CASE REPORT

Concomitant Juvenile Myasthenia *Gravis* and Polymyositis in a Child: A Case Report

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Abstract

Acute muscle weakness is a major neurological emergency with a vast differential diagnosis. Even though inflammatory myopathies and myasthenia *gravis* are rare causes of acute muscle weakness, especially in children, there have been descriptions of the coexistence of both diseases in adults, especially in association with thymoma. We report a clinical case of a pediatric patient with concurrent myasthenia *gravis* and inflammatory myopathy and comment on the relevant features and difficulty in diagnosing both diseases.

Keywords: Child; Myasthenia Gravis/diagnosis; Myasthenia Gravis/therapy; Muscle Weakness/etiology; Polymyositis/diagnosis; Polymyositis/therapy; Treatment Outcome

Introduction

Acute muscle weakness is a major neurological emergency in pediatrics. The approach to these children implies the differential diagnosis between disorders that compromise the descending motor pathway, from the motor upper neuron to the motor unit.[1]

Motor unit diseases include diseases of lower motor neuron, peripheral nerve, neuromuscular junction, and muscle. They are generally expressed as symmetrical weakness associated with diminished deep tendon reflexes.[1]

During the diagnostic approach, it is crucial to obtain a detailed case history, including past medical and family history, location of weakness at onset (ocular, bulbar, proximal, or distal muscles), sequence and rate of progression of paralysis, associated symptoms, exposure to drugs and toxins, immunizations, and previous episodes of weakness. In the child evaluation, it is mandatory to consider vital signs and respiratory function. Neurological examination must address the distribution of weakness, impaired cranial nerves, and sensory and autonomic dysfunction.[2-4]

Myasthenia *gravis* and inflammatory myopathies, including polymyositis, are two well-recognized and distinctive neuromuscular diseases.[3,4]

Myasthenia *gravis* is a very well-characterized antibody mediated disease that is frequently associated with antibodies against the acetylcholine receptor (AchR) or muscle-specific kinase (MusK). These antibodies contribute to the characteristic defects in neurotransmission at the neuromuscular junction.[3,5]

Inflammatory myopathies are a group of immune-mediated muscle diseases associated with proximal muscle weakness that can also present with systemic manifestations. Polymyositis is a rare entity, usually not seen in childhood.[4,6,7]

We report the clinical case of a pediatric patient with concurrent myasthenia *gravis* and inflammatory myopathy and comment on the relevant features that helped the diagnosis.

Case Report

A previously healthy 7-year-old boy with normal psychomotor development presented to the emergency department with frequent falls from his height, without an apparent trigger or daytime relation, lasting three weeks. The mother reported no other motor compromise, myalgias, altered mental status, dizziness, or headache. He had no fever or previous infections. No previous episodes of muscle weakness or choking were reported.

Physical examination showed global hypotonia, predominant symmetrical proximal muscle weakness (strength 3/5 in proximal hips and shoulders, strength 4/5 in wrist and ankle flexion/extension) with myopathic gait and normal deep tendon reflexes. Neurological

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examination showed no signs of muscle atrophy/hypertrophy, ophthalmoplegia or other cranial nerve deficits, sensory or autonomic abnormalities. No dyspnea, dysphagia, dysphonia, arthritis, Raynaud phenomenon, heliotrope rash or Gottron papules, nailfold capillary changes, or skin ulcerations were noted.

Clinical worsening was noted during the hospital stay with the progressive loss of the ability to walk and to raise both arms. He also developed fatigable intermittent ptosis and slurred/nasal speech. The worst childhood myositis assessment scale total score, performed after losing the ability to walk, was 8/52. Laryngoscopy and cardiac evaluation were normal.

Blood tests revealed slightly elevated creatine kinase (534.15 UI/L) and myoglobin (209 UI/L). Aspartate transaminase, alanine transaminase, lactate dehydrogenase aldolase, parathyroid hormone, vitamin D, calcium, phosphorus, and thyroid function tests were all normal. The main metabolic myopathies were excluded (normal blood gas test, lactate, pyruvate, carnitine, redox potential, and acid alpha-glucosidase) (Table 1). C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, complement components C3 and C4, and total complement (CH50) were in the normal range. Infectious causes were excluded (Table 1). Anti-AchR antibodies were positive (59.10 nmol/L). Electromyography was suggestive of primary muscle disease, but repetitive nerve stimulation was not performed due to non-compliance. The autoimmunity study revealed antinuclear antibodies (ANA) 1/320, with nuclear fine speckled pattern, and positive Anti-PL-12 (++) (Table 1). Other myositis-specific (Jo-1, PL-7, Mi-2, EJ, OJ and KS) and myositis-associated antibodies (SSA, SSB, PM-Scl75, PM-Scl100) were all negative.

