Neurophysiological Profiles of Chemotherapy-Induced Neuropathy in Acute Lymphoblastic Leukemia

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Abstract

Background: Early pregnancy loss, occurring before 10-13 weeks, often involves an empty or nonviable gestational sac. Vitamin D deficiency is linked to higher miscarriage rates. Between 10% and 20% of diagnosed pregnancies end in loss, with true rates potentially higher.

Aims of the study: To assess if there is a relationship between serum vitamin D level and the spontaneous termination of pregnancy that occurs before reaching 10 to 13 weeks of gestational age.

Methods: A case-control study at Basrah Maternity and Child Hospital conducted from October 2023 to April 2024, involved 104 women divided into case (early pregnancy loss) and control (normal delivery) groups. Data collected included sociodemographic factors, medical history, and serum 25(OH)D levels, using the AFIAS™ Vitamin D assay.

Results: The study compared two groups of women (n = 52 each). Serum vitamin D3 levels were significantly lower in the case group (17.24 ng/ml) compared to the control group (27.74 ng/ml, p = 0.001). There was a significant statistical difference between both groups (P value = 0.05) regarding the time spent outdoors.

Conclusion: The study found a significant disparity in serum vitamin D levels in women with early pregnancy loss compared to those with normal pregnancies. Cases spent less time outdoors, reducing sun exposure and vitamin D synthesis. Despite higher average BMI in controls, they had better vitamin D levels, suggesting lifestyle and supplementation play key roles.

Keywords: Pregnancy Loss, Vitamin D3, Deficiency

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introduction

Leukemia is a type of hematological malignancy that causes the accumulation of abnormal blood cells in the bone marrow and circulation [(1)]. Although leukemias have a lower prevalence than other types of cancer, they remain the main cause of cancer-related mortality in children and adults under the age of 39 [(2)]. Acute lymphoblastic leukemia (ALL) comprises about 15% of leukemia cases, however, it accounts for 30% of childhood cancer and 80% of childhood leukemia cases. In Europe, incidence rates range from 2 to 4 per 100,000 individuals annually, which are approximately comparable to those of other developed countries. All are relatively more prevalent among men than women [(3,4)]. Peripheral neuropathy (PN) is a common complaint among leukemia patients. This could be brought on by leukemia chemotherapy drugs like vincristine, which is one of the vinca alkaloids drugs that is believed to interfere with the growth of axonal microtubules and impair neuronal transmission [(5)]. Leukemic cells, on the other hand, rarely infiltrate the peripheral nerves causing PN. However, it can be the initial presentation of leukemia, leading to delayed diagnosis in some cases. It typically presents as painful, progressive sensory and motor deficits [(6,7)]. In approximately 30–40% of patients receiving neurotoxic chemotherapy,

chemotherapy-induced peripheral neuropathy (CIPN) develops. It is a common, unpleasant, dose-limiting consequence that dramatically reduces the patient's quality of life [8,9]. It appears a few weeks or months after starting chemotherapy, and it could last for several months or even years after treatment is over. Although its prevalence declines with time, at least 30% of patients suffer from CIPN six months or more after chemotherapy has been stopped [10]. Patients with CIPN experience sensory more often than motor symptoms. Sensory axonal degeneration, which lowers the amplitude of sensory action potentials, can cause CIPN patients to feel paresthesia, tingling, pain, or numbness. These symptoms usually start and worsen in the toes and feet, then spread to the fingers and hands. They advance symmetrically in the manner of a stocking-glove (loss of distal generally more rapidly than proximal). Motor symptoms include limb weakness that eventually makes it difficult to move around, pick up small objects, and perform fine motor tasks like buttoning clothes and the absence of deep tendon reflexes in the afflicted limbs. Injuries to the autonomic nerves, which control the body's internal functions, are unusual in CIPN [11,12]. CIPN is commonly diagnosed clinically, but electrophysiological testing verifies the diagnosis and rules out possible explanations of neuropathic symptoms. [13]. Electrodiagnostic testing includes several specialized examinations, such as NCS and EMG. They assess the function of nerves and muscles and therefore aid in the diagnosis of neuromuscular diseases [14]. The purpose of this study was to estimate the percentage of CIPN, as well as to evaluate the neurophysiological alterations of peripheral neuropathy in ALL patients receiving chemotherapy.

