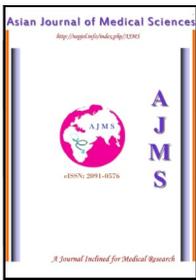


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## Association of Primary Biliary Cirrhosis with Opsoclonus Myoclonus Syndrome

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### Abstract

Primary biliary cirrhosis is an autoimmune disorder affecting exclusively liver. There has been association of this autoimmune disease with various other neurological counterparts, but Opsoclonus-Myoclonus Syndrome in conjunction with primary biliary cirrhosis is unreported yet. Opsoclonus-Myoclonus Syndrome is a disorder of eye movement with an ill-defined etiology. It may be idiopathic or present as a paraneoplastic manifestation with a low response to therapeutic modalities. We present a case of primary biliary cirrhosis that developed Opsoclonus-Myoclonus Syndrome during an exaggeration of disease process which responded well to intravenous corticosteroids. Knowledge of association of Primary biliary cirrhosis with Opsoclonus-Myoclonus Syndrome and its good response to treatment in this setting will help in reducing morbidity in similar situations.

**Key Words:** Primary biliary cirrhosis; Opsoclonus-Myoclonus Syndrome

### 1. Introduction

The word oculo-plas [Opsoclonus] was introduced in 1913 by the Polish neurologist Orzechowski to denote irregular, continual, conjugate, chaotic saccades of the eyes.<sup>1</sup> Since then, there have been many descriptions and terms coined to describe this phenomenon. It may be idiopathic; or a part of post-viral encephalitis or cancer-related. Although a small group of them have been reported in association with auto-antibodies, rarely have they described in association with autoimmune diseases. We report a patient diagnosed with primary biliary cirrhosis [PBC], who developed Opsoclonus Myoclonus Syndrome [OMS] with good therapeutic response to intravenous corticosteroids. To our knowledge, this is the first case of OMS in association with PBC.

### 2. Case History

A 40 year old woman presented with complaints of yellowish discoloration of eyes and skin since 10 days. He also complained of fever and vomiting since 5 days. Further, she gave history of easy fatigability, anorexia and diffuse pain abdomen since 2 months. Her past

medical and surgical history was not significant. There was no history of co-morbidities and her family history was non-contributory.

On examination, she was pale and icteric with bilateral pitting oedema. Per abdomen examination revealed tender hepatomegaly with a liver span of 16 cm. there was no splenomegaly and no free fluid in the abdomen. There were no other signs of chronic hepatic dysfunction. Other systemic examination was normal.

Complete blood examination revealed leucocytosis with high ESR [Hemoglobin-9.7 g%, Total Count- 17,500 cells/mm<sup>3</sup>, neutrophils-54, lymphocytes-40, eosinophils-04, monocytes-02, basophils-0, ESR- 75 mm/hr]. Liver function test showed predominant direct bilirubinemia with hypoalbuminemia and elevated liver enzymes, predominantly alkaline phosphatase [Total Bilirubin-6.69, Direct Bilirubin- 5.26, Total Protein- 5.1, SGOT-199 IU/L, SGPT-113 IU/L and Alkaline Phosphatase-604 IU/L]. Lipid profile showed dyslipidemia with very low HDL levels [Total cholesterol- 252 mg/dl, Serum triglycerides -231 mg/dl, Serum HDL- 03 mg/dl, Serum LDL-203 mg/dl, Serum VLDL-46 mg/dl]. Serology for viral markers [Human Immunodeficiency Virus, Hepatitis A Virus, Hepatitis B Virus, Hepatitis C Virus and Hepatitis E Virus]

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was negative. Coagulation and renal parameters were within normal limits. Ultrasound abdomen showed chronic parenchymal liver disease and splenomegaly. Upper gastro-intestinal endoscopy showed congestive gastropathy. She was provisionally diagnosed as a case of cholestatic liver disease; most likely PBC and was further evaluated. Anti-mitochondrial antibody [AMA] assay was positive with titre of 1:100, confirming the diagnosis of PBC. Tests for P-ANCA and Anti-Nuclear Antibodies [ANA] were negative. Thyroid profile was done in view of association of autoimmune thyroiditis with PBC, was normal.

The diagnosis of PBC was established and the patient was started on ursodeoxycholic acid. A day later, icterus deepened and the patient developed new symptoms of giddiness and difficulty in walking without support. Detailed examination revealed opsoclonus, ataxic gait and myoclonic jerks in both lower limbs. Patient was diagnosed to have OMS and was subjected to a full detailed investigation for the same. Magnetic Resonance Imaging [MRI] Brain, Visual evoked Potential [VEP] and Brainstem Auditory Evoked Potential [BAER] were normal. Chest X-ray and Computerized Tomography [CT] scan of the chest were done to rule out primary breast or lung carcinoma as OMS is mostly associated with small cell carcinoma lung and carcinoma breast as paraneoplastic manifestation in these conditions. Both investigations were normal.

