## Title

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## Journal

Pediatric Neurology, 154

## ISSN

0887-8994

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## Publication Date

2024-05-01

## DOI

10.1016/j.pediatrneurol.2023.12.028

Pediatric Neurology 154 (2024) 9–14

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

# Characteristics of Opsoclonus-Myoclonus Syndrome in Patients of the Largest Pediatric Hospital in Latin America

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ARTICLE INFO

*Article history:*
Received 29 November 2022
Accepted 30 December 2023
Available online 5 January 2024

*Keywords:*
Brazil
Children
Kinsbourne syndrome
Latin America
Opsoclonus-myoclonus syndrome
Paraneoplastic

ABSTRACT

*Background:* Opsoclonus-myoclonus syndrome (OMS) is a rare neuroinflammatory disorder characterized by ataxia, opsoclonus, and myoclonus. Clinical diagnosis of OMS has been challenging; therefore, we sought to determine the clinical and treatment profiles of patients with OMS at the largest pediatric hospital in Latin America.

*Methods:* We analyzed the data of patients diagnosed with OMS between 2010 and 2020 at Pequeno Principe Hospital (Brazil) to determine the corresponding clinical profile more accurately.

*Results:* Of the approximately 50,000 visitors to our pediatric neurology department from 2010 to 2020, 10 patients with OMS were observed. Five nontumor cases included three parainfectious and two idiopathic cases. The median time from symptom onset to diagnosis was 34 days. All patients with diagnostic OMS criteria in the idiopathic, nontumor group underwent whole-exome sequencing, with potentially pathogenic mutations identified in two cases. Nine patients were treated with methylprednisolone pulse, followed by oral steroids; eight received one or more intravenous immunoglobulin treatments; and six received azathioprine and cyclophosphamide. Complete symptomatic recovery was observed in only one patient.

*Conclusions:* OMS diagnosis remains challenging. Diagnostic suspicion is necessary to improve the management of these patients and allow early immunosuppressive treatment. Paraneoplastic etiology is the most prevalent. In idiopathic patients who do not respond to immunosuppressive treatment, tests, such as whole-exome sequencing, may reveal a differential diagnosis. Genetic alterations that increase the risk of tumors may be an important clue to the pathophysiology of OMS.



Ethics statement: This work was approved by the research ethics committee of the Pequeno Príncipe Hospital, registered under protocol number CAAE: 23549619.5.0000.0097.

Author contributions: M.S.Z., a physician neuropediatrician, participated in clinical management, conceptualized the study, drafted the initial manuscript, and reviewed and revised the manuscript. This report is, in part, her dissertation. D.A.d.V. and M.L.S.F.S are also attending physicians for the families of the participants and participated in the conceptualization of the study. T.S.B. helped with the neuropsychologic data gathering and did all the statistical analysis. M.L.C., the principal investigator, coordinated the study, helped conceptualize the study, revised the manuscript, and conducted critical reviews of the manuscript for key intellectual content. All authors contributed to the drafting of the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Funding: This work was supported in part by *Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior* (CAPES, grant #001 to M.S.Z., D.A.d.V., and T.S.B.).

Data statement: The data supporting this study's findings can be requested from the corresponding author, Dr. Cordeiro, upon reasonable request based on Data Transfer Agreement.

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https://doi.org/10.1016/j.pediatrneurol.2023.12.028

## Introduction

Opsoclonus-myoclonus syndrome (OMS) is a rare neuroinflammatory disorder, with an estimated incidence of 0.18 cases per 1 million inhabitants. OMS was first described in six children by Marcel Kinsbourne in 1962 as a myoclonic encephalopathy and long retained the eponym "Kinsbourne syndrome."[1,2]

OMS is characterized by the triad of ataxia, opsoclonus, and myoclonus. Symptoms of irritability, exaggerated response to stimuli, altered speech and sleep, behavioral changes, and cognitive impairment are common. This devastating disease has neurological and neuropsychiatric sequelae, such as speech alteration, neurobehavioral disorder, sleep disturbance, and intellectual disability.[3]

In approximately 50% of OMS cases, the etiology is identifiable and is associated with infection or neoplasia. Neuroblastoma is the main associated tumor.[4] Autoantibodies against various neuronal surface antigens, such as δ2 glutamate receptor, *N*-methyl-d-aspartate, nuclear antineuronal, and natural human killer 1,[5-8] have been described in OMS, but there is no single specific diagnostic autoantibody.[9]

Currently, there is no consensus regarding OMS diagnosis or any specific treatment protocol. However, existing publications indicate that multimodal immunosuppressive therapies hold promise.[10-12]

In this study, we aimed to evaluate the development and clinical course of the disease as well as the therapeutic response and clinical profiles in patients with OMS at the largest pediatric hospital in Latin America, located in Brazil, with the aim of correlating the etiologic causes and contributing to the scarce literature on OMS.

