REVIEW ARTICLE

Immune mediated myasthenia gravis in children, current concepts and new treatments: A narrative review article

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ABSTRACT

Myasthenia gravis (MG) is the most frequent transmission disease in the neuromuscular junction. Juvenile myasthenia gravis (JMG) is an autoimmune antibody-mediated disease of postsynaptic endplate defined as MG presentation in patients before the age of 18 years old. While many clinical features of JMG are identical to the adults, there are some significant differences between them regarding presentation, clinical course, antibody level, and thymus histopathology. In JMG, ocular symptoms are more frequent, the clinical course is comparably benign, and the outcome is better than adult MG. Antibodies attack the muscle endplate proteins in the postsynaptic membrane and interfere with transmission. These antibodies in most patients are against the acetylcholine receptors, but they may also be directed toward muscle-specific kinase, lipoprotein-related protein 4, and agrin. Findings show racial influences and genetic effects on the occurrence of JMG. The essential clinical symptom is fatigable weakness of muscles that can be in the form of isolated ocular type or more disseminated weakness. The diagnosis of JMG is essentially clinical, with fluctuating patterns of weakness and easy fatigability, but a series of diagnostic evaluations can confirm the diagnosis. Precise diagnostic evaluation and distinction from congenital myasthenic syndromes is critical. The treatment plan is conducted according to the clinical course (ocular or generalized), antibody type, and disease severity. The mainstay of treatment includes symptomatic therapy, long-lasting immunosuppressive treatment and treatment of myasthenic crisis. Novel medications are introduced and conducted to the specific pathophysiologic mechanisms of the disease, and they are used primarily in the refractory MG.

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Introduction

Myasthenia gravis (MG) is a chronic disorder of the neuromuscular junction (NMJ) presenting with weakness and easy fatigability of ocular, extremity, bulbar and respiratory muscles (1). Diurnal fluctuation in muscle weakness is a marker in all forms of the disease. If the respiratory muscles are involved, myasthenia may be life-threatening (2). MG in children is categorized into three types with different pathophysiological mechanisms (3), including 1. Transient neonatal MG produced by transplacental transmission of acetylcholine receptors (Ach R) antibodies from a myasthenic mother. Less commonly, muscle-specific kinase antibodies cause defective transmission in NMJ in this type of MG (4, 5). Transient neonatal MG is rare and may develop in 10-15% of neonates born from myasthenic mothers, either in remission or acute disease (5). 2. Congenital myasthenic syndromes (CMS), another form of MG, is a heterogeneous genetic group of diseases that cause functional or structural defects in NMJ proteins, leading to transmission abnormalities and muscle weakness (6). These syndromes often arise from molecular abnormalities in the nicotinic receptors of Ach in the muscle, but mutations in the presynaptic or synaptic proteins or developmental defects in the endplate could also be the reason (7). The prevalence of CMS in children under 18 years old is approximately 9.2 per 100,000. Nowadays, the distributed use of genetic tests has led to more frequent diagnoses of CMS, specifically in seronegative patients (6). On the other hand, the clinical presentations of CMS overlap with immune-mediated MG in some aspects. In very uncommon cases, CMS and autoimmune MG have been described in the same patient (6, 7). 3. Juvenile MG (JMG) is an autoimmune disorder with antibodies leading to dysfunction of the postsynaptic membrane. This type of MG is the subject of discussion in this review.

MG is the most frequently acquired transmission disease in NMJ (8). JMG is an autoimmune antibody-mediated disease of postsynaptic endplate defined as MG presentation in patients before age 18 (9). Usually, the onset of the disease is after infancy or two years old. While many clinical features of JMG are identical to the adult MG, there are some significant differences between them regarding presentation, clinical course, antibody level, and histopathology of the thymus (9, 10). Based on studies, in JMG ocular, symptoms are more frequent, the clinical course is comparably benign, and the outcome is better than adult MG (10, 11). Antibodies attack the muscle endplate proteins in the postsynaptic membrane and interfere with transmission. These antibodies in most patients are against the AchR, but they may also be directed toward muscle-specific kinase (MuSK), lipoprotein-related protein 4 (LRP4), and agrin (1, 9). The essential clinical symptom is fatigable weakness of muscles that can be in the form of isolated ocular weakness named “ocular myasthenia” or more disseminated weakness known as “generalized myasthenia” (9). The possibility of positive titers of antibodies in adults with ocular MG is less likely (nearly 50%) than in generalized MG (12). In most generalized JMG patients, detectable antibodies are against AchR (almost 85%); in the remaining patients, other types of antibodies are observed (nearly 8%). Residual JMG patients with no detectable serum antibodies or known responsible antigenic sites are named seronegative patients (13). MG patients with MUSK-positive antibodies usually have bulbar-dominant presentations with no abnormalities in the thymus (14). AchR antibodies

in the pre-pubertal children are less frequent than in older patients (15).

Materials & Methods

The main goal of this study was to organize a comprehensive review of recent available knowledge about immune-mediated myasthenia gravis in children. An extensive search of the PubMed database for related articles published from the January 2000 to December 2023 was done using the following query: ("Myasthenia Gravis"[Mesh] OR "Myasthenia Gravis"[tiab] OR Myasthenia[tiab]) AND ("Child"[Mesh] OR Child*[tiab] OR Pediatric*[tiab] OR "Pediatrics"[Mesh] OR juvenile[tiab]) AND ("Autoimmune"[tiab] OR "immune-mediated"[tiab] OR "Antibodies"[Mesh] OR Antibod*[tiab] OR "Autoantibodies"[Mesh] OR Autoantibod*[tiab]). All study designs were included. Reference lists of eligible articles were manually searched to take more data. A few of these references were published prior to 2000. The initial search consisted of 771 articles and only those with available full texts were included (n=596). After screening articles based on the title and abstract, 365 articles remained, and after excluding the papers in non-English language and non-human studies and non-relevant full-texts, 104 articles were selected. The correlated data on the epidemiology, pathophysiology, clinical manifestation, diagnostic evaluation, differential diagnosis, treatment strategies, and outcome of immune-mediated MG in pediatrics were extracted and described (Figure 1).

