NEUROLOGICAL MANIFESTATIONS IN CHILDREN WITH HAEMATOLOGICAL MALIGNANCIES

Sanjeev Kumar Verma[1], Mukesh Kumar Mishra[2], Rashmi Kumar[3], Archana Kumar[4], Nivedita Nimesh[5]

[1]Assistant Professor, Department of Paediatrics, King George Medical University, Lucknow, Uttar Pradesh, India.
[2]Resident, Department of Paediatrics, King George Medical University, Lucknow, Uttar Pradesh, India.
[3]Professor, Department of Paediatrics, King George Medical University, Lucknow, Uttar Pradesh, India.
[4]Professor, Department of Paediatrics, King George Medical University, Lucknow, Uttar Pradesh, India.
[5]Resident, Department of Ophthalmology, King George Medical University, Lucknow, Uttar Pradesh, India.

ABSTRACT

BACKGROUND

Neurological complications occur frequently in patients with cancer in all age groups. Few of these neurological complications are related to systemic effects of malignancy, and rest are related to treatment, but all of them contribute to disease course in terms of morbidity and mortality.

The objectives of the study are to evaluate the prevalence of neurological manifestations and complications among the children with haematological malignancies and also to look for the outcome of such manifestation.

MATERIALS AND METHODS

This retrospective observational study was done at the Department of Paediatrics, King George Medical University (KGMU), Lucknow, India. All available records of children admitted till 2015 (20 years) with haematological malignancy in the department of Paediatrics, KGMU were searched. Those with any form of neurological manifestations or complications were included in the study and tried to look for the cause of the neurological issues.

RESULTS

870 children with all types of haematological malignancies were found in dept. of Paediatrics, KGMU. Among all haematological malignancies, major contributors were Acute Lymphoblastic Leukaemia (ALL) 52.9%, Acute Myeloid Leukaemia (AML) 16.6% and Hodgkin Lymphoma 9.8%. About 82 (9.4%) Paediatric haemato-oncology patients had neurological manifestations or complications, among these 24.4% had intra cranial bleed, 9.8% with CNS relapse, 8.5% meningitis/ meningo-encephalitis, 7.5% with primary CNS involvement, 4.9% of cerebral atrophy and peripheral neuropathy, wherein 23.3% of the cases, diagnosis could not be established. Seizures, headache, altered sensorium/encephalopathy, cranial nerve[1] palsies and focal deficits were the common presentations. CNS involvement at presentation, posterior reversible encephalopathy syndrome (PRES), spinal metastasis, sinus thrombosis, hydrocephalus, gliosis and intra cranial bleed were associated with adverse outcome. Overall 73.2% of children with neurological manifestations expired.

CONCLUSION

Paediatric haematological malignancies with neurological manifestations have wide spectrum of complications and aetiologies. Most of these complications lead to either long term morbidity or poor outcome.

KEYWORDS

Children, Haematological Malignancy, Neurological Issues.

HOW TO CITE THIS ARTICLE: Verma SK, Mishra MK, Kumar R, et al. Neurological manifestations in children with haematological malignancies. J. Evid. Based Med. Healthc. 2019; 6(1), 56-60. DOI: 10.18410/jebmh/2019/10

BACKGROUND

Haematological malignancies are common in paediatric age group and among these Acute Lymphoblastic Leukaemia (ALL) contribute to 75% of the cases and one fourth of all Paediatric cancers.[2] Haematological malignancies can present with neurological manifestations due to primary involvement (Infiltration of the CNS by leukemic cells and Secondary complications due to disease per se and /or therapy). These manifestations could be due to cerebrovascular issues like haemorrhage, thrombosis or infarct, direct effect or CNS relapse, infections leading to meningitis or meningo-encephalitis, drug induced encephalopathy or Posterior Reversible encephalopathy syndrome (PRES), post radiation leukoencephalopathy, cerebral or cerebellar atrophy. Chemotherapy and stem cell transplant related CNS complications incidence is 5-10%.[3] These neurological issues decide the line of management and outcome. But there is paucity of data on neurological issues in the Paediatric Haematological malignancies from this most populated state of India, so this retrospective

Financial or Other, Competing Interest: None.
Submission 14-12-2018, Peer Review 16-12-2018,
Acceptance 24-12-2018, Published 07-01-2019.
Corresponding Author:
Dr. Nivedita Nimesh,
Resident, Department of Ophthalmology,
King George Medical University,
Lucknow, Uttar Pradesh, India.
E-mail: nivee02@gmail.com
DOI: 10.18410/jebmh/2019/10

study was planned to evaluate neurological manifestation with all Haematological cancers in Paediatric age group.

