

Clinical Profile, Prognostic Indicators, and Therapeutic Outcomes of Pediatric Opsoclonus-Myoclonus-Ataxia Syndrome: A Single-Center Experience from South India

Karthik Muthusamy, Maya Thomas, Sangeetha Yoganathan, Sniya Valsa Sudhakar¹

Department of Neurological Sciences, Pediatric Neurology Division, Christian Medical College, ¹Department of Radio Diagnosis, Christian Medical College, Vellore, Tamil Nadu, India

Abstract

Background: Opsoclonus myoclonus syndrome (OMS) is a neuroinflammatory disorder. Indian literature on its clinical profile and outcome is sparse. **Objectives:** The objective of this study is to describe the clinical profile and analyze outcomes and prognostic predictors in a cohort of children with OMS. **Materials and Methods:** This was a retrospective study of children with OMS between 2007 and 2017. **Results:** Twenty-two children were included in the study. The mean age at onset of symptom was 20.9 months (standard deviation [SD]: 7.5). The mean duration of delay in diagnosis was 8.4 months (SD 1.26) with acute cerebellitis being the most common misdiagnosis. Eleven children (50%) were diagnosed with tumor during evaluation and follow-up and 11 children (50%) belonged to idiopathic/postinfectious group. Magnetic resonance imaging brain was normal in all children except for one revealing cerebellar atrophy on follow-up. One child in the paraneoplastic group (neuroblastoma) had a positive PNMA2/Ta onconeural antibody. Children in the tumor group had an earlier age of onset (mean 15.5 vs. 26.3 months), shorter time to onset of opsoclonus from initial symptom (2.54 vs. 7.27 weeks), and higher severity score at presentation (13.7 vs. 11.3) compared to the nontumor group. Children in the nontumor group attained their first remission with treatment earlier (10.9 weeks, SD: 4.5) than the children with tumor (18.72 weeks, SD: 5.8). There was no significant difference in the outcome between the groups. Children with multiple relapses (>3) and late surgical intervention for tumor (>6 months after symptom onset) had a poor outcome. **Discussion:** A high index of suspicion coupled with early diagnosis and periodic tumor surveillance (even in the initially negative cases) along with aggressive combined multimechanistic immunotherapies is the key in improving outcomes. **Conclusion:** A high index of suspicion in appropriate clinical circumstances and early aggressive immunomodulation might lead to a better outcome.

Keywords: Neuroinflammation, neuroblastoma, opsoclonus-myoclonus-ataxia syndrome, opsoclonus myoclonus syndrome, paraneoplastic neurologic disorders

INTRODUCTION

Pediatric opsoclonus-myoclonus ataxia syndrome (OMS) is a devastating neuroinflammatory disorder with the core clinical criteria of ataxia/myoclonus, opsoclonus, and behavioral/sleep disturbances. OMS is an immune-mediated disorder with recent reports of various associated autoimmune antibodies. Frequently reported paraneoplastic association is an underlying neuroblastoma. Awareness of this entity among physicians, a high index of suspicion in appropriate clinical circumstances, early diagnosis, aggressive immunomodulation, and periodic tumor surveillance are essential in reducing the morbidity and improving the developmental outcome. In this article, we report the clinical profile, management, and outcomes of pediatric OMS in a tertiary care center in South India. This is the largest case series from the Indian subcontinent till date.

MATERIALS AND METHODS

A retrospective chart review of children (<15 years of age) diagnosed with opsoclonus-myoclonus-ataxia syndrome was done with a standard pro forma which included demographic details, clinical profile, investigations, treatment, and follow-up.

