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CASE REPORT

Misdiagnosis of Myasthenia Gravis and Subsequent Clinical Implication

A case report and review of literature

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الخطأ في تشخيص مرض الوهن العصبي والآثار السريرية اللاحقة

تقرير حالة ومراجعة الأدبيات

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الملخص: يمكن لمرض الوهن العضلي الوبيل المتعلق بالمناعة الذاتية محاكاة مجموعة متنوعة من الاضطرابات العصبية مما يؤدي إلى تأخير في التشخيص والعلاج. وفي بعض الأحيان يؤدي الخطأ في تشخيص المرض إلى تدخلات علاجية غير ضرورية وربما تكون ضارة. ندرج في هذا التقرير حالة طفل في الثانية عشرة من عمره مصاب بمرض الوهن العضلي الوبيل، حيث شخصت حالته خطأ على إنها مضاعفات ناتجة عن التهاب السحايا، وبالتالي نجم عن الاعتلال العصبي/العضلي معاناة هذا المريض من هذه الحالة مدة تقارب عقداً من الزمن. نتج عن التشخيص الصحيح للحالة المرضية والعلاج الأمثل لها تحسناً كبيراً في الحالة الوظيفية. وسوف نناقش في هذا التقرير أهمية أخذ مرض الوهن العضلي الوبيل في التشخيص التفريقي المحتمل للحالات المرضية الأخرى كحالة فشل المضخة التنفسية المتكرر، أو إحدى مضاعفات الشلل البصلي، إذ أن هناك نقصاً في الإثبات الوثائقي للتشخيصات المذكورة آنفاً والتي تتضمن إجراءات التشخيص لمرض الوهن العضلي الوبيل. كما نستعرض في هذا التقرير الأدبيات الطبية المنشورة عن خطأ تشخيص مرض الوهن العضلي الوبيل، وسنركز على مخاطر ذلك.

مفتاح الكلمات: مرض الوهن العضلي الوبيل، الشلل البصلي، التهاب الرئة، إلتهاب السحايا، مضاعفات مرض معين (عقابِيل)، تقرير حالة، عمان.

ABSTRACT: The autoimmune disease, myasthenia gravis (MG), can mimic a variety of neurological disorders leading to a delay in diagnosis and treatment. On occasions, misdiagnosis of MG could lead to unnecessary and potentially harmful therapeutic interventions. We report on a 12 year-old boy, in whom MG was mistaken for meningitic sequelae and subsequently for critical neuropathy/myopathy resulting in considerable morbidity for nearly a decade. Subsequent correct diagnosis and optimal management resulted in significant improvement in his functional status. We discuss the importance of considering MG as one of the potential differential diagnoses among cases of recurrent respiratory pump failure, or unexplained bulbar symptoms where documentary proof of the previous diagnoses including work-up for MG is lacking. We also review the literature on MG misdiagnosis and highlight the potential pitfalls in MG diagnosis.

Keywords: Myasthenia gravis; Bulbar palsy; Pneumonia; Meningitis, sequelae; Case report; Oman.

Acquired myasthenia gravis (MG) is an eminently treatable neuromuscular disorder characterised by autoimmunity against postsynaptic antigenic epitopes such as the skeletal muscle acetyl choline receptor or muscle-specific tyrosine kinase (MuSK).[1–3] While the typical clinical manifestations include ocular and generalised (with or without bulbar paresis) forms, occasional cases might pose diagnostic challenges with atypical manifestations.[4–9] A high index of clinical suspicion is required in these circumstances to avoid unnecessary delay in the diagnosis and treatment. Further, failure to reconsider the other diagnoses entertained on previous medical evaluation, but not based on solid clinical evidence (for instance, lack of documentation or inability to ascertain the diagnosis from previous clinical or laboratory records), could hinder further diagnostic and therapeutic endeavours. In this report, we provide the clinical account of a young

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Table 1. Differential diagnosis of oculo-bulbar syndrome with limb girdle weakness

