Pediatric Neurology 158 (2024) 128–134

Contents lists available at ScienceDirect

Pediatric Neurology

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

Research Paper

Inaugural Patient-Reported Registry of Pediatric Opsoclonus-Myoclonus-Ataxia Syndrome: Presentation, Diagnosis, and Treatment of 194 Patients

Sandra Jimenez Giraldo, MD [a, 1], Michael Michaelis, BS [b, 1], Lauren Kerr, BA [c], Christopher Cortina, MS [d], Bo Zhang, PhD [c, d, *], Mark P. Gorman, MD [c, *]

[a] Division of Child Neurology, Department of Pediatrics, Hasbro Children's Hospital, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island
[b] The OMSLife Foundation, Cypress, Texas
[c] Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts
[d] Biostatistics and Research Design Center, Institutional Centers for Clinical and Translational Research, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

ARTICLE INFO

Article history:
Received 16 February 2024
Accepted 16 June 2024
Available online 25 June 2024

Keywords:
Opsoclonus-myoclonus syndrome
Neuroblastoma
Rare diseases
Paraneoplastic neurological syndromes

ABSTRACT

Background: Opsoclonus-myoclonus-ataxia syndrome (OMAS) is a rare neuroimmune disease with peak onset at 18 months, associated with neural crest tumors in 50% of patients. In part due to its rarity, misdiagnosis at onset is common, can delay treatment, and may contribute to adverse outcomes. Patient-reported registries may overcome some of these challenges in rare disease research. In this context, the OMSLife Foundation collaborated with the National Organization of Rare Diseases to create a patient-reported registry in OMAS.
Methods: Retrospective analysis was performed of data entered by parents of patients with OMAS into nine online surveys assessing demographics, symptoms at onset, triggers, time of diagnosis, treatment, and additional therapies.
Results: A total of 194 patients were enrolled. There was a female predominance (54%) and high rate of parental autoimmunity (31%). Age at onset peaked between 12 and 18 months overall. The age of onset was older in female patients (median [interquartile range]: females 22 [15 to 31] vs males 18 [14 to 23], $P = 0.0223$, $P = 0.0223$). Symptoms at onset most commonly included ataxia (84%) and were typically severe. Initial misdiagnosis occurred in nearly 50% and tumor discovery was delayed in 18 patients, but overall median time to correct diagnosis was 25 days. Most patients (56%) received combination immunomodulatory therapies, and nearly all underwent supportive therapies.
Conclusions: Patient- and parent-powered research is feasible in OMAS and created the second largest published cohort of pediatric patients with OMAS. Results were similar to other large cohorts and also validated findings from prior case reports and smaller case series.

Introduction

Opsoclonus-myoclonus-ataxia syndrome (OMAS) is a chronic, typically relapsing, autoimmune central nervous system disorder with an incidence of 0.18 cases per million.[1] Disease onset peaks at age 18 months.[2] In addition to the hallmark symptoms, sleep disturbances and behavioral dysregulation are common at onset. Diagnosis is based on the presence of three of the following four features: opsoclonus, myoclonus or ataxia, behavioral change or sleep disturbances, and neuroblastoma.[3] The last of these is present in approximately 50% of pediatric patients with OMAS as a paraneoplastic disorder. The remaining 50% may be secondary to a regressed tumor, postinfectious causes, or idiopathic. Treatment includes tumor resection, immunotherapy, and supportive treatments. Despite advances in the field, many patients have residual lifelong neurological sequelae, often in cognitive and behavioral domains.[4]

* Communications should be addressed to: Dr. Gorman, or Dr. Zhang; Department of Neurology; Boston Children's Hospital; 300 Longwood Ave; Boston, MA 02115.
E-mail addresses: Bo.Zhang@childrens.harvard.edu (B. Zhang), Mark.Gorman@childrens.harvard.edu (M.P. Gorman).
[1] These authors contributed equally to this research article.