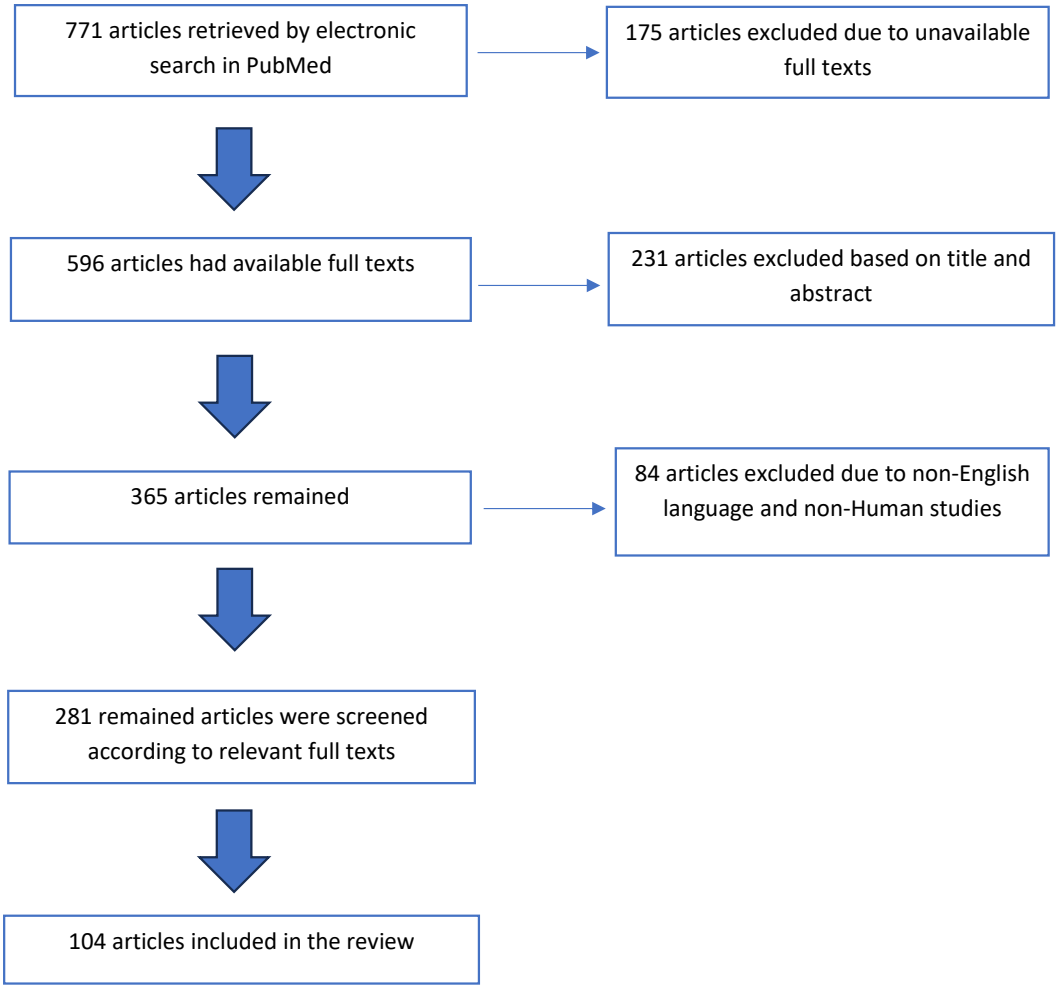

Fig 1. *Flow diagram that shows the selection of articles*

Epidemiology

MG is a recognized neuromuscular disease first described in the 16th century, but its immune-mediated origin is well-known from the 19th century to date (15). Even though MG is the most common NMJ disease (16), JMG is still a non-frequent disorder in children, and its prevalence and incidence vary in different countries (10). JMG encompasses 10%-15% of all antibody-mediated autoimmune myasthenias (17). Based on studies, the presentation of MG during childhood is more common in Eastern countries than inthe European population, whose post-pubertal presentation is more probable in them (10, 18). Childhood-onset of MG in European patients is lower than 10% of cases (10). Studies on Asian compared with European patients have shown that pre-pubertal (under the age of 12 years old) compared to post-pubertal onset proportion was more than twice in Asian children (≥74%). This proportion for African and European children was 40 to 48% and <33% respectively (19, 20) (Figure 2). Ocular MG was four times more common in Asian versus European childhood patients and 2-3 times more common in African children either in post-pubertal or pre-pubertal onset (19). Furthermore, the results of a pediatric multiracial study in England show MG was proportionally more frequent in African, Arabian and Asian compared with European children. The authors of in this study reported the mean incidence of 1.5 million children per year for seropositive patients (21). Similar results regarding the racial proportion of pre-pubertal JMG onset were reported in Canada and France (19, 22). Data from studies in China are broad-ranged and vary from 27% juvenile onset of MG in the north to 45% in the south of China, but generally, roughly 50% of children presented with MG in age under ten years old in these studies. The peak of incidence was under the age of five years (23, 24). A study from Japan reported that children presenting with

Fig 2. *Proportion of pre-pubertal to post-pubertal onset of juvenile myasthenia gravis in different races (19), (20).*

