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Research paper

# Without ENMG, detecting pediatric vincristine neuropathy is a challenge

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ABSTRACT

*Objective:* Vincristine, a widely used anticancer chemotherapy drug, may cause polyneuropathy (PNP), potentially resulting in permanent functional impairment. We characterized the occurrence and development of vincristine-induced neuropathy (VIPN) in early treatment of childhood leukemia.
*Methods:* This prospective study of 35 pediatric acute lymphoblastic leukemia (ALL) patients comprised systematic clinical and electrophysiological studies at both the time of diagnosis and at least one time point during the first months of treatment.
*Results:* After vincristine treatment, all patients had axonal sensorimotor PNP on electroneuromyography (ENMG) In 34/35 patients, the motor and in 24/35 the sensory responses were decreased. Interestingly, in 3 patients PNP was most prominent in the upper limb. However, some children had no PNP symptoms despite moderate ENMG findings, and not all clinical symptoms were correlated with abnormal ENMG.
*Conclusions:* Pediatric VIPN is a sensorimotor, predominantly motor axonal neuropathy. VIPN can be detected even in its early phase by ENMG, but it is difficult to detect by symptoms and clinical examination only.
*Significance:* Pediatric ALL patients treated with vincristine are at risk of developing VIPN. Since the clinical signs of PNP in acutely ill children are difficult to identify, VIPN can easily be overlooked if ENMG is not performed.


## 1. Introduction

Acute lymphocytic leukemia (ALL) is the most common cancer in children; fortunately, its survival rate has improved markedly in recent decades (Hunger et al., 2012). Chemotherapy-induced peripheral neuropathy (CIPN) is the most common side effect in pediatric ALL patients, affecting up to 78 % of patients. CIPN significantly impacts childhood cancer survivors' quality of life long after treatment (Jain et al., 2014; Kandula et al., 2016; Ramchandren et al., 2009; Tay et al., 2017). Thus, early and accurate identification of this harmful side-effect is important in preventing further damage.

The main cause of CIPN is exposure to vincristine (VCR) (Kandula et al., 2018), which is an antimitotic drug and an important component of ALL chemotherapy. Vincristine-induced peripheral neuropathy (VIPN) is known to be dose-related, and many individual characteristics also affect sensitivity to VIPN (van de Velde et al., 2017). Individual factors related to pharmacokinetics and genetics remain largely unknown and are under intensive investigation (Abaji et al., 2018; Carozzi et al., 2015; Ceppi et al., 2014; Triarico et al., 2021). Furthermore, some medicines, particularly antifungals, can interact with VCR and have an impact on VCR toxicity (Moore and Groninger, 2013; Moriyama et al., 2012; van de Velde et al., 2017).

Reliable clinical examination of polyneuropathy (PNP) includes sensory, muscle strength, and reflex testing, which are difficult to perform in young children. There are several peripheral neuropathy assessment tools, however, no gold standard exists. Based on available evidence, the pediatric–modified Total Neuropathy Scale (ped-m TNS) and the Total Neuropathy Score, pediatric version

*Abbreviations:* ALL, acute lymphocytic leukemia; CIPN, chemotherapy-induced polyneuropathy; CMAP, compound muscle action potential; EMG, electromyography; ENG, electroneurography; ENMG, electroneuromyography; MCV, motor conduction velocity; MUP, motor unit potential; PNP, polyneuropathy; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential; TNS-PV, Total Neuropathy Score Pediatric Version; VCR, vincristine; VIPN, vincristine-induced polyneuropathy.

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(TNS-PV) (Lavoie Smith et al., 2013) are the most recommended for the assessment of VIPN in children aged six years and over (Haryani et al., 2017; Smolik et al., 2018). TNS-PV consists of an interview-based questionnaire and a standardized physical examination. However, the reliable use of this tool requires trained assessors. No validated patient-reported outcome measure for pediatric CIPN exists, but a new and potentially useful measure, P-CIN (Pediatric Chemotherapy-Induced Neuropathy) has recently been introduced (Lavoie Smith et al., 2021).

The gold standard for detecting VIPN is ENMG (Kandula et al., 2016). ENMG in adults has revealed VIPN to be a typically symmetric, dose-related, and axonal and length-dependent peripheral PNP (Casey et al., 1973; Gulheneuc et al., 1980). In children, the findings of the type of PNP differ, most likely due to different study designs, timing, and methods used. ENMG studies have shown that in children there is predilection for motor disturbance in VIPN (Courtemanche et al., 2015; Dorchin et al., 2013; Kavcic et al., 2017; Li et al., 2023; Yildiz and Temucin, 2016). Furthermore, the findings can be asymmetric and even non-length-dependent (Courtemanche et al., 2015; Dorchin et al., 2013; Jain et al., 2014; Kandula et al., 2016; Toopchizadeh and Barzegar, 2009). In addition to symptoms due to peripheral nerve damage, autonomic dysfunction is a known feature of VCR toxicity (Anghelescu et al., 2011; Courtemanche et al., 2015) and rarely also weakness in cranial nerve functions (Bay et al., 2006; Mora et al., 2016). Typically, the onset of VIPN is sudden, occurring during the first months of treatment (Reinders-Messelink et al., 2000).

