www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i8.193

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Study of Neurological Manifestations in Hematolymphoid Neoplasms in A Tertiary Care Hospital In Eastern India

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Abstract
Objectives: *In the current study, we proposed to investigate neurological manifestations in patients with hematolymphoid neoplasms in a tertiary care centre in Kolkata*
Materials and Methods: *This was a prospective observational study from 1st February 2013 to 31st January 2015 among newly diagnosed 194 consecutive eligible cases of hematolymphoid neoplasms attending Institute of Hematology and Transfusion Medicine and/or Department of Neurology, Medical College and Hospital, Kolkata. All the patients were subjected to detailed clinical, biochemical, electrophysiological and radiological investigations.*
Results and Analysis: *Overall 22% of total patients of hematolymphoid neoplasms with neurological manifestations had NM at presentation. 28%, 15% & 22% of patients with myeloma, leukemia, and lymphoma respectively had NM at presentation of their HN. Therapy related causes were more (78.8% of patients with neurological manifestations had therapy related complications) than directly disease related causes (28.8%) & indirectly disease related causes (24%). Various neurological manifestations were noted. Most common neurological manifestation in all groups was peripheral neuropathy (40% of total 194 patients). 58.5%, 33.3%, 27.5% of patients with myeloma, leukemia, lymphoma respectively developed neuropathy.*
Conclusion: *Hematolymphoid neoplasms affect both the central and peripheral nervous system and their manifestations can be varied. Most of the patients develop neurological manifestations only during and after therapy. Some patients also have neurological manifestations at presentation and these may be the sole presentation. Therapy leads to more neurological complications than other causes in patients with hematolymphoid neoplasms. Peripheral neuropathy is the commonest neurological manifestation in all groups and shows temporal relationship with therapy.*
Keywords: *hematolymphoid neoplasms, myeloma, leukemia, lymphoma, Peripheral neuropathy.*

Introduction

Hematolymphoid neoplasms or tumors of the hematopoietic and lymphoid tissues or haematopoietic and lymphoid malignancies are tumors that affect blood, bone marrow, and lymph nodes[1,2]. Hematolymphoid neoplasms like leukemia, lymphoma, plasma cell dyscrasias, can affect central and peripheral nervous systems in a

number of different ways, producing a wide range of neurological disturbances. These neurological manifestations are common in different hematolymphoid neoplasms leading to therapeutic challenges in many situations. Neurological symptoms may be caused by disease itself directly/indirectly or may be consequence of therapeutic side effects[3,4]. Nowadays relatively high survival rate among patients with hematolymphoid neoplasm has focused more interest on the side-effects of the therapy and the possible development of long-term sequel particularly neurological ones. In our country large scale study data regarding this field are not available. Hence this study was undertaken in patients attending a tertiary health care centre in Kolkata to investigate neurological manifestations in hematolymphoid neoplasms.

Aims and Objectives

In the current study, we proposed to investigate neurological manifestations in patients with hematolymphoid neoplasms in a tertiary care centre in Kolkata and set out to explore the incidence and distribution of neurological manifestations at presentation and during initial intensive management of neoplasms, and to determine causes of neurological disorder.

Materials and Methods

This was a prospective observational study from 1st February 2013 to 31st January 2015 among newly diagnosed 194 consecutive eligible cases of hematolymphoid neoplasms attending Institute of Hematology and Transfusion Medicine, Medical College and Hospital, Kolkata and/or Department of Neurology, Medical College and Hospital, Kolkata. The study variables were incidence and distribution of neurological manifestations and causes of neurological disorders – disease related, therapy related, unrelated to these. We included only clinically and laboratory confirmed cases of hematolymphoid neoplasms of either sex and aged between 2- 70 years and followed for 6 months.

A pre-tested questionnaire was served to the chosen patients. Detailed histories of the patients were taken and a thorough clinical examination was done as per protocol and the findings were noted. Patient's history taking& clinical examination were done at presentation, at 1 month, at 3 months and 6 months after presentation.

Relevant blood tests (haemoglobin, total count of leukocytes, differential count of leukocytes, platelet count, metabolic profile), Serum M-protein (where indicated), 24 hours urinary M-protein (where indicated), bone marrow examination, CSF study were done at our centre at 0, 1, 3 and 6 months. Nerve conduction study of all 4 limbs were done in RMS NCS machine & Electroencephalography and relevant neuro-imaging studies which included X-ray skull, Computed tomography scan of brain, Magnetic resonance imaging of brain and Magnetic resonance imaging of spine (1.5 tesla) were also done for each participant.

