


## Pediatric Blood Disorders with Central Nervous System Complications

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### Abstract

Pediatric Hematology Oncology is a broad and complex area that encompasses perturbations of the several-formed elements of the blood and their precursors in the bone marrow, as well as the coagulation-fibrinolytic systems in the plasma, the reticuloendothelial system, and malignancies of the blood and solid tissues and organs. The most common non-malignant blood disorders in adolescents include the various forms of cytopenias, anemias, bleeding and clotting disorders, and hemoglobinopathies. Iron deficiency is the most prevalent nutritional deficiency affecting children and adolescents worldwide. But, anemia occurs frequently in children with cancer. Iron deficiency anaemia is commonly associated with thrombocytosis. Thrombocytopenia, or low platelets, can occur as an isolated finding or in conjunction with a multitude of underlying clinical conditions. Venous thromboembolism result in significant morbidity and mortality in children with cancer. Alpha-thalassemia major is the most common genetic variant of transfusion-dependent thalassaemia seen in the Indian subcontinent, the Mediterranean basin, Southeast Asia and China. Bleeding events still predominate as the diagnostic trigger in children, however, the sites of bleeding vary with age. Bone marrow failure is a rare but life-threatening disorder that usually manifests as (pan)cytopenia. Central nervous system tumors are the most common cancer diagnosed in children after leukemia, accounting for 20% of all pediatric malignancies. Fanconi anemia is an autosomal recessive disease characterized by developmental anomalies, bone marrow failure, cellular sensitivity to DNA cross-linking agents, and increased incidence of both hematologic and solid tumors. This narrative review focuses on the most suggestive symptoms of hematologic disorders with central nervous system complications in childhood.

**Keywords:** Central nervous system complications, blood disorders, children, pediatry

## 1. Introduction

The hematology oncology of infancy and childhood is a relatively recent area of study whose development depended upon the evolution of the science of Hematology and, especially, upon methods to study the blood and its elements. Pediatric Hematology Oncology has increasingly involved other allied medical sciences (genetics, immunology, and molecular biology). Pediatric Hematology Oncology has interactions and there are significant differences in same disease in pediatric and adult patients. Some pediatric diseases do not occur in adults and vice versa.

## 2. Pediatric Blood Disorders

### 2.1. Iron deficiency anemia

Iron deficiency is the most prevalent nutritional deficiency affecting children and adolescents worldwide. A consistent body of epidemiological data demonstrates an increased incidence of iron deficiency at three timepoints: in the neonatal period, in preschool children, and in adolescents, where it particularly affects females (Mattiello et al., 2020). Causes of anemia are increased loss or destruction of red blood cells (RBCs) or a significant decreased rate of production. When evaluating a child with anemia, it is important to determine if the problem is isolated to one cell line (e.g., RBCs) or multiple cell lines (i.e., RBCs, white blood cells [WBCs], or platelets). When two or three cell lines are affected, it may indicate bone marrow involvement (leukemia, metastatic disease, and aplastic anemia), sequestration (i.e., hypersplenism), immune deficiency, or an immune-mediated process (e.g., hemolytic anemia and immune thrombocytopenic purpura) (Hastings et al., 2021). Iron deficiency anemia is the most common and preventable cause of microcytic anemia. According to the World Health Organization, iron deficiency anemia is seen in 36% of developing countries and 8% in developed countries. The incidence of iron deficiency anemia in Mongolia is much higher than in developed

countries. One of the key findings of iron deficiency anemia is decreased appetite. There is a positive relationship between ghrelin, which stimulates appetite, and iron levels, and it has been reported that decreased appetite in iron deficiency anemia may be due to low ghrelin levels. The results of iron deficiency anemia and increased appetite in children taking iron supplements are conflicting. The causes of iron deficiency should be investigated and corrected, deficiencies should be eliminated, nutrition should be corrected, patient and family education should be provided. The clinical findings of anemia vary according to the age of the child, the etiology of anemia and the rate of development. However, it is determined that most anemic children are asymptomatic and there are abnormalities in hemoglobin and hematocrit values during routine screening. Although physical examination is very important, it may not be asymptomatic in most children with anemia. As a result of the body's compensation ability; chronic anemia presents with lesser symptoms than an acute anemia case with the same hemoglobin value (Babacan, 2021b). Anemia occurs frequently in children with cancer. A survey was conducted in 1998 in Europe by The Research Partnership with the objective of determining the incidence of anemia. Data were collected for 25,093 patients. Over 80% of patients were anemic (WHO: hemoglobin  $\leq 11$  g/dL; EORTC: hemoglobin  $\leq 12$  g/dL) regardless of tumor type; 97% of patients with leukemia, the most prevalent type of cancer (34% of the total population), were anemic. Decreases in hemoglobin levels to between 5.5 and 8.0 g/dL were the most common factor that precipitated anemia treatment. Treatment was almost exclusively blood transfusion; less than 5% of patients received drug treatment (which consisted mostly of folic acid or iron). Very few patients received recombinant human erythropoietin (rHuEPO, epoetin alfa) to treat anemia (Michon, 2002).