The current prospective study was designed to evaluate systematically the development of VIPN during the first three months of ALL treatment in children. We used repeated ENMG and clinical investigations to evaluate the appearance of abnormalities in ENMG in the early phase of the acute treatment and clinical symptoms and signs at the same time point.

## 2. Methods

This prospective study was conducted at Helsinki University Hospital (HUH) at Children's Hospital, Helsinki, Finland. The study recruited children diagnosed with ALL within the HUH healthcare district between 10/2016 and 2/2019. Inclusion criteria required a recent ALL diagnosis (within one week), age between 1 and 16 years at onset of the disease, and ability to communicate in Finnish, Swedish, or English independently without the use of an interpreter. Patients with relapsed ALL were excluded.

The study was approved by the HUH Ethics Review Board.

All patients were treated according to either the NOPHO (Nordic Society of Pediatric Hematology and Oncology) ALL 2008 (standard, intermediate, and high-risk groups) protocol or the EsPhALL protocol (patients with Philadelphia chromosome-positive ALL; 2017 International phase 3 trial in Philadelphia chromosome-positive acute lymphoblastic leukemia). In the NOPHO 2008 protocol, the VCR dosage is 2 mg/m$^2$ and in the EsPhALL protocol 1.5 mg/m$^2$. The treatment was started with the NOPHO 2008 ALL protocol in all patients. Of the patients, 25 belonged either to the standard-risk or intermediate-risk group and 7 to the high-risk group, and 3 patients changed to the Philadelphia EsPhALL protocol when the Philadelphia chromosome was found to be positive.

Our study protocol started with ENG and physical examination within two weeks of the ALL diagnosis; this period is referred to as the *baseline*. The next test point called *post-induction* was scheduled if the treating physician suspected PNP symptoms. This was done earliest at the end of induction treatment, which is approximately one month from the beginning of the treatment. ENMG and clinical examinations were conducted. The last examination called the *study point* was planned for all patients at three months from onset of the disease; it included ENMG and clinical status (see Fig. 1 for study scheduling).

Patients underwent a predefined electrodiagnostic ENMG protocol. All measurement points included ENG. The studied motor nerves were common fibular nerve bilaterally, tibial nerve distally, and median nerve on the right side. Sensory conduction measures included bilateral sural nerves and antidromic measurement of the median nerve unilaterally. The needle EMG was not performed at the first *baseline* measurement session, but at the *post-induction* and *study point* measurements the tibialis anterior muscle was examined unilaterally. If cooperation was insufficient, the follow-up electrodiagnostic studies were done under general anesthesia administered for intrathecal chemotherapy medication. The purpose of the *baseline* ENG at the beginning of the study was to determine the individual baseline for every patient. Normality of responses was first determined by comparing the values with laboratory normative values. In addition, the *post-induction* and *study point* measurements were compared with individual *baseline* values, and a decrease of more than 50 % in the amplitude of sensory nerve action potential (SNAP) or compound muscle action potential (CMAP) was considered abnormal.

The sensory and motor findings were graded based on ENMG as normal, mild, moderate, or severe. Motor findings: mild = only fibular CMAP amplitudes were decreased uni- or bilaterally; moderate = fibular and tibial CMAP amplitudes were decreased or there were abnormal motor unit potentials (MUPs) or spontaneous discharges in EMG or decreased median CMAP amplitudes; severe = all examined CMAP amplitudes were very low or absent. Sensory findings: mild = decreased SNAP amplitudes only in lower limbs; moderate = decreased SNAP amplitudes in both upper and lower limbs uni- or bilaterally or only in upper limb; severe = absent SNAPs.

The child's developmental and previous health histories were recorded according to the parents' interview. Medical report documentation was reviewed for the whole study period of each patient. Clinical symptoms were observed both by the research physiciańs clinical examination and by interviewing the parents and the treating physician. These evaluations were made before every electroneurodiagnostic investigation. Questioning included subjective sensory symptoms (numbness, tingling, hyperesthesia), pain, impaired performance in daily activities or motor skills, signs of cranial nerve impairment (strabismus, ptosis, problems in chewing or swallowing), and constipation or problems in urinary outflow. We checked the medical records for any notations of constipation or urinary or autonomic nervous system impairment. Physical examination was performed by a pediatric neurologist and included sensory testing, tactile, pinprick, warm-cold sensation, both upper and lower limb sensation (starting distally and proceeding proximally if abnormal findings were observed) and vibration (at least big toe and lateral malleoli), and joint position sense of the lower limbs of the lower limbs. Muscle strength was tested in both upper and lower limbs, as were reflexes. Cranial nerves III-VII and IX-XII were tested. Total Neuropathy Score Pediatric Vincristine (TNS-PV) was scored for patients aged six years or over. TNS-PV includes items quantifying vibration sense, muscle strength, deep tendon reflexes, subjective autonomic symptoms, and distal to proximal extension of subjective sensory and motor symptoms.

Statistical analyses were performed with the SPSS statistics software (version 25). Comparison of normally distributed conduction velocities was carried out with one-way ANOVA (analysis of variance) for repeated measures, and comparison of both amplitudes and distal latencies was done using non-parametric tests for related samples.

