Horizontal Gaze Palsy and Ipsilateral Facial Nerve palsy as Initial Manifestation of Relapsing-Remitting Very Late-Onset Multiple Sclerosis : a Case Report

Abstract

Introduction: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) and can be presented with various clinical manifestations. Impairment of eye movements is a common feature of MS but horizontal gaze palsy is a rare finding**,** that can be coupled with ipsilateral facial nerve palsy. Very late-onset multiple sclerosis (VLOMS) is an uncommon form of MS representing 0.5% of all MS patients. Late-onset multiple sclerosis commonly had a primary progressive course.

Purpose: To report a case of horizontal gaze palsy and ipsilateral peripheral facial palsy as the initial manifestation of VLOMS with relapsing-remitting course.

Case report: A 63-year-old man presented to outpatient clinic with sudden constant horizontal binocular diplopia and weakness of left facial muscle. On attempted left gaze, there was adduction deficit in right eye and abduction deficit in left eye. On rightward gaze was normal. Vertical eye movements were normal in both eyes. Convergence remained intact and no nystagmus is found during saccadic eye movements. Brain magnetic resonance imaging (MRI) showed small hyperintense lesion at pons, left paramedian pontine reticular formation (PPRF), and left medial longitudinal fascicle (MLF) that compatible with dissemination in time and space of 2017 revised McDonald's criteria for MS, and revealed disease course as relapsing-remitting multiple sclerosis (RRMS). Patient was given oral high dose corticosteroid along with its supportive medicine. Ophthalmic examination on the third week after treatment showed improvement of ocular movement in both eyes and gradual restoration of ipsilateral facial palsy.

Conclusion: Horizontal gaze palsy can be presented as an initial sign of RRMS. Neurological examination is important to localize the site of involvement in CNS and reveal other neurological finding like ipsilateral facial nerve palsy. Appropriate neuroimaging can be performed to support the diagnosis. High-dose oral corticosteroids reduce the severity of clinical impairment and hasten recovery of the deficits.

Keywords: multiple sclerosis, demyelination, horizontal gaze palsy, LOMS, RRMS, corticosteroids

I. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system (CNS), affecting between 2 and 2.5 million people throughout the world. This demyelinating disease predominantly affects young adults between 20 and 40 years of age. The late-onset multiple sclerosis (LOMS) accounts for 4.5% of the MS population and commonly presented as primary progressive course. Interestingly, data shows that very late-onset multiple sclerosis (VLOMS) represent only 0.5% of all MS cases.[1-3]

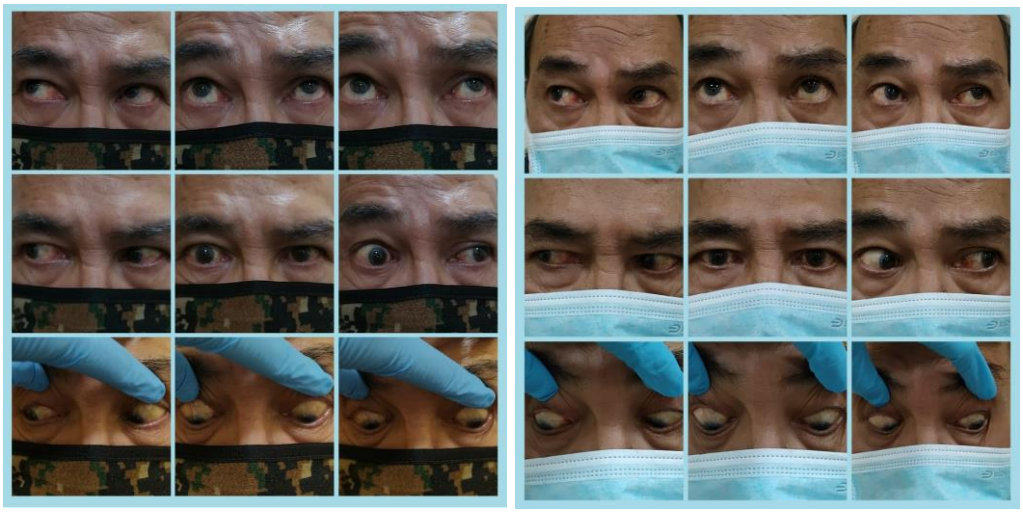
Multiple sclerosis can be presented with various clinical manifestations such as sensory problems, visual disturbances, weakness, gaze abnormalities, or changes in sphincter function, with some being more common and others less. In MS, although