## Materials and Methods

### *Collection of clinical data*

This retrospective analytical study investigated a series of patients diagnosed with OMS, attending the Children's Neurology Outpatient Clinic of the Pequeno Principe Hospital (Curitiba, Brazil) from 2010 to 2020. The Pequeno Principe Hospital, a centenary philanthropic center, is the largest pediatric hospital in Latin America (361 beds) and was recently ranked by Newsweek as one of the top 150 pediatric hospitals worldwide.

We selected patients in our research database who were diagnosed with OMS according to the clinical criteria defined at the Genoa meeting in 2004[13] and who met three of the following criteria: (1) opsoclonus, (2) ataxia and/or myoclonus, (3) behavioral alteration or sleep disorder, and (4) neuroblastoma.[14] Patients with incomplete medical records were excluded.

Participants were further divided into two groups: tumor (with any neoplasm associated with OMS) and nontumor (with no neoplasm identifiable). The nontumor group was subdivided into the parainfectious and idiopathic groups. This division was chosen according to the largest OMS cohorts to assess differences in relation to the severity score and neurological outcome, which is worse in patients with tumor-associated OMS,[15-17] and to search for possible genetic variants associated with immunologic alterations in the idiopathic group.

The medical records of patients were reviewed, and the following variables recorded: sex, age, city of origin, time of symptom onset, date of hospitalization in the referring hospital, date of diagnosis, association with neoplasia, initiation of treatment with immunosuppressants, disability, and therapeutic response based on the Mitchell-Pike OMS severity scale.[2,13] The tests requested and the disease course postdischarge were also evaluated.

The OMS severity score for each symptom was assessed individually in all patients at symptom onset and post-treatment. This scale evaluates the following symptoms: stance, gait, opsoclonus; arm and hand movement, sleep and mood disorders, and speech. Each symptom is scored on a scale ranging from 0 (normal) to 3 (severe) points, with a maximum score of 18 points (Supplementary Material).

Cerebrospinal fluid (CSF) examination, including cell count, lymphocyte percentage, protein, glucose, and lactate; brain magnetic resonance imaging (MRI); tumor screening, composed of chest, abdominal, and pelvic computed tomography (CT); and whole-exome sequencing (WES) were included in the review.

### *Statistical analysis*

Data were submitted to descriptive statistical analysis using SPSS for Windows version 23.0 (IBM Corp., Armonk, NY, USA). Next, the median age, severity scores, and intervals from the first symptoms to diagnosis and to treatment were compared between the two groups using the parametric *t* test. The significance level was established at $P < 0.05$.

## Results

### *Clinical characteristics*

From the approximately 50,000 visits to our department from 2010 to 2020, 14 patients were identified, 11 of whom had a clinical diagnosis of OMS (Fig). Three participants were excluded because they presented with isolated opsoclonus. OMS was associated with tumor in five cases, mostly neuroblastoma. The nontumor group consisted of five cases, three of which were parainfectious cases (cytomegalovirus, otomastoiditis, and acute diarrheal disease) and two of which were idiopathic cases. One case, despite meeting the clinical criteria for OMS, had some atypical characteristics and, therefore, was discussed separately.

Tables 1 and 2 summarize the main characteristics of the study participants. We also divided the patients into a tumor group (n = 5) and a nontumor group (n = 5). Of these 10 patients, five were girls (50%) with a median age at symptom onset of 4.5 (interquartile range [IQR]: 1.9 to 5.8) years. Ataxia was the most common initial symptom and was present in all patients. Irritability was described in four patients, of whom three were in the nontumor group.

The median time between symptom onset and diagnosis, as well as the start of immunosuppressive treatment, is described in Table 2. Patients with a longer interval between symptom onset and diagnosis were justified by the fact that the diagnosis of OMS was made only after hospitalization. The same principle was applied to the treatment before diagnosis, with the use of any immunosuppressant considered as treatment. Furthermore, in some cases, the diagnosis of OMS was made in the course of the disease. Some patients had to wait for a long time to be admitted after diagnosis owing to difficulties in accessing reference hospitals. Patient 4 (P4) had the longest time between the onset of symptoms and the start of immunosuppressive therapy. This patient required more lines of immunomodulatory treatment and had the highest score on the OMS severity scale at the end of the study (7 of 15 points).

