Detection of the Demylination Changes in patients with Chronic Viral Hepatitis B by the Evaluation of the Nerve Conduction Study

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بواسطة دراسة التوصيل العصب للكهربائية

خلاصة:
زوال النخعيين المقطعي يحدث نتيجت موت او قلت فعل خلايا شوان لافراز مادة النخعيين او تدمير الحاصل بطبقة النخع. وقد تؤدي هذه الحالة الى ضعف في استجابة وتوصيل العصب للتحفيز.
التهاب الكبد الفيروسي نوع بي مرض فيروسي شائع، يسب اعراض خارج الكبد نتيجة ترسبات مركبات مناعية معقدة على اجهزة الجسم. والتطورات العصبية واحدة من العراض الخارج الكبد التي تصيب هولاء المرضى. غالبا ما يكون مصحوبا بإصابة الجهاز العصبي المحيطي تسبب التهاب الأعصاب المحيطية الحسية والحركية أو التهاب العصب الاحادي، او التهاب الاعصاب الاحادية المركبة.
الغاية: تقييم الدراسة التوصيل العصب المحيطي لدى مرضى التهاب الكبد الفيروسي المزمن نوع بي.
الطريقة: الاستقصاء الكهربائي الفيزيولوجي فعال في تشخيص الاعراض العصبية واصابة الجهاز العصبي المحيطي. وقد جرى هذا الاستقصاء في وحدة تخطيط الاعصاب في مستشفى غازي الحريري للجراحات على ٢٧ شخصا سويا و(٣٠) مريض من نوع التهاب الكبد الفيروسي المزمن نوع بي، بما في ذالك دراسة وظائف العصب الحسي و وظائف العصب الحركي.
النتائج: لقد اوجدت الدراسة خلال الاستقصاء ان نسبة المرضى الذين يعانون من الخلل في العصب الحسي هم (56.7%) من مرضى التهاب الكبد الفيروسي بي . بينما كانت نسبة الخلل في العصب الحركي سجلت (٣.٣٣%) لمرضى التهاب الكبد الفيروسي المزمن نوع بي. ولقد سجل اعتلال عصبي احادي بنسبة (٢٦.٦%) لمرضى التهاب الكبد الفيروسي المزمن نوع بي.
الخاتمة: ضرر مقياس التوصيل العصبي الحسي والحركي لدى مرضى التهاب الكبد الفيروسي بي.

Summary
Bachground: Segmental demyelination occurs when there is dysfunction or death of the Schwann cell or damage to the myelin sheath Segmental demyelination with slowed nerve conduction, of these, wallerian and axonal degeneration cause denervation and reduce the amplitude of compound action potential, whereas demyelination slows the nerve conduction with or without conduction block.
Infection with HBV is one of the most common viral diseases affecting man; extrahepatic symptoms may result from deposition of antigen-antibody complexes formed when these particles are neutralized by anti-HBsAg antibodies. The pathogenesis of these extrahepatic disorders has not been fully elucidated but likely involves an aberrant immunologic response to extrahepatic viral proteins. The neurological manifestations of chronic hepatitis B viral are most often a peripheral sensory neuropathy characterized by numbness, burning and sensation of “pins and needles” peripheral motor neuropathy, mononeuropathy, mononeuropathy multiplex.
Objectives: To assess the peripheral nerves abnormalities and detected the segmental demylination in chronic viral hepatitis B patients by using Nerve conduction study and to evaluate the relation between the sensory and motor peripheral neuropathy on different type of chronic viral hepatitis B

Methods: This study was conducted at the neurophysiology unit Gazy AL-Harriry surgical specialties teaching hospital, thirty chronic viral hepatitis B patients included in these studies without treatment compare with Twenty-seven of the normal healthy subjects, by the evaluation of nerve conduction studies.
Results In our electrophysiological studies, sensory lesions were recorded in 17 (56.7%) out of 30 CVHB patients, while motor nerve lesions were recorded in 1(3.33%) out of 30 CVHB patients. The mononeuropathical changes where recorded on 8 (26.67%) out of 30 CVHB patients.
Conclusion: The sensory and motor nerves conduction measurements were frequently impaired in CVHB patients,

Keywords: chronic viral hepatitis B, sensory nerve conduction study, motor nerve conduction studies.