The study was conducted at the Pediatric Neurology division of the Department of Neurological Sciences at the Christian Medical College, Vellore, which is a tertiary care center catering to South India. The electronic records of children diagnosed with OMS from January 2007 to November 2017 (10 years) were reviewed and were analyzed further. Children with insufficient clinical details and follow-up of <1 year were excluded from the study. Children were classified into two groups – paraneoplastic and nontumor group (postinfectious and idiopathic). The severity of symptoms was graded as per the Genoa Opsoclonus Myoclonus syndrome symptom severity score.^[1] Treatment response and the

Address for correspondence: Dr. Karthik Muthusamy, Department of Neurological Sciences, Paediatric Neurology Division, Christian Medical College, Vellore, Tamil Nadu, India. E-mail: karthik@cmcvellore.ac.in

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course of the disease were classified as monophasic (attained sustained remission during the follow-up period, irrespective of the duration to attain remission), relapsing-remitting (near complete resolution of motor symptoms in-between except for mild behavioral/learning issues and recurrent relapses), and chronic relapsing (recurrent worsening by more than 3 scores compared to baseline and continues to have obvious baseline motor and behavioral symptoms).

Statistical analysis

Duration to attain the first remission, number of relapses, and the status at the last follow-up (remission/progression/relapse) were assessed as outcome measures. Various demographic data, etiology, time to delay in diagnosis/treatment initiation, and duration of symptoms before tumor removal were assessed as prognostic predictors. The tumor and nontumor group was further compared for its demographic details, clinical profile, and outcome. SPSS 16 was used for statistical analysis. Student's *t*-test, Chi-square test, and logistic regression analysis were used as appropriate for analysis. $P < 0.05$ was considered statistically significant. Statistical adjustments for multiple comparisons were done using Bonferroni correction.

RESULTS

Demographic profile

Twenty-seven children diagnosed to have OMS were found in the electronic records during the study period. Twenty-two children satisfying the inclusion criteria were enrolled in the study. Boys were 10 (45.5%) and girls were 12 (54.5%). All children underwent basic investigations and paraneoplastic workup in the form of computed tomography/magnetic resonance imaging (CT/MRI) of the neck, thorax, abdomen and pelvis, metaiodobenzylguanidine (MIBG) scan, and urine catecholamine metabolites. Children in whom initial paraneoplastic workup was noncontributory and not attaining remission with treatment at the time of follow-up visits underwent repeat paraneoplastic workup once yearly. Eleven children belonged to paraneoplastic group (50%) and 11 were nonparaneoplastic (7 postinfectious and 4 idiopathic).

Age at onset of symptoms and clinical presentation

The mean age at onset of symptoms was 20.9 months (standard deviation [SD]: 7.5, range: 10–38 months). The mean duration of delay in the diagnosis from the onset of first symptom was 8.4 months (SD: 1.26, range: 0–57 months). Misdiagnosis was common at the initial visit of the children with the general physicians, who are often the primary contact. Misdiagnosis was common which is tabulated in Table 1 along with other clinical features and investigations. Apart from seven children in the postinfectious group, one child in paraneoplastic group had a preceding respiratory infection. However, specific organisms were not isolated in any of them during the presentation to us or at the initial visit to the primary physician. Time to onset of opsoclonus from the initial presentation was 4.9 weeks (SD: 3.2, range: 1–12 weeks), and the mean severity of OMS at initial presentation was 12.5 (SD: 1.5, range: 9–15).

Brain imaging

MRI brain was done in 20 children, 2 children did not have MRI of the brain as CT thorax and abdomen had already revealed tumor in the appropriate clinical context. Only one MRI brain done at 2-year follow-up in postinfectious group revealed significant abnormality in the form of moderate diffuse cerebellar atrophy [Figure 1]. There were no abnormalities in the brain imaging in any of the children done during the acute period.