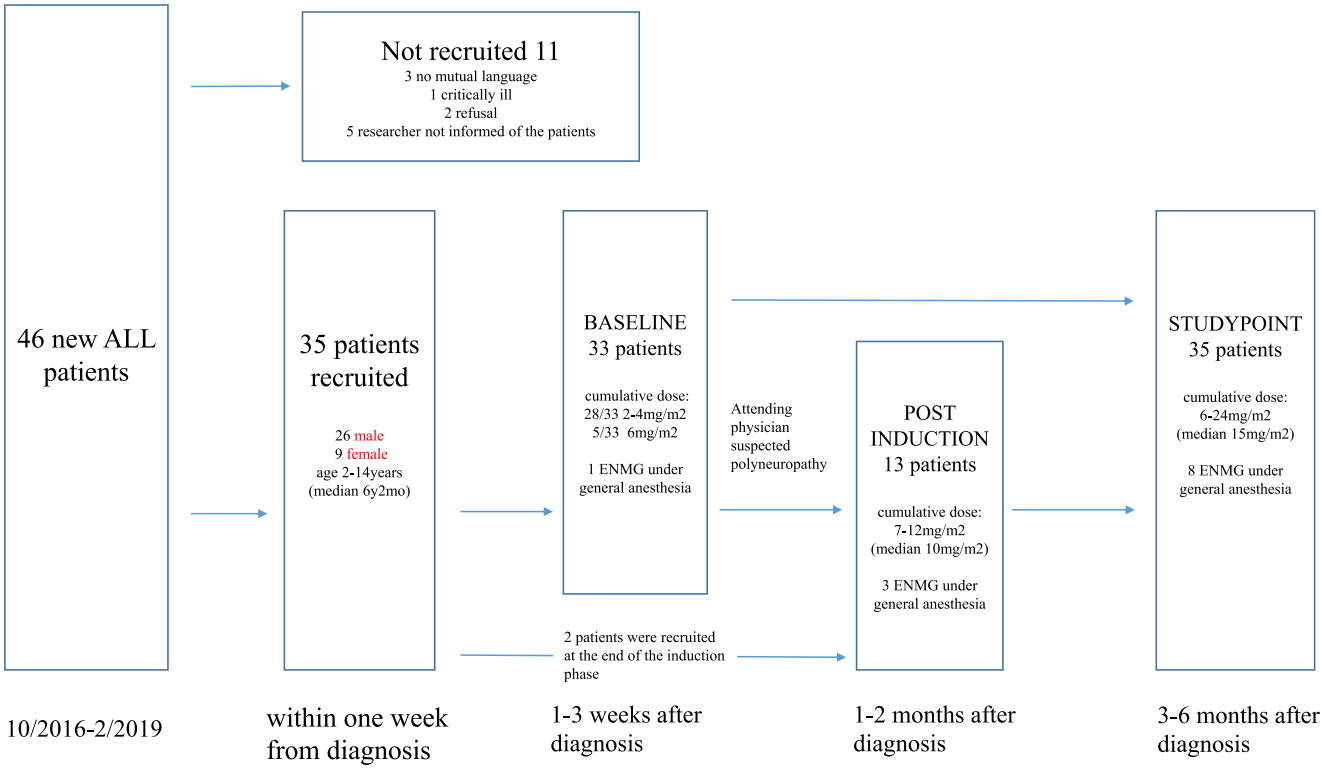


**Fig. 1.** Study structure and inclusion of patients.

## 3. Results

Altogether 46 patients aged 1–16 years were diagnosed with new ALL during the study period, and 35 of the patients met the inclusion criteria (see Fig. 1). All patients were of Caucasian ancestry.

None of the diagnosed children had any known susceptibility to genetic PNP. Of the 35 patients, 8 had a history of childhood motor developmental problems. One child had facial nerve palsy already at the time of ALL diagnosis.

All patients underwent at least two ENG/ENMG and clinical examinations as planned. The *baseline* evaluation was performed on 33/35 patients, five of whom had already been given 6 mg/m$^2$ of VCR at the time of the evaluation. Thirteen patients underwent *post-induction* phase studies based on clinical suspicion of VIPN. All patients were examined at the *study point.* These examinations were done within four months of disease onset for 28/35 patients, within five months for 34/35 patients, and within six months for 35/35 patients. Of the total of 81 examinations, 12 were performed under general anesthesia such that they were implemented in the same anesthesia as the intrathecal methotrexate administration, which is a part of routine ALL treatment protocol (see Fig. 1).

Patients' cumulative VCR amounts varied from 7 to 24 mg/m$^2$, with the median being 15 mg/m$^2$ at the end of the study protocol. This variation was due to three things. First, VCR dosages vary due to different treatment protocols. In the NOPHO 2008 ALL protocol, the VCR dosage is 2 mg/m$^2$ without any dose reductions, and it is given in five weekly infusions during the induction phase. After that, the dosage varies depending on which NOPHO 2008 ALL risk group the patient belongs or if the treatment was according to the EsPhALL protocol in which the VCR dose is 1.5 mg/m$^2$ without any reductions. Second, 15/35 patients received reduced VCR dosage due to neuropathy symptoms during the study. Third, the time point of the ENMG investigation varied due to practical issues (e.g. problems with scheduling, resources) between 2.5 months and 6 months (median 3.5 months). The clinical investigations were performed on the same schedule as the ENMG. See Fig. 1 for variation of cumulative VCR doses in general and Table 1 for individual patients' cumulative dosages at the end of the study.

