Clinical Characteristics of Pediatric Myasthenia: A Surveillance Study

AUTHORS: Juliana VanderPluym, MD, a Jiri Vajsar, MD, b Francois Dominique Jacob, MD, c Jean K. Mah, MD, c Danielle Grenier, MD, d and Hanna Kolski, MD  

aDivision of Neurology, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada; bDivision of Neurology, Department of Pediatrics, SickKids and University of Toronto, Toronto, Ontario, Canada; cDivision of Neurology, Department of Pediatrics, University of Calgary, Calgary, Alberta, Canada; and dCanadian Pediatric Society, Ottawa, Ontario, Canada

KEY WORDS
myasthenia gravis, congenital myasthenic syndromes, incidence

ABBREVIATIONS
AChR—acetylcholine receptor
DMS—congenital myasthenic syndromes
CPSP—Canadian Paediatric Surveillance Program
IVIg—intravenous immunoglobulin
JMG—juvenile myasthenia gravis
MuSK—muscle-specific kinase

Dr VanderPluym carried out the data analyses and drafted the initial manuscript; Dr Vajsar collaborated on the study design, obtained funding, and reviewed the manuscript; Dr Jacob participated in the design of the study and the data collection instruments and reviewed and revised the manuscript; Dr Mah collaborated on the study design, contributed to data collection, and reviewed the manuscript; Dr Grenier reviewed and commented on the initial study protocol and detailed questionnaire and reviewed and revised the manuscript; Dr Kolski conceptualized and designed the study, obtained funding, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-0814
doi:10.1542/peds.2013-0814

Accepted for publication Jul 2, 2013

Address correspondence to Dr Juliana VanderPluym, Department of Pediatric Neurology, University of Alberta, 3-574A ECHA 11405-87 Ave, Edmonton, AB T6G 1C9, Canada. E-mail: juliana.vanderpluym@albertahealthservices.ca

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2013 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: The authors gratefully acknowledge the monetary support of the Tara and Bobby Disenhouse Fund (Sick Kids Foundation, Toronto, Canada), Myasthenia Gravis Ontario Chapter, Muscular Dystrophy Canada, an unrestricted educational grant from Talecris Biotherapeutics, and a University of Alberta subspecialty residents research grant.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

WHAT’S KNOWN ON THIS SUBJECT: Pediatric myasthenia encompasses a group of rare and underdiagnosed conditions affecting the neuromuscular junction. Symptoms include fluctuating skeletal muscle weakness, which can progress to respiratory failure if left untreated. The autoimmune form of this condition, in particular, is treatable.

WHAT THIS STUDY ADDS: This study describes the incidence, clinical features, diagnostic testing, and treatment trends of pediatric myasthenia in Canada, which have not been previously reported in the literature.

abstract

OBJECTIVE: To evaluate the incidence, clinical features, diagnostic, and treatment trends of pediatric myasthenia in Canada.

METHODS: Through established Canadian Pediatric Surveillance Program methodology, physicians were anonymously surveyed for cases of pediatric myasthenia using a standardized clinical questionnaire containing deidentified data. Inclusion criteria were any child <18 years old with ≥1 of the following: (1) fluctuating ptosis or extraocular weakness, (2) skeletal muscle weakness or fatigue, and (3) any of the following supportive tests: clinical response to acetylcholinesterase inhibitor, positive antibodies, abnormal slow repetitive nerve stimulation, or single-fiber electromyography.

RESULTS: In 2 years of surveillance, 57 confirmed cases were reported. There were 34 generalized and 18 ocular reports of juvenile myasthenia gravis plus 5 congenital myasthenic syndrome cases. There were 14 incident cases in 2010 and 6 in 2011. Age of onset ranged from “birth” to 17 years for the generalized form compared with 18 months to 11 years for the ocular subtype. Positive acetylcholine receptor titers were found in 22 (67%) of 33 generalized cases and 8 (44%) of 18 ocular patients. Of patients started on pyridostigmine, improvement was noted in 33 (100%) of 33 generalized cases and 15 (88%) of 17 ocular cases.