## 2.2. Thrombocytopenia

Thrombocytopenia, or low platelets, can occur as an isolated finding or in conjunction with a multitude of underlying clinical conditions. Thrombocytopenia is typically subdivided into immune and nonimmune causes. Immune causes generally cause increased platelet destruction. Nonimmune causes may cause increased destruction or decreased bone marrow production. In patients with splenomegaly, platelet sequestration may also lead to thrombocytopenia. The initial evaluation of the child with suspected ITP begins with a complete history and physical examination. Other than a possible antecedent illness and the acute onset of minor bleeding and bruising, the child should be otherwise clinically well appearing. More significant bleeding may be associated with trauma. Bleeding into joints (hemarthroses) should lead one to consider an alternative bleeding disorder (e.g., congenital or acquired factor deficiency such as hemophilia). There should be no history of unexplained fevers, bone pain, or weight loss which would be concerning for an underlying malignancy or chronic infection. A medication history is critical as many drugs have been implicated in inducing drug-mediated immune thrombocytopenia (Hastings et al., 2021). General information about immune thrombocytopenic purpura and heparin induced thrombocytopenia/thrombosis will be given by considering the conditions that cause platelet deficiency in infants and young children separately. Causes of immune thrombocytopenia includes the destruction of platelets in the reticuloendothelial system, mainly in the spleen, due to antibodies against membrane antigens such as autoantibodies, alloantibodies or drug-induced antibodies. Immune damage due to platelet antibodies is mediated by an immune complex that directly targets the antigen on the platelet or binds to the Fc receptor on the platelet. Platelet antigens are divided into two classes. Platelet-specific antigens and

platelet non-specific antigens. Platelet-specific antigens are complexes such as GPIIb-IIIa or GPIb-IX-V in the glycoprotein structure that is only on the platelet membrane. Genetic structural differences in glycoproteins in the platelet membrane reveal platelet alloantigens (Babacan, 2021c).

## 2.3. Thrombocytosis

In healthy pediatric subjects normal count platelet ranges between 250,000  $\mu\text{L}$  and 450,000  $\mu\text{L}$ . An elevated platelet count greater than 2 SD defines a condition of thrombocytosis. On a clinical level, thrombocytosis is classified "mild" at a platelet count between  $> 500,000 \mu\text{L}$  and  $<700,000 \mu\text{L}$ ; "moderate" at a platelet count between  $>700,000/\mu\text{L}$  and  $<900,000/\mu\text{L}$ ; "severe" at a platelet count  $>900,000/\mu\text{L}$ ; and "extreme" at a platelet count  $>1,000,000/\mu\text{L}$ . Thrombocytosis can be classified as primary or secondary. Primary thrombocytosis is divided into familial and essential. Primary thrombocytosis is an extremely rare clonal disease in childhood with incidence of one per million children, i.e., 60 times lower than in adults. It is classified as a myeloproliferative disorder with polycythemia vera, chronic myeloid leukaemia and myelofibrosis and may be associated with thrombotic or haemorrhagic events. In the majority of cases no treatment is necessary, and the patient must be only closely monitored (Chiarello et al., 2011). Infections may be the cause of thrombocytosis. In addition to infections, sickle cell anemia and iron deficiency anemia should also be considered in the differential diagnosis of thrombocytosis (Babacan and Şenol, 2023). Iron deficiency anaemia is commonly associated with thrombocytosis, however cases of thrombocytopenia have been reported. In most cases of iron deficiency anaemia, the platelet count reactively increases or remains within the normal range. Only a few cases in the literature report the association between severe iron deficiency anaemia and thrombocytopenia. The exact mechanism of thrombocytopenia in this

setting is not well understood (Torrejon et al., 2018).

