Characterization of Misdiagnosed OMAS (Opsoclonus Myoclonus Ataxia Syndrome)

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ISPOR, Atlanta GA May 5-8, 2024

The authors have no conflicts of interest to report.

OMAS Primer

- Autoimmune disorder, usually paraneoplastic though may be parainfectious or idiopathic.
- Ultrarare, only ~2000 known cases worldwide. Est. incidence ~1 per 5MM.
- Most commonly presents in children, median age of onset 16-18 months.
- OMAS may cause long-term impairment in cognitive & motor functions.
- Prompt aggressive immunosuppressive treatments are effective.

The Diagnosis Challenge

Symptoms	Definition	Differentiate from
Opsoclonus	Rapid, involuntary, repetitive eye movements -- can be chaotic, multidirectional, arrhythmic	Nystagmus, ocular flutter, other abnormal eye movements
Myoclonus	Brief, jerky muscle contractions, twitch- or spasm-like	Epilepsies, metabolic issues
Ataxia	Impaired muscle control and coordination	Autoimmune diseases, cerebellar ataxia, hereditary ataxias

Other Symptoms

Hand Tremors
Sleep Disturbances
Temper Tantrums
Vomiting
Fever
Headache
Difficulty with Speech

Diagnosis Criteria

3 of 4 features:

- Opsoclonus
- Ataxia or myoclonus
- Behavior change or sleep disturbance
- Neuroblastoma

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The OMAS Natural History Registry

2016 NORD with FDA support initiates Natural History Registry development with 20 Rare Disease Foundations.

2017 OMAS Natural History Registry launched.

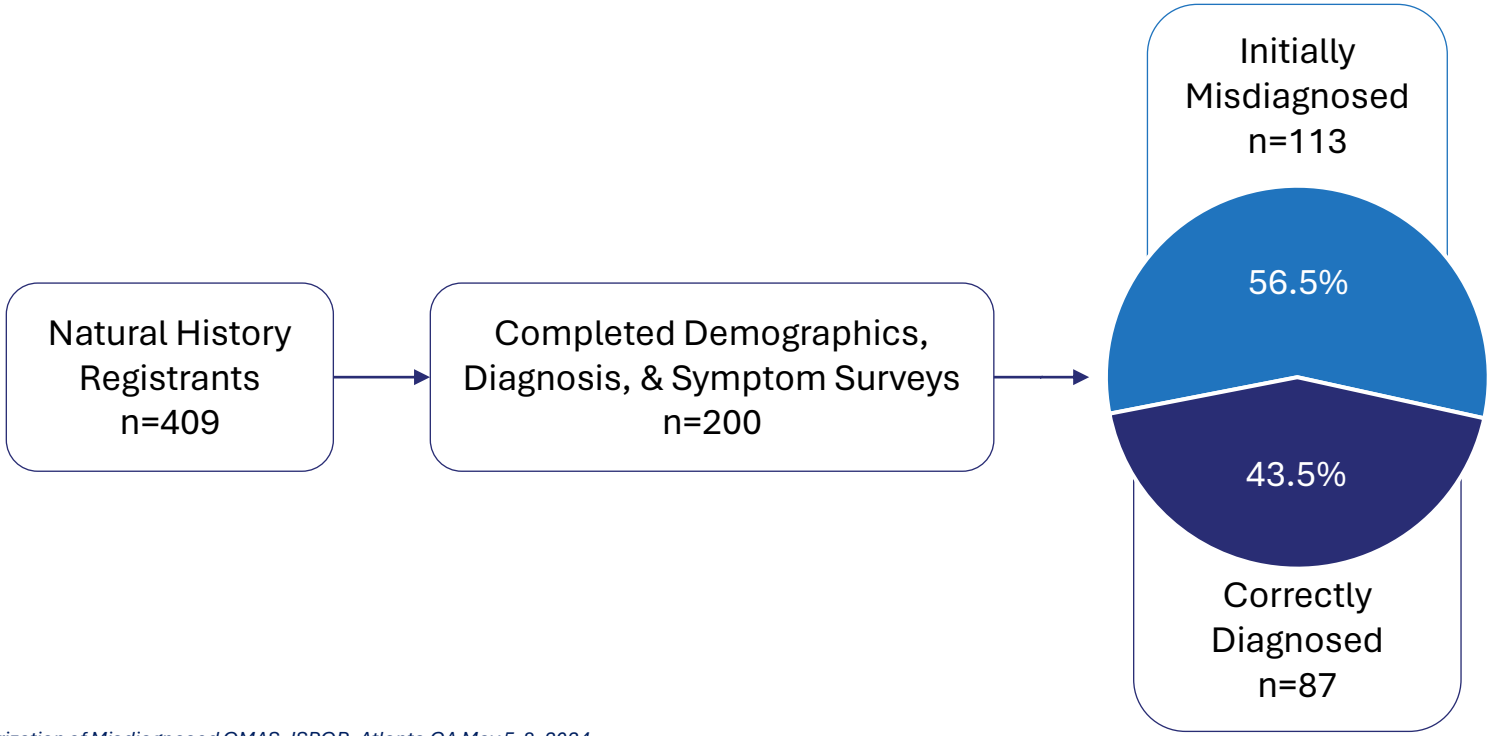
2024 >400 Patients with OMAS registered.

