European Review for Medical and Pharmacological Sciences 2016; 20: 2404-2408

Effect of glucocorticoid combined with gamma globulin in treatment of children with myasthenia gravis and its effects on immune globulin and complement of children

M.-G. WANG[1], X.-X. HUANG[1], D. YAO[1], Q. AN[2], X.-Q. DENG[1]

[1]Department of Neurology, Xuzhou Children's Hospital, Xuzhou, Jiangsu, P.R. China
[2]Department of Hematology, Xuzhou Children's Hospital, Xuzhou, Jiangsu, P.R. China

Abstract. – OBJECTIVE: To discuss the effects glucocorticoid combined with gamma globulins in the treatment of children with myasthenia gravis and its effects on immune globulin and complement of children.

PATIENTS AND METHODS: Clinical data of 70 cases of childhood myasthenia gravis in this hospital were retrospectively analyzed. These cases were randomly divided into observation group and control group. For observation group, there were methylprednisolone and gamma globulins while the only methylprednisolone in the control group. The clinical effects and changes in immune globulin and complement of two groups were observed.

RESULTS: The total effective rate for observation group was 94.3% and 74.3% for the control group, and this difference was statistically significant ($p < 0.05$) The time for relief of symptoms (6.55 ± 1.35 days) and total hospital stay (17.15 ± 3.65 days) in observation group was apparently shorter than the control group, with statistical significance ($p < 0.05$).

CONCLUSIONS: Glucocorticoid and gamma globulin can improve the symptoms and achieve satisfying clinical effects for the treatment of myasthenia gravis in children. Thus, it is valuable for further popularization and application.

Key Words:
Glucocorticoid, Gamma globulins, Myasthenia gravis, Clinical effects.

Introduction

Myasthenia gravis (MG) is an autoimmune disease caused by acetylcholine receptor (AchR) of post synaptic membranes of neuromuscular junction[1,2]. The main clinical manifestations are partial or systemic skeletal muscle weakness and fatigue. These symptoms are aggravated after activities and relieved after rest and treatment of acetyl cholinesterase inhibitors (AchEI). The current mainstream treatment method is impacted treatment of large doses of glucocorticoids[3,4]. However; this method could cause paralysis of respiratory muscles and become life-threatening. In this study, gamma globulins treatment was applied based on glucocorticoid impact treatment, which has achieved satisfying clinical effects as described below.

Patients and Methods

Patients

A total of 70 cases of childhood myasthenia gravis were treated in the Department of Neurology of this hospital and associated units from January 2008 to May 2013. The main diagnostic basis was pathological fatigue and daily unstable manifestation of myasthenia as well as the positive results of careful and accurate neostigmine test. Observation group and control group were divided based on random numbering, and there were 35 cases in each group. In the observation group, there were 18 male and 17 female cases, the age range was from 1 to 12 years and the mean age was 4 ± 1.5 years; the course of disease was from 1.5 months to 1 year. There were 15 cases of Type I, 16 cases of Type II and 4 cases of Type III of myasthenia. For the control group, there were 19 male and 16 female cases, the age range was from 1.2 to 13 years and the mean age was 4.1 ± 1.7 years; the course of disease was from 3 months to 1.5 years. For the types of myasthenia, there were 16 cases of Type I, 15 cases of Type II and 4 cases of Type III. There was no statistical significance in terms of the differences in sex ratio, age, mean age and course of the disease ($p > 0.05$) and both groups showed comparability.

Corresponding Author: Xingqiang Deng, MD; e-mail: dengxingqiang361@163.com

Methods

Patients in both groups received symptomatic treatment once admitted to the hospital. AChEI was applied to improve neuromuscular junction transmission of patients. The most frequently used medicine in this hospital was pyridostigmine bromide and the common dose used was: 5 mg/(kg·d) for children younger than 5 years old, 7 mg/(kg·d) for children older than 5 years and 3 to 4 times a day. Meanwhile, conventional nursing measures were adopted for children. For patients in control group, impact treatment of a large dose of methylprednisolone (15-20 mg/(kg·d), at the maximum dose was no more than 1000 mg/d) was applied by intravenous infusion continuously for 3 to 5 days. Furthermore, prednisone was taken orally (1.5-2 mg/(kg·d)) for 1 to 2 months and 2.5-5 mg can be reduced for every half to one month according to patient's condition until the minimum effective maintenance dose. The total treatment time should not be less than 1.5 years. Based on the control group, 0.4 g/(kg·d) gamma globulins (manufactured by Chengdu Institute of Biological Products) by intravenous infusion were applied to the observation group. The intravenous infusion speed is slow at the start and, then, 10-15 mL is added every 30 min. It increased quickly from 40 mL/h to 100 mL/h for a course of 5 days. Both groups were treated in the same way for the rest of the time[5,6].

