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ORIGINAL ARTICLE

Mild axonal neuropathy of children during treatment for acute lymphoblastic leukaemia

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Neurophysiological functioning was studied prospectively in children treated for acute lymphoblastic leukaemia with a low dose vincristine regime (8×1.5 mg/m^2/dose), to obtain more insight into vincristine neuropathy. A WHO neurotoxicity score was estimated and vibration sense and electrophysiological measurements were taken at standardized times during vincristine treatment. The WHO neurotoxicity score showed decreased or disappearance of Achilles tendon reflexes, and mild sensory disturbances, but a grade 3–4 neurotoxicity was not demonstrated by any of the children. Vibration perception thresholds increased progressively during treatment and amplitudes of action potentials of peroneal and sensory ulnar and median nerves decreased, whereas nerve conduction velocities stayed unchanged. Both vibration perception thresholds and the electrophysiological findings hardly exceeded the limits of normality. We conclude that children treated for acute lymphoblastic leukaemia with a low dose vincristine regimen have mild axonal neuropathy which may be responsible for the motor problems in these children.

Keywords: Neurophysiology. Vincristine neurotoxicity. Acute lymphoblastic leukaemia.

Introduction

Motor problems of children during and after treatment for acute lymphoblastic leukaemia (ALL) have been reported.[1–4] These problems are thought to be induced by vincristine neuropathy. Vincristine is commonly used in treatment for ALL, and peripheral neuropathy is its dose-limiting toxicity.[5,6] Clinical signs of vincristine neuropathy are early loss of Achilles tendon reflexes, followed by loss of other deep tendon reflexes and sensory disturbances (paresthesias, numbness). Motor impairment, specifically muscle weakness of the extensor muscles of fingers and wrists and dorsiflexors of the toes and ankles,[7] is the most severe manifestation of the neuropathy, often preceded by clumsiness of the hands and cramps in the legs. Electrophysiological studies have shown a decrease in amplitude of the sensory nerve action potentials (SNAPs) and compound muscle action potentials (CMAPs), while nerve conduction velocities remained normal or slightly reduced.[7–10] Pathological studies show axonal degeneration with some secondary myelin disturbances.[8–11] In contrast to demyelinating disorders, axonal

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neuropathies are renowned for poor prognosis for functional recovery, even if the original cause is successfully removed.[12] Vincristine neuropathy may therefore result in long-term motor problems.[2] Somatosensory evoked potential (SEP) studies have revealed disturbances in the distal as well as the proximal part of the nerves.[13,14] Limited data suggest that infants and adults are more susceptible than children.[5,15] In a study of 50 adults and children with acute leukaemia, weakness of the lower extremities was most apparent in children.[16] However, Bradley reported less neuropathy in children than in adults, probably because of relative differences in dosage.[8]

Children treated for ALL may therefore face a vincristine-induced axonal polyneuropathy with persisting neural damage and motor problems. Neurophysiological data, especially in children treated with a relatively low cumulative vincristine dose and low dose intensity, are limited. This prospective longitudinal study investigates the effect of low-dose vincristine on electrophysiologically measured motor and sensory nerve functioning of children with ALL before and during treatment at standardized test periods related to the administration of vincristine. Vibration sense measurements were taken to study subclinical neurological disturbances. Clinical assessment was undertaken using a WHO neurotoxicity score.

Subjects and methods

Subjects

Children admitted to the Children's Cancer Centres in Groningen and Nijmegen in the Netherlands from October 1994 to December 1996 were eligible if their age was between 4 and 12 years, and if they were treated according to the Dutch Childhood Leukaemia Study Group protocol (DCLSG-ALL-8, standard and medium risk group). Informed consent was obtained from the parents of all 17 eligible children (11 boys and 6 girls) with a median age of 5 years and 10 months (range 4.0–12.7 year/months). Six of the 17 children or their parents refused to participate in the electrophysiological measurements. One of these six children also did not want the vibration sense measurements. The neurotoxicity data were obtained from the parallel study of Gidding.[17] Six children in our study were not included in Gidding's study, thus the neurotoxicity score is missing. The gender, age and type of measurement we were able to obtain for each child are presented in Table 1.