eye movement abnormalities and bilateral internuclear ophthalmoplegia (INO) are frequent, a "one and half syndrome" and a unilateral or bilateral horizontal gaze palsy are rare.[1-6]

There is greater delay in diagnosis of LOMS compared to younger onset MS. Magnetic resonance imaging (MRI) is highly sensitive to detect characteristic lesions of MS. Corticosteroids can reduce the severity of clinical impairment and hasten recovery of the deficits.[1,3,7-9] The purpose of this study is to report a case of VLOMS with relapsing-remitting course presented as horizontal gaze palsy with ipsilateral peripheral facial nerve palsy that had improvement after being treated with high dose oral corticosteroids.

II. Case Report

A 63-years-old man presented to the outpatient clinic at Cicendo National Eye Hospital on May 28th 2021 with a complaint of sudden-onset horizontal binocular diplopia starting one week ago that was constant and worse in left gaze. The patient also noticed weakness in his left face muscles. There was no disturbance in visual acuity. No history of similar symptoms before. No headache, nausea, vomiting, weakness of extremities, slurred speech, seizure, urinary disturbance, paresthesia, fever, or flu-like syndrome before the diplopia happened. No history of trauma or previous surgical procedure. Patient had a history of hypertension for 10 years and regularly taking antihypertensive medicine, with his highest blood pressure had ever reached 200/100 mmHg. Patient had no diabetes or hyperlipidemia and denied using illicit drugs, tobacco, and alcohol. Patient had history of using glasses since elementary school. No family history related to this complaint.



(A) (B)

Figure 2.1 Cardinal eye position (A) on May 28th 2021, (B) June 25th 2021. Note the improvement of rigth eye adduction and left eye abduction.

Physical examination revealed blood pressure was 130/90 mmHg. Ophthalmic examination revealed visual acuity was 1/60 for both eyes, with best-corrected visual acuities using Snellen chart was 0.63 on the right eye and 0.1 on the left eye. Objective refractive with auto refractometer was S-6.25 C-1.00x145 for right eye and S-16.75 C-0.25x110 for left eye. His primary eye position was orthotropic. The red glass test revealed uncrossed diplopia. There was a restriction of ocular movement on attempted left gaze, -4 on right eye and -2 on left eye, with gaze-evoked nystagmus on both eyes. Patient had no contralateral dissociated nystagmus on saccadic eye movements. The accommodative convergent and vertical eye movements were normal. Patient had normal color vision examination and contrast sensitivity. No scotoma or metamorphopsia was found on Amsler grid examination. The confrontation visual field test was within normal limits in both eyes. The intraocular pressure was normal on both eyes. Direct and consensual light reflexes were normal and no relative afferent pupillary defect was found. There were mild lens opacities on both eyes. Other slit-lamp examinations on both anterior segment were within normal limit. Posterior segment examination revealed a myopic fundus and optic disc with defined margin on both eyes. Neurological examination shows that patient had left peripheral facial nerve paresis. Another cranial nerve, motoric and cerebellar examination were normal. The patient was then diagnosed with

horizontal gaze palsy and left peripheral facial nerve palsy suspected due to pons lesion caused by suspected ischemic lesion + myopia gravior of right and left eye + anisometropic amblyopia of left eye. Space-occupying lesion was considered as differential diagnosis. Patient was given oral cytidine-5-diphosphocholine 1000 mg daily. Further examination was planned including neuroimaging and ischemic laboratory tests.