Aims and Objectives

We aimed to study the prevalence of neurological manifestations and complications among the children with haematological malignancies retrospectively and also looked for the outcome of such manifestation.

MATERIALS AND METHODS

The study was done at department of Paediatrics, King George Medical University (KGMU), Lucknow, UP, India. All available records of children admitted till 2015 (20 years) with Haematological malignancies in department of Paediatrics, were searched and those with neurological manifestations or complication were included in the study and tried to look the cause of the neurological manifestations.

RESULTS

A total of 870 of all types of Haematological malignancies were found in dept. of Paediatrics, KGMU. Major contributors were acute lymphoblastic Leukaemia (ALL) 52.9%, Acute Myeloid Leukaemia (AML)16.6%, Hodgkin Lymphoma 9.8%.6.1% of children presented at < 1 year of age, 38% at 1-5 year, 39.7% at 5-10 year and 16.2% at >10 year of age, and 71.8% were male.

Sl. No.	Malignancy	No. of Patients	No. of Pts with Neurological Manifestations	%
1.	Acute Lymphoblastic Leukaemia	461	42	9.1
2.	Acute Myeloid Leukaemia	144	24	16.6
3.	Hodgkin's Lymphoma	129	7	5.4
4.	Non-Hodgkin's Lymphoma	85	6	7.0
5.	Chronic Myeloid Leukaemia	30	0	0
6.	Langerhans Cell Histiocytosis	21	3	14.2
	Total	870	82	9.42

Table 1. Contribution of all Haematological Malignancies with Neurological Manifestations

Among the aetiologies causing neurological manifestation in Paediatric Haematological malignancy, Intra cranial bleed 24.4%, CNS relapse 9.8%, meningitis/menigo-encephalitis 8.5%, primary CNS involvement 7.5%, cerebral atrophy and peripheral neuropathy 4.9% were leading cause where in 23.3% of the cases diagnosis cannot be established. CNS involvement at presentation, PRES, spinal metastasis, sinus thrombosis, hydrocephalous, gliosis were associated with 100% mortality, intracranial bleed 95%, CNS relapse 75% and peripheral neuropathy 75% were the other leading cause of adverse outcome. Overall 73.2% of those with neurological complications are expired.

Sl. No.	Malignancy	No. of Patients	%	Outcome (Expired)
1.	Intra Cranial Bleed	6 ALL 11 AML 2 HL 1 NHL=20	24.4	19/20=95%
2.	Meningitis/Menigo-Encephalitis	5 ALL 1 NHL 1 LCH=7	8.5	2/7=28.6%
3.	CNS Involvement (CSF Positive for Malignant Cells at Presentation)	1 ALL 3 AML 1 HL 2 NHL=7	7.3	6/6=100%
4.	CNS Relapse (CSF Positive for Malignant Cells after Initial Remission)	6 ALL 2 AML=8	9.8	6/8=75%
5.	Cerebral Atrophy	3 ALL 1 NHL=4	4.9	1/4 =25%
6.	Peripheral Neuropathy	3 ALL 1 HL=4	4.9	3/4=75%
7.	PRES	1 ALL=1	1.2	1/1=100%
8.	Granuloma	2 ALL 1 AML=3	3.7	1/3=33.3%
9.	Brain Abscess	1 ALL	1.2	0/1=0
10.	Cerebral Atrophy	1 ALL	1.2	0/1=0

11.	Deafness	1 ALL	1.2	0/1=0
12.	Spinal Metastasis	3 AML	3.7	3/3=100%
13.	Transverse Sinus Thrombosis	1 AML	1.2	1/1=100%
14.	Hydrocephalous	1 HL	1.2	1/1=100%
15.	Gliosis	1 LCH	1.2	1/1=100%
16.	Diagnosis Not Established	12 ALL 3 AML 3 HL 1 NHL 1 LCH=20	24.4	14/20=70%

Table 2. Aetiologies in Paediatric Haematological Malignancy with Neurological Presentation & Outcome

There is myriad of presentation as neurological ill complication in Haematological malignancies, among them Seizures, headache, altered sensorium/encephalopathy, cranial nerve palsies and focal deficits were the common presenting illnesses.