Evaluation (cerebrospinal fluid, electroencephalogram, immune markers, and tumor screening)

Cerebrospinal fluid (CSF) analysis and electroencephalogram findings are discussed in Table 1. MIBG scan was done in all children, and only one child in the paraneoplastic group had positive MIBG scan (1/11). Twenty-four-hour urinary catecholamine metabolites were normal in all

Table 1: Clinical and laboratory profile of children with opsoclonus myoclonus syndrome

Features	Results
Total number of children (<i>n</i>)	22
Etiology	Paraneoplastic: 11 (50%) Nonparaneoplastic: 11 (50%) (7 postinfectious and 4 idiopathic)
Sex	10 males: (45%) 12 females: (55%)
First diagnosis at presentation	2 (9%): OMS 12 (55%) infectious/postinfectious cerebellitis 2 (9%) neurometabolic disorder, 3 (14%) seizure disorder 2 (9%) encephalitis 1 (4%) Miller Fischer syndrome
History of preceding infection	8 (36%) (5: Nonspecific symptoms without any focus of infection, 2: Respiratory infection, 1: Gastrointestinal infection)
Evaluation	
CSF analysis (<i>n</i> =13)	Normal cells, protein, and sugar, OCBs not done
EEG (<i>n</i> =19)	Normal
MIBG scan (<i>n</i> =22)	Abnormal: 1 (4%) Normal: 21 (96%)
24-h urinary catecholamine (<i>n</i> =22)	Normal: 22 (100%)
Onconeural antibody profile (<i>n</i> =12)	Positive: 1 (8%) (PNMA2/Ta antibody) Negative: 11 (92%)
Treatment	
ACTH	14 (63%)
Methyl prednisolone	10 (45%)
Prednisolone	7 (32%)
IVIG	3 (13.6%)
Dexamethasone	6 (27%)
Rituximab	3 (13.6%)

OMS=Opsoclonus myoclonus syndrome, CSF=Cerebrospinal fluid, EEG=Electroencephalogram, MIBG=Metaiodobenzylguanidine, IVIG=Intravenous Immunoglobulin, ACTH= Adrenocorticotropic hormone

children (including the paraneoplastic group). Systemic autoimmune markers were done in 20 children and were negative in all. Antineuronal antibody profile was done in 12 children, out of which one child in paraneoplastic group (neuroblastoma) showed positivity for PNMA2/Ta antibody. Children in nonparaneoplastic group who did not attain sustained remission with treatment underwent tumor screening once yearly. One child with persistent symptoms initially diagnosed as postinfectious OMS (with a noncontributory CT thorax, abdomen, and pelvis) was subsequently detected to have a neuroblastoma during the follow-up visit. He eventually attained long-term remission following surgical intervention and follow-up immunotherapy. Representative images revealing tumors in selected cases have been depicted in Figure 2.

Treatment

None of the children with tumor in our group had clinical remission with tumor removal alone. Along with tumor removal, the initial treatment given was steroids (adrenocorticotropic hormone [ACTH]/corticotrophin injections, methylprednisolone injections, and oral prednisolone). These have been tabulated in Table 1. ACTH was the commonly used medication based on the physician's preference and experience. ACTH was used in a dose of 75 units/m² in two divided doses for the 1st week, then 75 mg/m² once daily for next week, and then on alternate days, gradually tapered over months to the minimum dosage possible to sustain remission. Methylprednisolone injections were initially given at 30 mg/kg/day for 5 days, followed by once weekly injections with gradual tapering based on response. Oral prednisolone was used in a dose of 2 mg/kg/day and gradual tapering over months. High-dose dexamethasone (20 mg/m²/day for 3 consecutive days every month) was used in 6 children who had a relapse with initial treatment. Intravenous immunoglobulin at the dose of 2 gm/kg was used in 3 children. Rituximab (375 mg/m² once weekly for 4 consecutive weeks) was used in 3 children who had frequent relapses with steroids. Cyclophosphamide, azathioprine, and mycophenolate were not used in our series.