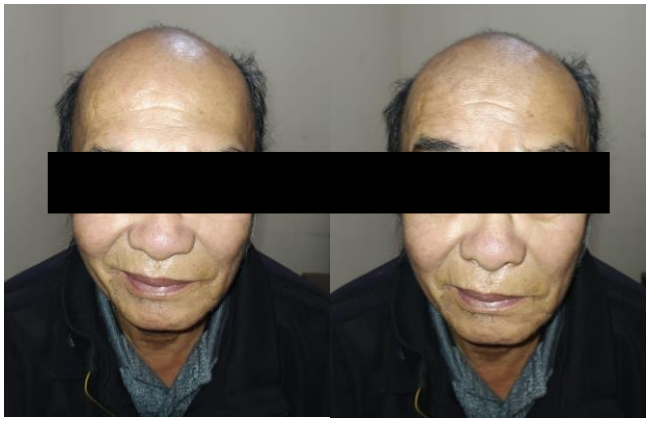


Figure 2.2 Left peripheral facial palsy as shown in examination at May 28th 2021

A week later on June 4th 2021, there was a subjective decrement of binocular diplopia. On attempted left gaze, restriction of ocular movement was -3 on right eye and -2 on left eye, with gaze-evoked nystagmus on both eyes. No other new neurological symptoms. Blood test results show normal blood sugar profile with low-density lipoprotein cholesterol was 132 mg/dL and triglyceride was 164 mg/dL. Another lipid profile was within normal limit. Magnetic resonance imaging (MRI) of brain and orbits with gadolinium contrast demonstrated there was Dawson's finger on left and right periventricular area, multiple small nodules on left and right cortex and juxtacortical cerebellar hemisphere, also small hyperintense lesion at pons, left paramedian pontine reticular formation (PPRF) and left medial longitudinal fasciculi (MLF) in posterior area that met McDonald's criteria of disseminated in time and space, as shown in figure 2.3.

The patient then diagnosed with horizontal gaze palsy and left peripheral facial nerve palsy et causa MS. Patient was given high-dose oral methylprednisolone 56 mg daily, cytidine-5-diphosphocholine 1000 mg daily, lansoprazole 30 mg daily,

and calcium hydrogen phosphate-cholecalciferol 400 mg bid. Patient was then referred to Neurologist for thorough neurological examination and management. Patient was also referred to Internist for regulation of his systemic hypertension and lipid profile. Further follow-up was planned for one week after treatment.

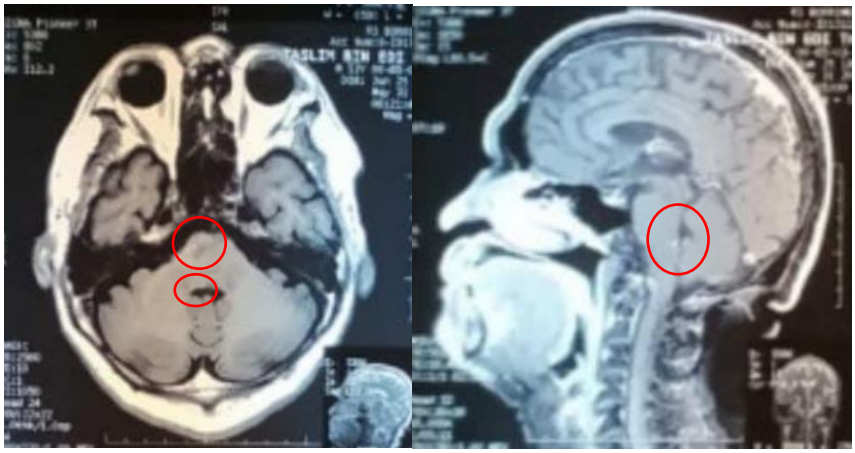


Figure 2.3 MRI findings support diagnostic criteria for multiple sclerosis. Note the hyperintense area (red circle).