Materials and methods

In Basrah governorate, southern Iraq, a cross-sectional study was carried out on ALL patients who visited the hematological center at Al-Sadar Teaching Hospital and Al-Sayyab Teaching Hospital from October first, 2022, to October first, 2023, and were referred to electrophysiological examinations (NCS, EMG) at the neurophysiology outpatient clinics. The study included 38 individuals, aged ≥18 years -ALL is more common in younger age groups, so we were able to collect only 38 adult patients in the study period-, of both genders, with confirmed diagnosis of ALL. The studied cases were on two chemotherapeutic protocols: UKALL (Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Dexamethasone, Etoposide, Cytarabine) and Hyper CVAD (Cyclophosphamide, Vincristine, Dexamethasone, Doxorubicin, Methotrexate, Cytarabine). The study excluded individuals who were less than 18 years old, had a history of diabetes, chronic renal disease, thyroid-induced neuropathy, vitamin B12 deficiency, alcoholism, or were critically ill, including those who were admitted to the ward or intensive care unit. Active surveying, detecting ALL patients getting chemotherapy, and evaluating their medical records from the statistics section were the initial stages in the data recruitment process. Direct interviews with patients provided the necessary information about malignancies, treatment plans, population demographics, medical and drug history, the recent neurological illness's clinical presentation and peripheral neuropathy diagnosis. Electrophysiological examinations by NCS of bilateral sensory nerves (sural and ulnar nerves) and motor nerves (tibial, peroneal and ulnar nerves), needle EMG for (extensor hallucis longus, tibialis anterior, vastus medialis, first dorsal interosseous, triceps, and deltoid muscles) Peripheral neuropathy was confirmed by Nihon Kohden Neuropack S3, with surface and needle electrodes. Normal value references were taken from Preston and Shapiro, 2020; Kimura, 2013 [15,16]. The test result was considered to be either normal or abnormal, and depending on the pathology, it was further divided into axonopathy and myelinopathy. Moreover, pure motor, pure sensory, or mixed neuropathy may be determined by the types of injured nerves. The statistical software package Statistical Package for Social Science (SPSS) version 26 (Armonk, NY: IBM Corp.) was used for analyzing the study results. The statistical

information was recorded as mean ± standard deviation (SD). Qualitative data, on the other hand, were recorded as numbers (percentages). Data analysis techniques included Chi-square, the Exact Fissure test, and the independent sample t-test. A statistically significant p-value is defined as ≤0.05.

Result

The results in Table 1 indicate that the duration of treatment and chemotherapy protocols do not significantly affect the results of EDX (p-value> 0.05).

Table (1): Treatment duration and protocols used among ALL cases with normal and abnormal EDX (n=38)

Treatment strategy		EDX		P- value
		Normal	Abnormal	
Duration	**≤ 6 months (induction and consolidation) (n=19)**	13 (68.4%)	6 (31.6%)	0.714
	>6 months (maintenance) (n=19)	15 (78.9%)	4 (21.1%)	
Treatment protocol	**UKALL (n=21)**	16 (76.2%)	5 (23.8%)	0.727
	Hyper CVAD (n=17)	12 (70.6%)	5 (29.4%)	

Chi-square test

EDX: electrodiagnostic study

UKALL: Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Dexamethasone, Etoposide, Cytarabine.

Hyper CVAD: Cyclophosphamide, Vincristine Dexamethasone, Doxorubicin, methotrexate, cytarabine.

None of the parameters of motor nerve conduction studies were significantly different between the patients who received the UKALL protocol and the hyperCVAD protocol Table (2).