Treatment

The treatment of children with ALL according to DCLSG-ALL-8[18] is almost identical to the German

Table 1 Gender and age of children treated for ALL eligible for for the study and their participation for the different measurements

Child no.	Gender	Age year/months	Neuro(physio)logical measurements		
			Nerve conduction studies	Vibration sense	WHO neurotoxicity
01	Boy	4.0	Refusal		No data[a]
02	Girl	4.1			
03	Girl	4.2			
04	Boy	4.5			
05	Boy	4.8	Refusal	Refusal	
06	Boy	5.3			
07	Girl	5.5			
08	Girl	5.6			No data
09	Girl	5.10			
10	Girl	5.10	Refusal		No data
11	Boy	7.2			No data
12	Boy	8.11			
13	Boy	9.1			
14	Boy	9.1	Refusal		No data
15	Boy	11.6	Refusal		No data
16	Boy	12.4	Refusal		
17	Boy	12.7			

[a]No data means the child was not included in the study of Gidding.[17]

Table 2 WHO neurotoxicity score

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Sensory	Normal	Paresthaesias/ decreased DTRs	Severe paresthaesia/ Mild objective sensory abnormality Absent DTRs	Intolerable paresthaesia Moderate objective sensory abnormality	Complete loss of sensation
Motor	Normal	Mild/transient weakness	Moderate weakness Able to ambulate	Unable to ambulate	Complete paralysis

ALL-BFM 90 protocol.[19] According to this treatment protocol, children are classified into the standard risk group (SRG, 30% of all children) or medium risk group (MRG, 60%). The remaining patients (10%) are classified as the high risk group (HRG) with a different vincristine treatment; therefore these children were not included in the study.

The participating children received 4 weekly vincristine doses (1.5 mg/m^2) during induction therapy (weeks 1–4) with a maximum of 2.5 mg/dose. Children received 4 doses (1.5 mg/m^2/week) again during reinduction therapy (weeks 17–20), with a maximum of 2.0 mg/dose. The maximum cumulative dose in these children was 18 mg vincristine. Besides vincristine the children received other medication including: prednisone, dexamethasone, daunorubicine, asparaginase, high-dose methotrexate (SRG: 2.0 g/m^2/24 h; MRG: 5.0 g/m^2/24 h), cytarabine, mercaptopurine, adriamycin, cyclophosphamide, thioguanine, and multiple (SRG: 9; MRG: 11) intrathecal injections with methotrexate, prednisone and cytarabine.

Methods

Electrophysiological techniques

Motor conduction velocities of the median, ulnar and peroneal nerves were determined by means of standard techniques using surface electrodes. Antidromic SNAPs were recorded from the index and little fingers with ring electrodes at the proximal and distal interphalangeal joints, stimulating the median nerve at the wrist and elbow and the ulnar nerve at the wrist, elbow and halfway up the upper arm. The sural nerve was stimulated at the dorsolateral side of the Achilles tendon approximately at the junction of the middle and lower thirds of the leg, the retrograde sensory nerve action potentials were recorded behind the lateral malleolus with surface electrodes (Medelec bar electrodes 18261).

The recording and stimulus apparatus was model Viking IV (Nicolet). Square wave stimulus pulses of 0.2 milliseconds (ms) duration were used. The amplitude of the CMAPs and the SNAPs were measured peak to peak. Before the measurements the legs and arms of the children were heated in a warm water bath (38°C) for 15 minutes. Skin temperature near the registration and stimulus points was also measured and the conduction velocities corrected for a skin temperature of 33°C.