### *Radiological and neurophysiological examinations*

All patients underwent brain MRI. Changes were noted in two patients, one with cerebellar atrophy (P4) and another one with periventricular leukomalacia (P5).

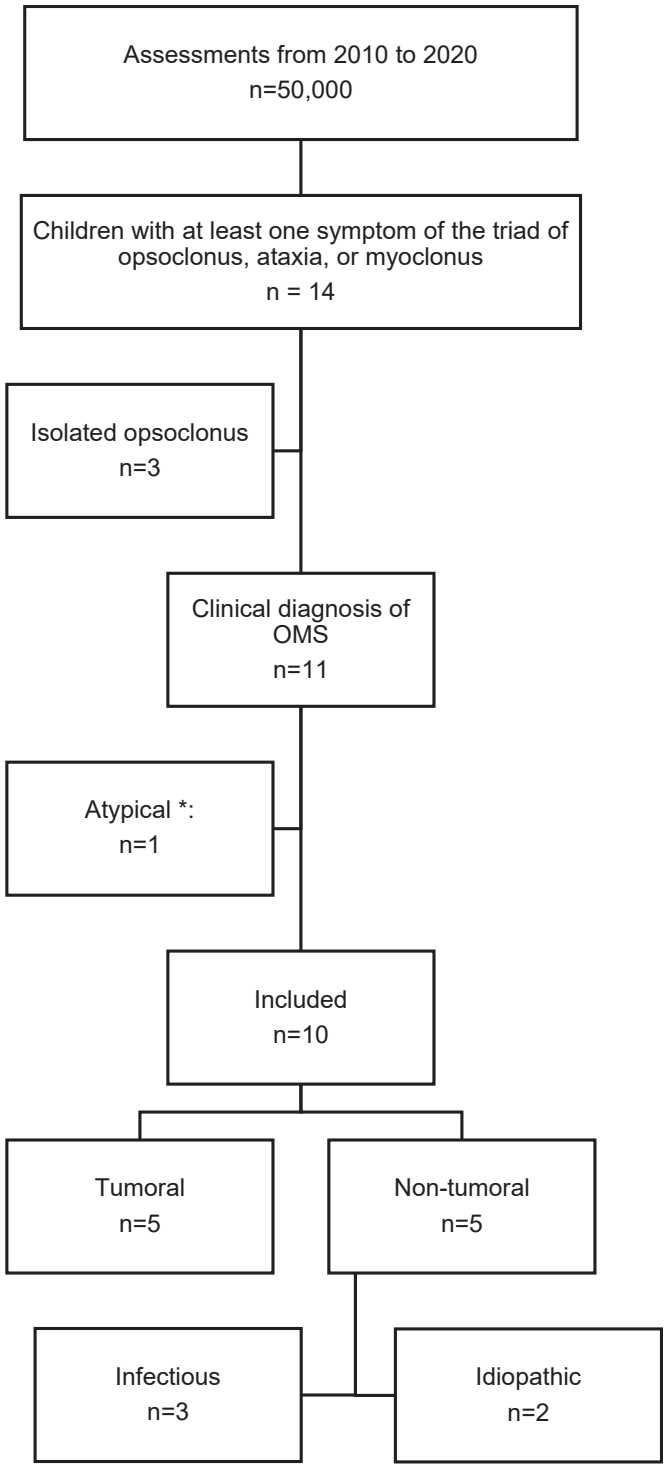


**FIGURE.** Study design. *One patient, despite meeting the clinical criteria for OMS, had some atypical characteristics and is therefore discussed separately. OMS, opsoclonus-myoclonus syndrome.

Chest, abdominal, and pelvic CT demonstrated extensive lesions in three patients having a right paravertebral expansive lesion (P1), an expansive nodular lesion in the right adrenal (P2), and a suggestive neuroblastoma mass located in the right adrenal gland (P5), respectively.

Of the nine patients who underwent CSF examination, one had cytomegalovirus encephalitis (P8) and one had significant pleocytosis and high protein levels (P5).

All analyzed patients had normal electroencephalograms and normal 24-hour vanillylmandelic acid levels. Two patients underwent a neuronal surface autoantibody panel test, which proved normal.

*Genetic evaluation*

All patients with idiopathic OMS in the nontumor group underwent WES. Pathogenic and potentially pathogenic mutations were identified in three patients (Table 3).