Results and Analysis

Total numbers of patients with hematolymphoid neoplasms (HN) recruited and followed up for 6 months in our study were 194. Among them neurological manifestations (NM) were seen in 104 (54%) cases. During study period total drop out cases were 37, number of death were 19. Those cases were excluded from study population. Among 194 cases, patients with plasma cell dyscrasias/myeloma were 65, patients with leukemia were 78 and patients with lymphoma were 51. 47 (72.3%) patients with myeloma, 34(43.5%) patients with leukemia, and 23 (45%) patients with lymphoma developed NM. Among 104 patients with NM, myeloma, leukemia, lymphoma constituted 45%, 33%, 22% respectively. Among 47 Myeloma patients with NM, 32 were male, female were 15. In 34 leukemia patients with NM, male were 20, female were 14. In 23 lymphoma patients with NM, male were 13, rest 10 were female. (Table 1)

Table 1 Sex distribution of the patients of Hematolymphoid neoplasms with neurological manifestations

Hematolymphoid neoplasms	Total patients recruited & followed up-194(100%)			Patients with neurological manifestations-104(54%)			
	Male	Female	Total	Male	Female	Total	%
Myeloma	38	27	65(45%)	32	15	47	72.3
Leukemia	49	29	78(33%)	20	14	34	43.5
Lymphoma	27	24	51(22%)	13	10	23	45

Regarding age group distribution of 104 patients with NM, major age group were 40- 59 yrs (35%), followed by 20-39 yrs (23%),<20 yrs &>60 yrs (21% each). Among patients with neurological manifestations(104), majority developed NM only during/after therapy (78%), followed by both at presentation and during/after therapy (16%), 6% of patients had NM during presentation without further features of new NM during follow up period. Overall 22% of total patients of hematolymphoid neoplasms with neurological manifestations had NM at presentation. 28%, 15% & 22% of patients with myeloma, leukemia, and lymphoma respectively had NM at presentation of their HN.

Regarding presumed etiological background of neurological manifestations, therapy related causes were more (78.8% of patients with neurological manifestations had therapy related complications) than directly disease related causes (28.8%) & indirectly disease related causes (24%). Myeloma, leukemia, lymphoma- in all groups, therapy related causes (83%, 85.3%, 60.9% of patients with neurological manifestations respectively) were more than directly disease related (31.9%, 26.5%, 26.1% of patients with neurological manifestations respectively)& indirectly disease related (14.9%, 26.5%, 39.1% of patients with neurological manifestations respectively)causes.

Among total patients with myeloma (65), neurological manifestations seen were 38(58.4%) peripheral neuropathy, 10(15.4%) spinal-cord compression, 4(6%) myopathy, 2(3%) metabolic encephalopathy, 2(3%) seizures, 2(3%) osteo-dural plasmacytoma leading to headache, 1(1.5%) stroke, 1(1.5%) cerebral venous sinus thrombosis , 1(1.5%) papilloedema.

Among 38 (58.4%) patients with peripheral neuropathy 1(1.5%) patient had demyelinating neuropathy, 2(3%) patients had carpal tunnel syndrome and rest 35 (53.8%) had length dependant axonal neuropathy. All myopathies (6%) were steroid induced. Among 2(3%) patients with metabolic encephalopathy, one had hyponatremia, rest had hypercalcemia. 2(3%) patients with seizure had generalised tonic clonic seizure. Spinal-cord compression only at presentation was seen in 9(13.8%) cases. (Table 2).

Table-2 Neurological manifestations of myeloma

Neurological manifestation of myeloma (n=65)	Frequency		
	At presentation	During/after therapy	Total
Spinal cord compression/ myeloradiculopathy	9(13.8%)	1(1.5%)	10(15.4%)
Osteo-dural plasmacytoma causing headache	2(3%)	0	2(3%)
Stroke	1(1.5%)	0	1(1.5%)
Cerebral venous sinus thrombosis	0	1(1.5%)	1(1.5%)
Papilledema	0	1(1.5%)	1(1.5%)
Metabolic encephalopathy	0	2(3%)	2(3%)
Seizures	0	2(3%)	2(3%)
Axonal neuropathy	0	35(53.8%)	35(53.8%)
Demyelinating neuropathy	1(1.5%)	0	1(1.5%)
Carpal tunnel syndrome	0	2(3%)	2(3%)
Myopathy	0	4(6%)	4(6%)