Vibration sense

Vibration threshold was measured by the method of limits, i.e. the threshold value first felt by the subject when the stimulus was increased from zero is defined as the vibration perception threshold (VPT).[20] Increased VPT means worse vibration sense perception. A commercially available device (Vibrameter type IV, Somedic AB, Sweden) was used. Measurements were taken at the dorsum of the metacarpal bone of the index finger and the dorsomedial aspect of the first metatarsal bone.[20] Measurements were taken three times on both the left and right side of the body. Analyses were performed on mean values of both sides. Data were compared with reference values developed by our laboratory. These reference values were obtained in a normative study where carpal and tarsal VPT of 167 children, 5–12 years old, were studied. The mean reference value of carpal VPT is 0.368 μm (SD: 0.16). The mean reference value of tarsal VPT is 0.468μm (SD: 0.24). (When applying a logarithmic transformation on the data, these reference values are slightly higher than the reference values of Meister[21]).

Neurotoxicity score

Sensory and motor neurotoxicity was graded according to a modified WHO-neurotoxicity score (Table 2).[22] The paediatric neurologists performing the assessments were blind to the results of the other tests.

Table 3 Protocol of vincristine dosages and test periods

		V	V	V	V			V	V	V	V		
Week after diagnosis	0	1	2	3	4	5	16	17	18	19	20	21	46
Test periods	t1					t2	t3					t4	t5

V: vincristine dose

Procedure

The measurements were carried out at five test periods. The test periods were chosen at specific periods of the vincristine protocol (Table 3). The test periods were chosen as follows:

- test period 1 (t1): in the week before the first vincristine dose, week 0;
- test period 2 (t2): 1 week after the fourth vincristine dose, week 5;
- test period 3 (t3): 1 week before the fifth vincristine dose, week 16;
- test period 4 (t4): 1 week after the eighth vincristine dose, week 21;
- test period 5 (t5): 6 months after the eighth vincristine dose, week 46.

The children were tested at the University Hospitals.

Data analysis

A repeated measures ANOVA would be the usual procedure to analyse the data. However, at some test periods, measurements could not be taken. This would have implied either listwise deletion, leading to the loss of valuable data, or imputation of many unknown values, leading to uncertain results. Measurements could not be taken for organizational reasons (i.e. children 4 and 12 received the last part of their treatment at home (Curacao) and therefore missed t5). Therefore it may be assumed that, from a statistical viewpoint, absence is random. (In Table 4 the exact number of children studied for each test period and measurement is shown.) In addition, the test periods are not equally spaced and there is some variation in the timing of the observations (the measurements were not always taken exactly 1 week before or after the vincristine dose). For all these reasons, multilevel regression analysis on the basis of the Hierarchical Linear Model[23] provides a good approach to analyse these data.[24] The analysis was carried out using the program MLn.[25]

We tested statistically if the electrophysiological variables and carpal and tarsal VPT changed significantly during treatment. There are *a priori* various regression effects that could represent the 'time' effect over the five repeated measures and three of them will be tested (Fig. 1):

- a cumulative neurotoxic effect of vincristine: *effect A* (score 0 at t1, score 1 at t2 and t3, score 2 at t4 and t5);
- a neurotoxic effect with recovery between the fourth and fifth vincristine dose, and between the last vincristine dose and 6 months later: *effect B* (score 0 at t1, t3 and t5 and score 1 at t2 and t4);
- a linear effect of test week (number of the week in which the children were tested; range 1–67).

Table 4 Number of children studied for each test period and measurement

		Test period				
Measurements		t1	t2	t3	t4	t5
Electrophysiological						
SNAP	median	9	9	10	9	8
	ulnar	7	7	8	10	8
	sural	9	10	10	10	8
CMAP	median	8	10	9	9	7
	ulnar	7	9	10	9	8
	peroneal	8	9	10	10	8
Vibration sense						
Tarsal VPT		7	13	12	14	11
Carpal VPT		9	15	14	14	13
WHO neurotoxicity		10	11	11	11	9

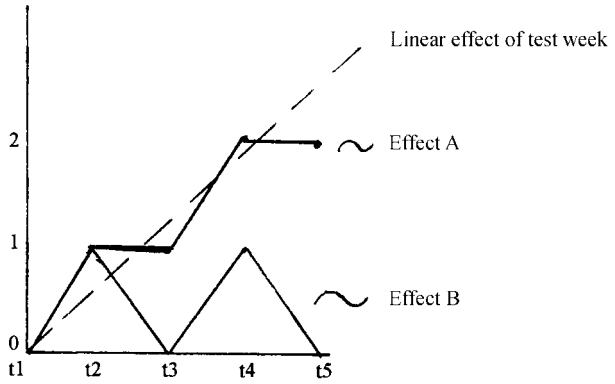

Fig. 1. Three possible regression effects representing the 'time' effect over the five repeated measures.