Evaluation Methods for Clinical Effects

The items were tested before and after treatment and the absolute scores items included: muscle strength of the upper eyelid, fatigue test of upper eyelid, horizontal eye movement, facial muscle strength, fatigue test of upper limbs, fatigue test of lower limbs, swallowing and respiratory function. The total score was 60. The relative score = (before treatment score – after treatment score)/score before treatment*100%. According to the results of relative score: the patients are recovered if the score is more than 0.95; a score between 0.80 and 0.95 indicates that the patients are basically cured; for score between 0.50 and 0.79, there are evident effects; for 0.25 to 0.49, the conditions of patients are improved; but the score below 0.25 suggests no effect. The condition of patients was scored once a day at 9:30 am for the first 2 weeks of treatment, and there after evaluations were done once a week. The total effective rate = recovery + basically cured + evident effects + improved.

Testing Index

The clinical symptoms of patients in two groups, their absolute score conditions before and after the treatment, the start time of symptoms relief, hospital stay and adverse reactions, etc. were recorded. Meanwhile, the immune globulins and complement C3 of patients in two groups were tested and recorded regularly.

Statistical Analysis

SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA) was applied to analyze data. The measurement data are presented by mean ± standard deviation (± S). Comparison between the groups was tested by t and the conditions before and after the treatment was tested by paired t. Enumeration data were tested by χ^2. The difference was considered of statistical significance when $p < 0.05$.

Results

Comparison of Clinical Effects Between Two Groups

For observation group, there were 11 basically cured cases, 6 cases with evident effects and 7 improved cases, the total effective rate was 94.3%, which is evidently better than 74.3% of control group. The comparison of two groups was with statistical significance ($\chi^2 = 5.285$, $p = 0.022$), details are shown in Table I.

Table I. Comparison of clinical effects in two groups (cases, %).

Group	Cases	Recovery	Basically cured	Evident effects	Improved	No effects	Total effective rate (%)
Observation group	35	9	11	6	7	2	94.29
Control group	35	5	8	7	6	9	74.29

Note: Compared to control group, $p < 0.05$.

Absolute Score Conditions Before and After the Treatment, Time of Symptoms Relief and Hospital Stay for Two Groups

The absolute score of observation group after the treatment was (9.15 ± 5.01), which is lower than the control group with statistical significance ($p < 0.05$); the time of symptoms relief (6.55 ± 1.35 days) and hospital stay (17.15 ± 3.65 days) of observation group were fewer than the control group, and the difference was statistically significant ($p < 0.05$). Please see the details in Table II.

Comparison of Changes in Terms of Immune Globulins and Complement Before and After the Treatment in Two Groups

The differences between before and after the treatment for observation group and control group had statistical significance ($p < 0.05$). However, the treatment effects in observation group were more evident and with statistical significance compared to the control group ($p < 0.05$) as presented in Table III.

Occurrence of Adverse Reactions

During the treatment process, there were 2 cases of numbness of respiratory muscle and 7 cases with more severe myasthenia, among them 3 cases of paralysis of respiratory muscle caused by numbness and ventilators were used. There was no statistical significance in terms of using breathing machines between two groups ($X^2 = 0.186$, $p = 0.666$). Please see more details in Table IV.

Discussion

Main pathological changes of myasthenia gravis occur in the neuromuscular junction. The synaptic cleft of neuromuscular junction gets widened and the wrinkles on subsynaptic membrane became smooth and decreased in number[7,8]. Under the immuno-electron microscope, it was observed that the subsynaptic membrane was disintegrated, the AchR were decreased, and there were deposits of IgG-C3-AchR combined immune complex[9-11]. No evident changes regarding the muscle fibers itself; how-

Table II. Comparison of the absolute score before and after the treatment, time of symptoms relief and hospital stay ($\bar{x}$ ± S).

Group	Cases	Absolute score before treatment (score)	Absolute score after treatment (score)	Time of symptoms relief (d)	Hospital stay (d)
Observation group	35	22.13 ± 5.35	9.15 ± 5.01*	6.55 ± 1.35*	17.15 ± 3.65*
Control group	35	23.01 ± 5.15	14.17 ± 5.13	15.05 ± 3.25	33.65 ± 5.75

Note: Compared to the control group, *$p < 0.05$.

Table III. Comparison of immune globulin IgG and complement before and after the treatment in two groups ($\bar{x}$ ± S).

