

Opsoclonus - Myoclonus in Children

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Opsoclonus-myoclonus (OPMS) is a rare neurological syndrome of children and adults. Association with neuroblastoma occurs in 20-50% of all cases. We have recently encountered an infant with this syndrome and detailed work up revealed her to have an underlying neuroblastoma. Etiology and pathogenesis of this syndrome have been reviewed, it is important for general paediatricians to recognise this entity in order to initiate investigations and possible treatment.

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Opsoclonus-myoclonus syndrome is a rare syndrome. Its presence is dramatic and should be recognised and appreciated by paediatricians because it is usually a manifestation of a remote malignancy, especially neuroblastoma (paraneoplastic). Such a syndrome is also known as dancing eye syndrome, myoclonic encephalopathy of infancy, infantile polymyoclonia of Kinsbourne and others.

Although Orzegliowski described it 80 years ago, it was only described fully in 1962 by Kinsbourne¹. The causal relationship between the syndrome and the tumour was only described in 1968 by Dyken and Kolar².

We have recently encountered an infant with this syndrome whose case report will be reviewed.

In addition, we will review briefly its clinical presentation, aetiology, pathophysiology, investigations, proposed treatment modalities and the outcome.

THE CASE

A one year old previously healthy girl, with normal perinatal and infantile period, presented for evaluation of ataxia and irritability. One month prior to presentation, she started to show signs of irritability manifested by tonic extension of body. Later on, developed abnormal multidirectional eye movements, generalised body tremor, followed by development of gait ataxia and loss of verbal skills. There was no history of seizure.

Past medical history was not significant. On examination, the child was very irritable with evidence of coarse head titubations. She was afebrile, blood pressure was 89/58 mmHg, weight, height and head circumference were in the 25th percentile.

General examination was unremarkable. Neurologic examination showed an alert child. She was able to

recognise her parents, but refused to verbally communicate in front of the examiner. Cranial nerves were intact. There were positive opsoclonic eye movements with prominent dyskinetic movement of mouth and lips. Motor tone and DTRs were normal with marked truncal and appendicular ataxia.

The results of urinalysis and complete blood count were normal, as were the values of renal profile, glucose, calcium, phosphorus and magnesium. Serum ferritin: 57 mg/L (10-291), VMA (vanillyl mandelic acid) screen was negative. Cerebral spinal fluid analysis was normal. A chest CT scan showed right sided paravertebral mass in the posterior mediastinum above the level of the carina, with no mass effect. Abdominal CT scan and brain MRI were normal. PET scan (positron emission tomography) of the brain was also normal except for relatively increased glucose uptake in the extraocular muscles, consistent with the excessive and rapid eye movements. Bone scan showed uptake only in the mediastinal regions with no evidence of bony abnormality. MIBG (metaiodobenzyl guanidine) revealed intense uptake only in the mediastinum. The pathologic study from mediastinal mass show small cells and multinucleated large cells with few mitoses, together with scattered ganglion cells consistent with ganglioneuroblastoma. The patient was treated with tumour resection, followed by cyclophosphamide according to neuroblastoma protocol. The patient evaluation one month after treatment showed continuity of opsoclonus symptoms. Unfortunately patient was lost to follow up after that.

DISCUSSION

The syndrome includes various symptoms: opsoclonus, myoclonus, ataxia and encephalopathy. The onset of the disease is usually between the first 18-20 months. The youngest reported case was a four month old and only 13% of paediatric cases are older than two years^{3,4}. Upper respiratory tract infection, gastroenteritis or history of vaccination are among the early preceding events in 36% of patients⁵.

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Opsoclonus, conjugate or semi-conjugate, rapid, randomly-directed eye movements are increased by verbal or tactile stimulation. Onset of myoclonus is acute and may precede opsoclonus by a few days. Its distribution may include the face, eyelids, head and trunk. Diaphragmatic myoclonus leading to respiratory impairment may occur. Usually the myoclonus is severe enough to affect sitting, standing, speech and feeding. Truncal ataxia has been reported in the majority of patients often associated with appendicular ataxia and sometimes so severe that the patient will be unable to stand or even sit without support. However, it has also been suggested that the ataxia is unlike cerebellar ataxia, but is instead due to repeated myoclonic jerks². Encephalopathy is not usually a feature of the disease in children. Yet other mental and emotional features such as nervousness, irritability and lethargy have been found almost in half of the patients reported⁴. Dysphasia, dysarthria or even mutism have been reported⁶. Other features like hypo or hypertonia, head nodding and even urinary retention and dysphagia may be present.