The comparison of the ENMG and clinical findings at different time points is summarized in Table 2, and the findings at the *study point* are detailed in Table 1.

Electroneuromyography examinations:

At the first *baseline* ENG, 30/33 patients had normal findings. Three patients had decreased CMAP amplitudes with normal conduction velocities; two were scored with mild and one with moderate motor PNP. Two of these patients had normal sensory measurements and one had mild sensory neuropathy as well (see Table 2). The two with decreased CMAPs had both received 2 mg/m$^2$ VCR before the examination and the one with both decreased SNAPs and CMAPs had received 3 mg/m$^2$.

Of the 13 patients selected for the *post-induction* examination, four had normal ENMG. Nine had decreased CMAP amplitudes and four (4/13) also decreased SNAP amplitudes. None had only sensory findings (see Table 2).

At the *study point,* none of the patients had normal ENMG, 34/35 patients had decreased CMAP amplitudes, and 24/35 patients had decreased SNAP amplitudes (see Table 1). At this point, 29/35 patients were scored with moderate or severe motor neuropathy and 22/35 with moderate or severe sensory neuropathy based on electrodiagnostic examinations. Fig. 2 shows the development of the PNP findings at the different examination points. Three patients had upper limb-predominant motor neuropathy, but it is noteworthy that at the *study point* the motor amplitudes of upper limbs were significantly decreased in 27 patients.

The motor and sensory measurements at different time points and the group comparisons between different visits are shown in Table 3. The most notable finding was the significant and marked

**Table 1**
Characteristics of study patients at the *study point.*

| Patient no | Gend | Age yrs | Motor findings | | | Sensory findings | | | Tendon reflexes | | Cranial nerve findings | TNS-PV score | Dose reduction | Cumulative dosage mg/m2 | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Patient reported | Clinical findings | ENG findings | Patient reported | Clinical findings | ENMG findings | ankle | patellar | | | | | |
| 1 | M | 2 | ++ | + | severe[i] | + | ++* | moderate | absent | absent | + | NA | + | 16 | |
| 2 | F | 2 | + | + | mild[ii] | – | –* | normal | absent | normal | – | NA | + | 15 | |
| 3 | M | 2 | + | –* | severe | – | –* | normal | absent | decreased | + | NA | – | 30 | |
| 4 | M | 2 | ++ | + | severe | – | –* | normal | absent | decreased | + | NA | + | 13 | infx[iiii] |
| 5 | M | 2 | + | + | severe | – | * | moderate | absent | decreased | – | NA | – | 18 | |
| 6 | M | 2 | + | + | severe | + | –* | moderate | normal | normal | – | NA | + | 15 | |
| 7 | M | 3 | + | + | severe | – | –* | moderate | absent | decreased | – | NA | – | 10 | |
| 8 | M | 3 | + | + | severe[i] | + | –* | moderate | decreased | absent | + | NA | + | 10 | |
| 9 | F | 3 | – | + | severe | – | +* | normal | absent | decreased | – | NA | – | 24 | |
| 10 | M | 3 | ++ | ++ | severe | ++ | +* | mild | absent | decreased | + | NA | + | 12 | |
| 11 | M | 4 | ++ | + | severe | ++ | +* | normal | absent | absent | – | NA | + | 18 | |
| 12 | M | 5 | – | – | mild | – | – | moderate | normal | normal | – | NA | – | 10 | |
| 13 | M | 5 | ++ | ++ | severe | + | +* | normal | absent | decreased | – | NA | | 14 | infx[iiii] |
| 14 | M | 5 | ++ | + | severe | – | –* | moderate | absent | decreased | + | NA | – | 20 | |
| 15 | F | 5 | + | + | severe | + | –* | normal | absent | normal | – | NA | – | 12 | infx[iii] |
| 16 | M | 5 | + | + | severe | – | – | modetare | absent | absent | + | NA | – | 18 | |
| 17 | F | 6 | ++ | + | severe | – | + | normal | absent | decreased | + | 7 | – | 20 | |
| 18 | M | 6 | + | +* | severe | – | –* | normal | decreased | decreased | + | NA | – | 15 | infx[iii] |
| 19 | M | 6 | + | + | severe | + | + | moderate | decreased | absent | – | 6 | + | 12 | |
| 20 | M | 6 | – | + | severe | – | – | normal | absent | decreased | – | 5 | – | 22 | |
| 21 | F | 6 | + | + | severe | + | +* | moderate | absent | decreased | – | 9 | – | 13 | infx[iii] |
| 22 | M | 6 | + | + | severe | + | – | moderate | normal | decreased | – | 3 | – | 18 | |
| 23 | M | 7 | ++ | ++ | severe | + | + | mild | absent | absent | – | 6 | + | 18 | |
| 24 | F | 7 | + | + | severe | – | – | moderate | decreased | decreased | – | 3 | – | 18 | |
| 25 | F | 7 | ++ | + | mild | – | +* | modetare | decreased | decreased | – | 3 | – | 18 | infx[iii] |
| 26 | M | 8 | ++ | + | moderate | – | – | moderate | absent | absent | + | 5 | – | 22 | |
| 27 | F | 8 | – | – | normal | + | – | moderate | decreased | normal | – | 3 | – | 16 | |
| 28 | M | 8 | ++ | +* | severe | + | NA | moderate | NA | NA | – | NA | + | 9 | |
| 29 | M | 9 | ++ | ++ | severe | + | – | moderate | absent | decreased | – | 6 | – | 20 | |
| 30 | M | 9 | + | + | severe | – | –* | normal | absent | absent | – | 6 | + | 17 | infx[iii] |
| 31 | M | 11 | – | + | moderate | + | + | moderate | absent | decreased | – | 6 | + | 11 | |
| 32 | F | 11 | + | + | mild | + | – | moderate | absent | decreased | – | 7 | – | 14 | |
| 33 | M | 12 | + | ++ | mild | – | – | moderate | absent | decreased | – | 4 | + | 10 | |
| 34 | M | 13 | + | + | severe[i] | + | + | moderate | decreased | decreased | + | 5 | – | 14 | |
| 35 | M | 14 | ++ | ++ | severe | ++ | ++ | severe | absent | decreased | – | 16 | + | 6 | infx[iiii] |

