Neurology Current Research

ISSN: 2687-6981

Case Report

Involvement of Frontal Lobes and Cingulate Gyri in Symptom Clusters of Fatigue and Pain in Myasthenia Gravis: Observation Based on Brain Perfusion SPECT

Shin-Tsu Chang[1,2*]

[1]Department of Physical Medicine and Rehabilitation, Kaohsiung Veterans General Hospital, Taiwan

[2]Department of Physical Medicine and Rehabilitation, School of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taiwan

Abstract

Myasthenia Gravis (MG) is an autoimmune disease without effective treatments. The clinical manifestation of MG is fluctuating and variable fatigue to a large extent in ocular, bulbar, limb, and respiratory muscles, which leads to major symptoms such as dysarthria, dysphagia, fatigable chewing, fatigable limb, or axial weakness. Half of these patients would progress to generalized disease within 2 years. However, symptom cluster of fatigue-pain have never been reported.

I herein report a case with MG, assessed with the Myasthenia Gravis Activities of Daily Living Scale, Quantitative Myasthenia Gravis Scale, as well as brain perfusion images with Single Photon Emission Computed Tomography (SPECT). This SPECT demonstrated the symptom cluster of fatigue-pain was highly correlated with involvement of frontal lobes and cingulated gyri, as well as with two clinical scores.

Keywords: Myasthenia gravis; Myasthenia gravis activities of daily living scale; Quantitative myasthenia gravis scale; Single photon emission computed tomography; Symptom cluster of fatigue-pain

Introduction

Myasthenia Gravis (MG) was first described by Dr. Thomas Willis in 1672 [1]. MG has received a great deal of attention after the mid-nineteenth century, and a large number of research articles have been published in the past 350 years. The updated prevalence of MG in the world today is 12.4 people per 100,000 populations [2]. MG has been known as one of autoimmune diseases caused by the failure of neuromuscular transmission. It creates antibodies against the acetylcholine receptor, Muscle-Specific Kinase (MuSK), Lipoprotein-Related Protein 4 (LRP4), or agrin in the postsynaptic membrane at the Neuromuscular Junction (NMJ) [3-6]. Useful in the assessment of respiratory failure in MG patients is the level of positive MuSK antibodies [7]. MG patients often present with ocular symptoms of ptosis and diplopia, and the core clinical manifestation of MG is fatigable muscle weakness, which may affect ocular, bulbar, respiratory and limb muscles [8,9]. An updated official consensus guidance of international MG connoisseurs, based on novel evidence in 2020, offers counsels to clinical doctors, staffs and faculty for MG patients worldwide [10]. Auxiliary bedside tests and laboratory routines help bear out the synaptic disorder, define its type and severity, classify MG according to the contributing antibodies, and assess the outcome of treatment objectively [11].

The symptom cluster of fatigue-pain is well known in cancer patients while they are facing disease entity and varying treatments, including drug administration [12,13]. However, the phenomenon of symptom cluster of fatigue-pain has never been reported in MG. I herein present a case diagnosed as MG with manifest deficit in cerebral cortex according to brain perfusion images.

Case Presentation

A business man, 59 years old, suffered from fatigue of muscles and fluctuating weakness in limbs for the past 4-5 year. His eyelid dropped soon after he woke up and double vision condition appeared spontaneously. Progressive changes of symptoms included severe ptosis, diplopia, and fibromyalgia. In order to maintain his daily sleeping, he needed a ventilator. He called at a neurologist in a local medical center, where laboratory testing revealed a positive acetylcholine receptor antibody and repetitive stimulation study showed abnormal. There was no evidence of a thymic mass from the magnetic resonance imaging of the chest. He was diagnosed with myasthenia gravis on August 5, 2018. He was prescribed acetylcholinesterase inhibitor and immunosuppressive drugs to improve the conditions. However, severe eyelid-dropping (ptosis), double vision (diplopia), and fibromyalgia persisted without any sign of recovery at all. The patient reported that fluctuating muscle weakness in a specific distribution, more severe in bilateral lower limbs caused walking disability. Sometime, the condition of fatigue-pain of muscles did not ameliorate, which affected his daily life severely. He then came to our Rehabilitation Clinics for further investigation.