#### **2.4. Thalassemia**

The thalassemias are a group of inherited hematological disorders characterised by early onset of anemia resulting from reduced synthesis of one or more globin chains which can be caused by many different globin gene mutations. Alpha-thalassemia major is the most common genetic variant of transfusion-dependent thalassaemia seen in the Indian subcontinent, the Mediterranean basin, Southeast Asia and China (Low, 2005). The alpha-thalassemias are caused by a decrease in the production of alpha-globin due to a deletion or mutation of one or more of the four alpha-globin genes located on chromosome 16. Beta-thalassemia is caused by mutations in the beta-globin gene. Although there have been hundreds of mutations identified within the beta-globin gene locus, about 20 different alleles make up about 80% of the mutations found worldwide (Hastings et al., 2021).

#### **2.5. Von Willebrand Disease**

Von Willebrand disease (VWD) is the most common inherited haemostasis disorder in humans with an estimated yearly incidence of 1 per 800–1,000 subjects (1). VWD is characterised by either a quantitative or a qualitative deficiency in von Willebrand factor (VWF) molecule and is divided into three categories; types 1, 2, and 3. Whereas type 1 VWD is characterised by a mild reduction in the amount of a functionally normal VWF, type 2 is characterised by the production of a dysfunctional protein, in which the ability to participate in mediating platelet adhesion, to bind to platelets or to act as a carrier protein for factor VIII in plasma is impaired. Type 3 is characterised by the virtual absence of VWF (Halimeh et al., 2011). Mucocutaneous bleeding symptoms, such as bruising and epistaxis, are common in childhood and do not always reflect the presence of an underlying bleeding disorder. A detailed bleeding

history is essential to distinguish symptoms that are abnormal from those that are normal. However, this is often done in an informal manner, the interpretation dependent upon the prior experience of the observer. It would be expected that some children with a significant inherited mucocutaneous bleeding disorder might not have bleeding symptoms until late in childhood due to the lack of exposure to hemostatic challenges such as surgery, dental extraction and menarche. Early childhood bleeding such as post-circumcision bleeding, cephalohematoma and bleeding from the umbilical stump may be of greater significance in this patient group (Biss et al., 2010). Treatment guidelines recommend the use of von Willebrand factor/factor VIII (VWF/FVIII) concentrate for VWD patients with type 2 or 3 VWD undergoing surgery, and type 1 patients undergoing surgery who are unresponsive, or for whom desmopressin acetate is contraindicated (Gill et al., 2011).

#### **2.6. Jaundice**

Jaundice is caused by an accumulation of bilirubin in the blood. The presentation in infants and children can be indicative of a wide range of conditions, with some self-limiting and others potentially lifethreatening. Infantile jaundice is a common but potentially lifethreatening condition. Referral to a specialist is necessary if jaundice persists beyond the neonatal period. The differentiation between medical and surgical causes should be made early on by measuring the blood level of conjugated and unconjugated bilirubin. Laparoscopy should be considered in any patient with persistent cholestatic jaundice to exclude BA that requires early intervention. Breast milk jaundice can persist for as long as 12 weeks before spontaneous resolution. Glucose-6-phosphate dehydrogenase (G-6-PD) is an enzyme found in all cells of the body. Apart from haemolysis (as evidenced by a falling haemoglobin with elevated reticulocyte count), diminished bilirubin clearance plays a role in the pathogenesis of

jaundice in G-6-PD deficiency infants. Serum conjugated bilirubin studies indicate diminished bilirubin conjugation in G-6-PD-deficient neonates, with impaired excretion of conjugated bilirubin into the small intestine in bile (Chee et al., 2018). While investigating the etiology of jaundice in newborns, it would be appropriate to check the G6PD levels in babies, and it should be considered that jaundice may improve in a long time in babies with low G6PD levels, and the necessary treatment should be planned in this way (Babacan, 2022c). Choledochal cyst is a congenital disorder characterised by cystic dilatation of the intrahepatic and/or extrahepatic bile duct. The estimated incidence is around 1 in 5000 live births and slightly more in Asians.<sup>44</sup> The diagnosis is usually made in the first few years of life when the patient presents with jaundice or abdominal pain. In recent years, antenatal diagnosis has become more common and more cysts are detected on prenatal scans. Occasionally, the disease can remain asymptomatic until adulthood when it presents with cholangitis. Malignant transformation into cholangiocarcinoma is a rare but possible sequelae of untreated choledochal cyst and thus, surgical excision is recommended (Madadi-Sanjani et al., 2019).

