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CLINICAL AND NEUROPHYSIOLOGICAL FEATURES OF VINCRISTINE-INDUCED PERIPHERAL NEUROPATHY IN INDONESIAN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT
Vincristine-induced peripheral neuropathy (VIPN) is a common complication clinical pattern vary across populations, and data from Indonesian children remain limited. Objectives to describe the clinical and nerve conduction study (NCS) features of VIPN in children with ALL treated at a tertiary hospital in Indonesia. We conducted a cross-sectional study of children with ALL receiving chemotherapy recruited consecutively at Mohammad Hoesin Hospital, Palembang, from November 2023 to August 2025. Data were collected from detailed neurological and NCS examinations. Diagnosis of VIPN was made using NCS. Severity was graded using the Common Terminology Criteria for Adverse Events (CTCAE v5.0). Clinical features and NCS findings were evaluated. Comparisons were made between induction and maintenance phases, including the proportions of severity groups, clinical symptoms, individual nerve involvements, number of symptoms and nerves, as well as the type of lesions. A total of 118 children were enrolled; 65 (55.1%) had VIPN by NCS criteria. Neuropathy incidence was similar in induction (56.9%) and maintenance (52.8%) phases (p=0.66). Most cases were CTCAE grade 2–3. Weakness was the most frequent symptom (56.9%), while paresthesia was significantly more common in the induction phase (p=0.008). Peroneal motor nerve involvement was the most frequent NCS abnormality (91.1%), followed by median motor (50.0%) and ulnar nerves (33.7%). The induction phase was characterized by additional upper extremity nerve involvement compared to the maintenance phase, including the median (p=0.004) and ulnar (p=0.025) nerves. Sural sensory nerve abnormalities were significantly more prevalent during the maintenance phases (p=0.002). All cases demonstrated axonal, motor-predominant neuropathy, with no isolated sensory cases. VIPN is highly prevalent among Indonesian children with ALL, with motor-predominant, axonal involvement. The induction phase has more widespread nerve involvement that includes upper extremities, while the maintenance phase has more sensory sural nerve involvement, albeit more likely asymptomatic or milder. Phase-specific patterns suggest distinct pathophysiological mechanisms.

Keywords: ALL children; vincristine; vincristine induced peripheral neuropathy

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, affecting 2 - 4 per 100.000 children annually.(Garniasih et al., 2022; Kaplan, 2019; Wang et al., 2025) Advances in chemotherapy and supportive care have improved survival of children with ALL. Chemotherapy induced peripheral neuropathy is a common side effect in childhood LLA that may negatively impact the quality of life of cancer survivors. Vincristine is one of the main components of

childhood ALL chemotherapy regimen that is often associated with peripheral neuropathy, termed vincristine induced peripheral neuropathy (VIPN). The reported incidence of VIPN varies widely between 4% to 100% depending on population and diagnostic methods.(Gunawan et al., 2023; Lopez-Lopez et al., 2016; Skiles et al., 2018; Uittenboogaard et al., 2022) The reported incidence in Indonesia is between 76,4-100%, which is particularly high.(Gunawan et al., 2023; Tunjungsari et al., 2021)

The manifestations of VIPN can be motor, sensory, or autonomic.(Tay et al., 2022) Diagnosis in children is often difficult because younger patients may have limited ability to report symptoms.(Smolik et al., 2018) Nerve conduction study (NCS) is the gold standard for diagnosing VIPN,(Viinikainen et al., 2024) but its availability is limited in resource-limited settings. Several clinical tools have been developed, such as the Total Neuropathy Score–Pediatric Vincristine (TNS-PV) and the pediatric-modified Total Neuropathy Score (ped-mTNS), which were adapted from adult scales. Unlike adults, who typically exhibit a balance of motor and sensory involvement, most children demonstrate motor-predominant neuropathy, with high variability of symptoms between studies.(Smith et al., 2020). Studies on VIPN in Indonesian children remain limited. NCS-based studies have reported a higher incidence of sensory neuropathy unlike international cohorts.(Gunawan et al., 2023; Tunjungsari et al., 2021) More study on VIPN in Indonesian children is needed to better understand this condition. The current study aimed to describe the clinical and NCS features of children with ALL and VIPN, to obtain more information to improve future diagnostic and management strategies.

