



ASSOCIATION OF CEREBRO VASCULAR ACCIDENT WITH SERONEGATIVE MYASTHENIA AND HERPES INFECTION

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| Dr. Billa Vikas | Post Graduate, Department Of General Medicine, Vinayaka Mission, S Research Foundation (Du) Karaikal, Pondicherry |
| Dr. T. Prabhu* | M.D,D.M, Neurology, Assistant Professor Vinayaka Mission's Research Foundation (Du) Karaikal, Pondicherry. *Corresponding Author |
| Dr. V. Sakthivel | M.D, Professor And Hod, Department Of General Medicine, vinayaka Mission's Research Foundation (Du) Karaikal, Pondicherry |

KEYWORDS :

INTRODUCTION

Cerebro vascular accident is the medical synonym of stroke. Stroke is defined as a condition where the blood flow to a part of brain is stopped due to blockage of blood vessel or rupture of blood vessel resulting in either ischaemic stroke or haemorrhagic stroke. Hypertension, hyperlipidemia, smoking, alcohol, diabetes, infections are the main causes of stroke.

Myasthenia gravis is a multisystem autoimmune neuromuscular disorder which affects skeletal muscles mainly resulting in muscle weakness, impaired muscle contraction, early onset of fatigue. Antibodies are produced against acetylcholine receptors at neuromuscular junction. Initially eye, facial muscles, oesophageal and pharyngeal muscles are involved. The subject may develop ptosis, diplopia and toneless voice. Striated cardiac muscle is also the target for immune reactive attack resulting in heart failure, arrhythmia and death.

Only less than 50% of patients with MG are likely to get heart disease.

The risk factors are
 - Age over 60 years
 - patients with thymoma
 - people with anti-Kv1 antibodies. These antibodies are the likely to result in damage and inflammation of heart muscle resulting in arrhythmias, cardiac failure, sudden cardio vascular death.

Acetylcholine receptor is made up of number of subunits acting as gating for flow of ions through the membrane and also for binding of acetylcholine neurotransmitter. and HuAChR alpha subunit residues 160-167 exert biological effect in Myasthenia gravis. In laboratory conditions when synthetic polypeptides similar to unique regions of alpha subunit of AChR are used with alpha-bungarotoxin showed accessible sites on AChR that bind with antibodies suggesting the chances of amino acid sequences shared between infectious agent and host protein. This indicates the ability of microbes to start an immunological response that subsequently reacts with self determinant resulting in autoimmune disease.

Even though myasthenia gravis is usually diagnosed in between 15-30 years, now a days the incidence of MG in elderly population after the age of 50 years is being increased 'Myasthenia gravis with late onset'. The disease is combined with other geriatric illness like somatic diseases making diagnosis more difficult. The main variation between early onset MG and late onset MG is presence of antibodies to "titin" protein of muscle in approximately 50% of patients. Seronegative myasthenia gravis is a condition in which there are no antibodies against AChR receptors. Double seronegative myasthenia gravis is a condition where there are no antibodies against AChR and MuSK. Therefore absence of detectable antibody or autoimmune biomarker hinders the diagnosis.

Herpes zoster is a viral disease caused by activation of varicella zoster virus in dorsal root ganglion (caused due to prior chicken pox virus infection). Primary infection is by varicella after which VZV remains dormant in ganglionic neurons. When cell mediated immunity is declined in immunocompromised and elderly results in reactivation causing serious neurological and ocular diseases like cranial nerve palsy, myelopathy, meningoencephalitis, giant cell arteritis etc. VZV

vasculopathy occurs after infection of cerebral arteries and vascular remodelling. The herpes virus infections results in manifestations like ischemic stroke, aneurysm, dissection etc. However exact incidence of vasculopathy is not clear.

The main causative etiology for stroke, heart failure, cardiovascular death, arrhythmia is atrial fibrillation. The rate of admission of patients with AF raised from 13.5% in 2006 to 30% by 2021. In the presence of stressors like hypertension, diabetes mellitus, any heart diseases may result in structural remodelling of heart. This will act as triggering factor for atrial fibrillation. It is known that atrial fibrillation leads to local conduction defect resulting in re-entry and amplification of AF. This loss of rhythm control is due to autonomic nervous system dysfunction.

It is seen that in majority of patients with myasthenia gravis have antibodies reactive against HuAChR alpha subunit receptors. Immunological cross reactivity of self epitope with herpes simplex virus indicates that this virus might be associated in causing myasthenia gravis in some patients.