P4, although classified in the tumor group, also underwent WES. At study inception, no tumor was identified in this patient, but Burkitt lymphoma was subsequently diagnosed. The genetic test result showed a pathogenic mutation in *BRCA1*, a genetic variant related to an increased risk of developing certain types of cancer.

*Treatments*

Only one patient did not receive immunosuppressive treatment. The other nine patients received methylprednisolone pulse 30 mg/kg/day followed by oral steroids (prednisolone 1 mg/kg/day and/or dexamethasone 0.1 to 0.4 mg/kg/day), eight received intravenous immunoglobulin (IVIG) (2 g/kg, divided as 400 mg/kg daily for five days), and six received azathioprine 2 to 5 mg/kg/day. Cyclophosphamide (750 mg/m$^2$, four cycles) was administered in two patients and cyclosporine in one patient. No patient underwent plasmapheresis.

*Severity assessment*

The median OMS severity scale score was 11 (IQR: 9 to 11) points in the tumor group and 10 (IQR: 9 to 10) points in the nontumor group. After the first line of treatment, the median score was 3 (IQR: 2 to 4) points in the tumor group and 2 (IQR: 0 to 2) points in the nontumor group.

*Follow-up*

The median follow-up period was 5.5 (IQR: 3.4 to 6.7) years. Only one patient showed complete symptom recovery. The main changes observed at the end of the study were in behavior and sleep disorders (eight of 10 patients). Two patients had intellectual deficiencies documented based on the Wechsler Intelligence Scale for Children (fourth edition).

*Atypical case (P11)*

One patient (P11) exhibited an atypical clinical course. Initial symptoms manifested at age 4.5 years, and the time span between symptom onset and diagnosis spanned 253 days. The patient's initial OMS severity score was 9 points, which eventually improved to 6 points. Initially, the patient presented with ataxia, myoclonus, and distinctive abnormal eye movements, specifically opsoclonus. Consequently, a clinical diagnosis of OMS was established. Subsequently, the child's condition progressed, leading to changes in behavior, psychomotor agitation, and developmental delay. Noteworthy symptoms also included irritability, vomiting, third cranial nerve palsy, and myasthenic syndrome. Initial cranial MRI results appeared normal during hospitalization, but signs of intracranial hypertension surfaced, accompanied by intraocular insinuation of the optic papillae and posterior eyeball wall distortion. Despite exhibiting a phenotype resembling OMS, genetic testing revealed an interstitial duplication spanning 219 kb at chr15q11.2 (chr15:22,820,239-23,039,543). This duplication encompassed the genes *TUBGCP5*, *NIPA1*, *NIPA2*, and *CYFIP1*.

**TABLE 1.**
Characteristics of the Study Participants

| Patients (P) | Group | Sex | Age at OMS Onset (years) | OMS Etiology | Interval Between OMS Onset and Diagnosis (Days) | Initial OMS Severity Score | Final OMS Severity Score |
|---|---|---|---|---|---|---|---|
| 1 | *1* | F | 1.4 | Infiltrative tumor* | 8 | 13/15 | 3/15 |
| 2 | *1* | F | 4 | Neuroblastoma | 37 | 11/15 | 2/15 |
| 3 | *1* | M | 6 | ALL | 42 | 11/15 | 4/15 |
| 4 | *1* | M | 13 | Burkitt lymphoma | 331 | 9/15 | 7/15 |
| 5 | *1* | F | 1.1 | Neuroblastoma | 5 | 9/15 | 2/15 |
| 6 | *2* | M | 1.7 | Probable postinfectious etiology (AOM) | 31 | 10/15 | 2/15 |
| 7 | ***2*** | M | 4.9 | Idiopathic | 206 | - | - |
| 8 | *2* | M | 2.3 | Probable postinfectious etiology (CMV) | 19 | 11/15 | 1/15 |
| 9 | *2* | F | 10 | Probable postinfectious etiology (enterovirus) | 31 | 6/15 | 0/15 |
| 10 | ***2*** | F | 5 | Idiopathic | 396 | 10/15 | 2/15 |

Abbreviations:
ALL = Acute lymphocytic leukemia
AOM = Acute otitis media
CMV = Cytomegalovirus
F = Female
M = Male
OMS = Opsoclonus-myoclonus syndrome
* Infiltrative tumor: tumor with paravertebral malignant characteristics without possibility of biopsy.