Which one of these provides the best fit is an empirical question. A backward model selection was carried out, starting with a model containing all effects, and deleting the least significant effects. The reported p values (Tables 5, 6) refer to this final model. This model selection process was carried out separately for the electrophysiological variables and tarsal and carpal VPT. If an effect of a test week fits better into the data than neurotoxic vincristine effects A or B, this means that the measured variable deviates proportionally with increasing number of test weeks. This would imply that the deviations are difficult to relate to the vincristine administration and likewise it would be hard to differentiate between a general effect of development or treatment or vincristine neurotoxic effects. Only when the nature of the deviation indicates an axonal degeneration, vincristine neurotoxicity may be thought to be responsible, because axonal degeneration contradicts development and none of the other agents received by the children cause peripheral (axonal) neuropathy. In addition, we controlled for age and gender and temperature. The significance level was set to 0.05. A lower value would lead, for this limited sample size, to an undesirable loss of power.[26]

Results

Electrophysiological measurements

The results of the MLn analysis of the nerve conduction studies are presented in Table 5.

On the SNAP of the median nerve, a cumulative neurotoxic vincristine effect (*effect A*) was found: after one block of four weekly doses of vincristine, median SNAP decreased, and decreased cumulatively after a second block of four weekly doses of vincristine.

On the SNAP of the ulnar nerve, the effect of a 'test week' was noted: with proceeding time (measured in number of 'test weeks') the amplitude of the ulnar SNAP decreased proportionally.

On the peroneal compound muscle action potential (CMAP), the results of the MLn-analysis were such that a reliable interpretation was not possible. Instead, to give optimal insight in the data, the CMAPs of the peroneal nerve of all individual children are outlined against a week in Fig. 2. With increasing number of test weeks a decreasing trend in CMAPs can be seen.

On the CMAPs of the upper extremity nerves and the sural SNAP, no significant effects of proceeding time or vincristine were found.

None of the conduction velocities of the measured nerves changed significantly during treatment.

The neurotoxic vincristine effect (*effect B*) with recovery did not fit well with any of the measured variables, meaning that no significant signs of recovery were found on any of the measured variables.

The co-variate gender showed significant effects on amplitude of the action potentials. Girls showed higher action potential amplitudes than boys for sural and median SNAP. For ulnar CMAP girls showed lower action potential amplitudes. Temperature had a significant effect on sural SNAP, as with decreasing temperature, sural SNAP became

Table 5 MLn-analysis of amplitudes of nerve action potentials (Exact p values)

	Sur	Smed	Mmed	Suln	Muln[b]
Test week	0.281	0.351	0.141	0.008[a]	0.171
Vincristine *effect A*	0.468	0.039[a]	0.118	0.391	0.307
Vincristine *effect B*	0.266	0.437	0.334	0.181	0.249
Gender	0.000[a]	0.000[a]	0.480	0.051	0.010[a]
Age at diagnosis	0.413	0.415	0.176	0.169	0.190
Temperature	0.018[a]	0.224	0.097	0.481	0.312

[a] $p < 0.05$
[b] Sur: sural nerve; Smed: sensor median nerve; Mmed: motor median nerve; Suln: sensor ulnar nerve; Muln: motor ulnar nerve.