Table (2): The association between the NCS characteristics of motor nerves and the protocols of chemotherapy in ALL patients (n=38)

Nerve	Parameter		UKALL (n=21)	Hyper CVAD (n=17)	P-value
Median nerve	Distal latency	Rt	3.43 ± 0.30	3.39 ± 0.29	0.646
		Lt	3.28± 0.30	3.33 ± 0.76	0.610
	Amplitude	Rt	8.41 ± 1.84	8.10 ± 2.18	0.639
		Lt	8.67 ± 1.79	7.88 ± 2.17	0.240
	Conduction velocity	Rt	60.45 ± 12.03	57.86 ± 5.23	0.382
		Lt	59.35 ± 10.35	58.27 ± 6.18	0.694
Ulnar nerve	Distal latency	Rt	2.25 ± 0.28	2.22 ± 0.17	0.646
		Lt	2.18 ± 0.29	2.18 ± 0.24	0.855
	Amplitude	Rt	7.40 ± 1.62	7.59 ± 0.98	0.669
		Lt	7.73 ± 1.32	7.29 ± 0.73	0.906
	Conduction velocity	Rt	57.75 ± 5.97	61.24 ± 9.32	0.193
		Lt	59.01 ± 5.73	62.06 ± 9.37	0.252
	F wave	Rt	27.57 ± 2.06	28.07 ± 1.99	0.451
		Lt	27.37± 1.84	27.93 ± 2.29	0.417
Peroneal nerve (EDB)	Distal latency	Rt	4.17 ±0.71	3.94 ± 0.27	0.182
		Lt	4.09 ± 0.66	3.87 ± 0.31	0.188
	Amplitude	Rt	3.20 ± 1.45	3.57 ± 1.62	0.474
		Lt	3.15 ± 1.35	3.54 ± 1.31	0.375
	Conduction velocity	Rt	52.94 ± 8.82	55.49 ± 13.61	0.510
		Lt	53.72 ± 9.68	54 .75 ± 12.48	0.783
Peroneal nerve (TA)	Distal latency	Rt	2.98 ± 0.51	2.75± 0.40	0.132
		Lt	3.03 ± 0.50	2.78 ± 0.44	0.110
	Amplitude	Rt	3.22 ± 0.79	3.55 ± 0.67	0.174
		Lt	3.28 ± 0.76	3.58 ± 0.58	0.169
Tibial nerve	Distal latency	Rt	3.88 ± 0.67	3.75 ± 0.46	0.506
		Lt	4.02 ± 0.55	3.83 ± 0.52	0.285
	Amplitude	Rt	8.34 ± 3.20	8.52 ± 3.05	0.861
		Lt	8.02 ± 3.35	8.11 ± 2.76	0.930
	Conduction velocity	Rt	53.83 ± 8.04	53.09 ± 3.62	0.709
		Lt	53.96 ± 8.10	53.01 ± 3.99	0.643
	F wave	Rt	52.05 ± 3.21	50.00 ± 3.06	0.078
		Lt	52.07 ± 3.21	50.05 ± 3.23	0.064

Independent sample t-test

UKALL: Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Dexamethasone, Etoposide, Cytarabine; Hyper CVAD: Cyclophosphamide, Vincristine, Dexamethasone, Doxorubicin methotrexate, cytarabine; Rt: right; Lt: left; EDB: extensor digitorum brevis; TA: Tibialis anterior.

Table 3 shows that there is no significant association between the NCS characteristics of sensory nerves and the chemotherapy protocols used among the ALL cases (p-value> 0.05).