## Discussion

In this study, we present the clinical and treatment profiles of patients with OMS from the largest pediatric hospital in Brazil. This is the most comprehensive study on OMS in Latin America to date.

OMS is a rare and poorly understood condition, with an estimated incidence of 0.03 to 0.18 per million in the total population.[18-21] Our study identified a similar incidence in terms of sex, with a slight predominance of females.[18-20,22] The median age at diagnosis was slightly above the range reported in the literature, which spans from birth to 3 years.[18,21] Additionally, our findings revealed a correlation between the age at symptom onset and prognosis. Opsoclonus was observed more frequently in younger children,[4] whereas cognitive deficits and speech delays were more prevalent in patients with an earlier onset of symptoms.[11,21]

OMS diagnosis often faces significant delays, with a mean time to a conclusive diagnosis of 3 months in Japan, 4.2 months in Tunisia, and 8.4 months in India.[18,21,23] These delays are typically attributed to erroneous initial diagnoses, with cerebellitis or acute ataxia being more commonly considered, or the presence of atypical symptoms in up to 20% of cases.[18,19,21,23] Therefore, OMS diagnosis can be particularly challenging, especially when the classic triad of symptoms is not fully present.[21] Our study observed that delayed diagnosis, exemplified by case P4, can also lead to delayed treatment, which may contribute to a less favorable prognosis.[11,18,19,21]

Opsoclonus manifested later in the course of the disease, in agreement with previous findings, where it can emerge up to 18 months after the initial onset of symptoms.[18,20,21,24] This underscores the importance of considering this condition in patients presenting with ataxia and the need for continued monitoring.

A paraneoplastic origin was confirmed as the primary cause of OMS, in line with the existing literature. The literature indicates tumor-related causes in approximately 50% of cases and infectious origins in 30%.[3,21,22,25,26] Despite exhaustive investigations, the etiology remains elusive in some cases.[21] Idiopathic forms of OMS typically present with a mild, self-limited, and single-phase clinical course. Patients often exhibit a positive response to immunotherapy, resulting in complete recovery,[21] as observed in P7, who underwent a single-phase treatment without the need for immunosuppression and fully recovered.

The finding of a variant in *SDHA* in P10, which causes a predisposition to neoplasms, reinforced the importance of investigating tumor. In their experience with 30 patients, Mitchell et al. reported that >80% of children with OMS who underwent extensive evaluation, including thin-slice CT, had neuroblastoma that escaped detection with the common diagnostic methods.[14] Therefore, it seems possible that OMS symptoms can occur even with very small

**TABLE 2.**
Characteristics of the Participants in the Tumor and Nontumor Groups

| Parameters | Tumor Group (n = 5) | Nontumor Group (n = 5) | *P* |
|---|---|---|---|
| Median age (years) | 4 (first quartile 1.40) | 4.7 (first quartile 2.85) | **0.702** |
| Sex (male: female) | 2:3 | 3:3 | – |
| Main inaugural symptoms | | | |
| Ataxia | 4 | 6 | |
| Myoclonus | 1 | 4 | |
| Opsoclonus | 0 | 1 | |
| Interval from initial symptoms to diagnosis | 37 days (IQR: 6-37) | 31 days (IQR: 25-31) | **0.852** |
| Interval from diagnosis to hospitalization | 90 days (IQR:12-40) | 82 days (IQR: 20-90) | **0.770** |
| Interval from diagnosis to treatment | 65 days (IQR: 20-26) | 25 days (IQR: 14-25) | **0.250** |
| Comparison of initial OMS severity score | 11 (IQR: 9-11) | 10 (IQR: 9-10) | **0.903** |
| Comparison of final OMS severity score | 3 (IQR: 2-4) | 2 (IQR: 0-2) | **0.351** |

Abbreviations:
IQR = Interquartile range
OMS = Opsoclonus-myoclonus syndrome.
Values in parentheses indicate S.D. unless otherwise noted.

