ORIGINAL ARTICLE

Electrophysiological changes of peripheral neuropathy with vincristine after a physical therapy program in pediatric patients with acute lymphoblastic leukemia

Cambios electrofisiológicos de la neuropatía periférica por vincristina posteriores a un programa de terapia física en pacientes pediátricos con leucemia linfoblástica aguda

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Abstract

Background. Vincristine is among the drugs used for the treatment of patients with acute lymphoblastic leukemia (ALL). It is a drug whose most feared effect is affection of the peripheral nerves because it is time- and dose dependent. It produces long-term physical incapacity that limits activities of daily living. We undertook this study to demonstrate that ALL patients who were enrolled in a supervised program of physical therapy (PT) presented confirmed improvement using the nerve conduction velocity (NCV) test of motor and sensorial nerves.

Methods. This was an experimental, comparative, longitudinal, and prospective study carried out in the Department of Rehabilitation of the Hospital Infantil of Mexico "Federico Gomez." Twenty four patients who fulfilled the inclusion criteria were included. Patients were divided into two groups: group 1-supervised group who received a program of regular, supervised PT for 3 months, and group 2-unsupervised group who received a regular program of PT. In both groups, NCV studies were carried out prior to and subsequent to the physical therapy regime. Latency, amplitude and NCV of sensorial and motor nerves of the four extremities were compared.

Resumen

Introducción: Dentro del los fármacos utilizados para el tratamiento de los pacientes con leucemia linfoblástica aguda (LLA) se encuentra la vincristina, medicamento cuyo efecto más temido es la afección de los nervios periféricos; al depender ésta de tiempo y dosis, produce a largo plazo una discapacidad física que limita las actividades básicas de la vida diaria (AVD). Objetivo: Demostrar que los pacientes con LLA sometidos a un programa de terapia física supervisada presentan mejoría que se confirma con el estudio de velocidades de neuroconducción (VNC) tanto de nervios motores como de nervios sensoriales.

Métodos: Estudio experimental, comparativo, longitudinal, prospectivo realizado en el departamento de Rehabilitación del Hospital Infantil de México. Se incluyeron 24 pacientes que reunieron los criterios de inclusión. Se dividieron en dos grupos: 1) supervisado, en el que recibieron un programa de terapia física de forma regular y supervisada por 3 meses, y 2) no supervisado en el que recibieron el programa habitual de terapia física. En ambos grupos se realizaron estudios de VNC previa y posteriormente a los programas de terapia física. Se compararon la latencia, amplitud y velocidad de neuroconducción de los nervios sensoriales y motores.

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Results. The peroneal nerve was affected in 98% of the cases and axonal degeneration was the most frequent neuropathy appearing in 96% of subjects. Relationship of the results obtained in the NCV studies (both prior and subsequent) in both groups was statistically non-significant (p >0.01), whereas the relationship of the NCV studies between groups was statistically significant (p <0.01). Under appropriate supervision and monitoring, the PT program for patients with leukemia and neuropathy treated regularly with vincristine displays major benefits that are able to be measured objectively by NCV studies.

Key words: acute lymphoblastic leukemia, vincristine, peripheral nerves, nerve conduction velocity test, physical therapy.

Resultados: La media de edad fue de 7.7 años, el género masculino representó el 75% de los pacientes. El nervio peroneo presentó afección en el 98% de los casos y la degeneración axonal fue la neuropatía más frecuente (96%). La relación de los resultados obtenidos en los estudios de VNC del primero y segundo estudio de ambos grupos fue estadísticamente no significativa (P >0.01), mientras que la relación en los estudios de VNC entre ambos grupos fue estadísticamente significativa (P <0.01). Concluimos que el programa de terapia física para pacientes con leucemia y neuropatía por vincristina realizado de forma regular, con adecuada supervisión y vigilancia, presenta mayores beneficios que pueden ser medidos de forma objetiva en los estudios de VNC.