Among total patients with leukemia (78), neurological manifestations were 26(33.3%) peripheral neuropathy (length dependant axonal neuropathy), 7(8.9%) infection related meningitis, 4(5.1%) intracranial hemorrhage, 4(5.1%) leukemic meningitis, 3(3.8%) myopathy, 2(2.5%) metabolic encephalopathy, 1(1.3%) leukemic restrictive ophthalmopathy. All myopathies (3.8%) were steroid induced. Among 7 (8.9%) infection related meningitis cases 2 patients had viral meningitis, 2 patients had fungal meningitis, and rest 3 had pyogenic meningitis. Among 2 (2.5%) patients with metabolic encephalopathy both had hyponatremia. Two patients with acute promyelocytic leukemia had intracranial hemorrhage at presentation of their HN and during /after therapy one patient with acute myeloid

leukemia and one patient with acute promyelocytic leukemia had intracranial hemorrhage. One patient with acute myeloid leukemia had leukemic restrictive ophthalmopathy at presentation of his HN. (Table 3).

Table-3 Neurological manifestations of leukemia

Neurological manifestations of leukemia(n=78)	Frequency		
	At presentation	During/after therapy	Total
Intracranial hemorrhage	2(2.5%)	2(2.5%)	4(5.1%)
Metabolic encephalopathy	1(1.3%)	1(1.3%)	2(2.5%)
Leukemic meningitis	1(1.3%)	3(3.8%)	4(5.1%)
Restrictive ophthalmopathy	1(1.3%)	0	1(1.3%)
Infection related meningitis	0	7(8.9%)	7(8.9%)
Peripheral neuropathy	0	26(33.3%)	26(33.3%)
Myopathy	0	3(3.8%)	3(3.8%)

Among total patients with lymphoma (51), neurological manifestations seen were 14(27.5%) peripheral neuropathy (length dependant axonal neuropathy), 5(9.8%) infection related meningitis, 3(5.9%) spinal cord/cauda equina compression, 3(5.9%) transient ischemic attacks/cerebral infarcts, 2(3.9%) metastatic intracranial disease, 1(1.9%) leptomeningeal metastases, 1(1.9%) paraneoplastic disorders. 1(1.9%) patient of Non–Hodgkin's lymphoma at presentation of HN had metastatic intracranial disease. Another patient (1.9%) of Non–Hodgkin's lymphoma had epidural metastases causing spinal cord compression at presentation. Among 5(9.8%) infection related meningitis cases, 2 patients had viral meningitis & rest 3 had pyogenic meningitis. 1(1.9%) patient with Hodgkin's disease had paraneoplastic cerebellar degeneration, manifested as subacute onset truncal and appendicular ataxia, dysarthria and bilateral gaze evoked nystagmus. (Table 4).

Table- 4 Neurological manifestations of lymphoma

Neurological manifestations of lymphoma (n=51)	Frequency		
	At presentation	During/after therapy	Total
Metastatic intracranial disease	1(1.9%)	1(1.9%)	2(3.9%)
Spinal cord/cauda equina compression due to epidural metastasis	1(1.9%)	2(3.9%)	3(5.9%)
Leptomeningeal mets	0	1(1.9%)	1(1.9%)
Paraneoplastic	0	1(1.9%)	1(1.9%)
Infection related meningitis	0	9(5.8%)	9(5.8%)
TIA/infarcts	0	3(5.9%)	3(5.9%)
Peripheral neuropathy(axonal)	0	14(27.5%)	14(27.5%)

Most common neurological manifestation in all groups was peripheral neuropathy (40% of total 194 patients). 58.5%, 33.3%, 27.5% of patients with myeloma, leukemia, lymphoma respectively developed neuropathy. Among neuropathies (78), sensory axonal 52%, sensory-motor axonal 44%, entrapment 3%, demyelinating 1% were noted.

Presumed therapy induced peripheral neuropathy were seen in 38.7% (75) patients. Bortezomib +Thalidomide induced neuropathy were seen in 66.67 %(24), Bortezomib +Lenalidomide induced neuropathy were in 37.9 %(11), Vincristine induced neuropathy were seen in 39.6 %(40) of patients who received above mentioned chemotherapy. (Table-5)

Table-5 Drugs causing neuropathy

Drugs	Frequency		
	Received	Neuropathy detected	%
Bortezomib +Thalidomide	36	24	66.67
Bortezomib+Lenalidomide	29	11	37.9
Vincristine	101	40	39.6

Discussion

Assessment of neurological manifestations (NM) in patients with hematolymphoid neoplasms (HN) are subject of interest of clinicians, research scholars across the world. In our study, we have included all types of hematolymphoid neoplasms - plasma cell dyscrasias /myeloma, leukemia and lymphoma and assessed neurological manifestations among them.