METHOD

We conducted a cross-sectional observational study of children with ALL treated at Mohammad Hoesin General Hospital, Palembang recruited consecutively between November 2023 and August 2025. These children received therapy according to the Indonesian National Childhood ALL Protocol 2018 or 2024, which included induction, consolidation, and maintenance phases. The chemotherapy regimen comprised intrathecal and intravenous methotrexate, vincristine, L-asparaginase, 6-mercaptopurine, doxorubicin, prednisolone, and dexamethasone. Vincristine was administered mainly during induction phase (weekly for 4-7 weeks) and maintenance phase (every 8–11 weeks for 95 weeks).(UKK Hematologi Onkologi IDAI, 2018, 2024). Study subjects were all children who underwent chemotherapy in accordance to the prescribed schedule, and completed a neurological and nerve conduction study (NCS) assessments. Neurological assessment included a detailed interview and neurological examination were performed by a senior pediatric resident to detect motor (weakness, foot drop, cramps, decreased reflexes), sensory (pain, paresthesia, tingling, hypesthesia), and autonomic (constipation, diarrhea, abnormal sweating) signs and symptoms.

Demographic and clinical data were recorded. NCS was performed by a pediatric neurologist using a Sierra Easy III System (Cadwell Industries Inc., Kennewick, WA). Motor studies included the median, ulnar, tibial, and deep peroneal nerves; sensory studies included the median and sural nerves. Collected parameters were distal latency, conduction velocity and compound motor action potential (CMAP) amplitude for motor nerves, and peak latency, conduction velocity and sensory nerve action potential (SNAP) amplitude for sensory nerves. Results were compared to normal values based from previous studies (Kang, 2007; Ryan et al., 2019). Peripheral neuropathy was defined as any abnormal NCS parameter, and classified as motor, sensory, or mixed, as well as symptomatic or asymptomatic. Patients were considered neuropathy-free only if all listed studies were completed and normal. If neuropathy was already established (≥1 NCS abnormality), incomplete testing was allowed in cases of difficult venous access or poor cooperation.

Severity was graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0: grade 1, asymptomatic (detected only on examination); grade 2, symptomatic but independent in activities of daily living (ADL); grade 3, severe symptoms limiting ADL; grade 4, life-threatening consequences.(Cancer Therapy Evaluation Program, 2017)

The incidence, classifications, and distribution of VIPN symptoms were described. Clinical and NCS characteristics were compared between induction and maintenance phases. Differences in proportions were tested using chi-square or Fisher's exact test; differences in the number of nerves involved and symptoms per patient were analyzed with the Kruskal–Wallis test. Analyses were conducted with SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL). The study protocol was approved by the Ethics Committee of Mohammad Hoesin General Hospital.

RESULT

A total of 118 children were enrolled during the study period, comprising 65 in the induction phase and 53 in the maintenance phase. Neuropathy, as determined by nerve conduction studies (NCS), was identified in 65 children (55.1%): 37 (56.9%) during induction and 28 (52.8%) during maintenance phases. When only symptomatic cases were considered, the incidence of neuropathy was 41.7%. There was no significant difference in the incidence of neuropathy between the two phases ($p = 0.66$). Demographic and baseline characteristics of the 65 children with VIPN are summarized in table 1.

Table 1.
Demographic and baseline characteristics of the 65 children with VIPN

Characteristics	f (%)
Age (months)	Median 79 (range 18-208) months
Sex	
Boys	39 (60%)
Girls	26 (40%)
Nutritional status	
Underweight	8 (12.3%)
Well nourished	49 (75.4%)
Overweight-Obesity	8 (12.3%)
Risk stratification	
Standard risk	19 (29.2%)
High risk	44 (67.7%)
T cell leukemia	2 (3.1%)
Treatment phase	
Induction	37 (56.9%)
Maintenance	28 (43.1%)
Cumulative vincristine dose (median)	
Induction phase	6 (range 3.2 – 12)mg/m^2
Maintenance phase	40.5 (12 – 54) mg/m^2
CTCAE grading	
Grade 1	23 (35.4%)
Grade 2	29 (44.6%)
Grade 3	13 (20.0%)
Grade 4	-

