Myasthenia Gravis and Its Aeromedical Implications

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BACKGROUND: Myasthenia gravis is an autoimmune condition where antibodies form against the acetylcholine receptors at the neuromuscular junction, eventually causing damage to the motor end plate. The clinical features include muscle fatigability as well as ocular, bulbar, and limb weakness, which can have implications on the role of a pilot or air traffic controller. This retrospective study reviewed the United Kingdom Civil Aviation Authority (UK CAA) experience of myasthenia gravis.

METHODS: A search of the United Kingdom Civil Aviation Authority medical records database from 1990 to 2016 identified 11 individuals with a diagnosis of myasthenia gravis. Data were extracted for the class of medical certificate, age at diagnosis, symptoms, acetylcholine receptor antibody status, treatment, the time from diagnosis to loss of medical certification, and the reasons for loss of certification.

RESULTS: There were two Class 1 certificate holders (for professional flying) and six Class 2 certificate holders (for private pilot flying) and three air traffic controllers. The mean and median ages at diagnosis were 53 and 57 yr, respectively, with a range of 28–67 yr. The mean and median intervals from diagnosis to loss of certification were 22 and 11 mo, respectively, with a range of 0 to 108 mo.

CONCLUSION: The aeromedical implications of myasthenia gravis, including complications, types of treatment, and functional impact, are considered. A policy for medical certification following a diagnosis of myasthenia gravis is proposed.

KEYWORDS: muscle fatigability, acetylcholine receptor antibodies, myasthenic crisis, pilots.

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Myasthenia was first described by Dr. Thomas Willis in 1672,[24] but it was not until 1877 that the first detailed clinical description was made by Sir Samuel Wilks.[23] The first use of anticholinesterase drugs to treat the condition was reported by Dr. Mary Walker in the *Lancet* in 1934[22] and the first successful thymectomy for myasthenia was performed by Alfred Blalock at Johns Hopkins University in 1936.[4] However, it was only in 1960 that myasthenia was recognized by Dr. John Simpson as an autoimmune disease in which antibodies form against the acetylcholine receptors at the neuromuscular junction, blocking neuromuscular transmission and eventually causing damage to the end plate.[19] It is a rare condition with an annual incidence of between 0.25 and 2 per 100,000.[21] There is no racial predominance and there are two age peaks for incidence: an early one in the fourth decade, which is mostly female, and a later one in the seventh and eighth decades, which is mostly male.[21] There are many different types of myasthenia: pure ocular, generalized, congenital, neonatal, juvenile, familial, the myasthenic syndrome (Lambert Eaton), and drug-induced myasthenia; however, the pure ocular and generalized types are most relevant to the pilot population.

About 50% of patients with myasthenia present with ocular symptoms from extraocular muscle weakness, causing ptosis and diplopia. Up to two-thirds of these patients will progress to develop generalized myasthenia, most within the first year (80%) and almost all (95%) by 3 yr.[3] Only about 15% of patients initially present with bulbar symptoms and less than 5% present with limb weakness alone.[11] In generalized myasthenia, the disease affects other systems in addition to ocular involvement and can include bulbar, facial, neck, limb, and respiratory muscles.

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Diagnostic investigations include the Tensilon test, where an intravenous injection of edrophonium may produce a dramatic symptomatic improvement in muscle strength that only lasts a few minutes. The test requires cardiac monitoring for arrhythmias and the ready availability of the reversal agent atropine.[12] Acetylcholine receptor antibodies (AChRAbs) are positive in about 85% of patients with generalized myasthenia and in about 50% of patients with pure ocular myasthenia. In those with generalized myasthenia who are AChRAb negative, about 40% have antibodies to muscle specific kinase receptors that are involved in neuromuscular junction development.[14] A CT scan or MRI of the chest should be performed as 60–70% have thymic hyperplasia and 10–15% have a thymoma.[18] Striated muscle antibodies are a useful marker for the presence of a thymoma, being positive 80% of the time.[7] Thyroid dysfunction is common in myasthenia, as both hyperthyroidism and hypothyroidism, so thyroid function and auto-antibodies tests should be undertaken. Electromyography can confirm the diagnosis, as there is a detriment on repetitive stimulation and concentric-needle single-fiber recording shows a characteristic 'jitter' pattern.[1,9]

Initial management of mild myasthenia gravis is with pyridostigmine, an acetylcholinesterase inhibitor that reduces the breakdown of acetylcholine, increasing bioavailability at the neuromuscular junction. The standard formulation has a half-life of 4 h and the long acting preparation of about 10 h. Plasmapheresis and intravenous immunoglobulin may be used in active disease to produce a rapid response; for example, in a patient awaiting thymectomy or in a myasthenic crisis. Immunosuppression is commonly required for long-term maintenance therapy and is usually with steroids combined with azathioprine as a steroid-sparing agent. If this does not produce a satisfactory response, other immunosuppressive drugs such as methotrexate, cyclosporin, mycophenolate, cyclophosphamide, or rituximab may be used.

