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# ADULT ONSET OPSOCLONUS-MYOCLONUS-ATAXIA SYNDROME WITH SEIZURE AND RELATED TO EPSTEIN BARR VIRUS

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## ABSTRACT

Paciente masculino, 49 anos, teve diagnóstico de faringite purulenta e recebeu azitromicina seguida de amoxicilina e clavulanato sem melhora da febre. Evoluiu com convulsão tônico-clônica, tremor generalizado, titubeação axial e cefálica, ataxia de tronco, mioclonia e opsoclonus. A análise do líquor mostrou pleocitose e hiperproteinorraquia. Os testes laboratoriais mostraram inflamação sistêmica, linfocitose e sorologia IgM e IgG anti-Epstein-Barr positiva. O ecocardiograma teve derrame pericárdico leve. Após a exclusão das lesões estruturais na ressonância magnética, fizemos o diagnóstico de síndrome de opsoclonia-mioclonia-ataxia relacionada à infecção por Epstein Barr. O paciente recebeu um pulso de 3 dias de metilprednisolona, com melhora clínica rápida e significativa.



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# INTRODUCTION

Opsoclonus-myoclonus syndrome (OMS), also known as opsoclonus myoclonus ataxia, is a syndrome that includes opsoclonus along with diffuse or focal body myoclonus and truncal titubation with or without ataxia and other cerebellar signs[1]. OMS can affect adults and can rarely be caused by nonimmune mechanisms. The incidence of OMS was 0.18 cases per million population per year in a prospective survey of United Kingdom pediatric neurology centers[2]. This article is to present a case report of adult onset opsoclonus myoclonus ataxia syndrome related to Epstein Barr virus (EBV) infection with a distinct feature in the presentation: the seizure.

# CASE REPORT

A 49 year-old-man previously healthy started with fever, headache, malaise, swallow pain and was fisrtly diagnosed purulent pharyngitis and treated with a three-day course of azitromicin and 5 days of amoxicillin clavulanate) without fever resolution. Twelve days after initial symptoms, he had a generalized tremor and, one day later, presented a tonic-clonic seizure and was hospitalized. The posterior day, he was unable to walk, but denied weakness. His wife complained about anxiety and irritability of the patient and the fever persisted. He worked with irrigation and claimed to have had asthma during childhood. His mother has heart disease and his father died due to gastric cancer. He seemed anxious, but had stable general condition, without remarkable features on cardiovascular, respiratory and abdominal exam. On neurological examination, he had generalized tremor with head and axial titubation, GCS 15, dysarthria, ocular motricity with saccades intrusions and opsoclonus, cerebellar ataxia, tremor with kinetic, postural and intention characteristics. He also had myoclonus during exam, which was present during sleep. Reflexes, vibration, proprioception and sensitivity were unremarkable and nucal stiffness was absent. He was started on acyclovir because history of fever and seizure. Brain MRI was normal and transthoracic echocardiogram showed mild pericardial effusion. CSF analysis showed pleocytosis (7 cells, 100% mononuclear) and high protein (62mg/dl). Laboratory tests showed ESR of 75mm, mild elevation of transaminases, normal renal function, normal ionogram. CBC had leukocytosis with lymphocytosis. HIV, HBsAg, VDRL and HCV serologies were negative. Cytomegalovirus (CMV) IgG serology was positive, but IgM was negative. HSV was positive for IgM and IgG,

however Epstein Barr IgM and IgG was positive as well. Based on history and neurological features and exclusion of structural lesions on MRI, we made the diagnosis of Opsoclonus Myoclonus Ataxia Syndrome. After that, CT of torax, abdomen and pelvis was performed, without abnormalities, to rule out hidden tumors. The patient received a 3-day-course of methylprednisolone with quick and significant clinical improvement. He has discharged of 60mg of prednisone to follow up.

# DISCUSSION

The case presented all four related symptoms of the syndrome: (1) opsoclonus; (2) myoclonus of trunk and extremities; (3) step ataxic; and (4) behavioral change such as generalized anxiety and sleep disturbance. This clinical spectrum facilitates earlier diagnosis and treatment. Meanwhile, the majority of published cases has only three of described symptoms, which impairs the recognition of the entity and contributes with delayed diagnosis. A british study reported an average of 11-week between the onset of the syndrome and the diagnostic elucidation, and suggested that a 11-week delay can severely compromise the prognosis of the condition and underlying cause[3]. In the pediatric population, the syndrome is more prevalent with a strong association with neuroblastoma and ganglioneur oblastoma and delayed diagnosis may impact overall patient survival[4]. In adults, up to 70% of cases are idiopathic[2]. There is also a strong paraneoplastic association, in particular with small cell lung carcinomas, breast and ovarian neoplasms[5]. Therefore, it is prudent to perform CT screening of chest, abdomen and pelvis, all negative in our case. Brain MRI with gadolinium is recommended to rule out structural lesions that could lead to symptoms similar to OMS, also normal in our case[1].

