Juvenile Myasthenia Gravis (JMG) is a neuromuscular disease, often characterized at onset by fatigue and fluctuating weakness. We report a case of a girl affected by severe mood disorder, in which the diagnosis of JMG and its treatment were challenged by the concomitant psychiatric condition. A 14-year-old girl, with a history of severe mood disorder and emotional dysregulation, had been treated with benzodiazepines, sertraline, and antipsychotics, reporting generalized fatigability, weakness, and drowsiness, first ascribed to her psychiatric condition and therapy. After a suicide attempt, she was hospitalized and a neurological assessment revealed a fluctuating ptosis and facial weakness, that improved with rest. The diagnosis of JMG was confirmed by repeated nerve stimulation test, and by the response to pyridostigmine. Antibodies anti-AChR and anti-MuSK were negative. JMG diagnosis may be harder in adolescents with psychiatric comorbidity. Moreover, the neurological condition limits the choice of the appropriate psychopharmacotherapy.

Key words: juvenile Myasthenia Gravis, psychiatric comorbidities, mood disorder

Introduction

Paediatric Myasthenic Syndromes (PMS), caused by defects of transmission at the neuromuscular junction, may manifests in three main distinct forms, with different pathophysiological mechanisms: the congenital myasthenic syndromes (CMS), a heterogeneous group of genetically inherited disorders of the neuromuscular transmission; the transient neonatal myasthenia, resulting from placental transfer of maternal antibodies to infants from mothers with autoimmune myasthenia; and the juvenile myasthenia gravis (JMG), an autoimmune acquired disorder in which antibodies are directed at the postsynaptic membrane of the neuromuscular junction, leading to varying degrees of muscle weakness and fatigability. The disease presentation is usually under 19 years-old.

All forms of PMS lead to muscle fatigue and weakness of varying degrees. Especially in JMG, fluctuations in weakness are a hallmark of this disease. The weakness can involve ocular, bulbar, respiratory, and skeletal...
muscles. Clinical diagnosis is confirmed by electromyography (EMG) and response to therapy, while serology is less helpful in children.  

In some cases, initial myasthenic symptoms may be underestimated, especially in presence of other medical conditions causing fatigability and exhaustion. Depressive features can also be a key confounder in JMG; as a consequence, the simultaneous onset of the two disorders adds to the risk of diagnostic confusion.  

The main objective of this presentation is to describe how a psychiatric condition, namely a severe mood disorder, challenged the diagnosis of JMG in a 14 year-old girl. This case highlights the importance of a careful neurological assessment in young psychiatric patients presenting confounding symptoms and signs, with an integration of neurological and psychiatric perspectives, causing a relevant impact on differential diagnosis and pharmacological options.

**Case report**

A 14 year-old girl was admitted in the psychiatric department for a suicide attempt with ingestion of metal objects. She had already been hospitalized twice during the previous year, because of eating dysregulation, recurrent panic attacks with depressive symptoms, and general emotional dysregulation. Her family history was positive for psychiatric disorders and substance addiction (her father had an history of alcohol abuse and depression), in the context of a poor family environment, complicated by a complex parental separation. Family and personal history was silent for neuromuscular diseases: in particular, perinatal conditions were reported as regular, and the development of motor milestones was normal. She had been treated with high-dose benzodiazepines (d lorazepam, lorazepam), sertraline, and an atypical antipsychotic (aripiprazole) for six months, with poor results on depressive symptoms and worsening of general fatigue, weakness, and drowsiness, considered in part as side effects of the therapy and in part as a manifestation of her psychiatric condition. Nocturnal respiratory distress was also described with mild desaturation and diagnosed as panic attacks.  

At admission, the neurological assessment revealed a myasthenic face, with asymmetric eyelid ptosis and facial muscle weakness, which were fluctuating during the day, and improving with rest. The patient showed a mild generalized weakness, and there were no other neurological signs nor bulbar involvement.  

Suspecting a myasthenic syndrome, neurophysiological and laboratory exams were performed. EMG showed a pathological decrement in the compound motor action potential after the 4 th stimulation (18%, 26%) of the right facial nerve (orbicularis oculi muscle). Both anti-AchR and anti-MuSK antibodies resulted negative. A chest TC was performed and excluded the presence of thymoma. A DNA sample was collected for genetic analysis in order to detect possible congenital myasthenic syndromes (still on-going). A clinical and neurophysiological diagnosis of seronegative JMG syndrome was made. First-line symptomatic therapy with low-dose pyridostigmine (15 mg, 5 times per day) was initiated, leading to a progressive reduction of eyelid ptosis, generalized fatigue, and drowsiness with positive subjective outcome. A multidisciplinary team composed by child neurologists and psychiatrists assessed different therapeutic options: steroids were avoided because of her psychiatric comorbidities, and for the good response to the symptomatic therapy alone (pyridostigmine).

