Incidence and Ocular Features of Pediatric Myasthenias

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• PURPOSE: **To report the incidence, demographics, and ocular findings of children with myasthenia.**
• DESIGN: **Retrospective cohort study.**
• METHODS: **The medical records of all children (< 19 years) examined at Mayo Clinic with any form of myasthenia from January 1 1966, through December 31, 2015, were retrospectively reviewed.**
• RESULTS: **A total of 364 children were evaluated during the study period, of which 6 children were residents of the Olmsted County at the time of their diagnosis, yielding an annual age- and sex-adjusted incidence of 0.35 per 100 000 < 19 years, or 1 in 285 714 < 19 years. The incidence of juvenile myasthenia gravis (JMG) and congenital myasthenic syndrome (CMS) was 0.12 and 0.23 per 100 000, respectively. Of the 364 study children, 217 (59.6%) had JMG, 141 (38.7%) had CMS, and 6 (1.7%) had Lambert-Eaton syndrome, diagnosed at a median age of 13.5, 5.1, and 12.6 years, respectively. A majority of the JMG and CMS patients had ocular involvement (90.3% and 85.1%, respectively), including ptosis and ocular movement deficits. Among children with at least 1 year of follow-up (JMG; median, 7.1 years, CMS; median, 7.0 years), improvement was seen in 88.8% of JMG patients (complete remission in 31.3%) and in 58.3% of CMS patients.**
• CONCLUSION: **Although relatively rare, myasthenia gravis in children has 2 predominant forms, CMS and JMG, both of which commonly have ocular involvement. Improvement is more likely in children with the juvenile form.** **(Am J Ophthalmol 2019;200:242–249. © 2019 Elsevier Inc. All rights reserved.)**

MYASTHENIA GRAVIS (MG) IS A CHRONIC AUTOIMmune disease characterized by fluctuating weakness and fatigability of the voluntary muscles of the body.[1] Pediatric myasthenia is a common term for disease onset prior to 19 years of age and includes both the autoimmune and inherited etiologies.[2] Pediatric myasthenia is divided into neonatal, congenital, and juvenile forms. Congenital myasthenic syndrome (CMS) includes a diverse group of inherited disorders, typically present at birth, caused by a defective signal transmission at the neuromuscular junction.[3] Juvenile myasthenia is caused by an ongoing production of autoantibodies directed against the postsynaptic membrane of the neuromuscular junction, whereas neonatal myasthenia is a transient condition occurring because of the passive transfer of antibodies from the myasthenic mother.[2]

Whereas adult MG is a more prevalent disease and has been studied in several populations, less is known about the juvenile form,[4,5] with incidence rates varying widely between geographic regions.[6–8] Even less is known concerning CMS. The purpose of this study is to describe the incidence, demographics, and ocular findings of MG observed in patients <19 years of age over a 50-year period.

METHODS

THE MEDICAL RECORDS OF ALL PATIENTS LESS THAN 19 YEARS of age who were diagnosed with any form of MG from January 1, 1966, through December 31, 2015, and examined at Mayo Clinic, Rochester, Minnesota, USA, were retrospectively reviewed. Patients diagnosed while residing in Olmsted County, Minnesota were identified using the resources of the Rochester Epidemiology Project, a medical record linkage system designed to capture data on any patient–physician encounter in Olmsted County, Minnesota.[9] The population of Olmsted County is relatively isolated from other urban areas and virtually all medical care is provided to its residents by Mayo Clinic, Olmsted Medical Group, and their affiliated hospitals. Institutional Review Board approval was obtained from Mayo Clinic and Olmsted Medical Group.

A diagnostic code search was performed using the Rochester Epidemiology Project and Mayo Clinic databases, applying a wide range of myasthenia-related codes so as to capture all patients with myasthenia. Of the 544 potential patients identified through the search, 145 were excluded because of incorrect diagnosis, 17 presented to Mayo Clinic facilities outside of Minnesota, 8 were not within the study period, 6 were 19 years or older at the time of diagnosis, and 4 had incomplete medical records. The remaining 364 patients were included in the study. Pediatric myasthenia patients included all patients with symptoms and/or signs of ocular or generalized weakness fulfilling the criteria of diagnosis of juvenile myasthenia

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TABLE 1. Historical and Demographic Characteristics of 364 Children Diagnosed With Myasthenia Gravis From 1966 Through 2015