Data collection includes:

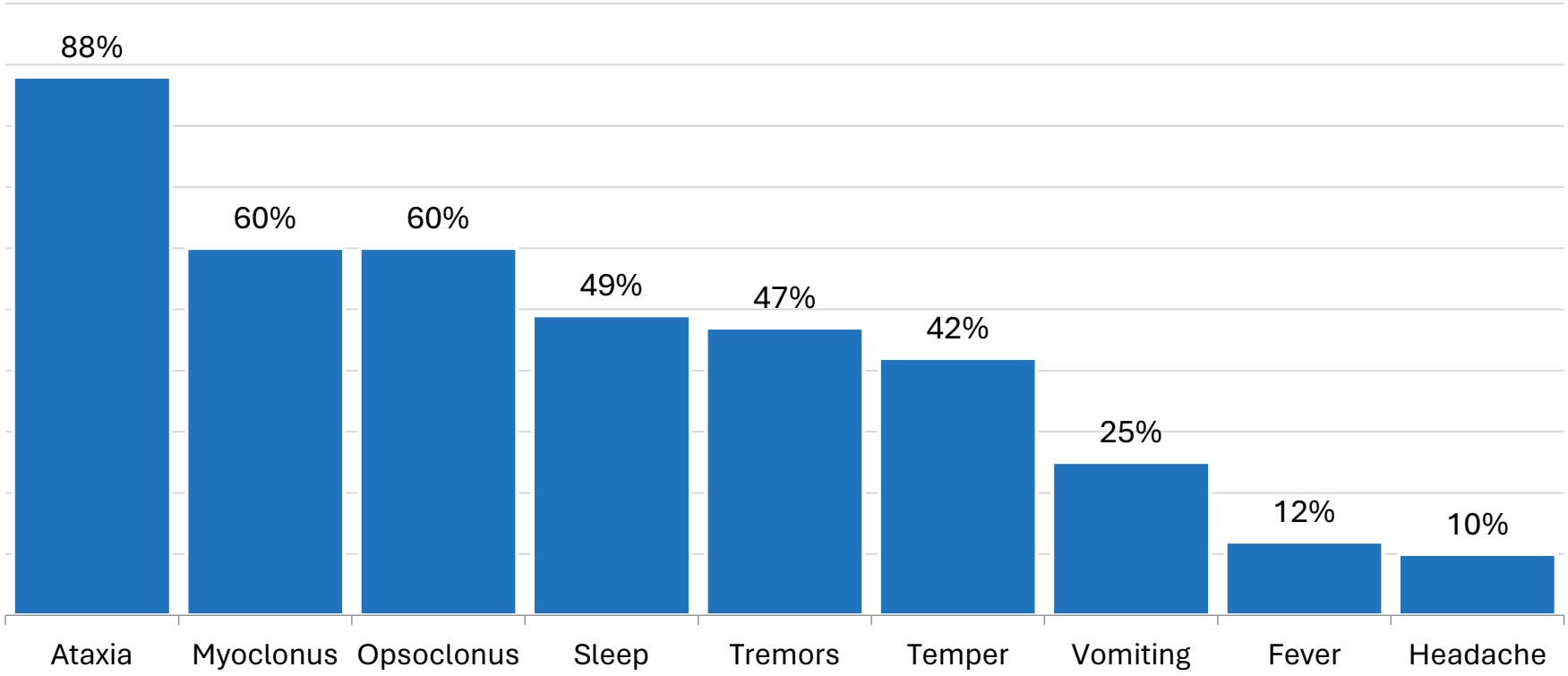
- Sociodemographics
- Family History
- Symptoms & Diagnosis
- Systems Review
- Functioning
- Treatment Types, Medications
- Disease Progression, Relapse
- Quality of life

Objective and Patient Selection

To characterize misdiagnosed OMAS for the purpose of raising disease awareness.