INTRODUCTION

Segmental demyelination occurs when there is dysfunction or death of the Schwann cell or damage to the myelin sheath; there is no primary abnormality of the axon. The process affects some Schwann cells, and their corresponding internodes, while sparing others. The disintegrating myelin is engulfed initially by Schwann cells and later by macrophages. The denuded axon provides a stimulus for remyelination, with a population of cells within the endoneurium differentiating to replace injured Schwann cells. These cells proliferate and encircle the axon and, in time, remyelinate the denuded portion. Remyelinated internodes, however, are shorter than normal, and several are required to bridge the demyelinated region. In addition to being shortened, remyelinated internodes have thinner myelin in proportion to the diameter of the axon than normal internodes With repetitive cycles of demyelination and remyelination, there is an accumulation of tiers of Schwann cell processes that, on transverse section, appear as concentric layers of Schwann cell cytoplasm and redundant basement membrane that surround a thinly myelinated axon (onion bulbs). In time, many chronic demyelinating neuropathies give way to axonal injury (21).
Segmental demyelination with slowed nerve conduction, of these, wallerian and axonal degeneration cause denervation and reduce the amplitude of compound action potential, whereas demyelination slows the nerve conduction with or without conduction block (1) Axons may degenerate in neuropathies after mechanical compression of the nerve, exposure to vibration (5, 19), application of toxic substances, or death of the cell body. Nerve ischemia also causes axonal degeneration, affecting large myelinated fibers first, followed by smaller myelinated fibers and unmyelinated axons. The extent of abnormality varies with location of occlusion. Electromyography reveals normal motor unit potentials that recruit poorly during the acute stage of partial axonal degeneration. Long-duration, high amplitude polyphasic potentials appear in the chronic phase. Fibrillation potentials and positive sharp waves develop in two to three weeks after the onset of illness (9, 16). The accessibility of many peripheral nerves makes nerve conduction useful for survey approaches to peripheral nerve involvement in generalized diseases, for defining the nature of injury, and for the prognosis in focal peripheral nerve injuries (35).
Infection with hepatitis B virus (HBV) leads to a wide spectrum of clinical presentations ranging from an asymptomatic carrier state to self-limited acute or fulminant hepatitis to chronic hepatitis with progression to cirrhosis and hepatocellular carcinoma. Infection

with HBV is one of the most common viral diseases affecting man (32). Progression to chronic active hepatitis is suggested by ongoing anorexia, weight loss, and fatigue, although most patients with chronic replication are asymptomatic. Physical findings may include persistent hepatomegaly. Other findings may include the persistence of hepatitis B surface antigens (HbsAg). The immune-mediated mechanisms of injury have been most closely studied in HBV. It is thought that the extent of inflammation and necrosis depends on the person's immune response (24). However, most patients with chronic infection are "healthy carriers" and have normal liver enzymes, no symptoms, are anti-HBe positive, and have normal or near normal liver histology (26). In the case of chronic HBV infection, if the humoral immune response is insufficient to overcome infection, then a chronic infection results, as occurs in 3–8% of adults. Hepatocytes with ground glass cytoplasm are seen, particularly in patients with little or no necroinflammatory activity. HLA-restricted cytotoxic T lymphocytes directed against the molecular complex of viral and histocompatibility antigens on the liver cell surface are the effector cells that mediate cell damage. Cytokine-mediated cell injury and other mechanisms may also be involved in cell damage (26). HBV causes liver diseases that vary greatly in severity from person to person (10). Some subjects control infection efficiently and clear the virus from the bloodstream either without clinically evident liver disease or with an acute inflammation of the liver (acute hepatitis) that can resolve without long-term clinical sequelae. Other patients fail to clear the virus and develop chronic infection. Most chronically infected patients remain largely asymptomatic without life-threatening liver disease but 10–30% develops liver cirrhosis with possible progression to liver cancer (18). The rate of HBV chronicity is low in adult infections (5% or lower) but age and route of infection influence the outcome with exposure in neonatal life leading to a high rate of HBV persistence (10, 18). Hepatitis B virus (HBV) is a small DNA virus and belongs to a group of hepatotropic DNA viruses (23,13). Extrahepatic symptoms may result from deposition of antigen-antibody complexes formed when these particles are neutralized by anti-HBsAg antibodies. The pathogenesis of these extrahepatic disorders has not been fully elucidated but likely involves an aberrant immunologic response to extrahepatic viral proteins (25). The neurological manifestations of chronic hepatitis B viral are most often a peripheral sensory neuropathy characterized by numbness, burning and sensation of "pins and needles". Peripheral motor neuropathy, mononeuropathy, mononeuropathy multiplex and transverse myelitis also occur (6).

