

Review Article

Integrative Clinical and Practical Hematology

Neurological Complications of Childhood Hematological Disorders and Solid Malignancies: A Brief Review

Panda PK*

Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

***Correspondence:** Prateek K Panda, Senior Resident, All India Institute of Medical Sciences, New Delhi, India, E-mail: drprateekpanda@gmail.com

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Abstract

Hematological disorders are often associated with various neurological complications during the course of the disease and often as adverse effect due to the treatment instituted. Iron deficiency anemia has definite role in the pathogenesis of breath holding spell and ischemic stroke in children. Sickle cell anemia is also associated with increased risk of arterial ischemic stroke and Moyamoya disease. Acute lymphoblastic and myelogenous leukemia are also associated with various neurological complications due to CNS spread, complications of chemotherapy, tumor lysis syndrome, hyperleukocytosis and opportunistic infections. Rarely, paraneoplastic complications like Ophelia syndrome and Opsoclonus Myoclonus Ataxia syndrome can be seen in children with Hodgkin lymphoma and Neuroblastoma respectively. This review article briefly describes individually various neurological complications associated with hematological disorders and malignancies in children, and their current evidence based management guidelines.

Introduction

Childhood Neurological Disorders (CND) often have hematological complications [1]. On the other hand, neurological complications are not uncommon in hematological disorders. Often the drugs used for treatment of childhood neurological disorders are associated with hematological adverse effects. Timely recognition of these adverse effects is imperative for proper management of these children. Hematological disorders are associated with immunocompromised status often during the course of illness and management [1]. These immunocompromised states often predispose the child to opportunistic central nervous system infections [2]. Hence it is important not only for the pediatric neurologists to have knowledge about these hematological complications, but also for hematologists to have knowledge regarding neurological complaints.

CND in iron deficiency anemia

Iron deficiency anemia as such has various neurological manifestations in childhood in the form of irritability, listlessness [3]. Often, it is associated with other micronutrient deficiency, failure to thrive. Many of these children are often found to have delay especially in social and cognitive milestones. Infants and toddlers with clinical and subclinical iron deficiency are often more prone to develop cyanotic and pallid breath holding spells and reflex anoxic seizures. Hence, iron supplementation is usually recommended in children with breath holding spells [3]. Children with iron deficiency also have thrombocytosis and hypercoagulable state and often regarded as a risk factor for pediatric stroke [4]. Hence, all children with acute cerebrovascular events should be screened for iron deficiency. Severe anemia due to iron deficiency often causes clinical and subclinical hypoxia to

CNS and it may present as developmental delay. Iron is required for neurotransmitter synthesis, hence deficiency of catecholamines and serotonins are often considered causative for neurological manifestations [4].

CND in sickle cell anemia

Sickle cell anemia children are also more prone to develop acute ischemic stroke and moyamoya disease [5]. In moyamoya disease, there is usually vasculopathy and nonthrombotic occlusion of distal part of internal carotid artery and proximal part of middle and anterior cerebral artery. These children can present with multiple cerebrovascular accidents involving bilateral upper and lower extremities. MRI brain and MRA films reveal attenuated flow voids of major intracranial arteries and collateral forming a "puff of smoke" around origin of middle cerebral artery. Children with sickle cell anemia are also predisposed to 10-20 times more risk of arterial ischemic stroke as compared to normal children and timely blood transfusion to keep sickled hemoglobin below 30% helps to reduce the risk of stroke significantly [6]. Rarely immune thrombocytopenic purpura can be associated with ischemic stroke [7].

CND in Vitamin B12 deficiency anemia

Pernicious anemia or anemia due to vitamin B12 deficiency is often associated with systemic complications like subacute combined degeneration of cord [8]. In this disease, on clinical examination signs due to involvement of posterior column and lateral column of spinal cord can be elicited, such as extensor plantars with decreased position and vibration sense, Romberg sign and decreased deep tendon reflexes [8]. It responds to vitamin B12 supplementation. In infants vitamin B12 deficiency can cause infantile tremor syndrome along with megaloblastic anemia [9]. There are rare case reports of west syndrome with epileptic spasms due to vitamin B12 deficiency.