Characteristic	N (%)			
	JMG (N = 217)	CMS (N = 141)	LEM (N = 6)	Overall (N = 364)
Sex				
Male	73 (33.6)	67 (47.5)	5 (83.3)	145 (39.8)
Female	144 (66.4)	74 (52.5)	1 (16.7)	219 (60.2)
Race				
African American	5 (2.3)	4 (2.8)	0 (0.0)	9 (2.5)
Asian	6 (2.8)	2 (1.4)	0 (0.0)	8 (2.2)
White	136 (62.7)	93 (66.0)	6 (100.0)	235 (64.4)
Unspecified	67 (30.9)	42 (29.8)	0 (0.0)	109 (29.9)
Prematurity[a]				
Yes	10 (4.6)	11 (7.8)	0 (0.0)	21 (5.8)
Family history				
Myasthenia	4 (1.8)	26 (18.4)	0 (0.0)	30 (8.2)
Consanguinity	0 (0.0)	3 (2.1)	0 (0.0)	3 (0.8)
Age at onset (years)				
Median (range)	12.8 (0.8-18.3)	0 (0.0-13.3)	9.5 (0.0-14.8)	5.8 (0.0-18.3)
Age at diagnosis (years)				
Median (range)	13.5 (0.9-18.8)	5.1 (0.0-18.9)	12.6 (7.6-18.7)	10.8 (0.0-18.9)
Symptoms at onset				
Weakness	71 (32.7)	37 (26.2)	5 (83.3)	113 (31.0)
Drooping of eyelids	111 (51.2)	45 (31.9)	1 (16.7)	157 (43.1)
Diplopia	52 (24.0)	0 (0.0)	1 (16.7)	52 (14.3)
Swallowing, chewing, speech difficulties	54 (24.9)	23 (16.3)	0 (0.0)	77 (21.2)
Floppy baby	1 (0.5)	21 (14.9)	0 (0.0)	22 (6.0)
Feeding difficulties	1 (0.5)	62 (44.0)	1 (16.7)	64 (17.6)
Respiratory difficulties	7 (3.2)	54 (38.3)	0 (0.0)	61 (16.8)
Involvement				
Ocular predominantly	49 (22.6)	0 (0.0)	0 (0.0)	49 (13.5)
Bulbar predominantly	4 (1.8)	0 (0.0)	0 (0.0)	4 (1.1)
Ocular and bulbar	16 (7.4)	0 (0.0)	0 (0.0)	16 (4.4)
Generalized	148 (68.2)	141 (100)	6 (100)	295 (81.0)
Vision				
Amblyopia	12 (5.5)	0 (0.0)	0 (0.0)	12 (3.3)
Ptosis at presentation				
Unilateral	29 (13.4)	8 (5.7)	1 (16.7)	38 (10.4)
Bilateral	113 (52.1)	95 (67.4)	2 (33.3)	210 (57.7)
Strabismus at presentation				
Esotropia	21 (9.7)	11 (7.8)	0 (0.0)	32 (8.8)
Exotropia	15 (6.9)	3 (2.1)	0 (0.0)	18 (4.9)
Vertical deviation	17 (7.9)	1 (0.7)	0 (0.0)	18 (4.9)
Strabismus, not specified	5 (2.3)	4 (2.8)	0 (0.0)	9 (2.5)
Limitation of (OD or OS or OU)				
Adduction	49 (22.6)	56 (39.7)	0 (0.0)	105 (28.9)
Abduction	54 (24.9)	66 (46.8)	0 (0.0)	120 (33.0)
Elevation	44 (20.3)	63 (44.6)	0 (0.0)	107 (29.4)
Depression	35 (16.1)	47 (33.3)	0 (0.0)	82 (22.5)

CMS = congenital myasthenic syndrome; JMG = juvenile myasthenia gravis; LEM = Lambert-Eaton myasthenia.
[a]Born at <37 weeks.

gravis (JMG), CMS, neonatal transient MG, or acquired Lambert-Eaton myasthenia (LEM).

