Incidence of peripheral neuropathy in a randomly selected newly diagnosed patient with hypertriglyceridemia, a cross sectional study in Karbala city

[1]Almhanna Mohanay Yahya, [2]AlMokhtar Amer Omran,[3] Harba Alkhansaa Sabah Ibrahim,

[1]Branch of medical physiology, College of medicine, Kerbala University, Iraq.

[2]Branch of medicine, College of medicine, Kerbala University, Iraq.

[3]Department of Neurophysiology, Al-Hussein teaching Hospital, Kerbala, Iraq

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Abstract:

Many researchers suggested that there is a relationship between hyperlipidemia and neuropathy as being a cause of neuropathy (focal or generalized poly-neuropathy). But few cases were reported and they are mostly involved people with other diseases that cause neuropathy, such as diabetes mellitus or other chronic illnesses. In this study we try to clarify if there is any correlation between hypertriglyceridemia and peripheral nerves lesion (peripheral neuropathy (PN)) in patients with a high triglyceride level and no neurological complaints. 68 patients were randomly selected (36 males and 32 females) whom having a high serum triglyceride level (above 300 mg/dl) with no neurologic complaints and no other common causes of peripheral neuropathy and they underwent an electroneurophysiologic study. The distal motor or sensory latencies, motor or sensory conduction velocities, and motor or sensory amplitudes were collected for the peripheral nerves including peroneal, posterior tibial, sural, median, and ulnar nerves and were compared with the reference values. The results showed that 40% of the patients had a significant neuropathic changes mainly of axonal degeneration type while 60% had normal nerve conduction study (NCS) parameters. The abnormalities affecting the peripheral nerves mainly of the lower extremities is suggestive of an early axonal polyneuropathy. So, it was concluded that hypertriglyceridemia affects the results of conduction parameters in peripheral nerves in a pattern suggestive of early peripheral neuropathy.

Keywords: Hypertriglyceridemia, hyperlipidemia, peripheral neuropathy

الخلاصه

اقترح العديد من الباحثين أن هناك علاقة بين فرط شحميات الدم والاعتلال العصبي كسبب للاعتلال العصبي (اعتلال الأعصاب البؤري أو المعمم). ولكن تم الإبلاغ عن عدد قليل من الحالات وهي في الغالب تتعلق بأشخاص يعانون من أمراض أخرى تسبب اعتلال الأعصاب ، مثل داء السكري أو غيره من الأمراض المزمنة. نحاول في هذه الدراسة توضيح ما إذا كان هناك أي ارتباط بين فرط شحوم الدم واصابة الأعصاب الطرفية (اعتلال الأعصاب المحيطية (PN)) في المرضى الذين يعانون من ارتفاع مستوى الدهون الثلاثية وعدم وجود شكاوى عصبية. تم اختيار 68 مريضًا بشكل عشوائي (36 من الذكور و 32 من الإناث) الذين لديهم مستوى مرتفع من الدهون الثلاثية في الدم (أعلى من 300 مجم / ديسيلتر) دون أي شكاوى عصبية ولا توجد أسباب أخرى شائعة لاعتلال الأعصاب المحيطية وخضعوا لدراسة الفيزيولوجيا العصبية الكهربية. تم جمع الكمون الحركي البعيد والقريب أو الكمون الحسي ، وسرعات التوصيل الحركية أو الحسية ، والسعات الحركية أو الحسية للأعصاب الطرفية بما في ذلك الأعصاب الشظوية ، الظنبوب الخلفي ، الربلي ، المتوسط ، والزندي وتمت مقارنتها مع القيم المرجعية. أظهرت النتائج أن 40٪ من المرضى عانوا من تغيرات اعتلال عصبي معنوي بشكل رئيسي من نوع التنكس المحوري بينما 60٪ لديهم معايير دراسة التوصيل العصبي الطبيعي (NCS). تشير التشوهات التي تصيب الأعصاب الطرفية بشكل رئيسي في الأطراف السفلية إلى اعتلال الأعصاب العصبي المحوري

المبكر. لذلك ، خلص إلى أن ارتفاع شحوم الدم يؤثر على نتائج معاملات التوصيل في الأعصاب الطرفية في نمط يوحي باعتلال الأعصاب المحيطية المبكر

1- Introduction

Hyperlipidemia involves abnormally elevated levels of any or all lipids and/or lipoproteins in the blood. Hyperlipidemias are divided into primary and secondary types. Primary hyperlipidemia is usually due to genetic causes, while secondary hyperlipidemia arises due to other underlying causes such as diabetes. [1]