From the psychiatric point of view, the therapy was re-assessed, avoiding drugs associated to the risk of myasthenic symptoms worsening, such as benzodiazepines. Sertraline was also suspended for the lack of efficacy, and aripiprazole was confirmed as a stabilizer agent, together with the diagnosis of severe mood disorder with emotional dysregulation. After reaching an adequate control of myasthenic symptoms, with an evident improvement of her neurologic condition, a better anxiety control and lower emotional lability were also observed.

**Discussion**

JMG represents a challenging diagnosis, which can result even harder in adolescents with psychiatric comorbidity, due to the difficulty of differentiating neurologic and psychiatric symptoms. To date, little is still known about the relationship between myasthenia and associated psychiatric disorders; however, it is known that psychiatric symptoms, such as fatigue, lack of energy and shortness of breath may coincide with those of the neurologic disease, leading to a misdiagnosis. The correct diagnosis is missed in up to 46% of myasthenic patients during the 1 st year of disease manifestation and depressive symptoms are a key confounder accounting for 20% of initial misdiagnoses.

In the literature, psychiatric comorbidities are reported as quite common in myasthenic patients, with a prevalence of mood disorders around 45% and a prevalence of anxiety disorders around 58%. Moreover, it is important to remark that many pharmacological treatments, including psychiatric ones, can cause myasthenic-like symptoms, or unmask a latent form of myasthenia. Therefore, psychiatric treatments must be carefully planned because of the risk of worsening myasthenic symptomatology. In particular, antipsychotics impair neuromuscular trans-
mission at presynaptic and postsynaptic levels; lithium, for instance, causes reduction in acetylcholine synthesis and release reduction in number of receptors, and sedatives like benzodiazepines, inducing central respiratory depression, which can be very dangerous for patients with bulbar symptoms or borderline respiratory reserve. In the presented case, immediate worsening of general fatigue and weakness was reported following initiation of high dose of benzodiazepines, initially interpreted as mood deflection.

On the other hand, regarding JMG as a chronic, debilitating, life-threatening disease with unpredictable progression, patients affected may have psychiatric consequences in terms of coping and adaptation to the disease. Thus, subject with JMG may be at increased risk of psychiatric disorders.

In the presented case, the diagnosis was suspected after a careful neurological clinical assessment, which is always recommended in the evaluation of psychiatric patients, particularly at onset or in the presence of a modification in symptoms. The clinical diagnosis was confirmed by the positive repetitive nerve stimulation test, which was performed on the orbicularis oculi muscle; the single-fiber electromyography (sfEMG), which is considered the gold standard for seronegative JMG, was not carried out due to discomfort and the length of the test, poorly tolerated in young patients. At the time of the first assessment, immunological analysis did not detect the presence of anti-AChR and MuSK antibodies. This finding is consistent with literature reports, as delayed seroconversion can be years after onset and particularly in pre-pubertal children. Therefore, it is suggested to repeat this test in seronegative young patients at 6 monthly intervals.

The final therapeutic strategy was discussed by a multidisciplinary team, and included pyridostigmine and aripiprazole, avoiding benzodiazepine, sertraline and steroids, with a good outcome both on neurological and psychiatric manifestations.

**Conclusions**

Mood and anxiety disorders symptoms may be a key confounder in JMG, leading to a diagnostic delay. Information on the relationship between JMG and psychiatric symptoms are limited, and misdiagnosis and under-treatment are actual issues in these patients. Although JMG is a rare disease if compared to juvenile psychiatric disorders, ‘red flags’ symptoms such as fluctuating weakness and fatigability should always prompt a neurological assessment. Moreover, clinically relevant guidelines for managing myasthenic patients in presence of psychiatric comorbidities are hardly available. This case outlines the need of further studies, especially about the safety of different therapeutical options for the comorbidities.

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**Conflict of interest**

The Authors declare no conflict of interest.

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**Author contributions**

AS, MV: data collection; AS, MV, RD: conceptualization, methodology, data curation, original draft preparation, writing; FSR, TEM: review and editing and supervision; FSR, TEM: validation

**Ethical consideration**

The study was conducted in accordance with the Declaration of Helsinki. The approval of the Ethics Committee was not necessary as no procedures other than those routinely performed were employed.

Parents gave their informed consent for the publication of this case report.

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