The diagnosis of JMG was assigned when symptoms typical for MG were present, such as fatiguable ocular or generalized weakness with onset before 19 years of age, along with 2 of the following 3 features[6]: (1) antibodies against acetylcholine receptors (AchR) or muscle-specific kinase (MuSK), (2) electrophysiologic findings of decrement on

repetitive stimulation and/or increased jitter of single-fiber electromyography, and (3) response to administration of acetylcholinesterase inhibitor and/or immunomodulating therapy. A diagnosis of "probable JMG" was made when 1 of the 3 criteria was met in the setting of a clinical picture consistent with the diagnosis JMG by the treating neurologist or ophthalmologist. CMS was diagnosed on the basis of ocular or generalized weakness present from birth or early life along with any 1 of the following[3]: (1) supportive clinical or in vitro electrophysiologic studies, (2) supportive muscle biopsy findings, and (3) molecular genetic testing showing mutations in the CMS genes. The diagnosis of "probable CMS" was assigned when there was no supportive testing, but the clinical picture was considered consistent with the diagnosis of CMS by the treating neurologist or ophthalmologist. The diagnosis of transient neonatal MG was assigned when there were findings of weakness in the neonate born to a mother with MG, with AchR antibodies with resolution of weakness within 3 months.[1]

Each record was meticulously reviewed for confirmation of MG based on the criteria listed above. The 364 medical records were reviewed for demographics including sex, race, date of diagnosis, history of prematurity, date of onset, symptoms at onset, date of presentation, symptoms and signs at presentation, laboratory tests, imaging, electrophysiologic studies, genetic tests, and recommended treatment. The ophthalmic record was reviewed for visual acuity, ocular misalignment, extraocular movement abnormalities, and anterior and posterior segment findings. Longitudinal findings were collected from follow-up examinations and letters of communication from referring physicians as well as parent and patient questionnaires that were part of the medical record.

An outcome was designated as "complete remission" when a patient had no symptoms or signs for at least 1 year and received no therapy for MG during the same period, while "pharmacologic remission" referred to those patients who were symptom-free on medical therapy. "Minimal manifestation" included those patients who had no symptom of functional limitations caused by MG but had findings consistent with muscle weakness owing to either the disease itself or the use of immunosuppression and/or cholinesterase inhibitors. Since the treatment drugs themselves can cause muscle weakness as a side effect, "minimal manifestation" was made a separate category. Patients experiencing an improvement in signs and symptoms not included in any of the above 3 categories were considered "improved," while "unchanged" or "worsened" was defined for no change or worsening of signs and symptoms, respectively, between the initial and final follow-up evaluation.[10]

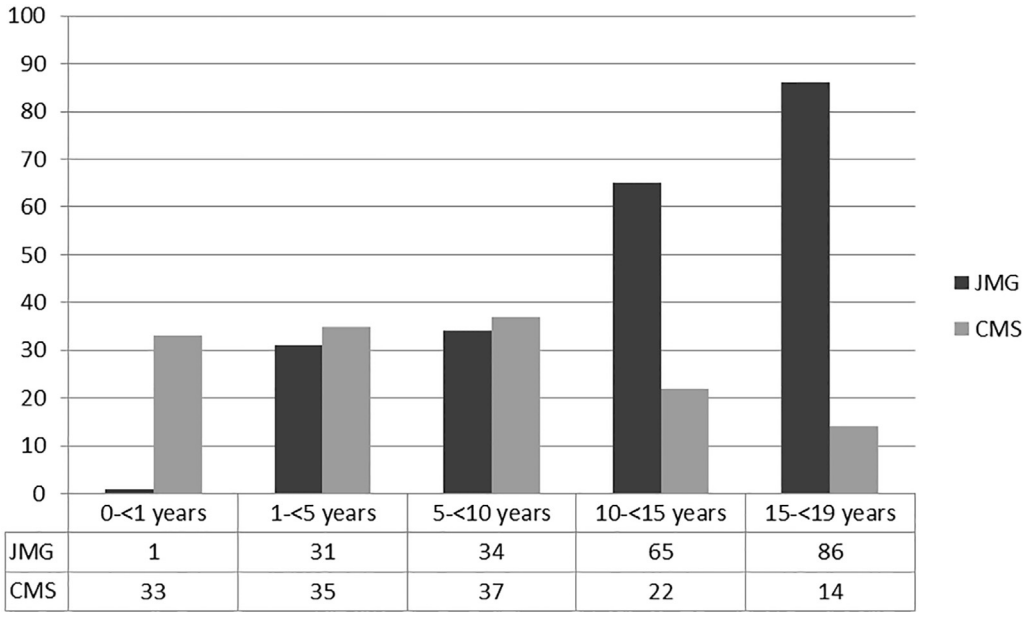
The prevalence and incidence of pediatric MG and its subtypes was estimated using the population figures in Olmsted County. Population figures for 1960, 1970, 1980, 1990, 2000, and 2010 were based on the U.S. census data, and population figures for the inter-census years were estimated by linear interpolation. These incidence rates were also age- and/or sex-adjusted to the 2010 census figures for the U.S. white population to enable comparison with national estimates. The 95% confidence interval for the overall incidence was then calculated to provide range of the true incidence. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc, Cary, North Carolina, USA).