Group	Cases	IgG (mg/mL)		C3 (g/L)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	35	12.27 ± 3.12	9.01 ± 0.05#,*	2.95 ± 0.23	1.47 ± 0.13#,*
Control group	35	12.21 ± 3.13	9.69 ± 0.09*	2.89 ± 0.21	1.97 ± 0.16*

Note: Compared to control group, #$p < 0.05$; compared to before treatment, *$p < 0.05$.

Table IV. Comparison of using breathing machines in two groups (cases, %).

Group	Cases	Number using breathing machine	Percentage (%)
Observation group	35	2	5.71
Control group	35	3	8.57

ever, sometimes solidification, necrosis and swelling of muscle fibers were observed. Also, muscle atrophy occurred for chronic lesions[12,13].

A distinctive feature of MG patients is that the patient's condition is mild in the morning and gets worse as the day progresses which could be due to fatigue and gets alleviated next morning or after rest[14-18]. Skeletal muscles of the whole body are fatigued, especially extraocular muscles, facial muscles, throat muscles and proximal muscles of four limbs[19-21]. Myasthenia often starts in one muscle group and gradually the range is extended. In this study, all above mentioned features were present in the children.

Currently, use of glucocorticoids is the most important method to treat MG. Whereas, for MG Type II B and Type III patients, the intervention of glucocorticoid is applied besides symptomatic treatment methods such as a large dose of immune globulin[22,23]. Meanwhile, for glucocorticoid therapy full dose, adequate duration of the treatment, slow dosage reduction and proper maintenance dose treatment principles should be followed[24,25].

Thus, it can be concluded from this study that hormone and gamma globulin can achieve better clinical effects as the total effective rate was 94.3%, compared to 74.3% in control group and the difference is statistically significant ($p < 0.05$). This indicates that the combined treatment of glucocorticoid and gamma globulin had better effects and could shorten the hospital stay and duration of symptoms relief. Meanwhile, there are two methods in terms of glucocorticoid treatment on MG, and these are regression method (downward method) and incremental method (upward method), which are selected and applied based on the actual conditions. This work also indicates that there are possibilities for increased symptoms of myasthenia and causing a crisis in terms of glucocorticoid treatment on MG. Therefore, there are more cases of adverse reactions in the control group and it is suggested that the incremental method should only be applied to severe Type II B and Type III patients in clinical practice, while for other mild conditions, gradual incremental treatment method should be applied[26-28].

Conclusions

Above all, combined method of glucocorticoid and gamma globulin for the treatment of childhood myasthenia gravis can achieve evident effects in a shorter time, which in turn will reduce treatment time and the hospital stay of patients as well as achieve satisfying clinical effects, and should be popularized and applied further.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Melbourne Chambers R, Forrester S, Gray R, Tapper J, Trotman H. Myasthenia gravisin Jamaican children: a 12-year institutional review. Pediatr Int Child Health 2012; 32: 47-50.
2) Tracy MM, McRae W, Millichap JG. Graded response to thymectomy in children with myasthenia gravis. J Child Neurol 2009; 24: 454-459.
3) Zhang X, Yang M, Xu J, Zhang M, Lang B, Wang W, Vincent A. Clinical and serological study of myasthenia gravis in HuBei Province, China. J Neurol Neurosurg Psychiatry 2007; 78: 386-390.
4) Chiang LM, Darras BT, Kang PB. Juvenile myasthenia gravis. Muscle Nerve 2009: 39: 423-431.
5) Koves IH, Cameron FJ, Kornberg AJ. Ocular myasthenia gravis and Graves disease in a 10-year-old child. J Child Neurol 2009; 24: 615-617.
6) Scheer BV, Valero-Burgos E, Costa R. Myasthenia gravis and endurance exercise. Am J Physi Med Rehabil 2012; 91: 725-727.
7) Wang R, Zhang P, Wang Y, Zhang L. Role of ubiquitin ligase Cbl-b in B-cell activation of dendritic cells loaded with Tα146-162 in the treatment of experimental autoimmune myasthenia gravis in mice. Eur Rev Med Pharmacol Sci 2014; 18: 1723-1734.
8) Scoppetta C, Scoppetta M. Common sense in treating persons suffering from myasthenia gravis. Eur Rev Med Pharmacol Sci 2014; 18: 937-938.
9) Bodack MI. Ptosis and cranial nerve IV palsy reveal juvenile myasthenia gravis. Optometry 2009; 80: 342-349.
10) Dejie W, Xingguo L, Dong Z. Research progress of glucocorticoid receptors. Prog Mod Biomed 2010; 10: 1592-1594.
11) Strober J, Cowan MJ, Horn BN. Allogeneic hematopoietic cell transplantation for refractory myasthenia gravis. Arch Neurol 2009; 66: 659-661.
12) Parikh K, Vaidya A, Jain R. Preliminary results of VATS thymectomy for pediatric myasthenia gravis. Pediatr Surg Int 2011; 27: 595-598.
13) Lo HP, Bertini E, Mirabella M, Domazetovska A, Dale RC, Petrini S, D'Amico A, Valente EM, Barresi R, Roberts M, Tozzi G, Tasca G, Cooper ST, Straub