Treatment response and follow-up

The mean duration of follow-up was 44 months (SD: 2.1, range: 20–90 months). The mean duration to attain the first

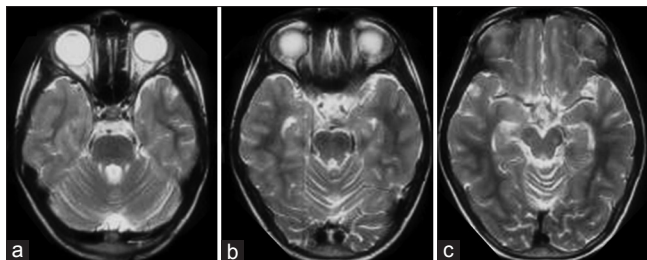


Figure 1: Magnetic resonance imaging T2 axial images of the brain (a-c) showing increased vermian and hemispheric interfolial distance (arrows) suggesting diffuse cerebellar volume loss

remission after initiation of treatment was 14.8 weeks (SD: 6.49, range: 2–30 weeks). Twelve children (54%) had a monophasic course irrespective of the duration to attain the first remission. Seven children (32%) had a recurrent relapsing disease course, before attaining complete remission. Three children (14%) had a chronic disease course with intermittent worsening of disease score and did not attain significant remission till their last follow-up, the results of which are tabulated in Table 2. The most common precipitating factor for a relapse was an intercurrent infection in 7 children and steroid tapering/withdrawal in 2 children. One child had a relapse without an obvious precipitating event while on stable treatment phase. All children except three were in the final remission at the time of last follow-up. Children in the final remission had no residual motor/sleep problems though they continued to have attention deficits and poor scholastic performance.

Statistical analysis

Mean age at onset of symptoms, delay in diagnosis, time to onset of opsoclonus from the initial symptom, severity of OMS at presentation, duration to attain the first remission, disease course, number of relapses, and final remission were analyzed between the tumor and nontumor group and are tabulated [Table 2]. The parameters which were statistically significant between the tumor and nontumor group were the age at presentation, time to onset of opsoclonus from the initial presentation, severity of symptoms at presentation, and the duration to attain the first remission. Children in tumor group developed neurological symptoms at an earlier age (mean 15.5 months, SD: 3.5) than the nontumor group (26.3 months, SD: 6.5), the time to onset of opsoclonus

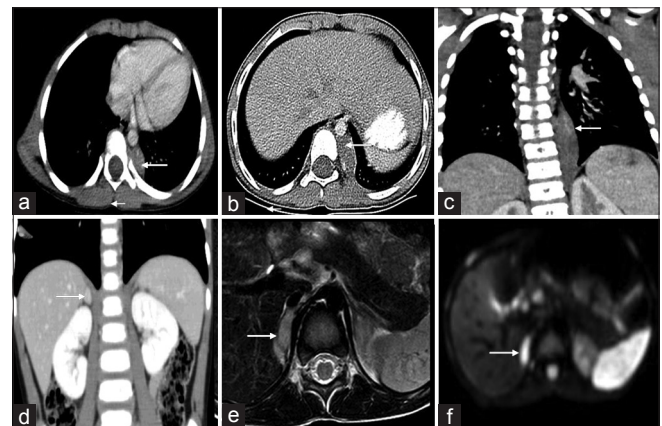


Figure 2: Case 1 with tumor (a-c): Computed tomography axial (a and b) and coronal (c) images of the thorax in venous phase shows a hypodense, mildly enhancing, faintly calcified, elongated lower left paravertebral lesion (arrows) in the posterior mediastinum extending into the retrocrural region (b) no intraspinal or intra-abdominal extension. Case 2 with tumor (d-f): Coronal (d) venous-phase computed tomography images of the upper abdomen show a small enhancing lesion in the medial limb of right adrenal gland (arrows). Magnetic resonance imaging T2 axial (e) image shows a corresponding T2 hyperintense lesion measuring ~ 16 mm × 8 mm. Note the restricted diffusion on diffusion-weighted imaging images (f)

Table 2: Comparison of the clinical profile of tumor versus nontumor group and results of statistical analysis