RESULTS

THREE HUNDRED SIXTY-FOUR CHILDREN WERE EVALUATED for myasthenia during the 50-year study, of which 217 (59.6%) had JMG, 141 (38.7%) had CMS, and 6 (1.7%) had Lambert-Eaton syndrome (LES). Demographic features and ocular characteristics of the 364 patients are summarized in Table 1. Fourteen of the 217 JMG patients (6.5%) were diagnosed as probable JMG and 1 of the 141 CMS patients (0.7%) was diagnosed as probable CMS. There were no children with the diagnosis of neonatal transient myasthenia. Two hundred nineteen (60.2%) were female: 144 (66.4%) in the JMG cohort, 74 (52.5%) in the CMS cohort, and 1 (16.7%) in the LES cohort. CMS was diagnosed at a median age of 5.1 years (range, 0-18.9 years), whereas JMG was diagnosed at a median age of 13.5 years (range, 0.9-18.8 years), as illustrated in Figure 1. LES was diagnosed at a mean age of 12.6 years (range, 7.6-17.7 years). The median duration from onset of symptoms to diagnosis was 5.0 months (range, birth to 18.9 years).

Six of the 364 study children were residents of the Olmsted County at the time of their diagnosis, yielding an annual age- and sex-adjusted incidence of 0.35 (95% confidence interval: 0.07-0.63) per 100 000 <19 years, or 1 in 285 714 <19 years. Four children were diagnosed with CMS and 2 had JMG, with an incidence of 0.23 and 0.12 per 100 000 <19 years, respectively (95% confidence intervals: 0.005-0.46 and 0-0.28). There were no cases of neonatal MG or pediatric LEM in Olmsted County over the 50-year period. Both JMG children had ocular myasthenia and included 1 male and 1 female child. Three of the 4 CMS children were siblings, 2 female and 1 male, with postsynaptic disease and an abnormal beta subunit of acetylcholine receptors on muscle biopsy. If the 3 siblings with CMS are counted as a single family unit, the corrected annual age- and sex-adjusted incidence is 0.12 (95% confidence interval: 0.000-0.28) per 100 000 <19 years, or 1 in 50 582 live births. The final female patient with CMS had a synaptic form of the disease, with muscle biopsy showing endplate acetylcholinesterase deficiency. All 4 patients with CMS had generalized disease including extraocular movement limitation and bilateral ptosis.

The ocular features observed among the cohort of 364 children are shown in Table 1. At the time of onset, 180 (49.5%) had ocular symptoms by history, with 25 children (6.9%) presenting to the ophthalmologist first. Drooping



	0-<1 years	1-<5 years	5-<10 years	10-<15 years	15-<19 years
JMG	1	31	34	65	86
CMS	33	35	37	22	14

FIGURE 1. Age at diagnosis for 217 children with juvenile myasthenia gravis (JMG) and 141 children with congenital myasthenic syndrome (CMS) from 1966 through 2015 at Mayo Clinic.

eyelids was the most common symptom at onset in the JMG and CMS groups (51.2% and 31.9%, respectively). Ocular signs and symptoms occurred in 90.3% of children with JMG and in 85.1% of those with CMS, while ocular features alone occurred in 22.6% and 0.0%, respectively. On examination, strabismus in primary position was present in 45 of the 217 children with JMG (20.7%) and 18 of the 141 (12.8%) with CMS (Table 1). Esotropia was the most frequent form of misalignment (JMG: 9.7% and CMS: 7.8%). Extraocular limitation of movements was found in 66 (30.4%) and 75 (53.2%) patients in the JMG and CMS groups, respectively. Ptosis was present in 65.5%, 73.1%, and 50% in the JMG, CMS, and LEM groups, respectively, with Cogan's lid twitch occurring in 14 (3.8%) children, all in the JMG group. Amblyopia occurred in 12 (5.5%) patients in the JMG group.