Hyperlipidemias may basically be classified as either familial (also called primary) caused by specific genetic abnormalities, or acquired (also called secondary) when resulting from another underlying disorder that leads to alterations in plasma lipid and lipoprotein metabolism. Also, hyperlipidemia may be idiopathic, that is, without known cause. [2]

The most common type is familial hypertriglyceridemia which is an autosomal dominant condition occurring in approximately 1% of the population. Triglyceride levels, but not cholesterol, are elevated as a result of excess hepatic production of VLDL or heterozygous LPL deficiency. [3]

Hypertriglyceridemia is defined as a fasting serum triglyceride (TG) level of >150 mg/dl. Serum TG elevations are designated as:

Borderline: 150 to 199 mg/dl,

High: 200 to 499 mg/dl,

Very high: 500 mg/dl.

When triglyceride levels exceed 500 mg/dL, patients may develop acute pancreatitis. Levels exceeding 1000 mg/dL define chylomicronemia, which may result in lipemia retinalis, eruptive xanthomas, hepatomegaly, and potentially fatal acute pancreatitis. [4]

Overweight/obesity and insulin resistance have been found to be associated with elevated triglyceride levels, and hypertriglyceridemia is a component of the metabolic syndrome.

Hypertriglyceridemia is often clinically silent and is typically detected by lipid screening in asymptomatic patients. [5]

Peripheral neuropathy is damage to or disease affecting nerves, which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected. Common causes include systemic diseases (such as diabetes or leprosy), some vitamin deficiency, medication (e.g., chemotherapy, or commonly prescribed antibiotics including Metronidazole and the Flouroquinolone class of antibiotics (Ciprofloxacin, Levaquin, Avelox etc.), traumatic injury, radiation therapy, excessive alcohol consumption, immune system disease, Coeliac disease, or viral infection. It can also be genetic (present from birth) or idiopathic (no known cause). [6-8]

A previous study [9] investigated the influence of HL on the function of sensory nerve fibers. Recently, substantial epidemiological research performed on diabetic patients in a retrospective or prospective manner found that individuals with HL have a significantly higher incidence of axonal distal polyneuropathy [10-12].

1-1- Mechanism of lipid impairment

Previous investigations have confirmed that hyperglycemia is harmful to dorsal root ganglion neurons via initiating the process of oxidative stress as reactive oxygen species (ROS), which are principally generated by mitochondrial overload, that eventually lead to the degeneration and death of neurons [13]

In addition to eliciting oxidative stress and inflammatory lesions to the nervous system directly, HL may lead to stenosis of the vascular lumen and disturb microcirculation, resulting in possible ischemia in peripheral nerves. [14-15].

Several lipid products, such as oxLDLs and oxysterols, are known to stimulate inflammatory cytokines and the expression of adhesion molecules on endothelial cells, which play a role in the recruitment of monocytes and the initiation of local inflammatory lesions. Recent studies found that HL may also initiate local inflammation in the PNS, and lead to inflammatory lesions in the etiopathology of neuropathies [16].

Early in 1997, Weigle had reported the possible causative role of adipocytokines in various human diseases related to energy homeostasis, insulin action, host defense and reproduction [17]. Recent studies have demonstrated that Hyperlipidemia (HL) and other systematic metabolic disturbances can alter the expression levels of local adipocytokines in adipocytes distributed in many tissues [18]. This is evidence that Hyperlipidemia (HL) plays a potential role in these diseases via the disturbance of local adipocytokines secretions that ultimately lead to clinical symptoms. This is also the case in the PNS. Adipocytokines play a critical role in the etiology of diabetic peripheral neuropathy [19]. Consequently, the precise mechanism of adipocytokines underlying the process of peripheral neuropathy caused by HL has become of great interest to many researchers. An early study has detected the presence of adipocytes in the epineurium of peripheral nerves [20].

2- Patient and Methods

The study was done in Al-Hussein teaching hospital and extend from January 2017 to February 2019

***Inclusion criteria*:** patients with newly diagnosed hypertriglyceridemia were randomly selected from the lipid clinic.

***Exclusion criteria*:** people whom were excluded from the study were those with diabetes mellitus, hyperthyroidism, renal failure, lumbosacral (L-S) radiculopathy, chronic drug usage (as anti TB drugs), patient with family history of hereditary neuropathies, patients with carpal tunnel, Guyon`s canal, tarsal tunnel syndromes and patient with some chronic disease (as chronic renal failure, malignancy or collagen disease).

