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Review Article

CRITICAL UNDERSTANDING OF MYASTHENIA GRAVIS ON THE BASIS OF *VYADHI GHATAK*

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ABSTRACT

Myasthenia gravis (MG) is an autoimmune neuromuscular junction (NMJ) disorder characterized by weakness and fatigability of skeletal muscles. Myasthenia gravis has prevalence as high 200 in 100,000. It affects individuals in all age groups, but peak incidences occur in women in their twenties and thirties and in men in their fifties and sixties. Overall, women are affected more frequently than men, in a ratio of 3:2. It has bimodal age distribution. In MG, the fundamental defect is a decrease in the number of available AChRs at the postsynaptic muscle membrane. It presents with fluctuating skeletal muscle weakness and fatigue most commonly affecting the ocular muscles, although any muscle may be affected. In modern science treatment of Myasthenia gravis include anti-cholinesterase medications, glucocorticoids and other immunosuppressive agents. Long term use of steroid and immunomodulators with immunosuppressant drugs has many adverse effects on other system of body. Ayurvedic therapies can give much more promising results. Comparison between myasthenia gravis and diseases explained in Ayurveda is difficult and exact correlation is not possible. But based on critical understanding of *Vyadhighataka*, a probable diagnosis can be made and treated accordingly. In this article, attempt is made to understand the pathogenesis of myasthenia gravis by considering the concepts of *Dosha* (vitiated *Dosha*), *Dushya* (vitiated *Dushya*), *Aama*, *Agnimandya,* and *Srotovaigunya*. For any disease pathology to begin, all components must be present. Pathogenesis of any disease will not occur without these elements.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune neuromuscular junction (NMJ) disorder characterized by weakness and fatigability of skeletal muscles. The underlying defect is a decrease in the number of available acetylcholine receptors (AChRs) at NMJs due to auto antibodies directed against acetylcholine receptors (AChRs) at neuromuscular junction.[1] The word Myasthenia gravis is derived from the Greek word. Here MYS means “muscle”, ASTHENIA means “weakness” and the word GRAVIS is Latin which means “serious”.

MG is an autoimmune disorder most commonly caused by anti AChR antibodies. The anti-AChR antibodies reduce the number of available AChRs at NMJs by three distinct mechanisms: (1) Cross-linking and rapid endocytosis of the receptors; (2) Damage to the postsynaptic muscle membrane and (3) Blockage of the active site of the AChR.

In MG, the postsynaptic folds are flattened, or “simplified.” These changes result in decreased efficiency of neuromuscular transmission. Therefore, although ACh is released normally, it produces small end-plate potentials that may fail to trigger muscle action potentials. This will result in impair neuro muscular transmission at post synaptic membrane.[2]

In this disease there are two types of the auto antibodies produced against receptor at post synaptic membrane. In 85% of the patients have auto antibodies which produced against nicotinic AChRs and in remaining 15% of the patients having autoantibodies against muscle-specific kinase (MuSK). MuSK is a protein involved in regulation of concentration of AChRs at postsynaptic membrane.

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The thymus gland appears to be involved in this condition. The thymus is abnormal in 75% of patients with AChR antibody–positive MG; in 65%, the thymus is "hyperplastic," with the presence of active germinal centres detected histologically, although the hyperplastic thymus is not necessarily enlarged. An additional 10% of patients have thymic tumors (thymomas). Myoid cells, which are muscle-like cells within the thymus that express AChRs on their surface, may serve as a source of autoantigen and initiate the autoimmune reaction within the thymus gland.[3]

The cardinal features are weakness and fatigability of muscles. The weakness increases during repeated use (fatigue) or late in the day and may improve following rest or sleep. The course of MG is often variable. Exacerbations and remissions may occur, particularly during the first few years after the onset of the disease. The cranial muscles, particularly the lids and extraocular muscles (EOMs), are typically involved early in the course of MG; diplopia and ptosis are common initial complaints. Facial weakness produces a "snarling" expression when the patient attempts to smile. Weakness in chewing is most noticeable after prolonged effort, Speech may have a nasal timbre caused by weakness of the palate or a dysarthric "mushy" quality due to tongue weakness. Difficulty in swallowing may occur as a result of weakness of the palate, tongue, or pharynx.

The weakness becomes generalized in 85% of cases, affecting the limb muscles as well. If the weakness is limited to the EOMs for three years, it is unlikely to become generalized, and these patients are termed to have ocular MG. In MG, limb weakness is frequently proximal and may be asymmetric. Deep tendon responses are retained despite muscular weakness. If ventilatory weakness becomes requires respiratory assistance, the patient is said to be in crisis.

