CASE REPORT

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Ethical statement

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ABSTRACT

Miller-Fisher syndrome is a rare, acute, autoimmune, demyelinating disorder which is considered a variant of Guillain-Barré syndrome. The pathologic mechanism is unclear, but acute demyelinating polyneuropathies may be triggered by bacterial or viral infections, major surgical interventions, or vaccination. Pregnancy may be a trigger of the immune response causing the onset of the syndrome. Miller-Fisher syndrome is characterized by acute onset, with predominant involvement of the facial cranial nerves resulting in ophthalmoparesis, ataxia, and areflexia/hyporeflexia. Diagnosis is based on clinical suspicion together with the determination of specific ganglioside antibodies and other laboratory and imaging tests. Treatment consists of intravenous immunoglobulin and plasmapheresis, together with supportive measures. There are few reports of the syndrome occurring in pregnant women. A case of Miller-Fisher syndrome during pregnancy is presented.

Key words: Miller-Fisher syndrome, Guillain-Barré syndrome, Ophthalmoparesis, Ataxia, Pregnancy.

RESUMEN

El síndrome de Miller-Fisher es un trastorno agudo, autoinmune y desmielinizante poco frecuente que se considera una variante del síndrome de Guillain-Barré. El mecanismo patológico no está claro, pero las polineuropatías desmielinizantes agudas pueden ser provocadas por infecciones bacterianas o virales, intervenciones quirúrgicas mayores o vacunación. El embarazo puede ser un desencadenante de la respuesta inmunaria que causa la aparición del síndrome. El síndrome de Miller-Fisher está caracterizado por la aparición aguda, con afectación predominante de los nervios faciales y craneales que resulta en oftalmoparesia, ataxia y areflexia/hyporeflexia. El diagnóstico se basa en la sospecha clínica junto a la determinación de anticuerpos gangliósidos específicos y otras pruebas de laboratorio e imágenes. El tratamiento consiste en el uso de inmunoglobulina endovenosa y plasmaderesis, junto a medidas de apoyo. Existen pocos informes de aparición del síndrome en embarazadas. Se presenta un caso de síndrome de Miller-Fisher durante el embarazo.

Palabras clave. Síndrome de Miller-Fisher; Síndrome de Guillain-Barre; Oftalmoparesia; Ataxia; Embarazo.

INTRODUCTION

Miller-Fisher syndrome (MFS) is a rare disorder that is characterized by acute onset of ophthalmoparesis, ataxia and hyporeflexia / areflexia(1). It was recognized 60 years ago as a variant of Guillain-Barré syndrome (GBS). The annual incidence is 0.09 per 100,000 persons and affects more males than females with a 2:1 ratio(2).

GBS usually follows Campylobacter jejuni, cytomegalovirus, Epstein-Barr and influenza virus infections or secondary to major surgery, pregnancy, or vaccination(3,4). MFS accounts for 5%-10% of GBS cases and may have a major autoimmune component due to the presence of anti-ganglioside antibodies. During the acute phase of the disease, these antibodies have a diagnostic sensitivity and specificity of 92% and 97%, respectively(5). MFS during pregnancy is rare and there are only reports of 5 cases in pregnant women. A case of Miller-Fisher syndrome during pregnancy is presented.
CLINICAL CASE

The patient was 16 years old, primigravida of 20 weeks, who was referred for presenting nausea and incoercible vomiting of five days of evolution, accompanied by double vision, generalized weakness, ataxia, difficulty walking, dysphonia for 2 days. She denied a history of respiratory and/or gastrointestinal infections or neurological diseases during pregnancy. She also denied any important family history.

On physical examination the patient was in fair condition, afebrile and slightly dehydrated. Vital signs were blood pressure 145/82 mmHg, heart rate 88 beats per minute and temperature 36.9°C. She was anxious and uncomfortable on questioning but was oriented in all three spheres. Higher mental functions were preserved with coherent and congruent language, preserved anterograde and retrograde memory. Bilateral ophthalmoparesis with non-fluctuating deconjugate eye deviation was noted, with restriction of left eye abduction and limitation of bilateral eye movement in all other directions, with no evidence of ptosis and nystagmus. Pupils were isometric, mydriatic and normoreactive with normal fundus. No evidence of alteration of the rest of the cranial nerves was found.