Sixty eight patients were included in this study, who were referred from the lipid clinic with serum triglyceride levels above 300 mg/dl, the patients were told about the research and their informed consent was taken.

These patients were newly diagnosed as having hypertriglyceridemia and none of them was on any lipid lowering therapy before the electrophysiological examination.

The electroneurographic study were done for all the patient in the classical manner. The peroneal, posterior tibial, sural, median, and ulnar nerves were studied in both lower and one extremities.

The peroneal nerves stimulation were at the ankle and the fibular head recording from the extensor digitorum brevis muscles. The tibial nerves were stimulated behind the medial malleolus and at the popliteal fossa with recording from the abductor hallucis muscles. The sural nerves stimulation were between the heads of the gastrocnemii with recording from the lateral malleolus. The median nerves were stimulated at the wrist and elbows with recording from the abductor pollicis brevis muscles. The ulnar nerves were stimulated at the wrist and elbows with recording from the abductor digit quinti muscle. The distal motor or sensory latencies (DL), motor or sensory conduction velocities (CV), and motor or sensory amplitudes were collected for each of the above mentioned nerves. We compared the results with the normal values and considered them abnormal if they fall above or below 2 standard deviations (SD) of reported normal distal latencies, amplitudes, and conduction velocities [21].

3- Statistical analysis

Statistical analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Normally distributed data were analyzed by parametric tests (-test and -test for dependent samples). The gender distribution of the two groups was assessed by a chi-square test. Compound muscle action potentials and sensory nerve action potenital latency and duration were established as the mean from four recordings. The mean, median, standard deviation, and minimal and maximal values were calculated. Statistical significance level was accepted as a p-value of <0.05.

4- Results:

68 patients were included in our study (32 females and 36 male), with an average age of (45.3 ± 11.4 years and an average weight of (82.5 ± 13.7 kg).

The average blood cholesterol level of 226.5±49.8 mg/dl and the average triglyceride level of 566.1±367.4 mg/dl.

The results show that 40% of the patients had a significant neuropathic changes mainly of axonal degeneration type while 60% had normal NCS parameters. The difference in the means was most pronounced in the peroneal and sural nerves. There was no significant correlation between the triglycerides levels and any of the measured electrophysiological parameters.

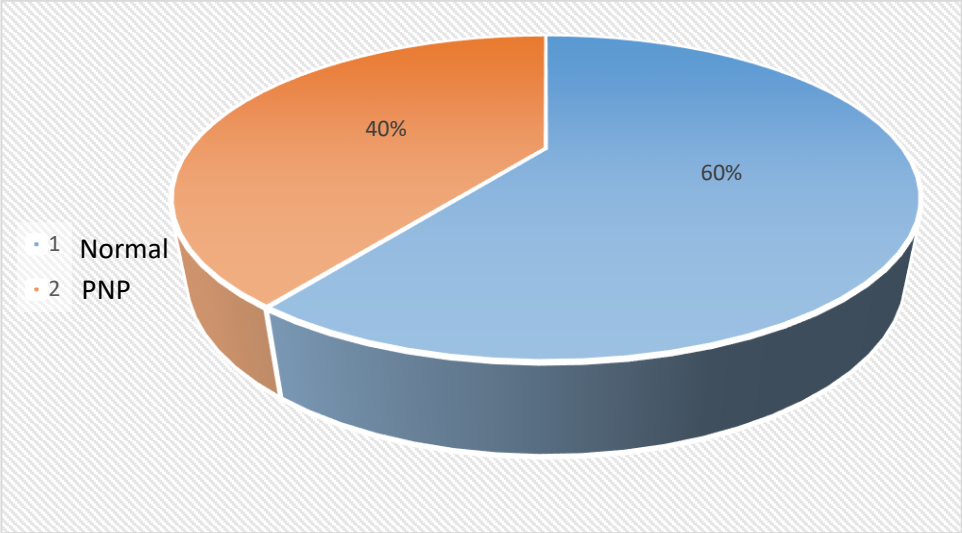

Figure (1) Pie figure show the percentage of neuropathy among the participant.

Table2: Results of SNC Study of Patients and Controls with their Level of Significance.