https://doi.org/10.1016/j.pediatrneurol.2024.06.007
0887-8994/

TABLE 1.
Name, Source, Description, and Completion Rates of Surveys

Survey Name	Author	Description	Completed N (%)
Participant profile	NORD	Basic demographic information including sex, race, ethnicity, etc.	194 (100%)
OMS onset	OMSLife	Symptoms at onset, time to diagnosis, type of doctor diagnosing OMAS, etc.	166 (85.6%)
Treatment of OMS	OMSLife	Medications (routes, frequency, duration, side effects, etc.)	148 (76.3%)
Neuroblastoma	OMSLife	Timing of tumor detection and tumor type	133 (68.6%)
Other therapies	OMSLife	Participation in and results of speech, physical, behavioral, and occupational therapies	136 (70.1%)
Triggers	OMSLife	Tumors and their diagnostic evaluation, environmental triggers, etc.	128 (66.0%)
Medical and diagnostic data	NORD	Height, weight, tobacco, and alcohol consumption, etc.	129 (66.5%)
Treatment and return of symptoms	NORD	Medications, dietary issues, current status of patient, etc.	125 (64.4%)
Family medical history	OMSLife	Family history of autoimmune diseases	94 (48.5%)

Abbreviations:
NORD = *National Organization of Rare Disorders*
OMAS = Opsoclonus-myoclonus-ataxia syndrome

Owing to its rarity, overlap with acute cerebellar ataxia, and lack of a definitive biomarker, OMAS diagnosis can be delayed. Improving recognition of OMAS may shorten the time to diagnosis and treatment with the potential to improve outcomes. However, awareness of rare diseases and related funding and research may be limited. Single-site studies often have small sample sizes, limiting their scope and generalizability. In this context, the support organization *OMSLife Foundation* (https://omslifefoundation.org) collaborated with the *National Organization of Rare Disorders* (NORD; https://www.nidcd.nih.gov/directory/national-organization-rare-disorders-nord) to create a patient registry on the NORD IAMRARE Registry platform. Through an online platform, patients or their legally authorized representatives can directly enter data, which researchers can analyze to examine the natural history, treatment, and outcomes of OMAS.

In this study, we characterized the demographic findings, clinical features, etiology, and treatment of 194 patients with pediatric OMAS enrolled in the OMSLife Foundation registry, the second largest cohort published to date. We also compared our findings with previous publications to determine if patient- and family-reported data generate similar findings to studies utilizing clinic and hospital data.

Methods

Study design

Retrospective data were obtained on patients with OMAS onset at age less than 18 years occurring between 1990 and 2020 using three NORD-developed standardized templates (Participant Profile, Medical and Diagnostic Data, Treatment and Return of Symptoms) and six OMAS-specific surveys (Onset of OMAS, Treatment of OMAS, Neuroblastoma, Other Therapies, OMAS Triggers, Family Medical History). Surveys were completed from May 2017 to November 2020 by parents or the patient's legally authorized representative who consented to the study and possibility of sharing deidentified data. A total of 194 subjects completed the Patient Participant Profile survey. Partially overlapping subsets of the total cohort completed the additional eight surveys (Table 1). Respondents were not required to answer all questions in a given survey, leading to varying rates of unknown categories. OMAS severity was assessed with the Mitchell and Pike OMAS severity scale, with items (scored 0 to 3) for stance, gait, arm/hand function, opsoclonus, mood/behavioral changes, and speech changes with higher scores indicating more severe symptoms. The study was approved by the independent central Hummingbird Institutional Review Board (IRB). Deidentified data were transferred from the OMSLife Foundation to study authors at Boston Children's Hospital for analysis (IRB exempt, BCH IRB-P00031016).

Statistical analysis

Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary NC, USA). Patient demographic features and clinical characteristics were reported using mean with S.D., median with range and interquartile range, and count number with frequency. We evaluated associations between clinical variables with a focus on biological sex and presence or absence of tumors. Differences of continuous variables between these groups were evaluated using Welch-Satterthwaite t test or its nonparametric alternative Wilcoxon rank-sum test. Association of categorical variables was evaluated using chi-square test or Fisher exact test. A P value less than 0.05 was considered statistically significant. Frequencies were demonstrated by bar plots for graphical visualization.

Results

Demographic and socioeconomic characteristics (N = 194)

The majority of patients were female (54.1%), white (87.3%), non-Hispanic (78.1%), had a tumor present (55.4%), and had health insurance (96.3%) (Table 2). There were 29 (14.9%) international patients included in the study.