We have found 54% of patients with HN had NM in 6 months follow up. 72.3% patients with myeloma, 43.5% patients with leukemia, 45% patients with lymphoma developed NM. Among 104 patients with NM, myeloma, leukemia, lymphoma constituted 45%, 33%, 22% respectively. So we have seen patients of myeloma had higher incidence of NM in comparison to lymphoma & leukemia. We have found most of the patient's neurological manifestations developed only during/after therapy (78%), while 6% had only at presentation of their HN. Results were similar in all neoplasms. We have observed that 28%, 15% & 22% of patients with myeloma, leukemia, and lymphoma

respectively had NM at presentation of their HN. Overall 22% of total patients with Hematolymphoid neoplasms developed NM at presentation. Hence patients may present with NM only.

As per etiology is concerned, we have observed therapy related causes were most significant contributor (78.8%) than directly disease related (28.8%) and indirectly disease related (24%) causes in all patients with HN. Myeloma, leukemia, lymphoma-in all groups, therapy related causes were more (83%, 85.3%, 60.9% of patients with neurological manifestations respectively) than directly disease related (31.9%, 26.5%, 26.1% of patients with neurological manifestations respectively) and indirectly disease related (14.9%, 26.5%, 39.1% of patients with neurological manifestations respectively) causes.

Among total patients with myeloma, we have observed peripheral neuropathy was most common neurological manifestation (58.4%). According to Malhotra P et al, peripheral neuropathy is present at diagnosis in approximately 12 % of patients, and up to 50–62 % of MM patients present with subclinical neuropathy when exhaustive neurologic examination and nerve conduction studies are performed [5]. In our study, we have seen 1.5% of patients presented with peripheral neuropathy. 53.8% patients with myeloma had length dependant axonal neuropathy during/after therapy. Sonneveld P et al described that up to 50% of patients with plasma-cell dyscrasia having peripheral neuropathy[6]. This study result is similar to our findings. All myopathies (6%) were steroid induced (developed during/after therapy) in our study. Development of myopathy presumed to be due to steroid containing regimen (Bortezomib +Thalidomide + Dexamethasone) in our study. Anderson H et al[(7)] study revealed 8 % incidence of steroid myopathy in high-dose dexamethasone schedules, as with the classical VAD protocol (vincristine, adriamycin, and dexamethasone).

Among patients with leukemia, we have observed peripheral neuropathy was most common neurological manifestation (33.3%) in our study. The most common peripheral neuropathy that occurs in leukemic patients is a length dependent axonal sensorimotor neuropathy caused by vinca alkaloids as reported in several studies [(8)]. In our study, peripheral neuropathy (axonal) developed in 33.3% cases during/ after therapy presumed to be related to therapy. Among patients with lymphoma, we have observed peripheral neuropathy (Length dependant axonal neuropathy) was most common neurological manifestation (27.5%) in our study.

In our study, we have found 5.9% of patients with lymphoma had spinal cord/cauda equina compression. This finding was similar to retrospective review by Wood and Coltman[9]. We have observed peripheral neuropathy was the most common neurological manifestation in all groups of hematolymphoid neoplasms (40%). 58.5%, 33.3%, 27.5% of patients with myeloma, leukemia, lymphoma respectively developed neuropathy. Among neuropathies (78), 52% sensory axonal, 44% sensory-motor axonal, 3% entrapment, 1% demyelinating neuropathy was noted.

In our study, we have observed that 66.67% of patients receiving Bortezomib + Thalidomide, 37.9% of patients receiving Bortezomib +Lenalidomide and 39.6% of patients receiving Vincristine developed length dependant axonal neuropathy during/after therapy. A systematic review of thalidomide monotherapy in relapsed multiple myeloma reported an overall peripheral neuropathy (PN) incidence of 12% to 44%[10]. Thalidomide combined with dexamethasone in relapsed/refractory multiple myeloma is associated with a slightly lower overall PN incidence of 27% in some studies [10,11]. Rajkumar SV et al, in their study reported incidence thalidomide induced neuropathy of grades 2 and 4 are up to 31% with TAD regimen (thalidomide/ adriamycin / dexamethasone) [12]. In our study, patients of Myeloma received Bortezomib + Thalidomide +Dexamethasone regimen instead of Thalidomide + Dexamethasone regimen, which

might be responsible for high occurrence of drug induced neuropathy in our study in comparison to above mentioned study.

