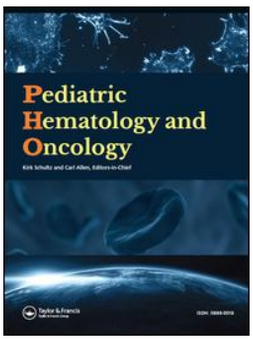

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Incidence of vincristine induced neurotoxicity in children with acute lymphoblastic leukemia and its correlation with nutritional deficiencies

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ABSTRACT

Injection vincristine is an important component of therapy for acute lymphoblastic leukemia (ALL). An important adverse effect of vincristine is neurotoxicity. The incidence of this adverse effect is well studied. The present was undertaken to determine the incidence of vincristine-induced neurotoxicity in children with ALL after the induction of remission phase of chemotherapy and to ascertain its correlation with undernutrition, vitamin B12, folate and iron deficiency. Thirty children (1–18 years) with ALL were enrolled at the commencement of chemotherapy. The electrophysiological evaluation was done at baseline and repeated after four doses of vincristine (1.5 mg/m^2/dose). Clinical evaluation was done regularly. Anthropometry and serum B12, folate and ferritin levels were assessed at baseline. Twelve children over a 4-week period of observation had peripheral neuropathy clinically. The autonomic system was most commonly involved followed by motor and sensory system respectively. On electrophysiological testing, half of the patients had evidence of neuropathy. Micronutrient deficiencies were present in a significant number of patients—63.3% had a B12 deficiency, 20% were deficient in folate and 43.3% in iron. The incidence of vincristine-induced neuropathy in patients with/without these micro-nutrient deficiencies was not statistically significantly different. Vincristine-induced neuropathy is common in Indian children with ALL. The present study did not find any correlation between the occurrences of vincristine-induced neuropathy and nutritional deficiencies. Larger studies are warranted to evaluate the contribution of micronutrient deficiencies to the development of peripheral neuropathy in childhood ALL.

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Introduction

Leukemia is the most frequent cancer in children. It constitutes approximately one-third of cancers in children and 10% in adolescents.[1] Survival in acute lymphoblastic

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leukemia (ALL) has improved over the last few decades. This has been attributed to the utilization of risk-adapted therapy, better combination chemotherapy regimens, effective central nervous system (CNS) prophylaxis, post induction intensification of chemotherapy and improved supportive care.[2] The improved survival, however, comes with the price of chemotherapy-induced toxicity and the nervous system is frequently the target of toxicity.

Treatment of childhood ALL involves a minimum of 2 years of chemotherapy with multiple administrations of vincristine, a neurotoxic drug. Chemotherapy-induced peripheral neuropathy is the most important dose-limiting toxicity of vincristine. Chemotherapy-induced peripheral neuropathy manifests as tingling, numbness, difficulty in walking, jaw pain, constipation, urinary retention, or paralytic ileus.[3] Patients with preexisting neuropathy can develop life-threatening paralysis, even with low doses of vincristine.[4] In western countries, the pattern of vincristine-induced neuropathy varied from no dose-limiting toxicity, mild axonal neuropathy (on nerve conduction study), or isolated fine motor abnormalities.[5,6]. However, there is a paucity of data on the incidence of vincristine-induced neuropathy in India. Given the high incidence of undernutrition in India and possible concomitant micronutrient deficiencies, the incidence of vincristine-induced neuropathy could be higher than in the western countries. The present study is a prospective study to determine the incidence of neuropathy in patients with Acute Lymphoblastic Leukemia (ALL) after completion of induction of remission phase and to correlate its incidence with undernutrition, vitamin B12, folate and iron deficiency.

Materials and methods

The study was a prospective observational study carried out over a period of 2 years at the Hematology ward, at a children hospital in North India. All new diagnosed cases of ALL, aged (1–18 years) were eligible if they did not have the following exclusion criteria, which included-overt CNS disease or CSF status 3 at the time of diagnosis (clinical signs and symptoms or >5 WBCs/mm^3 with detectable blasts in CSF), preexisting neurological disease, co-infection with HIV and not consenting to participate. At baseline, anthropometry was performed and weight for age and BMI were calculated and compared to WHO standards.[7] The serum sample for vitamin B12, folate and ferritin levels were taken before commencement of chemotherapy. Serum Ferritin was measured using Enzyme-linked Immunosorbent Assay (ELISA) (Calbiotech). Serum B12 and folate were measured using automated chemiluminescent immunoassay (Beckman Coulter Access-2). Under-nutrition as defined by weight for age less than 3rd centile for children <5 years and BMI for age less than 5th centile for children aged ≥ 5 years. Iron deficiency was taken as ferritin <10 ng/ml. Vitamin B12 deficiency was defined as levels below 200 pg/ml and folate deficiency was defined as levels below 5 ng/ml.[8] At baseline, electrophysiological studies were also performed using a Cadwell Sierra II electromyography unit. The test was done in bilateral median, sural and common peroneal nerves at baseline.