MG under ten years comprised 9% of all cases of myasthenic patients, compared to China, which is much less (19,25). This peculiar data from Italy was 2% (19). Consequently, regardless of different methodologies in epidemiological data studies, these findings show racial influences and genetic effects in the JMG occurrence (9). The frequency of MG in children, either post-pubertal or pre-pubertal, compared with adults, is lower in European populations compared with African and Asian populations. The rate of transformation from ocular to generalized type of disease is much higher in European children, with more HLADRB1*04 among them (19). The Prevalence of MG in adults is about 1 in 5000, and older men and younger women have a higher prevalence of the disease (26). Most of the studies have a female priority in both pre-pubertal and post-pubertal JMG patients (9, 19, 27, 28). However, some other studies, including a survey from South Africa, have reported an equal proportion of M/F pre-pubertal compared with female preponderance in post-pubertal patients (9, 10). According to studies, the autoimmune regulator gene is downregulated in the thymus by the estrogen effect in young women, causing more delivery of autoreactive T-cells (28, 29).

Pathophysiology

Disruption of synaptic transportation by autoantibodies against NMJ elements results in MG (9). Genetic vulnerability and environmental factors such as infectious disease are responsible for autoimmunity (1). Rheumatologic and autoimmune disorders also can trigger MG (30). In AchR-MG, self-tolerance within the thymus is defective because the equilibrium between generating immune cells and eliminating lymphocytes showing auto-reactivity is disrupted. Therefore, in addition to genetic factors, thymus pathology has an essential role in MG's immune malfunction and development (31). In AchR –JMG, follicular hyperplasia occurs in the thymus, and autoimmunity originates from the centers of these follicles with abnormal cytokines synthesis and imbalanced T cell function that activates B cells to produce autoantibodies (1, 32, 33). The function of regulatory B cells to suppress autoantibodies in MG is also abnormal. In the MuSK-MG, no obvious thymus pathology has been reported (34). Ach release in NMJ is provoked by the motor neuron impulse that turns on voltage-gated calcium channels. In the postsynaptic muscle membrane, Ach attaches to the receptors in the synaptic folds and induces the sodium channels that are activated by voltage change, resulting in muscular contraction. Typically, an enterokinase enzyme called MuSK induces AchR clustering in the synaptic folds that is necessary for normal function. The interaction of two proteins named agrin, which is delivered from motor nerve axons, and LRP4, a protein in the postsynaptic membrane, is mandatory for the stimulation of MuSK.

Finally, the clustering of AchR is completed by employment of Rapsyn and Dok7 in a chain of phosphorilative reactions which are also induced by MuSK (35, 36). Pathogenic IgG antibodies to AchR, which are IgG1 and IgG3 subtypes, interfere with post-synaptic membrane function in three manners: direct prevention of binding Ach to receptors, degradation, and internalization of receptors, and complement-mediated membrane destruction. The latter is the essential mechanism that induces damage to postsynaptic sodium channels and raises the excitation threshold (9, 37). MuSK antibodies are IgG4 subclass and unable to fix the complement. Instead, these antibodies, along with LRP4 antibodies act in the presynaptic

membrane by interfering with AchR clustering (38). These pathogenic mechanisms of responsible antibodies in MG are identical in adults and children. In some aspects of disease pathogenesis, the role of racial effect is significant. In Asian and African JMG patients, ophthalmoplegia with treatment resistance is more common compared to European individuals. Genetic dysregulation of muscle atrophy signaling and metabolic pathway of mitochondria are responsible pathogenetic mechanisms in susceptible patients (19).

Clinical presentations

JMG may present with pure ocular manifestations or with generalized muscular weakness. In most children, specifically in pre-pubertal ages, the first manifestation is ptosis and ophthalmoplegia, manifesting in variable extents (9). In a recent systematic review, authors reported that in 60.6% of JMG patients, the first manifestations were ocular symptoms such as ptosis, strabismus, and diplopia, and the most frequent initial manifestation was ptosis occurred in 77% (28). On examination, patients often have fatigue following a 45-60 second up gaze. Holding an eyebrow against the brow bone is better to prevent the activation of frontalis muscle for compensation. Children manifested with ocular MG may convert to generalize JMG, which often develops within six months of the onset of symptoms. If pure ocular features continue for more than 24 months, the development of generalized JMG is rare (27, 39). As mentioned earlier, the frequency of ocular JMG and its progression to generalized JMG differs in various studies. There is a robust racial influence. As in Asian studies, up to 90% of patients have a pure ocular form (21, 25, 27, 40). Manifestation of JMG in post-pubertal children resembles adults and is more likely to present with generalized symptoms and has less chance to remit spontaneously (9). In ocular MG, the muscles of orbicularis oculi, palpebral superiors, and extra ocular muscles are involved. On examination, a few signs exist that can be helpful for the diagnosis of ocular MG, such as:" Coggan's lid twitch," a mild overshoot twitch of the upper lid when looking straight from a sustained downward gaze (30). In a study, the specificity and sensitivity of this test were 99% and 75%, respectively, and false positive proportion was 1% (41). "Ice pack test "(application of an ice pack on the ptotic lid for 2-5 min and improvement of 2 mm or more as a positive result), probable mechanisms are increased sensitivity of postsynaptic receptors to Ach, induction of Ach release and transport in the presynaptic membrane, decreased activity of Ach esterase, decreased calcium ion removal from the nerve endings after stimulation. Cooling also has a more prolonged influence on excitation-contraction coupling via the increased calcium ions release and promoting contraction (42). The studies reveal that the ice test is specific and relatively sensitive for ocular MG, but in complete ptosis, its sensitivity reduces (43). Placing an icepack for 5 min over the eye also may cause an improvement in diplopia and extraocular weakness (44). "Curtain sign" or enhanced ptosis sign, correlates to all forms of ptosis and is not characteristic of MG. When opening the eyes, both lids get an equal range of impulses. Therefore, in unilateral ptosis, lifting the ptotic lid obviates any ptosis in the other lid and is a helpful test to assess if the other lid is involved (30, 44). If MG is suspected without obvious ptosis, the physician can induce ptosis by up gazing for 1 min to exhaust the levator pulpebral muscle (43).