NA = not applicable because of age or co-operation; * = The examination could only be performed partially due to coopetration; [i] = upper limb more affected; [ii] = vitamin B treatment for ptosis; infx[iii] = bacterial; infx[iiii] = bacterial spepsis and fungal infection during the treatment sepsis during the treatment.
TNS-PV scoring for patients over six years of age: The median score at *studypoint* was six points the cut-off point for PNP being score $\geq 4$ (E. M. Lavoie Smith et al., 2015). In was noteworthy that most of the points in our patients came from decreased or absent reflexes 2,7 ± 1,2 points (nearly half on the median score). So alteration in reflexes is a significant clinical sign to detect.

decrease in motor and sensory amplitudes. Motor distal latencies were slightly prolonged, but motor conduction velocities (MCVs) of deep fibular nerves were not altered. Fig. 3 shows an example of the progression of distal deep fibular nerve responses in one patient at different examination points. Notably, the upper limb motor median nerve responses were also significantly altered; amplitudes were decreased, distal latencies prolonged, and MCV slowed. Despite the significant decrease in sensory amplitudes with follow-up, the sensory nerve conduction velocities (SCVs) were not changed in lower or upper limbs.

Clinical symptoms:

At *baseline*:

At the *baseline,* none of the patients had any abnormal neurological findings, but six patients had subjective sensory symptoms (three of whom had jaw pain, others pain in the knees or legs) and three had subjective motor symptoms (perceived weakness in walking or difficulty getting up from the floor). One patient with sensory symptoms had also decreased sensory amplitudes in ENG. The other patients with subjective symptoms, either motor or sensory, revealed no ENMG abnormalities.

During the *post-induction* phase:

The treating physician suspected PNP in 13 patients at the *post-induction* phase. The symptoms that lead to the suspicion were as follows: 12 had walking difficulties (weakness of dorsiflexion in eight), seven had problems in fine motor skills, five had neuropathic pain, three had paresthesia or hyperesthesia, five had ptosis, three had jaw pain and/or unclear speech, and two had difficulty in urinating. Nine of these 13 patients had findings in ENMG (decreased CMAPs in all and four also had decreased SNAPs, none had pure sensory findings) (see Table 2). However, three of the nine patients with normal SNAPs had self-reported sensory symptoms (numbness or pain in feet), and of the four who had decreased SNAPS only three reported symptoms. Therefore, the clinical findings were partially inconsistent with ENMG findings. However, the combination of weakness of dorsiflexion and decreased Achilles reflex was clearly indicative of PNP; of the seven patients with this combination, five had abnormalities in ENMG.

At the *study point*:

In interviews of all 35 patients at the *study point* (Table 1), six patients or their caregivers reported sensory symptoms of the upper extremity (pain, tingling, hyperesthesia), 13 had sensory symptoms of the lower extremity, 19 had problems in fine motor skills, 25 had walking difficulties, five had ptosis, and 25 had constipation.