### 2.7. Hemophilia

The hemophilias are the most common X-linked inherited bleeding disorders, which if not properly managed can lead to chronic disease and lifelong disabilities. The challenges and issues in newborns are different from that in older children and adults. Bleeding events still predominate as the diagnostic trigger in children, however, the sites of bleeding vary with age. While delivery-associated intracranial hemorrhage (ICH), circumcision, and venipuncture bleeding are common in the newborn period, joint disease and head trauma occur in the older child and adolescent. Awareness of clinical manifestations and treatment complications are crucial in instituting appropriate management and implementing preventive

strategies. Currently, inhibitors and ICH are the most challenging complications and prophylaxis is emerging as the optimal preventive care strategy (Kulkarni and Soucie, 2011).

### 2.8. Bone marrow failures

Bone marrow failure (BMF) is a rare but life-threatening disorder that usually manifests as (pan)cytopenia. BMF can be caused by a variety of diseases, but inherited BMF (IBMF) syndromes are a clinically important cause, especially in children. IBMF syndromes are a heterogeneous group of genetic disorders characterized by BMF, physical abnormalities, and predisposition to malignancy. An accurate diagnosis is critical, as disease-specific management, surveillance, and genetic counselling are required for each patient. The major differential diagnoses of IBMF syndromes are acquired aplastic anemia (AA) and refractory cytopenia of childhood (RCC). These diseases have overlapping features, such as BM hypocellularity and/or dysplastic changes, which make the differential diagnosis challenging. RCC has been defined as a histomorphologically distinct entity. Therefore, understanding the BM histopathology of these diseases is essential for the differential diagnosis (Iwafuchi, 2018). Patients with dyskeratosis congenita are at increased risk of marrow failure, myelodysplastic syndrome, acute myelogenous leukemia and pulmonary fibrosis. Allogeneic hematopoietic stem cell transplantation is a curative procedure in patients with Shwachman–Diamond syndrome with bone marrow abnormalities (Babacan, 2022b).

### 3. Central nervous system tumors with blood disorders and epilepsy

Central nervous system tumors are the most common cancer diagnosed in children after leukemia, accounting for 20% of all pediatric malignancies. The most common location is infratentorial in children up to 14 years of age, while supratentorial tumors are more common in

adolescents. Spinal cord tumors are also more common in adolescents than in younger children. Brain tumors are the most common solid tumor in childhood. Most of the symptoms of childhood cancer are either due to a mass and its effect on the surrounding tissues, invasion of the marrow, or secretion of a substance by the tumor that disturbs normal function. A careful family history should be elicited and include familial cancers. Certain conditions can predispose to malignancy such as genetic diseases (e.g., Down syndrome, Beckwith–Wiedemann syndrome, neurofibromatosis), prior history of a malignancy, or radiation therapy. Environmental and genetic factors have been associated with the development of malignancy; genetic factors are known to play a significant role in the development of pediatric cancer, whereas environmental factors are postulated to play a role in the increasing incidence of certain cancers. Headache is one of the most common complaints in the pediatric population, the majority of which are attributable to nonmalignant conditions. Although few headaches are caused by intracranial masses, primary brain tumors or metastases must be ruled out when dealing with a patient with repeated or persistent headaches. Back pain in young people is pathologic and may be due to a tumor in the spinal cord or one causing external compression such as neuroblastoma, rhabdomyosarcoma, or a leukemic chloroma. The most common malignant tumors in young children are neuroblastoma and Wilms tumor (Hastings et al., 2021).

### 3.1. Tumors with anemia

Anemia is a common finding in children presenting with malignancy. Up to 80% of children presenting with ALL will be anemic at diagnosis. This can result from bleeding, inflammation, or marrow infiltration by tumor. It is rarely an emergency; children can tolerate a hemoglobin level as low as 2 to 3 g/dL if it develops slowly from decreased production (Hastings et al., 2021). Fanconi anemia

