



Childhood-Onset Myasthenia Gravis, a Troublesome Clinical Entity with Heterogeneity in China

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Received Date: January 03, 2018

Published Date: January 11, 2019

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Abstract

Myasthenia gravis (MG) is a well-known autoimmune disease involving neuromuscular transmission leading to fluctuating muscle weakness and fatigability. With the advent of immunotherapy, majority of MG sufferers will have a good outcome. However, the childhood onset MG (CMG) in China is quite different from that reported in the Western countries in light of onset age distribution, clinical types, responsiveness to immunotherapy and the long-term outcome. The mini-review focuses on the differences of Chinese CMG patients from European cases.

Keywords: myasthenia gravis; Child; Juvenile; Heterogeneity; Chinese; Drug-resistance

Introduction

Myasthenia gravis (MG) is a T cell dependent, antibody-mediated neuromuscular junction disease with complement system activation [1], often presenting with muscle weakness and fatigability of affected muscles. The distribution of affected muscles varies significantly from case to case, and the same regarding the onset ages. Some studies reported the bimodal distribution of ages at onset in the Western countries, with a peak of onset 20-40 years old in females and 50-60 years old in males [2,3]. However in China, the disease tends to more frequently affect children than adults [4-6]. In literatures, the term, juvenile MG (JMG) is frequently used to describe the disease happened before age of 19 years [7], which are subdivided into prepubertal and postpubertal patients, according to occurrence of the first symptoms before or after puberty [8]. Childhood onset myasthenia gravis (CMG) depicts the condition that MG patients who develop the disease before age of 14 years and accounted for more than half of MG population in China and harbored unique features different from the cases of JMG in the Western countries or the ones of adult onset myasthenia gravis (AMG). The following paragraphs focus on the research concerning the CMG.

Demographic Differences

The estimated incidence of MG ranges from 15 to 179/1,000,000/year in the Western countries [9,10], of which the incidence of JMG is between 1 and 5/1,000,000/year accounting for 10-15% of all MG population [10-14]. The onset age distribution in

Western JMG population has one peak in postpubertal, aged from 12 to 18 years, accounting for 66-90% [12,15]. Unfortunately, the epidemiology of MG is generally lacking in China, and a survey in Yiyang county in Hunan Province in 1986 discovered 60 MG patients in 590,000 residents (incidence was 10/100,000), with CMG 48 cases (80%) [16]. The Chinese hospital-based reports stated that CMG patients were estimated to account for more than 50% of the MG population, with a peak of onset age before 10 years, mainly aged 2-5 years [4-6,17].

Distinct Features

In the Western countries, the prepubertal patients have distinctive clinical characteristics compared with the postpubertal cases, who shared more features with AMG, such as presentations, transformation to the generalized types, immunological profiles, thymic abnormalities and responses to therapy [8,18-22].

Presentations and transformation

In prepubertal MG children, similar to late-onset AMG (LOMG) cases, no sex predominance has been observed [23]. While the postpubertal MG children had a predilection for females, just like early-onset AMG (EOMG) patients [24,25]. As reported, the prepubertal children are more likely to present with isolated ocular symptoms compared with the overwhelming generalized presentations among the postpubertal children and AMG patients [18-20]. Out of those prepubertal cases with initial ocular

presentations, 50-60% would develop into generalized muscle weakness within 2 years, similar to the patients of AMG [22,26]. But in a sharp contrast, the Chinese CMG children only present with ocular type in as high as 71-95% of the CMG population with a pretty low rate of transformation to generalized types [6,27]. The conversion rate of CMG was significantly lower than that of AMG in our retrospective studies over 10 years follow-up (12.4% vs. 32.5%) [6], and much lower than that of JMG or AMG in the Western countries (50-60% and 80%, respectively) [22,28]. Interestingly, a cohort of study in Thailand disclosed the similar results in the JMG patients [29]. Though the risk factors for transformation have not been clearly pulled out yet [6,30], the long disease duration and onset age older than 10 years were reported to be associated with the transformation [31].

Immunological profiles

50-71% of the prepubertal children were AChR antibodies positive when compared with 80-90% seropositivity among the postpubertal or adult patients [15,18,20]. Numerous studies have demonstrated a high percentage of seronegativity among CMG children, especially in the prepubertal or those with isolated ocular symptoms [7,18-20,32-34]. MuSK-positive cases were very rare in seronegative children [13,35], while 40-50% of AMG patients who were negative for AChR antibodies had elevated titers of antibodies against MuSK [36]. Other antibodies profiles were not routinely determined in the literatures, such as LRP4, Titin, etc, in CMG patients. The possibility of other neuromuscular diseases mimicking CMG had been thoroughly investigated and ruled out, including the congenital myasthenic syndromes, mitochondrial myopathies, congenital myopathies or pure Graves disease in the CMG children.

Thymus abnormalities and thymectomy

Thymus abnormalities in CMG and JMG around the world are similar, of which thymic hyperplasia is the most common one, accounting for 73-89%, while thymoma is particularly rare, accounting for 0-3.8% [4,6,7,15,19,37,38]. However, in AMG patients, thymic hyperplasia is common in EOMG (46.6-80%), and thymoma is frequently observed in LOMG (50-75%) [1,39-41]. Indications for thymectomy are less clear for prepubertal JMG, and for seronegative children and the ones with isolated ocular symptoms. There are concerns that thymectomy performed at a young age may result in premature immunosenescence [42]. Nonetheless, thymectomy constitutes an important option in children if the pharmaceutical treatment proves unsatisfactory. According to a wide consensus, thymectomy is indicated in seropositive postpubertal children with moderate to severe generalized symptoms [43]. Thymectomy is mandatory if thymoma is present, but this situation is rare in children. The benefit of thymectomy to the children remains controversial. Popperud et al reported the efficacy of thymectomy in the prepubertal onset patients who presented severe generalized symptoms or even frequent myasthenic crisis [22]. Similarly, Heng et al considered the trans-sternal thymectomy was effective in improving the outcome of 24 severe generalized children with positive AChR-ab in the United Kingdom [44].

