Thieme

Juvenile Myasthenia Gravis

Authors
Adela Della Marina, Ulrike Schara

Affiliation
Myasthenie Zentrum für Kinder und Jugendliche, Abteilung für Neuropädiatrie, Kinderklinik I, Universitätsklinikum Duisburg- Essen

Key words
juvenile myasthenia gravis, clinical symptoms, therapy

Bibliography
DOI https://doi.org/10.1055/s-0043-120334
Neurology International Open 2018; 2: E6–E9

ISSN 2511-1795

Correspondence
Dr. med. univ. Adela Della Marina
Neuropädiatrie
Entwicklungsneurologie und Sozialpädiatrie
Klinik für Kinderheilkunde I
Universitätsklinikum Essen
Hufelandstr. 55
45122 Essen
Germany
Adela.Dellamarina@uk-essen.de

ABSTRACT

Juvenile myasthenia gravis (JMG) is an autoimmune disorder of neuromuscular transmission caused by production of antibodies against the postsynaptic membrane of the neuromuscular junction. Clinical signs in young children and adolescents range from isolated ocular symptoms to general muscular weakness and respiratory insufficiency. Clinical presentation of JMG in young children and adolescents shows distinct features compared to adults. Young children may show generalized muscular weakness already during the first two years of life, and in this group specific antibodies can be only slightly increased. Because of existing therapeutic options, an early diagnosis is important. In case of negative specific antibodies and onset of the first symptoms during infancy or early childhood, the diagnosis of a congenital myasthenic syndrome (CMS) must be considered and is not always clear to differentiate. Clinical symptoms, diagnostic procedures and therapeutic strategies with consideration of specificities of this age group are discussed.

Introduction

Autoimmune childhood and juvenile myasthenia gravis (JMG) is defined with the occurrence of the first symptoms before the age of 19. Prevalence and incidence of JMG in Germany are not known. In Norway, incidence was calculated at 1.6 per million population, with a prevalence of 3.6–13.8 per million [1]. According to the occurence of their first symptoms, the patients are divided into prepubertal (symptom onset prior to the age of 12) and postpubertal (symptom onset after the age of 12) group. Clinical manifestations are similar to those of adults: children may exhibit isolated fluctuating ocular symptoms (ptosis, ophthalmoplegia) as well as generalized muscular weakness and respiratory insufficiency. Symptom onset even in the first two years of life is possible.

The influence of ethnic origin on the clinical course in children and adolescents with JMG is represent with a higher proportion of isolated ocular presentation in Asian countries (up to 93 %) [2]. Younger children often show only ocular symptoms (unilateral or bilateral ptosis, with possible changes of side); these symptoms can progress into generalized weakness, even after a symptom-free interval of up to two years. On the whole, the literature shows a lower rate of generalized symptoms in JMG compared to adults, which varies, depending on the study, between 29 and 75 % [2, 3]. Likewise, a rate of spontaneous remission (among patients with and without drug therapy) of up to 34.7 % has been reported [3–5], but this is transient [6].

Gender predominance is not present in prepubertal children, 50–86 % of patients with JMG are female [2, 4, 5, 7].

Clinical symptoms

The onset of first symptoms is possible already during infancy, in neonatal patients the diagnosis of congenital myasthenic syndrom (CMS) or transient neonatal myasthenia are more likely. Isolated ocular symptoms (ptosis, opthalmoplegia, double vision, insecurity when climbing stairs) are common in children (in 27–93 % of cases depending on the study author, see overview in [2]), generalization of symptoms are possible in the course of disease (facial hypomimia, bulbar symptoms, generalized muscle weakness). Gen-

eralized muscle weakness at onset is more frequent in school children and adolescents (in up to 90 %, [7]). Post-pubertal children and adolescents show a similar disease course as adults, likewise a predominance among females is evident [2].