CND in acute hematological malignancy

Children with acute lymphoblastic and myelogenous leukemia are also at risk of developing intracranial hemorrhage as well as ischemic strokes due to various hemodynamic and hematological alterations. Thrombocytopenia and disseminated intravascular coagulation (especially in M3 variety of AML) predisposes these children for cerebral parenchymal and subarachnoid hemorrhages. Certain chemotherapeutic drugs like L-asparaginase also increase the risk of arterial and venous ischemic stroke [10]. Apart from intracranial bleed, these

children are also at risk for the dreaded complication of CNS spread of malignancy or isolated CNS relapse. Many chemotherapeutic drugs do not penetrate blood brain barrier and CNS acts as a sanctuary site for malignant cells. In previous days, although radiation therapy was used to curb the risk of CNS relapse, but it was associated with significant cognitive decline and behavioral issues among various long term neurological complications in these children. Currently, intrathecal chemotherapeutic drugs like methotrexate are used at various intervals along with routine monitoring of CSF cytology to reduce the risk of CNS spread. Moreover, if blast cells are found in CSF, than the disease is considered to be high risk and introduction of more intensive chemotherapy regimens is usually recommended [10].

Central nervous system spread of hematological malignancy

CNS spread of acute hematological malignancy can present with features resembling acute meningoencephalitis in children like poor sensorium, persistent headache, recurrent projectile vomiting, meningeal signs like neck rigidity, often associated with features of raised intracranial pressure like vision impairment, papilledema, bilateral sixth cranial nerve palsy [10]. In rare cases it can present as an acute neurological emergency with seizures, tonic posturing and signs of intracranial herniation. Rarely leukemic deposits can also be found along the arachnoid membrane covering spinal cord and it can cause lower motor neuron type of weakness in lower limbs with radicular pain. It is worthwhile to mention that bone pain is a common clinical feature associated with hematological malignancy due to extramedullary hematopoiesis and it can mimic a condition resembling acute flaccid paralysis in children. This is actually "pseudoparalysis" due to significant bony pain [10].

Complications due to chemotherapeutic drugs

Certain chemotherapeutic drugs like Cytarabine can cause cerebellar toxicity, especially when administered in high doses and can present with acute onset ataxia and other cerebellar signs [11]. On the other hand, Vincristine can cause motor neuropathy in children with leukemia and can cause foot drop in these children along with constipation in variable proportion of cases [12,13]. Cyclophosphamide and Ifosfamide can also rarely cause acute CNS complications. Intrathecal methotrexate can cause damage to periventricular white matter. It can rarely present acutely with altered sensorium, seizures

and recurrent vomiting. However, the more common form of the chemotherapy induced leukoencephalopathy is usually insidious onset, can even occur years after the chemotherapy was completed. Slowly progressive cognitive decline, behavioral abnormalities, spasticity and rarely seizures are hallmark findings of this entity, often associated with white matter signal changes in MRI brain films [11].

Opportunistic infections in hematological malignancies

Immunosuppression associated with hematological malignancy and due to chemotherapy predisposes the child to various CNS infections due to atypical organisms, including fungal and parasitic infections. In low and middle income countries, reactivation of tuberculosis with tubercular meningitis is not uncommon to be found in children with malignancy [14]. Herpes group of organisms like Herpes simplex virus type 1 and 2, Varicella Zoster virus, Cytomegalovirus all can cause CNS infection in children with hematological malignancies [15]. Hence, when any child with hematological malignancy presents with suspected CNS infection, these clinical possibilities needs to be considered and appropriate therapy with Acyclovir and Ganciclovir along with proper antibacterials like ceftriaxone needs to be reinstated to treat them. Specific tests like polymerase chain reaction are available to diagnose them whenever suspicion arises. Cryptococcus and Acanthamoeba infection also rarely needs to be ruled out in these children with India ink stain and wet slide mount test to detect motile amoebas in these children [15].

Paraneoplastic syndromes in hematological malignancies leading to neurological disorders

Last but not the least, paraneoplastic complications are also found in hematological malignancies and lymphomas and they can rarely involve CNS. Ophelia syndrome is the term used for autoimmune encephalitis like picture in a child with Hodgkin lymphoma. In this entity, the child presents with subacute onset alteration of cognition, behavior, sleep disturbance and occasional positivity for antibodies to metabotropic glutamate receptor [16]. These diseases need to be treated with institution of corticosteroid pulse or intravenous immunoglobulin. Rarely, long term use of steroids can cause hypertension and subsequent hypertensive encephalopathy in children with acute leukemia [17]. In these cases MRI brain shows features suggestive of "Posterior Reversible Encephalopathy Syndrome" with white matter hyper

intensities in periventricular regions, with parietooccipital predilection.