Symptoms at Onset (n=200)



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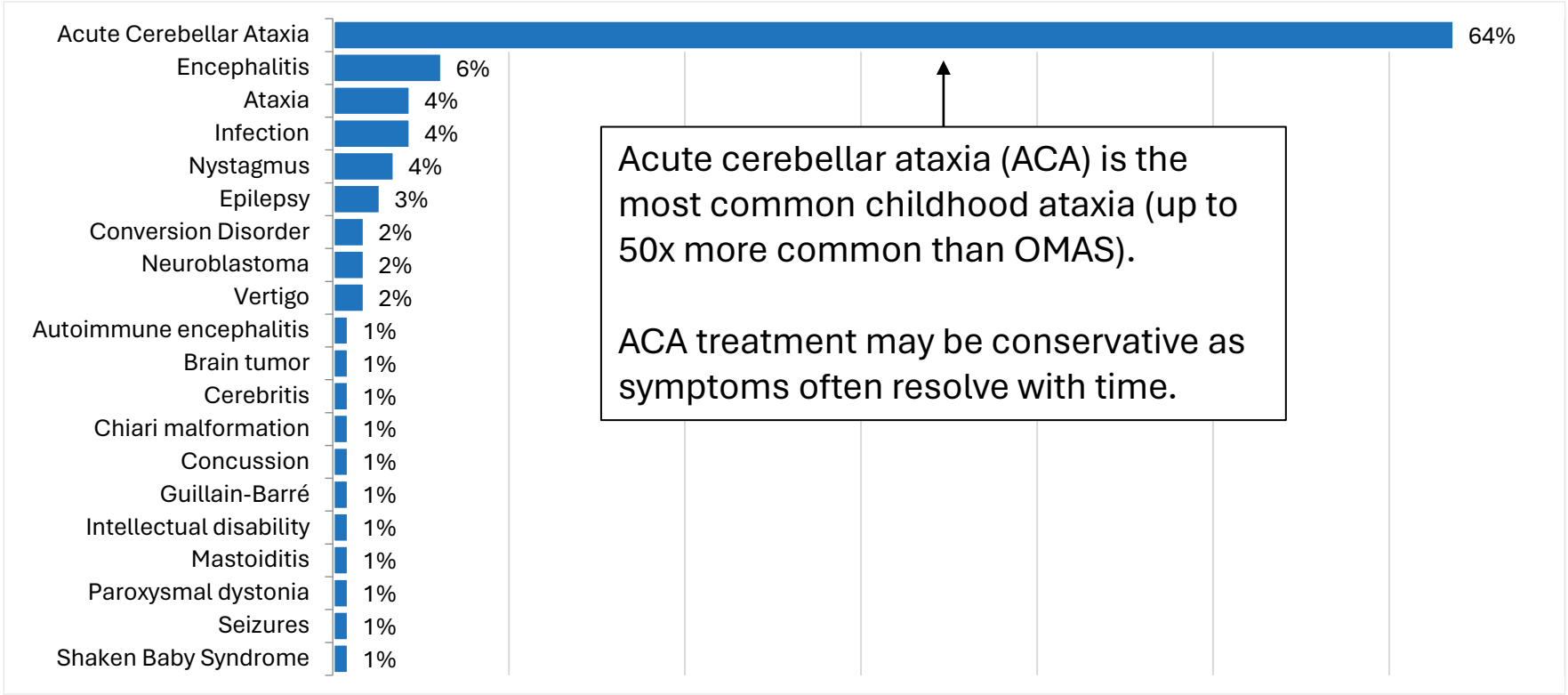
Misdiagnoses (n=113)



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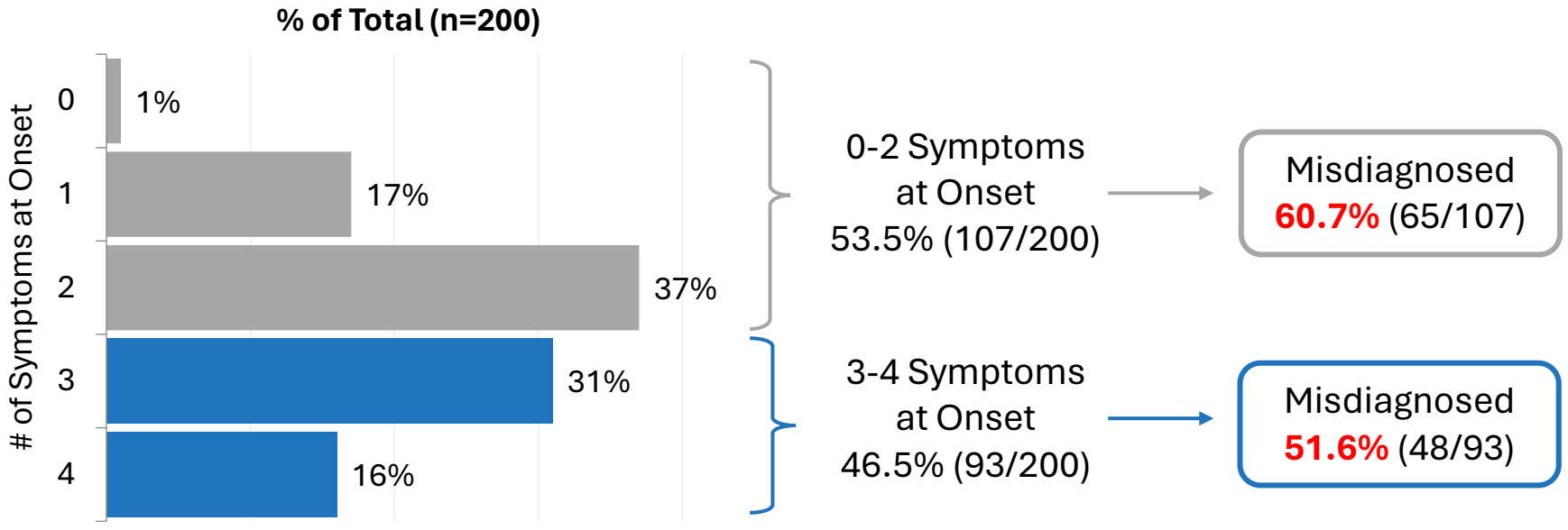
Cohort Comparisons