At follow up visit in June 11th 2021, there was an improvement in ocular movement to left gaze, -2 on right eye and -1 on left eye. Oral prednisolone then tapered to 48 mg daily for one week and 40 mg daily for further week. Two weeks later on June 25th 2021, there was an improvement in ocular movement to left gaze, -1 on right eye and -1 on left eye. Patient says that his double vision is almost gone and there is gradual restoration of his left facial palsy. Oral prednisolone then tapered to 32 mg daily for one week and 24 mg daily for further week. The next visit scheduled two weeks later with expected restoration in ocular movement and his facial palsy.

III. Discussion

Multiple sclerosis is a brain- and spinal cord-specific chronic autoimmune process that affects the CNS, damaging myelin sheaths produced by oligodendroglia. Myelin sheaths, wrapped around axons, enable rapid saltatory conduction of action potentials and contribute to the maintenance of axonal integrity. This demyelination disease predominantly affects young adults between

20 and 40 years of age. The LOMS is an uncommon form of MS in which symptoms start at 50 plus years of age and represent roughly 4.5% of the MS population. Interestingly, in a study by de Campos Lotti et al, very late onset multiple sclerosis (VLOMS), defined as first symptom at 60 years or above, represent only 0.27% of their cohort. In other literature VLOMS accounts for 0.5% of all MS diagnoses. Initial presentation of LOMS is often a motor dysfunction.[1,3,6,7,10] Our case is a man who reports his first complaints related to MS at age 63-years-old, met the age criteria of the uncommon VLOMS. The patient initial presentation was brainstem symptom in a form of horizontal gaze palsy and ipsilateral peripheral facial nerve paresis. There is no motor dysfunction like previous reports in other studies.

The horizontal gaze center is specifically housed in the dorsal tegmental pons and comprises PPRF, abducens nucleus, MLF, and projection fibers to the contralateral oculomotor nerve medial rectus subnucleus. Paramedian pontine reticular formation send input into the ipsilateral abducens nucleus. The abducens nucleus then inputs into the ipsilateral lateral rectus muscle via the abducens nerve and also to the contralateral oculomotor medial rectus subnucleus in the midbrain via the MLF. When functioning properly, these connections structures allow conjugate horizontal gaze to occur. Disruption at one or more of these areas can result in characteristic eye movement disorders. Regardless of the type of the lesion, the clinical features will be developed based on lesions' site.[2,11,12]

Gaze palsy are defined as a reduction or complete elimination of conjugate eye movements in a particular direction and can include horizontal, vertical, or total gazes. With unilateral horizontal gaze palsy, lesions typically will involve the contralateral frontal eye fields (FEF), ipsilateral PPRF, or ipsilateral abducens nucleus. Interestingly, more superior PPRF lesions have been shown to cause loss of horizontal eye movements, whereas more inferior PPRF lesions lead to loss of both horizontal and vertical eye movements. If the lesion affects the inferior PPRF, ipsilateral abducens nerve palsies can be present as the abducens nerve fascicle passes through the inferior aspect of the PPRF. Ewe et al suggest that the vertical and horizontal gaze pathways run separately through their lower course and merge

in their rostral course, with the vertical gaze inputs running anterolateral to the horizontal gaze inputs. They may cross in their ascent, probably substantially, such that bilateral lesions are required to produce vertical gaze palsy. This would explain the sparing of the direct pathway for vertical gaze from the lateral PPRF in the presence of a unilateral lesion. A lesion of the abducens nucleus results in an ipsilateral horizontal gaze palsy, and not an isolated sixth nerve palsy.[2,5,11-13]