Sl. No.	Clinical Presentation	No. of Patients	%
1.	Seizure	12 ALL 07 AML 04 HL 03 NHL 01 LCH=27	32.9
2.	Headache	6 ALL 5 AML 2 HL 1 NHL=14	17.1
3.	Altered Sensorium	2 ALL 6 AML 2 HL 2 NHL	12.2
4.	Cranial Nerve Palsy 3rd Cranial Nerve Palsy 7th Cranial Nerve Palsy 9th/10th/11th Cranial Nerve Palsy	1 ALL 1 AML=2 4 ALL 1 AML=5 3 ALL	10.9
5.	B/L Hearing Loss	1 ALL	
6.	Loss of Vision	2 ALL 1 LCH=3	3.7
7.	Ptosis	1 ALL 1 AML=3	3.7
8.	Aphasia	1 ALL	1.2
9.	Para/Hemi/Quadriparesis	5 ALL 4 AML=9	10.9
10.	Raise Intra Cranial Tension	1 HL	1.2
11.	Pain/Tingling, Numbness in Limb	1 ALL 1 HL 1 LCH= 3	3.7
12.	Asymptomatic	3 ALL	1.2

Table 3. Clinical Presentations in Paediatric Haematological Malignancy with Neurological Involvement

DISCUSSION

In this study 82 (9.4%) of 870 children have neurological manifestations either as systemic disease or neurotoxicity while on chemotherapy which is comparable to 8.4% from a German study.[4] Incidence of neurotoxicity is reported to be 3-13% in various studies.[5,6] Whereas incidence of neurological abnormalities in systemic cancer reported to be 15-20% in adult studies.[7] A Turkish study of 154 children with malignancy excluding Leukaemia and lymphoma showed 33% of children have neurological issues. CNS metastasis was the commonest one (15.6%) followed by CNS infection (11%) while 7.7% patient had peripheral or cranial neuropathy. In current study primary CNS involvement and CNS relapses accounted for 17.1% of the cases, while peripheral neuropathy and cranial nerve involvement accounted for 4.9% and 10.9% of the cases

respectively. CNS infections related manifestations are 28.6%, which are also close to German study of 26.8%.[4]

There is increased incidence of cerebrovascular accidents during the course of Haematological malignancies as well as those with survivors. The relative risk of Intracerebral haemorrhage and infarcts for Leukaemia survivors compared with sibling controls was 6.4 at a median of 9.8 years from cancer diagnosis; the relative risk of stroke for brain tumour survivors compared with siblings was 29 at a median of 13.9 years from cancer diagnosis.[8] Another retrospective study of 700 children with systemic malignancy where primary CNS neoplasm were excluded found the incidence of cerebrovascular accident 4%, very close to this study where overall 2.3% of all haematological malignancy developed intracranial bleed during the course of illness.[9] In a study of 203 ALL children by Kuskonmaz B et al 9.9% of the children developed neurological complications and among the common ones were meningitis in 25% and CNS thrombosis or infarct in 21% of the cases.[10] Current study has 24.4% of the cases developed CNS vascular events.

One of the mechanisms of neurological complication in children with malignancy with CNS vascular events is hyperleukocytosis, resulting in hyper viscosity, leading to vascular events like haemorrhage and infarction. A US and a Korean study showed that severity of hyperleukocytosis proportionate with chances of getting a vascular event.[11,12] we are unable to document hyperleukocytosis in our patients due to retrospective methodology.

Chemotherapy related neurotoxicity is another cause for neurological manifestations and incidence varies from 3 to 13%.[4,5] Vincristine is associated with mixed sensorimotor neuropathy and sometimes with autonomic involvement, rarely this drug is implicated with serious events like encephalopathy, coma and cranial nerve palsies.[13] Systemic or intrathecal methotrexate can cause acute cerebral oedema manifesting as seizures, while L-asparaginase have increased risk of intracerebral haemorrhage or thrombosis by alteration in coagulation cascade and fibrinolysis, leading to focal seizures.[14] cytarabine, ifosfamide are other agents related with chemotherapy related neurotoxicity. In this study we failed to make exact contribution from chemotherapy related neurotoxicity because of temporal association of toxicity and retrospective method of study.