Correctly Diagnosed (n=87)	Misdiagnosed (n=113)	Characteristic
20% (↓)	**40% (↑)**	Immediate Family History of Autoimmune Disease
70% (↑)	**52% (↓)**	Opsoclonus at Onset

Misdiagnosed and correctly diagnosed groups were similar for gender, race, ethnicity, insurance type, age at onset, family history of cancer and/or psychiatric disorder, and most symptoms at onset. *US residency was significantly different between cohorts though this finding needs further review.

Symptoms Necessary for Diagnosis

OMAS diagnosis may be made by presence of 3 of the following: opsoclonus, ataxia or myoclonus, behavior change or sleep disturbance, and/or tumor.



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Summary

- Most patients with OMAS are initially misdiagnosed.
- Cerebellar ataxia is the most common misdiagnosis.
- Misdiagnosis is higher for patients with a family history of autoimmune disease.
- Misdiagnosis is lower when opsoclonus is recognized at symptom onset.
- Even when evidence for diagnosis is present at onset, half of patients are still misdiagnosed.

Key Points

- Time is of the essence.
- What if it isn’t Acute Cerebellar Ataxia??
- Opsoclonus recognition may be the key. A squeeze test to elicit opsoclonus movement could literally change a life.
- Much work remains to be done.

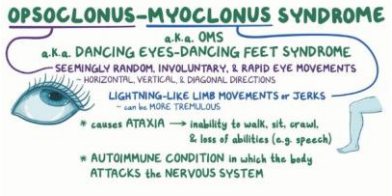
Special Thanks to

The Patients and Caregivers

The National Organization of Rare Disorders

To learn more about OMAS…

OMS *life* Foundation



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Characterization of Misdiagnosed Opsoclonus Myoclonus Ataxia Syndrome (OMAS)

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P51

Tuesday, May 7
5:00PM-6:00PM

BACKGROUND/OBJECTIVE

The neurologic disorder Opsoclonus Myoclonus Ataxia Syndrome (OMAS) is an ultrarare disease that may result in motor, cognitive, and/or behavioral dysfunction. Though OMAS develops infrequently in adults, most patients have symptom onset by 3 years of age. As with other rare diseases, challenges to OMAS care include misdiagnosis and lack of provider knowledge. Here, we leverage information from the OMAS Natural History Registry to characterize a misdiagnosed population for the purpose of raising OMAS awareness.

METHODS

The OMAS Natural History Registry contains demographics and family history, symptoms, diagnosis and disease severity, therapies (behavioral, occupational, physical, speech), and medication details input from the patient and/or caregiver. Study Population: 200 patients with completed demographic, symptoms, and diagnosis surveys as of Nov 2023. [FIGURE 1] Univariate comparisons: two-sided independent sample t-test (continuous), Pearson $\chi 2$ or Fisher's exact tests (categorical) with subsequent z-test of column proportions. Variables approaching significance ($p \leq 0.1$) in univariate analyses or of clinical interest were further assessed by forward stepwise logistic regression.

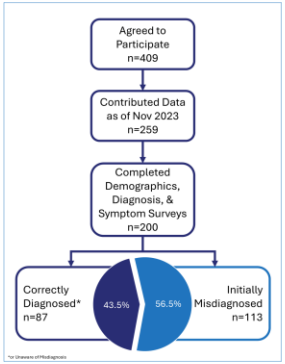
RESULTS

Of 200 study patients, 113 (57%) were initially misdiagnosed; the remaining 87 (44%) were correctly diagnosed and/or not aware of misdiagnosis. [FIGURE 1] Twenty different misdiagnosed conditions were recorded with Cerebellar Ataxia most common (72/113, 64%). [FIGURE 2] In univariate analyses, the misdiagnosed group had a higher proportion with US residence (91% v. 80%, p=0.028) and autoimmune disease in immediate family (40% v. 20%, p=0.025) and lower proportion of opsoclonus at symptom onset (52% v. 70%, p=0.010). [TABLES 1,2] These variables were retained as significant in multivariate analysis. Odds ratio (OR) and 95% confidence interval lower and upper values for misdiagnosis were opsoclonus at onset (0.310 [0.132-0.730] p=0.007), US residence (6.154 [1.288-29.413] p=0.023), and immediate family history of autoimmune disease (2.998 [1.222-7.357] p=0.016). An assessment of conditions necessary for OMAS diagnosis at symptom onset (3 of 4 conditions: opsoclonus, ataxia or myoclonus, behavior change or sleep disturbance, and/or tumor) did not find significant differences between groups in proportions of patients with 1, 2, 3, or 4 of these criteria. [TABLE 3b] In the subset with sufficient conditions (≥3) for diagnosis (47%, 93/200), 52% (48/93) were misdiagnosed. [FIGURE 3]