TABLE 2.
Demographic Features of Survey Respondents

Parameter (Number of Respondents)	N (%)
Biological sex (n = 194)	
Male	89 (45.9)
Female	105 (54.1)
Tumor presence (n = 175)	
Yes	97 (55.4)
No	78 (44.6)
Race (n = 189)	
White	165 (87.3)
Black or African American	3 (1.6)
Asian	4 (2.1)
American Indian/Alaskan Native	1 (0.5)
Other	16 (8.5)
Ethnicity (n = 155)	
Hispanic or Latino	23 (14.8)
Not Hispanic or Latino	121 (78.1)
Unknown	11 (7.1)
Health insurance status (n = 188)	
Insured	181 (96.3)
Not insured	6 (3.2)
Unknown	1 (0.5)
Region (n = 194)	
United States	165 (85.1)
International (non-US)	29 (14.9)

TABLE 3.
History of Autoimmune Disorders in First-Degree Relatives of 94 Patients With OMAS

Autoimmune Disease	N (%)
Autoimmune thyroid disease (Hashimoto thyroiditis, Graves disease)	17 (18.1)
Rheumatoid arthritis	4 (4.3)
Systemic lupus erythematosus	0
Insulin-dependent diabetes mellitus (type 1)	2 (2.1)
Inflammatory bowel disease	2 (2.1)
Psoriasis	7 (7.5)
Other	10 (10.8)
Addison disease	0
Celiac disease	1 (1)
Multiple sclerosis	1 (1)
Pernicious anemia	1 (1)
Vitiligo	2 (2.1)
Other (lichen planus, ulcerative colitis, autoimmune hepatitis, inflammatory polyarthritis, ankylosing spondylitis)	7 (7.6)
Any autoimmune disease	29 (30.9)

Abbreviation:
OMAS = Opsoclonus-myoclonus-ataxia syndrome
Some first-degree relatives reported more than one autoimmune disorder.

Family history of autoimmunity (N = 94)

Rates of specific autoimmune diseases in first-degree relatives are presented in Table 3. Rate of familial autoimmunity did not differ between the tumor (36.1%) and no tumor (30.8%) subgroups ($P = 0.5212$).

OMAS triggers (N = 128)

It was found that 53.5% of patients reported a potential trigger within 30 days of the initial OMAS presentation, including viral illnesses alone (22%), vaccines alone (15.8%), both viral illness and vaccine (11.8%), and accidents and/or emotional stressors (3.9%). No trigger was identified in 46.4%. Nineteen patients with a tumor also reported a trigger (12 viral illness, seven viral illness and vaccine); 44.2% (19 of 79) of patients with viral trigger had a tumor, and 24.1% (19 of 43) of patients with a tumor had a viral trigger.

Age, symptoms, and severity at OMAS onset (N = 166)

OMAS symptom onset (Table 4, Fig) peaked at age 12 to 18 months (27.8%) with an older age in females (22 months [15 to 31] vs 18 [14 to 23], $P = 0.0223$) and no significant differences between the tumor and no tumor subgroups. Ataxia was the most frequent symptom at onset (81.7%), followed by opsoclonus (58.9%), myoclonus (56.6%), sleep disturbances (43.4%), tremors (43.4%), temper tantrums (37.1%), and vomiting (22.3%). Myoclonus was more frequent in the tumor subgroup (65.9% vs 44.9%, $P = 0.0059$) (Supplemental Table 1). Nearly 40% of patients with OMAS did not have opsoclonus or myoclonus as one of the initial presenting symptoms. OMAS severity scale score was ≥15 in 41.8%, 10 to 14 in 28.9%, 5 to 9 in 13.9%, and 0 to 6 in 1.0% of patients. Severity of individual signs and symptoms did not differ between the tumor and no tumor subgroups (Supplemental Table 2).