Table (3): The association between the NCS characteristics of sensory nerves and the protocols of chemotherapy in ALL cases (n=38)

Nerve	Parameter		UKALL (n=21)	Hyper CVAD (n=17)	p-value
Ulnar nerve	Distal latency	Rt	2.03 ± 0.25	1.95 ± 0.33	0.440
		Lt	2.00 ± 0.11	1.92 ± 0.26	0.489
	Amplitude	Rt	24.30 ± 3.83	25.38 ± 8.71	0.640
		Lt	25.67 ± 5.17	25.88± 10.93	0.994
	Conduction velocity	Rt	57.43 ± 5.58	57.38 ± 2.76	0.974
		Lt	57.72 ± 5.87	57.45 ± 2.79	0.853
Sural nerve	Distal latency	Rt	2.47 ± 0.85	2.56 ± 0.29	0.626
		Lt	2.51 ± 0.85	2.58 ± 0.29	0.740
	Amplitude	Rt	7.54 ± 3.69	8.77 ± 3.37	0.290
		Lt	7.65 ± 3.44	8.66 ± 2.98	0.344
	Conduction velocity	Rt	50.39 ± 18.84	52.99 ± 5.37	0.553
		Lt	52.77 ± 20.87	53.55 ± 4.64	0.870

Independent sample t-test

UKALL: Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Dexamethasone, Etoposide, Cytarabine; Hyper CVAD: Cyclophosphamide, Vincristine, Dexamethasone, Doxorubicin methotrexate, cytarabine; Rt: right; Lt: left.

Although neurogenic MUAPS in lower limb muscles (EHL and TA) were detected more in UKALL cases, this difference was statistically not significant. Whereas no abnormal MUAP was detected in VM muscle or upper limb muscles in either group (Table 4)

Table (4): The association of needle EMG of muscles of the lower and upper limbs and protocols of chemotherapy among ALL patients (n=38)

Muscles	Parameter	UKALL (n=21)	Hyper CVAD (n=17)	p-value
EHL	Normal	18 (85.7%)	16 (94.1%)	0.613
	Neurogenic	3 (14.3%)	1 (5.9%)	
TA	Normal	18 (85.7%)	17 (100%)	0.238
	Neurogenic	3 (14.3%)	0 (0%)	
VM	Normal	21 (100%)	17 (100%)	-
FDI	Normal	21 (100%)	17 (100%)	-
Triceps	Normal	21 (100%)	17 (100%)	-
Deltoid	Normal	21 (100%)	17 (100%)	-

Chi-square test; EHL: Extensor halluces longus, TA: Tibialis anterior, VM: Vastus medialis, FDI: first dorsal interosseous; UKALL: Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Dexamethasone, Etoposide, Cytarabine; Hyper CVAD: Cyclophosphamide, Vincristine Dexamethasone, Doxorubicin, methotrexate, cytarabine.

Table (5) shows that six (60%) cases exhibited pure sensory neuropathy, while the remaining cases developed mixed motor and sensory neuropathy. In addition, all of the above cases developed axonopathy (100%).

Table (5) The electrodiagnostic study of ALL patients

Electrodiagnostic study		Frequency (n=10)	Percentage (100%)
Function	Mixed motor-sensory neuropathy	4	40%
	Purely sensory neuropathy	6	60%
	Purely motor neuropathy	0	0%
Pathology	Axonopathy	10	100%

Discussion

The most widely used protocols for treating ALL in Basrah are UKALL and Hyper CVAD, they are given as induction, consolidation phase for about 6 months and maintenance phase later on. We didn't find any significant difference in the duration of treatment below and above 6 months (Table 1).

However, patients in the maintenance phase (more than 6 months) were found to have less abnormal EDX. This might be the result of the protocol's decreasing vincristine doses, which reduce neurotoxicity, as the treatment goes on. And according to studies conducted by Alwhaibi et al., (2023) and Okada et al. (2014), peripheral neurotoxicity is associated with both the dose and frequency of medication administration [17,18]. Li et al. (2020), Argyriou et al., (2012) and Verstappen et al. (2005) in their studies on vincristine-induced peripheral neuropathy, all confirmed that vincristine neurotoxicity increased with increasing the dose [19-21]. Additionally, the neuronal defect may have been cured, as vincristine neuropathy is usually reversible when vincristine is decreased to one dose every 3 months as Verstappen et al. (2005) suggested [21].