Neuromuscular junctional disorder
Autoimmune myasthenia gravis
Congenital myasthenia
Eaton Lambert myasthenic syndrome
Botulism
Tick paralysis
Snake bite with envenomation
Organo-phosphorus compound poisoning
Myopathy
Oculo-pharyngeal dystrophy
Limb girdle muscular dystrophy
Inclusion body myositis
Critical illness myopathy
Radiculo-neuropathy
Guillain-Barré syndrome (including polyneuritis cranialis)
Chronic inflammatory demyelinating polyradiculoneuropathy
Heavy metal poisoning
Diphtheritic neuropathy
Critical illness neuropathy
Central nervous system disorders
Motor neuron disease
Mutiple sclerosis
Brain stem lesion: posterior circulation stroke, glioma
Sequelae of basal meningitis
Locked-in syndrome
Psychiatric disorders
Conversion disorders

man with MG in whom the bulbar symptom was attributed to the sequelae of basal meningitis in childhood and subsequently to critical neuropathy/myopathy which was followed by a prolonged delay in reaching the ultimate diagnosis. We highlight the importance of early diagnostic consideration of MG and provide a review of English language medical literature on MG misdiagnosis; for this we used search terms such as myasthenia gravis, misdiagnosis, and diagnostic errors in PubMed for the period 1988 to 2010.

Case Report

A 12 year-old boy developed hoarseness of voice and dysphagia with nasal regurgitation for liquids following a febrile illness. Basal meningitis was suspected and the bulbar symptoms (dysphagia, difficulty in chewing and dysarthria) were attributed to lower cranial nerve palsies as part of meningitic sequelae. Full details of this diagnostic evaluation and management could not be ascertained at a later date. At age 18, he underwent flexible laryngoscopy that was reported to have shown bowing of the left vocal cord. Following that finding, augmentation and medialisation of the left vocal cord and palatapexy were performed with questionable improvement of his voice and dysphagia.

At age 19, he developed lethargy, weight loss, nocturnal dyspnoea of 2 month duration and aspiration pneumonia in the left mid-zone and type II respiratory failure. He required prolonged ventilatory assistance followed by tracheostomy despite adequate antibiotic coverage. Neurologically, he demonstrated intermittent confusion, ophthalmoparesis, bifacial weakness, reduced palatal movements with hypoactive gag reflex, and mild to moderate proximal weakness in arms and legs. Critical illness neuropathy/myopathy was suspected at that point in time because of a difficulty in weaning him off the ventilator. Phrenic nerve conduction was within normal limits and needle electromyography (EMG) did not reveal any evidence of denervation or myopathic changes. Serum creatine kinase and a computed tomography (CT) scan of the brain were normal. Apart from an abnormal blood gas study, suggestive of type II respiratory failure prior to mechanical ventilation and elevated C reactive protein, his other laboratory parameters, including basic metabolic profile, were within normal limits. To prevent further episodes of aspiration, he underwent percutaneous endoscopic feeding gastrostomy. After weaning him off the ventilator and subsequent hospital discharge, he later required multiple hospitalisations for optimisation of his respiratory care and care of the permanent tracheostomy.

At age 21, he required ventilatory assistance (through a miniventilator connected through the tracheostomy) and was evaluated in our institution. Neurologically, he was conscious and demonstrated bilateral ophthalmoparesis (but no blepharoptosis)

Table 2: Literature review on misdiagnosis/masquerade of myasthenia gravis (MG)