CONCLUSIONS

The OMS registry developed by The OMSLife Foundation and NORD has proven to be a successful endeavor for this ultrarare disease, providing large samples of data for researchers and clinicians to use to identify care opportunities in OMS. The results from this study highlight a need for greater OMAS awareness, as even when sufficient diagnostic criteria are present, misdiagnosis occurs in half of the cases. Additional insight is anticipated as the registry continues to grow in participants and type of data collected.

FIGURE 1: Patient Disposition



*or Unaware of Misdiagnosis

FIGURE 2: Misdiagnoses (n=113)

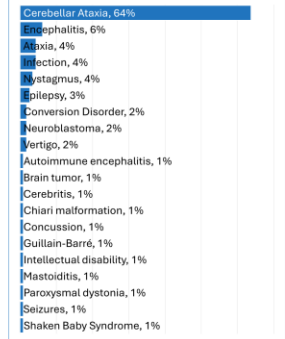


TABLE 1: Patient Demographics

Characteristic	Correct Diagnosis* (n=87)		Misdiagnosed (n=113)		Total (n=200)		p
	No. Patients	% Patients	No. Patients	% Patients	No. Patients	% Patients	
Female	46	53%	66	58%	112	56%	0.434
Race							0.525
American Indian, Alaska Native	1	1%	0	0%	1	1%	
Asian	3	3%	3	3%	6	3%	
Black or African American	1	1%	3	3%	4	2%	
Other	8	9%	9	8%	17	9%	
White	74	85%	98	87%	172	86%	
Ethnicity							0.807
Hispanic or Latino	9	10%	14	12%	23	12%	
Non-Hispanic or Latino	55	63%	73	65%	128	64%	
Not Specified	23	26%	26	23%	49	25%	
Insurance Type (US only)[†]	n=70		n=103		n=173		0.572
Medicaid/SCHIP and/or Medicare	27	39%	34	33%	61	35%	
Military health care (Tricare/VA)	4	6%	4	4%	8	5%	
Not Specified	2	3%	7	7%	9	5%	
Private health insurance	37	53%	58	56%	95	55%	
Country of Residence							0.275
Australia	1	1%	1	1%	2	1%	
Belgium	0	0%	1	1%	1	1%	
Brazil	0	0%	1	1%	1	1%	
Canada	2	2%	4	4%	6	3%	
Germany	4	5%	1	1%	5	3%	
Greece	1	1%	0	0%	1	1%	
Ireland	1	1%	0	0%	1	1%	
Netherlands	1	1%	0	0%	1	1%	
Paraguay	1	1%	0	0%	1	1%	
Spain	1	1%	0	0%	1	1%	
Sweden	1	1%	0	0%	1	1%	
Taiwan	1	1%	0	0%	1	1%	
Ukraine	0	0%	1	1%	1	1%	
United Kingdom	3	3%	1	1%	4	2%	
United States	70	80%	103	91%	173	87%	0.028[‡]

*or Unaware of Misdiagnosis. [†]Significant differences by z-test of proportions. [†]Insurance type was assigned by hierarchy of Medicaid/SCHIP and/or Medicare -> Military Health Care -> Private health insurance.