SUBJECTS AND METHODS

This study was conducted at the neurophysiology unit Gazy AL-Harriry surgical specialties teaching hospital thirty chronic viral hepatitis B patients included in these studies without treatment chosen according to these criteria:

History of chronic viral hepatitis disease for more than 6 months.

Had records in Iraqi hepatic center.

Have not recieved treatment for this disease.

Patients with diabetes, kidney disease as uremia, any blood disease as thallasemia, Amyloidosis, alcoholic abuse, nutrition or lipid metabolism disorders or with a family history of peripheral or central nerve disorders were excluded.

They had no known history of peripheral or central nerves involvement.

All patients were diagnosed and referred by a consultant physician and were examined by a consultant Neurologist.

Compare with Twenty-seven of the normal healthy subjects, by the evaluation right median, ulnar, tibial and common peroneal nerves underwent an electrophysiological examination according to a simplified nerve conduction study (NCS) at the neurophysiology unit, Gazy AL-Harriry Surgical Specialties Teaching hospital, Medical City from January 2009 to November 2009. The EMG Machin use on this study is Nicolet Biomedical EMG system (Viking Quest Neurodiagnostic system).

The sensory nerve conduction velocity (SNCV) was studies by the surface stimulating and recoding electrodes were used in the sensory conduction studies of median, ulnar, tibial and common peroneal nerves. The stimulus intensity was adjusted by gradually increasing the stimulating current until maximum and stable potentials were evoked on the screen. The antidromic method was used for SNCV determination. The nerve was proximally stimulated from the trunk and the evoked activity was distally recorded from a finger.

The motor nerve conduction velocities (MNCV) for the median, ulnar, common peroneal and posterior tibial nerves were measured. The stimulates intensity was adjusted by gradually increasing the stimulating current until maximum and stable potentials were evoked on the screen, and in order to ensure supramaximal stimulation, the intensity was increased by 50% from the point where the recorded action potential increases no further with the increase in stimulus intensity.

All statistical analysis was obtained using statistical package for social sciences (SPSS) version 17.0 computer soft ware. All data of each set used the Descriptive statistics expressed as mean ± SD (standard deviation).

The percent of abnormal values in any test was calculated as mean ± SD of the normal values for the control group.

Data from each patient and control group were compared using independent sample T-test, chi-square and ANOVA tests to calculate differences between groups.

RESULTS

All the patients were examined by consultant neurologist and the results showed that 10 patients (33.3%) had symptomatic neuromuscular manifestation, related to the peripheral nerve or muscles. 7 patients (23.3%) presented with signs of mononeuropathy and 3 patients (10%) presented with signs of neuropathy.