A neurological examination that is often unremarkable after physical rest requires various provocation methods to prevent overlooking symptoms: a long glance upwards to provoke ptosis (Simpson test), physical stress in case of generalized muscle weakness (e.g., bicycle riding, climbing stairs), repeated examination in the course of the day. Typically, symptoms worsen in the course of the day and improve after rest (such as midday nap). Provocation/deterioration of symptoms due to heat and infectious disease is possible. In adults, the Myasthenia Gravis Foundation of America (MGFA) classification as well as the Quantitative Myasthenia Gravis Score (QMG) have been established to determine the severity of disease [8]. This Scoring requires a good compliance from the patient and can be used with modification for younger children (below eight years of age), but is not verified in this patient population. The QMG score is a useful parameter in the clinical evaluation of the patients undergoing therapy or after its termination, if there is corresponding compliance.

Suspected diagnosis is assured by electrophysiological studies and detection of specific antibodies (acetylcholine receptor antibody (AChR-Ab), muscular tyrosine kinase (MuSK), and low density lipoprotein receptor-related protein 4 (LRP4)). The latter has yet to be reported in JMG. The proportion of patients with positive AChR-Ab varies between 31–96 %; especially in prepubertal patients the proportion of seronegativity is high [3, 4, 7, 9–12]. MuSK-positive JMG is rare; only few case reports are available. Thymomas also play a minor role in JMG, but they should be ruled out by imaging. In newborns, the antibodies of the mother (transient neonatal myasthenia in maternal myasthenia gravis) can circulate in the bloodstream until the 5th month of life. During the postnatal period, newborns often show generalized but fluctuating muscle weakness, respiratory symptoms or sucking weakness; ptosis and external opthalmoplegia are also possible. The onset of symptoms is often directly postpartum, but can show a latency up to the third day of life and persist for up to three weeks, in rare cases up to three months [6].

The creatine kinase (CK) level is in the normal range or slightly elevated [13].

In case of suggestive clinical symptoms and negative antibody findings, repetitive nerve stimulation testing (low-frequency, 3 Hz) can support the diagnosis of JMG. This can be performed at any nerve; the measurement site is strongly dependent on the age of the patient and his/her cooperation (personal observation). If the result is positive, a pathological decrement (decrease of the amplitude from 1st to 5th stimulus response) of more than 10 % is to be expected. If the findings are unremarkable and the patients exhibit mild symptoms, the examination should be repeated after physical stress.

Single-fiber EMG is more sensitive and in the case of negative findings can disclose abnormalities in low-frequency single stimulation. Both high-frequency single-stimulation and single-fiber EMG can only be used to a limited extent in children (no cooperation).

If there is a pathological decrement (> 10 %) during repetitive 3 HZ stimulation, it is impossible to distinguish between seropositive, seronegative JMG and CMS.

Intravenous administration of edrophonium chloride (formerly known as ,,Tensilon test“) is indicated above the age of one and should only be performed on children under intensive care condition (overdose can result in bradycardia, brochospasm, hypotonic circulatory reaction). This is reserved for the cases in which the diagnosis of JMG is uncertain (antibody findings and/or elektrophysiology show negative results) but does not contribute in the differential diagnosis of a congenital myasthenic syndrome if there is a positive response. The clinical symptoms should be sufficiently pronounced (e.g., distinct ptosis or opthalmoparesis), otherwise the assessment of a definite clinical effect is difficult. A positive effect results in clear improvement of clinical symptoms within minutes.

A slow oral dosage (single doses distributed throughout the day) of pyridostigmine bromide in a weight-adjusted dose represents a good alternative for younger children. This should also be done only by monitoring of vital signs (at least 60 min after administration) in an in-patient setting. Improvement of symptoms within 30–60 min after drug administration is considered a positive response.