CONCLUSIONS: This study represents the largest descriptive series of pediatric myasthenia in North America and provides valuable information about clinical characteristics. A high index of suspicion is important for this treatable disease. Children generally respond promptly to readily available therapies. Pediatrics 2013;132:1–6
Pediatric myasthenia, first described by Erb in 1879, is a heterogeneous group of acquired and genetic conditions of the neuromuscular junction. These rare and underrecognized disorders are classified broadly into 3 categories: juvenile myasthenia gravis (JMG), congenital myasthenic syndromes (CMS), and transient neonatal myasthenia gravis. JMG is the most common myasthenic disorder affecting children, representing 10% to 15% of all myasthenia gravis cases in North America and up to 50% of cases from Asia. JMG encompasses a group of autoimmune antibody-mediated disorders targeting neuromuscular junction proteins, preventing nerve impulse transmission to muscle. The most commonly identified antibodies target the acetylcholine receptors (AChRs) or, more rarely, the muscle-specific kinase (MuSK) receptors. The clinical hallmark of the disease is fluctuating and fatigable skeletal muscle weakness, which improves with rest. Clinical features may include predominantly ocular symptoms with ptosis, ophthalmoplegia, and/or diplopia; bulbar symptoms with dysphagia and/or dysphonia; and/or general symptoms with exercise intolerance and weakness. If left untreated, JMG may progress to respiratory distress and subsequent respiratory failure. Affected children are also at an increased risk for other autoimmune diseases, such as rheumatoid arthritis, juvenile diabetes mellitus, asthma, thyroid disease, and chronic inflammatory demyelinating polyneuropathy. Transient neonatal myasthenia gravis refers to the self-limited condition caused by the transfer of maternal AChR antibodies across the placenta. Affected infants may exhibit ptosis, facial weakness, a weak cry, feeding difficulty, generalized weakness, hypotonia, and/or respiratory insufficiency. Treatment is largely supportive, with resolution typically within a few weeks.

The CMS represent a group of rare genetic conditions affecting proteins expressed at the neuromuscular junction. They have been classified based on the site of neuromuscular transmission defect: presynaptic, postsynaptic, or synaptic. Clinical features may include hypotonia, limb contractures, and delayed motor milestones in children with weak and small underdeveloped muscles. In some cases, the presentation may mimic congenital myopathies, muscular dystrophies, or metabolic myopathies.

The diagnosis of myasthenic disorders in children is based mainly on clinical presentation and supported by serum antibody testing, genetic testing, positive edrophonium chloride (Tension) testing, and/or abnormal electrodiagnostic studies, including single-fiber electromyography and/or repetitive nerve stimulation. These conditions are often underrecognized and misdiagnosed, with pediatric patients often being symptomatic for years before the diagnosis is made. A strong index of suspicion is needed for appropriate investigation and prompt diagnosis, as there are effective treatments for the autoimmune form and some CMS. There is limited information on the incidence and clinical features of pediatric myasthenia in the Canadian population and, hence, the objectives of this study were to (1) determine the incidence of JMG and (2) characterize the clinical features, diagnostic, and treatment trends of pediatric myasthenia gravis in Canada.

METHODS

Cases of pediatric myasthenia were reported to the Canadian Pediatric Surveillance Program (CPSP) from January 1, 2010, through December 31, 2011. The CPSP is a national active surveillance program using a voluntary 2-tiered reporting process that tracks a variety of pediatric illnesses. More than 2500 practicing Canadian pediatricians and pediatric subspecialists, including neurologists, are surveyed by the CPSP on a monthly basis for cases. The initial “check-form” is returned on a monthly basis to the CPSP office even if no new cases are identified. A detailed clinical questionnaire is completed for reported cases to gather additional anonymous information about patient demographics, family medical history, clinical presentation, investigations, initial treatments, and short-term outcome for the patient. During 2010 and 2011, the CPSP overall reporting rate was 80% for the initial “check-form” and 86% for the detailed questionnaire.