In clinical examination at the *study point,* two patients had findings in upper extremity sensory testing, 13 in lower extremity sensory testing, and seven in upper extremity motor function, 32 had weakness of dorsiflexion, 27 had walking difficulties, 32 had decreased reflexes (absent Achilles reflex in 24), and ten had findings in cranial nerves (seven ptosis, two strabismus, two unclear

**Table 2**
Summary of the prevalence of findings in nerve conduction studies and correlation with clinical findings.

| | *Baseline* | *Post induction* | *Studypoint* |
|---|---|---|---|
| **Number of patients (out of total 35)** | 33 | 13 | 35 |
| **Cumulative VCR dosage mg/m2** | 2–6 (median 4) | 5–12 (median 10) | 7–24 (median 15.5) |
| **Normal ENG/ENMG** | 30/33 | 4/13 | 0/35 |
| **Decreased CMAP without clinical motor symptoms** | 3/33 | 0/13 | 2/35 |
| **Decreased CMAP with clinical motor symptoms** | 0/33 | 9/13 | 32/35 |
| **Normal CMAP but clinical motor symptoms** | 3/33 | 4/13 | 0/35 |
| **Decreased SNAP without clinical sensory symptoms** | 0/33 | 1/13 | 8/35 |
| **Decreased SNAP with clinical sensory symptoms** | 1/33 | 3/13 | 16/35 |
| **Normal SNAP but clinical sensory symptoms** | 5/33 | 3/13 | 5/35 |
| **Decreased of absent lower extremity reflexes** | 0/33* | 11/13* | 32/35* |
| **Cranial nerve symptoms** | 2/33 | 7/13 | 11/33 |
| **TNS-PV score (over 6 years old patients)** | N = 17 0–4 (median 0)<br>* 4/33 unreliable, cooperation unoptimal | N = 4 3–10 (median 6)<br>* 3/13 unreliable, cooperation unoptimal | N = 17 3–16 (median 6)<br>* 6/35 unreliable, cooperation unoptimal |

VCR = vincristine; ENG = electroneurography; ENMG = electroneuromyography; CMAP = compound muscle action potential; SNAP = sensory nerve action potential; TNS-PV = Total Neuropathy Score Pediatric Version

speech and hoarseness). A summary of *study point* findings is presented in Table 1.

Of all clinical findings, the most obvious was the decrease or abolishment of lower extremity deep tendon reflexes over time (see Table 2).

TNS-PV assessment:

At the beginning of the study, 19 patients were aged over six years and TNS-PV was also used to evaluate their symptoms. Two of the patients were excluded from scoring for developmental reasons (developmental disability and autism spectrum disorder), and thus, 17 patients were scored at the beginning of the study and at the *study point* and four patients were scored at the *post-induction* phase. At *baseline,* the TNS-PV score was 0–4, at *post-induction* the score was 3–10, and at the *study point* the score was 3–9 points in 16 patients and 16 points in one patient. See Tables 1 and 2 for TNS-PV scores.

## 4. Discussion

In this prospective study, we evaluated systemically the development of VIPN during ALL treatment in children. To our knowledge, this cohort of 35 pediatric ALL patients is the largest study of repeated clinical evaluations and systematic electrophysiological investigations (see Fig. 1). Our study confirmed the earlier finding that motor symptoms are initial and more predominant than sensory symptoms in pediatric VIPN (Courtemanche et al., 2015; Dorchin et al., 2013; Kandula et al., 2016). When sensitive methods like nerve conduction studies are used, VIPN can be demonstrated to affect many pediatric patients receiving VCR (Toopchizadeh and Barzegar, 2009). However, we did not expect to observe findings this severe; 77 % of patients had very low or absent CMAP amplitudes and/or absent SNAPs. The finding of progressing axonal sensorimotor neuropathy was systematic throughout the study, and