On the contrary, we have performed a trans-sternal thymectomy in a cohort of 34 CMG patients (27 ocular type cases and 7 generalized type cases) who failed to respond well to drug therapy

and have found thymoma in 6 cases and hyperplasia in 28 patients. But unfortunately, the general outcome of the cohort did not improve significantly, only slight improvement in the 7 generalized CMG patients [6]. The results may hint at the difference of CMG with isolated ocular type from those with generalized MG types.

Refractory cases

At present, the definition of refractory MG is not definitely delineated [45]. Although related researches are few, we have found that about 20% of ocular CMG patients in our database were resistant to drug therapy [6]. The longer follow-up observation of the Chinese CMG children disclosed that the majority of the cases had a tendency to relapse (over 50%) after they had achieved the status of being symptom-free for months or years. Slowly, the relapsing-remising cases could become resistance to oral corticosteroids and pyridostigmine [6]. The resistant or refractory cases would have troublesome symptoms such as symmetric or asymmetric ptosis, strabismus and amblyopia, which profoundly compromise the sufferers' social and personal activities and social-psychological behavior as well. It is urgent for physicians to improve their symptoms. All the treatment of CMG has largely been extrapolated from adults' data, so for refractory children, there is no clear guidance yet. Thymectomy may be beneficial to the CMG cases with generalized types, but no significant efficacy was observed in the cases with isolated ocular symptoms [38,43,46]. FK506 was initially tried to significantly improve the symptoms unresponsive to oral corticosteroids and pyridostigmine and had achieved satisfactory improvement in majority of the CMG cases who had the troublesome ocular symptoms [47,48]. Rituximab was occasionally used to treat both the intractable children and adults with generalized types and showed efficacy [49-52], but the data in CMG patients with sole isolated ocular symptoms is lacking. Based on the pathogenesis of autoimmunity, seeking more accurate novel immunosuppressive agents and biomarkers which may actually represent the severity and activity of the disease are needed in the refractory children.

Response to therapy and prognosis

There have been no large-scale prospective studies on the long-term outcome of CMG population all over the world except for some cross-sectional studies or retrospective studies [6,22,53-57]. Thus, the disease course and prognosis of MG children remained poorly defined. Even though spontaneous remission was reported to be high in children (15-34.7%) [19,58], especially in the prepubertal sufferers [18], or sole administration of acetylcholinesterase inhibitors may achieve satisfactory prognosis [53], the nature course has not been clearly depicted. Corticosteroids are the first-line immunosuppression therapy in treating MG, and both the ocular and generalized MG usually respond well to steroids. In order to avoid the side effects of long-term use of corticosteroids or to further improve the symptoms, cytotoxic agents, such as azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, as steroid-sparing or alternative therapy would be probably added on and achieved improvement in some case [7,38,54,59].

Most studies suggested a high remission rate after thymectomy in JMG [18,44,60,61], especially in postpubertal cases (29-68%) [38,56,62,63], similar to AMG population. Whereas the data about thymectomy in prepubertal was scarce [21]. In China, CMG children

showed a good response to acetylcholinesterase inhibitors and immunotherapy initially, but majority of the patients would develop acquired drug-resistance or take a remising-relapsing course. These CMG children may relapse after they had achieved a complete clinical stable remission or pharmaceutical remission for years [6]. After multiple relapses, the symptoms will fail to respond to the therapy again (acquired drug-resistance) with unknown pathogenesis. Thus, the relapses after remission and acquired resistance to corticosteroids constitute the major concern in Chinese CMG populations.

Multidisciplinary Management

The ocular symptoms, such as symmetric or asymmetric ptosis, strabismus, diplopia or eyeball fixation, etc., with poor therapeutic efficacy would persist in a considerable group of patients with or without fluctuation and immensely affect the sufferers' facial appearance, social activity and psychological status [19]. What is more, the chronic side effects of steroids such as growth-stunting and weight gain, would superimpose the MG symptoms and aftereffects [19]. In dealing with the sufferers with the intractable MG symptoms, it should be emphasized that multidisciplinary cooperation including neurologists, pediatricians, psychotherapists, and ophthalmologists is needed to improve the outcome of the CMG patients [20].

The Possible Reasons for the Chinese CMG

Up to now, the reasons for the distinctive Chinese autoimmune CMG patients remain elusive, although the CMG-mimics have been ruled out. Genetic background probably constitutes the cardinal factors [31,64]. HLA DRw9 and DRw13 were strongly associated with Japanese MG [31], Bw46DR9 with Chinese [27,65], DQ8 and DR3 with Caucasian, and DR5 with African descents [66]. Besides, environmental factors may play as a trigger to activate the autoimmunity by way of molecular mimicry, supra-antigen or by-stander mechanism [17]. In all, CMG is a clinical entity with worldwide heterogeneity concerning the clinical presentations and the responses to therapy. The Chinese CMG presents unique predominant ocular symptoms which harbor the remising-relapsing course and acquired resistance to corticotherapy. More attention should be paid to elucidate the reasons why the CMG is likely to affect the Chinese and to investigate more accurate therapeutic methods to improve the ocular symptoms.

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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