Sensory parameters including the distal sensory latency, sensory amplitude and sensory nerve conduction velocity of five nerves (right median, right ulnar, right common peroneal and right tibial nerves) were measured in 30 chronic viral hepatitis patients and compared to that of 27 control group. The percent of CVHB patients with sensory abnormalities, expressed as prolongation in distal sensory latency were calculated as 2SD above the mean of the normal values for control group, while the reduction of sensory amplitude and sensory nerve conduction velocity (SNCV) calculated as 2SD below the mean of the normal values for control group, is illustrated in Table1.

Table1: Percent of patients with sensory parameters abnormality in CVHB.

NERVES	No.	Delayed DSL No. %	Reduced Amplitude No. %	Reduced SNCV No. %
Median N	30	12 40%	5 16.66%	14 46.66%
Ulnar N	30	10 33.33%	3 10%	9 30%
Peroneal N	30	13 43.33%	5 16.66%	13 43.33%
Tibial N	30	14 53.33%	3 10%	13 50%

Statistically, there was a significance deference of these parameters of CVHB patients and the control group (P<0.05), these findings are illustrated in (table 2).

Table2: sensory parameters values of 4 nerves

parameter	**subject**	**No**	**Rt. Medi N Mean ±SD**	**Rt. ulnar N Mean ± SD**	**Rt.peroneal N Mean ±SD**	**Rt.Tibial. N Mean ±SD**
DSL (m se	**CVHB**	30	2.74 ± 0.53	2.44 ± 0.59	4.44 ± 1.28	5.32 ± 0.97
	Contro	27	2.24 ± 0.15	2.01 ± 0.14	3.94 ± .28	4.15 ± 0.32
Amplitude (µv)	**CVHB**	30	16.50 ± 8.2	22.86 ± 10.8	12.00 ± 8.27	10.97 ±4.8
	Contro	27	17.68 ± 7.4	17.96 ± 5.65	13.44 ± 4.32	11.00±4.56
SNCV (m/sec)	**CVHB**	30	45.73 ± 6.8	48.50 ± 8.37	34.70 ± 9.45	33.47±6.04
	Contro	27	54.48 ± 1.9	55.56 ± 2.34	46.08 ± 3.97	44.80±2.79
P-value f DSL	**CVHB**		>0.0001 S	0.001 S	0.153 N	>0.0001 S
P-value fo Amplitude	**CVHB**		0.597 NS	0.070 N	0.421 N	0.980 NS
P-value fo SNCV	**CVHB**		>0.0001 S	>0.0001 S	>0.0001	>0.0001 S

Significantly in relation to the control group S = Significant NS= Non significant
The mean difference is significant at the 0.05 level (P≤ 0.05).

Analysis of motor parameters including distal motor latency (DML) and motor nerve conduction velocity (MNCV) was measured in right median, right ulnar, right common peroneal and right tibial nerves.

The percent of patients with motor abnormalities expressed as prolongation in DML were calculated as 2SD above the mean of the normal values of control group and reductions in MNCV were calculated as 2SD below the mean of the normal values of control group, are illustrated in table3.

Table3: Percent of patients with motor parameters abnormalities in CVHB.

NERVES	No.	Delayed DML No. %	Reduced MNCV No. %
Median N	30	11 36.67%	1 3.33%
Ulnar N	30	1 3.33%	1 3.33%
Peroneal N	30	4 13.33%	1 3.33%
Tibial N	30	12 40%	1 3.33%

Measurements were compared between CVHB patients and the control group and we found a significant deference (P<0.05), these findings are illustrated in (table4),

Table4: Motor parameters values of 4 nerves.