Most affected children were male and well nourished, with the majority classified as high-risk ALL. Based on CTCAE grading, most children had grade 2 or 3 neuropathy, indicating impairment in daily activities. Considering the entire cohort (including those without neuropathy), the overall incidences of CTCAE grade 1, 2, and 3 neuropathies were 19.5%, 24.6%, and 11%, respectively. Clinical characteristics and NCS findings are presented in Tables 2 and 3. Children in the induction phase tended to have more severe neuropathy, with fewer grade 1 and more grade 2–3 cases, although the difference was not statistically significant. No cases of grade 4 neuropathy were observed. Weakness was the most frequently reported symptom and was more common during the induction phase. Paresthesia and hypoesthesia were also more prevalent in the induction phase, though only paresthesia reached statistical significance. The median number of symptoms per child was 1 (range 1–4), with no significant phase difference (Mann–Whitney U, $p = 0.059$). A higher proportion of children in the maintenance phase were asymptomatic, though again not statistically significant.

Table 2.
The clinical characteristics of 65 ALL children with neuropathy

Characteristics	Total (n=65)	Induction phase (n=37)	Maintenance phase (n=28)	p*
CTCAE grading				
Grade 1	23 (35.4%)	10 (27.0%)	13 (46.4%)	0.208
Grade 2	29 (44.6%)	19 (51.4%)	10 (35.7%)	
Grade 3	13 (20.0%)	8 (21.6%)	5 (17.9%)	
Grade 4	-	-	-	
Clinical symptoms				
Weakness	37 (56.9%)	28 (75.7%)	15 (53.8%)	0.062
Paresthesia	8 (12.3%)	8 (21.6%)	0	0.008
Hypesthesia	4 (6.2%)	4 (10.8%)	0	0.128
Pain	21 (32.3%)	12 (32.4%)	9 (32.1%)	0.980
Cramps	9 (13.8%)	5 (13.5%)	4 (14.3%)	<0.999
Number of symptoms				
None	17 (26.2%)	7 (18.9%)	10 (35.7%)	0.360
1	23 (35.4%)	13 (35.1%)	10 (35.7%)	
2	15 (23.1%)	9 (24.3%)	6 (21.4%)	
3	8 (12.3%)	6 (16.2%)	2 (7.1%)	
4	2 (3.1%)	2 (5.4%)	0	
5-6	0	0	0	

*Induction vs maintenance phase, chi square or Fisher's exact test

Table 3.
Summary of NCS findings of 65 ALL children with neuropathy

Findings	Total	Induction phase	Maintenance phase	p*
Nerves examined (abnormal/total)				
Tibial nerve	37/120 (30.8%)	20/66 (30.3%)	17/54(31.5)	0.889
Peroneal nerve	113/124 (91.1%)	63/68 (92.6%)	50/56 (89.3%)	0.542
Median motor nerve	41/82 (50.0%)	29/45 (64.4%)	12/37 (34.2%)	0.004
Ulnar nerve	28/83 (33.7%)	20/45 (44.4%)	8/38 (21.1%)	0.025
Sural nerve	25/122 (20.5%)	7/68 (10.3%)	18/54 (33.3%)	0.002
Median sensory	4/81 (4.9%)	2/45 (4.4%)	2/36 (5.6%)	>0.999
Number of nerve abnormality per subject				
1	4 (6.2%)	2 (5.4%)	2 (7.1%)	0.057
2	17 (26.2%)	7 (18.9%)	10 (35.7%)	
3	12 (18.5%)	9 (24.3%)	3 (10.7%)	
4	12 (18.5%)	8 (21.6%)	4 (14.3%)	
5	7 (10.5%)	5 (13.5%)	2 (7.1%)	
6	6 (9.2%)	3 (8.1%)	3 (10.7%)	
>6	7 (10.8%)	3 (8.1%)	4 (14.3%)	
Distribution of NCS abnormalities				
One lower extremity	4 (6.2%)	2 (5.4%)	2 (7.1%)	0.154
Bilateral lower extremities	20 (30.8%)	8 (21.6%)	12 (42.8%)	
Bilateral lower and upper extremities	41 (63.1%)	27 (73.0%)	14 (50.0%)	
Motor or sensory nerve involvement				
Motor	53 (81.5%)	33 (89.2%)	20 (71.4%)	0.067
Motor sensory	12 (18.5%)	4 (10.8%)	8 (28.6%)	
Sensory	-	-	-	
Axonal or demyelinating lesion				
Axonal	58 (90.6%)	33 (91.7%)	25 (89.3%)	>0.999
Axonal and demyelinating	6 (9.4%)	3 (8.3%)	3 (10.7%)	
Demyelinating	-	-	-	