Different extraocular muscles or various defects may occur during the course of the disease. Hence, a precise examination of these muscles is essential,

especially in seronegative patients (43). Diplopia on examination could be provoked by sustained gaze (Simpson's sign) (43). Orbicularis oculi muscle weakness seen in MG prevents complete eye closure. Ocular symptoms cause significant complications in children. Hence, the correct diagnosis, in-time treatment, and consultation with an ophthalmologist are essential to prevent persistent amblyopia (10, 45). A considerable percentage of patients with MG, particularly JMG, may develop persistent ophthalmoplegia and have duction failure on examination (19, 39, 46, 47).

In generalized MG, weakness in the proximal muscles of limbs occurs, such that running, climbing stairs, getting up from a sitting position or raising the arms becomes difficult. Dysarthria, dysphagia, swallowing problems, and difficulty breathing may develop due to involvement of the bulbar and respiratory muscles. Diurnal fluctuations of weakness may be evident, as symptoms become severe through the day and improve after sleep or rest. There is a risk of choking and aspiration pneumonia in children (10, 19). Severe weakness of respiratory muscles leads to myasthenic crisis, and ventilation support is needed. The generalized form of the disease is less frequent in JMG, particularly in pre-pubertal disease, than in adults. In the pre-pubertal onset of the disease, the pure ocular form is more common, and the disease prognosis is better. Post-pubertal JMG patients have more similarities to adults. Up to 80% of adult patients, with an ocular type of disease at onset will evolve to a generalized form. Progression to generalized MG is less frequent in children compared with myasthenic adults, especially in pre-pubertal patients (10, 19).

Disease onset in MuSK –JMG patients may be acute, along with severe involvement of bulbar and respiratory muscles and early myasthenic crises (48). In a large pediatric study, 89% of patients with MuSK –MG were female, identical to adults (49). In adult patients with ocular MG, up to 80% will develop generalized weakness. The generalization rate is lower in children, particularly at pre-pubertal ages (10). Pre-pubertal myasthenic children have a better prognosis and a higher chance for spontaneous remission (10, 19). In a Norwegian study, the rate of spontaneous remission in pre-and post-pubertal patients were 14% and 5%, respectively, and 51% had complete stable remission (remission for at least one year without treatment and any MG features), greater in the pre-pubertal patients (27). In Chinese reports, 17% of children had complete stable remission during 5-year follow-up, and in 55%, the disease relapsed after one year, mostly due to treatment discontinuation (50). Again, it shows the racial and genetic influence of disease. A recent meta-analysis regarding JMG reported limb weakness at presentation in 64 of 769 myasthenic children (8.3%) and bulbar involvement at presentation in 55 of 732 children (7.5%), and respiratory crisis in seven of 492 children (0.1%) (28). This study also reported the generalization of myasthenic symptoms in 21.9% of patients, showing a greater frequency of pure ocular MG in this population.

In MG patients, including JMG, comorbidity of autoimmune diseases is common, particularly thyroid diseases (19, 27, 50, 51, 52). Hyperthyroidism is more common (28). Other comorbid disorders are: systemic lupus erythematosus, idiopathic thrombocytopenic purpura, Crohn's disease, ulcerative colitis, juvenile rheumatoid arthritis, vitiligo, psoriasis, alopecia areata, and diabetes mellitus type 1 (28). The incidence of comorbid autoimmune diseases in studies is different. Reports from England

and Canada, and also Hong Kong, China, and Thailand are 4-19% (21, 23, 25, 39, 50, 53, 54), and in the Norwegian study is 30%(27) and in African children is 7% (22,55).

Thymoma is rare in JMG (19, 28) and varies between 0 and 17% in Asian studies (19). This is one of the causes that accounts for less mortality in patients with JMG (28). Studies have reported that DRB1* 09 and HLA-B*46 are overexpressed in Asian children with ocular MG versus HLADRB1*04 overrepresentation in European children more prone to progression to a generalized type of MG (19).

Diagnosis

The diagnosis of JMG essentially is clinical, with fluctuating patterns of weakness and easy fatigability (9, 10). A series of diagnostic evaluations can confirm the clinical diagnosis. The most common tests are:

-Serological tests: antibodies against AchR are detected by radioimmunoprecipitation, and their identification supports the diagnosis. The frequency of AchR antibodies in JMG is less than in adult patients and varies between 50% and 95% in studies (19). Positive results are more probable in generalized JMG compared with pure ocular type (21, 27, 55). Most JMG patients have an ocular type, which is why a more significant proportion of seronegative patients are among them (21, 56). Both pure ocular type and negative AchR antibodies give a better prognosis for remission (19, 21). In seronegative patients, the test should be repeated every six months up to five years after the onset of the disease for detection of delayed positivity (27, 56). Some seronegative children have low-affinity type antibodies not identified with standard techniques. Detection of antibodies to clustered Ach with cell-based assay may be helpful in these seronegative cases (10, 21, 57, 58). These antibodies are shown in all ages and may be identified in 60% of seronegative patients (10). Children with negative results for AchR antibodies may have antibodies to MuSK and should be tested. Positive results are rare in JMG and are detected in 5-8% of patients (9, 10, 48). This subgroup of patients, which are more females, have a peculiar feature of disease with more severe presentations such as marked bulbar and facial involvement and recurrent respiratory crisis (10,48,59). An IgG-specific cell-based assay has been established to detect low-affinity MuSK antibodies and has increased the positive results (60). Antibodies against other proteins, including COLQ, agrin, and LRP4, have been reported in adults, but their specificity and exact pathogenicity are not truly determined (9, 61), and their relation to JMG has not been confirmed (10). Seronegative myasthenic patients resemble AchR-positive patients more than MuSK-positive patients regarding either clinical manifestations or treatment response (10). In a small group of AchR-positive patients, seroconversion occurs after thymectomy along with the development of MuSK seropositivity (62). In seronegative patients, specifically in pre-pubertal children and in pure ocular forms of the disease, differentiation between congenital myasthenic syndromes and autoimmune MG is significant. Precise evaluation is necessary, as their treatment and outcomes are very different. Beginning the symptoms from early infancy or at birth, positive family history, and resistance to symptomatic treatments or immunotherapy are in favor of CMS diagnosis (9). Supportive characteristics for autoimmune MG are progressive and subacute disease onset, asymmetrical ptosis, and diurnal variations in ophthalmoplegia (63). Several forms of CMS cases may present in childhood (RAPSN, DOK7,

GFPT1, COLQ, and CHNRE), adolescence (DPAGT1), or adulthood (64). Although, the majority of them have associated characteristics such as weakness in limb-girdle pattern, dysmorphic features, absence of extraocular muscle involvement, or ptosis.

-**Pharmacological test:** Intravenous administration of edrophonium, a short-lived, fast--acting cholinesterase inhibitor, induces a transient remission of symptoms such as ophthalmoplegia, ptosis, and dysarthria, which could be assessed. Due to cholinergic side effects of edrophonium causing hypersecretion and bradycardia, this test should be performed with heart monitoring and pediatric resuscitation equipment available. Nowadays, the application of edrophonium test is limited due to their potential side effects and the more significant promotion of antibody detection and electrophysiological tests (9, 10).

- **Neurophysiological tests:** They are invaluable tests in diagnosing MG, although their use in young children is technically difficult, and interpretation of the results relates to operator experience (65). In the repetitive nerve stimulation test (RNS), recurrent stimulation by the 4th or 5th drive leads to a compound motor action potential to decrease > 10%. Single fiber EMG (SFEMG) is particularly efficient in the recognition of CMSs and in seronegative MG. Its appliance is more difficult in children due to the pain and degree of cooperation needed and could be done under anesthesia. The sensitivity of the test is 95-97% (9, 10). Furthermore, stimulated potential analysis using concentric needle electrodes (SPACE) is another method without child cooperation needed. It has 92% sensitivity (66). However, the specificity of the SFEMG is less than that of RNS. Hence, the normal result of SFEMG makes the diagnosis of MG very implausible, and a positive RNS strongly confirms the diagnosis (9).

- **Imaging:** The thymus should be scanned, although thymoma is uncommon in children, particularly in pre-pubertal ages. Patients with positive AchR antibodies frequently have pathological changes in the thymus of which hyperplasia is the most common. Thymus abnormalities are not common in MuSK-positive and seronegative patients (67).

Differential Diagnosis

A wide differential diagnosis should be considered in pediatric MG, consisting of congenital myopathies and muscular dystrophies, mitochondrial cytopathies, acquired neuropathies, acute disseminated encephalomyelitis, multiple sclerosis, brain stem tumors, hypothyroidy and CMSs, which are most challenging. Therefore, meticulous evaluation regarding these differential diagnoses is needed, especially in seronegative or pure ocular cases (9, 10).

Treatment

The treatment plan is conducted according to the clinical course (ocular or generalized), antibody type, and disease severity. The mainstay of treatment includes symptomatic therapy, long-lasting immunosuppressive treatment, and treatment of myasthenic crisis. A multidisciplinary team should manage patients consisted of pediatric neurologist, ophthalmologist, occupational therapist, physiotherapist, psychologist and dietitian. Supportive therapy included encouraging a healthy diet and lifestyle, avoiding obesity, exercise program, proper and in-time vaccination, particularly before the beginning of the immunosuppressive treatments, managing concurrent infections, regular ophthalmologic and psychiatric consults to prevent depression and associated fatigue that may be erroneously diagnosed as myasthenic feature and

overtreatment, explaining the families to avoiding certain drugs that could potentially exacerbate the symptoms by affecting NMJ. Some drugs trigger autoimmunity and then symptomatic MG, such as tyrosine kinase inhibitors, interferons, and immune checkpoint inhibitors, prescribed for the cancer treatment, but a number of medications affect neuromuscular transmission and worsen the MG symptoms through the induction of myasthenic crisis or obviating an undiagnosed MG such as fluoroquinolones, macrolides, aminoglycosides, muscle relaxants, magnesium, antipsychotics, some antiepileptics, chorticosteroides and the like (68). A rational way, especially in generalized MG, is to consider that initiation of any new drug may worsen the symptoms and should be used cautiously.