Among the 217 children with JMG, electromyography was positive in 154 (82.8%), anticholinesterase serum antibodies occurred in 100 (68.5%), autoantibodies to muscle-specific tyrosine kinase (anti-MuSK) in 5 (26.3%), and antistriational antibodies in 2 (8.3%) (Table 2). Of the 194 (89.4%) children who were imaged, thymus enlargement was present on imaging in 15 (7.7%). Among the 141 children with CMS, electromyography was positive in 136 of 139 tested children (97.8%) and a causative gene mutation was identified in 37 of 45 children tested (82.2%). Of the 93 (66.0%) children in whom the level of transmission abnormality was identified by combined electrophysiologic and structural or genetic studies, postsynaptic acetylcholine receptor defect was the most common, seen in 51 patients (54.8%), followed by defects in endplate development and maintenance in 16 (17.2%). Fourteen (15.1%) had abnormalities in synaptic basal lamina associated proteins, 11 (11.8%) had abnormal presynaptic proteins, and 1 (1.1%) had defects in glycosylation. The ocular features among children with CMS were analyzed based on the level of transmission abnormality and are depicted in Table 3. All the children with LEM had diagnostic electromyographs, although only 2 of the 6 had positive Lambert-Eaton antibodies to the P/Q type calcium channels.

The median follow-up duration for the 364 cases was 3.0 years (range, birth to 50.4 years) and 3.7 years (range, birth to 46.1 years) for the JMG and CMS cohorts, respectively. One hundred thirty-four of the 217 children with JMG (61.8%) were followed for a minimum duration of 1 year with a median follow-up of 7.1 years (range, 1-50.4 years), while 96 of the 141 CMS patients (68.1%) were followed for a similar minimum duration, with a median of 7.0 years (range, 1.2-46.1 years). Sixty-seven of 134 JMG patients (50.0%) and 34 of 96 patients with CMS (35.4%) were determined by actual visits, while 67 of 134 (50.0%) and 62 of 96 (64.6%) were determined by letters of communication.

One hundred nineteen (88.8%) and 56 (58.3%) of patients with JMG and CMS, respectively, experienced some degree of improvement in symptoms from the initial presentation to the final follow-up. During this observation interval, complete remission occurred in 42 (31.3%) patients with JMG and in none of the patients with CMS, as expected. Figure 2 depicts the outcomes for the subgroups. Among the entire cohort of 364 children, 52

TABLE 2. Clinical Investigations of 217 Children Evaluated for Juvenile Myasthenia Gravis From 1966 Through 2015 at Mayo Clinic

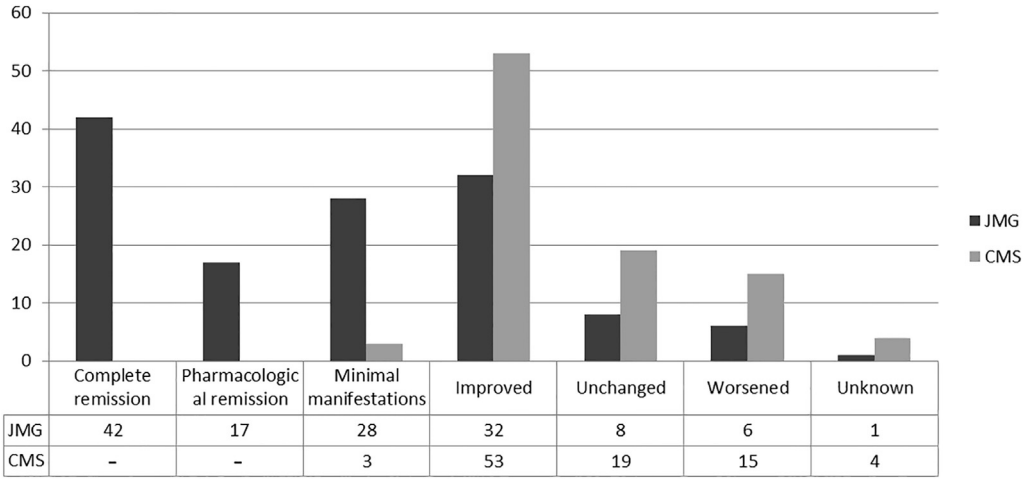
	N (%)				
	Ocular Myasthenia N = 49	Generalized Myasthenia N = 148	Predominantly Bulbar[a] N = 4	Predominantly Ocular and Bulbar[a] N = 16	Overall N = 217
Tensilon test					
Positive	36 (94.7)	86 (96.6)	3 (100)	8 (80.0)	133 (95.0)
Electromyography					
Positive	19 (47.5)	115 (91.3)	4 (100.0)	16 (100.0)	154 (82.8)
Imaging					
Thymus enlargement	2 (6.3)	13 (9.4)	0 (0.0)	0 (0.0)	15 (7.9)
Antibodies					
Anticholinesterase	20 (60.6)	73 (72.3)	1 (100)	6 (54.6)	100 (68.5)
Anti-MuSK	0 (0.0)	3 (2.0)	0 (0.0)	2 (12.5)	5 (2.3)
Antistriational	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	2 (0.9)
Seronegative	13 (39.4)	26 (25.7)	0 (0.0)	5 (45.5)	44 (30.1)