Initial misdiagnosis/ masquerade (with reference no.)	Number of patients	Age (in years) at MG diagnosis	Gender M or F	Time to MG diagnosis after symptom onset	Comments
Posterior circulation stroke[4,6]	4	91 77 66 58	All F	1 yr 3 wks; several mos; 9 days; 3 days	Initial treatment included anticoagulation for the stroke mimic. MG diagnostic consideration was prompted by negative brain imaging, along with thymic lesion, when present, and subsequently confirmed by electrophysiological studies, or positive edrophonium test, or elevated serum acetyl choline receptor antibody titre. *Lesson*: Incidental brain infarcts should be interpreted with caution in elderly patients.
Blepharospasm[8]	2	74 57	Both M	4 yrs, 3 mos; 7 yrs, 9 mos	Periocular injection with botulinum toxin for the initial treatment resulted in prolonged and complete ptosis. Blinking that returned after wearing-off of the toxin effect and the subsequent fluctuating ptosis was confirmed to be due to MG by electrophysiological study. Further, the ptosis improved with MG treatment. *Lesson:* Isolated blinking mimicking blepharospasm could be the initial atypical presentation of MG in occasional patients.
Amyotrophic lateral sclerosis[9]	1	38	F	4 yrs	Bulbar symptoms, ventilatory assistance and muscle denervation in leg muscles simulated amyotrophic lateral sclerosis. Symptoms and signs were confirmed to be due to MG by electrophysiological study and improved with MG treatment. Initial finding of muscle denervation was attributed to functional nerve and muscle disconnection in that the spontaneous muscle activity disappeared with MG treatment. *Lesson:* MG may masquerade as other neuromuscular disorders.
Velopharyngeal incompetence[9]	1	17	F	3.5 yrs	Bulbar symptoms, especially nasal speech was misdiagnosed with velopharyngeal incompetence, though the patient lacked the associated findings of cleft (or submucosal cleft) palate. Subsequent generalised weakness with fatiguability and a positive edrophonium test clinched the diagnosis of MG. *Lesson:* A broader differential diagnosis for bulbar symptoms would avoid missing the diagnosis of MG.
No diagnosis of MG[9]	1	18	F	2.5 yrs	Fatiguable ptosis, diplopia and bulbar symptoms in pregnancy were ignored and the clinical status was presumed to be normal. Subsequently MG diagnosis was confirmed with a positive edrophonium test, electrophysiological study and elevated titer of serum acetyl choline receptor antibody. *Lesson:* Careful clinical evaluation, including tests for fatiguability and ordering the appropriate tests for MG would avoid diagnostic uncertainty.
Myofacial pain syndrome[7]	1	20	F	3 mos	The primary symptom was facial pain and cheek swelling with worsening in the later part of the day. Presence of bilateral ptosis, weakness of jaw closure and fatiguability while speaking along with a positive edrophonium test and electrophysiological study confirmed MG diagnosis. *Lesson:* Occasionally, non-specific musculo-skeletal symptoms might override the classical MG symptoms. So, the advice is to look carefully for MG clinical signs and arrange the appropriate tests.
Hysteria[5]	1	54	M	Several mos	Initial complaint of generalized weakness was associated with over-reactivity and anxious behaviour. Subsequent progressive dysphagia and limb weakness prompted diagnostic evaluation and confirmation of MG. *Lesson:* Neurotic symptoms could be present along with MG or be a reaction to MG signs and symptoms.

with good pupillary reaction, bifacial weakness, bulbar palsy, neck muscle weakness and mild to moderate weakness (with subtle fatiguability of weakness) in his upper and lower limbs. There was no family history of neuromuscular disorders. In view of subtle fatiguability of limb weakness, pupil-sparing ophthalmoparesis, recurrent exacerbation of cranial-motor symptoms, and well preserved cognitive function, a possibility of myasthenia gravis was considered. Repetitive nerve stimulation test at 3 Hertz revealed significant decremental response from the right facial nerve (recording from nasalis: a decrement of 47% between the first and fourth compound muscle action potentials at rest) and right accessory nerve (recording from trapezius: a decrement of 38%). On pharmacological testing with edrophonium, there was significant improvement of ocular mobility and limb weakness. Chest imaging did not reveal thymoma. He was subsequently treated with immunoglobins (as we did not at that time have access to plasma exchange) and pyridostigmine to which the immunosuppressive medications (prednisolone and azathioprine) were added. The serum anti-acetylcholine receptor antibody test later turned out to be negative. However, the anti-MuSK antibody titer was elevated (14.2 nmol/l; normal range <0.4 nmol/l). This result was obtained in a reference laboratory in France at a later date. The patient had improvement of his bulbar symptoms, ocular motility and limb weakness and was discharged with a home ventilator. After discharge, he could breathe spontaneously without the need to use the home ventilator and he successfully pursued college education. The prednisolone was subsequently tapered and he was maintained on azathioprine. Later, he was hospitalised twice for pneumonia and at the time of his latest hospitalisation, the sputum grew *Pseudomonas aeruginosa* that was successfully treated with antibiotics, ventilatory support, and intravenous immunoglobulins. The MG medications were further optimised. He was subsequently discharged with significant improvement in his functional status. The MG was classed as Myasthenia Gravis Foundation of America Clinical Class IIa and he was treated with pyridostigmine, prednisolone and azathioprine. Regular follow-up in the ambulatory clinic was planned.

Discussion

Our patient had anti-MuSK antibody positive MG with prominent bulbar symptoms that were mistaken for meningitic sequelae and critical illness neuropathy/myopathy. This case illustrates the diagnostic challenges posed by MG and the importance of entertaining the diagnosis in the first place in the case of patients presenting with rather unexplained bulbar symptoms, aspiration pneumonia and respiratory insufficiency. Such an atypical presentation, in the absence of ptosis, does not exclude MG. Careful evaluation for other ocular-motor and facial weaknesses and clinical tests for fatiguability would aid in the clinical diagnosis, as well as arranging for appropriate pharmacological, electrophysiological, serological and imaging studies. Further, the management pathways should include reconsideration of previous diagnoses at different times, specifically in the context of a poorly documented diagnostic entity in the past. Timely diagnosis of MG is crucial and would obviate the need for needless surgical procedure(s), or potentially harmful interventions with significant morbidity and negative influence on the quality of life.