Apart from CNS and spinal metastasis, cranial irradiation in advanced disease can have neurological complication in Haematological malignancies. Radiotherapy can lead to white matter destruction, vascular damage resulting in haemorrhage, calcification and enlargement of ventricles suggestive of cortical atrophy.[15] Long term neurological complication including late occurring strokes are much higher in those receiving radiotherapy greater than 30 Gy.[8,16]

These neurological issues have ultimately final impact on outcome; few of them lead to immediate mortality up to 23% from CNS infection related complications and 24% mortality with chemotherapy related CNS complications.[4] Our data shows 24% mortality related to cerebrovascular accident related complications, 3.7% succumbed to CNS infections, 10.9% with CNS involvement at presentation and 7.3% with relapse related complications with neurological manifestations in children with Haematological malignancies. Intracranial bleed, thrombosis, CNS and spinal extension of malignancy were associated with very high mortality.

CONCLUSION

Haematological malignancies with neurological manifestations in children have wide variety of underlying causes and some of them like intracranial bleed, advanced disease carry grave prognosis.

REFERENCES

[1] Taşdemiroğlu E, Patchell RA, Kryscio R. Neurological complications of childhood malignancies. Acta Neurochir (Wien) 1999;141(12):1313-1321.

[2] Pui CH. Acute lymphoblastic Leukaemia. Pediatr Clin North Am 1997;44(4):831-846.

[3] Huang LT, Hsiao CC, Weng HH, et al. Neurologic complications of Paediatric systemic malignancies. J Formos Med Assoc 1996;95(3):209-212.

[4] Schmidt K, Schulz AS, Debatin KM, et al. CNS complications in children receiving chemotherapy or hematopoietic stem cell transplantation: retrospective analysis and clinical study of survivors. Pediatr Blood Cancer 2008;50(2):331-336.

[5] Ochs JJ. Neurotoxicity due to central nervous system therapy for childhood Leukaemia. Am J Pediatr Hematol Oncol 1989 Spring;11(1):93-105.

[6] Ray M, Marwaha RK, Trehan A. Chemotherapy related fatal neurotoxicity during induction in acute lymphoblastic Leukaemia. Indian J Pediatr 2002;69(2):185-187.

[7] Clouston PD, DeAngelis LM, Posner JB. The spectrum of neurological disease in patients with systemic cancer. Ann Neurol 1992;31(3):268-273.

[8] Bowers DC, Liu Y, Leisenring W, et al. Late-occurring stroke among long-term survivors of childhood Leukaemia and brain tumors: a report from the childhood cancer survivor study. J Clin Oncol 2006;24(33):5277-5282.

[9] Packer RJ, Rorke LB, Lange BJ, et al. Cerebrovascular accidents in children with cancer. Paediatrics 1985;76(2):194-201.

[10] Kuskonmaz B, Unal S, Gumruk F, et al. The neurologic complications in Paediatric acute lymphoblastic Leukaemia patients excluding leukemic infiltration. Leuk Res 2006;30(5):537-541.

[11] Lowe EJ, Pui C, Hancock ML, et al. Early complications in children with acute lymphoblastic Leukaemia presenting with hyperleukocytosis. Pediatr Blood Cancer 2005;45(1):10-15.

[12] Kong SG, Seo JH, Jun SE, et al. Childhood acute lymphoblastic Leukaemia with hyperleukocytosis at presentation. Blood Res 2014;49(1):29-35.

[13] Kellie SJ, Koopmans P, Earl J, et al. Increasing the dosage of vincristine: a clinical and pharmacokinetic study of continuous-infusion vincristine in children

with central nervous system tumors. Cancer 2004;100(12):2637-2643.
[14] Foreman NK, Mahmoud HH, Rivera GK, et al. Recurrent cerebrovascular accident with L-asparaginase rechallenge. Med Pediatr Oncol 1992;20(6):532-534.
[15] Waber DP, Silverman LB, Catania L, et al. Outcomes of a randomized trial of hyper-fractionated cranial radiation therapy for treatment of high-risk acute lymphoblastic Leukaemia: therapeutic efficacy and neurotoxicity. J Clin Oncol 2004;22(13):2701-2707.
[16] Waber DP, Tarbell NJ, Fairclough D, et al. Cognitive sequelae of treatment in childhood acute lymphoblastic Leukaemia: cranial radiation requires an accomplice. J Clin Oncol 1995;13(10):2490-2496.