Peripheral neuropathy afflicted 23.8% and 29.4% of patients on the UKALL protocol and the Hyper CVAD protocol, respectively, in our study (Table 1). Statistically, there was no difference

between them as both protocols contain vincristine, which has the most detrimental effects on peripheral nerve fibres, the only difference in the component of these protocols is etoposide in the UKALL protocol which has less impact on the peripheral nerves, Imrie et al. (1994) reported that it causes peripheral neuropathy in 6/142 [22].

In light of the assessment of nerve conduction in the lower and upper extremity nerves of patients diagnosed with acute lymphoblastic leukemia using the UKALL and Hyper CVAD protocols, no statistically significant differences in electrophysiological findings related to the motor and sensory nerves under investigation were identified between the two protocols (Table 2,3). Given that both studied protocols comprise nearly identical drugs, their impact on the peripheral nerves is essentially equivalent.

Although all the data were within normal limits, the amplitude of the sural nerve approached the borderline, suggesting the presence of sensory peripheral neuropathy that is also length-dependent. In the majority of electrophysiological studies examining peripheral neuropathy induced by vincristine administration, sensory deficits were found to be more pronounced than motor deficits. NCS reveals SNAPs with absent or low amplitude, as well as CMAPs with normal or low amplitude as reported by Custodio (2017) and Balayssac et al. (2011) [23,24].

Concerning the needle EMG examination of the lower and upper extremities, neurogenic findings (long duration and high amplitude of MUAPs accompanied by reduced recruitment) are predominantly observed in the distal lower limbs muscles (EHL muscle), with the TA muscle following (Table 4). Again, these modifications, however, did not differ significantly between protocols. These alterations corroborate the hypothesis of length-dependent peripheral neuropathy, according to which the peripheral neuropathy starts in the lower limbs' most distal muscles and progresses proximally.

In the electrophysiological evaluation of polyneuropathy, the needle EMG demonstrates greater sensitivity than the nerve conduction study. While NCSs and EMG both reveal distal abnormalities in typical polyneuropathy, certain mild polyneuropathies may only exhibit abnormalities detected on the EMG. Even if only a few axons are lost, the resulting abnormalities may be readily detectable on the EMG, but they may have little effect on the motor and sensory NCSs [15].

The results of Schouten et al. (2020), Custodio (2017), and Argyriou et al. (2012) are consistent with our own, as they also reported that vincristine induces axonal neuropathy, with a greater degree of involvement observed in the lower extremities compared to the uppers. In the distal limb muscles, they found fibrillation potentials, reduced recruitment, and large, polyphasic MUAPs in needle EMG; these are pronounced in the lower extremities [25,23,20].

In summary, the electrodiagnostic tests applied to diagnose peripheral neuropathy in ALL patients within various protocols identified peripheral polyneuropathy in 10 out of 38 (26.31%) patients. This polyneuropathy was predominantly axonal in nature and symmetrical bilaterally; 60% of these cases involved pure sensory neuropathy 40 % involved mixed motor and sensory neuropathy, and none involved pure motor polyneuropathy (Table 5). Mora et al (2016), Okada et al., (2014) and Windebank et al., (2008) reported that the incidence of peripheral neuropathy induced by vincristine is about 30%–40%, respectively which is nearly the same as ours [26,18,27].

Balayssac et al. (2011) histologically confirmed axonal degeneration associated with vincristine-induced peripheral neuropathy and found that Wallerian degeneration affects both small and large myelinated fibers [24].

Following the findings of Li et al. (2020), Schouten et al. (2020) and Boyette–Davis et al. (2018), vincristine primarily induces length-dependent, symmetrical, bilateral axonal sensory or sensorimotor peripheral neuropathy [19,25,28].