Table 1 shows other neurological disorders and competing diagnoses that MG could mimic. The oculopharyngeal symptoms, with or without limb weakness, could be mistaken for oculo-pharnygeal muscular dystrophy, or mitochondrial cytopathy. In the acute setting, differential diagnoses include: posterior circulation stroke;[4,6] atypical Guillain-Barré syndrome (polyneuritis cranialis); botulism (distinguished by pupillary involvement in botulism); heavy metal poisoning; tick paralysis, and snake bite with envenomation. In the absence of ocular symptoms and signs, limb girdle myasthenia could be misdiagnosed as muscular dystrophy. Rarely, the condition could be confused with central nervous system disorder such as demyelinating disorder—especially in the presence of pseudo-internuclear ophthalmoplegia[10] and easily elicitable deep tendon reflexes. A PubMed search revealed 11 cases of MG which were initially misdiagnosed, or had atypical presentations, leading to a delay in the ultimate diagnosis and treatment.[4–9] The patients with initial misdiagnoses had bulbar symptoms that prompted consideration of posterior circulation stroke in the acute setting,[4–6] or amyotrophic lateral

sclerosis, or velopharyngeal incompetence[9] when the bulbar and associated symptoms were of longer duration. Other misdiagnoses include hysteria,[5] myofascial pain syndrome[7] and blepharospasm[8] [Table 2]. In our patient, there was a delay of nine years in reaching the diagnosis. This delay was compounded by the following issues: 1) occurrence or precipitation of symptoms after febrile illness, myasthenic symptoms being well known to be precipitated by systemic illness, especially infectious diseases; 2) failure to reconsider the initial diagnosis considered several years previously with unavailable documentary evidence. It is interesting to note from Table 2 that many patients with initial misdiagnosis had bulbar symptoms that prompted consideration of posterior circulation stroke in the acute setting,[4,6] or amyotrophic lateral sclerosis, or velopharyngeal incompetence[9] when the bulbar and associated symptoms were of longer duration. Fluctuating weakness would favour a diagnosis of myasthenia gravis over stroke, meningitic sequelae and critical illness neuropathy or myopathy.

Potential pitfalls in the diagnosis of MG include, first, a variable response to cholinesterase inhibitors; in fact, MG associated with anti-MUSK antibodies may, at times, not significantly benefit from treatment with cholinesterase inhibitors.[2] However, pharmacological testing with edrophonium or neostigmine for unequivocal objective benefits is warranted in all patients with oculo-bulbar symptoms with limb weakness. More importantly, the target weak muscle for such outcome should be pre-specified. A second diagnostic pitfall is subjective improvement of symptoms with cholinesterase inhibitors in occasional patients with brainstem glioma[11] or amyotrophic lateral sclerosis; this underscores the importance of considering unequivocal objective benefits while performing diagnostic testing with edrophonium or neostigmine. A third pitfall is the absence of decremental response to 3 hz repetitive nerve stimulation test in occasional patients. Volitional or stimulated single fibre electromyography (SFEMG) would be useful in this setting; normal findings (absence of abnormal jitters or block) in a clinically weak muscle virtually rules out the diagnosis of MG. However, SFEMG is not available widely and is technically demanding requiring physician patience and patient's cooperation. A fourth diagnostic pitfall is heterogeneity in clinical progression and course. Diurnal variation of symptoms may not always be apparent and the clinical tests for fatiguability may not be performed in busy clinical practice. The final pitfall is that the anti-acetyl choline receptor antibodies test, although specific for the diagnosis of autoimmune MG, is not positive in all cases of MG. These seronegative cases may harbour anti-MuSK antibodies, or low affinity anti-acetyl choline receptor antibodies.[1] Anti-MuSK antibody is most often present in women, with peak onset of the disease in the third to fourth decade.

Conclusion

In conclusion, we underscore the importance of entertaining the timely diagnosis of MG in obscure cases with oculo-bulbar-limb girdle paresis to obviate the need for unnecessary or potentially harmful therapeutic procedures. Previous diagnostic consideration with uncertain documentation should be reviewed with an open mind for the diagnosis of potentially treatable conditions such as MG, as the diagnosis could be otherwise delayed or missed.

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