Myasthenia gravis has prevalence as high 200 in 100,000. It affects individuals in all age groups, but peak incidences occur in women in their twenties and thirties and in men in their fifties and sixties. Overall, women are affected more frequently than men, in a ratio of 3:2. It has bimodal age distribution.[4]

In modern science treatment of Myasthenia gravis include anti-cholinesterase medications, gluco-corticoids and other immunosuppressive agents, thymectomy, plasmapheresis. Long term use of steroid and immune modulator drugs has many adverse effects on other system of body.

Ayurvedic treatments have significantly more positive outcomes. It can be difficult to compare myasthenia gravis to diseases described in Ayurvedic medicine, and an accurate correlation is not possible. Aggravated *Dosha* may cause manifold diseases depending upon the various etiological factors and the sites of manifestations. Hence nomenclature of all types of diseases in definite terms is not always possible. If a physician is not able to name a particular disease, he should not feel ashamed on that account.[5] There are few concepts in Ayurveda like *Vatakshaya, Udanavrita Vyana, Aama* and *Mansa Kshaya* etc; by means of these concepts we can able to understand the pathogenesis of myasthenia gravis. Understanding the Myasthenia gravis in Ayurveda involves the hypothetical understanding of the *Vyadhighataka.*

AIMS AND OBJECTIVE

1. To study the pathophysiology Myasthenia gravis of from Ayurvedic perspective.
2. To understand pathophysiology through *Vyadhi Ghatak* (*Dosha, Dushya, Aama, Agnimandya,* and *Srotovaigunya)* concept mentioned in Ayurveda.

MATERIALS AND METHODS

The Ayurvedic literature includes *Brihatrayee*. The number of published research, articles, and books on the subject are a testimony to importance of the topic. All the available sources have been included as a source material for critical understanding of Myasthenia gravis on the basis of *Vyadhi Ghatak*.

Vyadhi Ghatak involved in Pathogenesis of Myasthenia Gravis

Vyadhi Ghatak are the factors that contribute to the pathogenesis (*Samprapti*) of any disease. There are five elements: *Dosha (*vitiated *Dosha*), *Dushya* (vitiated *Dushya*), *Aama*, *Agni,* and *Srotovaigunya*. For any disease pathology to begin, all components must be present. Pathogenesis of any disease will not occur without these elements.

Samprapti explains the entire process of how a disease develops, starting with the exposure to the causative factors and continuing through the initial disturbances in those factors. It is a mechanism for assessing each disease in sequential order, starting from the *Dosha Vaishamya* and continuing till the full extent of the disease manifests. It includes *Dosha, Dushyas, Agni, Aama,* and *Srotovaigunya.*

The ability to diagnose a patient's condition accurately and choose the best course of therapy, it depends greatly on the physician's knowledge of these *Vyadhi Ghatakas*.

Dosha

तत्र त्रयः शरीरदोषा वातपित्तश्लेष्माणः, ते शरीरं दूषयन्ति; [6]

Dosha is the one who does the *Dushti* of *Mana* and *Shareera*. Disease always requires the *Vaishamya* of the *Dosha* to emerge. Similarly, the way a soaring bird's shadow continually follows it, *Doshadushti* and *Vyadhi* are associated and dependent on each other. *Vata, Pitta*, and *Kapha* are essential elements that must exist either separately or in combination with the other two or three to establish a disease's etiology.

When *Doshas* are in there normal state, disease is not bring on by them. As a result, the first point of

the *Vyadhi Ghataka* is considered the permutation and combination of *Doshas.*

On the basis of symptoms in myasthenia gravis, we can see the involvement of *Vata Dosha.* Here in this disease fatigue and weakness of skeletal muscle is the cardinal symptoms. Diplopia, ptosis, difficulty in chewing and swallowing, dysarthria, and dysphonia etc symptoms are present due to impaired neuro muscular transmission.

कृत्स्नदेहचारी महाजवः|
गत्यपक्षेपणोत्क्षेपनिमेषोन्मेषणादिकाः|
प्रायः सर्वाः क्रियास्तस्मिन् प्रतिबद्धाः शरीरिणाम्| [7]

Among all the five types of *Vata Dosha*, especially *Vyana Vayu* is responsible for all actions like- Apkshepan*, Utkshepan, Nimesh, Unmesh* etc. In myasthenia gravis, these activities are hampered due to impaired neuro muscular junction, so from ayurvedic perspective *Vyan Vayu Dusti* is responsible for the pathogenesis of the disease.