The thymus is a source of antibodies and thymectomy may be a very effective treatment. Thymectomy is indicated in all patients with a thymoma. If complete excision of the thymus gland is not possible, it is followed by radiotherapy. Thymectomy for patients without a thymoma or thymic hyperplasia may also be beneficial, particularly if they are AChRAb positive.[6,25]

METHODS

The UK CAA medical database holds personal details and medical history on all applicants and medical certificate holders from 1990 to 2016. A search of this database was undertaken for the diagnostic terms 'myasthenia' and 'myasthenia gravis'. For each subject identified, the medical record was reviewed for gender, age at diagnosis, symptoms, acetylcholine receptor antibody status, treatment, time from diagnosis to loss of medical certification, and the reasons for loss of certification. Ethical approval was not required for this anonymized study.

RESULTS

There were 11 cases of myasthenia gravis identified. Eight were pilots, two of whom were European Union Class 1 certificate holders (for professional flying) and six were European Union Class 2 certificate holders (for private flying). There were three air traffic control officers (ATCOs) who held European Class 3 certificates. All subjects were men. At diagnosis, the mean age was 53 yr, the median age was 57 yr, and the range was 28 to 67 yr.

There was a lack of data on four subjects. This is a problem when using a regulatory medical database as an individual may choose not to seek recertification on declaration of a medical condition, so the regulator may not receive further medical details. Of the seven remaining subjects, none had pure ocular myasthenia and all had generalized myasthenia: four with ocular symptoms, three with bulbar symptoms, six with limb symptoms, and two with facial symptoms. Five subjects were AChRAb positive. Four had undergone a thymectomy, six had been treated with pyridostigmine, three with azathioprine, and two with prednisolone.

The mean time from first symptoms to diagnosis was 5 mo. Reasons for this delay included the length of time taken to complete all investigations to reach a definitive diagnosis and individuals ignoring and not realizing the significance of early symptoms, which were often intermittent. Anecdotal reports in the medical notes were indicative of this; for example, one subject only noticed mild fatigue after running and did not seek medical attention until 6 mo later. Most subjects informed the regulator at the time of diagnosis and not when they initially developed symptoms. The normal certificatory process is that the medical certificate is temporarily suspended on declaration of the diagnosis and following the regulatory assessment, recertification can proceed if the medical requirements are met.

There were two Class 1 certificate holders; one had not yet pursued a flying career and chose to lapse to Class 2 certification for private flying following the diagnosis at the age of 32. The other held a private pilot's license and was undergoing professional flying training when diagnosed at the age of 28. He regained Class 1 certification with a multicrew restriction and has continued to pursue flying training for the last 2 yr.

There were six Class 2 certificate holders: three diagnosed at the ages of 57, 60, and 63 who did not reapply for medical certification and three diagnosed at the ages of 47, 65, and 67 who did regain certification. Of the latter three, one gained unrestricted certification and resumed flying for 4 yr, another had a safety pilot restriction for the first year and then unrestricted certification for a subsequent 8 yr, and another gained a lower standard of medical certification for a light aircraft pilot's license (LAPL) 12 yr later.

Of the three ATCOs, diagnosed at the ages of 53, 56, and 58, one was recertificated with 'A Proximity Condition' limitation, which is a UK restriction mandating the presence of another suitably qualified ATCO nearby to take over controlling expeditiously in the event of a medical incapacitation. This ATCO continued controlling for almost 3 yr until disease progression

resulted in loss of certification. The other two ATCOs relinquished certification on declaration of the diagnosis; however, one successfully gained a LAPL for private flying 8 yr later.

The mean time from diagnosis to loss of certification for all subjects was 22 mo and the median was 11 mo. The large difference between the median and mean reflects the wide variation in the severity of the disease and the small number of subjects. All subjects who presented with ocular symptoms lost certification on declaration of the diagnosis. The longest that a pilot continued to fly after a diagnosis was 9 yr, which was in a private pilot diagnosed at the age of 47 who had been treated with a thymectomy and prednisolone.

DISCUSSION

Concerns for aeromedical certification are clinical features that could affect any aspect of the flying or controlling role. These include visual impairment with ocular involvement, difficulties with speech and the interaction with pilots or air traffic control with bulbar involvement, and limb weakness that could affect the use of aircraft controls and controller switches. A particular problem in myasthenia is muscle fatigability, which is difficult to assess, partly due to the diurnal and between day variability and the fluctuating course of the disease. Furthermore, the exacerbating factors are unpredictable and include infections, systemic illnesses, excessive heat, exercise, and stress. Certain drugs can exacerbate the condition, such as beta-blockers, including atenolol and bisoprolol, antimalarials, including chloroquine and doxycycline, and antibiotics, such as ciprofloxacin and erythromycin, and certificate holders should be warned of this.