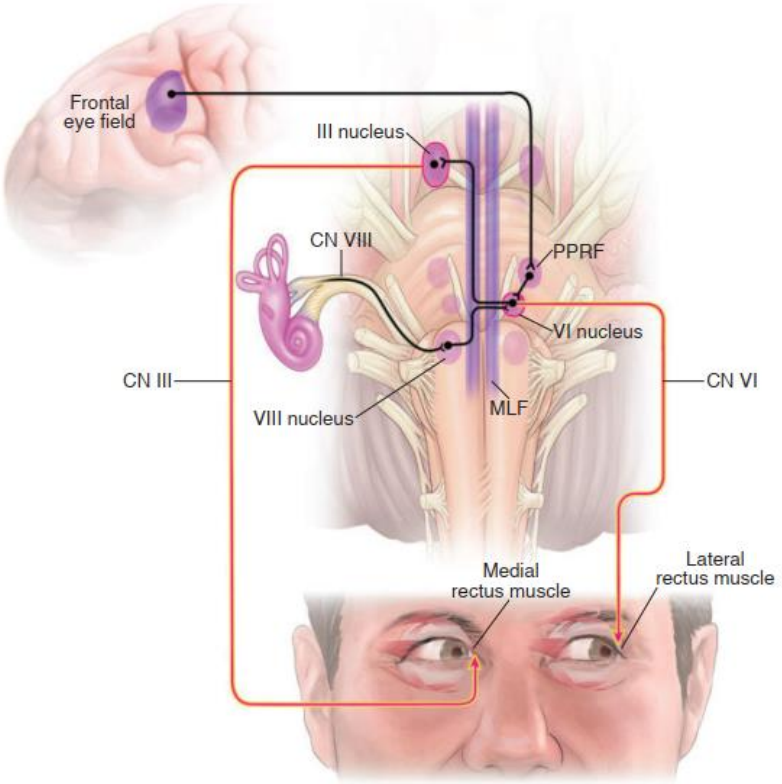


Figure 3.1 Anatomical scheme of horizontal gaze pathway. Abbreviations include the following: medial longitudinal fasciculus (MLF), paramedian pontine reticular formation (PPRF)
Source: Cantor et al[14]

In this patient, based on clinical examination there is adduction deficit in right eye and abduction deficit in left eye on attempted leftward gaze. Attempted rightward gaze was normal. Vertical eye movement were normal in both eyes. Brain MRI showed small hyperintense lesion at pons, left PPRF and MLF in posterior area. Posterior part of pons is region of abducens nucleus. This finding supports the diagnosis of horizontal gaze palsy implies lesions of the posterior pontine

tegmentum involving the complex of PPRF and abducens nucleus, sparing the vertical gaze pathway.

The abducens nucleus is located in the facial colliculus on the floor of the fourth ventricle at the level of the mid to lower portion of the pons. It's nucleus is surrounded by the looping fibers (genu) of facial nerve, and it's adjacent to the PPRF and the MLF. Then an ipsilateral facial weakness often accompanies conjugate horizontal gaze palsy. In previous literature, Henderson described a patient with horizontal diplopia on left lateral gaze and adduction weakness. Brain MRI demonstrated a solitary T2 hyperintense brain-stem lesion adjacent to the fourth ventricle, and a diagnosis of MS was made.[5,12-14] Our patient also complaint about weakness of his facial muscle that compatible with left peripheral facial nerve palsy.

Because of the close proximity of the seventh nerve fascicles to the sixth nerve nucleus and fascicles as well as the MLF and the PPRF, a single lesion may affect these and adjacent structures, leading to several variations of this finding. Similar to findings in this case, Green et al report a case of 62-year-old woman with partial right horizontal gaze palsy without an INO (1 ½ - ½ = 1) coupled with ipsilateral intra-axial fascicular seventh nerve palsy caused by ischemia. Tsuda et al described a similar case of sixth nuclear palsy and fascicular seventh nerve palsy occurring without an INO from a facial colliculus lesion. Green et al have named this pattern of an MLF-sparing nuclear and seventh nerve fascicular palsy as the "eight syndrome"— combination of the 1 ½ syndrome with the addition of a seventh nerve facial palsy, a neuroanatomical variant of the eight-and-a-half syndrome. The absence of an INO indicates sparing of MLF fibers.[4]