* Induction vs maintenance phases, chi square or Fisher's exact test

Based on the NCS results, peroneal motor nerve abnormality was the most frequent finding, followed by median motor nerve involvement. Upper extremity motor nerves (median and ulnar) were more often affected in the induction phase, while sural sensory abnormalities were

significantly more common in maintenance phase. The median number of nerves affected per child was 4 (range 1–8), with no statistically significant difference between phases. Children in the induction phase were more likely to have both upper and lower extremity involvement, whereas in the maintenance phase, involvement was mostly limited to lower extremities. Isolated upper extremity neuropathy was not observed. Motor nerves were involved in all cases, either alone or with concomitant sensory abnormalities. No cases of isolated sensory neuropathy were detected. All patients had axonal lesions, with some also showing demyelinating features; no purely demyelinating neuropathies were found. There was no correlation between the number of symptoms and the number of nerves affected (Spearman's rho, $r = –0.011$, $p = 0.930$), nor between the number of nerve involvements and CTCAE grade (Kruskal–Wallis, $p = 0.252$).

DISCUSSION

Vincristine is one of the main chemotherapeutic drugs in the treatment of childhood ALL. Vincristine induced peripheral neuropathy (VIPN) is one of the most common side effects of vincristine. There are several possible mechanisms of vincristine peripheral neurotoxicity. Vincristine can disrupt axonal transport by its effect on the formation of microtubules. It can also cause mitochondrial damage through its influence on Ca^{2+} homeostasis. Lastly, vincristine may activate an inflammatory process through CXCL12 upregulation.(Starobova & Vetter, 2017; Triarico et al., 2021) Younger age, micronutrient deficiencies, concomitant use of other neurotoxic agents, and higher cumulative vincristine dose may increase the susceptibility to VIPN. Genetic susceptibility is believed to play a significant role. Motor, sensory, and autonomous peripheral nerve systems can all be affected in VIPN.(Tay et al., 2022; Triarico et al., 2021).

The incidence of VIPN in this study was higher than rates reported in many other populations, which ranged between 4% to 30%.(Diouf et al., 2015; Gutierrez-Camino et al., 2016; Skiles et al., 2018; Uittenboogaard et al., 2022) Even when we restricted to only symptomatic cases, which might likely be detected without NCS, the incidence reported by the current study remained higher. Previous Indonesian studies using NCS reported similarly high or higher prevalence, suggesting that Indonesian children may be more vulnerable to VIPN.(Gunawan et al., 2023; Tunjungsari et al., 2021) Methodological differences (clinical vs NCS-based diagnosis, cross-sectional vs longitudinal follow-up) explain some variation,(Smolik et al., 2018; Viinikainen et al., 2024) but the significant differences between populations suggest genetic predispositions may have significant contributions.(Abaji et al., 2018; Diouf et al., 2015; Gutierrez-Camino et al., 2016; Uittenboogaard et al., 2022)

A notable finding in this study was the comparable incidence of VIPN between the induction and maintenance phases. Prior reports in other populations have described more neuropathy in induction (Gutierrez-Camino et al., 2016; Lopez-Lopez et al., 2016) or maintenance phases,(Abaji et al., 2018; Diouf et al., 2015) but not both. These results again suggest possible specific factors, including genetic susceptibility, that may influence vulnerabilities at the different phases of treatment. Most patients in our cohort had milder neuropathy (CTCAE grade 1–2), with grade 3 neuropathy only in 11%. A similar severity distribution was found in other large series.(Abaji et al., 2018; Gutierrez-Camino et al., 2016; Lopez-Lopez et al., 2016) The use of NCS enabled us to detect asymptomatic cases, which were 14.4% in our study. Previous reports have shown a wide range of asymptomatic cases, from 3% to 54%.(Li et al., 2023; Viinikainen et al., 2024) More sensitive clinical detection, thus a lower rate of "asymptomatic" cases, may be associated with several factors, including older age of the children, use of more specialized bedside tools (monofilaments, tuning fork), structured examinations (TNS-PV, ped-mTNS), and using longitudinal instead of cross-sectional observation.(Li et al., 2023; Smolik et al., 2018; Viinikainen et al., 2024). We also observed a trend toward milder neuropathy during the maintenance phase, with a greater proportion of asymptomatic cases, although this did not reach statistical significance.

