Neurological complications in children with non-neurological malignancies: A single institution experience

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Short running title: Neuro-complications in non-neurological cancers

Funding: None

Declarations of Interest of authors: None

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Declarations

Funding: The authors did not receive support from any organization for the submitted work.

Conflicts of interest: The authors declare they have no financial interests.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of King George's Medical University, Lucknow, Uttar Pradesh

Word count of abstract:250

Word count of manuscript: 2999

Number of tables: 4

Number of figures: 1

Keywords: neurological complications, malignancy, children, haematological malignancy, solid tumour

Authors' contributions: Conceptualization: RK, Methodology: RK, AK, Software: MM, AA, Validation: RK, AK, RKG, formal analysis: MM, AA, Funding acquisition: None, Investigation: None, Data curation: MM, RKG, Writing – original draft: AA, MM, Writing-Review & Editing: RK, AA, AK, RKG, Supervision and project administration: RK. All authors read and approved the final manuscript.

Abbreviations

NC	neurological complications
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BAER	brainstem auditory evoked response
CNS	central nervous system
CVD	cerebrovascular diseases
CSF	cerebrospinal-fluid
ES	Ewing's sarcoma
GCT	Germ cell tumour

HL	Hodgkin's lymphoma
LCH	Langerhans cell histiocytosis
NCV	nerve conduction velocity
NB	Neuroblastoma
NHL	Non-Hodgkin's Lymphoma
PRES	posterior reversible encephalopathy syndrome
RB	Retinoblastoma
RMS	Rhabdomyosarcoma
WT	Wilm's tumour

Abstract

Purpose: Central nervous system (CNS) involvement usually confers poor prognosis in cancer. We aimed to estimate prevalence of neurological-complications (NC) in children presenting with non-neurological malignancy and to describe type, aetiology and outcome of such complications

Methods: A bidirectional cohort study of children (1 month-15 years) with non-neurological malignancy was conducted at tertiary-care teaching hospital, North India. Prevalence and spectrum of NC was determined. Etiological diagnosis was made using neuroimaging, cerebrospinal-fluid analysis, nerve-conduction velocity, history and clinical examination.

Results: A total of 1572 patients (870 with haematological-malignancy; 55.6% and 702 with solid tumours; 44.4%) were enrolled. Most of them presented within 5-10 years of age and were males (72%). Overall frequency of NC was 10.5% (Haematological: 9.4%; solid: 11.8%). Highest proportion of NC was seen in RB (17.2%), followed by Neuroblastoma (16.6%), acute myeloid-leukaemia (AML) (16.6%), Ewing's sarcoma (16.1%) and Langerhans cell histiocytosis (LCH) (14.2%). Frequent symptoms were seizures (30.9%),

headache (18.2%), bilateral lower-limb weakness (13.3%), altered sensorium (9.7%), cranial nerve palsy (9.1%), loss of vision (3.0%), pain in lower-limbs (1.2%), aphasia (0.6%), ataxia (0.6%) and bilateral hearing loss (0.6%). Common aetiologies of NC included CNS metastasis or intracranial extension (in RB, Rhabdomyosarcoma), spinal metastasis (in Neuroblastoma, Ewing's-sarcoma, germ cell tumour), intracranial bleed (in AML, Hodgkin's-lymphoma, ALL), CNS relapse (ALL), CNS leukaemia (in Non-Hodgkin's-lymphoma), cerebral atrophy (Wilm's-tumor) and Meningo-encephalitis (in LCH). Mortality was high in affected children (80%).

Conclusions: Cancer-specific information about NC may be beneficial for early recognition and judicious management in order to prevent neurological or cognitive morbidity.

Keywords: neurological complications, malignancy, children, haematological malignancy, solid tumour

Introduction

Neurological complications (NC) are often responsible for hospitalization in children with systemic cancers.[1] Advanced therapeutic interventions leading to longer survival rates and enhanced imaging modalities have increased duration of risk along with possibility of detecting such complications. Central nervous system (CNS) complications of systemic malignancy may occur due to cerebrovascular events, direct-cancer related toxicities (local compression, metastatic disease and leptomeningeal carcinomatosis), indirect-non metastatic effects (paraneoplastic disorder, seizures, vascular disorders, movement disorders and non progressive encephalopathy), chemotherapy-related iatrogenic toxicities (neuropathy, toxic encephalopathy, cerebral infarction, drug specific side effects) or as complications to radiation and stem-cell transplantation.[2]