तत्र, वातक्षये मन्दचेष्टताऽल्पवाक्त्वमप्रहर्षो मूढसञ्ज्ञता च... [8]

In condition of *Vata Kshya* there are some symptoms like- *Manda Chestata, Alpavaktvam, Apraharsha, Mudhasangnyata* are seen which can be correlate with symptoms of Myasthenia gravis. In *Udanvrita Vyana* there are some symptoms like – *Alpaagnita, Chestahani* and *Nimilinam* which can also corelate with Myasthenia gravis.

Dushya

This is the second element that is frequently linked to *Doshas.* Together, *Saptadhatus* and *Malas* form the *Dushyas*. Additionally, other bodily components like *Lasika, Udaka,* and *Vasa* are contained in the *Dushyas* itself. The subsequent pathological process is started by various *Dushita Avastha* of *Dosha* and *Dushya* with various permutations and combinations. *Doshadushya Sammurchana* is the initial stage of any *Vyadhi,* is the association of *Dushta Dosha* and *Dooshita Dushyas*.

As per this concept, *Rasa Dhatu* and *mamsa dhatu* are *dushya* which are responsible for the pathophysiology of myasthenia gravis.

In *Astang Hridaya Sutrasthan*, *Acharya* explain *Mansa Kshaya Lakshna* **-मांसे क्षीणेऽक्षग्लानिः,** which correlate with ocular manifestation of disease. In *Rasa Kshaya Lakshan, Acharya* states that-**रसे रौक्ष्यं श्रमः शोषो ग्लानिः शब्दासहिष्णुता|**[9]**.** Here *Glani* and *Shram* represent as muscular fatigue which are cardinal symptoms of the myasthenia gravis.

Agni

For every physiology, *Agni* is the essential part of the organism. *Agni* is a factor that has the power to transform substances or pierce through even the smallest gaps. It includes numerous elements that contribute and regulate the process of digestion, metabolism, or any other modifications to an organism's tissue.[10] All of the chemical and energy modifications that take place in the body are collectively referred to as metabolism, and they are nothing more than *Agni's* function.[11] *Agni* is influenced by the *Dosha* and results in *Vishamagni* (irregular digestive capacity), *Tikshanagni* (intense digestive capacity), *Mandagni* (low digestive capacity), and *Samagni* (normal digestive capacity). *Jatharagni, Panchabhutagni* and *Dhatvagni* are main three *Agni* in the body.

Role of *Agni* in Improving Immunity

आयुर्वर्णो बलं स्वास्थ्यमुत्साहोपचयौ प्रभा|
ओजस्तेजोऽग्नयः प्राणाश्चोक्ता देहाग्निहेतुकाः||[12]

Normal functioning of *Agni* leads to longevity. The condition of Agni in the body determines the quality of life, appearance, strength, health, sustenance, luster, *Ojas*, *Teja* (energy), and *Prana* (living energy). Here in this *Shloka*, *Bala* and *Oja* represents as immunity which is depends upon *Agni*.

Immunity is a necessary component of life and an essential tool in the battle against harmful microorganisms for survival. The innate immune system and the adaptive immune system are the two main parts of the human immune system.

Sahajabala may be correlated to innate immunity. The innate immune system allows for the quick induction of inflammatory reactions based on the identification of chemicals expressed by bacteria or molecules that serve as "danger signals" secreted by infected cells (either at the cell surface or within cells). These receptor interactions trigger signaling events that ultimately lead to inflammation. Innate immune responses encompass almost all cell lineages, not just immune cells, however myeloid cells, such as neutrophils and macrophages, play a significant role due to their phagocytic ability. Adaptive immune system and *Yuktikritabala* may be connected. An immune activation program is carried out by the adaptive immune system after clonal identification of antigens, which is followed by a sharp proliferation of cells that react to the antigen.[13]

Life requires immunity, which is a vital defense mechanism against dangerous microbes. To resist harmful etiological agents and maintain health, one needs a strong immune system. We must be aware of the significance of keeping *Agni* protected in order to improve immunity. As a result, adopting healthy eating and lifestyle practices will help one protect their *Agni* and increase their resistance to disease.

In myasthenia gravis, When the Agni becomes weak, due to improper digestion *Ama* produced in the body. *Ama* act as antigen and modulate signaling at cellular levels leading to incompatible autoimmune response by producing auto-antibodies against Ach

receptor. AChR availability is decreased by anti-AChR antibodies. This will result in impair neuro muscular transmission at post synaptic membrane.

Aama

"ऊष्मणोऽल्पबलत्वेन धातुमाद्यमपाचितम्। दुष्टमामाशयगतं रसमामं प्रचक्षते।।"[14] (वा. सू. अ. १३)

Ayurveda science elaborated different concepts related to disease pathogenesis and *Aama* is one of them described as toxins or antigen which can trigger diseases pathogenesis. It is believed that hypo-functioning of *Agni* leads production of *Aama* which can combine with *Dosha, Dhatu* and *Mala* and induces various pathological conditions.