Multiple sclerosis is classified as either relapsing-remitting multiple sclerosis (RRMS) or primary progressive multiple sclerosis based on initial disease course. Among the phenotype subtypes of MS, RRMS is the most common and comprises approximately 85% to 90% of cases at disease onset. It is characterized by periods of exacerbation followed by periods of remission. The RRMS typically affects young adults and women are affected three times more often than men but most of LOMS presented as primary progressive MS. Low prevalence LOMS may because the patient may die of other causes before diagnosis of MS can be made, or since

some patient may have vasculopathic comorbid conditions that may present with similar symptoms. This may cause delay in patients being referred to specialized MS center. The delayed in diagnosis can reach three to five years in almost 40% of LOMS patients.[1,3,9] Our case is a man diagnosed as LOMS with RRMS course confirmed by MRI results. This could indicate an earlier unrecognised attack.

An early and accurate diagnosis of MS is essential to prevent irreversible neurological disability. Horizontal gaze palsy can also have various other etiologies such as infarction, vasculitis, inflammation/demyelination as part of MS or neuromyelitis optica spectrum disorders, hemorrhage, and metastasis. Therefore, in assessing a patient with suspected MS, it is important to determine the onset and evolution of their symptoms and to seek details of previous neurological symptoms that could indicate an earlier unrecognized attack and thus help to establish the diagnosis and disease course.[2,3,13] In our case, the patient has a long history of hypertension and with consideration of patient's age at initial symptoms, we initially suspect his horizontal gaze palsy was caused by an ischemic lesion.

When a patient presents with symptoms or signs that could indicate MS, an MRI is highly recommended because an abnormal brain MRI is present in nearly all patients with established MS and in more than 80% of patients with clinically isolated syndrome (CIS) who develop MS. The diagnosis of MS requires objective evidence of CNS lesions disseminated in time and space. Using the McDonald 2010 criteria, a diagnosis of MS can still be made on clinical grounds alone; however, MRI is used to provide evidence for dissemination in time and space, including in patients with CIS. For RRMS, MRI evidence of dissemination in space requires at least one T2 lesion in at least two of four sites, periventricular, juxtacortical, and infratentorial regions and the spinal cord, with symptomatic lesions in the brainstem and spinal cord excluded. Dissemination in time requires either asymptomatic gadolinium-enhancing and non-enhancing lesions on the same MRI scan or a new lesion on a follow-up scan. Using the McDonald 2010 criteria, a diagnosis of RRMS can be made in up to a third of patients with CIS with a single MRI scan.[3] Our patient's MRI shows multiple T2 lesions on periventricular and pons area, met the criteria of disseminated in space. There is also gadolinium-enhancing lesion in

cortex and juxtacortical, indicate active lesion that met the criteria of disseminated in time. This finding compatible with the RRMS.

Establishing a diagnosis of MS can be more difficult in older adults because white matter lesions due to small vessel cerebrovascular disease are often found on brain MRI. Astringent interpretation of brain MRI criteria is mandatory and spinal cord MRI is helpful because spinal cord lesions do not occur with healthy aging. At symptom onset, spinal cord imaging is recommended in patients with clinical features suggestive of spinal cord involvement to exclude alternative cord pathology (eg, compression, spinal cord tumor, neuromyelitis optica, or vasculitides) and in those with nonspinal CIS that do not fulfill brain MRI criteria for dissemination in space. Further targeted laboratory tests to exclude mimics of MS might be indicated if the history, examination, or MRI findings are atypical.[1,3,15] Our patient had systemic hypertension that can lead to ischemic etiology. We do perform an MRI with results compatible with MS. In this patient we do not perform spinal cord imaging and further targeted laboratory test because MRI shows the typical finding of MS.