During his visit, he was evaluated according to two scales of negative indicators. The first is the Myasthenia Gravis Activities of

Citation: Shin-Tsu Chang. Involvement of Frontal Lobes and Cingulate Gyri in Symptom Clusters of Fatigue and Pain in Myasthenia Gravis: Observation Based on Brain Perfusion SPECT. Neurol Curr Res. 2022;2(2):1013.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Apr 11th, 2022

***Corresponding author:** Shin-Tsu Chang, Department of Physical Medicine and Rehabilitation, Kaohsiung Veterans General Hospital and School of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, 114201, Taiwan, Tel: +886-7-3422121; E-mail: ccdivlaser1959@gmail.com

Daily Living (MG-ADL) Scale [14], which includes eight criteria, recording as talking (2), chewing (2), swallowing (2), breathing (3), brushing teeth or combing hair (2), arising from a chair (3), double vision (3), and eyelid droop (3), with total score 20/24, Table 1. The second is the Quantitative Myasthenia Gravis (QMG) Scale [15], which includes 13 items, and measured as score 32/42, Table 1.

The regional cerebral perfusion scan with Tc-99m Ethyl Cysteinate Dimer (ECD) Single Photon Emission Computed Tomography (SPECT) was arranged, and it showed a decreased perfusion in frontal regions and anterior cingulate gyri (Figures 1 and 2).

Discussion

To the best of my knowledge, this is the first report regarding the relationship between the symptom clusters of fatigue-pain and such novel findings in brain perfusion images in patients of MG. With respect to the causes of fatigue, most studies have attributed muscle weakness to deficits in peripheral nervous system, while it is rare description to attribute to central nervous system. I used regional perfusion brain SPECT images to assess the brain function. Notably, there are two important findings in the study of this MG patient.

Firstly, there was an obviously decreased perfusion in frontal lobes (Figure 1 upper panel), which indicates a strong relationship between motor function and frontal lobe activity. The motor cortex comprises three different areas of the frontal lobe, immediately anterior to the central sulcus. These areas are the primary motor cortex (Brodmann's area 4), the Premotor Cortex (PMC), and the Supplementary Motor Area (SMA) [16]. In a study of 14 patients with MG and evaluated with 99mTc-HM-PAO SPECT, Henkes et al. [17] found 9 out of 14 having single or multiple areas of hypoperfusion in cerebral cortex (without revealing cingulate gyrus). In the context of an impaired ADL performance of these patients, imaging findings might be a correlate between a primary cerebral manifestation and ADL performance. More importantly, the SPECT image shows perfusion significantly decreased in both SMA and PMC, suggesting those areas contributing to the muscle weakness and fatigue.

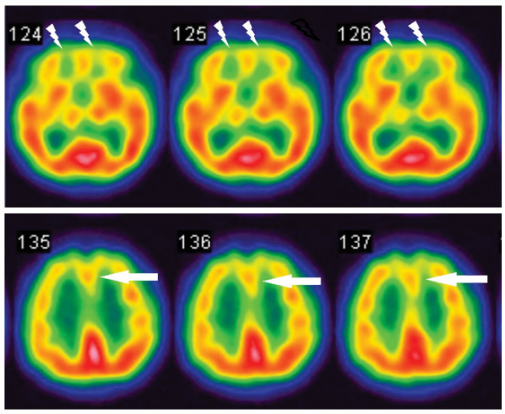

Figure 1: Regional perfusion brain SPECT (axial sagittal view). The color gradient in white to red area is normal and healthy perfusion, and in green to blue is worse. Upper panel is the perfusion deficit at the frontal lobe (flash-light). Lower panel is the perfusion deficit in anterior cingulated gyri (white arrow). On the opposite, there is red in the posterior cingulated gyri, meaning no deficit at all.
SPECT: Single-Photon Emission Computed Tomography

Table 1: Myasthenia gravis activities of daily living scale and quantitative myasthenia gravis scale.

Two Scores	Measured score of the patient
Myasthenia Gravis Activities of Daily Living Scale	
Breathing	3
Chewing	2
Double vision	3
Eyelid droop	3
Impairment of ability to brush teeth or comb hair	2
Impairment of ability to arise from a chair	3
Swallowing	2
Talking	2
Total	20
Quantitative Myasthenia Gravis Scale	
Head, lifted (45° supine) sec.	2
Double vision (lateral gaze) sec.	3
Ptosis (upwards gaze) sec.	3
Facial muscles	3
Swallowing	2
Speech following counting aloud from 1-50 (onset of dysarthria)	1
Right arm outstretched (90° standing) sec.	2
Left arm outstretched (90° standing) sec.	2
Right hand grip (Kg force)	3
Left hand grip (Kg force)	3
Right leg outstretched (45° supine)	3
Left leg outstretched (45° supine)	3
Vital capacity (Male)	2
Total	32

Numbers in each item represent grades from the maximum of 3 to the minimum of 0, total full as 24 in the front score and 42 in the latter. Some modifications of item sequence of the two scores were made.