Each treatment modality carries its own neurological risks. Most common neurological complications include cerebrovascular diseases (CVD), posterior reversible encephalopathy syndrome (PRES), peripheral neuropathy, and long-term neuro-cognitive defects.[3] CVDs majorly accounts for increased morbidity and need for critical care services.[4] Presence of tumor per se and coagulation disturbances due to its direct effect or as adverse effect to chemotherapy is responsible for CVD. Radiation therapy to extra-cranial or cranial sites can also contribute to vessel stenosis or thrombosis.[5] Children's Oncology Group showed that stroke risk is increased in survivors of Hodgkin lymphoma (HL) and acute lymphoblastic leukaemia (ALL) who received radiation to brain and/or neck.[6]

These complications range in severity from relatively trivial to fatal. At time of diagnosis, most CNS lesions are symptomatic as seizures, localized motor deficits, or headaches.[7] Patients may also present with pleomorphic and subtle neurological signs, sometimes difficult to differentiate between brain metastases and treatment- related adverse effects.[8] Metastasis typically occurs late during the course of systemic malignancies.[9] Cancer cells infiltrating cerebrospinal-fluid (CSF) can lead to neoplastic meningitis, a rapidly progressive and fatal condition characterized by serious neurologic deficits.[10]

It is estimated that up to 30% of patients with non-neurological cancer develop brain involvement.[11] Early recognition of a problem and prompt institution of therapy may improve quality of life by preventing further deterioration and permanent disability in cancer patients.[12] Literature on neurological manifestations in common childhood non-neurological malignancies is scanty[13-15] and no such studies could be found from India. Therefore we aimed to study prevalence of NC among children presenting with non-neurological malignancy and to describe the type, aetiology and outcome of such complications at our centre.

Materials and Methods

A bidirectional cohort study was conducted at Department of Pediatrics, King George's Medical University (KGMU), Lucknow, UP, India for a period of one year (September 2014-August 2015). It included prospective follow up (cohort study) and retrospectives analysis of case records of children aged 1 month to 15 years diagnosed as non-neurological malignancy presenting to Paediatric Oncology division from 2010 to 2015. Children whose parents refused to give consent were excluded from study. Ethical clearance for study was obtained from institutional Ethics review committee. A subset of collected data was presented in our previous work.[16]In this paper; we intend to provide a comprehensive overview of all cancers admitted to our centre during study period.

Study setting

KGMU, Lucknow is a large, multispeciality, 3000-bed tertiary care teaching hospital in North India. It is a major pediatric oncology centre in state encompassing area of 243286 km^2 and harbouring 204 million people. [17]Majority of our patients come from rural areas and belong to lower socio-economic status.

Data Collection

1. Prospective study

Patients diagnosed as systemic malignancy during September 2014 to August 2015 were followed up prospectively till 2016 for development of any neurological symptoms or signs. If occurred, it was documented on a predesigned data collection form and investigated with neuroradiology, nerve conduction velocity (NCV), EEG or any other investigation as required. Detailed work up for cause was attempted.

2. Retrospective analysis of case records

Records of children admitted from January 2010 to August 2014 were availed from record section of Oncology division and information regarding any neurological manifestation was abstracted. Attempt was made to find cause of neurologic manifestation from history, examination and investigations as entered in case records. Neurological diagnosis was made on basis of neuroimaging (computed tomography/ magnetic resonance imaging), cerebrospinal fluid analysis, and NCV. CNS involvement at presentation was confirmed by CSF cytology showing malignant cells. Deafness was investigated by brainstem auditory evoked response (BAER) and diagnosed when BAER showed increased latency in 8^{th} nerve.

Statistical Analysis

Data was entered into Microsoft Excel sheet. Prevalence and spectrum of NC as a whole and for individual malignancies was described as proportion. Aetiologies' of NC and outcome of children with NC were also presented as proportions. All collected data was analysed using SPSS (Statistical Package for Social Sciences) version16 software (SPSS, Chicago, IL, USA).

Results

A total of 1572 patients were admitted during study period. Out of 1572, 311 patients were enrolled prospectively from September 2014 to August 2015 and 1261 cases were enrolled retrospectively from records of January 2010 to August 2014.

Year wise distribution showed that there was yearly increase in number of patients (Fig 1) Most common age of presentation was 5-10 years of age followed by 1-5 years age. Male preponderance in patients was seen (>70%). (Table1)

The most common malignancy noted was ALL (29.3%) followed by retinoblastoma (12.6%), although, highest proportion of neurological manifestations were evident in retinoblastoma

(RB, 17.2%) followed by acute myeloid leukaemia (AML), Neuroblastoma (NB) (16.6% each) and Ewing's sarcoma (ES) (16.1%). (Table2) Spectrum of neurological symptoms and its etiological diagnoses in each malignancy is depicted in Table 3. Spectrum of neurological manifestations and underlying aetiology in prospectively collected cases are shown in Table 5.