Research ethics board approval for this study was obtained through the University of Alberta Health Research Ethics Board.

Patients were considered eligible for inclusion if they were <18 years old with >1 of the following clinical features: unilateral or bilateral fluctuating ptosis, unilateral or bilateral fluctuating extraocular muscle weakness, and/or skeletal muscle weakness or fatigue and any of the following supportive tests: Tension test or other acetylcholinesterase inhibitor administration demonstrating reversal of weakness, elevated AChR or MuSK antibody levels, abnormal nerve conduction studies demonstrating defect in neuromuscular junction transmission, or abnormal single-fiber electromyography. Exclusion criteria included underlying primary muscle, nerve, or metabolic diseases. Cases of transient neonatal myasthenia were excluded as they were beyond the scope of this study.

RESULTS

Over the 2-year study period, 64 suspected cases of pediatric myasthenia were reported to the CPSP, of which 57 were confirmed as per the study case definition. Reports were received from Alberta, Manitoba, Ontario, Quebec, and Newfoundland. The remaining 7 were
excluded for the following reasons: duplicate reporting (4 cases), insufficient information to confirm a case diagnosis (2 cases), and an alternate diagnosis (1 case). There were 34 cases of generalized JMG, 18 cases of exclusively ocular JMG, and 5 cases of CMS. The 5 cases of CMS included 1 genetically confirmed case of choline acetyltransferase deficiency, 1 slow-channel CMS, 1 Rapsyn mutation, and 2 of unknown subtype.

The clinical characteristics of the 52 cases of JMG are presented in Table 1. Of these, 20 were newly diagnosed cases in the 2-year study period, including 14 incident cases in 2010 (10 generalized and 4 ocular) and 6 in 2011 (3 generalized and 3 ocular). Reported age of symptom onset for JMG ranged from “birth” to 17 years (median 10 years) for the generalized form compared with 18 months to 11 years (median 3½ years) for the ocular type. The ratio of girls to boys was 1.1:1 in the generalized group and 2.6:1 in the younger ocular group. Children in the generalized group were predominantly white (59%) compared with the ocular group, which was predominantly Asian (44%). Two antibody-positive patients also had a diagnosis of Graves disease (1 generalized case and 1 ocular case). Another patient with generalized JMG had elevated antimicrosomal antibodies. Two patients (1 generalized and 1 ocular) had a family history of thyroid disease. Ptosis was the most common symptom reported among both the patients with generalized and with ocular JMG (82% and 100%, respectively). Among the patients with generalized JMG, swallowing/chewing difficulty (65%) and fatigue (62%) were the next most commonly reported symptoms. In regard to physical examination, bilateral ptosis was the most common physical finding in both the patients with generalized (76%) and ocular (56%) JMG. Among the patients with generalized JMG, 18% presented with respiratory distress and 6% in respiratory failure.

As shown in Table 2, 97% of patients with generalized JMG and 100% of patients with ocular JMG were tested for AChR antibodies, and positive titers were found in only 67% and 44%, respectively. Twelve patients with JMG (10 generalized and 2 ocular) were tested for MuSK antibodies; all were negative. The Tensilon test was performed in 47% of generalized cases and in 39% of ocular cases and results were abnormal in 88% and 100%, respectively. Nerve conduction studies were performed in 76% of generalized cases and 39% of ocular JMG cases, with abnormal results found in 65% and 43%, respectively.