[a]Oropharyngeal muscle involvement.

TABLE 3. Ocular Findings Among 141 Children Diagnosed With Congenital Myasthenic Syndrome From 1966 Through 2015 at Mayo Clinic

	N (%)			Overall N = 141
	Ptosis	Extraocular Movement Limitation	Strabismus	
Presynaptic (n = 11)	7 (63.6)	2 (18.2)	2 (18.2)	
ChAT deficiency	1	1	1	1
SNAP25B	1	0	0	1
Unknown	5	1	1	9
Postsynaptic (n = 51)	46 (90.2)	46 (90.2)	4 (7.8)	
Alpha subunit defect	1	2	0	2
Beta subunit defect	3	3	0	3
Delta subunit defect	1	1	0	1
Epsilon subunit defect	9	9	1	9
Slow channel	11	12	3	14
Fast channel	2	2	0	2
Unknown	19	17	0	20
Synaptic (n = 14)	11 (78.6)	8 (57.1)	0 (0.0)	
Collagen Q mutation	1	0	0	1
Laminin B2 deficiency	1	1	0	1
Unknown	9	7	0	12
Endplate development and maintenance (n = 16)	12 (75.0)	3 (18.8)	7 (43.8)	
Dok- 7 myasthenia	3	1	0	4
Rapsn deficiency	8	2	7	11
MuSK deficiency	1	0	0	1
Defects of glycosylation (n = 1)				
DPAGT1 myasthenia	0	0	0	1
Indeterminate (n = 48)	36 (75.0)	22 (45.8)	8 (16.7)	48

(14.3%) received prolonged intubation (>7 days) at some point during their follow-up (JMG 10.1% and CMS 26.2%). Twelve patients (5.5%) with JMG required strabismus surgery, 2 (0.9%) were treated with botulinum toxin injections for strabismus, and 1 patient (0.5%) underwent ptosis repair surgery. Among the CMS patients, 3 (2.1%) underwent strabismus surgery, while 6 (4.3%) had surgery for ptosis.



	Complete remission	Pharmacological remission	Minimal manifestations	Improved	Unchanged	Worsened	Unknown
JMG	42	17	28	32	8	6	1
CMS	-	-	3	53	19	15	4

FIGURE 2. Outcomes for 134 children with juvenile myasthenia gravis (JMG) and 96 children with congenital myasthenic syndrome (CMS) followed for at least 1 year from 1966 through 2015 at Mayo Clinic.

DISCUSSION

IN THIS POPULATION-BASED STUDY OF CHILDREN OBSERVED over a 50-year period, the incidence of childhood myasthenia was 0.35 per 100 000 <19 years. The incidence of JMG and CMS were 0.12 and 0.23 per 100 000, respectively. Of the 364 study children, about 60% were found to have JMG while nearly 40% had CMS. LEM comprised less than 2% of the study cohort. Ocular involvement occurred in approximately 9 out of 10 patients with both JMG and CMS. Among those children observed for at least 1 year, most children improved including complete remission in only one third of children with JMG.