Palabras clave: Leucemia linfoblástica aguda, vincristina, nervios periféricos, velocidades de neuroconducción, terapia física.

Introduction

Malignant hematological diseases comprise the greatest percentage of cancer in the pediatric population (31% of all neoplastic diseases in Caucasian children and 24% in Afro-American children).[1,2] Acute lymphoblastic leukemia (ALL) is a malignant disease that produces accumulation of immature lymphoid cells of the bone marrow (lymphoblasts), which displace normal hematopoetic elements.[3-5] These cells are released in peripheral blood and are scattered throughout the body by infiltrating every organ system.[1,2] It is the most common pediatric neoplasm and comprises 80% of all acute leukemia cases detected in children.[4-6] In the Hospital Infantil of Mexico Federico Gomez (HIMFG) there were more than 326 cases diagnosed from 2000 to 2008. During the last 2 years there were 62 cases.

Before this incidence, the treatment objective was to eradicate the leukemia clone by replacing the bone marrow, which allows for repopulation by normal stem cells. Among the multiple pharmaceuticals used for treatment is vincristine, a medication whose most feared effect is peripheral nerve damage resulting in motor, sensory or autonomous system disturbances. These symptoms tend to be diffuse, symmetrical and predominantly distal. Muscle weakness may be limited to distal zones or extended regions in chronic cases. The spectrum of sensory symptoms ranges from a total loss of sensation and slight tingling sensation to major dysesthesia.[7-9] This effect is exacerbated by the combination of other anticarcinogens.[10]

There are different treatment modalities and, depending on the response and the severity of the disease, it is possible to decrease the neuropathy,[10,11] although in the long term this produces physical disability that limits the basic activities of daily living, (ADL). This, in turn, hinders the rapid reintegration of the patient to their social environment.[12] The dose and duration of vincristine treatment are directly proportional to the damage, which is evident clinically as well as electrophysiologically.[13]

A noninvasive, objective, measurable and practical method for obtaining information on nerve function in order to observe the pathophysiological changes that occur in patients with neuropathy is the measurement of nerve conduction velocity (NCV).[14] Changes are characterized by axonal damage and neuronal loss with demyelination. Axonal damage reduces the amplitude of the action potentials, whereas demyelination produces

prolonged latencies and eventually may also produce decrease in amplitude. This is reflected in the decrease in NCVs.[12]

Physiotherapy is the treatment of problems with the possibility of improvement and that cannot be reversed or treated, but always identifying the specific problems during evaluation. The important aspects of physiotherapy in acute neuropathy are the prevention of contractures, pain management and respiratory support. In chronic neuropathies, early remissions are important to recommend activities to maintain ambulation and avoid preventable complications such as foot deformities, among others. Therefore, management is based on strengthening exercises, stretching, mobilization and pain relief.[15]

The main objective is to demonstrate that patients who underwent a supervised physical therapy (PT) program have improvement confirmed in NCV studies, for both motor as well as sensory nerves.

Patients and methods

The study design was experimental, comparative, longitudinal and prospective and was comprised of pediatric patients diagnosed with ALL who attended the Department of Rehabilitation of the HIMFG.

Inclusion criteria were as follows: 1) pediatric patients 4-16 years of age, 2) diagnosis of ALL, 3) received chemotherapy with vincristine at the HIMFG and 4) had NCV study done before and after the PT program. Excluded were severely immunosuppressed patients who, due to their general condition, were unable to enter the PT program, did not receive management with vincristine or were in monitoring stages. Those patients with no discussion about entering a PT program were also excluded. Patients who completed chemotherapy before scheduling the second NCV study, those who did not complete the NCV study in any of the stages, those who presented life-threatening adverse effects to chemotherapy, those who voluntarily left the program, those who attended <3 PT programs, or those who died were eliminated. There were 78 pediatric patients recruited with diagnosis of ALL from 2006 to 2008. A total of 30 patients who met the inclusion criteria were contacted by telephone. They received verbal information regarding the study and the importance of carrying out a supervised PT program in order to sensitize patients to the need of a home program. They also signed a letter of consent to participate in the study.