Parameters	Tumor-related OMS	Nontumor OMS	Significance P
Sex	6 males, 5 females	4 males, 7 females	0.67
Mean age at presentation in months (SD, range)	15.5 (3.5, 10-20)	26.3 (6.5, 18-38)	<0.001
Mean duration of delay in diagnosis in months (SD, range)	10.3 (16.9, 0-57)	6.54 (6.3, 1-18)	0.492
Time to onset of opsoclonus from initial symptom in weeks	2.5 (1.03, 1-4)	7.27 (2.8, 4-12)	<0.001
Severity of OMS at presentation	13.72 (0.78, 12-15)	11.36 (1.02, 9-12)	<0.001
Duration to attain the first remission (weeks)	18.72 (5.8, 6-30)	10.9 (4.5, 2-18)	<0.02
Disease course	Monophasic: 7 Recurrent relapsing: 3 Chronic relapsing: 1	Monophasic: 5 Recurrent relapsing: 4 Chronic relapsing: 2	0.66
Number of relapses	≤3 relapses: 10 ≥4 relapses: 1	≤3 relapses: 7 ≥4 relapses: 4	0.12
Final remission	Attained final remission: 10 Not attained remission: 1	Attained final remission: 9 Not attained final remission: 2	0.53

OMS=Opsoclonus myoclonus syndrome, SD=Standard deviation

from initial symptom was relatively shorter in the tumor group (2.54 weeks, SD: 1.03) than in the nontumor group (7.27 weeks, SD: 2.8), as shown in Figure 3 and the severity of OMS score at presentation was higher in the tumor group (13.7, SD: 0.78) than in the nontumor group (11.3, SD: 1.02). Children in the nontumor group attained their first remission with treatment earlier (10.9 weeks, SD: 4.5) than the children with tumor (18.72 weeks, SD: 5.8). It can be seen that many children in the tumor group had a monophasic disease course though the duration to attain the first remission was longer when compared to the nontumor group.

Outcome

There were no significant differences in the outcome when the tumor and nontumor group were compared ($P = 0.557$). However, children with frequent relapses (>3) had an adverse outcome, not attaining final remission, which was statistically significant ($P = 0.001$). Twelve children were diagnosed and treated within 4 months of symptom onset and 10 were delayed by >4 months; the mean duration to attain the first remission was 14.8 weeks in both groups ($P = 0.99$). Six children had their tumor removed within 6 months of symptom onset and 5 had tumor removal after 6 months of symptom onset. It was observed that those children with delay in diagnosis of >4 months after symptom onset and those with tumor removal >6 months of symptom onset had frequent relapses and lesser chances of attaining final remission though the data were not statistically significant.

DISCUSSION

Opsoclonus-myoclonus-ataxia syndrome is a rare and devastating inflammatory disorder affecting central nervous system of young children and is often of paraneoplastic etiology. The syndrome was first recognized and described by Kinsbourne in 1962 as myoclonic encephalopathy in infants.^[2] OMS is rare with an estimated incidence of 0.18–0.4/million of total population, as reported in a prospective study in the United Kingdom and Japan, respectively.^[3,4] Prodromal

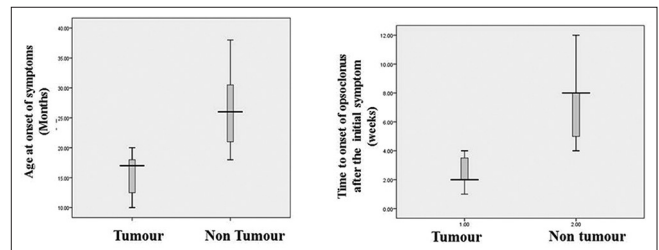


Figure 3: Box plot showing distribution of age at onset of symptoms (months) and time to onset of opsoclonus after initial onset of initial symptom (weeks) in tumor versus nontumor group

symptoms are usually nonspecific which often lead to misdiagnosis and thereby delay in treatment initiation and increase in eventual developmental disability and morbidity. To avoid delay in diagnosis, international consensus criteria have been proposed^[1] in Box 1.