All children in this study had motor neuropathy, with a small number of children having combined motor and sensory involvement. This finding is similar to the previous reports using NCS. This may be explained by several factors including nerve length, less motor reserve in children, and the immaturity of the neuromuscular system.(Courtemanche et al., 2015; Jeong et al., 2023; Viinikainen et al., 2024) The peroneal motor nerve was the most frequently affected in this study. This finding is consistently found across multiple studies.(Gunawan et al., 2023; Jeong et al., 2023; Madsen et al., 2019) As previously mentioned, vincristine disrupts axonal transport through its effect on microtubules. Longer nerves, including the peroneal motor nerve, require efficient axonal transport due to the long distances, making them more susceptible to vincristine toxicity.(Madsen et al., 2019; Triarico et al., 2021) Interestingly, during the induction phase, we observed more widespread nerve involvement, with significantly more upper extremity motor nerves being affected (median and ulnar), whereas the sural sensory nerve was significantly more affected in the maintenance phase. Induction phase vincristine dosing is more frequent, leading to higher peak exposure and less recovery time. This may drive broader, non-length-dependent injury with more nerve involvement on both upper and lower extremities.(Courtemanche et al., 2015; Jeong et al., 2023; Madsen et al., 2019).

The maintenance phase dosing, though associated with higher cumulative vincristine exposure, is less frequent. This allows partial recovery and results in the more classic length-dependent pattern with predominant lower limb involvement. Dorsal root ganglia of the sensory nerve are especially susceptible to cumulative toxicity due to lack of a protective blood–nerve barrier, particularly through microtubular disruption and mitochondrial dysfunction. This explains the increased sural sensory involvement in the maintenance phase. Clinically, weakness, paresthesia, and hypoesthesia were more common during the induction phase, consistent with more extensive and severe nerve involvement at that stage.(Au et al., 2014; Han & Smith, 2013; Zajaczkowską et al., 2019) By contrast, the greater sensory nerve involvement in the maintenance phase was accompanied by milder, often asymptomatic disease, explaining fewer sensory symptoms found in this study despite more sural nerve involvement on NCS. All of these findings suggest that induction- and maintenance-onset VIPN may represent distinct entities, driven by differing predominant pathophysiological mechanisms (e.g., microtubule disruption vs mitochondrial damage), as suggested by genetic association studies.(Abaji et al., 2018; Diouf et al., 2015; Gutierrez-Camino et al., 2016; Lopez-Lopez et al., 2016).

This study has limitations. First, because baseline assessments were not performed, some cases identified in the maintenance phase may actually represent prolonged induction-phase neuropathy. Second, NCS assessments were occasionally incomplete due to practical barriers (e.g., venous access, child cooperation), the true distribution of nerve involvement may not be accurately represented by the results of this study. Finally, younger children may have difficulties in conveying symptoms, leading to inaccurate assessment of clinical severity and even the onset of neuropathy. Despite these limitations, this study is one of the largest studies that utilized NCS and may provide important insights into VIPN in children with ALL, particularly treatment phase-related differences in clinical and electrophysiological features.

CONCLUSION

In conclusion, similar to previous studies, we found that VIPN is highly prevalent among Indonesian children with ALL. The predominant NCS findings consist of axonal and motor lesions. Differences in the extent of nerve involvements and severity are found between induction and maintenance phases. The induction phase has more widespread nerve involvement that includes upper extremities, while the maintenance phase has more sensory sural nerve involvement, albeit more likely asymptomatic or milder. These phase-specific patterns may be caused by differences in pathophysiological mechanisms.

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