TABLE 2: Disease and Diagnosis Characteristics

Characteristic	Correct Diagnosis* (n=87)		Misdiagnosed (n=113)		Total (n=200)		p
	No. Patients	% Patients	No. Patients	% Patients	No. Patients	% Patients	
Diagnosis Specialist							0.667
Neurologist	71	82%	99	88%	170	85%	
Oncologist	11	13%	10	9%	21	11%	
Ophthalmologist	1	1%	2	2%	3	2%	
Other	2	2%	1	1%	3	2%	
Pediatrician	2	2%	1	1%	3	2%	
Age at Onset	n=86		n=112		n=198		0.295
0-3y	79	92%	94	84%	173	87%	
4-11y	5	6%	13	12%	18	9%	
12-17y	0	0%	2	2%	2	1%	
>=18y	2	2%	3	3%	5	3%	
Year of OMAS Onset	n=85		n=113		n=198		0.093
<2011	18	21%	39	35%	57	29%	
2011-2015	34	40%	33	29%	67	34%	
2016-2023	33	39%	41	36%	74	37%	
Immediate Family History	n=49		n=73		n=122		
Autoimmune Disorder	10	20%	29	40%	39	32%	0.025[‡]
Cancer	6	12%	7	10%	13	11%	0.641
Psychiatric Disorder	21	43%	34	47%	55	45%	0.689
OMAS Diagnosis Determination							
Symptoms	30	34%	35	31%	65	33%	0.592
Symptoms, Lab Tests	20	23%	36	32%	56	28%	
Tumor, Symptoms	28	32%	30	27%	58	29%	
Tumor, Symptoms, Lab Tests	8	9%	8	7%	16	8%	
Other/Unknown	1	1%	4	4%	5	3%	
Symptoms at Onset							
Ataxia	74	85%	102	90%	176	88%	0.261
Myoclonus	57	66%	62	55%	119	60%	0.128
Opsoclonus	61	70%	59	52%	120	60%	0.010[‡]
Tremors	43	49%	50	44%	93	47%	0.467
Sleep	39	45%	59	52%	98	49%	0.300
Temper	35	40%	48	42%	83	42%	0.749
Vomiting	19	22%	31	27%	50	25%	0.365
Fever	11	13%	12	11%	23	12%	0.656
Headache	8	9%	11	10%	19	10%	0.897

*or Unaware of Misdiagnosis. [‡]Indicates significant differences at p<0.050.

TABLES 3A,B: Symptoms Necessary for Diagnosis

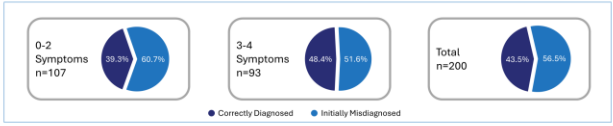
A: Individuals Symptoms for Diagnosis

Symptoms	Correct Diagnosis* (n=87)			Misdiagnosed (n=113)			Total (n=200)		
	No. Patients	% Row	% Column	No. Patients	% Row	% Column	No. Patients	% Row	% Column
Ataxia or Myoclonus	79	43%	91%	105	57%	93%	184	100%	92%
Opsoclonus	61	51%	70%	59	49%	52%	120	100%	60%
Temper or Sleep	47	42%	54%	65	58%	58%	112	100%	56%
Tumor	36	49%	41%	38	51%	34%	74	100%	37%
Denominator	87			113			200		

B: No. Symptoms for Diagnosis (at least 3 of 4 are necessary for diagnosis)

No. Symptoms	Correct Diagnosis* (n=87)			Misdiagnosed (n=113)			Total (n=200)		
	No. Patients	% Row	% Column	No. Patients	% Row	% Column	No. Patients	% Row	% Column
0	0	0%	0%	1	100%	1%	1	100%	1%
1	12	36%	14%	21	64%	19%	33	100%	17%
2	30	41%	34%	43	59%	38%	73	100%	37%
3	29	48%	33%	32	52%	28%	61	100%	31%
4	16	50%	18%	16	50%	14%	32	100%	16%
Total	87	44%	100%	113	57%	100%	200	100%	100%

Figure 3: Misdiagnosis based on No. of Diagnostic Symptoms at Onset



The OMS Natural History Registry was developed by OMSLife Foundation with assistance by the National Organization for Rare Disorders (NORD) and supported in part by a cooperative agreement with the U.S. Food and Drug Administration. SM is an employee of Trio Health Analytics though Trio Health Analytics is not associated with this work.

Consequences of Misdiagnosed Opsoclonus Myoclonus Ataxia Syndrome (OMAS)

Michaelis M[1], Milligan S[2]
[1]The OMSLife Foundation, Cypress TX USA; [2]Trio Health Analytics, Louisville CO USA

PCR97

Monday, May 6
3:30PM-6:30PM

BACKGROUND/OBJECTIVE

OMAS may be diagnosed by the presence of 3 out of 4 conditions (opsoclonus, ataxia or myoclonus, behavior change or sleep disturbance, and tumor), though the expression and timing of these conditions are varied between patients. As a result, ultrarare OMAS is often misdiagnosed as acute cerebellar ataxia, the most common type of ataxia in children. To evaluate the impact of misdiagnosis on patients with OMAS, we assessed time to, and disease severity at, OMAS diagnosis in comparison to correctly diagnosed patients.

METHODS

The OMAS Natural History Registry contains demographics, family history, symptoms, diagnosis, disease severity, therapies (behavioral, occupational, physical, speech), and medication details input by the patient and/or caregiver. Study Population: 122 patients with demographic, family history, symptom & disease information. Statistics: Pearson χ^2, Fisher's exact (categorical), z-test (proportions), Mann-Whitney U test (continuous), Shapiro-Wilk (normality). Matched pairs by exact propensity score matching (PSM) without replacement. "Correctly diagnosed" defined as patient not aware of any initial misdiagnosis.