It should be noted that children with OMS need not fulfill all the criteria at the time of initial presentation and the syndrome usually evolves over a couple of weeks to its full-blown clinical presentation, and many atypical presentations have also been reported. Hence, the index of suspicion should be high in appropriate clinical scenarios to avoid delay in diagnosis and misdiagnosis. Misdiagnosis is common even with experienced clinicians due to its rarity and nonspecific symptoms at initial presentation. In our series, the most common misdiagnosis was acute cerebellitis, which is the universal misdiagnosis reported,^[5] followed by neurometabolic disorder, seizure disorder, and encephalitis and one case with Miller Fisher syndrome.

Age at onset and presentation

The mean age at onset of symptoms in our group was 1.74 years with the range of 0.8–3.16 years. It is in accordance with the largest cohort reported till date by Pranzatelli,^[5] where the mean age at symptom onset was 1.5 years with range of 0.17–9.8 years; only 2% had their symptom onset at <6 months of age in this largest cohort. None of the children in our group

had the onset of symptoms at <6 months of age. Girls (55%) slightly outnumbered the boys (45%) in our series, as also seen in other studies.^[5] Gait ataxia was the initial presentation in all our children. Atypical presentations with stridor, rage attacks, and dysphagia have been reported in previous studies^[6,7] though none of our children had these presentations.

Etiology

The etiologies of OMS described are paraneoplastic, postinfectious, and idiopathic, where a yet unidentified antigenic stimulation leads to inflammatory activation and the resultant neurological symptoms. Infections triggering OMS are common and include viruses such as Epstein–Barr virus, adenovirus, enterovirus, varicella zoster virus, West Nile virus, hepatitis C virus, and Japanese encephalitis virus and bacterial agents such as streptococci, mycoplasma, and rickettsial infections.^[8–10] There has been a case report of immune reconstitution syndrome in a child with HIV infection presenting with OMS.^[11] There were 7 (31%) children with postinfectious etiology in our group though no organisms could be isolated in them. One child in our study who had symptoms of recent infection and initially classified as a probable postinfectious etiology turned out to have tumor at evaluation. Hence the presence of infection should not preclude a detailed paraneoplastic workup in appropriate clinical circumstances. Neuroblastoma though a rare solid tumor of childhood is the most common tumor associated with OMS in pediatric-onset OMS, whereas in adult-onset cases, varieties of tumors including small cell lung carcinoma, breast carcinoma, ovarian carcinoma, and nasopharyngeal carcinoma have been reported.^[12–14]

Conversely, around 36%–50% of children presenting with OMS were diagnosed to have neuroblastoma^[5] at presentation and follow-up. Fifty percent of children in our series belonged to paraneoplastic group and all of them had neuroblastoma. Periodic tumor surveillance is essential in children without tumor at initial presentation as most of them eventually turn out to have tumor at follow-up. In our experience, one child who was initially classified as postinfectious after an extensive paraneoplastic workup and managed appropriately was diagnosed with tumor, at repeat screening after a period of 1 year. In the cohort described by Pranzatelli,^[5] tumor detection was comparably higher in the second and third study period, than in the first study period.

Pathogenesis of OMS

Exact pathogenesis of this disorder is unknown; however, an immune-mediated dysfunction of the brainstem and cerebellum