Secondly, another finding from SPECT was the lower activity in Anterior Cingulate Cortex (ACC) (Figure 1, lower panel), which denotes a correlation between pain-arousing and ACC. In the group of patients with chronic pain, SPECT study showed blood flow reduction in ACC [18]. Watanabe et al. [19] have confirmed that altered cerebral blood flow in the anterior cingulate cortex is associated with neuropathic pain. Hence, lower activities in ACC, considered a complicated integrative center, revealed the development of symptom cluster of fatigue-pain (pain in both arms and the decreased power of skeletal muscle).

Approximately half of these patients progress to generalized disease within 2 years [20]. The clinical manifestation of this disorder is fluctuation and variable weakness in ocular, bulbar, limb, and respiratory muscles, which lead to major symptoms such as dysarthria, dysphagia, fatigable chewing, fatigable limb, or axial weakness. The fatigue of skeletal muscle is manifested by weakened contractile force of the muscle [21-23]. Further symptom cluster of fatigue-pain was observed for the first time in my case.

The role of peripheral mechanism contributing for the muscle fatigue has no doubt at all. To sustain muscle contraction, ATP needs to be regenerated at a rate complementary to ATP demand. There are three major ways to replenish ATP in muscles: phosphagen, glycolytic, and mitochondrial respiration, which differ in the substrates used, products, maximal rate of ATP regeneration, capacity of ATP regeneration, and their associated contributions to fatigue [24,25]. In contrast, the role of central mechanism contributing for muscle fatigue should be highly correlated with the frontal lobes as described earlier.

One latest study initiated by Zhou et al. [26] aimed at investigating

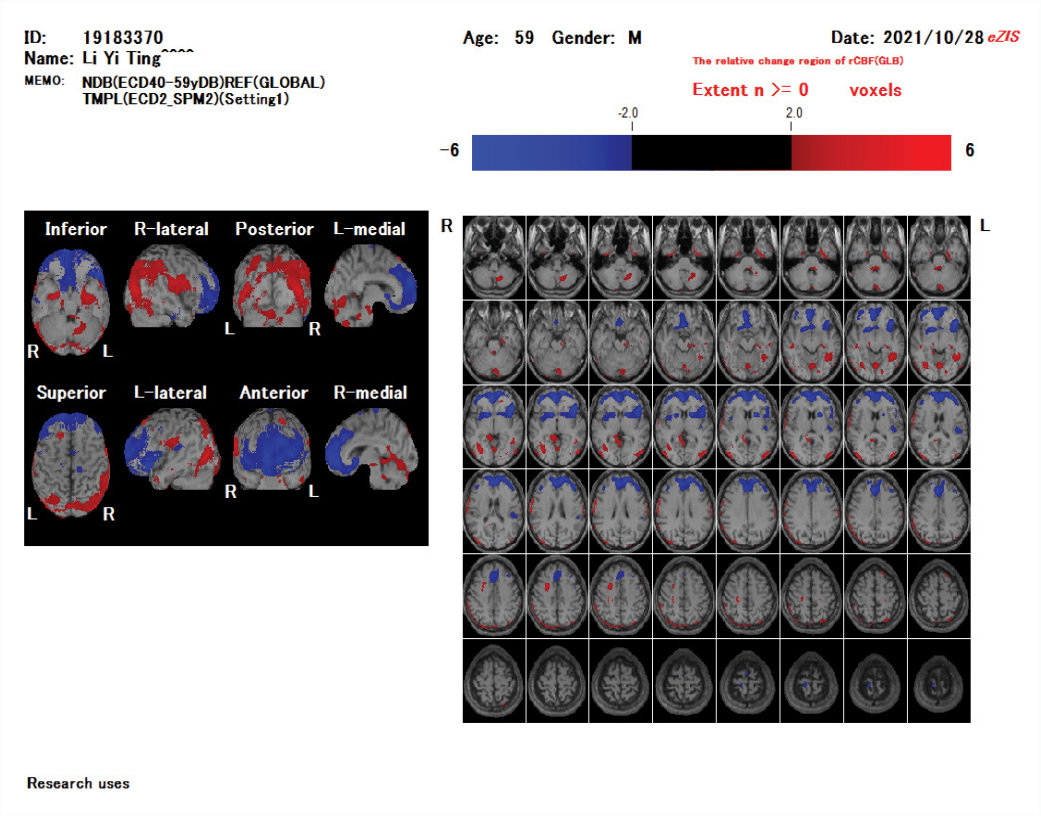

Figure 2: Difference of change of perfusion of whole brain in axial view of perfusion brain SPECT. Red means increased uptake and blue decreased uptake. SPECT: Single-Photon Emission Computed Tomography

the association between MG and cognitive function, especially for the cognitive domains of memory, showed that patients with MG showed lower memory performance, such as both immediate and delayed recall ability, but there was no association between the severity of MG and memory [26]. Future studies should delineate whether these associations are casual and modifiable, and fortunately, my patient did not have such a problem of memory right now.