**Fig. 2.** Progression of polyneuropathy over time.

**Table 3**
Results of nerve conduction studies at different time points of the study.

| **Motor conduction studies** | | *Baseline* | *Post induction* | *Studypoint* | *P* value Baseline - Post Induction | *P* value Baseline - Studypoint |
|---|---|---|---|---|---|---|
| Fibular right | MCV (m/s) | 48.42 ± 4.53 | 46.55 ± 13.50 | 47.62 ± 12.02 | 0.091 | 0.48 |
| | Ampl (mV) | 2.34 ± 1.03 | 1.60 ± 1.34 | 0.86 ± 0.84 | 0.028 | < 0.001 |
| | DL (ms) | 3.20 ± 0.72 | 4.86 ± 4.53 | 3.10 ± 0.84 | 0.033 | < 0.001 |
| | n | 33 | 12 | 35 | | |
| Fibular left | MCV (m/s) | 45.80 ± 4.95 | 46.60 ± 17.65 | 46.74 ± 11.87 | 0.060 | 0.019 |
| | Ampl (mV) | 2.61 ± 1.12 | 1.41 ± 1.07 | 0.92 ± 0.77 | 0.033 | < 0.001 |
| | DL (ms) | 3.10 ± 0.84 | 4.71 ± 4.67 | 3.88 ± 1.25 | 0.033 | 0.001 |
| | n | 32 | 13 | 35 | | |
| Tibial right | Ampl (mV) | 10.29 ± 4.40 | 9.20 ± 6.28 | 8.01 ± 3.22 | 0.041 | < 0.001 |
| | DL (ms) | 3.09 ± 0.78 | 3.23 ± 0.93 | 3.11 ± 0.74 | 0.248 | 0.801 |
| | n | 33 | 13 | 35 | | |
| Tibial left | Ampl (mV) | 10.07 ± 4.47 | 8.94 ± 6.89 | 7.76 ± 3.12 | 0.155 | 0.002 |
| | DL (ms) | 3.07 ± 0.73 | 3.18 ± 0.93 | 3.12 ± 0.86 | 0.386 | 0.969 |
| | n | 32 | 13 | 33 | | |
| Median right | MCV (m/s) | 54.79 ± 4.67 | 50.83 ± 5.04 | 51.73 ± 4.33 | 0.050 | < 0.001 |
| | Ampl (mV) | 5.03 ± 1.53 | 2.67 ± 2.13 | 1.98 ± 1.54 | 0.028 | < 0.001 |
| | DL (ms) | 2.60 ± 0.33 | 3.08 ± 0.58 | 3.26 ± 0.68 | 0.007 | < 0.001 |
| | n | 33 | 12 | 34 | | |
| **Sensory conduction sudies** | | *Baseline* | *Post induction* | *Studypoint* | *P* value Baseline - Post Induction | *P* value Baseline - Studypoint |
| Sural right | SCV (m/s) | 54.14 ± 6.34 | 51.88 ± 3.88 | 54.12 ± 5.69 | 0.200 | 0.434 |
| | Ampl (mV) | 20.94 ± 6.97 | 22.39 ± 10.00 | 16.55 ± 5.68 | 0.959 | <0.001 |
| | DL (ms) | 1.56 ± 0.39 | 1.60 ± 0.55 | 1.61 ± 0.38 | 0.169 | 0.829 |
| | n | 33 | 13 | 33 | | |
| Sural left | SCV (m/s) | 53.46 ± 5.30 | 50.17 ± 5.26 | 53.22 ± 6.02 | 0.016 | 0.975 |
| | Ampl (mV) | 23.17 ± 8.95 | 22.18 ± 9.13 | 17.75 ± 6.12 | 0.285 | 0.001 |
| | DL (ms) | 1.49 ± 0.40 | 1.66 ± 0.54 | 1.60 ± 0.45 | 0.037 | 0.233 |
| | n | 33 | 13 | 35 | | |
| Median right | SCV (m/s) | 58.82 ± 3.82 | 54.05 ± 6.66 | 56.40 ± 5.41 | 0.076 | 0.062 |
| | Ampl (mV) | 54.33 ± 14.71 | 33.93 ± 13.08 | 25.43 ± 8.82 | 0.005 | < 0.001 |
| | DL (ms) | 1.85 ± 0.27 | 1.97 ± 0.42 | 1.84 ± 0.36 | 0.074 | 0.983 |
| | n | 33 | 12 | 35 | | |

MCV = motor conduction velocity; Amp = amplitude; DL = distal latency; n = number of patients.

all patients were affected. Motor predominance was observed in both the *post-induction* and *study point* examinations, but the sensory findings increased over time. Not all findings were pure length-dependent type PNP: three patients had upper extremity-dominant sensorimotor neuropathy, as described earlier by Courtemanche et al. (2015) and Kandula et al. (2016).

The challenge in clinical settings is to treat ALL effectively, while preventing permanent damage due to severe pediatric VIPN. The difficulty lies in clinical recognition and identification of the early often motor-predominant PNP symptoms when there are several confounding factors causing weakness, most importantly systemic illness and concurrent use of steroids as part of ALL treatment. It is challenging—if not impossible—to differentiate only by clinical examination whether the motor disturbances are due to neuropathy, myopathy, or pain. Young children especially have difficulties expressing tactile symptoms, numbness, tingling, and neuropathic pain (Kandula et al., 2016; Mora et al., 2016; Smolik et al., 2018). It is noteworthy that assessment tools for VIPN are mainly based on what is known about adults' VIPN, which is typically a sensorimotor, length-dependent PNP (Cornblath et al., 1999; Gilchrist et al., 2009; Lavoie Smith et al., 2008).

The reasons for the different presentation of VIPN in children and adults are most likely multifactorial and not fully understood. It has been suggested that the motor dominance in pediatric VIPN, at least in the early phase of exposure to vincristine, is due to different biophysical properties of motor and sensory nerves in adult and children (Kandula et al., 2020). Also, the pathomechanisms in VIPN are diverse and conditioned by patient-related risk factors and treatment-related risk factors (Triarico et al., 2021).

In this study, in contrast to marked ENMG findings, the clinical manifestations of neuropathy were difficult to detect clinically, even in those patients who had moderate PNP in ENMG. Of the clinical signs, the most reliable finding was the abolishment of reflexes. Nearly all our patients (32/35) had decreased or absent lower extremity reflexes at the *study point*. Furthermore, at the *post-induction* phase the decreased reflexes were also one of the initial findings, causing the treating physician to suspect VIPN. This is in line with Kavcic et al. (2017) who found decreased or absent myotatic reflexes (89 %) as the most common sign of VIPN (Kavcic et al., 2017). Our sensory findings were partly conflicting. At the *study point* examination, there were nine patients who had decreased SNAPs but no clinical sensory symptoms or findings, and vice versa, seven patients who had clinical sensory symptoms but normal SNAPs (as seen in Table 2). No obvious difference was found in the incidence or severity of either sensory or motor PNP in patients aged under six years and in those aged over six years.