Chest computed tomography was performed and showed no thymus abnormalities or lung disease.

Lower limbs magnetic resonance showed no evidence of myositis. Biopsy from lateral vastus muscle revealed T-cell infiltrates with muscle fiber necrosis and healthy muscle fibers expressing major histocompatibility complex class I antigen, all usual pathological findings in polymyositis.

His clinical presentation associated with positive anti-AchR antibodies was attributed to myasthenia *gravis*. The patient was treated with a trial of pyridostigmine (1 mg/kg/dose, four times per day) with significant clinical improvement at 48 hours after the initial dose, regaining the ability to walk. Intravenous immunoglobulin (1 g/kg/day in two consecutive days) was added 48 hours after the initiation of an acetylcholinesterase inhibitor.

Six days later, after the biopsy results were known, the diagnosis of concurrent polymyositis and myasthenia *gravis* was established, and he started methylprednisolone (five doses of 30 mg/kg/day) followed by oral prednisolone (2 mg/kg/day) and subcutaneous methotrexate (17 mg/m^2/week). Prednisolone was gradually tapered off over nine months.

At the three-week follow-up, he had almost normal strength with a childhood myositis assessment scale total score of 44/52.

At one year of follow up and two months off prednisolone, he is in clinical and laboratory complete remission with a childhood myositis assessment scale total score of 52/52, treated with the same doses of methotrexate and pyridostigmine.

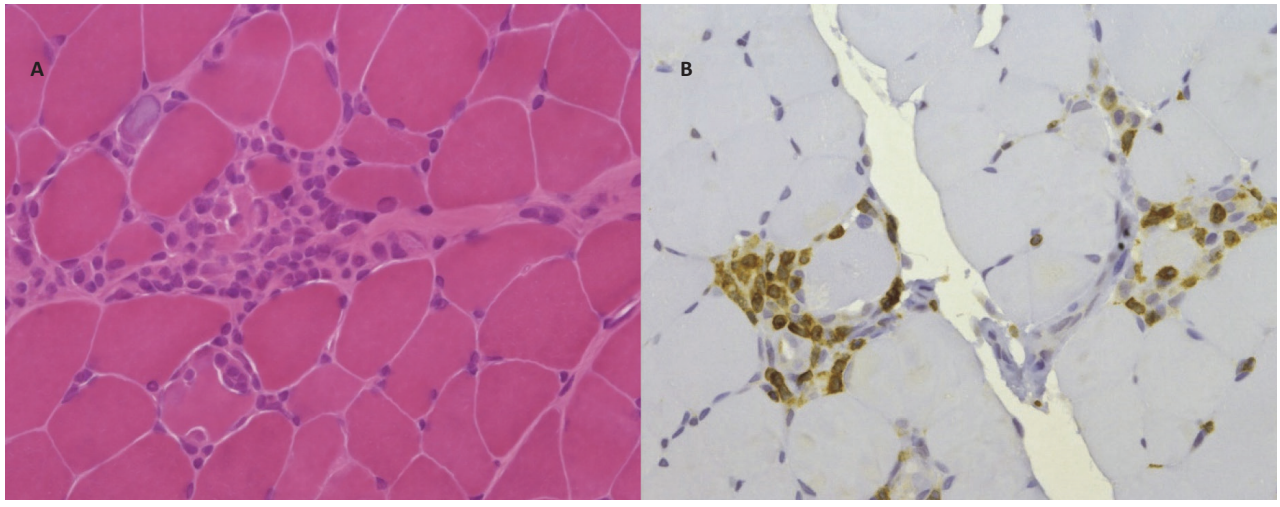

Figure 1. A. Endomysial infiltrate and mononuclear inflammatory cells surrounding viable fibers (hematoxylin-eosin, 40 x 100). B Immunohistochemical staining with T-cell infiltrates (CD3, 40 x 100).