A major concern is the risk of a myasthenic crisis, which is a life-threatening condition that occurs from a combination of respiratory and bulbar muscle weakness, causing respiratory failure requiring mechanical ventilation. Berrouschot[2] reported a group of 235 myasthenic patients in which 19% had experienced one or more crises. Of these, 57% had only one crisis, 32% had two, and 11% had three or more. The average annual risk of a myasthenic crisis was 2.5%; however, this included those who had more than one crisis. The time from deterioration of symptoms to ventilation was 1 d to 3 wk, with two-thirds (68%) requiring ventilation within 3 d. The commonest causes of myasthenic crises were progressive myasthenic weakness (32%), respiratory infection (27%), and post-thymectomy (17%).[2] Another study showed that in 30% of patients who had experienced a myasthenic crisis, it was the initial presenting feature.[15] Most crises occurred within the first year of disease onset,[16,20] but these have been reported up to 6 yr after diagnosis.[15] However, myasthenic crises are usually seen in patients with severe and poorly controlled disease who would not be eligible for certification.

A cholinergic crisis can occur with excessive anticholinesterase medication, usually due to over self-medication by the patient and the treatment is to reduce the dose. Both muscarinic and nicotinic toxicity can occur and symptoms include nausea, vomiting, diarrhea, bradycardia, fasciculations and an increase in pulmonary secretions, lacrimation, and salivation. Cholinergic crises are most likely in the first year of treatment and are avoidable with appropriate patient education.

The adverse effects of medication need to be considered. Pyridostigmine may cause abdominal pain, diarrhea, nausea, sweating, and bradycardia. There is the potential for a wearing-off effect at the end of each dose. Prednisolone can cause psychiatric effects; however, this is usually only seen at doses of greater than 40 mg per day.[5] Immunosuppressants, such as azathioprine, mycophenolate mofetil, and cyclosporin, have adverse effects specific to the drug, including hepatotoxic and nephrotoxic effects, which require appropriate monitoring.

The policies of civilian regulatory authorities vary worldwide: Transport Canada allows certification once the applicant is in remission and stable, with little or no medication, 2 yr after thymectomy.[13] The U.S. Federal Aviation Administration requires assessment of functional status, including the degree of impairment as measured by strength, range of motion, and pain.[10] Australia's Civil Aviation Safety Authority has no specific published guidance for the disease. The United Kingdom follows the European Union Regulations issued by the European Aviation Safety Agency for pilots[8] and the European Class 3 Requirements issued by Eurocontrol for ATCOs,[17] neither of which have specific guidance for myasthenia gravis.

A certificatory policy for myasthenia is proposed. If clinically indicated, a thymectomy is undertaken prior to certification. Ocular symptoms preclude medical certification, including ocular symptoms controlled on medication, due to the risk of possible breakthrough visual symptoms. A history of ocular involvement, which is in prolonged remission and no longer dependent on medication, may be considered for certification. A history of previous myasthenic crises is disqualifying for all classes of certification, as this usually indicates severe and poorly controlled disease and is associated with a risk of recurrence. The condition must be stable and in remission for at least 3 mo, with no, or only minimal and nonocular symptoms, before a return to flying or air traffic control. If on maintenance medication, there must be no adverse effects and no end of dose effects. Acceptable maintenance medication is pyridostigmine up to 360 mg daily, prednisolone up to 10 mg a day, and immunosuppressants with acceptable side effect profiles and appropriate monitoring. A medical flight test in an aircraft or a simulator check is required to assess for any functional impairment in the relevant working environment, with special attention paid to the possibility of fatigability throughout the duration of the test. In all cases, even for those without obvious ocular involvement, specialist assessments with both a neurologist and an ophthalmologist are required prior to certification.

Professional pilots require a multicrew restriction as a long-term limitation in view of the risk of muscle fatigue, myasthenic crisis, and progression of the disease. In those individuals who have had a history of pure ocular myasthenia, there remains a risk of relapse, which precludes unrestricted professional certification. Private pilots with a diagnosis of myasthenia can gain unrestricted medical certification; however, consideration may

be given to whether a safety-pilot restriction is appropriate in some cases.

Follow-up specialist neurology and ophthalmology reviews are required on a 3-mo basis for the first year, as this is when disease progression and problems with medication are most likely to occur, and thereafter on a 6-mo basis. Functional assessments in the form of medical flight tests in the aircraft or simulator checks are required at least every 6 mo. Any change in medication requires a period of disease stability without side effects for at least 3 mo prior to a return to flying and air traffic control. In conclusion, the UK CAA experience is that pilots and ATCOs with a diagnosis of myasthenia gravis can be granted certification with close medical surveillance, depending on the clinical features, treatment, and functional impact of the disease.

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