Comparison of features of prepubertal JMG (age <12 years at symptom onset; 40 patients) and pubertal/postpubertal JMG (age ≥12 years at symptom onset; 12 patients) are described in Table 3. The prepubertal group demonstrates an almost 50:50 split between generalized and ocular presentation and a 1.4:1 female-to-male ratio compared
with the pubertal/postpubertal group, which has 100% generalized presentation and a 2:1 female-to-male ratio. Among the patients with generalized JMG who were tested for AChR antibodies, there was higher percentage of seropositivity in the pubertal/postpubertal group (92% vs 52%). However, there is a higher percentage of short-term remission in the prepubertal group (63% vs 25%).

Treatment information (Table 2) was available for 33 of 34 patients with generalized JMG. All were started on pyridostigmine and all demonstrated improvement. Of the 18 patients who received steroids, improvement was cited in 94%. Of the 21 patients administered intravenous immunoglobulin (IVIg), there was reported improvement in 88%. For patients with exclusively ocular presentations, 17 of 18 patients received it.

TABLE 2 Diagnostic Tests and Treatment of Generalized and Ocular JMG

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Generalized JMG n = 34 (%)</th>
<th>Ocular JMG n = 18 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performed</td>
<td>Percent Abnormal</td>
<td>Performed</td>
</tr>
<tr>
<td>AChR antibody</td>
<td>33 (97)</td>
<td>67</td>
</tr>
<tr>
<td>MuSK antibody</td>
<td>10 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Tension test</td>
<td>16 (47)</td>
<td>88</td>
</tr>
<tr>
<td>Nerve conduction study</td>
<td>26 (76)</td>
<td>65</td>
</tr>
<tr>
<td>Electromyography</td>
<td>4 (12)</td>
<td>75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Short-term treatment</th>
<th>Administered</th>
<th>Percent Response</th>
<th>Administered</th>
<th>Percent Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridostigmine</td>
<td>33 (97)</td>
<td>100</td>
<td>17 (94)</td>
<td>88</td>
</tr>
<tr>
<td>Steroid</td>
<td>18 (53)</td>
<td>94</td>
<td>10 (56)</td>
<td>100</td>
</tr>
<tr>
<td>IVIg</td>
<td>21 (62)</td>
<td>81</td>
<td>2 (11)</td>
<td>50</td>
</tr>
</tbody>
</table>

TABLE 3 Comparison of Prepubertal and Pubertal/Postpubertal Features of JMG

<table>
<thead>
<tr>
<th>Type of JMG</th>
<th>Prepubertal Onset of JMG n = 40 (%)</th>
<th>Pubertal/Postpubertal Onset of JMG n = 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized</td>
<td>22 (55)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Ocular</td>
<td>18 (45)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (43)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (57)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>AChR-positive titers in generalized JMG</td>
<td>11/21 (52)</td>
<td>11 (92)</td>
</tr>
<tr>
<td>Short-term remission</td>
<td>25 (63)</td>
<td>3 (25)</td>
</tr>
</tbody>
</table>

DISCUSSION

The national minimum incidence of JMG is 2.0 and 0.9 new cases per 1 million children per year in 2010 and 2011, respectively, based on estimates of the total Canadian pediatric population (0 to 17 years old) as reported by CANSIM from Statistics Canada. The only other study to report the incidence of myasthenia gravis in a North American population was Phillips et al, which reported a total population incidence for all ages (pediatric and adult) of 9.1 per 1 million total population. Among the patients presented by Phillips et al, 4.2% were between 0 and 9 years of age at presentation and 9.5% were between 9 and 19 years of age at presentation. The majority of previous studies describing the incidence of myasthenia gravis relied on retrospective chart reviews from European countries. None of the previous studies focused on the incidence of pediatric myasthenia gravis but rather all ages with subsequent division into age groups. A study conducted in Croatia from 1976 to 1996 found the incidence of myasthenia gravis among patients aged 0 to 19 years to be 1.4 per 1 million per year based on retrospective review of database records looking for typical history with appropriate clinical features, improvement with acetylcholinesterase drugs, reduction in muscle amplitude on repetitive nerve stimulation and detection of AChR antibodies. A similar estimate for patients aged 0 to 19 years of 2.2 per 1 million per year with 95% confidence limits of 1.4 and 3.4 was obtained in Tanzania, Africa, based on prospective study from 1988 to 1998 looking at clinical diagnosis based on positive fatigue test or Tensilon test.