Table 6 MLn-analysis of vibration perception thresholds (exact p values)

	carpal	tarsal
Test week	0.476	0.172
Vincristine *effect A*	0.003[a]	0.400
Vincristine *effect B*	0.343	0.043[a]
Gender	0.235	0.474
Age at diagnosis	0.481	0.325

[a] $p < 0.05$

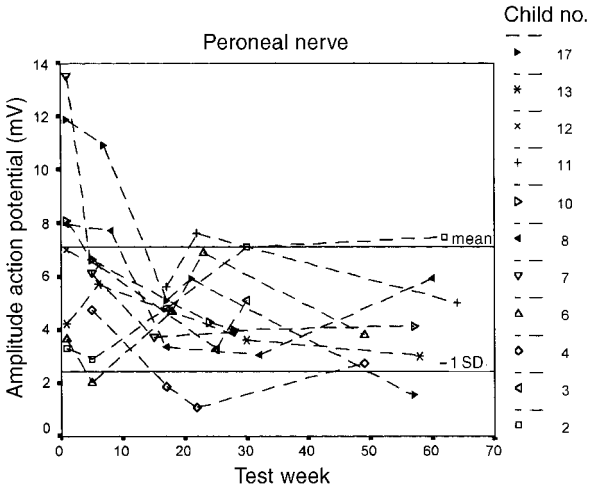

Fig. 2. Action potential amplitudes of peroneal nerves of individual children are outlined against test weeks (week number in which the measurement was done). Child numbers are in accordance with Table 1. Reference lines (solid lines; mean and −1 standard deviation (SD)) according to Parano[29] are presented.

higher. Age did not have a significant effects on the measured variables.

Nerves that were found to have significantly decreasing amplitudes were compared with reference values.[27–29] However, reference values for children of antidromic measured median and ulnar SNAPs were not available in the literature. For the peroneal nerve, at diagnosis (t1) the mean CMAP of the children with leukaemia (7.46 mV; SD: 3.78) was in accordance with the mean reference value of Parano (7.10 mV; SD: 4.67).[29] Over the course of time most amplitudes dropped below the mean reference value, and four measurements dropped below the clinically relevant range of >1 SD (see also Fig. 2).

Vibration perception thresholds

The results of the MLn-analysis of the vibration perception thresholds (VPT) are presented in Table 6. On carpal VPT a cumulative neurotoxic effect of vincristine (*effect A*) was found. This means that after one block of four weekly vincristine doses, carpal VPT increased, and increased still further after a second block of four weekly doses.

On tarsal VPT an effect of vincristine with recovery (*effect B*) was found: tarsal VPT increased after four doses of vincristine, but this recovered when vincristine was withdrawn.

The co-variates age and gender did not have significant effects on carpal or tarsal VPT.

Carpal and tarsal VPT were also compared with the reference values developed by our laboratory (see ***Methods***). At diagnosis (t1) mean tarsal (0.712 μm; SD: 0.18) and carpal VPT (0.452 μm; SD: 0.09) differed from these reference values ($p < 0.01$). From t2 to t5, for tarsal VPT 22% and for carpal VPT 23% of the measurements reached above the clinical range of >2 SD of the reference values.

WHO neurotoxicity score

The results of the modified WHO neurotoxicity score are presented in Table 7. At diagnosis (t1) nine of ten children showed no signs of neurotoxicity. The number of children with grade 2 neurotoxicity was highest at the second (t2) and fourth test period (t4), each directly after a block of 4 weekly vincristine doses. At t4 (1 week after the eighth vincristine dose) most deviations were seen: a grade 2 neurotoxicity in eight of 11 children. None of the children reached a neurotoxicity grade 3 or higher.

The neurotoxicity grades are compound scores. More detailed information showed at t2 (1 week after the fourth vincristine dose) Achilles tendon reflexes have disappeared in seven of 11 measured children. Over all measurements Achilles tendon reflexes disappeared in a total number of ten children. From t2 to t5 transient paresthesias were found in four and transient objective sensory loss (mostly vibration sense) in six of 11 children. Transient mild motor weakness was seen in three of 11 children; in two of these children this weakness concerned proximal parts of lower extremities. The grade 2 neurotoxicity in three

Table 7 Number of children with WHO neurotoxicity score at each test period

Test period		t1	t2	t3	t4	t5
n		10	11	11	11	9
Grade	0	9	2	3	2	6
	1	1	3	6	1	0
	2	0	6	2	8	3
	>2	0	0	0	0	0

children at t5 consisted of mild objective sensory abnormalities in these children, and Achilles tendon reflexes were still absent in one and decreased in an other child.