Patients were divided into two groups. The first group was referred to as the supervised group (SG) and was comprised of patients who agreed to participate in the study and met the following aspects: 1) attended the initial discussion, 2) entered the PT program and received instructions for performing it at home, 3) received a booklet as a guide, 4) attended the review and supervision of the PT program at least three times. The second group was referred to as the unsupervised group (USG) and was comprised of patients who agreed to participate in the study and who met the initial discussion of awareness, but for different circumstances were unable to attend the review and supervision of the PT program. However, they attended outpatient rehabilitation where they were sent to a regular PT program.

In both groups, NCV studies were conducted in the Department of Rehabilitation of the HIMFG before the beginning of the PT program by the staff specialized in the area of electrodiagnosis. All studies were performed and analyzed by the same specialist physician. We evaluated the following parameters: 1) amplitude, 2) latency, and 3) NCV of action potentials. The nerves assessed were a) motor (median and ulnar nerves for upper extremities and tibial and fibular for lower extremities) and b) sensory (median and ulnar for upper extrmities and sural for lower extremities).

Electromyographic equipment used for the studies was a Nicolet electromyograph (Viking Select Model 4-channel). As to the technical specifications

of the equipment for each of the velocities done, the recommendations from the International Federation of Clinical Neurophysiology (IFCN) were accepted as the standards. Results were compared and analyzed based on the reference ranges established by Jones et al. for pediatric patients.[16]

PT program monitoring was conducted for 6 months by a PT technician. At the end of the period established for the PT, the second NCV study was scheduled for both groups, with 3 months between each study. This was done under the same conditions as previously and the same parameters of the nerve action potential of sensory and motor nerves of the four extremities were evaluated.

PT program for the SG consisted of four phases: 1) warm-up phase, 2) training phase, 3) stretching and cooling-down phase and 4) use of textures for management of sensitivity. The number of repetitions and the resistance was related to age and to patient characteristics with an average of 10 repetitions for each exercise.

Data analysis was performed using SPSS v.11.5 software. Descriptive statistics were carried out based on measures of central tendency and dispersion (mean ± SD, respectively) for quantitative variables. Frequencies for qualitative variables were determined. In addition, relationship between dose, administration of neuroprotector, relationship between the study differences of the same group and relationship between groups was analyzed with Student t-test.

Results

A total of 30 patients participated in the study. Six patients were eliminated due to not meeting inclusion criteria. SG was comprised of 13 patients and USG 11 patients.

The ages of both groups ranged between 4 and 16 years (mean 7.7 years) in both groups. The mean age of the SG was 7.6 years and mean age of the USG was 8.8 years.

There was a predominance of males in both groups (75%) corresponding to 18 patients. Meanwhile, females represented 25% with six patients. Median number of cycles of vincristine for each patient was 11. The average dose for both groups was 1.5 mg in each cycle. A total of 10 patients received drug treatment with a neuroprotector and represented 41% of patients in both groups. In the SG, two patients received treatment (15%), whereas in the USG eight patients were treated (72%).

Results of electrodiagnostic (ED) studies

In the SG, 15% of patients had sensory condition during the first study and 4% in the second study. The condition of the latency of the motor nerves was affected by 46% during the first assessment and 11% during the second assessment.

The condition of the motor amplitude was 48% of cases in the first study and 48% in the second study. NCV was affected in 38% during the first study and 4% during the second assessment. The most common type of neuropathy in both studies was axonal degeneration, accounting for 84% of the total cases; 46% presented during the first survey and 38% during the second assessment. Mixed neuropathy characterized by axonal degeneration and demyelination was present in 7% cases in both studies, whereas 3% of the cases had incipient neuropathy during the second study. In the USG, 18% had sensory condition in the first survey and 18% in the second survey.