During the induction of remission phase, the children received four doses of vincristine in the dosage of 1.5 mg/m^2 (maximum dose per injection—2.0 mg). They did not receive any other neurotoxic drug during this period. Neurological evaluation was done

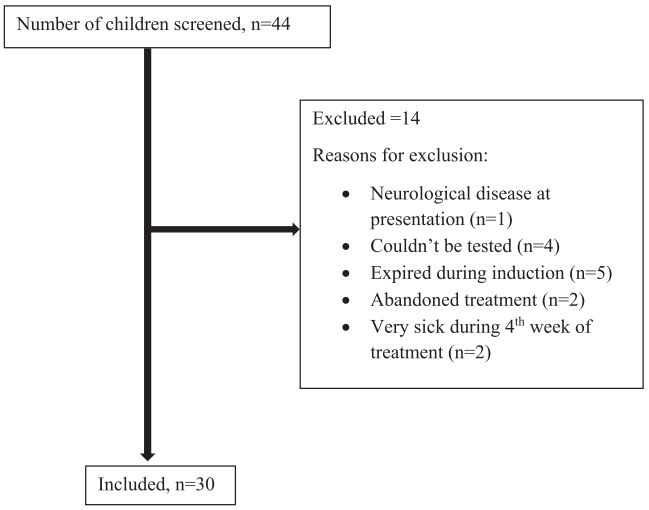

Figure 1. Flow of patients in the study.

regularly to look for symptoms and signs suggestive of neuropathy. The electrophysiological studies were done after completion of induction of remission phase of chemotherapy and compared to baseline. Subsequently, reduced total neuropathy score (rTNSr) score was calculated for more accurate assessment and quantification of peripheral neuropathy in the study population.[9] The institutional ethical committee approved the study.

Statistical analysis

All data analysis was performed using Statistical Package for the Social Sciences (SPSS) (version 14.0) for windows. The incidence of electrophysiologically defined peripheral neuropathy and as per TNSr, was calculated in percentage. The baseline characteristics were compared between the children with and without electrophysiologically defined neuropathy to look for associations. The continuous variables were compared using "*t*-test" (for normally distributed data). The skewed data were analyzed by the Wilcoxon rank-sum test. The categorical data were analyzed using the chi-square test. The statistical significance was considered at $p < 0.05$.

Results

Forty-four children met the eligibility criteria—14 were excluded from statistical analysis for reasons listed in Figure 1—predominantly because of the inability to do follow up electroneurologic testing. Twenty-eight (93.3%) had B-cell ALL (Pre-B or Pro-B), and remaining two (6.7%) had T-cell phenotype. Of the children screened during study period, 30 children (M:F = 3.3:1), with mean age at the time of diagnosis of 5.1 ± 2.7 years were included in the study. Twenty-eight (93.3%) had B-cell (Pre-B or Pro-B), remaining (6.7%) had T-cell phenotype. The baseline characteristics of the study population have been described in Table 1. Twelve children over a 4-week period of observation had peripheral neuropathy clinically (Figure 2). All the three systems—

Table 1. Baseline characteristics of the study population ($n = 30$).

Baseline characteristic	Value
Blood counts at diagnosis:	Mean/Median (SD/IQR):
– Hemoglobin (g/dL)	6.4 (2.5)
– Total leukocyte count (mm^3) (median)	24,750 (IQR 7390–692000)
– Platelet count (mm^3) (median)	23,500 (IQR 14,000–46,000)
Severe anemia (<7 g%)	18 (60%)
Hyperleukocytosis (>100,000 cells/mm^3)	7 (23.3%)
Thrombocytopenia (<100,000 cells/mm^3)	26 (86.7%)
CNS Leukemia (by CSF examination)	None
Undernutrition*	14 (46.7%)

*Weight for age <3rd centile for children less than 5 years old; BMI <5th centile for children aged 5 years or more.