CASE

A 73 year old male hypertensive patient was brought to emergency department of Vinayaka Mission's Research Foundation, Karaikal, Pondicherry with chief complaints of weakness in left upper limb and lower limb and slurring of speech since morning 5am which is of sudden onset and patient developed difficulty in opening both eyes and difficulty in swallowing to liquids, slurring of speech. Informed consent is taken. Investigations are done. MRI BRAIN showing Acute infarct in M2 and M3 segment of right MCA, carotid artery doppler findings is without any significant stenosis and ECG showing atrial fibrillation with controlled ventricular rate and patient has B/L Ptosis, subsequently tested with ice pack test then patient opened eyes spontaneously then suspected of myasthenia gravis but serum acetylcholine receptor antibodies and serum musK receptor antibodies were negative. CT Thorax was done to ruled out Thymoma. 2D Echocardiography showed grade I diastolic dysfunction with EF-65%. Routine blood investigations total counts, renal function test, liver enzymes were in normal range and serological tests for HIV, HbsAg, HCV were negative, and on examination patient is having a raised rash appearing as band on right side of waist with itching suggestive of herpes zoster shingles, patient did not show improvement for dysphagia, bilateral ptosis when he is on beta blockers, statins and flouroquinolones then he improved symptomatically once these drugs are withheld and treated as seronegative myasthenia and improved with pyridostigmine, CCB, anticoagulant and antiplatelets and regular physiotherapy and pathophysiology might be herpes infection causing development of autoantibodies having molecular mimicry causing myasthenia and atrial fibrillation leading to cerebro vascular accident with history of hypertension.

INVESTIGATIONS

Edrophonium test-Edrophonium (2-10mg) given slow i.v shows dramatic improvement of symptoms in patients with myasthenia gravis but not in other dystrophies.

DISCUSSION

Myasthenia gravis being autoimmune disorder characterised by presence of auto antibodies against Acetyl choline receptors. Even though the disease mainly effects skeletal muscle, in long duration may effect other tissues of body like cardiac muscle resulting in various cardiac abnormalities. The incidence of MI in Myasthenia gravis is unknown. The presence of overlapping of symptoms between MG and cardiac disease like poor tolerance to exercise, easy fatigability and dyspnea results in failure of noticing cardiac manifestations.

On the other hand chicken pox virus is most commonly effected childhood viral infection. This virus became dormant in dorsal root ganglion and remains latent in immunocompetent subjects. When the subject becomes immunologically weak this virus reactivates and results in herpes zoster.

Atrial fibrillation is the most common cardiac disorder encountered generally. This is caused by various factors like external stress, hypertension, diabetes, local conduction defects, electrical dissociation between muscle fiber bundles. AF is the main cause of stroke, cardiac failure and sudden death. Autonomic nervous system plays an important role in initiation and modulation of AF. Herpes zoster infection results in autonomic dysfunction resulting in activation of c-reactive protein, IL-2, IL-6, IL-8 etc, all these inflammatory mediators results in atrial fibrillation.

In the study in Journal of Korean Medical Science by Cha et al regarding the risk of AF after severe Herpes zoster infection in 2 year follow up revealed a relation between atrial fibrillation and increased inflammatory mediators by viral infections. In case study by Young Soo Lee about the risk of AF after Herpes Zoster revealed that HZ infection is significantly associated with increased risk of stroke/transient ischaemic attack and myocardial infection.

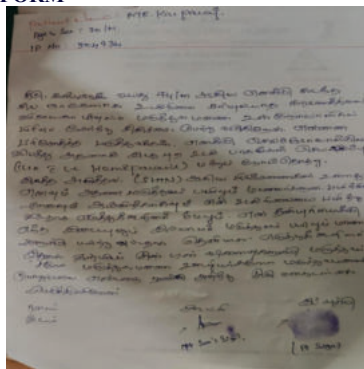
In a study by Peter L. Schwimbeck et al, where they collected sera from 40 patients with myasthenia gravis, 6 out of 40 patients with the disease have shown HuAChR alpha subunit sequence and the antibodies purified from sera of 2 patients showed cross reaction with HSV.

The patient has no detectable antibodies against AChR receptors and MusK receptors making the diagnosis much difficult in seronegative myasthenia gravis. Complete seronegative myasthenia gravis is rare <10% of all the myasthenia gravis. There is possibility that the antibodies are still to be discovered in these patients. For diagnosis of myasthenia gravis in these patients repetitive nerve stimulation and single-fibre electromyography (EMG) can be helpful in these patients.

For molecular mimicry to be considered as a cause of autoimmune disease the following criteria should be fulfilled-the amino acid sequences between microbe and self protein must be different and immunological reaction is initiated against the microbe, the two must be similar structurally so the immune response produced against infectious agent cross react with self protein and lastly the self determinant can be active part of molecule.

There are studies showing immunological cross reactivity between herpes virus epitope glycoprotein D residues 286-293 and HuAChR alpha subunit residues 160-167 which exert biological effect in Myasthenia gravis. So there is some molecular mimicry where herpes zoster can result in myasthenia gravis, atrial fibrillation finally resulting in stroke.

CONSENT FORM



CONCLUSION

The molecular mimicry concept gives us a scope of identifying or exploring the etiological agents for various human diseases.

Herpes Zoster epitope has immunological cross reactivity with autoantibodies having molecular mimicry causing myasthenia and atrial fibrillation leading to cerebro vascular accident with history of hypertension. So a regular ECG follow up must be done in patients with HZ irrespective of their symptoms.

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