TABLE 4.
Age of OMAS Onset as a Function of Biological Sex and Tumor Status

Age Category at OMAS Onset				
Entire Cohort	Overall (n = 194)	Male (n = 89)	Female (n = 105)	*P* value (Wilcoxon rank-sum test)
Median (IQR)	18 (14-29)	18 (14-23)	22 (15-31)	0.0223
<12 months	23 (14.6)	10 (14.1)	13 (14.9)	
12-18 months	44 (27.8)	25 (35.2)	19 (21.8)	
18-24 months	40 (25.3)	20 (28.2)	20 (23.0)	
24-30 months	12 (7.6)	5 (7.0)	7 (8.1)	
30-36 months	21 (13.3)	5 (7.0)	16 (18.4)	
36 months-18 years	18 (11.4)	6 (8.5)	12 (13.8)	
Missing in age	36	18	18	
Tumor status reported	Overall (n = 175)	Male (n = 79)	Female (n = 96)	
Tumor status unknown	Overall (n = 19)	Male (n = 10)	Female (n = 9)	
Tumor	Overall (n = 97)	Male (n = 43)	Female (n = 54)	*P* value (Wilcoxon rank-sum test)
Median (IQR)	18 (14-23)	16 (14-18)	19 (14-25)	0.0804
<12 months	15 (16.9)	5 (12.8)	10 (20.0)	
12-18 months	29 (32.6)	18 (46.2)	11 (22.0)	
18-24 months	25 (28.1)	11 (28.2)	14 (28.0)	
24-30 months	6 (6.7)	1 (2.6)	5 (10.0)	
30-36 months	9 (10.1)	2 (5.1)	7 (14.0)	
36 months-18 years	5 (5.6)	2 (5.1)	3 (6.0)	
Missing in age	8	4	4	
No Tumor	Overall (n = 78)	Male (n = 37)	Female (n = 42)	*P* value (Wilcoxon rank-sum test)
Median (IQR)	22 (16-32)	20 (14.5-28)	29 (17-35)	0.0872
<12 months	8 (11.6)	5 (15.6)	3 (8.6)	
12-18 months	15 (21.7)	7 (21.9)	8 (21.6)	
18-24 months	15 (21.7)	9 (28.1)	6 (16.2)	
24-30 months	6 (8.7)	4 (12.5)	2 (5.4)	
30-36 months	12 (17.4)	3 (9.4)	9 (24.3)	
36 months-18 years	13 (18.8)	4 (12.5)	9 (24.3)	
Missing in age	9	4	5	

Abbreviations:
IQR = Interquartile range
OMAS = Opsoclonus-myoclonus-ataxia syndrome

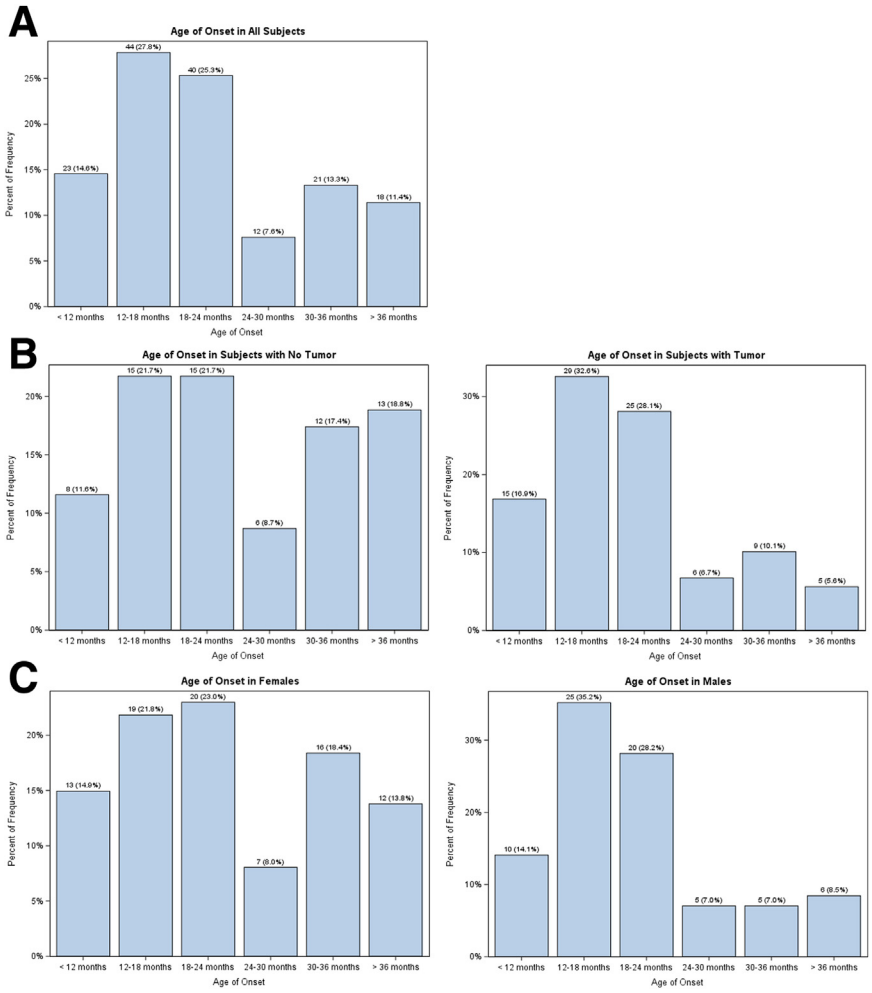

FIGURE. (A) Age of OMAS onset, (B) age of onset by tumor status, and (C) age of onset by gender. The color version of this figure is available in the online edition.