**TABLE 3.**
Genetic Data of Patients

| Group | Patient | Sex | Age (years) | Gene(s) | Location | Variation | Consequence | Copies | ACMG |
|---|---|---|---|---|---|---|---|---|---|
| Nontumor idiopathic | ***P7*** | M | 4.9 | *F8* | chrX:154.929.411 | delA | p.Asn1460fs | Hemizygote | Pathogenic |
| | | | | *SCNN1B* | chr16:23.380.568 | C>T | p.Gln564* | Heterozygote | Probably pathogenic |
| | ***P10*** | F | 5 | *SDHA* | chr5:240.459 | C>T | p.Arg512* | Heterozygote | Pathogenic |
| Tumor | ***P4*** | M | 13 | *BRCA1* | chr17:43.092.646 | T>C | p.Glu962Gly | Heterozygote | VUS |

Abbreviations:
ACMG = American College of Medical Genetics and Genomics
delA = Deletion
F = Female
M = Male
VUS = Variant of unknown significance

neuroblastic tumors, undetectable using standard investigation methods, or in cases where tumors have already regressed completely.[14]

An interstitial 219-kb duplication on chr15q11.2 in a patient initially diagnosed with OMS suggests that certain genetic conditions can mimic OMS. This genetic variation is linked not only to susceptibility to neurodevelopmental disorders (e.g., developmental delay, intellectual disability, epilepsy, and autism spectrum disorder) but also to ataxia, gait issues, balance problems, and dyspraxia.[24] This fact underscores the need to consider these genetic factors as potential differential diagnoses for OMS,[26] especially when there is an inadequate response to immunotherapy.

In most studies, including this study, brain MRI and CSF analysis were normal in most patients. Neuroimaging abnormalities identified in P8 may be better explained by prematurity. In P11, the signs of intracranial hypertension were likely attributed to the underlying disease and may have been caused by the use of methylprednisolone as the first line of treatment, as the patient had a normal brain MRI.[2,4]

Clinical management of OMS is varied, with corticosteroids and immunoglobulin being common first-line treatments.[11,18-21] However, there is no definitive evidence favoring one treatment over another, because of inconsistencies in standardization across studies. Multimodal approaches, combining corticosteroids, IVIG, and additional agents such as azathioprine, rituximab, and cyclophosphamide, have shown better responses.[12,15,25,27,28] Enhanced immunosuppression is associated with improved neurodevelopment.[8,9,19,29,30,31] Notably, over 50% of patients treated with steroids or IVIG alone experience OMS recurrence, emphasizing the need for aggressive initial therapy to improve prognosis and reduce relapse rates.[10,11,25,29,30] In tumor-associated cases, timely surgical intervention and concurrent immunosuppression are crucial, with tumor resection advised within six months of OMS onset for a better prognosis.[23]

Complete remission was rare, and the highest scores of the OMS severity scale scores were mainly observed in patients with a parainfectious cause, consistent with prior findings.[23] Behavioral and sleep disturbances persisted during the evaluation period, with neurodevelopmental issues observed in up to 70% of cases, irrespective of other factors.[24,31,32] One patient exhibited cerebellar atrophy during follow-up, a phenomenon previously reported in some OMS cases.[22] Evidence suggests that OMS, whether tumor-associated or not, shares an immune-mediated etiology,[4,19,22] and delayed diagnosis and treatment are linked to poor cognitive and behavioral outcomes.[2,18-21,25] Recent studies have indicated a progressive encephalopathy aspect of OMS, with significant long-term cognitive deficits.[33,34]

An important finding of this research was the genetic evaluation of patients with no defined etiology (idiopathic) for OMS. Pathogenic variants in *BRACA1*, *SDHA*, and *SCNN1B* were observed. The finding of genes causing a predisposition to neoplasms reinforces the importance of tumor investigation because OMS symptoms may arise with very small neuroblastic tumors, undetectable by the usual methods of investigation or that have already completely regressed in the presence of the disease. This finding allowed for a differential diagnosis in one patient.

Our study has some limitations, including the lack of standardized screening and the difficulty of performing neuronal surface autoantibody panels and WES throughout the sample.

## Conclusion

OMS diagnosis remains challenging, particularly in the presence of atypical or incomplete symptoms in the early stages. Diagnostic suspicion is necessary to improve patient management and allow early immunosuppressive treatment. Delayed diagnosis and treatment can result in a worse prognosis. Paraneoplastic etiology is the most prevalent; therefore, when symptoms are present, careful tumor screening is mandatory, with thin-section examinations, regular follow-up of these patients, and reinforcing that some tumors can spontaneously regress. In idiopathic patients unresponsive to immunosuppressive treatment, tests such as WES may reveal a differential diagnosis. Genetic alterations that cause a greater tumor predisposition may be an important clue to the pathophysiology of OMS, requiring further studies.

## CRediT authorship contribution statement

**Michelle Silva Zeny:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Daniel Almeida do Valle:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Mara Lúcia Schmitz Ferreira Santos:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Tiago S. Bara:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Mara L. Cordeiro:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

None.

## Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2023.12.028.

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