In addition, proximal predominant quadriparesis was found with diminished osteotendinous reflexes (1/4) in all four extremities, bilateral negative Babinski with absence of abnormal movements and signs of meningeal irritation. Proprioception was impaired, but vibration and temperature perception were normal. Ataxia was prominent in the lower extremities during standing and walking, despite preservation of motor strength. Obstetric examination showed single, live fetus, with uterine height of 21 centimeters compatible with gestational age, and fetal heart rate of 149 beats per minute, without evidence of cervical changes and/or loss of amniotic fluid.

Hematology, liver and renal function, coagulation profile, urine test and electrolytes were within normal limits. Computed tomography and magnetic resonance imaging, computed tomography angiography and magnetic resonance venogram showed no abnormalities. Electromyography showed evidence of severe sensory-motor demyelinating polyneuropathy, length-dependent and symmetrical, with greater involvement of the lower extremities, but without signs of presynaptic junction disorder. Cerebrospinal fluid analysis obtained by lumbar puncture denoted absence of albumin-cytologic dissociation with protein concentrations of 0.60 g/L and glucose of 70 mg/dL (central glucose of 81 mg/dL). Gram stain, cultures and serology panel for bacteria, herpes simplex virus and cytomegalovirus were negative. In view of the findings the patient was treated with supportive care.

Serological studies showed positive antiganglioside antibodies (anti-GQ1b, anti-GD1b and anti-GT1a), while determination of antibodies against myelin-associated glycoprotein, oligoclonal bands, autoantibody screening (antinuclear, small nuclear antiribonucleoproteins, antimitochondrial, antireticulin, anti-gastric parietal cell and anti-neutrophil cytoplasm) were negative. Tests for connective tissue disorders, antibodies against thyroid peroxidase and thyroglobulin, Lyme disease serology, mycoplasma IgM and syphilis tests were negative. In view of the findings a diagnosis of MFS was made.

48 hours after admission, the patient developed absence of deep tendon reflexes, respiratory failure, hypoxemia, and hypercapnia progressively associated with bulbar weakness, so she was intubated and transferred to the intensive care unit. Treatment was started with plasmapheresis (with total replacement of 5 volumes of plasma) and intravenous immunoglobulin (400 mg/kg/day). Significant clinical improvement was observed after the second exchange. After 5 sessions the patient was transferred to hospitalization and was discharged 18 days after admission. There was no evidence of alterations in fetal well-being during hospitalization.

The patient was treated by the neurology service during follow-up. An outpatient control was performed one month after hospital discharge with the result of the electromyographic study, with improvement of muscle strength in lower limbs is 4/5 and upper limbs 5/5, both distal and proximal. Six months after the onset of symptoms, she still needs help to stand up.

The patient was followed up weekly at the high-risk prenatal clinic without complications. At 38 weeks she presented spontaneous vaginal delivery without complications, obtaining a live female newborn of 3200 grams, with Apgar scores at 1
Miller-Fisher syndrome during pregnancy

Discussion

MFS is an acute autoimmune and demyelinating polyneuropathy characterized by acute onset of ophthalmoparesis, ataxia, and areflexia/hyporeflexia, but may also present with signs and symptoms indicative of generalized neuropathy. Demyelinating polyneuropathies can be triggered by an acute inflammatory response with evidence of inflammatory infiltrates and areas of segmental demyelination. In some cases, these have been associated with respiratory / gastrointestinal infections, acute cytomegalovirus infection, influenza vaccination, calcineurin inhibitor neurotoxicity and allograft rejection.

The etiopathogenesis of MFS is associated with a phenomenon of molecular mimicry between gangliosides (important components of peripheral nerves) and some infectious agents. Gangliosides are ceramides bound to hexoses and N-acetyleneuraminic acid, linked to an oligosaccharide core. Four gangliosides, GM1, GD1a, GT1a and GQ1b, differ in number and position of sialic acids. The most common hypothesis about the underlying mechanism is humoral immune response with deposition of activated complement and immunoglobulins with cellular response of macrophages and infiltrating T cells. Furthermore, the localization of these ganglioside antigens is associated with distinct clinical patterns.