OMAS diagnosis (N = 166)

In this cohort, 32.1% of patients were diagnosed based solely on symptoms; 32.1% by the presence of tumor accompanied by typical OMAS symptoms; 26.5% by symptoms and laboratory testing; 8.6% based on symptoms, presence of a tumor, and laboratory testing; and 0.6% by other approaches. OMAS was diagnosed by a neurologist in 82.4%, oncologist in 11.5%, pediatrician or ophthalmologist in 3.6%, and other specialist in 2.4% of cases.

Initial misdiagnosis at the time of OMAS onset occurred in 48.5% of cases. The most common misdiagnosis was acute cerebellar ataxia or postinfectious cerebellitis (71.3%), followed by other causes (8.5%), encephalitis (5.3%), epilepsy (4.3%), abnormal eye movements (4.3%), ear infection (3.2%), and trauma (3.2%).

Etiology of OMAS and tumor detection timing

Of those reporting these data, 97 patients (55.4%) had a tumor detected, the majority of which were neuroblastomas (70.9%) and stage 1 or 2 (64.1%). Tumor was detected at the time of OMAS diagnosis in 76.9% (N = 60) of cases with these data available. The time from OMAS onset to tumor detection ranged from <1 month to >12 months. In 18 patients, a tumor was not detected at OMAS onset, but later in tumor surveillance follow-up scans in eight, by unclear methods in seven, and by second opinion on initial scans in three (Table 5).

Interval from symptom onset to OMAS diagnosis and treatment regimens

The median time from symptom onset to a correct diagnosis was 25 days and from diagnosis to treatment was 7 days, which did not significantly differ between the tumor and no tumor subgroups (Table 6).

Of the 148 patients reporting treatment data, 18.2% received one, 12.2% received two, and 56.1% received three or more agents without significant differences between the tumor and no tumor subgroups. The most common medications received were steroids (79.7%), intravenous immunoglobulin (IVIG) (64.9%), and rituximab (52.7%) (Table 7). There were no significant differences in the number or type of treatment in patients diagnosed before and after 2013 (median calendar year of diagnosis).

Other Therapies (N = 136)

Physical, occupational, and speech and language therapies were utilized by the majority of patients for more than one year, with >95% of respondents finding them beneficial. Nearly 51% of patients used an assistive device, such as a wheelchair, walker, or brace, at some point in their disease course. Swallowing difficulties were reported in 53.4% of patients, and only 11.7% received feeding therapy. Only 23.5% of patients received behavioral therapy, which was perceived as beneficial in 90.6% (Supplemental Table 3).

TABLE 5.
Tumor Histology and Characteristics

Variable	N (%)
Tumor present (n = 97)	
Neuroblastoma	61 (70.9)
Ganglioneuroblastoma	14 (16.3)
Ganglioneuroma	9 (10.5)
Other	2 (2.3)
No response	11
Tumor stage (n = 78)	
Stage 1	31 (39.7)
Stage 2	19 (24.4)
Stage 3	7 (9.0)
Stage 4	4 (5.1)
Unknown	17 (21.8)
No response	19
Tumor discovered at time of diagnosis? (n = 78)	
Yes	60 (76.9)
No	18 (23.1)
No response	19
If No: time from OMAS onset to detection of tumor (n = 18)	
1-3 months from OMAS onset	4 (22.2)
3-6 months from OMAS onset	2 (11.1)
6-9 months from OMAS onset	1 (5.6)
9-12 months from OMAS onset	3 (16.7)
>12 months from OMAS onset	8 (44.4)
If No: method of tumor discovery (n = 18)	
Routine scans as part of OMAS follow-up	8 (44.4)
Second opinion on initial set of scans taken at diagnosis	3 (16.7)
Other/unclear from available data	7 (38.9)

Abbreviation:
OMAS = Opsoclonus-myoclonus-ataxia syndrome

Discussion

Our study reports parent-provided data from 194 pediatric patients with OMAS, making it the second largest published cohort to date. The demographic and clinical data in our cohort are overall similar to the data in the US National Pediatric Myoclonus Center cohort (n = 356) and a cohort from the United Kingdom (n = 101 patients) suggesting that patient-derived data are likely comparable to clinician-entered data (Supplemental Table 4).[5,6] The rate of detection of neuroblastoma and related tumors in our cohort (55.4%) is consistent with the reported ongoing trend toward increased tumor detection over time, likely reflecting improved imaging techniques.[7]

