John might then have had a better chance.

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