Table 1. Etiologic laboratory investigation

	Results	Reference values
Lactate (mmol/L)	0.84	0.50-2.20
Pyruvate (mg/dL)	0.50	0.30-0.90
Beta-hydroxybutyrate (mM)	0.06	0.03-0.3
Acetoacetate (mM)	0.03	< 0.15
Lactate/pyruvate (mM)	13	10-14
Beta-hydroxybutyrate/acetoacetate (mM)	2	2.00-3.00
Free fatty acids/ketone (mM)	4.40	0.60-5.50
Serum carnitine and acylcarnitine	Normal	
Purine and pyrimidine screen test, urine	Normal	
Mitochondrial respiratory chain enzymatic complexes evaluation	Normal	
Complex I (nicotinamide adenine dinucleotide - ubiquinone reductase) (nmol/minute/mg)	28.6	8.8-30.8
Complex II (succinate - ubiquinone reductase) (nmol/minute/mg)	19.8	12.0-35.0
Complex III (ubiquinol - cytochrome c reductase) (nmol/minute/mg)	28.7	22.2-62.2
Complex II+III (succinate - cytochrome c reductase) (nmol/minute/mg)	4.4	2.6-12.0
Complex IV (cytochrome c oxidase) (nmol/minute /mg)	11.1	11.5-34.5
Acid alpha-glucosidase	0.14	0.12-0.70
C-reactive protein (mg/dL)	0.47	< 0.3
Erythrocyte sedimentation rate (mm/hour)	10	< 13
Ferritin (ng/mL)	96	14-124
Immunoglobulin G (mg/dL)	1,510.00	650.00-1,600.00
Immunoglobulin A (mg/dL)	84.40	35.00-250.00
Immunoglobulin M (mg/dL)	53.60	45.00-200.00
Immunoglobulin E (UI/mL)	33.30	< 90.00
Anti-acetylcholine receptor antibodies (nmol/L)	59.10	< 0.25
Antinuclear antibodies	1/320 (nuclear fine speckled)	
Rheumatoid factor (UI/mL)	< 9	< 16
Antibody anti-SSA	Negative	
Antibody anti-SSB	Negative	
Antibody anti-PM-Scl75	Negative	
Antibody anti-PM-Scl100	Negative	
Antibody anti-Mi-2	Negative	
Antisynthetase antibodies		
Antibody anti Jo-1	Negative	
Anti-PL-12	**Positive (++)**	
Anti-PL-7	Negative	
Anti-EJ	Negative	
Anti-OJ	Negative	
Anti-KS	Negative	
C3 (mg/dL)	136	90-180
C4 (mg/dL)	26.7	10-40
Total complement CH50 (UI/mL)	42.7	41.7-95.1
Angiotensin-converting enzyme (UI/L)	42.05	8-52
Human immunodeficiency virus type 1 and 2 antibodies	Negative	
Hepatitis C antibody	Negative	
Hepatitis B surface antigen	Negative	
Venereal disease research laboratory	Negative	
Cytomegalovirus antibody immunoglobulin M/immunoglobulin G	Negative/positive	
Epstein-Barr virus viral capsid antigen immunoglobulin M/immunoglobulin G	Negative/positive	
Epstein-Barr virus nuclear antigen immunoglobulin G	Positive	
Enterovirus polymerase chain reaction, nasopharynx	Negative	
Enterovirus D68-specific reverse transcriptase polymerase chain reaction	Negative	

Discussion

Proximal muscle weakness is a characteristic feature of both myasthenia *gravis* and polymyositis. However, fluctuating weakness with fatigability is a hallmark of myasthenia *gravis,* whereas patients with polymyositis usually have consistent weakness.[8,9] Although bulbar symptoms, such as the weakness of the palatal muscles, can be present in both diseases, they are more typical of myasthenia *gravis*. Ocular symptoms are the most differentiating features between inflammatory myopathies and myasthenia *gravis* with diplopia and ptosis almost never encountered in patients with inflammatory myopathies alone.[8,9] Our patient developed fluctuating bilateral ptosis without diplopia and slurred and nasal speech, which was possibly related to palate muscle weakness, and all the clinical findings were suggestive of myasthenia *gravis*.