Differential Diagnoses

The most important differential diagnosis is a congenital myasthenic syndrome (CMS). In case of seronegative JMG, CMS should always be considered as a differential diagnosis, in particular if the symptom onset occurs during the first two years of age or familial clustering. Even in late symptom manifestation (adolescents), the presence of CMS is possible (for example, in mutations in the *DOK7, GFPT1* gene). Children with CMS may also show isolated ocular symptoms (for example, mutations in the *CHRNE* gene); in the case of negative antibody findings, the presence of symptoms since birth is sometimes indicative. An absence of evidence of the specific antibodies and the lack of response to immunosuppressive therapy are also indirect indications of CMS (see the review article by Schara et al. [14]). In newborns transient neonatal myasthenia may result from maternal antibodies.

Lambert-Eaton myasthenic syndrome should be considered when patients exhibit noticeable lower extremities weakness; however, it is rare among children and adolescents. In mitochondriopathies, symptoms may also be worsened by infection or fever. In this case, mitochondriopathy has to be confirmed or ruled out by specialized metabolic, muscle bioptic and molecular genetic examinations. In cases of prominent ocular symptoms, JMG can be misinterpreted as chronic progressive external ophthalmoplegia (CPEO). Juvenile dermatomyositis shows specific inflammatory changes in the MRI of the muscle as well as in the muscle biopsy. In case of primarily facial and bulbar symptoms, progressive bulbar palsy of childhood, Fazio-Londe disease (FLD), may resemble JMG especially at the onset of the disease. Botulism frequently affects several persons in the immediate environment; accompanying vegetative symptoms (pupillary rigidity, constipation) as well as verification of the toxin lead to a diagnosis.

Since patients with narcolepsy can exhibit facial hypomimia, ptosis and generalized muscle weakness, it is important to inquire

whether excessive daytime sleepiness or cataplexy is present as an important distinguishing feature.

Therapy

Therapy for JMG is derived from national gudelines for adults [15]; to date, there are no specific guidlines for JMG in Germany. Depending on clinical manifestation (ocular or generalized) and antibody status (AChR-Ab-positive or negative), a combination of acetylcholinesterase (AChE) inhibitors, drug immunosuppression/immunomodulation and surgical therapy (thymectomy) is used.

AChE inhibitors are the first therapeutic choice (pyridostigmine bromide, dose range between 1–10 mg/kg/day is distributed over 4 daily doses, in this case, as with adults, the absolute maximum dose should be considered). The immunosuppression with steroids (prednisone, prednisolone, dose up to 2 mg/kg/day, maximum 60–80 mg / day) plays a primary role, short-term administration (few months) ist requested due to the long-term side-effects on the growing organism. High-dose methylprednisolone therapy in JMG cannot be recommended due to absence of data regarding its effect. Azathioprine is the first choice as steroid sparing drug and has been used in most studies of JMG (up to 2.5 mg/kg/day, maximum 150–200 mg/day) [2, 16]. In severe cases of adult MG, cyclophosphamide has been used, but cannot recommended for children due to known nephrotoxicity. Based on current data, mycophenolate mofetil (MMF) and rituximab can be presumed to be effective for adults [15]; there are only few reports of the use of MMF as a steroid sparing drug as well as rituximab in case of severe forms of JMG [17–20].

If isolated ocular symptoms are present, primary therapy with pyridostigmine should be initiated in combination with steroids in the absence of improvement. In the case of a generalized form, this combination should be extended by azathioprine. In case of bulbar symptoms or respiratory deterioration as well as myasthenic crisis, intensification of treatment using immunoglobulins and plasmapheresis/immunoadsorption is necessary. There are currently no data available regarding immunoadsorption for treating JMG. The data on the effectiveness and timing of thymectomy in children and adolescents are inconclusive and usually involve mixed groups with seropositive and seronegative patients who exhibit both isolated ocular symptoms and a generalized form of the disease. The only study observing a clearly defined group of patients with a generalized form of JMG and positive AChR-Ab with thymectomy over a median of 2.7 years demonstrated positive effects of thymectomy on the course of the disease, especially if the procedure was performed in the first year after symptom onset [17]. We could see a similar result in our cohort of AChR-Ab-positive patients with generalized JMG; however non-steroidal drugs were started earlier (generally pre-thymectomy) and continued for up to 2 years post-thymectomy [21]. Regarding seronegative patients or patients with isolated ocular symptoms, the pros and cons of thymectomy should be weighed and individually considered if immunosuppressive therapy (especially steroids) must be given over a longer period; up to now, there is no clear evidence of its positive effect in this patient group.

