Juvenile Myasthenia Gravis

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 occurrence 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 represented 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 syndrome (CMS) or transient neonatal myasthenia are more likely. Isolated ocular symptoms (ptosis, ophthalmoplegia, 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 chil-
dren 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 over-
looking symptoms: a long glance upwards to provoke ptosis (Simp-
son 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/de-
terioration 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 pa-

tient 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 electrophysiologic studies
and detection of specific antibodies (acetylcholine receptor anti-
body (AChR-Ab), muscular tyrosine kinase (MuSK), and low densi-
ty 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 pa-
tients the proportion of seronegativity is high [3, 4, 7, 9–12].
MuSK-positive JMG is rare; only few case reports are available. Thy-

momas 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 postna-
tal period, newborns often show generalized but fluctuating mus-

cle weakness, respiratory symptoms or sucking weakness; ptosis
and external ophthalmoplegia are also possible. The onset of symp-
toms 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 ampli-
tude from 1st to 5th stimulus response) of more than 10 % is to be
expected. If the findings are unremarkable and the patients exhib-
it mild symptoms, the examination should be repeated after phys-
ical stress.

Single-fiber EMG is more sensitive and in the case of negative
findings can disclose abnormalities in low-frequency single stimu-
lation. 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 seroposi-
tive, 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 condi-
tion (overdose can result in bradycardia, bronchospasm, hypotonic
circulatory reaction). This is reserved for the cases in which the di-
agnosis of JMG is uncertain (antibody findings and/or electrophys-
ology show negative results) but does not contribute in the differ-
ential diagnosis of a congenital myasthenic syndrome if there is a
positive response. The clinical symptoms should be sufficiently pro-
nounced (e.g., distinct ptosis or ophthalmoparesis), 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 administra-
tion) in an in-patient setting. Improvement of symptoms within
30–60 min after drug administration is considered a positive re-

Differential Diagnoses

The most important differential diagnosis is a congenital myasthen-
ic syndrome (CMS). In case of seronegative JMG, CMS should always
be considered as a differential diagnosis, in particular if the symp-
tom onset occurs during the first two years of age or familial clus-
tering. Even in late symptom manifestation (adolescents), the pres-
ence of CMS is possible (for example, in mutations in the DOK7,
GEPT1 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 anti-
bodies 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; how-
ever, it is rare among children and adolescents. In mitochondriopa-
thies, symptoms may also be worsened by infection or fever. In this
case, mitochondriopathy has to be confirmed or ruled out by spe-
cialized metabolic, muscle biopic and molecular genetic examina-
tions. In cases of prominent ocular symptoms, JMG can be misin-
terpreted 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 pri-
marily facial and bulbar symptoms, progressive bulbar palsy of
childhood, Fazio-Londe disease (FLD), may resemble JMG especi-
ally 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 guidelines for adults [15]; to date, there are no specific guidelines 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 thymectomy 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 treatment 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 development.
- 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