The patient was started on intravenous corticosteroids, following which Opsoclonus and myoclonus subsided. The patient improved after 3 weeks of treatment with ursodeoxycholic acid for PBC. Repeat liver function test done after 3 weeks of treatment was normal.

### **3. Discussion**

PBC is an autoimmune disease with the characteristic AMA. Although the target in this autoimmune disease is all nucleated cells, the disease is organ specific with focus only on the liver. There are reports showing association of PBC with various neurological autoimmune diseases. Anantharaju et al reported a case of transverse myelitis occurring in association with PBC and Sjogren's syndrome.<sup>2</sup> Sato and colleagues reported a case of PBC with mitochondrial encephalomyopathy.<sup>3</sup> Escalante et al reported a case of sensory neuropathy in association with PBC.<sup>4</sup> Blaes et al reported a case of adult OMS with Anti-mitochondrial antibody but there was no evidence of clinical or laboratory signs of PBC or

any other liver disease; otherwise there is no reported case of OMS associated with PBC.<sup>5</sup>

Opsoclonus is a disorder of eye movement characterized by involuntary, chaotic saccades that occur in all directions of gaze; it is frequently associated with myoclonus and ataxia. When it is a paraneoplastic manifestation, the most common tumours are Small Cell Lung Carcinoma and Breast Cancer in adults; and neuroblastoma in children.<sup>6</sup> In addition to its association with tumour and post-viral encephalitis, opsoclonus has been associated with many other conditions ranging from vascular events to severe head trauma.<sup>1</sup>

Auto-antibodies in association with OMS have been reported with a small group of paraneoplastic OMS. Anti-Ri and anti-Hu antibodies are the most common auto-antibody seen in paraneoplastic OMS, commonly seen with breast cancer. The other antibodies infrequently seen with this paraneoplastic manifestation are anti-Ma2 and anti-Yo antibodies.<sup>6</sup> However, there is increasing recognition that both humoral and cell mediated immune mechanisms are involved in the pathogenesis of Opsoclonus.<sup>7</sup> Blaes and colleagues studied in detail regarding an autoimmune aetiology of OMS in children and concluded that a humoral immune-mediated process is the underlying cause for OMS.<sup>8</sup> A variety of auto-antibodies have been reported in association with OMS and a number of newer auto-antibodies have been added to this list over last few years.

Blaes et al have reported a case of SCLC-associated OMS with high titre AMA in serum and CSF in a 58 year old Caucasian woman.<sup>5</sup> They suggested presence of AMA in adult onset OMS indicates an underlying tumour. In the present case, the patient did not have any preceding history of viral infection or clinical evidence of viral infection of the CNS and CSF/MRI examination was normal. Normal CT and MRI ruled out Breast and Lung Malignancy. The pathogenesis of OMS was considered secondary to worsening PBC since the symptoms appeared with increase in bilirubin levels. Resolution of symptoms with falling bilirubin levels and intravenous corticosteroids further supports this theory.

Review of previously reported case-reports of idiopathic OMS suggest that the condition is associated with an age dependent prognosis and immunotherapy seems to be associated with a faster recovery particularly in those cases with a severe neurological dysfunction.

A retrospective study of idiopathic OMS found that 82% of the cases resolved without any neurological sequel in an average eight weeks.<sup>1</sup> Similarly, there was complete remission of OMS in the present case. The good response to the treatment may be due to a short delay between onsets of symptoms. The treatment and control of the possible underlying cause could also have contributed to the good prognosis.

Paraneoplastic OMS is usually resistant to steroids, plasmapheresis, or intravenous immunoglobulins.<sup>9</sup> In contrast, Blaes et al reported an almost complete remission of SCLC-associated OMS with AMA after steroid therapy.<sup>5</sup> The association of AMA with the good prognosis in both these situation could not be considered as a mere coincidence but again, an in-depth study of the same is needed to prove this hypothesis.

#### 4. Conclusion

We present a case of PBC presenting with OMS. The patient condition improved following intravenous corticosteroid therapy. Hence, an adult onset OMS should not only raise suspicion for underlying malignancy but a detailed work-up has to be done for any underlying and associated immunological disorders as the prognosis is fairly good with early initiation of treatment.

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