RESULTS

Most (60%) study patients [FIGURE 1] were initially misdiagnosed; this group had a higher proportion of family history autoimmune disease (40% v. 20% correctly diagnosed, p=0.025) and lower proportions of onset by age 3 (82% v. 96% correctly diagnosed, p=0.024) and opsoclonus at onset (52% v. 73% correctly diagnosed, p=0.018). [TABLE 1] Final PSM, based upon opsoclonus, US residence, onset age, and family history autoimmune disease, yielded 31 pairs. Matched cohorts of misdiagnosed v. correctly diagnosed were not significantly different by demographics, symptoms, or family history. Aggregate Mitchell-Pike severity scores at diagnosis were not significantly different between cohorts in study or matched samples. [TABLE 2, FIGURE 3] Misdiagnosed groups had higher proportions with abnormal mood (value >0; study: 100% v. 88% correctly diagnosed, p=0.003; matched: 100% v. 84% correctly diagnosed, p=0.053), impaired arm/hand coordination or fine motor function (value >0; study: 99% v. 90% correctly diagnosed, p=0.038; matched: 100% v. 93% correctly diagnosed, p=0.492), and impaired speech (value >0; study: 85% v. 67% correctly diagnosed, p=0.027; matched: 87% v. 68% correctly diagnosed, p=0.127) though differences did not reach significance in the matched set. Differences by component score distributions are shown in FIGURE 3. Mean (median) months to diagnosis was greater in misdiagnosed groups (study: 5.9 (2.0) v. 2.8 (1.0) correctly diagnosed, p<0.001; matched: 4.7 (2.0) v. 3.2 (1.0) correctly diagnosed, p=0.048). [FIGURE 4]

CONCLUSIONS

In the OMAS Natural History Registry, patients initially misdiagnosed were delayed in receiving the accurate OMAS diagnosis. Impaired speech, arm/hand motor function, and abnormal mood were more common in misdiagnosed cohorts, though significance was only achieved in the starting study population. Enrollment into the registry is ongoing.

FIGURE 1: Patient Disposition

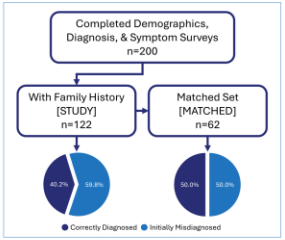


TABLE 2: Mitchell-Pike Severity

The Mitchell-Pike (MP) Severity scale is assigned at diagnosis based on 6 factors, each ranked from 0-3 where 0 is "normal" and 3 is most severe. Aggregate MP scores ≥6 reflect mild disease, 7-12 moderate, and 13-18 severe.

Group	Description	score
stance	Standing and sitting balance normal for age	0
	Mildly unstable standing for age, slightly wide based	1
	Unable to stand without support but can sit without support	2
	Unable to sit without using hands to prop or other support	3
gait	Walking normal for age	0
	Mildly wide-based gait for age, able to walk in/outdoors independently	1
	Walks only or predominantly with support from person or equipment	2
	Unable to walk even with support from person or equipment	3
hand	Normal for age	0
	Mild, infrequent tremor or jerkiness without functional impairment	1
	Fine motor function persistently impaired for age, but less precise manipulative tasks normal or almost normal	2
	Major difficulties in all age-appropriate fine motor & manipulative tasks	3
opsoclonus	None	0
	Rare or only when elicited by change-in fixation or "squeeze test"	1
	Frequent, interferes intermittently with fixation or tracking	2
	Persistent, interfering continuously with function and tracking	3
mood	Normal	0
	Mild increase in irritability but consolable; and/or mild sleep troubles	1
	Irritability and sleep disturbances interfering with child and family life	2
	Persistent severe distress	3
speech	Normal for age, no loss	0
	Mildly unclear, plateaued in development	1
	Loss of some words or some grammatical constructs (i.a. from sentences to phrases) but still communicates verbally	2
	Severe loss of verbal communication and speech	3