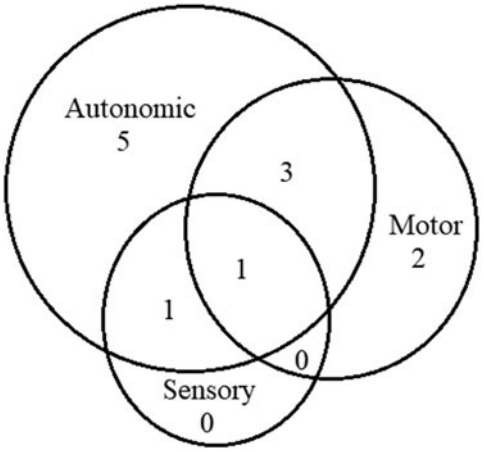

Figure 2. Distribution of symptoms based on system. ($n = 12$).

sensory, motor, and autonomic—were involved, autonomic system being the most common. Constipation was present in 26.7% children. One child developed orthostatic hypotension. Seven children (23.3%) had depressed ankle jerks. Two children reported sensory symptoms. None of the children had any cranial nerve deficit. On electrophysiological testing, fifteen children (50%) were found to have neuropathy. All the affected children had axonal neuropathy (reduced Compound Motor Action Potential and normal conduction velocities & distal latencies). The incidence of peripheral neuropathy as detected by TNSr score ≥ 1, was 56.7% (17/30). The TNSr ranged from 1 to 12 (Mean 2.53). Abnormal scores were obtained in five items—peroneal amplitude (15/30), tendon reflexes (7/30), motor symptoms (3/30), strength (3/30), and sensory symptoms (2/30). Pin sensibility, vibration sensibility and sural amplitude was normal in all subjects. The evaluation of peripheral neuropathy is summarized in Table 2.

Substantial number of children had undernutrition and micronutrient deficiencies at baseline. Almost half of the children (46.7%; 14/30) had under nutrition as per WHO standards of weight for age or BMI. The study had found no difference in incidence of vincristine-induced neuropathy in children with undernutrition ($n = 7$) and without undernutrition ($n = 8$). There was no correlation of presence of undernutrition with the development of neuropathy ($p = 1.0$). There was difference in levels of vitamin B12 in children with and without neuropathy [185.7(56.5) pg/mL vs. 196.7(66.7) pg/mL;

Table 2. Evaluation of peripheral neuropathy.

Clinical characteristics	*N* (%)
Motor symptoms/signs ($n = 30$)	7 (23.3%)
• Weakness	3 (10%)
• Depressed ankle jerks	7 (23.3%)
Sensory symptoms/signs ($n = 30$)	2 (6.7%)
• Tingling/numbness	2 (6.7%)
• Sensory deficit	None
Autonomic symptoms/signs ($n = 30$)	9 (30%)
• Constipation	8 (26.7%)
• Postural hypotension	1 (3%)
• Others	None
Cranial neuropathy	None
Electrophysiological characteristics	
Incidence of peripheral neuropathy electrophysiologically	15 (50%)
Type of neuropathy ($n = 15$)	15 (100%)
• Axonal	0
• Demyelinating	
Fiber involvement (n = 15)	15 (100%)
• Motor	0
• Sensory	
Number of nerves involved per affected child ($n = 15$)	1.46 (mean)
Number of children with a single nerve involvement	8
Number of children with two nerves involved	7
Specific nerves involved ($n = 30$)	15 (50%)
• Common peroneal	7 (23.3%)
• Median motor	0
• Sural	0
• Median sensory	
Incidence of neuropathy as per TNSr	17 (56.67%)
Mean TNSr score in children with neuropathy ($n = 17$)	2.53 (range 1–12)

$p = 0.63$] (Mean (SD)). The folate levels also did not show significant difference in two groups [8.6 (3.2) ng/mL vs. 9.5 (3.0) ng/mL; $p = 0.44$] (Mean (SD)). The median serum ferritin levels in children with and without neuropathy were not significantly different [98.8 (9.8–132.7) ng/mL vs. 14.7 (7.0–141.5) ng/mL)] (Median (interquartile range)). We also analyzed the incidence of vincristine-induced neuropathy in patients with/without these micro-nutrient deficiencies and the difference was not statistically significant.

Discussion

The incidence and burden of vincristine-induced neuropathy have been poorly documented in childhood ALL patients. Small sample sizes, limited clinical neurological evaluation, insufficient electrophysiological data and most importantly, retrospective nature of studies are a few of the drawbacks of the previously done studies.