Most patients with RRMS will eventually enter a secondary progressive phase in which neurological deficits become fixed and accumulate. Pharmacological therapies are expected to reduce the yearly incidence and/or decrease the length and severity of relapses, halt or slow down disability progression, and prevent or delay transition to secondary progressive MS. Disease-modifying therapies (DMT) have decreased the risk of accumulation of new focal lesions, but when relapses occur, high-dose intravenous corticosteroids are commonly used. Glucocorticoids are recommended as the standard of care for acute MS flares, since their proven effectiveness to reduce the severity of clinical impairment, hasten the recover, and reduce the risk of exacerbations. It have potent anti-inflammatory and immunosuppressive properties. There are two main effects relevant to MS immunopathogenesis. First, facilitation of apoptosis of activated immune cells and inhibition of T cell activation. Second, reduction of the adhesion and transmigrating capacity of peripheral blood mononuclear cells into the CNS by down-regulating

the expression of adhesion molecules on the surface of both T cells and endothelial cells.[8,9,16,17]

Several studies have shown that there is no difference in efficacy and safety between oral methylprednisolone and intravenous methylprednisolone. Barnes et al found no difference in Expanded Disability Status Scale between a 3-week oral regimen with, respectively, 48 mg - 24 mg - 12 mg of MP and a cumulative dose of 580 mg versus 1000 mg intravenous methylprednisolone during 3 days. Oral delivery is simpler and less invasive, more convenient for the patient, and allows obvious savings in costs and logistics. The choice of oral rather than intravenous steroid therapy results in savings to the healthcare system. Furthermore, the use of intravenous glucocorticoids will increase costs, require hospitalization and interfere with daily life.[8,9,16,17] In this patient we give oral high dose corticosteroid 1 mg/kg body weight daily with weekly tapering of scheme and result in markedly improved of ophthalmoplegia and facial palsy. Patient also was given neuroprotector citicoline 1000 mg daily.

Relapses in RRMS are caused by immune cells invading CNS and damaging myelin, while remissions involve activation of oligodendroglia and oligodendroglial precursors, and remyelination, which protects axons from degeneration. Citicoline, or cytidine 5'-diphosphocholine (CDP-choline) has been shown to possess several protective functions including promoting membrane stability, and inhibiting glutamate excitotoxicity, apoptosis, and oxidative stress, then enhance and accelerate remyelination.[6,19]

Annual relapsing rate was higher in younger MS than LOMS. In a study by Mirmosayyeb, compared to younger onset MS, individuals with LOMS more often had no relapses in the first two years. This low annual relapse rate in older patients could be attributed to more inflammatory disease in young patients. Recovery after the first relapse is better in younger patients and the chances of full recovery after a relapse decreases by 1% for each year older the patient is at onset while LOMS patient are more common to acquire sustained severe neurological disability in a short period of time. But considering RRMS form of LOMS, respectively, 70% had their second relapse less than a year after the first symptom.[1,7] Further long term

follow-up even after complete resolution of patient restriction of eye movement is important.

The prognosis of this patient, *quo ad vitam* is *dubia ad bonam* due to his diagnosis of hypertension. Further general examination is needed since longterm hypertension can lead to potential complications that include heart disease, stroke, or kidney damage; *quo ad functionam* is *dubia* because patient's good response to corticosteroid treatment but there is possibility of further demyelination in other area that can result in another disability; *quo ad sananctionam* is *dubia* since the natural course of RRMS.

III. Conclusion

Horizontal gaze palsy can be presented as an initial sign of relapsing-remitting VLOMS. Neurological examination is important to localize the site of involvement in CNS and reveal another neurological finding like ipsilateral facial nerve palsy. Appropriate neuroimaging can be performed to support the diagnosis. High-dose oral corticosteroids reduce the severity of clinical impairment and hasten recovery of the deficits.

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