The incidence of JMG in this study is similar to Popperud and associates and Parr and associates, who reported an incidence of 1.6 per million and 1.5 per million, respectively,[6,11] but less than the 3.85-7.85 per million children reported by Tsai and associates in the Taiwanese population.[8] However, Asian populations have described a higher proportion of childhood-onset MG.[4] An epidemiologic study from Virginia in the United States describes the incidence of autoimmune MG as 9.1 per million per year, with 13.7% having onset prior to 19 years of age, although they did not report the incidence in the pediatric population.[12] A study based on voluntary reporting of cases from Canada reported an incidence of 0.9-2.0 per 1 million children per year, which was similar to our rate.[7]

Our incidence rate of CMS was as high as the rate of JMG in the current population. There are limited epidemiologic studies with which to compare these findings. One report from the United Kingdom observed a prevalence of 9.2 genetically confirmed cases per million under 18 years of age.[11] They included identified children from the laboratory performing genetic testing for CMS for all of the UK, and therefore they could have missed patients with clinical findings and other testing indicating CMS, but who had not had the CMS mutation determined.

The initial clinical and ocular features of the 217 children with JMG were generally similar to prior reports. Popperud and associates[6] and Parr and associates,[11] reporting on children diagnosed at a mean age of 13 years, reported similar findings in predominantly white populations, while Tsai and associates[8] reported younger age at diagnosis (mean 8.7 years) in an Asian population. There was, similar to prior studies,[8,11] a preponderance of female subjects in this cohort of patients. Atopic diseases and asthma were found to be more common in children with myasthenia in a previous study.[8] Though our study had no comparison cohort, the 6 (2.8%) and 10 (4.6%) of the JMG cohort had allergies and asthma, respectively. Fifteen (7.9%) of the study patients had evidence of thymic enlargement, while Tsai and associates found that none of their patients had benign or malignant tumor of the thymus.[8] This difference could be explained by referral patterns to our institution of complex myasthenia or for thymus surgery. Seventy-five percent of the children in our study had ocular symptoms of ptosis and diplopia at the time of onset of the disease. This finding is similar to Popperud and associates, who found that 69% had an initial ocular manifestation.[6] Amblyopia in our cohort was uncommon (5.5%) compared to Pineles and associates, who reported that 26% had amblyopia initially, declining to 3% after treatment.[10] Antibodies to acetylcholine receptors were positive in 82.8% of our patients overall and in 47.5% of our patients with ocular myasthenia, similar to the diagnostic sensitivity in adult populations.[13] Rates of remission reported in literature vary widely from 12% to 70% in various populations, with our findings (31.3%) being similar to Pineles and associates (26%), although they included only ocular myasthenia patients.[14–16]

Similarly, the clinical and ocular features of CMS in this cohort were not unlike prior reports. Among our CMS

group, the median age at onset was at birth, which is similar to previous studies.[17] There was, similar to previous studies, nearly equal distribution among the 2 sexes.[11] A previous study performed from Mayo Clinic described a series of 295 patients with CMS, which included patients that were investigated at Mayo using DNA sent by other centers but not necessarily examined. Among the CMS study cohort, a large majority had ptosis across most subtypes, while about half demonstrated ophthalmoparesis, similar to what has been described previously in literature.[17,18] We found that three fourths of our patients had an unchanged or improved course. Regarding other types of myasthenia, we found no patients in the population-based cohort with LES and very few patients with confirmed antibody-positive LEM overall (2 cases over a 50-year period), similar to a recent report.[19] We did not report a single case of neonatal autoimmune myasthenia, similar to a study in the UK that found neonatal myasthenia to be extremely rare (3 children per year).[11]

There are a number of limitations to the findings of this study. Its retrospective design is limited by incomplete data and variable follow-up. Second, serology studies to detect anticholinesterase antibodies were not available during the early years of this study and thus, many children at that time were diagnosed based on clinical features alone. Additionally, because the definition of pediatric myasthenia gravis evolved over the 50-year study period, we retrospectively applied diagnostic criteria in a uniform manner to each medical record to establish the diagnosis. The incidence rate from this cohort may be lower than the true value because some children with mild disease may have gone unnoticed and some residents of Olmsted County may have sought care outside the study catchment area. Similarly, not all patients were examined by an ophthalmologist. While this report is only the second study to assess epidemiologic data on CMS, the measured confidence interval was wide and included the value of zero. A small total population like that of Olmsted County makes it difficult to study rare diseases and therefore, we chose to extend the database over a 50-year period. Additionally, longitudinal data collected from local physician letters and patient communications may be prone to inaccuracies. However, because our institution is a referral center, we felt it important to include data from the referring physician letters to minimize the referral bias inherent in including only those patients seen in follow-up at our institution. If the letter of communication did not contain sufficient evidence to categorize an outcome based on our definitions, the patient was excluded from our outcome assessment. Finally, given the small number of Olmsted County residents, the findings in this population may not be generalizable to other populations.