In the present study, on history and clinical examination, 40% (12/30) children had peripheral neuropathy. The autonomic system was most commonly involved followed by motor and sensory system respectively. Previous studies have also shown that close to one-third of patients receiving vincristine develop symptoms involving autonomic nervous system dysfunction in the form of constipation, paralytic ileus, urinary retention or erectile dysfunction.[10,11] Autonomic involvement is commoner because these fibers are poorly myelinated and thus more vulnerable. Seven children (23.3%) had motor system involvement in the form of depressed ankle jerks. Of these, three children

(10%) also had difficulty in walking and motor examination was suggestive of distal muscle weakness in lower limbs. One child had so severe paresis that further doses of vincristine had to be withheld. These observations are consistent with the fact that ankle jerks vanish early in the course of neuropathy and distal muscle weakness occurs only in advanced stages of vincristine-induced neuropathy. Harila-Saari et al have reported the clinical signs of nerve injury such as depressed deep tendon in approximately 33% of patients receiving vincristine.[5] Similarly, Pal et al have reported an 18.7% incidence of motor abnormalities in patients who received vincristine.[12] In the literature, 30–75% of patients treated with vincristine reported paresthesias and distally predominant numbness.[12–14] In the present study, surprisingly, only two children reported neuropathic symptoms. These symptoms were mild and not disabling. This low incidence of sensory symptoms in our study may be due to the inability of young children to report these symptoms. On electrophysiological testing, half of the patients had neuropathy. Brigo et al in a study of 17 children with ALL, reported a 23.5% incidence of vincristine-induced neuropathy.[15] Studies done in India, however, have reported a similar or even higher incidence of vincristine-induced neuropathy. Gomber et al have reported 71.4% incidence of electrophysiologically defined neuropathy in children with ALL.[16] Pal et al have reported 46.7% incidence of electrophysiological abnormalities in lymphoma patients who received vincristine.[12] While our study cohort did not demonstrate any association between vincristine-induced neuropathy and nutritional deficiencies, our evaluation of potential nutritional deficiencies was not comprehensive. Also, the difference in expression of CYP3A5 enzyme (which metabolizes vincristine) among Indian children may also be responsible for the difference of incidence of neurotoxicity. It is known that expression of CYP3A5 enzyme varies considerably with race, with low expression having a higher incidence of vincristine-induced neurotoxicity.[17] Also, all electro-physiologically affected children had motor neuropathy. The evaluation of sensory nerves was normal in all the children. VCR is known to cause mixed sensory-motor neuropathy. Two children (2/37) had depressed median nerve SNAPs in the study by Ramchandren et al[13] This study showed that there is relative sparing of sensory nerves, both clinically and electrophysiologically in Indian children, although the reasons for the same are not clear. Common peroneal nerve was the most commonly affected nerve (15/30; 50%) followed by the median motor nerve (7/30; 23.3%). Similar, results have been reported by Ramchandren et al.[13]

Children with cancer are particularly vulnerable to undernutrition because of poor oral intake due to loss of appetite, nausea, and vomiting. At the same time, these children exhibit elevated substrate needs due to the disease. This problem may be of major concern in resource-poor countries like India where the incidence of undernutrition in general population is already very high. Moulik et al conducted a study to examine the prevalence of pretreatment malnutrition, hypoalbuminemia, folate and B12 deficiency in Indian children with ALL. They observed baseline malnutrition in 66%, hypoalbuminemia in 28%, folate deficiency in 38% and B12 deficiency in 34% children with ALL.[18]

Since the optimal functioning of nerves is dependent on a constant supply of macro- and micro-nutrients, we had hypothesized that the incidence of neuropathy would be more in children who have co-existing nutritional deficiencies. However, no significant difference was found in the incidence of neuropathy in children with or without these

nutritional deficiencies. The current study had inadequate power to detect this correlation. The expression status of CYP3A5 enzyme and serum albumin levels in this cohort were not evaluated. The use of ferritin to assess iron deficiency at the time of diagnosis of ALL is fraught with potential error due to the fact that ferritin is an acute phase reactant, hence falsely elevated ferritin levels may be observed. Thus, other indices for iron deficiency evaluation must be concomitantly evaluated. Larger studies with adequate power are warranted to evaluate the contribution of micronutrient deficiencies to the development of peripheral neuropathy in childhood ALL.

Notes on contributors

Conceptualization: JC; Methodology: JC, SD; Data Acquisition & Interpretation: SD, SS, PJ, SS, AJ, SA, JC; Supervision: JC, SA; and Writing, Review & Editing: SD, SG, JC.

Declaration of interest

The authors declare that they have no competing interests.

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