Symptomatic therapy

The first-line medication for the majority of patients with mild to moderate JMG are cholinesterase inhibitors that provide symptomatic improvement (69). The most commonly used is pyridostigmine, which has a long-acting effect. These drugs decreased the Ach degradation in NMJ, prolonging its binding to nicotinic receptors in the post-synaptic membrane. The studies show a significant improvement in MG symptoms by pyridostigmine (69, 70, 71). However, the treatment response is not equal in all patients, and some patients have a faint response to the drug, particularly patients with MuSK-positive MG that may even deteriorate. In these patients, the rate of cholinergic adverse effects of the drug is also higher (48). The remission of symptoms may be variable. Ocular symptoms, particularly diplopia, improve less than limb weakness and bulbar manifestations such as dysarthria and dysphagia (72). The effect initiation of pyridostigmine is 15-30 min. and continues for 3-4 hour. The starting dose is 0.5-1 mg /kg, 3-4 times daily with meals, increasing to 1.5 mg/kg 5 times daily depending on the treatment response and adverse effects. Doses and times must be individualized and modified according to the child's life programs. Physicians should consider immunosuppressive treatment if symptom improvement is not obviated in doses of about 1 mg/kg 4 times daily or the adverse effects limit efficient doses (9). The assessment of the effect of the drug could be completed in several weeks. Therefore initiation of the immunosuppressive treatment should not be postponed if needed (9). Side effects of pyridostigmine are due to excessive stimulation of the cholinergic system and are dose-dependent. Muscarinic effects include diarrhea and abdominal cramping, increased bronchial secretions, hypersalivation, bradycardia, blurred vision, bronchoconstriction, and decreased blood pressure. Nicotinic effects include muscle cramps and fasciculations. Adding an oral anticholinergic agent without binding to nicotinic receptors, such as glycopyrrolate or propantheline, blocks these bothersome side effects. Differentiation of cholinergic crisis with severe weakness from the MG may be difficult. However, this side effect is rare, and the observation of increasing weakness in the patient should raise suspicions of worsening of the underlying MG rather than cholinergic crisis, and then the proper treatment should be started. Intravenous atropine or glycopyrolate is used in the setting of the cholinergic crisis (8).

Immunotherapy

In mild myasthenic patients, anticholinesterases can induce rapid resolution of symptoms. However, some patients, particularly those with generalized form, need immunosuppressive therapy to reduce antibody production. No official guidelines are available in JMG; expert

opinions and adult guidelines are models for ongoing practice (9, 10, 73). Prednisolone is often effective and is the first-line immunosuppressant in the treatment, but its high doses in the first days of treatment can worsen the symptoms (9, 10). The initial dose is 0.5 mg/kg alternating days and is increased if needed gradually to a maximum dose of 1.5 mg/kg alternating days (upper limit: 1000 mg) or 1 mg/kg daily (upper limit: 60 mg). The improvement is usually obvious in several weeks, and the complete effect of treatment may be prolonged to six months. After the remission, the cholinesterase inhibitor can be discontinued, and the prednisolone tapered off monthly to the lowest effective dose (9). The Majority of experts recommend a short period of treatment with anticholinesterase before the initiation of corticosteroids in patients with mild JMG and concurrent use in the moderate and severe forms of the disease, specifically with bulbar involvement (73). The vulnerability of children to the side effects of steroids should be in mind, such as infections, growth retardation, delay in live vaccination, sleep disturbances, behavioral problems, diabetes, weight gain, hypertension, and osteoporosis. Therefore, a steroid-sparing medication is used concurrently as the second line treatment regarding the intolerable steroid side effects or when the treatment response to steroids is poor, or steroid dose reduction to a minimum efficient dose is impossible (9,10). Some of these steroid-sparing drugs are azathioprine, cyclosporine, cyclophosphamide, tacrolimus, mycophenolate mofetil, and rituximab. Plasmapheresis and intravenous immunoglobulin (IVIG) also have been implemented for long-term treatment (74).

Experts' opinions advocate the use of azathioprine in JMG (10, 73, 75). It is an analog of purine that functions through the suppression of B and T cells. It can be used alone or in conjunction with prednisolone. Azathioprine is metabolized to 6-mercaptopurine via the thiopurine methyltransferase enzyme. Screening of this enzyme is suggested in all patients before initiating azathioprine because myelosuppression is more probable given the enzyme deficiency (9). The starting dose is 1 mg/k/day, which can be titrated monthly to 2.5 mg/kg/day. Its efficient treatment response may take one year to be obvious (73, 75, 76). Patients on maintenance treatment should be checked for myelosuppression and liver function weekly for eight weeks and every three months afterward. Azathioprine is not a teratogen and can be used in female patients with long-term therapy requirements (77).

Mycophenolate mofetil suppresses the proliferation of activated T and B cells, inhibiting purine synthesis. There are some reports of its efficacy in patients with AchR antibodies, both as monotherapy or in combination with prednisolone (78), but based on studies in children, it is suggested as a second-line drug in patients with poor treatment response or intolerability to azathioprine. The greatest efficacy may not be shown until 12 months after treatment (78). Notably, it is not safe in pregnancy (9).

Tacrolimus modulates T lymphocyte activity and B cell antibody synthesis and is a calcineurin inhibitor. It is less nephrotoxic than cyclosporine (9). Studies have shown its efficacy in adults and post-pubertal patients with MG, leading to a decrease or discontinuation of prednisolone (79, 80). Greatest effect of tacrolimus is seen during six months (81).

Cyclosporine A and cyclophosphamide are alternatives for other immunosuppressive drugs. The mechanism of the effect of cyclosporine is

similar to tacrolimus, but its use has been limited due to the high probability of nephrotoxicity. Some studies have reported symptom resolution of MG during seven months of cyclosporine use alone or in combination with steroids (82). The effects of methotrexate is not well established in reports of adult MG as monotherapy (83). Cyclophosphamide, although is effective in adults with refractory MG, has been associated with elevated relapse risk (84). Besides, it has hazardous side effects such as hematological and bladder malignancies and doubtful infertility, drug accumulation in the disease course increases its risk.