(FA) is an autosomal recessive disease characterized by developmental anomalies, bone marrow failure, cellular sensitivity to DNA cross-linking agents, and increased incidence of both hematologic and solid tumors. Fanconi anemia is a rare, genetic disease resulting in impaired response to DNA damage in the FA/BRCA pathway. Although it is a very rare disorder, study of this and other bone marrow failure syndromes has improved scientific understanding of the mechanisms of normal bone marrow function and development of cancer. The breast cancer susceptibility gene BRCA2 was recently found to be associated with Fanconi anemia complementation group D1 (FA-D1). The co-occurrence of brain tumors, Fanconi anemia, and breast cancer observed in one of these kindreds constitutes a new syndromic association. Individuals who carry a germline BRCA2 mutation and who plan to have children with a partner of Ashkenazi Jewish descent should consider undergoing genetic counseling (Offit et al., 2003). Central nervous system complications are among the most common, devastating sequelae of sickle cell disease occurring throughout the lifespan. Recommendations immediately impact clinical care include: use of transcranial Doppler ultrasound screening and hydroxyurea for primary stroke prevention in children with hemoglobin SS (HbSS) and hemoglobin S $\beta$ 0 (HbS $\beta$ 0) thalassemia living in low-middle-income settings; surveillance for developmental delay, cognitive impairments, and neurodevelopmental disorders in children; and use of magnetic resonance imaging of the brain without sedation to detect silent cerebral infarcts at least once in early-school-age children and once in adults with HbSS or HbS $\beta$ 0 thalassemia. Individuals with sickle cell disease, their family members, and clinicians should become aware of and implement these recommendations to reduce the burden of central nervous system complications in

children and adults with sickle cell disease (DeBaun et al., 2020).

### 3.3. Tumors with von Willebrand disease

Wilms' tumor also known as nephroblastoma is the most common primary renal tumor in children, usually presenting between 6 months and 5 years of age. The majority of patients present with an abdominal mass, abdominal pain, hypertension or hematuria. One recognized yet uncommon presentation is a disturbance in coagulation function related to acquired von Willebrand syndrome (AvWS). Bleeding episodes due to AvWS have been reported in patients affected by lymphoproliferative, myeloproliferative, cardiovascular, neoplasia, and autoimmune disorders. AvWS in association with Wilms' tumor is characterized by bleeding related to platelet dysfunction and disturbances of coagulation function including an elevated partial thromboplastin time (PTT) (Kedir et al., 2018). Autoimmune causes of AVWS in children include postviral antibody production similar to immune thrombocytopenic purpura (ITP), lymphoproliferative diseases, systemic lupus erythematosus, other autoimmune disorders, and some cancers, most commonly Wilms tumor. Wilms tumor patients may have acquired von Willebrand disease at presentation increasing bleeding risk (Hastings et al., 2021).

### 3.3. Tumors with thrombosis

Venous thromboembolism (VTE) result in significant morbidity and mortality in children with cancer. The cause of VTE in children with cancer is multifactorial and includes genetic predisposition (thrombophilia), disease-related factors, and treatment-related factors including use of central venous catheter (CVC), surgery, and chemotherapy. The pathogenesis of VTE in cancer is complex involving multiple interactions between tumors and components of the hemostasis system. A number of general prothrombotic mechanisms occur related to the host

response to cancer including hemodynamic compromise, inflammation, necrosis and para protein production. However, the development of a persistent hypercoagulable state mediated by tumor activity is considered a key feature in VTE pathogenesis (Bordbar et al., 2018). Pediatric patients may have both congenital and acquired risk factors underlying thrombus formation. The single most common acquired risk factor for venous thromboembolism is the presence of a central venous catheter (e.g., endothelial injury). Other acquired risk factors include trauma, surgery, infection, nephrotic syndrome, inflammatory syndromes, diabetes, complex congenital heart disease, liver disease, and malignancy (e.g., acute lymphoblastic leukemia in association with the use of asparaginase or solid tumors with tumor thrombus) (Hastings et al., 2021).

### 3.4. Tumors with neutropenia

Chemotherapy-induced neutropenia is known to be a major risk factor for infections in patients with cancer. For decades, routine management for patients with cancer presenting with fever and neutropenia (FN) has been emergency hospitalization and empirical broad-spectrum intravenous antimicrobial therapy with or without escalation to include antifungal therapy until resolution of FN and signs of infection. Invasive infections are detected in a minority of patients with FN. This has stimulated the development of risk-adapted treatment guidelines, which are internationally established in adult oncology. In children with FN, presenting characteristics and outcome differ significantly from those found in adult oncology. Different risk prediction rules based on clinical and laboratory parameters were developed in prospective pediatric studies. Yet, an international consensus on when and how to assess the risk of which kind of adverse events (AEs) in pediatric FN is still lacking (Ammann et al., 2010). Neutropenia can also be seen in the setting of overwhelming bacterial infection as well as with typhoid fever, Rocky Mountain

spotted fever, and tuberculosis. Phagocytosis of microbes leads to release of toxic metabolites, which then activate the complement system, inducing neutrophil aggregation and adherence of leukocytes to the pulmonary capillary bed. Tumor necrosis factor and interleukin-1, released by macrophages, likely accelerate this process (Hastings et al., 2021).

