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Case Report

Statin-Induced Diplopia: A Rare Side Effect

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***Abstract*— Statin is one of the most effective medication to date in treating dyslipidemia. Moreover, statin is the most available in health clinics due to its cost-effectiveness. However, statin must be used with caution due to its severe rare side effects. Ocular disorder secondary to statin is rarely reported. In this case, statin-induced lateral gaze diplopia, worst on the left lateral gaze, was noted in a middle-aged Malay man. He had underlying dyslipidemia and was started on simvastatin 20mg at night three days before developing diplopia. He was otherwise well and had no other medical illnesses. There were no other neurological signs and abnormal ocular signs. Investigations were done and revealed no other abnormalities. The patient's symptom resolved gradually over eight weeks after discontinuation of the statin. Thus, this case highlights the important key point of anticipating this severe rare side effect of statin, which may be irreversible.**

***Keywords*— statin; diplopia; dyslipidemia; HMG-CoA reductase; neurology.**

I. INTRODUCTION

In dyslipidaemia, statins, which are readily available in health clinics, are the drug of choice to control low-density lipoprotein (LDL) and triglyceride. Statin acts by inhibiting the cholesterol synthesis by blocking the enzyme 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase (1). Thus, statin is used as primary and secondary prevention of cardiovascular disease. However, like other medications, statin has its side effects. The most known side effects are myopathy and drug-induced hepatitis. Based on the European Atherosclerosis Society Consensus Panel, about 10-30% of patients developed statin-induced muscle symptoms such as myalgia or myositis (2). Mild elevation on alanine transaminases enzyme was reported in less than 3% of the patients (3).

Rarely do we hear about statin-induced ocular adverse events. However, it has been reported as one of the side effects (4). Hence, treating doctors may not be aware of this adverse risk of statin. Diplopia is an ophthalmologic condition characterised by seeing two images instead of one. This case highlights statin-induced diplopia, which was successfully reversed after eight weeks of dechallenging with statin.

II. CASE REPORT

A 49-years-old Malay man with underlying dyslipidaemia and Grade 1 obesity complained of double vision for a one-week duration. It was gradual onset, constant, progressively worsening, and subsequently affected his daily activity such as driving and reading signage on the road. The diplopia was greatest with the left lateral gaze compared to any other directions, which resolved by closing one eye. In other words, the patient had binocular and horizontal diplopia. The separation of images was horizontal and worse at distance vision. Otherwise, the patient did not complain of drooping of the eyelid, blurred vision, eye pain, tearing, headache, or vision loss. He denied any weakness, facial asymmetry, slurred speech, numbness, or instability. A review of his medication history revealed that he was started on Tablet Simvastatin 20 mg at night, three days prior to this event.

His past medical history revealed that he had a history of left-sided Bell's palsy more than ten years ago, which resolved completely. He also had a history of pleural tuberculosis and completed treatment in February 2018. On examination, his vital signs were all normal. There was no facial asymmetry noted, and he had a normal gait. His external eyes appearance was normal. Bilateral conjunctiva was not injected, and the cornea appears clear. Pupils were symmetrical and reactive to light. The Relative Afferent Pupillary Defect (RAPD) test was negative. Visual acuity was 6/6 bilateral, and the visual field was intact. Upon assessment of the eye movement, the double vision worsened with the left lateral gaze. Otherwise, no ptosis and other cranial nerves were intact. Fundus examination revealed a cup disc ratio of less than 0.5, with a normal macula appearance and retina.

The peripheral neurological examination was normal. Basic blood investigations such as Full Blood Count (FBC) and serum Erythrocyte Sedimentation Rate (ESR) were done at the health clinic to look for haematological parameters and inflammatory markers to identify the possible cause such as infection or tumour. The FBC result was normal, and the ESR was only 26 mm/hour. The patient was referred to the Ophthalmology Department, Hospital Putrajaya. Computed Tomography (CT) imaging of the brain and Hess test were done. The CT Brain was normal, and the Hess test showed sixth nerve palsy. Hence, the provisional diagnosis was mononeuritis multiplex, whereas a rare possibility of statin-induced diplopia was also considered.

Consequently, the statin was discontinued. The patient fully recovered after eight weeks of discontinuation of statin. This case was subsequently reported as an adverse drug reaction (ADR) to the Malaysian National Pharmacovigilant Unit. The unit informed that there were two statin-related ophthalmologic cases reported in Malaysia, whereas there were 113 cases related to simvastatin worldwide.

III. DISCUSSION

Statin-induced diplopia is a rare drug-induced ophthalmologic condition. However, there is no clear consensus on the exact mechanism. There are few postulated pathogenic mechanisms, like myositis of the extraocular muscles causing myopathy (5). Since statin has a role in reducing the cholesterol level, this might change the function and integrity of the cell membrane at a cellular level (6).