Neuroblastoma and CNS complications

Neuroblastoma is another malignancy, which is often associated with CNS complications due to metastatic disease spread and also due to paraneoplastic complications like "Opsoclonus-Myoclonus-Ataxia" syndrome. In OMA syndrome, often the tumor is very small and detected only after the child develops the ataxia and other neurological features [18]. About 50% of OMA syndrome is due to paravertebral neuroblastoma or ganglioneuroblastomas and rest are due to parainfectious complications to various viral infections like CMV, EBV and Mycoplasma. OMA syndrome is usually characterized by acute onset ataxia and tremulousness in a child associated with bilateral dancing, chaotic, multidirectional eye movements also called opsoclonus. This entity is often associated with excessive irritability and sleep disturbance in these children. OMA syndrome, whenever detected it should be treated with injection ACTH and there should be a diligent search at yearly interval to detect the occult neuroblastoma with CT scan of the abdomen and MIBG scan, which is specific for detection of neuroblastoma [18].

Apart from OMA syndrome, paravertebral large neuroblastomas often cause compressive myelopathy by invading spinal canal through vertebral foramen and can cause weakness of bilateral lower limbs [19]. This is an acute emergency and often needs institution of emergency chemotherapy and radiotherapy. Neurofibromas or malignant peripheral nerve sheath tumors are other tumors which can spread through vertebral foramen to cause compression of spinal cord structures and ensuing weakness. Neuroblastoma are also likely to spread into CNS and present with seizure and features of raised intracranial pressure [19]. Extraocular retinoblastomas are another entity which are likely to spread inside CNS and can rarely cause a clinicoradiological picture suggestive of "Carcinomatous Meningitis" [20].

Miscellaneous neurological complications

Non-Hodgkin lymphomas are more likely to spread into CNS as compared to Hodgkin lymphoma [21]. Especially, in solid tumors like Burkitt's lymphoma institution of chemotherapy often leads to tumor lysis syndrome. This tumor lysis syndrome is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia and often associated with seizures,

along with life threatening cardiac complications like ventricular arrhythmias. Tumor lysis syndrome is usually treated with institution of hemodialysis to acutely reverse the metabolic complications responsible for clinical symptoms, along with Rasburicase, a Xanthine oxidase inhibitor to reduce the production of uric acid [22]. Similarly, hyperleukocytosis which is often seen with T-cell acute lymphoblastic leukemias and acute myelogenous leukemias is associated with vascular complications involving CNS [23]. It is usually treated with hydration, sodium bicarbonate (although its usefulness is still not proved in larger clinical trials) and exchange transfusion in life threatening cases [24].

Conclusion

Natural course of various hematological and nonhematological malignancies, as well as treatment related complications are likely to involve central and peripheral nervous syndrome. Timely recognition of these entities with institution of disease specific treatment, and often modifying the chemotherapy regimens is imperative for favorable outcome in these children. Iron deficiency and Sickle cell anemia are also often associated with cerebrovascular complications. Neuroimaging, CSF examination, clinical, hematological and biochemical findings most of the time help clinicians to determine the causative etiology for acute neurological complications in children with hematological disorders.

Conflict of interest

None

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References

1. Andersen MH. The targeting of immunosuppressive mechanisms in hematological malignancies. *Leukemia*. 2014;28(9):1784-1792. doi: <https://doi.org/10.1038/leu.2014.108>
2. Bhatt VR, Viola GM, Ferrajoli A. Invasive fungal infections in acute leukemia. *Ther Adv Hematol*. 2011;2(4):231-247. doi: <https://doi.org/10.1177/2040620711410098>
3. Hamed SA, Gad EF, Sherif TK. Iron deficiency and cyanotic breath-holding spells: The effectiveness of iron therapy. *Pediatr Hematol Oncol*. October 2018;1-10. doi: <https://doi.org/10.1080/08880018.2018.1491659>
4. Kaiafa G, Savopoulos C, Kanellos I, et al. Anemia and stroke: Where do we stand? *Acta Neurol Scand*. 2017;135(6):596-602. doi: <https://doi.org/10.1111/ane.12657>
5. Marks LJ, Munube D, Kasirye P, et al. Stroke prevalence in children with sickle cell disease in sub-saharan africa: A systematic review and meta-analysis. *Glob Pediatr Health*. 2018;5:2333794X1877497. doi: <https://doi.org/10.1177/2333794X18774970>
6. Talahma M, Strbian D, Sundararajan S. Sickle cell disease and stroke. *Stroke*. 2014;45(6):e98-100. <https://www.ahajournals.org/doi/abs/10.1161/strokeaha.114.005144>
7. Mihalov J, Timárová G. A seeming paradox: Ischemic stroke in the context of idiopathic thrombocytopenic purpura. *Clin Appl Thromb Hemost*. 2016;22(2):115-120. doi: <https://doi.org/10.1177/1076029614545213>
8. Rojas Hernandez C, Oo T. Advances in mechanisms, diagnosis, and treatment of pernicious anemia. *Discov Med*. 2015;19(104):159-168. <https://www.ncbi.nlm.nih.gov/pubmed/25828519>
9. Glaser K, Girschick HJ, Schropp C, Speer CP. Psychomotor development following early treatment of severe infantile vitamin B12 deficiency and west syndrome – Is everything fine? A case report and review of literature. *Brain Dev*. 2015;37(3):347-351. doi: <https://doi.org/10.1016/j.braindev.2014.05.006>
10. Berg SL, Chamberlain MC. Systemic chemotherapy, intrathecal chemotherapy, and symptom management in the treatment of leptomeningeal metastasis. *Curr Oncol Rep*. 2003;5(1):29-40. doi: <https://doi.org/10.1007/s11912-003-0084-9>
11. Soffiatti R, Trevisan E, Rudà R. Neurologic complications of chemotherapy and other newer and experimental approaches. *Handb Clin Neurol*. 2014;121:1199-1218. <https://www.ncbi.nlm.nih.gov/pubmed/24365412>
12. Jongen JLM, Broijl A, Sonneveld P. Chemotherapy-induced peripheral neuropathies in hematological malignancies. *J Neurooncol*. 2015;121(2):229-237. doi: <https://doi.org/10.1007/s11060-014-1632-x>
13. Wang B, Yang L, Yu L, Chen X, Hu Y. Clinical analysis of adverse drug reactions between vincristine and triazoles in children with acute lymphoblastic leukemia. *Med Sci Monit*. 2015;21:1656-1661. doi: <https://doi.org/10.12659/MSM.893142>
14. Inaba H, Pei D, Wolf J, et al. Infection-related complications during treatment for childhood acute lymphoblastic leukemia. *Ann Oncol*. 2017;28(2):386-