Rituximab is one of the B cell-depleting agents used in MG immune treatment. Dysregulation of T cells and cytokines initiates the pathogenesis of MG, but reactive B lymphocytes also have an essential role in developing dysfunction and releasing antibodies. Agents can directly deplete B cells by targeting B lymphocytes or indirectly inhibiting cytokines (1). Rituximab is a monoclonal antibody that binds to CD20 on the B lymphocyte surface and causes the cell apoptosis. Its effect prolongs approximately six months until peripheral CD19+ and CD20 + B cells are produced from the bone marrow (85). Current doses are 375mg/m2 infused weekly for four weeks or 750 mg/m2 (upper limit: 1 gr) two weeks apart. Repeated doses may be required. Some systematic reviews and case reports have shown its efficacy in refractory JMG, which has resulted in clinical remission, steroid dose reduction, and withdrawal of oral immunosuppressant (86, 87, 88). Rituximab does not diminish the long-living plasma cells without CD20, while it reduces the short-living B cells and plasma cells with CD20. Because MuSK antibodies are released from the short-lived plasma cells, patients with MuSK-positive MG may respond better to rituximab than AchR-MG patients (1, 9). Susceptibility to unusual infections like progressive multifocal leukoencephalopathy and hypogammaglobulinemia are significant side effects (9). Side effects have been reported in 4-26.1% of cases (1). Other new B-cell depleting agents undergoing clinical trials for MG include inebilizumab, tolebrutinib, a Burton's Tyrosine Kinas inhibitor, and Bortezomib. A clinical trial in pediatric patients is currently underway (NCT03759366). As MuSK antibodies are predominantly IgG4, which do not activate complement pathways, Eculizumab may not be an effective treatment in this group.

IVIG has different mechanisms of action, including complement pathway inhibition, reducing cytokines and antibody synthesis, and FC-receptor-mediated cytotoxicity modulation (9). The treatment response is usually seen in less than one week, and maximized in two weeks, and lasts 3-6 weeks (8, 9). Therefore, IVIG is used more in life-threatening myasthenic exacerbations or as a pre-operative therapy before thymectomy (89). Furthermore, reports are available regarding its use as a maintenance treatment (90). The recommended dose is 1gr/kg for two days. The maintenance dose is 1gr/kg every 4-6 weeks, according to the patient's status.

Plasmapheresis clears autoantibodies directly from circulation and also plays a role in the proliferation of lymphocytes. Its indications of use resemble IVIG in disease exacerbations and crises and pre-operative stabilization. Seemingly, plasma exchange is more efficient in most severely ill patients than IVIG and acts quicker despite reports regarding equal clinical results of both studies (91). The effect of plasmapheresis is seen in days and lasts 3-6 weeks. Antibodies rise more

during weeks if no combination immunotherapy exists (8). The usual course is 3-5 exchanges every other day. In young children, lack of appropriate vascular access is a limiting problem, and IVIG is particularly preferred. Significant complications include catheter-related thrombosis and infection, hypotension, arrhythmia, bleeding, muscle cramps, and citrate reactions (92).

Thymectomy is a significant part of management due to the identified role of the thymus in MG pathogenesis. By thymectomy, germinal centers in the thymus are remove, and antibody synthesis is disrupted (8). Thymoma is rare in JMG, but hyperplasia of the thymus is not infrequent (40). Despite the clinical manifestations, thymic imaging should be done in all children (9). Thymectomy is considered in all patients with generalized JMG with AchR antibodies and in the ocular AchR positive antibodies patients with poor response to appropriate immunosuppressive therapy or immunosuppressive dependent patients (due to the side effects of long-term immunosuppression). Earlier surgery during two years of disease onset has a better outcome (9). The risk of evolving generalized MG in ocular MG patients has been proven to be reduced by thymectomy (93). Because the symptom remission occurs more in pre-pubertal patients, and also according to the time necessary for immune maturation in early childhood, the benefit of thymectomy should be considered against the age of children. There are a few reports of increased risk of developing other autoimmune, particularly rheumatologic diseases in MG patients undergoing thymectomy (94). Thymectomy is not indicated MuSK antibodies positive JMG due to lack of benefit. Moreover, no indication exists for thymectomy in patients with LDL4 or agrin-positive antibodies (95). The risk of antimuscarinic adverse effects of anticholinestrases is increased following thymectomy and should be used cautiously (8). Minimal invasive thymectomy techniques seem to have the same outcomes as more aggressive procedures (8, 9, 96).

Myasthenic crises

Transient worsening of neuromuscular weakness may be triggered by surgery, coinciding infections, certain drugs, decrement of immunosuppressant drugs, or occurs spontaneously in the course of the disease and leads to the life-threatening respiratory failure named myasthenic crisis (73, 75). This can also result from laryngeal collapse due to bulbar weakness. The frequency of myasthenic crisis is similar to that of adults and is estimated to be 10% (27, 28). JMG patients with a generalized form and patients with an ocular form of less than two years of disease onset (since they are yet susceptible to developing a generalized form) are more vulnerable to respiratory crisis following respiratory infections. Patients with a pure ocular form for two years or more are less likely to progress to a generalized form and are not at increased risk of respiratory failure. Worsening of bulbar weakness, severe generalized weakness, dyspnea, and lethargy are warning signs of a crisis. Superimposed respiratory infections may bring the patient into assisted ventilation if noninvasive ventilation has been used in the early phases (97). The initial treatment step is recognizing and eliminating any triggering factors, including infections. Any recent alteration in drugs, either up or down titration of myasthenic treatments, as well as using the new medications, should be considered. IVIG and plasmapheresis are the treatments of choice because of their rapid onset of effects within days. Plasmapheresis is particularly helpful, although access to the

appropriate venous lines may be problematic in young children. Pyridostigmine and steroids can be prescribed at high effective doses while the patient has ventilator support. Intravenous methylprednisolone is not recommended for maintaining short-term remission due to the potential of MG exacerbation and increased vulnerability to critical illness myopathy; it is better to delay prescribing it for several days after initiation of plasmapheresis or IVIG effects (98). However, there are some reports of prescribing pulsed methylprednisolone with significant improvement in the less severe exacerbations of the disease (8). The mild or moderate exacerbations of symptoms frequently are seen in MG patients but may not be severe enough to be considered a crisis. Treatment strategy should be planned according to the severity of symptoms and the speed of neurologic worsening, along with considering any triggering factor of exacerbation (8). In the mild forms, incrementing the dose of pyridostigmine, starting or titrating steroids, or close observation and treatment of concurrent infection may be the only proper approach, while in the severe exacerbations with progressing dyspnea or dysphagia, admission into the intensive care unit and close monitoring for impended myasthenic crisis is necessary (8).