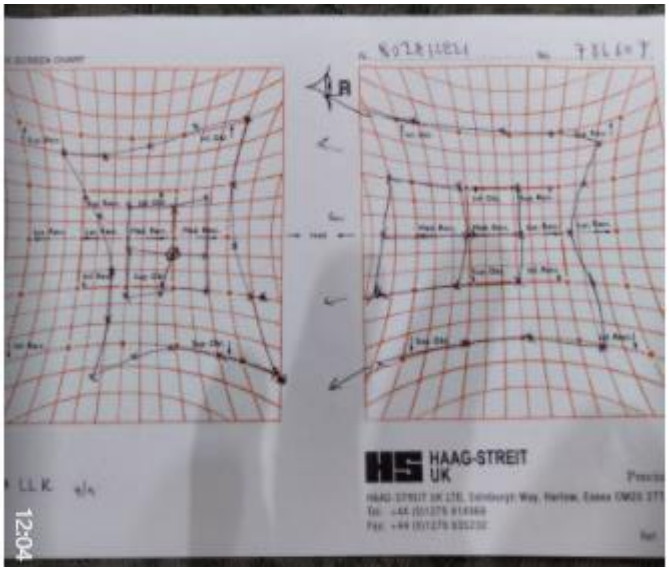

Fig. 1 Hess Test Chart at two weeks of diplopia onset. This test shows left lateral rectus palsy

Data from the Food and Drug Administration (FDA), the USA, in 2015 reported 1.8% of ocular adverse events related to statin. Most reported cases were blurred vision (48.4%), while some had visual impairment (25.7%). About 30.3% were related to ocular muscles. Those taking atorvastatin and simvastatin had more ocular problems compared to rosuvastatin, pravastatin, and lovastatin (8). In Australia, a retrospective study from Food and Drug Administration (FDA) and Adverse Drug Reactions Advisory Committee (ADRAC) year 1988 to 2013 reported 136 cases of statin-induced ocular adverse events. Again, blurred vision and visual impairments were the most typical adverse event reported (8). Nevertheless, which type of statin can exactly induced diplopia is still unknown. In Malaysia, there are not many cases of statin-induced diplopia reported.

Diplopia is caused by the dysfunction of the extraocular muscles, which can be due to the abnormality of the muscle itself or defects in the nerve involving the third, fourth, or sixth nerves supplying the extraocular muscles. Diplopia is divided based on binocular or monocular. It can also be divided based on its direction that is either horizontal, vertical, or oblique gaze (8). Binocular vision is the most common double vision, which disappears when either one eye is closed. The main cause is the misalignment of the visual axis (7). In contrast, monocular means diplopia persists when one eye is closed, suggesting local eye disorder or refractive error (6).

Horizontal diplopia affecting the lateral rectus (medical and lateral movement) is caused by the sixth nerve or intranuclear ophthalmoplegia. Vertical diplopia (superior and inferior) is usually caused by thyroid eye disorder. Meanwhile, oblique diplopia involving superior and inferior muscle impairment is caused by lateral medullary syndrome (6). As for statin, it is not stated which diplopia is commonly seen. In relation to this case study, this patient develops horizontal diplopia.

The eye examination, in this case, focuses on establishing which particular extraocular muscles were affected. The presence of pupillary reflex, other cranial nerve abnormalities and establishing other ocular findings were also performed to

determine the possible causes of diplopia. When the pattern of muscle weakness upon examination suggested that the problem was isolated to a single cranial nerve, the differential diagnosis was tailored to that specific individual nerve. Patients with sixth nerve palsy primarily complain of horizontal diplopia, commonly caused by vascular disease, malignancy and trauma (6). This patient has horizontal diplopia but has no history of trauma or constitutional symptoms.

Preferred neuroimaging in cases of diplopia is Magnetic Resonant Imaging (MRI). Alternative to this modality includes a Contrast-enhanced CT scan and the expected neuroimaging findings, including neoplasm, brain stem infarction, and giant cell arthritis (8). In this case, the CT scan was normal. There was no evidence of brain neoplasm or vascular event. The serum ESR, a non-specific marker that elevates inflammatory reaction, was also normal. Ocular Hess test aids in diagnosing ocular motility defect (9). The Hess test (Figure 1) showed left lateral rectus palsy. Thus, a history of double vision due to sixth nerve palsy with no other causal factors was reported in this case. Hence, statin was suspected as the cause of diplopia.

Since the diplopia improved eight weeks after statin was withdrawn, this patient was diagnosed with statin-induced sixth nerve palsy. This diagnosis was further supported by few reported case studies. Larebs reported 17 cases of statin-induced diplopia especially involving pravastatin and simvastatin, from July 1996 to July 2015, with a latency period from one day to several months after statin was taken by patients (10). Among them, only ten patients recovered after discontinuation of statin. Hence, a physician must be aware of the possibility of the irreversibility of statin-induced diplopia.

Clinical suspicion of statin-induced diplopia should be made in patients with unexplained diplopia, even though there is no specific time frame for this adverse event. In this case, it happened after three days of therapy. Therefore, a correlation between clinical history, including drug history, physical examination and investigations with the latest evidence is key to ease the diagnosis and management of statin-induced diplopia.

IV. CONCLUSIONS

Statin has played an important role in the primary and secondary prevention of cardiovascular diseases. However, physicians should be vigilant in observing for adverse drug events. If any ocular adverse effect was observed post statin initiation, a thorough history, with a comprehensive drug history, and examination are required to find the cause. If no cause is found after a thorough work-up, the symptoms may be attributed to statin-induced diplopia and withdrawal of the statin is indicated. Reporting the adverse event to the National Pharmaco-vigilant Unit in Malaysia is essential for monitoring this rare side effect of statins.

CONSENT TO PARTICIPATE

Written informed consent was obtained from the patient for the anonymized information to be published in this article.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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