Conclusion

This is the first paper to disclose such novel finding in brain perfusion images, which demonstrated the symptom cluster of fatigue-pain in patients with MG revealed involvement of frontal lobes and cingulated gyri. SPECT images act a good monitor for any deficit in brain. As for chronic fatigue-pain of MG and its correlation with clinical features such as a decreased score in MG-ADL Scale and QMG Scale, the relationship might be investigated by functional neuroimaging studies. In summary, brain SPECT image could provide direct evidence of a positive correlation between focal brain areas and clinical performance of MG.

References

1. Deymeer F. History of myasthenia gravis revisited. Noro Psikiyatr Ars. 2020;58(2):154-62.
2. Salari N, Fatahi B, Bartina Y, Kazeminia M, Fatahian R, Mohammadi P, et al. Global prevalence of myasthenia gravis and the effectiveness of common drugs in its treatment: a systematic review and meta-analysis. J Transl Med. 2021;19(1):516.
3. Vincent A, Palace J, Hilton-Jones D. Myasthenia gravis. Lancet. 2001;357(9274):2122-8.
4. Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: past, present, and future. J Clin Invest. 2006;116(11):2843-54.
5. Zhang B, Tzartos JS, Belimezi M, Ragheb S, Bealmear B, Lewis RA, et al. Autoantibodies to lipoprotein-related protein 4 in patients with double-seronegative myasthenia gravis. Arch Neurol. 2012;69(4):445-51.
6. Koneczny I, Herbst R. Myasthenia gravis: pathogenic effects of autoantibodies on neuromuscular architecture. Cells. 2019;8(7):671.
7. Tsai C, Howard JF Jr, Mehrabyan A. A case of MuSK myasthenia gravis presenting with persistent respiratory insufficiency. J Clin Neuromuscul Dis. 2021;23(1):39-42.
8. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve. 2008;37(2):141-9.
9. Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia gravis: epidemiology, pathophysiology and clinical manifestations. J Clin Med. 2021;10(11):2235.
10. Narayanaswami P, Sanders DB, Wolfe G, Benatar M, Cea G, Evoli A, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. Neurology. 2021;96(3):114-22.
11. Rousseff RT. Diagnosis of myasthenia gravis. J Clin Med. 2021;10(8):1736.
12. Aktas A, Walsh D, Rybicki L. Symptom clusters: myth or reality? Palliat Med. 2010;24(4):373-85.
13. Kirkova J, Aktas A, Walsh D, Davis MP. Cancer symptom clusters: clinical and research methodology. J Palliat Med. 2011;14(10):1149-66.
14. Muppidi S. The myasthenia gravis--specific activities of daily living profile. Ann N Y Acad Sci. 2012;1274:114-9.
15. Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. Neurology. 1999;52(7):1487-9.
16. Schlaug G, Renga V. Transcranial direct current stimulation: a noninvasive tool to facilitate stroke recovery. Expert Rev Med Devices. 2008;5(6):759-68.

17. Henkes H, Jäger H, Dewes W, Hierholzer J, Piepgras U. [MRT and 99mTc-HM-PAO SPECT of the brain in myasthenia gravis]. Bildgebung. 1991;58(4):208-14.

18. Honda T, Maruta T, Takahashi K. Brain perfusion abnormality in patients with chronic pain. Keio J Med. 2007;56(2):48-52.

19. Watanabe K, Hirano S, Kojima K, Nagashima K, Mukai H, Sato T, et al. Altered cerebral blood flow in the anterior cingulate cortex is associated with neuropathic pain. J Neurol Neurosurg Psychiatry. 2018;89(10):1082-7.

20. Kupersmith MJ, Latkany R, Homel P. Development of generalized disease at 2 years in patients with ocular myasthenia gravis. Arch Neurol. 2003;60(2):243-8.

21. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol. 2009;8(5):475-90.

22. Hehir MK, Silvestri NJ. Generalized myasthenia gravis: classification, clinical presentation, natural history, and epidemiology. Neurol Clin. 2018;36(2):253-260.

23. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren JJGM. Myasthenia gravis. Nat Rev Dis Primers. 2019;5(1):30.

24. Baker JS, McCormick MC, Robergs RA. Interaction among skeletal muscle metabolic energy systems during intense exercise. J Nutr Metab. 2010;2010:905612.

25. Hargreaves M, Spriet LL. Skeletal muscle energy metabolism during exercise. Nat Metab. 2020;2(9):817-28.

26. Zhou X, Zhou Y, Hua J, Xue Q. Association between myasthenia gravis and memory: A systematic review and meta-analysis. Front Neurol. 2021;12:680141.