स मूलं सर्वरोगाणामाम इत्यभिधीयते।।" इति। तथा चापरे-
"आममन्नरसं केचित्, केचित्तु मलसञ्चयम्।
प्रथमां दोषदुष्टिं च केचिदामं प्रचक्षते।।[15]

Ama is the prime cause for diseases. Some *Acharya* consider indigested and improperly formed *Ahar Rasa* as *Ama,* while others assume it to be the accumulation of waste products in body *(Mala)* and few others consider it as early stage of *Dosha* vitiation *(Dosha Dusti).*

Autoimmune diseases occur due to the harmful response of self-immune system when immune system stated attacking of body tissue as anticipated response against antigen/toxins or *Aama.* The inflammatory response occurs in autoimmune disorders triggered by *Aama* or antigen at cellular level. Antigens disrupt the immune system, which further destroys tissues by vitiating the *Dosha*.

The *Aama* enters the circulation i.e., it impairs the *Bhutagni* due to its *Gurvadi* properties, and reduces its function. Due to *Bhutagni* impairment, the *Vijatiya* (heterogenous) *Ahara rasa* will not be able to become *Sajatiya* (homogenous) and act as antigen in circulation.[16] Free radicals may also be considered as *Ama* substance in circulation as it does not undergo final change in configuration thereby causing damage to proteins, vitamins and lipids. So, most of the diseases like gastrointestinal disorders, allergic and auto-immune diseases, and various metabolic disorders have hypo functioning of *Agni* and *Aama* formation as primordial factor in their manifestation.[17]

In myasthenia gravis, there are two types of the auto antibodies produced against receptor at post synaptic membrane. In 85% of the patients have auto antibodies which produced against nicotinic AChRs and in remaining 15% of the patients having autoantibodies against muscle-specific kinase (MuSK). In this condition *Ama* act as antigen and that antigen/ *Aama* modulate signaling at cellular levels leading to incompatible autoimmune response and the auto antibodies produced against receptor at post synaptic membrane.

Strotovaigunya

Srotovaigunya means that condition of *Srotas* which is susceptible for pathological changes to produce a disease. *Kha Vaigunya* comprises of 2 words: *Kha- akasha, Indriya, Pura, Kshetra, Khaga[18], Srotas* and *Vaigunya* means *Vigunata/Vikruti. Acharya Sushrutha* explains as

कुपितानां हि दोषाणां शरीरे परिधावताम्।
यत्र सङ्गः खवैगुण्याद्व्याधिस्तत्रोपजायते।।[19]

The term "*Kha Vaigunya*" refers to a defect in the channels of transmission and transformation. The phenomenon known as *Kha Vaigunya* helps Ayurvedic practitioners to recognize changes in microtissues that contribute to disease. While these changes alone do not cause a disease, they do contribute to create the basis for potential diseases that may arise in the near future. They could be caused by faults from prior treatment, untreated toxins in the tissues, hereditary defects, microcellular defects, persistent inflammation in the tissues, or defects at the cellular level. The six-stage pathophysiology of disease progression (*Shatkriyakala*) includes *Kha Vaigunya* as a significant milestone. The defective body system is where the vitiated *Dosha* is localized, resulting in disease to develop.

Srotovaigunya stands for some inherent weakness or lack of natural immunity to some particular type of disease or Susceptibility to disease formation process and loss of resistance to disease producing factor. *Srotovaigunya* need not necessarily produce any disease until there is *Dosha-DushyaSammurchana*. It may not get an opportunity to show its existence and hence we may not find any clinical manifestations and in such cases, it has no pathological importance. *Srotovaigunya*, however, is a crucial element in the development of disease, making it impossible to ignore.

व्यानेन रसधातुर्हि विक्षेपोचितकर्मणा।
युगपत् सर्वतोऽजस्रं देहे विक्षिप्यते सदा।।
क्षिप्यमाणः खवैगुण्याद्रसः सज्जति यत्र सः।
करोति विकृतिं तत्र खे वर्षमिव तोयदः।।
दोषाणामपि चैवं स्यादेकदेशप्रकोपणम्।[20]

Acharya Charaka explains that *Rasa Dhatu* that moves all over the body gets obstructed where there is *Srotovaigunya* and there leading to manifestation of diseases.

In myasthenia gravis we can assume that *Khavaigunyata* is found in post syneptic cleft.