Parameter	Subjec	No	Rt.MedianN Mean ±SD	Rt. ulnar N Mean ± SD	Rt per. N Mean ±SD	Rt. Tib. N Mean ±SD
DML (m sec)	CVHB	30	3.68 ± 0.67	2.98 ± 0.42	4.19 ± 0.53	4.93 ± 0.77
	Contro	27	3.51 ± 0.44	3.04 ± 0.44	4.11 ± 0.46	4.61 ± 0.46
MNCV (m/sec)	CVHB	30	59.03 ± 5.85	62.57 ± 6.0	46.40 ± 3.4	45.46 ± 4.2
	Contro	27	59.44 ± 5.62	62.08 ± 5.0	45.40 ± 3.1	46.32 ± 3.2
P-value for DML	CVHB		0.637 NS	0.310 NS	0.740 NS	0.501 NS
P-value for MNCV	CVHB		0795 NS	0.817 NS	0.895 NS	0.577 NS

Significantly in relation to the control group S=Significant NS= Non significant
The mean difference is significant at the 0.05 level (P≤ 0.05).

The electrophysiological findings showed that 17 CVHB patients (56.8%) had changes of demylination. which was statistically significant difference on comparison of the CVHB and control group. (P-value>0.0001), the distribution of these abnormalities was according to the type of demylination illustrated in table5

Table5: comprise between chronic viral hepatitis B and subject group on Segmental Demylination changes (SD)

subje	Percenta	Segmental Demylination (SD) changes				Total of subject
		Norma	Sensory SD	Mixed SD	Mononeuropath	
B virt	Number	13	8	1	8	30
	Percent	43.3%	26.7%	3.3%	26.7%	100%
Contr	Number	27	0	0	0	27
	Percent	100%	0.00%	0.00%	0.00%	100%
Total	Number	40	8	1	8	57
	Percent	63.8%	19.2%	1.3%	10.8%	100%

The relationship between the neurological examination and the electrophysiological findings in CVHB patients included in this study showed that of the 10 patients having clinical findings of neuropathy. The results are illustrated in (Table 6).

Table 6: Relationship between neurological signs and demylination changes in patients with chronic viral hepatic B

Segmental Demylination	percent	NEUROLOG SIGN			Total
		Normal	Neuropathy	Entrapment neuropathy	
Normal	Number	13	0	0	13
	Percent	43.33%	0.00%	0.00%	43.33%
Sensory demylination	Number	4	1	3	8
	Percent	13.33%	6.67%	6.67%	26.7%
Mixed demylination	Number	0	1	0	1
	Percent	0.00%	0.00%	3.33%	3.33%
Mononeuropathy	Number	3	1	4	8
	Percent	6.66%	3.33%	13.33%	26.7%
Total	Number	20	3	7	30
	Percent	66.67%	10%	23.33%	100%

DISCUSSION

The neurological complication one of extrahepatic manifestation on chronic viral hepatitis, Shim (2006) reported the involvement of the peripheral nervous system is frequent in patients with CVH, whereas central nervous system (CNS) impairment has been rarely reported (28).

Sterling and Bralow (2006) and other authors show the sensory deficiencies are more common than motor Polyneuropathies (30). Sterling 2006 reported the sensory symptoms may persist for months to years before any motor defect becomes clinically evident. Electromyography can demonstrate an axonal involvement of the sensory potentials and later a delay in motor conduction; motor abnormalities alone have not been reported (3, 12, 30, 31, and 36).

Therefore, electrodiagnostic testing is a useful technique in detecting the subclinical neurological manifestation that has electrophysiological findings of peripheral nerves damage even in the absence of clinical evidence of peripheral and central nerves involvement. In patients with CVHB, a variety of peripheral nervous system disorders may be seen, including focal disorders mononeuropathy, mononeuropathy multiplex, generalized neuropathies such as sensorimotor demylination polyneuropathy and axonal degeneration peripheral neuropathy. (22, 33)

Thus clinical electrodiagnosis may provide essential information for the clinician managing a patient with a peripheral neuromuscular disorders as well as it, can not only document the presence or absence of peripheral neuropathy and/or myopathy, but the principal pathologic process, whether demyelination or axonal degeneration and/or muscle fiber damage, may be defined (15).