New immunotherapies for MG and other treatments

About 10% of adult generalized MG patients have refractory disease or are intolerant of conventional immunotherapies (8). Some new medications affecting the immune pathogenesis of MG have been reported. The effects of these drugs are in three ways:

1. Complement cascade inhibition: Complement pathway activation in MG is accomplished by autoantibodies, especially anti-AchR IgG1 and IgG3 antibodies (but not anti-MuSK IgG4). This results in forming a membrane attack complex that finally disturbs the posterior synaptic membrane and is the essential pathogenesis in AchR-MG (99). Therefore, drugs inhibiting key agents in the complement pathway (C5, C3, and C1) can treat MG (100). According to the clinical trials, the most effective drugs of this group are: eculizumab, ravulizumab, and zilucoplan. Eculizumab, a monoclonal antibody against the C5 protein of complement, was approved for treating refractory generalized AchR-antibody MG in adults in 2019 (1, 9). Rapid and significant remission of the manifestations and improvement in the quality of life scores have been reported in studies (101). A clinical trial in children with MG is currently ongoing (NCT03759366) (9). Eculizumab is not effective in treating MuSK antibody-positive patients because these antibodies are from the IgG4 subtypes that do not trigger the complement cascade (9). Zilucoplan is another medication with terminal inhibition of the complement system. It is small in size and suitable for end plate irradiation. It can be used concomitantly with IVIG because it is not an antibody (102).

2. Targeting neonatal FC receptor (FcRn) and inhibiting IgG synthesis: FcRn with binding to IgG protects it from degradation enzymes. Blocking of the FcRn decreases the IgG autoantibodies level. The effect of these drugs resembles the plasmapheresis. Other subtypes of antibodies remain in normal concentrations. Besides, IgG levels return to normal values faster than B-cell-depleting treatments and a lower chance of infection is expected (103). These agents include efgartigimod and monoclonal FcRn antibodies such as rozanolixizumab, nipocalimab, orilanolimab, and batoclimab. Efgartrigimod was

approved in 2021 for refractory generalized MG in adults. Studies have shown a 40-70% decrease in AchR antibodies and improvement in most patients 12 weeks after starting the drug (103,104). Recently, few clinical trials have been conducted to evaluate the safety of intravenous efgartigimod in generalized MG in children (NCT06392386, NCT04833894).

3. B-cell depleting mechanisms, which were mentioned earlier. Furthermore, cytokine and chemokine-depleting agents such as interleukin-6 antagonists and other medications have been administered in refractory MG patients. Satralizumab and tocilizumab are interleukin-6 antagonists that have been approved for else chronic immune-mediated diseases such as neuromyelitis optica spectrum disorders. These two drugs are currently developing as treatments for generalized MG in adults.

In a recent study, subcutaneous immunoglobulin was administered during four weeks in adult patients with worsening MG. Significant improvement effects were seen at six weeks, and the effects were comparable to those of intravenous IVIG (1). A recent study in 10 adult MG patients with MuSK antibody reported that 3,4 diaminopyridine (3,4-DAP), a voltage-gated potassium channel inhibitor that increases the Ach release in the neuromuscular junction, with 30–60 mg daily dose during a trial period of 21 days (in combination with placebo at alternating days) was effective and safe in the treatment (9).

Outcome

JMG outcomes have been remarkably raised regarding more effective treatments. In JMG, the clinical course is relatively benign, the prognosis is better than in adults, and the rate of spontaneous remission is also higher, particularly in the pre-pubertal group (9, 10). Despite the equal incidence of myasthenic crisis in adults and children, the mortality rate of adult patients is remarkably higher, which may be partly due to the frequency of thymomas in adults. This is one cause of the lower mortality in JMG (28). Based on studies, ocular MG children of Asian and African ethnicity have a higher risk of evolving refractory ophthalmoplegia (19). Ethnic origin also seems to affect the remission rate (10). Compared with JMG, ocular MG has a better prognosis, a higher remission rate, and a lower rate of myasthenic crisis (28).

In conclusion

JMG is an autoimmune antibody-mediated disease of postsynaptic endplate that is defined as MG presentation in patients before the age of 18 years old. While many clinical features of JMG are identical to the adult MG, there are some significant differences between them regarding presentation, clinical course, antibody level, and histopathology of the thymus, as explained in this article. Precise diagnostic evaluation and distinction from CMS is crucial. In JMG, ocular symptoms are more frequent, the clinical course is comparably benign, and the outcome is better than adult MG. The treatment plan is conducted according to the clinical course, antibody type, and disease severity. The mainstay of treatment includes symptomatic therapy, long-lasting immunosuppressive treatment, and treatment of myasthenic crisis. The newer medications are conducted to the specific pathophysiologic mechanisms of the disease and are used primarily in the refractory MG.

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Azita Tavasoli: Study design, data acquisition, interpreting and discussing results and Manuscript writing.

Conflict of interest

The author declare that there is no conflict of interest.

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