Discussion

Many non-neurological cancer patients have symptomatic NC during course of their illness which is a common reason for hospitalization in both adults and children. It is estimated that up to 30% of patients with non-neurological cancer develop brain involvement.[11] Description of incidence and spectrum of neurologic features in childhood-cancer have been limited to observational studies in individual cancers and isolated case reports. Our medical pediatric oncology unit caters to all types of non-neurological malignancies. The purpose of this study was therefore to outline incidence, aetiology and outcome of CNS manifestations of systemic pediatric cancers.

Amongst 1572 included children, 870 (55.6%) children had haematological-malignancy and 702 (44.4%) were diagnosed with solid-tumors. Overall frequency of neurological manifestations in our cohort was 10.5% (haematological-malignancies: 9.4%; solid-malignancies: 11.8%). Similar proportion (11.4%) was reiterated by another Indian adult study.[18] A study on 200 patients with systemic-cancer in China found similar prevalence of neurological disorders (12.5%).[13] However, a Turkish study on 154 non-CNS malignancies excluding leukemias and lymphomas reported that 33% of cases had NC.[14] Aysun et al identified neurological features as initial presentations of systemic-malignancies in his cohort of 30 patients.[15] Apart from these far-dated studies [13-15, 18] we could not identify any recent

study in literature evaluating NC in combined cohort of systemic malignancies. Most reports of NC have been focussed on individual systemic malignancy.

Highest proportion of neurological manifestations were reported in RB (17.2%), followed by NB (16.6%), AML (16.6%), ES (16.1%), LCH (14.2%), ALL (9.1%) and GCT (8.9%). No neurological manifestation was seen in CML and Hepatoblastoma. ALL and Neuroblastoma have contributed to maximum proportion of neurological-cases in Chinese and Turkish children.[13,15,18] Neuroblastoma was found to be most common solid cancer presenting with NC closely followed by sarcomas, WT, GCT in previous studies.[14,15] RB contributed to very few cases in other centres[14] in contrast to our centre because ours is a National Retinoblastoma Registry of Indian Council of Medical Research and most of cases are referred to us from periphery. In our study, children commonly presented within 5-10 years of age with male preponderance which is similar to other studies.[13, 15]

In present study, common symptoms were seizures in 51 (30.9%), headache in 30 (18.2%), bilateral lower-limb weakness in 22 (13.3%), altered-sensorium in 16 (9.7%), cranial nerve palsy in 15 (9.1%), loss of vision in 5 (3.0%), pain in lower limbs in 2 (1.2%), and aphasia (0.6%), ataxia, bilateral hearing loss in one patient each. NC was maximally reported in **RB** patients (17.2%). Optic nerve involvement was considered as stage of disease and not a neurological complication. Headache (13/34, 38.2%) and seizures (12/34; 35.2%) were frequent features in RB. Other clinical features noted were altered-sensorium, ptosis and paraparesis. Nearly 80% of cases were due to CNS metastasis or intracranial-extension of tumour. Other aetiologies were 3rd nerve palsy, meningitis, spinal metastasis and hydrocephalus. Mortality was quite high in these children (91.2%; 31/34). No other study in literature could be found on acute neurological manifestations in retinoblastoma.

Proportion of NC was 16.6% (14/84) in children with **Neuroblastoma** in our study. Paraparesis, due to spinal metastasis and spinal glioma, was found in 5/14 (35.7%) cases. Second common symptom was seizures (4/14), mostly due to brain metastasis followed by intracranial bleed and meningo-encephalitis. Other features included headache in 2 (14.2%), loss of vision in 1 (7.1%) and altered sensorium in 1. A study on 53 children observed NC in higher proportion (30.1%).[19] Another study from Turkey documented greater proportion of NC in 25 pediatric NB cases (68%).[20] Most of children demonstrated symptoms, similar to our findings like lower limbs paresis and bladder/bowel sphincter dysfunction. Few also suffered from severe back pain.[19, 20] Outcome of such cases in our study was dismal with 100% mortality, after excluding cases lost to follow up, which was similar to Turkish data (83%), however, much higher than that seen in Polish study (20%).[19] Astigarraga et al from Spain reported 4 patients with secondary meningeal metastases in primary-extracranial Neuroblastoma, all of whom died and hence, they concluded that possibility of CNS relapse in NB should be considered when neurological symptoms/signs appear.[21]