Another relevant etiologies in adults are infectious or parainfectious[5]. The most frequent infectious entities related are the EBV, CMV, HCV, mycoplasma, HIV, HSV 6, post-streptococcal, after Rubella vaccination, salmonella, and intoxication of venlafaxine[6]. In our case, the onset was compatible with infectious mononucleosis, due to a documented pharyngitis refractory to antibiotics, with mild elevation of transaminases, lymphocytosis, high ESR and IgM/IgG positivity for EBV. The presence of IgM and IgG antibodies for HSV is probably a cross reaction, because HSV and EBV belong to same family of virus. We performed echocardiogram due to persistent fever and possible endocarditis. It showed a mild pericardial effusion, probably another systemic repercussion of EBV infection. The pathophysiological mechanisms underlying the syndrome are still unknown[7]. Necropsy studies of brain tissues revealed mild perivascular lesions without associated lymphocytic infiltrate nor neural degeneration, suggesting a probable immunomediated cause via antibodies, such as anti-Ri, NMDAr, GABA-A, GABA-B, DPPX, HNK-1 and GlyR[2]. CSF should be obtained if there is concern for acute central nervous system infection; in OMS this may be normal or show mild elevations of protein or mild lymphocytic pleocytosis[1]. In the present case, indeed there was a mild pleocytosis of 6 cells and mild elevation of CSF protein of 62mg/dl. Several studies have been searching for biomarkers that may facilitate the diagnosis, but none studied biomarker has ever shown significant sensitivity or specificity[2]. A remarkable characteristic of the case is the seizure. We didn't find any case report of OMS in literature associated with tonic-clonic seizure. The patient didn't have encephalopathy, hypersomnolence or mental confusion, excluding encephalitis. Anxiety and irritability may occur in classic OMS. Because of this, our explanation about the seizure was a cortical disfunction without classical pattern of encephalitis. Thus, our case report is the unique to literature with this specific type of presentation. In treatment, corticosteroids and ACTH therapy are first choice, although there are no studies that indicate the superiority between them, clinical efficacy for motor improvement or impact on prognosis[5]. The majority of authors use oral prednisone or prednisolone (2mg/kg/day), but dexametasone pulsotherapy (20mg/ $m^2$/day for 3 days monthly) or methylprednisolone (1g/day for 3 days)[4,8]. A 5-day course of immunoglobulin (0,4g/kg/day), cyclophosphamide or rituximab can also be used[4,8]. The dose of ACTH proposed is 75 IU per dose twice for 52 weeks[8]. We decide to use methylprednisolone 1g/day for 3 days following 60mg oral prednisone according to our experience and drug availability. Literature data on long-term prognosis followed up a child population[8]. Although it is reported significant improvement in motor symptoms, 80% of children maintain minor impairments, such as dysarthria, ataxia or myoclonus, and 100% of these develop some neuropsychological symptom such as language, memory or attention disorders. The most obvious neurological impairment in this population translates to a significant fall in IQ, with an average decrease in IQ score of 78 points 1 to 4 years after OMS[8]. In adults, the recurrence of neurological symptoms is common, with about 2 to 4 episodes, specially during the decrease of oral corticosteroids[9]. The average oral corticosteroid treatment is 1 to 2 years, but some cases need corticosteroid therapy for up to 8 years. Due to the preponderance of neurological impairment and relapse of the syndrome in the short run, several other therapies have been employed. Italian studies suggest corticotherapy associated with multimodal immunosuppression such as monthly immunoglobulin[5]. Cyclophosphamide pulses have more improvement of motor symptoms compared to standard therapy, but similar for neuropsychiatric symptoms[5]. Most authors has been suggested immunosuppression in recurrence form, using chronically mycophenolate, rituximab or cyclophosphamide[8].

# CONCLUSION

OMS is a rare entity of exuberant clinical manifestation, but difficult diagnosis. Standard therapy with corticosteroids and ACTH shows a significant improvement in motor symptoms, but not in the neuropsychological impairment, especially in children. Recurrence is common, especially in adults, and there are few studies on prognosis of this population in the long term. In our case, a detailed history and neurological examination was crucial to suspect OMS, using opsoclonus as an important feature to accurate diagnosing. We ruled out tumors and the treatment was as early as possible, resulting in good clinical improvement.

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