has been proposed. Opsoclonus may reflect disinhibition of the fastigial nucleus of the cerebellum or disordered interaction between omnipause and burst neurons. However, the cognitive and behavioral elements of the condition, as well as recent imaging studies, suggest a diffuse cerebral dysfunction. There are several antibodies described as association with OMS in various studies though no antibody has been proven to be consistently associated with this disorder with childhood onset. Few of the antibody associations mostly described in adult-onset cases though occasionally in childhood are anti-glutamic acid decarboxylase antibodies, voltage-gated potassium channel antibody, anti-Hu, antineuronal nuclear autoantibody, antibodies to dendritic neuronal surface antigens, anti-NMDAR antibodies, Ri/ANNA2, glycine receptor antibodies, human natural killer-1 antibodies, and ganglionic acetylcholine antibodies.^[15–18] In our series, commercially available onconeural antibody profile was done in 12 children, of whom one child in paraneoplastic group (neuroblastoma) showed positivity for PNMA2/Ta, which has not been described earlier. Systemic immune markers such as erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, and dsDNA were negative in all the children. One child in the idiopathic group had incidental proteinuria during the acute presentation which went into spontaneous remission with the treatment of OMS, the association which has not been described earlier. This could represent a wider spectrum of systemic immune activation in this disorder.

Brain imaging in OMS

MRI of the brain in the acute presentation is usually normal. Imaging during the chronic phase can reveal cerebellar atrophy. Twenty children in our study had an MRI brain, of which MRI of one child revealed cerebellar atrophy at 2 years of follow-up. There have been several studies focused on voxel-based morphometry and tract-based spatial statistics revealing cerebellar atrophy particularly in vermis and flocculonodular lobes, severity of which has been correlated with persistent symptomatology. There were also differences in cerebral cortical thickness indicating disease beyond cerebellum explaining the cognitive deficits.^[19] Resting state functional MRI has revealed reduced connectivity between the cerebellum and motor cortex but increased connectivity with occipitoparietal regions.^[20] There are PET studies describing cerebellar vermis hypermetabolism in OMS.^[21]

Choice of imaging for tumor surveillance

Neuroblastoma is usually detected by detailed MRI/CT with particular focus on the paraspinal regions, carotids, mediastinum, adrenals, abdomen, and pelvis. Tests for functional tumors including urinary vanillylmandelic and homovanillic acids and MIBG scan should be performed but may produce a false-negative result as neuroblastomas in OMS are usually low grade and therefore not metabolically active. CT/MRI has the highest sensitivity for detecting neuroblastoma in children presenting with OMS, and this should be reflected

Box 1: Diagnostic criteria of opsoclonus-myoclonus ataxia syndrome

3 out of 4 features must be present for a diagnosis of OMS

- Opsoclonus
- Ataxia and/or myoclonus
- Behavioral changes or sleep disturbances
- Neuroblastoma

OMS=Opsoclonus myoclonus syndrome

in investigation protocols for initial diagnosis and also for periodic rescreening.^[22]

Cerebrospinal fluid biomarkers

CSF analysis with cells, protein, and sugars was normal in our series, and oligoclonal bands (OCBs) were not done in our cases. In several studies, CSF can reveal minimal CSF pleocytosis of around 4–11 cells/mm³, which was found predominantly in untreated patients. Immunophenotyping of CSF cells has been found to be of benefit in several studies by Pranzatelli.^[23,24] B-cell frequency was elevated in CSF and not in blood. CSF OCBs in that study revealed positivity in 58% of patients with pathologically increased frequency of CSF B-cells (93% of patients), while with treatment, OCB positivity was only 27%.^[5] There has been a search for disease biomarker to guide therapy. Recent research had shown that the two critical B cell modulating cytokines namely B cell activating factor and proliferation inducing ligand are potential biomarkers for monitoring disease activity.^[25]

Treatment

Tumor removal alone rarely leads to remission of the neurological symptoms. None of the children in our group went into remission with tumor removal alone. This could be attributable to immune reconstitution self-perpetuating in CSF leading to refractory symptoms, in spite of the fact that the initial immunogenicity triggered by the tumor is removed completely. Early and aggressive immunotherapy is the key in reducing morbidity and improving the developmental outcome. ACTH/corticotrophin is the commonly used treatment in our series. Refractory cases were treated with high-dose dexamethasone and rituximab. There has been a clear trend toward early use of multimodal immunotherapy and early use of rituximab. There are several anecdotal reports of utility of cyclophosphamide, mycophenolate, and plasmapheresis in refractory cases.^[26-29] The absence of tumor in initial screening in children with OMS warrants periodic tumor surveillance, especially in cases who remain refractory in spite of optimal treatment.