Thymectomy should always be carried out at an early stage and in clinical stable patient, since severe complications (for example provocation of a myasthenic crisis) may occur intra- and postoperatively. In very young children, thymectomy must be considered on a case-by-case basis and weighed against long-term immunosuppression and its associated side effects.

To date, surgical options include open and endoscopic thymectomies (also robotic-assisted). The endoscopic approach is preferable in children (except thymoma, in which open thymomectomy is the procedure of choice) after appropriate preoperative imaging of the thymus (in children MRI should be favoured). However, the procedure should only be performed in a center with proven expertise. Patients with a long period of illness and severe symptoms also need intensive physiotherapeutic and often – psychotherapeutic – support.

Case History

Patient history

At the age of 18 months, two weeks after a febrile infection, the female patient first developed bilateral ptosis as well as ophthalmoplegia. Due to her young age, the diagnosis of CMS was suspected; AChR-Ab was first negative. Initially tretment with pyridostigmine bromide resulted in an improvement of ptosis. After a new afebrile infection, she also developed bulbar symptoms with hypersalivation, dysphagia and facial hypomimia as well as generalized muscle weakness that worsened in the evening or after physical activity.

Therapy and follow-up

Increasing the dose of pyridostigmine (4 mg/kgBW/day) did not alleviate the symptoms; in addition, the cholinergic side effects resulted in increased salivation and diarrhea. Now, minimal elevated AChR-Ab (0.6 mmol/l, norm up to 0.4 mmol/l) suggested autoimmune JMG; therefore immunosuppression with prednisone was started, resulting in improvement of symptoms over the period of three weeks. At the same time, steroid sparing medication (azathioprine) was started resulting in discontinuation od steroid therapy 11 months later (side effects included significant weight gain and tendency to aggressive behavior). In the course of the disease, at the age of 3 she again developed alternating ptosis and noticeable swallowing difficulty during febrile infections. Subsequently steroid therapy was restarted (prednisone) and the azathioprine dosage was adapted to the child's weight, resulting in clinical remission. At the age of 4 she underwent robotic-assisted thymectomy, and steroid therapy was subsequently discontinued. She is showing stable clinical presentation; occasionally unilateral ptosis can be observed after long-lasting physical activity.

SUMMARY

- The possibility of JMG should be considered in the case of a combination of diurnal fluctuation in symptoms (muscular weakness, ocular symptoms such as double vision) that worsen under physical activity or during the course of the day in children with prior normal psychomotor developement.
- Due to current therapeutic options, an early diagnosis is important in this patient group.
- The diagnosis of JMG is confirmed by the combination of suggestive clinical symptoms, abnormal neurophysiological findings and, in the most cases, detection of specific antibodies.
- There is currently little evidence-based data regarding therapeutic options in this population group, as they are based on recommendations for adults. In children with JMG, attention must be paid to the appropriate weight-adjusted dose in the selection of the medication and the long-term side-effects of immunosuppression on growth and physiological development as well as on fertility.
- In patient with generalized symptoms of JMG and positive AChR-Ab, early thymectomy (within the first two years after symptom onset) appears to have a positive effect on the course of the disease and duration of immunosuppression.

Conflict of Interest

The authors declare no conflicts of interest.