With respect to motor latency, 60% of patients were affected in the first study and 35% in the second study. Amplitude action potential was affected in 90% of patients in the first survey and 86% in the second survey. Conduction velocity was affected in 53% during the first study and 40% during the second study. The most common type of neuropathy in both studies was axonal degeneration, accounting for 81% of total cases; 45% presented during the first survey and 36% during the second assessment.

Demyelinating type of neuropathy occurred in 9% of cases, both during the first study, whereas mixed sensory-motor neuropathy occurred in 9% of the cases, also during the first study.

The relationship between the dose of vincristine and changes in NCV studies was not statistically significant ($p > 0.01$). The relationship between changes in NCV and neuroprotective administration was also not statistically significant ($p > 0.01$).

The relationship of the results obtained in the three parameters of the action potential in both studies of the SG was not statistically significant ($p > 0.01$). The relationship in the results of both studies in the USG was also not statistically significant ($p > 0.01$). Finally, the relationship of the NCV studies obtained in both study groups was statistically significant ($p < 0.01$) (Tables 1 and 2).

Discussion

Leukemias are the most common malignancies in childhood and are a health concern due to the consequences of the disease. They restrict the patient's reintegration to their social environment. Peripheral problems during treatment are well known and result in different clinical manifestations. In this study we believe that a physiatrically supervised program focused on the management of neuropathy results in improvement in the patient's condition and is demonstrated by NCV studies of sensory and motor nerves.

Regarding gender distribution, patients in this study are predominantly male in both groups, coinciding with that reported by Donat and Goldberg, who claim that males are more susceptible to leukemia (1.2-1.3 times higher) than females.[2,7] Average age of our patients is 7.7 years, higher than that reported in the literature as the peak of dis-

Table 1. Measurements obtained in SG and USG in latencies, amplitude and NCV of motor nerves

Nerves Groups	Latency (msec)				Amplitude (uV)				NCV (m/sec)			
	SG		USG		SG		USG		SG		USG	
Studies	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Median	2.6	3.2	4.4	3.5	5.5	5	4.7	4.8	45.5	47.3	55.5	58.7
Cubital	2.2	2.6	2.8	2.6	4.1	4.3	5.4	4.5	47.4	51.6	60.5	52.7
Tibial	3.2	3.2	3.4	3.5	9	8.8	7.7	7.6	42.2	42.4	47.4	48.5
Peroneal	3.2	3.8	4.6	4.8	1.5	1.5	1.2	1.1	42.4	41.6	48.1	47.8

SG, supervised group (n = 13); USG, unsupervised group (n = 11).

Table 2. Measurements obtained in SG and USG in latencies, amplitude and NCV of sensorial nerves

Nerves Groups	Latency (msec)				Amplitude (uV)				NCV (m/sec)			
	SG		USG		SG		USG		SG		USG	
Studies	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Median	2.5	2	2.2	2.2	26.4	25.5	19	21	41.7	39.9	49.2	41.3
Cubital	1.6	1.9	2.1	2.1	17.3	20.1	17.2	14.8	35.7	38.7	46.6	43.1
Sural	1.9	1.7	1.9	2	14.1	14	13.6	13.1	41	35.5	45.8	43.8

SG, supervised group (n = 13); USG, unsupervised group (n = 11).

ease onset and is related to the fact that many of our patients were diagnosed for the first time at least 1 year prior to the study. The type of leukemia that occurred most frequently in our patients was ALL L2, which does not correspond to that described by Biondi, who reported that ALL L1 is, by far, the most common type of cell in children with leukemia.[3]