In this cohort, physicians established a diagnosis of pediatric myasthenia based on clinical features and supportive testing including the presence of antibodies, Tensilon test or robust response to acetylcholinesterase inhibitor administration, and/or abnormal electrodiagnostic studies. AChR antibody testing is often the first investigation pursued, as it is widely available to pediatricians and pediatric specialists. While AChR antibodies are found in 80% of adults with myasthenia gravis, numerous studies including this current study have demonstrated a high percentage of seronegativity among pediatric myasthenia patients, especially in prepubertal patients or those with isolated ocular JMG. If a child is negative for AChR antibodies and has a history of early onset of symptoms, the possibility of CMS should be raised. Between 40% and 50% of adult patients who are negative for AChR are found to have antibodies against MuSK. MuSK-positive myasthenia gravis appears to be a distinct subtype of myasthenia gravis, which is
more common in female patients and has a more severe disease course with prominent bulbar and respiratory muscle involvement. MuSK-positive myasthenia gravis is very rare in children.\textsuperscript{21} All of the 12 children in this cohort tested for MuSK antibodies were negative. Additional diagnostic testing, including Tensilon and electrodiagnostic testing, may be complicated in pediatric patients. This is partly due to patient tolerability and compliance with testing, sometimes requiring sedation for electrodiagnostic testing. Also, it is limited by availability of specialists to perform the tests. For example, Tensilon testing requires adjusted dosing, cardiorespiratory monitoring, and extra caution if there is any suspicion of CMS (e.g., AChR slow channel mutation or \textit{COLQ} mutation) as such patients may clinically worsen with exposure to acetylcholinesterase inhibitors.\textsuperscript{18}

The clinical features of JMG in the current study revealed a predominance of generalized (65%) compared with exclusively ocular (35%) JMG. Of those with generalized presentation, there was a subtle female predominance, older age of onset (median 10 years), and predominantly white ethnicity (59%). The ocular patients had a more pronounced female predominance, younger age of onset (median 3½ years), and predominantly Asian ethnicity (44%). The female predominance and younger age of onset of ocular JMG are in keeping with the results reported by Sriudomkajorn et al in Thailand. Their patients presented mainly with ocular symptoms (84.3%) at a mean age of 4.1 years.\textsuperscript{22} Compared with studies describing pediatric myasthenia from China, Korea, Jamaica, Europe, and India,\textsuperscript{23–27} whose populations are more ethnically uniform, the current study is unique in that the Canadian population is ethnically diverse. Consequently, the differences in terms of gender, age of onset, and subtype of myasthenia gravis likely reflect differences in the ethnic backgrounds and associated genetic susceptibility between the populations. HLA antigen plays a key role in several autoimmune diseases and has been associated with myasthenia gravis. For example, HLA-DR3 and -B8 are associated with 60% of white adult myasthenia gravis patients.\textsuperscript{19,26} Given the higher incidence of other autoimmune diseases in individuals with myasthenia gravis, especially those that are seropositive for AChR,\textsuperscript{29} it is prudent to perform basic screening especially for diabetes and thyroid disease; we reported 2 patients with a concurrent diagnosis of Graves disease and 2 patients with family history of thyroid disease.