Vincristine causes peripheral neuropathy by binding to tubulin and inhibiting polymerization into microtubules. Vincristine binds to intracellular tubulin modifies cellular microtubular structures

and limits fast and slow actional transport. Microtubules serve as tracks for the transport of organelles and proteins along axons. By destabilizing these structures, vincristine impairs both anterograde and retrograde transport, which is crucial for neuronal function and survival, leading to distal axonopathy [29]. Vincristine also causes ultrastructural alterations in the cytoskeleton of large myelinated axons as well as neurofilament buildup in dorsal sensory ganglion neurons [30].

Conclusions and recommendations

About 26.31% of ALL treated cases experienced peripheral neuropathy as a result of their chemotherapy regimen. The pattern tends to be distal, symmetrical, length-dependent axonal polyneuropathy, purely sensory followed by mixed sensory-motor polyneuropathy. Sural nerve amplitude in NCS reached the borderline, and needle EMG revealed neuropathic changes in the distal muscles of the lower limbs. We suggest a screening program before starting and during chemotherapy treatment for ALL by NCS and EMG test for the early identification of PN, as well as additional longitudinal research using bigger sample size and longer follow-up periods to compare pre- and post-treatment changes.

Conflicts of interest

Regarding this work, the authors declare any conflicts of interest.

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الخصائص الفسيولوجية العصبية للاعتلال العصبي الناجم عن العلاج الكيميائي في سرطان الدم الليمفاوي الحاد

الخلاصة

المقدمة: يعد الاعتلال العصبي المحيطي الناجم عن العلاج الكيميائي (CIPN) من المضاعفات الشائعة لدى مرضى اللوكيميا الذين يعالجون ببعض العلاجات الكيميائية السامة للأعصاب وخاصة فينكريستين. عادة ما يتم تشخيص CIPN سريريًا. ومع ذلك، تؤكد الاختبارات الفيسيولوجية العصبية التشخيص وتستبعد الأسباب المحتملة الأخرى للاعتلال العصبي.

الاهداف: تهدف هذه الدراسة إلى تقدير النسبة المئوية لـ CIPN وتقييم التغيرات الفسيولوجية العصبية للاعتلال العصبي المحيطي لدى مرضى اللوكيميا الذين يتلقون العلاج الكيميائي.

الطريقة: تم اجراء دراسة مقطعية متعددة المراكز في مدينة البصرة، جنوب العراق. وشملت الدراسة ٣٨ مريضا مع تشخيص مؤكد لمرض اللوكيميا (ALL). وقد تم تسجيل الخصائص السريرية والفيزيولوجية العصبية باستخدام دراسات تخطيط الاعصاب وتخطيط كهربائية العضل بالإبرة.

النتائج: كانت نسبة CIPN بين مرضى اللوكيميا ٢٦,٣١٪. جميع الحالات كانت عبارة عن اعتلال أعصاب محوري، حيث كانت ٦٠٪ منها عبارة عن اعتلال عصبي حسي نقي يليه ٤٠٪ اعتلال عصبي حسي حركي مختلط. وفي دراسة تخطيط الاعصاب اقترب العصب الربلي من الحد الادنى للقيمة الطبيعية. بينما أظهرتخطيط العضلات تغيرات عصبية عضلية في الأطراف السفلية البعيدة.

الاستنتاجات: العلاج الكيميائي المستخدم لمرضى اللوكيميا (ALL) يسبب الاعتلال العصبي المحيطي المحوري, حسي نقي يتبعه حسي حركي مختلط يبدأ من الاطراف السفلى بشكل متماثل. نوصي بجدول الفحص للكشف المبكر عن الاعتلال العصبي المحيطي وإجراء مزيد من الدراسةا لمقارنة التغييرات قبل وبعد العلاج مع حجم عينة أكبر ومدة متابعة أطول.

الكلمات المفتاحية: اعتلال الاعصاب الناتج عن العلاج الكيميائي ، تخطيط الاعصاب ، تخطيط العضلات، لوكيميا، سرطان الدم الليمفاوي الحاد، الفسلجة العصبية.