Pediatric myasthenia gravis was found to occur rarely in this population and was principally composed of 2 predominant forms: congenital myasthenic syndrome and juvenile myasthenia gravis. JMG was more prevalent among girls while CMS was nearly equally distributed among the sexes. Eighty-five percent to 90% had ocular involvement during the course of the disease. Complete remission occurred in about one third of the children with JMG and in none of the children with CMS during the study period.

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REFERENCES

1. Berrih-Aknin S, Frenkian-Cuvelier M, Eymard B. Diagnostic and clinical classification of autoimmune myasthenia gravis. *J Autoimmun* 2014;48-49:143–148.
2. Evoli A. Acquired myasthenia gravis in childhood. *Curr Opin Neurol* 2010;23(5):536–540.
3. Engel AG, Shen X-M, Selcen D, Sine SM. Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. *Lancet Neurol* 2015;14(4):420–434.
4. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in myasthenia gravis. *BMC Neurol* 2010;10:46.
5. Lee HN, Kang H-C, Lee JS, et al. Juvenile myasthenia gravis in Korea: subgroup analysis according to sex and onset age. *J Child Neurol* 2016;31(14):1561–1568.
6. Popperud TH, Boldingh MI, Brunborg C, et al. Juvenile myasthenia gravis in Norway: a nationwide epidemiological study. *Eur J Paediatr Neurol* 2017;21(2):312–317.
7. VanderPluym J, Vajsar J, Jacob FD, Mah JK, Grenier D, Kolski H. Clinical characteristics of pediatric myasthenia: a surveillance study. *Pediatrics* 2013;132(4):e939–e944.
8. Tsai J-D, Lin C-L, Shen T-C, Li T-C, Wei C-C. Increased subsequent risk of myasthenia gravis in children with allergic diseases. *J Neuroimmunol* 2014;276(1-2):202–206.
9. Kurland LT, Molgaard CA. The patient record in epidemiology. *Sci Am* 1981;245(4):54–63.
10. Pineles SL, Avery RA, Moss HE, et al. Visual and systemic outcomes in pediatric ocular myasthenia gravis. *Am J Ophthalmol* 2010;150(4):453–459.e3.
11. Parr JR, Andrew MJ, Finnis M, Beeson D, Vincent A, Jayawant S. How common is childhood myasthenia? The

UK incidence and prevalence of autoimmune and congenital myasthenia. *Arch Dis Child* 2014;99(6):539–542.
12. Phillips LH, Torner JC, Anderson MS, Cox GM. The epidemiology of myasthenia gravis in central and western Virginia. *Neurology* 1992;42(10):1888–1893.
13. Evoli A. Myasthenia gravis: new developments in research and treatment. *Curr Opin Neurol* 2017;30(5):464–470.
14. Morita MP, Gabbai AA, Oliveira AS, Penn AS. Myasthenia gravis in children: analysis of 18 patients. *Arq Neuropsiquiatr* 2001;59(3-B):681–685.
15. Raksadawan N, Kankirawatana P, Balankura K, Prateepratana P, Sangruchi T, Atchaneeyasakul L-O. Childhood onset myasthenia gravis. *J Med Assoc Thai* 2002;85(Suppl 2):S769–S777.
16. Gui M, Luo X, Lin J, et al. Long-term outcome of 424 childhood-onset myasthenia gravis patients. *J Neurol* 2015;262(4):823–830.
17. Aharoni S, Sadeh M, Shapira Y, et al. Congenital myasthenic syndrome in Israel: genetic and clinical characterization. *Neuromuscul Disord* 2017;27(2):136–140.
18. Abicht A, Dusl M, Gallenmuller C, et al. Congenital myasthenic syndromes: achievements and limitations of phenotype-guided gene-after-gene sequencing in diagnostic practice: a study of 680 patients. *Hum Mutat* 2012;33(10):1474–1484.
19. Morgan-Followell B, de Los Reyes E. Child neurology: diagnosis of Lambert-Eaton myasthenic syndrome in children. *Neurology* 2013;80(21):e220–e222.