In this patient, although clinical presentation and anti-AchR antibodies positivity were suggestive of myasthenia *gravis*, creatinine kinase elevation and myopathic changes on electromyography are not common features of this entity. In addition, he had elevated ANA titles (1/320) and positive Anti-PL-12, an antisynthetase antibody. Myositis-associated antibodies and myositis-specific antibodies are not frequently found in patients with polymyositis associated with myasthenia *gravis*.[8,9]

The diagnosis of myositis requires a histopathologic assessment of a skeletal muscle biopsy.[7,10,11] Characteristic findings of polymyositis are the partial invasion of muscle fibers by CD8+ cytotoxic T cells and activated macrophages and widespread upregulation of major histocompatibility complex class I.[4,6,7] The tissue biopsy results supported the diagnosis of possible inflammatory myopathies according to the American College of Rheumatology and European League Against Rheumatism classification criteria.[10]

There have been descriptions of adult patients with both myasthenia *gravis* and inflammatory myopathies,[8,9,12-14] mostly in association with thymoma, suggesting that aberrant T cell activation in the thymic tumor underlies the pathogenesis of both diseases.[8,12] In our literature review, we found only one case with myasthenia *gravis* and polymyositis overlap below the age of 18, and it occurred in the presence of thymoma. The association of myasthenia *gravis* and polymyositis in the absence of thymoma in a child emphasizes the importance of this case report.

The management of juvenile myasthenia *gravis* and polymyositis involves a multidisciplinary team comprising pediatric neurologist, pediatric rheumatologist, physiotherapist, psychologist, speech therapist, and dietician.[5-7,11]

The treatment of myasthenia *gravis* is based on symptomatic treatment with anticholinesterase inhibitors, such as pyridostigmine. A trial of pyridostigmine can also work as a diagnostic testing of myasthenia *gravis*.[3,5,15,16] Significant clinical improvement of our patient within 48 hours after the initial dose of pyridostigmine supported the diagnosis of myasthenia *gravis*. However, like inflammatory myopathies, myasthenia *gravis* has inflammatory pathogenesis and frequently requires immunosuppressive or immunomodulatory therapies such as corticosteroids, azathioprine, mycophenolate mofetil, and intravenous immunoglobulin.[3,5,7] Corticosteroids are the mainstay of therapy in both diseases.

A combination of high-dose prednisolone and methotrexate has demonstrated to be the most effective and safe treatment for inflammatory myopathies.[6,11]

On the other hand, in myasthenia *gravis*, corticosteroids can induce deterioration, particularly if started in high doses.[15] When a high dose of steroids is required, concurrent treatment with intravenous Immunoglobulin should be considered.[9] There was no clinical deterioration after treatment with corticosteroids in our case.

In conclusion, this case demonstrates the difficulty in diagnosing the co-existence of two distinct neuromuscular inflammatory diseases due to the sudden onset of weakness and clinical overlap of both autoimmune disorders in the absence of typical features.

WHAT THIS CASE REPORT ADDS

- There can be an overlap between myasthenia *gravis* and polymyositis making diagnosis difficult, especially in the absence of typical features.
- Acute simultaneous presentation of both polymyositis and myasthenia *gravis* is extremely rare, especially in pediatric patients.
- As polymyositis and myasthenia *gravis* both have an inflammatory pathogenesis, the management of these diseases requires immunosuppressive treatment. Myasthenia *gravis* treatment also includes anticholinesterase inhibitors.
- Childhood myositis assessment scale is a useful tool to monitor the response to therapy and follow-up in idiopathic inflammatory myopathies.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

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Miastenia *Gravis* Juvenil e Polimiosite Concomitante numa Criança: Caso Clínico

Resumo:
A fraqueza muscular de início súbito é uma emergência médica com um vasto diagnóstico diferencial. As miopatias inflamatórias e miastenia *gravis* são causas raras de fraqueza muscular aguda, especialmente na idade pediátrica. No entanto, têm sido descritos casos de coexistência de ambas as patologias em adultos, particularmente na presença de timoma. Apresentamos o caso clínico de uma criança que se apresentou simultaneamente com miastenia *gravis* e polimiosite e comentamos as particularidades e dificuldades no diagnóstico destas patologias.

Palavras-Chave: Criança; Fraqueza Muscular/etiologia; Miastenia Gravis/diagnóstico; Miastenia Gravis/tratamento; Polimiosite/diagnóstico; Polimiosite/tratamento; Resultado do Tratamento