Studied patients had ongoing management, receiving cycles of vincristine regularly. Ueberal notes that the changes found were related to the number of cycles of drug administration.[17] The average dose of vincristine received by our patients was 2 mg. This is in relation to patient's weight and age at the time of initiation of the chemotherapy cycle. We found no statistically significant relationship between the amount of vincristine administered and the degree of affection within the parameters of the NCV, although a decrease in amplitude and latency existed in all cases. This coincides with that reported by Hartman et al. who found no differences between dose and changes in NCV and clinical data,[18] whereas Verstappen et al. observed a marked difference in the cumulative dose between electrophysiological and clinical changes.[19]

Forty one percent of our patients received some neuroprotective pharmacological management at some point. This was indicated after treatment with vincristine due to presentation of significant symptomatology. We found no significant differences in the results of the NCV between patients who received treatment and those without, regardless of the PT management. This is consistent with that described by Harila-Saari who compared the NCV in three groups with different pharmacological management, but always respecting the dose of vincristine, and noted that these remained prolonged without being significantly different between them.[14] This is also consistent with that described by Verstappen et al. who reported that, despite not quantifying changes in the clinical picture, no improvement in ED studies was observed.[19]

Sensory and motor affection was found in 96% of patients from the first study, which coincides with that reported by Vainionpaa et al. They confirmed the presence of neuropathy in >90% of the patients studied, which started from the first cycle and persisted even 2 years after the last administration.[20]

Axonal degeneration was the type of neuropathy that occurred most frequently in our study, which corresponds to the affection in the amplitude of nerve action potential. This is consistent with that described by Harila-Saari who noted that the changes that occur in neuropathies as a result of vincristine are characterized by axonal damage and neuronal loss with demyelination.[14] Axonal damage reduces the amplitude of action potentials, whereas demyelination produces prolonged latencies and eventually decrease in amplitude occurs. All this is reflected in the decrease of NCVs. Furthermore, Ueberal showed that axonal degeneration is the main alteration observed in histopathological studies in both animal and human models and, secondarily, there are also changes in the conformation of myelin.[17] This condition still remains even after treatment completion.

Our study showed higher affection in motor nerves than in sensory nerves. The nerve that showed the highest affection according to the three parameters measured in NCV was the peroneal, followed by the median and the tibial nerves. These data are consistent with the data of Verstappen et al. who noted that sensory changes occur more often because there is heightened sensitivity of thin myelinated and unmyelinated fibers, which correspond to sensory fibers as well as to fibers of the autonomic nervous system.[19]

In our study we observed that there was no significant difference when comparing the results of NCV studies in each group. This may relate to the time difference in which the studies were conducted. The average length of time of nerve regeneration is ~1 mm/day[12] and is related to the conditions that caused the neuropathy. With recurrent

administration of vincristine, the period of nerve regeneration is not carried out, so that changes in ED studies are imperceptible.

We found that the difference in the ratio of the NCV between the SG and the USG was due to proper monitoring of the PT program that was conducted regularly, concentrating on the home program. This presented greater benefits than that which was done sporadically, without review and without regular monitoring. These differences were able to be quantified by ED studies.

Measurement of NCV is an objective, measurable and practical method for obtaining information on nerve function in order to observe the pathophysiological changes that occur in patients with neuropathy.

The few changes evidenced in NVC studies can be related to the short duration of the PT program and the number of patients. Therefore, we propose conducting studies with the same characteristics. We suggest increasing the time period for conducting NCV studies in order to allow additional time for further nerve regeneration that can be reflected in all parameters of the action potential.

This study allowed us to conclude the following: 1) the PT program for patients with leukemia and neuropathy due to vincristine conducted regularly and with proper supervision and monitoring is of greater benefit than can be measured objectively with NCV studies, 2) the most commonly affected nerve in neuropathy due to vincristine is the peroneal nerve, 3) decrease in amplitude of the action potential in both sensory and motor nerves is the most affected in the NCV studies and expresses axonal degeneration, characteristic of this type of neuropathy, 4) dose of vincristine and neuroprotective administration did not affect the development of neuropathy.

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