Consequences of Misdiagnosed Opsoclonus Myoclonus Ataxia Syndrome (OMAS)

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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 based upon opsoclonus at symptom onset, age at onset (4 levels), US residence, and immediate family history of autoimmune disease. "Correctly diagnosed" defined as patient and/or caregiver 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 of 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 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.

FIGURE 1: Patient Disposition

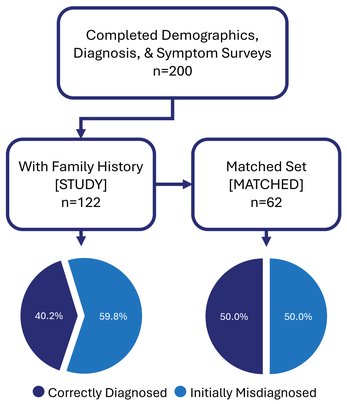


TABLE 2: Mitchell-Pike Severity

Mitchell-Pike (MP) Severity 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
	Can sit, but not stand, without support	2
	Requires using hands to prop or other support to sit	3
gait	Walking normal for age	0
	Mildly wide-based gait for age, walks independently	1
	Walks only or predominantly with support	2
	Unable to walk even with support	3
hand	Normal for age	0
	Mild, infrequent tremor or jerkiness, no functional impairment	1
	Fine motor function persistently impaired for age, but less precise manipulative tasks normal or almost normal	2
	Major difficulties in age-appropriate fine motor & manipulative tasks	3
opsoclonus	None	0
	Rare or only by fixation change or "squeeze test"	1
	Frequent, interferes intermittently with fixation or tracking	2
	Persistent, interfering continuously with function/ tracking	3
mood	Normal	0
	Mild irritability increase but consolable; and/or mild sleep troubles	1
	Irritability & 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 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

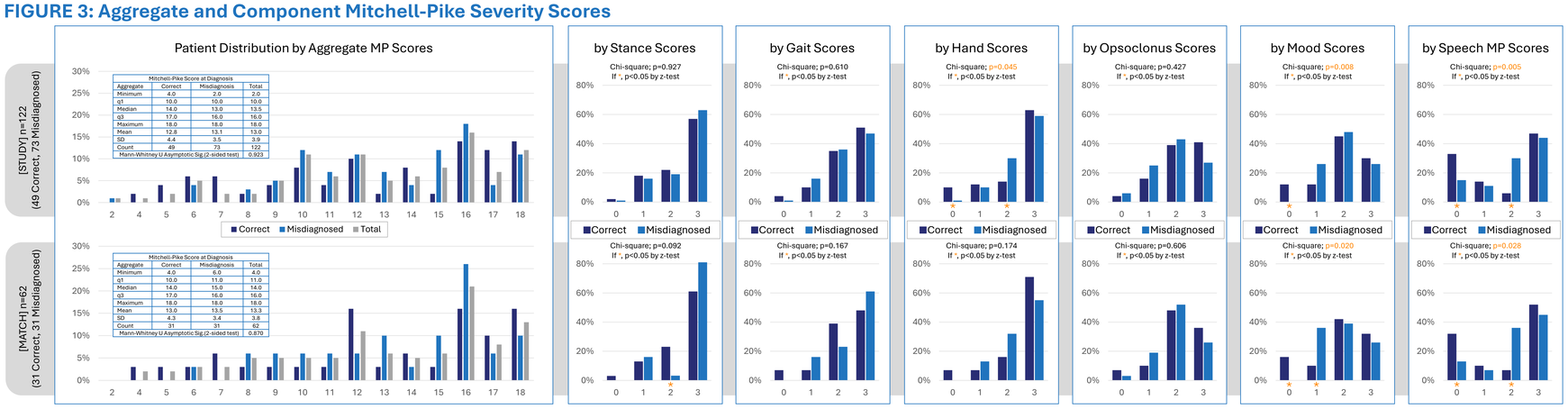
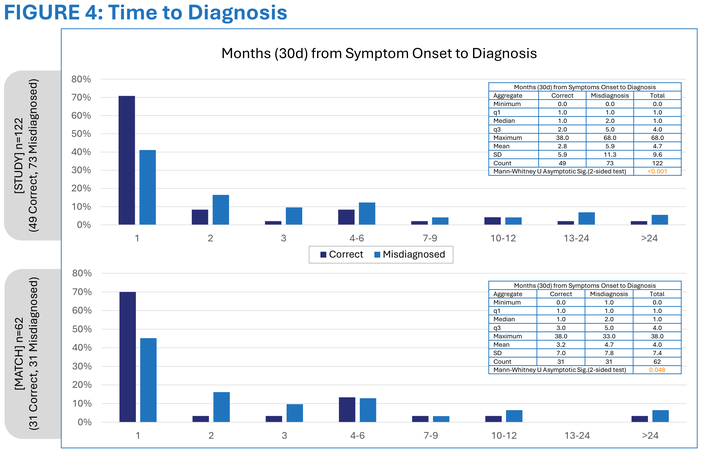


FIGURE 4: Time to Diagnosis



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