	Group	**Rt. Median N. mean±SD**	**P value**	**Rt. Ulnar N. mean±SD**	**P value**	**Rt.Com. Per.N. mean±SD**	**P value**	**Rt. Post Tib.N. mean±SD**	**P value**
DSL (m/sec)	**Control**	2.65 ± 0.58	NS	2.44 ± 0.5	NS	3.52 ± 0.88	HS	3.6 ± 0.69	HS
	patient	2.44 ± 0.17		2.29 ± 0.16		3.05 ± 0.22		3.12 ± 0.27	
Amplitude (µV)	**Control**	22.63 ± 5.5	HS	20.75 ± 3.6	S	9.65 ± 2.97		9.92 ±3.75	HS
	Patient	25.25 ± 2.2		22.04 ±1.7		11.07 ± 1.37		11.66 ± 1.81	
C.V. (m/sec)	**Control**	57.34 ± 7.1	S	57.55 ± 6.7	NS	47.7 ± 8.19	HS	47.88± 8.01	HS
	patient	59.67 ± 3		59.41 ± 3.4		51.48 ± 4.55		51.61 ± 3.97	

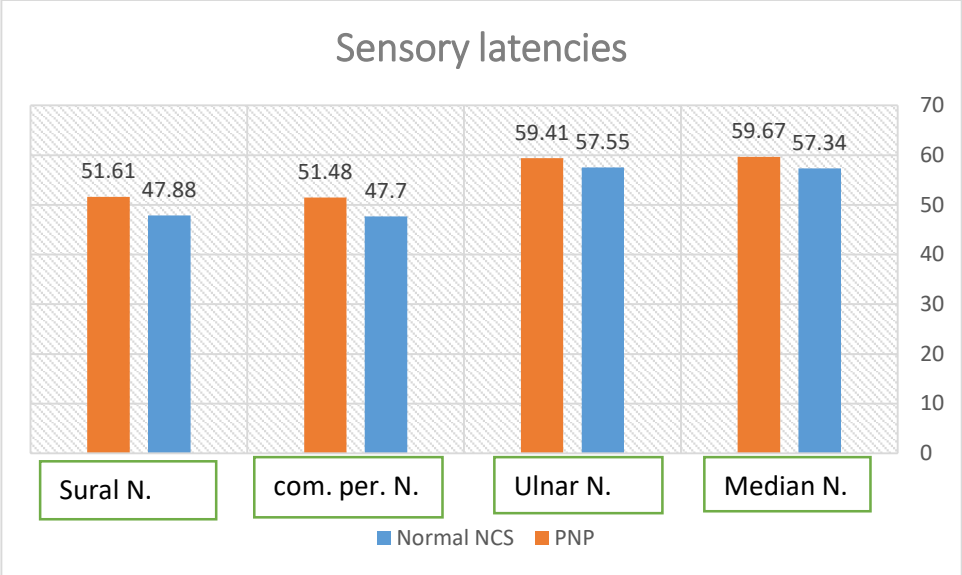

Figure (2) Results of SNAP distal latency of Patients and Controls

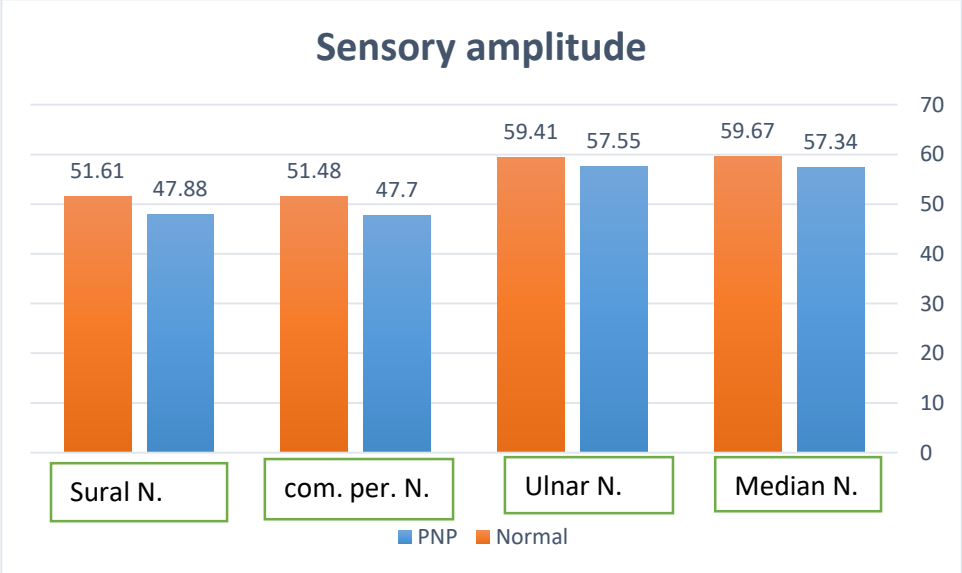

Figure (3) Results of SNAP amplitude of Patients and Controls.