Fifteen (16.1%) patients of **ES** had some neurological manifestation. Paraparesis (8/15, 53.3%) was frequently noted, mostly due to spinal metastasis (6/15, 40%). Other NC included seizures in 3 (20.0%), and headache, loss of vision, facial nerve palsy and diplopia in one patient (6.6%) each. Intracranial extension in 2 (13.3%), cerebral atrophy in 2, and intracranial bleed, meningitis and calcified granuloma in one (6.6%) each were responsible for these symptoms. Mortality was high (12/15), especially in children with spinal metastasis as all these children (n=6) succumbed to their illness. Neurological manifestations like paraparesis are not unusual in primary Ewing's sarcoma of spine but as a secondary presentation are less reported in literature.[22, 23] Aysun et al reported a single case of Ewing's among their 30 children who had neurological features. This patient had spinal cord compression.[15]

Neurological manifestations were found in 24 out of 144 children (16.6%) with **AML** in current study. Seizures (29%) and altered-sensorium (25%) accounted for 13/24 cases. Headache (20.8%) was noted in five children. Limb weakness (hemiparesis/ paraparesis) (4, 16.6%) was an important presenting complaint in children with AML. Other features were ptosis, facial nerve palsy and hemiparesis in one case each. Intracranial bleed was responsible for nearly 50% of these complaints. Limb weakness was mostly accounted by spinal metastasis. Other 3 cases (12.5%) had CNS involvement at presentation, 3 had isolated CNS relapse, 1 had hepatic encephalopathy, 1 had transverse sinus thrombosis, 1 had calcified granuloma and in 2 children (8.3%) cause of CNS symptoms was not established. Hepatic encephalopathy is not unusual in children with cancers since they are repeatedly exposed to blood products and can contract hepatitis B or C viruses. NC worsened prognosis resulting in 100% mortality. *Campbell et al* found that intracranial haemorrhage occurred in similar proportion as ours (7%) in their children.[24]

In **ALL**, 9.1% of patients (42/461) had neurological manifestations. Other studies reported NC ranging from 7%-15%.[3, 24-27] At our centre, seizure was most common presentation (12, 28.5%), followed by cranial-nerve involvement (9, 21.4%) (facial n=5, VIII nerve n=1, bulbar n=2, shoulder drooping n=1). Convulsions were also identified as commonest feature in ALL in other pediatric studies.[25, 28]Other symptoms in our children included headache (6, 14.3%), limb weakness (5, 11.9%), vision loss (2, 4.8%), ptosis, and altered-sensorium in one each. Neuropathies were predominant complaint in a Spanish study [26] and limb weakness were common presentation after seizures in a study from Argentina.[28] In one-third of cases, aetiology was undiagnosed (28.6%) in our cohort despite appropriate investigations and among diagnosed, CNS relapse (14.2%) and intracranial bleed (14.2%) were usual causes followed by chemical meningitis in 5 (11.9%), cerebral atrophy and peripheral neuropathy in 3 (7.1%) each. Similar spectrum of aetiologies was noted from Bangladesh[29], UK[24] and

India.[18] Cerebral hemorrhage was maximally reported CT finding [27] and responsible for 1% of neurological cases.[24] Chemical meningitis due to intrathecal chemotherapy has previously been a primary cause of neurological concern in children with ALL.[30] Other etiological diagnoses in present study were calcified granuloma in 2 (4.7%), CNS leukemia, PRES, brain abscess, cerebellar atrophy and deafness due to 8th nerve palsy in 1 (2.3%) child each. On contrary, PRES was frequent aetiology in Italian[27] and Turkish cohorts.[25] Sixty four percent (27/42) of our children with NC expired which was higher than that seen in another study (21%).[24]

Among renal tumours, only **Wilm's tumor** (WT) presented with NC (6/145, 4.1%) in form of seizures (4, 66.6%), altered-sensorium (2, 22.2%) and hemiparesis (1, 11.1%). On investigation, patients had cerebral atrophy, cerebral edema, intracranial bleed, CNS metastasis in one patient each whereas aetiology was unknown in a third. Quite similar to our data (1/145; 0.7%), seven of 1249 (0.6%) children with WT developed CNS metastases in UK.[31] Previous case reports on CNS metastases in WT, rare occurrence in children, documented signs of raised intracranial pressure[32], headache and hemiparesis as presenting complaints.[33] Excluding lost-to-follow-up; mortality was 75% (¾) in our cohort which is higher than that seen in UK cohort (60%).[31]

In **Hodgkin's-lymphoma**, 7 of 129 (5.4%) patients had NC with seizures noted in majority (4/7). Others included headache, limb pain and raised ICP in one each. Aetiology could not be established in nearly 50% of children and in remaining, intracranial bleed (28.5%) was typical diagnosis along with hydrocephalus and sciatic neuropathy (one each). Previous case reports have depicted back pain, leg pain associated with lower limb weakness ± sphincter dysfunction as chief complaints in HL.[34] Headache, seizures and proptosis were also reported in individual case reports.[34] Five out of seven affected children expired in our study (71.4%).