References

[1] Popperud TH, Boldingh MI, Brunborg C et al. Juvenile myasthenia gravis in Norway: A nationwide epidemiological study. Eur J Paediatr Neurol 2017; 21: 312–317

[2] Chiang LM, Darras BT, Kang PB. Juvenile myasthenia gravis. Muscle Nerve 2009; 39: 423–431

[3] Ashraf VV, Taly AB, Veerendrakumar M et al. Myasthenia gravis in children: A longitudinal study. Acta Neurol Scand 2006; 114: 119–123

[4] Evoli A, Batocchi AP, Bartoccioni E et al. Juvenile myasthenia gravis with prepubertal onset. Neuromuscul Disord 1998; 8: 561–567

[5] Rodriguez M, Gomez MR, Howard FM Jr et al. Myasthenia gravis in children: Long-term follow-up. Ann Neurol 1983; 13: 504–510

[6] Sanders DB. MJ. Clinical features of myasthenia gravis. In: Engel AG.ed. Handb Clin Neurol l. München: Elsevier; 2008: 229–252

[7] Lindner A, Schalke B, Toyka KV. Outcome in juvenile-onset myasthenia gravis: A retrospective study with long-term follow-up of 79 patients. J Neurol 1997; 244: 515–520

[8] Jaretzki A III, Barohn RJ, Ernstoff RM et al. Myasthenia gravis recommendations for clinical research standards. Neurology 2000; 55: 16–23

[9] Andrews PI, Massey JM, Howard JF et al. Race, sex, and puberty influence onset, severity, and outcome in juvenile myasthenia gravis. Neurology 1994; 44: 1208–1214

[10] Batocchi AP, Evoli A, Palmisani MT et al. Early-onset myasthenia gravis: Clinical characteristics and response to therapy. Eur J Pediatr 1990; 150: 66–68

[11] Zhang X, Yang M, Xu J et al. Clinical and serological study of myasthenia gravis in HuBei Province, China. J Neurol Neurosurg Psychiatry 2007; 78: 386–390

[12] Hong Y, Skeie GO, Zisimopoulou P et al. Juvenile-onset myasthenia gravis: Autoantibody status, clinical characteristics and genetic polymorphisms. J Neurol 2017; 264: 955–962

[13] Schara U, Schneider-Gold C, Schrank B. Klinik und Transition neuromuskulärer Erkrankungen. 1. Aufl. Heidelberg: Springer; 2015

[14] Schara U, Della Marina A, Abicht A. Congenital myasthenic syndromes: Current diagnostic and therapeutic approaches. Neuropediatrics 2012; 43: 184–193

[15] AWMF. S2k Leitlinie 030-087: Myasthenia gravis und Lambert-Eaton-Syndrom, Diagnostik und Therapie 2014;www.awmf.org

[16] Ionita CM, Acsadi G. Management of Juvenile myasthenia gravis. Pediatr Neurol 2013; 48: 95–104

[17] Heng HS, Lim M, Absoud M et al. Outcome of children with acetylcholine receptor (AChR) antibody positive juvenile myasthenia gravis following thymectomy. Neuromuscul Disord 2014; 24: 25–30

[18] Castro D, Derisavifard S, Anderson M et al. Juvenile myasthenia gravis: A twenty-year experience. J Clin Neuromuscul Dis 2013; 14: 95–102

[19] Koul R, Al Futaisi A, Abdwani R. Rituximab in severe seronegative juvenile myasthenia gravis: Review of the literature. Pediatr Neurol 2012; 47: 209–212

[20] Tzaribachev N, Koetter I, Kuemmerle-Deschner JB et al. Rituximab for the treatment of refractory pediatric autoimmune diseases: A case series. Cases J 2009; 2: 6609

[21] Della Marina A, Kölbel H, Müllers M et al. Outcome after robotic-assisted thymectomy in children and adolescents with acetylcholine receptor antibody-positive juvenile myasthenia gravis. Neuropediatrics 2017; 48: 315–322