We used also TNS-PV scoring for patients over six years of age. The median score at *study point* was six points (cut-off point for PNP being a score $\geq 4$; Lavoie Smith et al., 2015). It was noteworthy that most of the points in our patients came from decreased or absent reflexes. Two of 35 patients scored 3 and still had severe motor and moderate sensory PNP based on ENG. In our cohort, TNS-PV was not sensitive enough to detect pediatric VIPN in time for individual modifications to chemotherapy. The overall grade of TNS-PV emphasizes more sensory than motor findings, and this reduces its sensitivity in the early phase of pediatric VIPN because motor symptoms appear first and are more dominant than sensory symptoms.

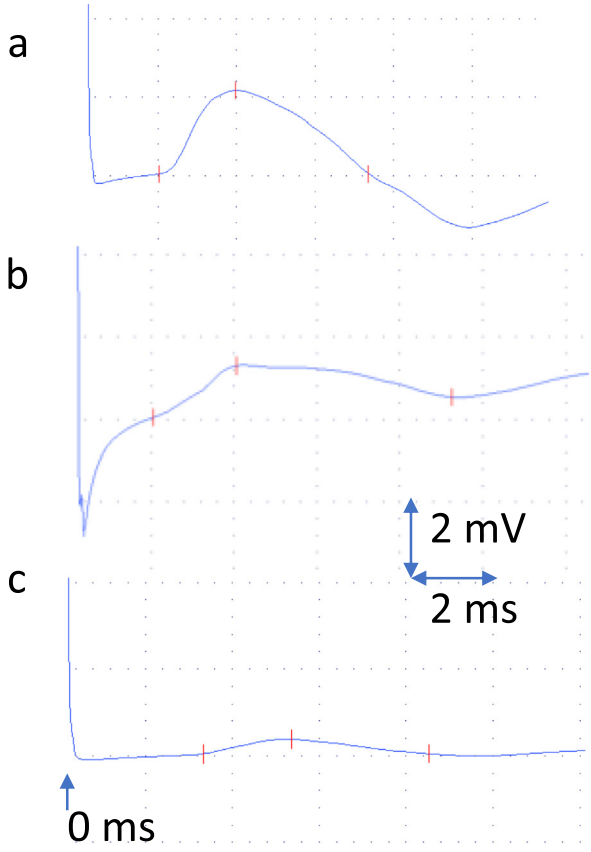


**Fig. 3.** Distal deep fibular nerve responses in one patient at different examination points: at baseline (a), post-induction (b), and studypoint (c). Note the decrease of the amplitude of the response with the advancement of vincristine induced polyneuropathy.

Bjornard et al. (2018) pointed out in their review that screening for neuropathy should be done on an ongoing basis in all pediatric patients receiving neurotoxic therapy. If functional changes or pain are suspected, an evaluation by a trained specialist is needed and electrodiagnostic studies should be considered (Bjornard et al., 2018). Our findings support this. However, it should be noted that in our study the dosage of VCR was 2 mg/m$^2$ according to the NOPHO 2008 ALL protocol, which is higher than the more commonly used 1.5 mg/m$^2$, likely having an effect on the high incidence of PNP in this study.

Our study has limitations, most of them due to the clinical setting of the study. Due to lack of information, five eligible patients could not be recruited, which might cause a minor selection bias. The *baseline* investigations were done as early as possible, but in practice the VCR treatment had already started. However, 30/33 *baseline* ENGs were normal, so the sample is reliable enough to consider as a baseline. The timing of the *study point* investigations was not as accurate as planned, but the findings are consistent, and all patients were still at the stage of the treatment protocol in which VCR was continued. Some of the nerve conduction studies were done under general anesthesia: 1/33 at *baseline*, 3/13 at *post-induction,* and 8/35 at *study point*. Since no muscle relaxants had been used, the ENG could be reliably conducted, and its results compared with *baseline* measures. EMG was restricted to evaluating possible spontaneous discharges. In the upper extremity, the nerve conduction was studied only unilaterally, which hampers the evaluation of the non-length-dependent type of VIPN. It is possible that ENMG underestimates sensory findings due to large variation in sensory measurements in children, but in this study the *baseline* measurement allowed individual assessment of changes in values and improved the reliability of the evaluation.

## 5. Conclusion

Pediatric vincristine-induced polyneuropathy typically presents first with motor symptoms and during early treatment of acute lymphocytic leukemia. Manifestations of neuropathy are difficult to detect by clinical evaluation in pediatric patients. Nerve conduction studies and electromyography are reliable for detecting polyneuropathy and can be done also under general anesthesia.

We recommend that if a child receiving vincristine has decreased lower extremity reflexes and any other symptom suggestive of polyneuropathy, nerve conduction studies should be considered. Reflex testing before vincristine treatment is very useful for follow-up.

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## Author contributions

The authors designed the prospective study. LL designed the electrodiagnostic study protocol / KV and TL designed the clinical outcome measures. KV and LL analyzed the ENMG data. KV performed the clinical examinations. KV and LL performed the statistical analyses. KV drafted the manuscript. All authors contributed to the interpretation of results, critically reviewed the manuscript, and approved the final version to be published.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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