Systemic tumours and viral infections constitute the principal aetiologies for opsoclonus myoclonus in children, but other aetiologies such as toxic and metabolic causes could play a role. Different types of infections have been reported to be associated with opsoclonus myoclonus, with viral infection leading the way. Such viruses include Epstein-Barr, mumps, rubella, Coxsackie-B, polio virus and some other viruses^{7,8}. Neurosyphilis, salmonella typhi and tuberculous meningitis have also been implicated. Paraneoplastic movement disorders are uncommon, except for opsoclonus myoclonus. There are a variety of associated neoplasms described in children; neural crest-derived tumours predominate and out of these, neuroblastoma is the most common. Two or three percent of neuroblastoma can present as OPM⁹. The syndrome has never been so far reported with pheochromocytoma.

Drug induced myoclonus is quite uncommon. It usually occurs at toxic doses. Tricyclic antidepressants, phenytoin and diazepam are most commonly implicated¹⁰. Other drugs may reversibly exacerbate pre-existing opsoclonus myoclonus such as ketamine hydrochloride. Multiple carboxylase deficiency in children and hyperosmolar nonketotic hyperglycaemia have been described to induce OPM incidentally. The reported pathologic findings have so far been supportive for an immune mechanism as a cause for OPM based on the presence of different types of antineurofilament antibodies¹¹, lymphocytic infiltrate in the tumour, and finally the response to ACTH in some of the patients. Abnormal high level of neurotransmitter have not been implicated in the pathophysiology of OPM, hence Pranzatelli et al's study of 27 affected patients with OPM showed that the level of CSF 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) were lower by 30-40% in OPM patients compared to control subjects¹².

The diagnosis is established on pure clinical grounds, occasional slowing in the EEG and delay in V-wave and prolonged interpeak latencies on brain stem auditory evoked potential testing has been noted. Cerebrospinal fluid may show pleocytosis with increased protein when encephalitis and CNS tumours are implicated. Tumor markers both cellular and circulating markers for neuroblastoma have been described but their relation to OPM is not well documented. Some of the monoclonal antibodies, such as CD2 (cell surface glycosphingolipid diganglioside), have been identified in neuroblastoma patients¹³, but none of these markers have been described in neuroblastoma induced

OPM patients. A search for remote neoplasm as a cause for OPM is mandatory. Various imaging studies have been proposed that are necessary to be done and that include abdominal radiography, IVP and bone scan, but out of these, Farrelly et al, found CT scans to be the most sensitive test for tumour detection¹⁴. However, occult neuroblastoma can easily be missed by the use of the various imaging studies mentioned. MIBG (metaiodobenzyl guanidine, a norepinephrine analogue), is radiolabeled with either ¹²³I or ¹³¹I. MIBG normally localise in the heart, liver, salivary glands, bladder, colon and normal adrenal gland. Osseous uptake is not expected. Thus MIBG scanning can easily identify sites of osseous metastasis in addition to detecting the primary mass¹⁵.

ACTH has been shown to be effective in alleviating the symptoms in 80-90% of patients with a latency period of up to two weeks. It was postulated that ACTH either functions as neurotransmitter or modulating the activity of neurotransmitter, namely serotonin. The majority of patients will show recurrence of their symptoms as ACTH is being tapered off. Comparative study of the use of ACTH versus prednisone proved that the latter was ineffective in controlling OPM symptoms⁵. Several other drugs have been tried, and were found to be ineffective. Few reports mentioned a relatively good response to clonazepam and 5-hydroxytryptine in alleviation of myoclonus. Thiamine responsive OPM was reported in a case of bronchogenic carcinoma, but not with other paraneoplastic opsoclonus. Biotin showed its effectiveness for OPM symptoms in multiple carboxylase deficiency. Plasmapheresis has been determined to be ineffective. Immunoabsorption was successfully used in an adult patient with OPM and underlying lung cancer¹⁶. Tumour therapy by surgical resection with chemotherapy has no effect in decreasing OPM symptoms. Yet, the abnormal movement may disappear spontaneously between three months and one year from the onset. The prognosis is not affected by aetiology, age of onset or even early treatment. The most chronic motor abnormality is ataxia. Cognitive dysfunction manifested by hyperactivity, impulsivity and emotion lability was reported in 61-82% of cases, regardless of the aetiology¹⁷.

CONCLUSION

Though OPM is a rare neurological syndrome, its presence should be appreciated by paediatricians, because it is usually a manifestation of a remote malignancy, especially neuroblastoma. Appropriate investigation should be done and accordingly early treatment of such malignancy can be initiated with the ultimate aim of improving the prognosis.

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