In **rhabdomyosarcoma**, 7.3% (6/82) of patients had NC out of which 2 (33.3%) had intracranial extension whereas cerebellar atrophy, calcified granuloma, hydrocephalus and undiagnosed cause was noted in 1 patient each. Similar to our data, in another analysis of 59 pediatric RMS, prevalence of CNS involvement was 11.9%.[35]However, a combined study on soft-tissue and osseous sarcomas identified NC in higher proportion (26.5%) (43/162) including intracranial metastatic disease (27.9%) and seizures (23.2%).[36] Symptomatic peripheral neuropathy (10%) also occurred in children with RMS[36] as reported in current study where seizure, ataxia, foot drop, facial nerve palsy, headache and altered-sensorium were presenting features (in 1case each; 16.6%). Headache, altered-sensorium and seizures were main symptoms described in recent study.[35] Ogose et al from Japan observed 15.4% (2/13) brain metastases in RMS.[37] Prognosis was grave as 5 out of 6 children died in our study, a finding supported by other authors.[35, 37]

Six out of 67 (8.9%) patients with **GCT** had neurological manifestations. Paraparesis (3, 50%) was frequent complication, seen in half of cases followed by backache in 1(16.6%) and headache in 1. Mostly (4, 66.6%) it was due to intra-spinal metastasis. Brain metastases and cerebral atrophy was found in 1 patient each. *Garg et al* from New Delhi, India observed that 16% of GCT had intra-spinal extension and presented in form of lower-limb paresis (80%) and bowel, bladder (20%) incontinence.[38] Outcome of our affected children was poor with 5 dying out of 6 (83.3%) which is in contrast to study from New Delhi where all were alive and showed improvement.

Six of our 85 patients of **NHL** had NC (7.1%) in form of seizures in 3 (50%), altered sensorium in 2 (33.3%), and headache in 1(16.6%). It was attributed by CNS involvement at presentation in more than third cases. Other causes were cerebral atrophy, intracranial bleed, cerebral edema and un-established cause in 1(16.6%) patient each. These neurological manifestations negatively impacted the course causing death in 5/6 children. Thirty percent of

children had NC in a Turkish cohort which is much higher than present cohort. Most common symptom was altered sensorium followed by seizure and hallucination.[39] Mortality in neurologically-affected children in Turkish cohort (14.2%) was quite undersized than present study.[39]

In **LCH**, 14.2% (3/21) of patients had NC in form of vision loss, tingling, numbness in arms and seizures. The child with seizures who was diagnosed as meningoencephalitis died and rest two (cause; gliosis and unknown etiology) survived. Higher proportion of CNS involvement in pediatric LCH was noted in a Swedish population based study (24%).[40] Grois et al (1993) from California, USA had observed 4 patients in which one patient had blindness, and 3 had progressive neurological disorder.[41]

Strengths

Our study provides a comprehensive overview of neuro-complications of various systemic malignancies in children at tertiary care cancer centre in a developing country. Patients were followed over years and assessed during dedicated hospital visits till the outcome.

Limitations

Major limitation is lack of few useful data like stage of cancer when neurological involvement occurred. Some children were lost to follow-up and we could not gather their outcome, however, their number was not significant.

Conclusions

Neurological problems constitute a considerable number and pose a significant concern in children with systemic-cancers. Overall mortality was 80% in patients with systemic-cancers who had neurological manifestations. Causes of neurological manifestations cover most of the recognized complications of malignancy. Certain causes predominate in each type of

malignancy and knowledge of these entities is imperative for practitioners to prevent delays, wrong diagnoses and to initiate early necessary treatment in order to maintain neurologic and cognitive function.

Conflict of interest: None

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Legends

Fig1 Distribution of year wise admissions of non-neurological malignancies

TABLE 1 Distribution of age, sex and malignancies in children

TABLE 2 Proportion of neurological manifestations in various types of malignancies

TABLE 3 Spectrum of Neurological manifestations and its aetiologies' in different systemic cancers

TABLE 4 Proportion and spectrum of neurological complications among 311 prospectively enrolled non-neurological malignancies