TABLE 1: Patient Demographics and Clinical Characteristics

Characteristic	[STUDY] n=122							[MATCHED] n=62						
	Correct Diagnosis* (n=49)		Misdiagnosed (n=73)		Total (n=122)		p	Correct Diagnosis* (n=31)		Misdiagnosed (n=31)		Total (n=62)		p
	No. Patients	% Patients	No. Patients	% Patients	No. Patients	% Patients		No. Patients	% Patients	No. Patients	% Patients	No. Patients	% Patients	
Female	28	57%	42	58%	70	57%	0.966	18	58%	12	39%	30	48%	0.127
Race							0.530							0.306
American Indian, Alaska Native	1	2%	0	0%	1	1%		1	3%	0	0%	1	2%	
Asian	2	4%	1	1%	3	2%		2	6%	0	0%	2	3%	
Black or African American	0	0%	1	1%	1	1%		0	0%	1	3%	1	2%	
Other	4	8%	7	10%	11	9%		2	6%	4	13%	6	10%	
White	42	86%	64	88%	106	87%		26	84%	26	84%	52	84%	
Ethnicity							0.667							0.197
Hispanic or Latino	7	14%	11	15%	18	15%		2	6%	7	23%	9	15%	
Non-Hispanic or Latino	30	61%	49	67%	79	65%		24	77%	20	65%	44	71%	
Not Specified	1	2%	4	5%	5	4%		5	16%	4	13%	9	15%	
Insurance Type (US only)†	n=43		n=70		n=113		0.354	n=30		n=30		n=60		0.600
Medicaid/SCHIP and/or Medicare	16	37%	24	34%	40	35%		12	40%	9	30%	21	35%	
Military health care (Tricare/VA)	3	7%	3	4%	6	5%		3	10%	2	7%	5	8%	
Not Specified	1	2%	5	7%	6	5%		0	0%	2	7%	2	3%	
Private health insurance	23	53%	38	54%	61	54%		15	50%	17	57%	32	53%	
Country of Residence							0.155							1.000
Ex-US	6	12%	3	4%	9	7%		1	3%	1	3%	2	3%	
US	43	88%	70	96%	113	93%		30	97%	30	97%	60	97%	
Diagnosing Specialist							0.387							0.468
Neurologist	39	80%	66	90%	105	86%		26	84%	27	87%	53	85%	
Oncologist	8	16%	5	7%	13	11%		5	16%	3	10%	8	13%	
Ophthalmologist	1	2%	1	1%	2	2%		0	0%	0	0%	0	0%	
Other	1	2%	1	1%	2	2%		0	0%	1	3%	1	2%	
Age at OMAS Onset	n=48		n=72		n=120		0.123							na
0-3y	46	96%	59	82%	105	88%	0.024‡	31	100%	31	100%	62	100%	
4-11y	1	2%	9	13%	10	8%	0.043‡	0	0%	0	0%	0	0%	
12-17y	0	0%	2	3%	2	2%		0	0%	0	0%	0	0%	
>=18y	1	2%	2	3%	3	3%		0	0%	0	0%	0	0%	
Immediate Family History														
Autoimmune Disorder	10	20%	29	40%	39	32%	0.025*	8	26%	8	26%	16	26%	1.000
Cancer	6	12%	7	10%	13	11%	0.641	5	16%	3	10%	8	13%	0.449
Psychiatric Disorder	21	43%	34	47%	55	45%	0.686	13	42%	12	39%	25	40%	0.796
Symptoms at Onset														
Ataxia	44	90%	64	88%	108	89%	0.718	28	90%	27	87%	55	89%	0.688
Myoclonus	33	67%	41	56%	74	61%	0.215	21	68%	22	71%	43	69%	0.783
Opsoclonus	36	73%	38	52%	74	61%	0.018*	21	68%	21	68%	42	68%	1.000
Tremors	23	47%	36	49%	59	48%	0.797	16	52%	19	61%	35	56%	0.442
Sleep	23	47%	37	51%	60	49%	0.685	14	45%	16	52%	30	48%	0.611
Temper	22	45%	31	42%	53	43%	0.790	12	39%	13	42%	25	40%	0.796
Vomiting	9	18%	21	29%	30	25%	0.191	5	16%	6	19%	11	18%	0.740
Fever	4	8%	10	14%	14	11%	0.347	2	6%	5	16%	7	11%	0.229
Headache	4	8%	7	10%	11	9%	0.788	1	3%	1	3%	2	3%	1.000

*p<0.05 by chi-square or exact test. ‡Column proportions that are significantly different by z-test. †Insurance type was assigned by hierarchy of Medicaid/SCHIP and/or Medicare -> Military Health Care -> Private health insurance.

FIGURE 3: Aggregate and Component Mitchell-Pike Severity Scores

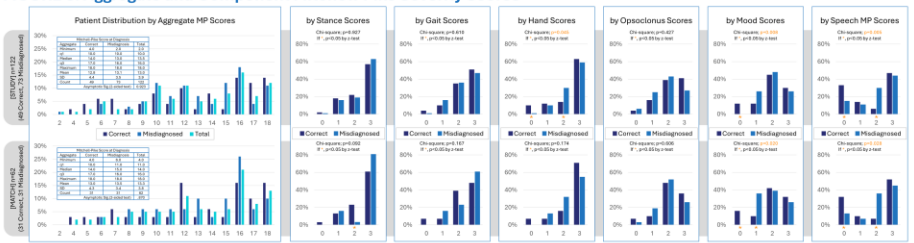
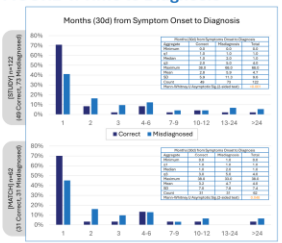


FIGURE 4: Time to Diagnosis



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