Discussion

The purpose of the present prospective longitudinal study was to describe the effect of low-dose vincristine on neurophysiological functioning of children with ALL before and during treatment at standardized test periods related to the vincristine administration. A modified WHO-neurotoxicity score was obtained to acquire detailed information about clinical neurological functioning. Objective information about peripheral nerve functioning was collected by electrophysiological measurements allowing a discrimination between axonal degeneration and demyelination. Vibration sense measurements were performed to study early signs of polyneuropathy.

From the ***Methods*** section it is clear that we had to deal with a rather small sample size and varying missing data for the different measurements. To facilitate an optimal interpretation of the data we choose to analyse and present all data.

Most knowledge about vincristine neuropathy results from studies in adult patients and animals. Only a few neurophysiological studies have been undertaken in children with vincristine neuropathy. In these studies clinical neurological findings were about the same as in adult studies. Only weakness of the lower extremities seemed more apparent in children than in adults.[14] Our clinical neurological findings are similar to those described earlier. The WHO neurotoxicity score showed an increase in number of children with a grade 2 neurotoxicity: from none of the children at diagnosis, to eight of 11 children after 12 mg/m^2 cumulative vincristine (t4). From t2 to t5 Achilles tendon reflexes decreased or disappeared in 10 of 11 children and motor weakness was found in three children. In two of these three children the weakness concerned the *proximal* musculature of the lower extremities, which could be diagnosed as a corticosteroid myopathy rather than a vincristine neuropathy according to the neurologist.[10] Three children still had sensory abormalities 6 months after the last vincristine dose, but all other children recovered. In agreement with the study by Ferrante[30] none of the children reached a dose-limiting grade of neurotoxicity.

Besides clinical neurological findings, a few studies of electrophysiological measurements of children treated with vincristine have been reported earlier.[8,13,14,30] Bradley[8] measured three children (with medulloblastoma) treated with vincristine (0.05 mg/kg/week) for several months and found progressively decreasing SNAP amplitudes (median and ulnar nerve), which became unrecordable after 4 months. Ferrante[30] measured six girls, 3–11 years old, treated for ALL with six doses of vincristine (1.5 mg/m^2/week) followed by 12 doses (1.5 mg/m^2/month). No significant electrophysiological changes were found from diagnosis until after 1 year of follow-up, although slight neural disturbances consistent with an axonal neuropathy were detected. Vainionpää *et al.*[13,14] measured prospectively SEPs of median and tibial sensory nerves of 38 children (median age: 5.3 years, range: 1.4–15.3) during and after treatment for ALL. They found significantly increased latencies of children with ALL compared with controls, mainly in the proximal nerve part. However, the actual differences were below 10%.[13] Significantly decreased amplitudes were only found in the median nerve cortical SEPs. No measurements at diagnosis were available. Although the possibility of vincristine axonal neuropathy is not excluded, demyelineating toxicity of treatment for ALL (e.g. methotrexate) should also be considered.

In the present study, motor and sensory peripheral nerves of upper and lower extremities of 11 children were measured prospectively at diagnosis and during treatment for ALL. In accordance with Bradley[8] decreased SNAPs of the median and ulnar nerve (upper extremities) were found. That sensory potentials changed, while motor potentials did not, might be explained by the fact commonly known that sensory potentials are often more sensitive indicators for peripheral neuropathy. This is because of reinnervation of the denervated muscle fibres by sprouting of the remaining motor fibres.

In addition, a decreasing trend in CMAPs of the peroneal nerve (lower extremities) was seen. Surprisingly no sural potential changes were found. We had the impression that the variation of the measurements were *such* that a possible fall in potential amplitude did not exceed the limits of 'systematic measurements failures'. On the other hand, loss of ankle jerk along with normal sural potentials might suggest involvement of muscle spindle disturbances (see also below).