Our findings point to potential risk factors for the development of OMAS. First, female sex was more prevalent in both the tumor and nontumor subgroups, confirming the findings of the above US and UK studies. The female predominance in our tumor subgroup contrasts with the male predominance (54%) in prior epidemiologic studies of neuroblastoma (not restricted to those with OMAS).[8] Regarding the nontumor subgroup, other cohorts of prepubertal children with autoimmune neurological conditions, such as acute disseminated encephalomyelitis, have shown a male predominance.[9] If female sex is confirmed as a risk factor for OMAS, additional research into the underlying biological mechanisms may yield novel insights into OMAS pathogenesis. Second, 30.9% of patients had at least one first-degree relative with an autoimmune disease, similar to the findings of two prior smaller studies in which the rate was 40% and 16%, respectively.[10,11] Furthermore, the rate of autoimmunity in first-degree relatives did not significantly differ in the tumor versus nontumor subgroups, confirming the findings of a prior study.[10] Collectively, these studies suggest a genetic predisposition to OMAS, regardless of the presence of a neuroblastoma. Further research into the genetic basis of this finding may yield important insights into the pathways involved in OMAS and potential treatment targets.

Our study also points to areas of potential improvement in the diagnosis of OMAS and associated neuroblastomas. Ataxia was the most common symptom at onset in both paraneoplastic and nonparaneoplastic OMAS groups. However, opsoclonus and myoclonus were absent at onset in 39.4% and 41.8% of patients, respectively, likely contributing to the high rate of initial misdiagnosis, which was most commonly acute cerebellar ataxia or cerebellitis. Even more challenging, eight patients never developed opsoclonus. Although this finding has been previously reported in case reports,[12] our cohort suggests that this may be a more common finding. Therefore, until a specific biomarker for OMAS is discovered, clinicians need to maintain a high index of suspicion for OMAS in children presenting with ataxia. Educational efforts to increase awareness of the heterogeneity of OMAS presentation among pediatric providers are warranted.

In addition, 23.1% of patients had delayed tumor detection, including eight who had a tumor detected later than 12 months after the initial presentation. Routine follow-up scans and second opinion on initial set of scans both led to tumor detection in our cohort. Delayed tumor detection can potentially lead to worse oncologic and neurological outcomes in OMAS. A prior study demonstrated that the combination of urine catecholamines, chest radiography, abdominal ultrasound, and iodine meta-iodobenzylguanidine would miss approximately 20% of neuroblastoma cases in the setting of OMAS, emphasizing the importance of cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) covering the entire sympathetic chain from the neck through pelvis.[7] Although the optimal frequency and duration of longitudinal surveillance imaging for neuroblastoma in the setting of OMAS with normal baseline

TABLE 6.
Time From Onset to Correct Diagnosis and From Diagnosis to Treatment

Characteristics	Overall	Tumor	No Tumor	*P* Value (Wilcoxon Rank-Sum Test)
Time from onset to diagnosis				
Number of patients	164	90	74	0.4011
Median time (days) (IQR, range)	23 (7, 74) (7287, 3432)	18.5 (8, 61) (−7287, 988)	30 (6, 95) (−329, 3432)	
Time from onset to diagnosis excluding negative values				
Number of patients	159	89	70	0.1704
Median time (days) (IQR, range)	25 (8, 78) (0, 3432)	19 (8, 61) (0, 988)	31 (8, 108) (0, 3432)	
From diagnosis to treatment				
Number of patients	106	61	45	0.4317
Median time (days) (IQR, range)	1 (−6, 19) (−358, 5387)	2 (−6, 19) (−358, 676)	0 (−5, 23) (−299, 5387)	
From diagnosis to treatment excluding negative values				
Number of patients	75	43	32	0.2440
Median time (days) (IQR, range)	7 (0, 31) (0, 5387)	10 (1, 31) (0, 676)	3.5 (0, 30.5) (0, 5387)	