In MG, the fundamental defect is a decrease in the number of available AChRs at the postsynaptic muscle membrane due to antibody production against Ach receptor. The postsynaptic folds are "simplified," or flattened. The effectiveness of neuromuscular transmission is diminished as a result of these modifications. Therefore, although ACh is released

normally, it produces small end-plate potentials that may fail to trigger muscle action potentials. Muscle contraction becomes weak as a result of transmission failure.

DISCUSSION

Myasthenia gravis (MG) is an autoimmune neuromuscular junction (NMJ) disorder characterized by weakness and fatigability of skeletal muscles.

Nidan Sevan

⇓

Agnimandya

Aama utppatti → Due to *Bhutagni* impairment, the *Vijatiya* (heterogenous) *Ahara rasa* will not be able to become *Sajatiya* (homogenous) and act as antigen in circulation.

⇓

Aama enters in the circulation (Act as antigen that modulate signaling at cellular levels leading to incompatible autoimmune response)

⇓

Aama further vitiate *Vata Dosha* (*Vyana Vayu*) and *Dhatu* (*Rasa Dhatu & Mansa Dhatu*)

⇓

Vitiated *Dosha* and *Dhatu* gets obstructed where there is *Khavaigunya* (post synaptic cleft)

⇓

Decreased number of AChrs at post synaptic fold and eventually these folds are flattened (due to *Aama*)

⇓

Impaired function of *Vyana Vayu* and *Mansa Dhatu* (impaired neuromuscular transmission)

⇓

Weakness in muscle contraction

⇓

Myasthenia gravis

In the view of Ayurveda, it is mainly due to *Khavaigunya* and *Agnidusti*. *Agni Dusti* leads to the formation of *Aama* in the body. In this condition *Ama* act as antigen and that antigen/*Aama* modulate signaling at cellular levels leading to incompatible autoimmune response and the auto antibodies produced against receptor at post synaptic membrane. *Aama* further vitiate *Vata Dosha (Vyana Vayu)* and *Dhatu (Rasa Dhatu & Mansa Dhatu*).

Aama hampers the proper functioning of *Dosha* and *Dhatu* (*Rasa Dhatu & Mansa Dhatu*). Since *Vata dosha (Vyana Vayu*) is mainly responsible for the proper functioning of neurotransmissions, here *Khavaigunyata* present at neuromuscular junction at that place vitiated *Dosha* and *Dhatu* gets obstructed and the functioning of *Vata* is obstructed by the *Aama*. Here *Aama* act as anti-AChR antibodies which reduces the number of available AChRs at NMJs by three distinct mechanisms: (1) cross-linking and rapid endocytosis of the receptors; (2) damage to the postsynaptic muscle membrane and (3) blockage of the active site of the AChR. The effectiveness of neuromuscular transmission decreases as a result of these modifications. Therefore, although ACh is released normally, it produces small end-plate potentials that may fail to trigger muscle action potentials. Failure of transmission results in weakness of muscle contraction.[21]

Comparison between myasthenia gravis condition and diseases explained in Ayurveda is difficult and exact correlation is not possible. Hence to understand the probable pathogenesis an attempt has been made as below.

Table 1: Table Showing *Vyadhighataka* Involved in Myasthenia Gravis

Vyadhi ghatak	**Critical understanding of *Vyadhighatakas* in Myasthenia Gravis**
Dosha	***Vata Kshya*** *Manda Chestata* (weakness and fatigability of muscles), *Alpavaktvam* (dysarthria, and dysphonia), *Mudhasangnyata* ("snarling" expression) ***Vyana Vayu Karma Dusti-*** unable to do normal functions like; *Apkshepan* (downward movement), *Utkshepan (*elevation), *Nimesh- Unmesh* (eyelid movements) results into Diplopia, ptosis, difficulty in chewing and swallowing, weakness and fatigability of muscles. ***Udanvrita Vyana-*** *Chestahani* (weakness and fatigability of muscle) and *Nimilinam* (Diplopia, ptosis)
Dushya	***Mansa Kshaya Lakshna*** *-Akshiglani* (Diplopia, ptosis)

	Rasa Kshaya- *Glani* and *Shram* (muscular fatigue and weakness)
Agni	***Agnimandyata***
Ama	*Aama* enters in the circulation and act as antigen that modulate signalling at cellular levels leading to incompatible autoimmune response.
Strotovaigunya	*Khavaigunyata* is found in post synaptic cleft.

CONCLUSION

There is no definite cure for autoimmune diseases in contemporary sciences. In Ayurveda, we can play a vital role in management of the symptoms without further derangement of the body by applying the concepts mentioned. This may help in the overall health status of such patients.

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