Comparison of tumor with nontumor group

In our study [Table 2], we found that there was a statistical significance in age at onset of symptoms in tumor versus nontumor group, which was also seen in the largest cohort described by Pranzatelli. Children with tumor tend to present at an earlier age compared to nontumor group (mean age: 15.5 and 26.3 months, respectively). A novel finding seen in our cohort was that there is a significant difference in the time of appearance of opsoclonus from the initial symptom onset and the severity of OMS (Genoa OMS severity scale) between the tumor and the nontumor group. Comprehensive motor scale for OMS was not used in view of retrospective nature of the study.^[5] Children with tumor tend to have early appearance of opsoclonus and higher severity of symptoms during the initial presentation. However, this needs to be further validated in a prospective larger cohort and across different ethnic groups.

Outcomes

There are several Indian studies with variable outcomes in the tumor versus nontumor group.^[30,31] It can be seen in our study that there is a tendency for paraneoplastic OMS for monophasic course after tumor removal though the duration to attain initial remission was longer when compared to the nontumor group. Nontumor group tends to have multiphasic course, usually with relapses precipitated by intercurrent infections and medication tapering. Children with tumors operated more than 6 months after symptoms onset appear to have an increased number of relapses, than those who are operated early, though there was no significant statistical difference. There is no significant difference in the final outcome and it is comparable between both the groups. Children in the final remission had no significant motor deficits though they tend to have attention issues and poor scholastic performance.

There are children in the gray area between those in remission with residual deficits and active disease when only clinical assessments are made for follow-up. Further research on the ideal biomarker for monitoring disease activity would help us in long run for guiding management decisions and in the duration of treatment. National and international collaboration on prospective studies of this neurological rarity is needed for elucidating the pathophysiology and further research for biomarkers and for drug trials. We propose several prospective recommendations which are given below and the need for national guidelines for this potentially treatable disorder.

Prospective recommendations for approach to OMS

- National registry is recommended for this rare disorder and institutional collaboration for randomized controlled studies for various immunomodulatory therapies to arrive at unifying treatment protocols and follow-up as there could be ethnic differences in presentation and treatment response
- Awareness need to be created among general physicians and paediatricians, who are often the first contact in most situations
- There is a felt need for active research into biomarkers for disease activity and treatment response as there is a gray zone where it is clinically difficult to differentiate children in remission with residual sequel and ongoing disease activity
- Periodic tumor surveillance is essential in initial tumor-negative cases who are not attaining remission
- High index of suspicion and application of diagnostic criteria is essential as the diagnosis remains clinical
- MRI/CT thorax and abdomen is the diagnostic modality of choice for tumor screening as the most circumstances; the tumor is well differentiated and inactive
- Early and aggressive combined immunomodulatory therapy is the key in reducing morbidity and improving developmental outcomes.

Limitations

The limitation of the study is that it is a retrospective study and few cases with incomplete documentation had to be

excluded. OMS motor severity scale which is much more objective assessment of clinical severity is not used in view of retrospective nature of the study. The conclusion about differences between the tumor and nontumor group should be interpreted cautiously given the small sample size, and this needs to be validated with prospective multicenter studies due to its low incidence.

CONCLUSION

OMS is a rare yet potentially treatable disorder. Early diagnosis, periodic tumor surveillance, and aggressive combined multimechanistic immunosuppressive therapy are the key modalities in reducing morbidity. A search for biomarkers to assess disease activity and international collaboration on assessing the phenotypic spectrum and management is the current need in optimizing clinical care and improving outcome in children with OMS.

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Conflicts of interest

There are no conflicts of interest.

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