Precubertal patients had distinctive clinical features compared with the pubertal/postpubertal group, who share more features with adult-onset myasthenia gravis. As reported in the literature, the precubertal patients were more likely to present with isolated ocular symptoms compared with the overwhelming generalized presentation among pubertal/postpubertal patients.\textsuperscript{14,16,17} An emerging female preponderance in the precubertal/postpubertal group (female-to-male ratio 2:1) compared with the prepubertal group (ratio 1.4:1) was noted. Among patients with generalized JMG tested for AChR antibodies, 92% of the pubertal/postpubertal patients were positive compared with 52% of the precubertal group, in keeping with reports of 50% to 71% seropositivity among precubertal patients, 68% to 92% seropositivity among pubertal patients, and 80% to 90% seropositivity among postpubertal/adult patients.\textsuperscript{14,17,30}

As well, the precubertal group showed a higher rate of short-term remission compared with the pubertal/postpubertal group, in keeping with reports by Andrews et al\textsuperscript{14} and Evoli et al.\textsuperscript{30} This study has a number of limitations. The estimated minimum incidence of pediatric myasthenia is based on a survey given to pediatricians and pediatric subspecialists, including neurologists. Consequently, patients who are followed by family physicians or adult neurologists could be missed. Additionally, despite the survey being nationally administered, responses were received from only 5 of 10 provinces and none of the 3 territories. However, the provinces that responded are among the most highly populated, representing 78% of the total Canadian population based on estimates of population per year (2010 and 2011) per province as reported by CANSIM from Statistics Canada.\textsuperscript{31} Though mechanisms are in place to improve the level of reporting, such as reminders to physicians, it nonetheless requires physicians to voluntarily participate. In addition, the reporting system relies on the primary care physician to accurately report all the pertinent data, as it is not possible for the study group to review each patient chart to confirm the data. It is clear, however, that the diagnosis in reported cases would be accurate as part of the inclusion definition required positive supportive testing. This included a convincing positive therapeutic response to acetylcholinesterase inhibitors, which would capture a small but documented subset of children who have negative supportive testing by antibodies and electrodiagnostic studies but have an appropriate clinical history and respond to treatment with pyridostigmine.\textsuperscript{19} Given the survey design, long-term follow-up of treatment outcome and disease progression was not available and both warrant investigation in the future.

**CONCLUSIONS**

This study represents the largest exclusively pediatric descriptive series in North America and the first population-based study to systematically evaluate
incidence of pediatric myasthenia gravis across Canada. The CPSP study results validate data currently reported in the literature. Given Canada's ethnic diversity, physicians will see patients from a variety of ethnic backgrounds with varying genetic susceptibilities and consequently see differences in terms of gender, age of onset, and type of myasthenia gravis in the different patient groups. A high index of suspicion is important for this treatable disease as a significant percentage of patients, especially in the exclusively ocular subtype, demonstrated negative titers of AChR antibodies, which is often the first and may be the only diagnostic test pursued. Pediatric patients generally respond to standard therapies in the short term, including pyridostigmine, prednisone, and IV Ig.

ACKNOWLEDGMENTS
The authors wish to thank all the physicians who reported patients to the CPSP as well as Bobby and Tara Disenhouse for their support of this project.

REFERENCES
Clinical Characteristics of Pediatric Myasthenia: A Surveillance Study
Juliana VanderPluym, Jiri Vajsar, Francois Dominique Jacob, Jean K. Mah, Danielle Grenier and Hanna Kolski
Pediatrics originally published online September 9, 2013;

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/early/2013/09/04/peds.2013-0814">http://pediatrics.aappublications.org/content/early/2013/09/04/peds.2013-0814</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="https://shop.aap.org/licensing-permissions/">https://shop.aap.org/licensing-permissions/</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://classic.pediatrics.aappublications.org/content/reprints">http://classic.pediatrics.aappublications.org/content/reprints</a></td>
</tr>
</tbody>
</table>
Clinical Characteristics of Pediatric Myasthenia: A Surveillance Study
Juliana VanderPluym, Jiri Vajsar, Francois Dominique Jacob, Jean K. Mah, Danielle Grenier and Hanna Kolski

Pediatrics originally published online September 9, 2013;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/early/2013/09/04/peds.2013-0814