In our study, prevalence of Bortezomib +Thalidomide induced neuropathy was more than Bortezomib +Lenalidomide induced neuropathy (66.67% vs 37.9%). Large clinical trials with lenalidomide in relapsed/refractory multiple myeloma have shown a significant reduced overall incidence of PN compared with thalidomide by Dimopoulos M et al[13]. Peripheral neuropathy is the main non-haematological dose-limiting side effect of bortezomib, thalidomide, and vincristine, which may impair the quality of life of myeloma patients observed in different study reports[14]. Bortezomib induced neuropathy was observed in 37% cases in several studies [14, 15,16]

Conclusion

Neurological manifestations are quite common in hematolymphoid neoplasms. Of these patients with myeloma more commonly develop neurological manifestations. Hematolymphoid neoplasms affect both the central and peripheral nervous system and their manifestations can be varied. Most of the patients develop neurological manifestations only during and after therapy. Some patients with hematolymphoid neoplasms also have neurological manifestations at presentation and these may be the sole presentation. Therapy leads to more neurological complications than other causes in patients with hematolymphoid neoplasms. Peripheral neuro-pathy is the commonest neurological manifesta-tion in all groups and shows temporal relationship with therapy. Anti Myeloma drugs Bortezomib and Thalidomide are commonly associated with peripheral neuropathy which might sometimes lead to discontinuation of their use.

Familiarity with the various neurologic disorders related to hematolymphoid neoplasms is critical to make the correct diagnosis and institute early and appropriate treatment. Early diagnosis and treatment of neurological complications can prevent disabling outcomes in many cases.

Financial support and sponsorship

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest

All contributors receive salary from Government and nobody is getting any financial assistance from any commercial agencies. Thus, we declare that there is no competing interest involved in this study.

References

1. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood.2009 Jul 30; 114(5):937-51.
2. World Cancer Report 2014. World Health Organization. 2014. pp. Chapter 5.13.
3. Martin, H.E., and Courville, C.B.: Hodgkin's Disease With Involvement of the Cranial Dura Mater , Bull Los Angeles Neurol Soc 1:145.
4. Winkelmann, N.W., and Moore, T.M.: Lymphogranulomatosis (Hodgkin's Disease of the Nervous System) , Arch Neurol Psychiat 45:304.
5. Malhotra P, Choudhary PP, Lal V, et al. Prevalence of peripheral neuropathy in multiple myeloma at initial diagnosis. Leuk Lymphoma 2011; 52: 2135–8.
6. Sonneveld P, Jongen JL. Dealing with neuropathy in plasma-cell dyscrasias. Hematology Am Soc Hematol Educ Program 2010: 423–430.
7. Anderson H, Scarffe JH, Lambert M, et al. VAD chemotherapy – toxicity and efficacy – in patients with multiple myeloma and

other lymphoid malignancies. Hematol Oncol 1987; 5: 213–222.

8. Lavoie Smith EM, Li L, Hutchinson RJ, Ho R, Burnette WB, Wells E, Bridges C, Renbarger J. Measuring vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia. Cancer Nurs. 2013 Sep-Oct;36(5):E49-60.
9. Wood NL, Coltman CA. Localized primary extranodal Hodgkin's disease. Annals of Internal Medicine. 1973;78 (1):113–118.
10. Glasmacher A, Hahn C, Hoffmann F, et al. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. Br J Haematol. 2006 Mar;132(5):584-93.
11. Von Lilienfeld-Toal M, Hahn-Ast C, Furkert K, et al. A systematic review of phase II trials of thalidomide/ dexamethasone combination therapy in patients with relapsed or refractory multiple myeloma. Eur J Haematol. 2008; 81:247–252.
12. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2006; 24:431– 436.
13. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007; 357:2123–2132.
14. Richardson PG, Briemberg H, Jagannath S, et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. J Clin Oncol 2006; 24: 3113–20.
15. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med. 2005; 352:2487–2498.
16. Jagannath S, Barlogie B, Berenson J, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol. 2004 Oct;127(2):165-172.