392. doi: <https://doi.org/10.1093/annonc/mdw557>
15. Caniza MA, Odio C, Mukkada S, et al. Infectious complications in children with acute lymphoblastic leukemia treated in low-middle-income countries. *Expert Rev Hematol*. 2015;8(5):627-645. doi: <https://doi.org/10.1586/17474086.2015.1071186>
16. Juneja M, Kaur S, Mishra D, Jain S. Ophelia syndrome: Hodgkin lymphoma with limbic encephalitis. *Indian Pediatr*. 2015;52(4):335-336. <https://www.ncbi.nlm.nih.gov/pubmed/25929634>
17. Tang J-H, Tian J-M, Sheng M, et al. Study of posterior reversible encephalopathy syndrome in children with acute lymphoblastic leukemia after induction chemotherapy. *J Child Neurol*. 2016;31(3):279-284. doi: <https://doi.org/10.1177/0883073815589758>
18. Blaes F, Dharmalingam B. Childhood opsoclonus-myooclonus syndrome: diagnosis and treatment. *Expert Rev Neurother*. 2016;16(6):641-648. doi: <https://doi.org/10.1080/14737175.2016.1176914>
19. Trahair T, Sorrentino S, Russell SJ, et al. Spinal canal involvement in neuroblastoma. *J Pediatr*. 2017;188:294-298. doi: <https://doi.org/10.1016/j.jpeds.2017.05.051>
20. Gündüz K, Müftüoğlu O, Günalp I, Unal E, Taçyıldız N. Metastatic retinoblastoma clinical features, treatment, and prognosis. *Ophthalmology*. 2006;113(9):1558-6. [https://www.aajournal.org/article/S0161-6420\(06\)00452-0/abstract](https://www.aajournal.org/article/S0161-6420(06)00452-0/abstract)
21. Kose D, Paksoy Y, Koksall Y, Unal E. Neurological complication of non hodgkin lymphoma in childhood: experience from a single center in turkey. *Childs Nerv Syst*. 2014;30(4):639-645. doi: <https://doi.org/10.1007/s00381-013-2267-5>
22. Firwana BM, Hasan R, Hasan N, et al. Tumor lysis syndrome: A systematic review of case series and case reports. *Postgrad Med*. 2012;124(2):92-101. doi: <https://doi.org/10.3810/pgm.2012.03.2540>
23. Abla O, Angelini P, Di Giuseppe G, et al. Early complications of hyperleukocytosis and leukapheresis in childhood acute leukemias. *J Pediatr Hematol Oncol*. 2016;38(2):111-117. doi: <https://doi.org/10.1097/MPH.0000000000000490>
24. Cruz ML, Farooq S, Testai FD. Neurological and neurosurgical emergencies in patients with hematological disorders. *Curr Neurol Neurosci Rep*. 2017;17(3):24. doi: <https://doi.org/10.1007/s11910-017-0728-z>



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