V, North KN. Mosaic caveolin-3 expression in acquired rippling muscle disease without evidence of myasthenia gravis or acetylcholine receptor autoantibodies. Neuromuscul Disord 2011; 21: 194-203.

14) Sankhyan N, Chakrabarty B, Sharma S, Ramesh K, Gulati S. Limb-girdle myasthenia gravis in a 10-year-old girl:a case report. J Child Neurol 2011; 26: 1434-1437.

15) Katzberg HD, Barnett C, Bril V. Predictors of response to immunomodulation in patients with myasthenia gravis. Muscle Nerve 2012; 45: 648-652.

16) Soltys J, Kusner LL, Young A, Richmonds C, Hatala D, Gong B, Shanmugavel V, Kaminski HJ. Novel complement inhibitor limits severity of experimentally myasthenia gravis. Ann Neurol 2009; 65: 67-75.

17) Barnett C, Grinberg Y, Ghani M, Rogaeva E, Katzberg H, St George-Hyslop P, Bril V. Fcγ receptor polymorphisms do not predict response to intravenous immunoglobulin in myasthenia gravis. J Clin Neuromuscul Dis 2012; 14: 1-6.

18) Soltys J, Halperin JA, Xuebin Q. DAF/CD55 and Protectin/CD59 modulate adaptive immunity and disease outcome in experimental autoimmune myasthenia gravis. J Neuroimmunol 2012; 244: 63-69.

19) Yuqiang C, Yuan W. Gamma immunoglobulin Fc glycosylation and biological activity and function. Prog Mod Biomed 2008; 8: 1368-1370.

20) Ware TL, Ryan MM, Kornberg AJ. Autoimmune myasthenia gravis, immunotherapy and thymectomy in children. Neuromuscul Disord 2012; 22: 118-121.

21) Ren J, Bai Y, Hao L, Dong Y, Pi Z, Jia L. Amelioration of experimental autoimmune myasthenia gravis rats by blood purification treatment using 4-mercaptoethylpyridine-based adsorbent. J Biomed Mater Res A 2011; 98: 589-595.

22) Takahashi Y, Sugiyama M, Ueda Y, Itoh T, Yagyu K, Shiraishi H, Ukeba-Terashita Y, Nakanishi M, Nagashima T, Imai T, Motomura M, Saitoh S. Childhood-onset anti-MuSK antibody positive myasthenia gravis demonstrates a distinct clinical course. Brain Dev 2012; 34: 784-786.

23) Heatwole C, Johnson N, Holloway R, Noyes K. Plasma exchange versus intravenous immunoglobulin for myasthenia gravis crisis: an acute hospital cost comparison study. J Clin Neuromuscul Dis 2011; 13: 85-94.

24) Foldvari A, Kovacs N, Sipos V, Merth G, Vincze F, Szucs M, Sandor J. Estimation of incidence, prevalence, and age-at-diagnosis of myasthenia gravis among adults by hospital discharge records. Wien Klin Wochenschr 2015; 127: 459-464.

25) Alahgholi-Hajibehzad M, Kasapoglu P, Jafari R, Rezaei N. The role of T regulatory cells in immunopathogenesis of myasthenia gravis: implications for therapeutics. Expert Rev Clin Immunol 2015; 14: 1-12.

26) Gomez AM, Van Den Broeck J, Vrolix K, Janssen SP, Lemmens MA, Van Der Esch E, Duimel H, Frederik P, Molenaar PC, Martínez-Martínez P, De Baets MH, Losen M. Antibody effector mechanisms in myasthenia gravis-Pathogenesis at the neuromuscular junction. Autoimmunity 2010; 43: 353-370.

27) Kang SY, Oh JH, Song SK, Lee JS, Choi JC, Kang JH. Both binding and blocking antibodies correlate with disease severity in myasthenia gravis. Neurol Sci 2015; 36: 1167-1171.

28) Yamamoto T, Yokozeki H. Discoid lupus erythematosus in a patient with myasthenia gravis. Int J Rheum Dis 2015 May 12. DOI: I0.III/1756-185X.12624 [Epub ahead of print].