Abbreviation:
IQR = Interquartile range

TABLE 7.
Pharmacologic Treatment Received in Patients With OMAS

Feature	N (%)					*P* Value (Fisher Exact Test for Comparing Tumor vs No Tumor)
	All Patients n = 148	Before 2013 n = 59*	2013 and After n = 84*	Tumor n = 84	No Tumor n = 64	
Treatment categories						
Missing agent information	20 (13.5)	8 (13.6)*	10 (11.9)*	11 (13.1)	9 (14.1)	0.6702
One agent	27 (18.2)	10 (17)	17 (20.2)	17 (20.2)	10 (15.6)	
Two agents	18 (12.2)	6 (10.2)	12 (14.3)	8 (9.5)	10 (15.6)	
Three or more agents	83 (56.1)	35 (59.3)*	45 (53.6)*	48 (57.1)	35 (54.7)	
Treatment agents						
Corticosteroids (prednisolone, dexamethasone, methylprednisolone) or corticotropins (ACTH)	118 (79.7)	46 (78)*	69 (82.1)*	67 (79.8)	51 (79.7)	1.000
IVIG	96 (64.9)	41 (69.5)*	53 (63.1)*	53 (63.1)	43 (67.2)	0.7284
Cyclophosphamide	30 (20.3)	15 (25.4)*	13 (15.5)*	19 (22.6)	11 (17.1)	0.5365
Rituximab	78 (52.7)	31 (52.5)*	44 (52.4)*	44 (53.1)	34 (52.4)	1.000
Mycophenolate mofetil	7 (4.7)	5 (8.5)*	1 (1.2)*	4 (4.8)	3 (4.7)	1.000

Abbreviations:
ACTH = Adrenocorticotropic hormone
IVIG = Intravenous immunoglobulin
OMAS = Opsoclonus-myoclonus-ataxia syndrome
* In the year of diagnosis, there were five instances of no response, leading to the absence of responses in various categories: missing agent information (two cases), three or more agents (three cases), corticosteroids (three cases), IVIG (two cases), cyclophosphamide (two cases), rituximab (three cases), and mycophenolate mofetil (one case).

imaging is unclear, we recommend at least one follow-up cross-sectional imaging at six months from onset, including in patients with adequate control of OMAS disease activity. This approach is supported by recent consensus guidelines in OMAS.[13] We are planning a follow-up study of the patients with delayed tumor detection to determine whether CT or MRI were not obtained at onset or whether the tumor escaped detection on CT or MRI, which could be due to technical factors, diagnostic error, or sub-radiographic size.

Finally, our study highlights potential questions and gaps in OMAS treatment. In our cohort, there was much higher usage of combination therapy (56.1% vs 16%), IVIG (64.9% vs 1%), and rituximab (52.7% vs 0%) compared with the prior UK study[6] The higher rate of IVIG use in our cohort may reflect regional practice differences, as well as the influence of a randomized controlled trial of IVIG in paraneoplastic OMAS, which showed improved outcomes when it was added to steroids and cyclophosphamide.[14] The higher rate of rituximab use may reflect the influence of open-label studies suggesting that its use in OMAS may improve outcomes.[15] Although our study was not designed to assess treatment efficacy, further research using international data can capitalize on regional differences in treatment to power real-world comparative effectiveness studies, which we are planning in our international clinician-entered database.[16] In addition, our study suggests that whereas physical, occupational, and speech therapies are commonly used and perceived as beneficial in more than 90% of patients, behavioral therapy is underutilized and reflects an unmet need in OMAS care.

Limitations of our study include low number of patients in some surveys, the subjective report from parents, and missing data for variable numbers of patients in different surveys. Nonetheless, the similarities in patient characteristics between our cohort and two prior large cohorts support the validity of parent-driven data compared with clinician-derived data. In addition, we acknowledge that parents who do not speak English, have less education, and/or have less access to the internet may have been less likely to enroll in the study, which may limit generalizability. We plan to utilize translated surveys in the future to partially address this issue. Despite these limitations, our report demonstrates the potential for parent-driven data registries to assemble large cohorts in OMAS with our study highlighting important insights into risk factors, diagnosis, and treatment of OMAS.

CRediT authorship contribution statement

Sandra Jimenez Giraldo: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Michael Michaelis:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lauren Kerr:** Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Investigation, Data curation, Conceptualization. **Christopher Cortina:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Investigation, Formal analysis. **Bo Zhang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mark P. Gorman:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

None.

