

Chronic Inflammatory Demyelinating Polyradiculoneuropathy Association With Low Cholesterol Levels: A Case Report in a Patient Taking PCSK9 Inhibitor

Diana Carolina Franco^{a, b}, Neelam Neupane^{a, b}, Maria Riaz^a,
Sanaz Mohammadzadeh^a, Issac Sachmechi^a

Abstract

A 57-year-old woman with history of prediabetes and dyslipidemia treated with PCSK9 inhibitors due to statin intolerance presented to the clinic with complaints of bilateral thigh pain, weakness and numbness. During the physical exam, the patient exhibited stocking loss of vibratory and cold temperature sensation in both legs, absent ankle reflexes and tandem imbalance with normal cranial nerve functions. After all the clinical studies, the patient was diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as an exclusion diagnosis. A link with medications (Praluent) was determined to be the most possible offending agent. With this case, we present a rare case of CIDP in the setting of low level of low-density lipoprotein cholesterol (LDL-C) due to PCSK9 inhibitors. This case opens the door to a new and unrecognized adverse effect of this type of medication.

Keywords: CIDP; Low cholesterol levels; PCSK9 inhibitor

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), which is sometimes called chronic relapsing polyneuropathy, is an acquired peripheral neuropathy due to an autoimmune attack of peripheral nerve myelin characterized by symmetrical motor predominant polyneuropathy characterized by both distal and proximal weakness, numbness and sensory ataxia [1, 2]. There is also associated impaired sensation, absent or diminished tendon reflexes, an elevated cerebrospinal fluid protein level, demyelinating nerve conduction studies

and signs of demyelination in nerve biopsy specimens [3].

Case Report

A 57-year-old woman with history of prediabetes and dyslipidemia with a poorly controlled low-density lipoprotein cholesterol (LDL-C) level was started on subcutaneous injection of Praluent 75 mg/mL every 2 weeks due to statin intolerance. Patient had been on statins for 15 years and four different statins were tried, which were always getting switched because of intolerance in the setting of terrible muscle pain from each of statin. Due to this fact, she was started on PCSK9 inhibitor, Praluent while LDL-C was 203 mg/dL and level dropped to 121 mg/dL after 3 months of Praluent use. Eventually it went down to 106 mg/dL after 6 months of treatment. While on Praluent, patient developed symptoms of polyneuropathy after 1-year use of PCSK9 inhibitor. She presented to the clinic with complaints of bilateral thigh pain, weakness and numbness. Tingling and stabbing pain was started in feet initially, which then progressed to thighs bilaterally. Later on, patient also developed imbalance and started having leg cramps while rising from a chair and climbing stairs with severe fatigue. Ibuprofen use helped her pain with minimal relief. Physical examination was significant for weakness of bilateral hip flexors with strength 2/5 on right side and 3/5 on the left side. Patient exhibited stocking loss of vibratory and cold temperature sensation in both legs, absent ankle reflexes and tandem imbalance with normal cranial nerve functions and rest of physical exam. Patient did not have any significant findings in upper extremities. Patient was referred to a neurologist who performed basic blood tests, electromyography (EMG), nerve conduction studies, skin biopsy, magnetic resonance imaging (MRI) and computed tomography (CT) of the pelvis. The results revealed abnormal asymmetric distal demyelination more pronounced on right side. Neurologist reported that findings were consistent with peripheral distal demyelinating axonal neuropathy and lumbar radiculopathy. Patient underwent various other tests to rule out any rheumatological and musculoskeletal disorders. She had a positive antinuclear antibody (ANA) but had a negative anti-dsDNA antibody and anti-Sm antibody with positive SCL-70 (> 8 h). She followed up with a rheumatologist for ANA (1:640) and SCL-70. The rheumatologist confirmed that patient had no clinical features of scleroderma. Other test re-

Manuscript submitted September 3, 2019, accepted September 28, 2019

^aDepartment of Internal Medicine, Endocrinology Services, Icahn School of Medicine at Mount Sinai, Queens Hospital Center, Jamaica, NY 11432, USA

^bCorresponding Author: Diana Carolina Franco and Neelam Neupane, Department of Internal Medicine, Endocrinology Services, Icahn School of Medicine at Mount Sinai, Queens Hospital Center, Jamaica, NY 11432, USA.
Email: dfrancob7@hotmail.com, neeru819@gmail.com

doi: <https://doi.org/10.14740/jnr552>

sults such as ribonucleoprotein (RNP), human leukocyte antigen (HLA) B27, HLA DRQ, rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), creatine phosphokinase (CPK), Lyme ABs, thyroperoxidase (TPO), cortisol and immunoelectrophoresis were all negative.