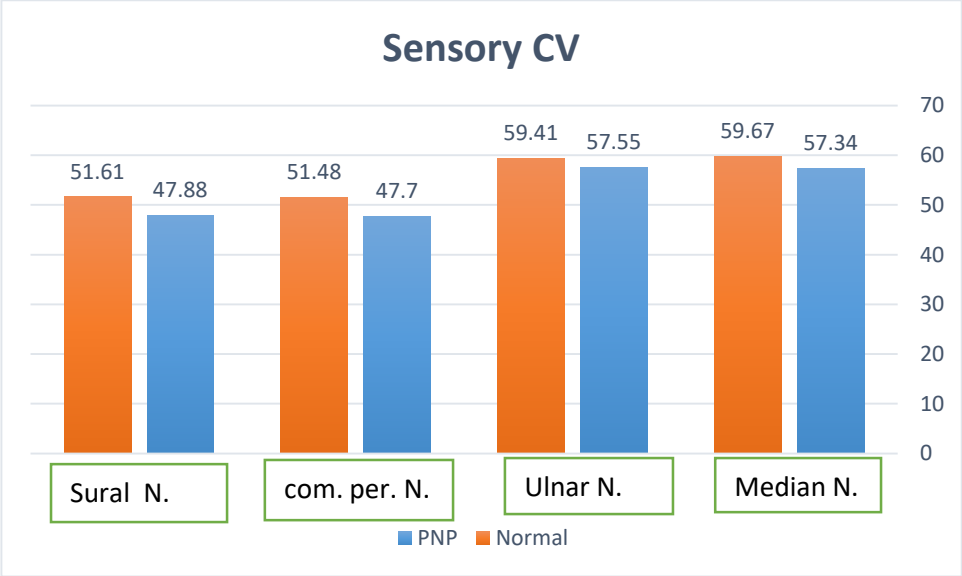

Figure (4) Results of SNAP conduction velocity of Patients and Controls

5- Discussion:

McManis P.G. *et al* in 1994 also described six patients with painful polyneuropathy and markedly increased levels of triglycerides. They concluded that the hypertriglyceridemia caused the peripheral neuropathy in these patients and they recommended that serum lipid levels should be assessed in patients with unexplained peripheral neuropathy to determine curable cause for this condition [22]. Another study that investigate the etiology of chronic idiopathic axonal polyneuropathy (CIAP), found that there was significant hypertriglyceridemia in patients with CIAP as compared to control subjects. The authors documented that a logistic regression analysis identified environmental toxin exposure and hypertriglyceridemia as significant risk factors that should be further investigated as possible causes of CIAP [23].

In 1971 Sandbank et al. observed severe electron microscopic alterations of myelin sheaths in the sural nerve obtained by biopsy in a patient with hyperlipemia and peripheral neuropathy [24]. In this study the degree of abnormality in the nerves differed from the reference values mainly in the measurements of the DLs than the measurements of the CVs and much more in the longer nerves of the lower extremities than the shorter nerves of the arm. These findings suggest an axonal pathology rather than focal demyelination. It is not possible without needle EMG analysis or nerve biopsy to ascertain whether there is actual axonal damage or only metabolic dysfunction secondary to elevated triglycerides levels [25]. The amplitude of the sensory nerve action potential was affected more than the distal sensory latency and conduction velocity which was the first parameter to be affected; the underlying mechanism of that is mixed axonal degeneration and segmental demyelination [26 – 28].

In this study it was found that hypertriglyceridemia affects conduction parameters in peripheral nerves and the effect is more commonly seen distally and primarily in the sensory nerves.

6- Conclusion and Recommendations:

It was concluded from this study that hypertriglyceridemia affects conduction parameters in peripheral nerves and the effect is more commonly seen distally and primarily in the sensory nerves. This is consistent with early peripheral neuropathy. So it might be useful to check triglecyride serum levels in patients with a suspicion of peripheral polyneuropathy (clinically or electrophysiologically) especially in the absence of other causes. We recommend to do a prospective studies to establish the long-term effect of hypertriglyceridemia on peripheral nerves and whether these changes are treatable or not.

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