Acknowledgments

The authors would like to thank the National Organization for Rare Disorders (NORD) for their developmental grant for the OMAS Natural History Study. With their guidance and funding, the OMSLife Foundation was able to develop the OMAS Patient Reported Registry on the NORD IAMRARE Registry platform. We express our gratitude to Drs. Tim Lotze and Wendy Mitchell for their invaluable guidance and expertise throughout the development of the OMAS surveys. We also want to thank the many OMAS caregivers and patients who completed the numerous surveys in the registry and updated them over the past four years. Without their assistance, the publication of these findings would not be possible. We thank Shanshan Ding for her efforts in initial data configuration and exploratory data analysis. Finally, we would like to thank the developers of the surveys, Christy Khoury-Dennis, Shandi Ricciotti, Kelly Miller, and Brooke D'Souza, as well as members of our medical

advisory team, Dr. Wendy Mitchell (Children's Hospital Los Angeles) and Dr. Tim Lotze (Texas Children's Hospital).

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2024.06.007.

References

1. Ki Pang K, de Sousa C, Lang B, Pike MG. A prospective study of the presentation and management of dancing eye syndrome/opsoclonus–myoclonus syndrome in the United Kingdom. Eur J Paediatr Neurol. 2010;14:156–161.
2. Hero B, Schleiermacher G. Update on pediatric opsoclonus myoclonus syndrome. Neuropediatrics. 2013;44:324–329.
3. Matthay KK, Blaes F, Hero B, et al. Opsoclonus myoclonus syndrome in neuroblastoma a report from a workshop on the dancing eyes syndrome at the advances in neuroblastoma meeting in Genoa, Italy, 2004. Cancer Lett. 2005;228:275–282.
4. Sheridan A, Kapur K, Pinard F, et al. IQ predictors in pediatric opsoclonus myoclonus syndrome: a large international cohort study. Dev Med Child Neurol. 2020;62:1444–1449.
5. Pranzatelli MR, Tate ED, McGee NR. Multifactorial analysis of opsoclonus-myoclonus syndrome etiology ("Tumor" vs. "No tumor") in a cohort of 356 US children. Pediatr Blood Cancer. 2018;65, e27097.
6. Brunklaus A, Pohl K, Zuberi SM, de Sousa C. Outcome and prognostic features in opsoclonus-myoclonus syndrome from infancy to adult life. Pediatrics. 2011;128:e388–e394.
7. Brunklaus A, Pohl K, Zuberi SM, Sousa C de. Investigating neuroblastoma in childhood opsoclonus-myoclonus syndrome. Arch Dis Child. 2012;97:461–463.
8. Heck JE, Ritz B, Hung RJ, Hashibe M, Boffetta P. The epidemiology of neuroblastoma: a review. Paediatr Perinat Epidemiol. 2009;23:125–143.
9. Pohl D, Alper G, Van Haren K, et al. Acute disseminated encephalomyelitis: updates on an inflammatory CNS syndrome. Neurology. 2016;87:S38–S45.
10. Santoro JD, Kerr LM, Codden R, et al. Increased prevalence of familial autoimmune disease in children with opsoclonus-myoclonus syndrome. Neurol Neuroimmunol Neuroinflamm. 2021;8, e1079.
11. Krasenbrink I, Fühlhuber V, Juhasz-Boess I, et al. Increased prevalence of autoimmune disorders and autoantibodies in parents of children with opsoclonus-myoclonus syndrome (OMS). Neuropediatrics. 2007;38:114–116.
12. Herman TE, Siegel MJ. Ataxia without opsoclonus: right lumbar sympathetic trunk neuroblastoma. Clin Pediatr (Phila). 2009;48:336–340.
13. Rossor T, Yeh EA, Khakoo Y, et al. Diagnosis and management of opsoclonus-myoclonus-ataxia syndrome in children. Neurol Neuroimmunol Neuroinflamm. 2022;9, e1153.
14. de Alarcon PA, Matthay KK, London WB, et al. Intravenous immunoglobulin with prednisone and risk-adapted chemotherapy for children with opsoclonus myoclonus ataxia syndrome associated with neuroblastoma (ANBL00P3): a randomised, open-label, phase 3 trial. Lancet Child Adolesc Health. 2018;2:25–34.
15. Mitchell WG, Wooten AA, O'Neil SH, Rodriguez JG, Cruz RE, Wittern R. Effect of increased immunosuppression on developmental outcome of opsoclonus myoclonus syndrome (OMS). J Child Neurol. 2015;30:976–982.
16. Kerr LM, Ryan ME, Lim M, et al. An international pediatric-onset opsoclonus- myoclonus ataxia syndrome registry and clinical research Network development, Progress, and vision. Pediatr Neurol. 2023;148:145–147.