In contrast with the studies of Vainionpää *et al.*[13,14] no significant conduction velocity changes were found in any of the studied nerves. This difference with the Finnish studies may be explained at least in part by differences in

population and measurements. The differences in population mainly concern age of the children and differences in treatment. For example, some of the children in the Finnish studies received cranial irradiation (CI), but none of the children in our study did. With regard to the difference in measurements: Vainionpää *et al*. used SEPs whereas in the present study distal SNAPs and CMAPs were measured because we focused on the origin of the axonal degeneration of vincristine peripheral neuropathy.

The nature of our findings, i.e. a combination of decreased action potential amplitudes with unchanging conduction velocities, indeed suggests an axonal neuropathy rather than a demyelinating neuropathy. However, besides axonal neuropathy, a decrease in CMAPs may also imply muscle pathology.[8,31]

From a clinical point of view, unchanging conduction velocities are unexpected, because the disappearance of Achilles tendon reflexes is often considered an indication of disturbed conduction velocities and demyelination. However, when Achilles tendon reflexes disappear concomitantly with unchanging H-reflexes, these data together are known to indicate damage to the muscle spindles. This is exactly what was found by Sandler.[16] He found absence of Achilles tendon reflexes but unchanged H-reflexes and hypothesized that vincristine may mainly affect muscle spindles. We did not measure H-reflexes and therefore cannot give a definite answer to this problem.

Vibration sense measurements are considered a useful instrument for early detection of peripheral neuropathy.[12] Vibration sense measurements of children with vincristine neuropathy, however, have not been reported before. Studies of vibration sense measurements in adults reported inconsistent results. Sandler[16] reported intact vibration sense and Casey[7] found only mild impairment. However, Postma[32] reported vibration sense disturbances in 50% of adult patients 1 year after treatment with vincristine (12 mg/m^2 cumulative dose, 18–24 weeks). Haim[33] found vibration sense disturbances in 44% of 32 adult lymphoma patients 3–12 months after eight doses vincristine (1.4 mg/m^2/dose). Our study revealed significantly increased carpal and tarsal VPTs. From 1 week after the first four vincristine doses until 6 months after the eighth vincristine dose (t2–t5) 22–23% of all values were over 2 SD from the clinical normal range. However, already at diagnosis (t1) VPTs differed from the reference values. In contrast, at diagnosis, the electrophysiological data in children with ALL were in accordance with the reference values. Therefore, psychosomatic factors may have caused an increased VPT already at diagnosis, whereas the electrophysiological measurements are independent of such factors.

Vincristine neuropathy is thought to be largely reversible.[17] We also found evidence of recovery. Six of nine children had a grade 0 neurotoxicity 6 months after the last vincristine gift (t5). In addition, for tarsal VPT, a neurotoxic vincristine effect with recovery was found, meaning that at t5 the baseline VPT was reached. However, three of nine measured children had a grade 2 neurotoxicity at t5 and for carpal VPT, peroneal CMAP and median and ulnar SNAP no signs of recovery were found. Furthermore, axonal neuropathies are known to have poor recovery. Neurophysiological follow-up measurements are necessary to give a definite answer on whether children treated for ALL will recover completely from vincristine neuropathy or will have to deal with persisting peripheral neural damage. In the end, the neural disturbances shown in the present study may at least partly be responsible for the motor problems reported elsewhere.[4]

Conclusions

In conclusion the standardization of the test periods closely related to the vincristine protocol allowed us to test two possible neurotoxic effects of vincristine. Significant neurotoxic vincristine effects on the measured variables were found and this suggests a relation between the neurological disturbances and neurotoxicity by vincristine, consistent with the literature. Additional or other neurotoxical effects of other agents are hard to exclude. Children treated for ALL according to protocol DCLSG-ALL-8, a BFM-oriented treatment, with a relatively low dose vincristine regimen do not suffer from dose-limiting neurotoxicity, but rather a mild axonal neuropathy.

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