The diagnosis of MFS is based on symptomatology. Symptoms usually have acute onset within hours or days and clinical signs are diplopia (63%), sensory disturbance (52%), blepharoptosis (35%), facial palsy (35%), ataxia (33%), muscle weakness (25%) and dysesthesias (17%). Diplopia is a consequence of ophthalmoparesis, which is an early finding. Pupillary abnormalities are also common and may include pupillary asymmetry and slow reactivity to light. Moreover, ataxia is usually severe and makes independent ambulation difficult, despite preservation of muscle strength.

Most patients with MFS have normal imaging findings, especially those with partial symptomatology. Cerebrospinal fluid analysis, although initially normal, may show cytologic-albumin dissociation. However, its results are only useful to exclude other pathologies with similar symptomatology. Nerve conduction studies and electromyography can help in the diagnosis, but have a limited role, since only in some cases abnormalities appear, which are more pronounced two weeks after the onset of symptoms.

Differential diagnoses are with other infectious or autoimmune neurological pathologies, such as Bickerstaff’s encephalitis, multiple sclerosis, Tolosa-Hunt syndrome, paraneoplastic syndromes (Eaton-Lambert syndrome), botulism, myasthenia gravis, poliomyelitis, and diphtheria. The main differential diagnosis during pregnancy is Wernicke’s encephalitis, which is characterized by a clinical triad (nystagmus and ophthalmoplegia, mental status changes and ataxia) usually associated with thiamine deficiency. Magnetic resonance images show symmetrical T2 signal intensity alterations in medial thalamus, mammillary bodies, tectal plate and periaqueductal area.

Approximately 80% to 90% of patients with MFS have antibodies against GQ1b. These play a key role in the pathogenesis of the syndrome, as ophthalmoparesis and ataxia are strongly associated with the presence of antibodies. In addition, there are reports of higher concentrations of the antibodies in the cerebrospinal fluid during the first 3 weeks of the disease.

Treatment data from clinical trials of MFS are scarce, so management is based on the same guidelines used for GBS and should be initiated as early as possible to prevent irreversible nerve damage, mainly in patients with rapidly progressive weakness. Intravenous administration of high-dose immunoglobulin has been shown to be as effective as plasmapheresis in GBS and its variants, along with supportive care. Several reports indicate decreased nerve damage and more rapid clinical improvement after treatment. Good response to treatment has been reported in two-thirds of patients when initiated within two weeks of symptom onset, with full recovery of function within three to five months.

Demyelinating polyneuropathies during pregnancy are rare and occur most frequently in the second and third trimester of pregnancy and in the first postpartum month, due to the predominance of Th1 cells that produce proinflammatory cytokotoxic cytokines during this period. Prior to the advent of immunotherapies, obstetric patients
experienced significant morbidity and mortality with 20% of patients on disability, 35% on ventilatory support and a mortality rate of 13%. The frequency of preterm delivery also increased in severe cases. Both the rapidity of disease onset and the severity and duration of paralysis are indicators of poor prognosis\textsuperscript{14}. To date, the impact of MFS during pregnancy and long-term perinatal outcomes is unknown.

All patients with MFS should remain under hospital observation until it has been established that there is no evidence of clinical progression. Patient management should include prevention of deep vein thrombosis, identification and management of infections, pain management, bladder catheterization in case of urinary retention, laxatives in case of constipation, management of psychosocial stress resulting from the disease, and implementation of early, active and individualized rehabilitation programs. These measures can help to achieve a favorable outcome\textsuperscript{15}.

In conclusion, MFS, a variant of GBS, is a rare condition during pregnancy. It is characterized by ophthalmoparesis, ataxia and areflexia/hyporeflexia and can be successfully treated with intravenous immunoglobulin or plasmapheresis. It is necessary to achieve accurate diagnosis and timely treatment and to be alert for unexpected autoimmune neurological disorders during pregnancy.

References