Sensory nerve conduction studies are essential component of the electrodiagnostic study, several components might be analyzed and are of diagnostic importance, these include, latency, amplitude and conduction velocity. Sensory action potentials that had been studied in control subject and in CVHB patients are of right median, right ulnar, right common peroneal, right tibial nerves, in CVHB patients we found statistically highly significant changes in the DSL and SNCV ($P< 0.01$) of the median nerve, ulnar nerve, right common peroneal nerve and tibial nerve (excluding DSL of right common peroneal nerve).

The sensory lesion is recorded in 17 (56.7%) out of 30 CVHB patients, these findings are either similar or near to that reported by other authors (4, 22, 29).

Sensory nerves are more sensitive than motor nerves conduction studies to pathophysiologic processes involving mixed nerves; they may be the only abnormal nerve conduction study since some PNS lesion affect only sensory axons. In general, axonal damage or dysfunction of sensory fibers, result from axonal degeneration causing reduced amplitude, where as prolongation of DSL and slowing of SNCV is consistent with demyelination (15).

The assessment of conduction characteristics depends on the analysis of compound evoked potentials recorded from the muscle in the study of the motor fibers, on this study showed that CVHB patients had a statistically non significant deference ($P>0.05$) of prolong DML and reduced MNCV in the four nerves examined (median, ulnar, common peroneal and tibial nerves) excluding the MNCV of right tibial nerve ($P=0.025$) as compared with the values of the control group. Motor nerve lesion is recorded 1 (3.33%) out of 30 CVHB patients These result are similar or near to that recorded by other author (4, 8, 22, 29).

In some CVHB patients the prolongation of DML with normal or mildly abnormal MNCV in median nerve point to Carpal Tunnel Syndrome (CTS) and in the posterior tibial nerve refers to tarsal tunnel syndrome (TTS), these abnormality recorded on 8 (26.67%) out of 30 CVHB patients, these result are similar or near to that recorded by other author [8, 11, 20, 22, 27)

Generally it has been found that latencies don‘t correlated very well with symptoms in patient with mononeuropathy. This is not surprising since slowing of conduction doesn‘t by itself cause symptoms (17).

The values of nerve conduction parameter in our control group (sensory and motor) are compatible with the values by other authors (7 &14).

Demyelination lead to prolongation of conduction time, incomplete proximal compressive lesion may also give rise to slowed conduction with a reduction in external fiber diameter distal to the site of constriction.

However the conduction slowing along the distal nerve segment results from distal paranodal demyelination. Slow conduction accompanies relatively normal amplitude when stimulation occurs above the lesion; these changes generally imply segmental demyelination without conduction block affecting a majority of the nerve fibers (2).

A prolonged latency or slowing of the conduction velocity may also result from axonal neuropathy with loss of the fast conducting fibers (38), in general, axonal damage or dysfunction results in a reduction of amplitude, where as demyelination lead to prolongation of conduction time (15).

The mixed sensorimotor demylination polyneuropathy is recorded in 1 (3.33%) out of 30 CVHB patients, these findings are either similar or near to that reported by other authors (28, 34).

Where as the pure sensory demylination neuropathy is recorded in 8 (26.67%) out of 30 CVHB patients, these findings are either similar or near to that reported by other authors (4, 8, 22, 28).

In our study the percentage of these abnormalities in electrophysiology was 7 (23.3%) out of 30 CVHB patients had subclinical electrophysiological abnormality and 10 (33.3%) out of 30 CVHB patients had clinical abnormality signs and electrophysiological signs, according to my knowledge; I was not able to find similar studies which deals with the correlation and percentage of changes on clinical and subclinical electrophysiological peripheral neuropathy in CVHB patients

Conclusion

The sensory and motor nerves conduction measurements were frequently impaired in CVHB patients,. It could be of mono or multiple nerve impairment and even without any clinical signs and symptoms of neuropathy.

Abnormalities and significant changes are more commonly observed in the sensory than in the motor fibers, recorded on both the upper limbs and lower limb.

Electrophysiological changes on peripheral nervous system are recorded in 7 CVHB patients out of 30 patients including in this study without neurological manifestation abnormality.

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