Patient was diagnosed with CIDP as an exclusion diagnosis. It was thought that perhaps her CIDP was caused by medication and Praluent was found to be the most possible offending agent because it was the only one medicine patient was on. She was taken off Praluent and started on gamma globulin, IVIG biweekly, after which symptoms improved dramatically. As expected, following discontinuation of Praluent, LDL-C spiked up to 350 mg/dL in 3 months, for which the cardiologist put her on Repatha (PCSK9 inhibitor) 140 mg/mL every 2 weeks. LDL-C dropped to 93 mg/dL after 3 months use of Repatha. While patient was on Repatha, symptoms of polyneuropathy such as pain and weakness of distal muscles returned after two doses. As PCSK9 inhibitor was again thought to be a cause of polyneuropathy relapse, she was taken off Repatha. There was a marked improvement in her leg weakness, 15 days after discontinuation of Repatha. It has been 4 months since the patient has been off Repatha and has not had a relapse. Patient is being treated with IVIG biweekly. Cardiologist has restarted low-dose statin, crestor 5 mg every other day since LDL-C level was 206 mg/dL. She goes for physiotherapy and is currently working on muscle strength, balance and range of motion.

Discussion

Myelin is a fatty protective cover of nerves. The lipid composition of myelin is believed to have a pivotal role in membrane morphology and transmission of nerve impulses [4]. Lipid depletion can lead to synaptic and dendritic spine degeneration, failed neurotransmission and decreased synaptic plasticity [3].

Studies have shown that when compartmented cultures of Rat's sympathetic neurons are incubated with pravastatin, in the absence of exogenously supplied lipids, cholesterol synthesis is inhibited, and axonal growth is impaired [5]. The addition of cholesterol to the axons or cell bodies of neurons treated with this inhibitor restores normal axonal elongation [6]. PCSK9 inhibitors in dyslipidemia primarily focus on reduction of plasma LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (ApoB) PP levels [7].

Since PCSK9 inhibitors promote an aggressive lowering of total serum cholesterol levels and decrease the LDL-C, we assume that low levels of total serum cholesterol and LDL-C are associated with demyelinating nerve lesions because cholesterol is not produced in the axon and needs an external supply of HDL-C and LDL-C. Lowering cholesterol levels with the use of medications such as PCSK9 inhibitors would result in the use of different lipid compositions to develop myelin [6]. This alteration in lipids would therefore result in nerve swelling attributable to reactive thickening of the myelin sheath, with impaired nerve conduction and an increasing severity of a patient's clinical symptoms [5].

PCSK9 inhibitors usual side effects are: allergic reactions,

insulin resistance, new onset diabetes in prediabetic, predisposition to colon cancer in animal studies and rarely neurocognitive and muscular disorders. CIDP has not been known to be a side effect of PCSK9 inhibitors. To the best of our knowledge, no case has been reported about the association between use of PCSK9 inhibitors and demyelinating polyneuropathy.

It is possible that genetics may play a role, leading to some patients being more susceptible than others to the demyelinating effects of aggressive cholesterol lowering since not everyone on PCSK9 inhibitors developed this disorder [8]. It is not known if there is a cutoff LDL-C that needed in order to develop this disorder. Also, it is unclear why this adverse effect has a predilection for lower extremities and not upper [8].

Further studies should be done for better understanding of demyelinating neuropathy with the use of PCSK9 inhibitors.

Conclusion

In patients who are taking PCSK9 inhibitors, one should watch for the possibility of adverse effects of CIDP.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors have no conflict of interest.

Informed Consent

Informed consent was obtained from the patient.

Author Contributions

The authors all equally contributed to, had access to and interpreted the data, drafted the manuscript and approved the final version for submission.

References

1. Dyck PJB, Tracy JA. History, diagnosis, and management of chronic inflammatory demyelinating polyradiculoneuropathy. *Mayo Clin Proc.* 2018;93(6):777-793.
2. Mathey EK, Park SB, Hughes RA, Pollard JD, Armati PJ, Barnett MH, Taylor BV, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: from pa-

- thology to phenotype. *J Neurol Neurosurg Psychiatry*. 2015;86(9):973-985.
3. Koller H, Kieseier BC, Jander S, Hartung HP. Chronic inflammatory demyelinating polyneuropathy. *N Engl J Med*. 2005;352(13):1343-1356.
 4. Orth M, Bellosta S. Cholesterol: its regulation and role in central nervous system disorders. *Cholesterol*. 2012;2012:292598.
 5. Vance JE, Campenot RB, Vance DE. The synthesis and transport of lipids for axonal growth and nerve regeneration. *Biochim Biophys Acta*. 2000;1486(1):84-96.
 6. de Chaves EI, Rusinol AE, Vance DE, Campenot RB, Vance JE. Role of lipoproteins in the delivery of lipids to axons during axonal regeneration. *J Biol Chem*. 1997;272(49):30766-30773.
 7. Dijk W, Cariou B. Efficacy and safety of proprotein convertase subtilisin/kexin 9 inhibitors in people with diabetes and dyslipidaemia. *Diabetes Obes Metab*. 2019;21(Suppl 1):39-51.
 8. Perez-Matos MC, Morales-Alvarez MC, Mendivil CO. Lipids: a suitable therapeutic target in diabetic neuropathy? *J Diabetes Res*. 2017;2017:6943851.