### 3.5. Tumors with bone marrow failure

Bone marrow failure occurs during early adulthood and is associated with a high risk of developing aplastic anemia, MDS, leukemia, and solid tumors (Hastings et al., 2021). Inherited bone marrow failure syndromes (IBMFSs) are multisystem genetic disorders with varying degrees of single-lineage or multilineage cytopenias due to defective production of blood cells and a high risk of benign and malignant neoplasms. IBMFSs are caused by *de novo* or inherited germline gene mutations. Over 80 IBMFS genes have been identified, which are crucial for fundamental cellular processes such as DNA repair, telomere maintenance, cell survival, and others. Most of IBMFSs such as Fanconi anemia, dyskeratosis congenita, Diamond–Blackfan anemia, and Shwachman–Diamond syndrome are associated with wide range of physical anomalies. However, some of the disorders are not associated with physical anomalies or the malformations develop later in life. The prevalence of the IBMFSs has not been accurately determined. Because of the increasing availability of genetic testing, patients with novel presentations or partial phenotypes are increasingly found (Alabbas et al., 2017).

### 3.6. Tumors with thrombocytopenia

Thrombocytopenia due to decreased production may be a result of an acquired or inherited disease process. Decreased production may be a direct effect of marrow crowding due to malignancy (leukemia or metastatic solid tumors such as lymphoma, Thrombocytopenia, neuroblastoma, medulloblastoma, and rhabdomyosarcoma) or storage diseases (Gaucher, Neimann-

Pick, etc.) (Hastings et al., 2021). Kasabach-Merritt phenomenon (KMP) is a rare potentially life-threatening, consumptive coagulopathy associated with the vascular tumors: kaposiform hemangioendothelioma (KHE) and tufted angioma (TA). KMP was first described in 1940 by Kasabach and Merritt in a 2-month-old boy who presented with what was diagnosed as a capillary hemangioma with profound thrombocytopenia and hypofibrinogenemia. These rare vascular tumors when associated with KMP typically arise in early infancy and are rapidly growing, large (>5 cm), locally invasive solitary lesions that most commonly manifest on the extremities, trunk, and face or neck. The clinical course is characterized by severe thrombocytopenia, microangiopathic anemia, hypofibrinogenemia, and elevated fibrin split products in the presence of an underlying vascular tumor. The coagulopathy is believed to be triggered by sequestration of platelets and clotting factors within the vascular lesion, which may lead to a systemic disseminated intravascular coagulation (Tlougan et al., 2013). High-grade gliomas in childhood are difficult to treat and have a very poor prognosis. For decades, reliable radical surgery and radiation therapy have been the cornerstones of treatment for these cancers. For most children, however, these treatments provide short-term clinical benefits and disease control, and most patients relapse within 2 years. Infiltration properties and resistance to radiation therapy are considered characteristics that determine the unpleasant course of these tumors. The presence of infiltrative properties and intrinsic radiotherapy resistance are thought to be the features that determine the unfavorable course of these tumors. There is currently no effective chemotherapy regimen to treat these cancers, but many new treatment options are being actively explored. The current belief is that high-grade childhood gliomas can be treated with multi-agency therapies.



With the emergence of tumor biology more and more, the importance of biological agents is increasing and they seem to be a beacon of hope in treatment (Babacan, 2021a). Both early radiotherapy initiation and high-dose chemotherapy with autologous stem cell rescue were important components in the treatment of pediatric atypical teratoid rhabdoid tumor. Gross total resection is the major predictor of survival especially in choroid plexus carcinoma (Babacan, 2022a).

### 3.7. Tumors with epilepsy

In the Global Burden of Disease 2010 study, severe epilepsy ranked fourth among 220 health conditions in terms of disability weight. The classification emphasises the importance of aetiology, which allows the optimisation of management. Antiepileptic drugs (AEDs) are the main approach to epilepsy treatment and achieve seizure freedom in about two-thirds of patients. More than 15 second generation AEDs have been introduced since the 1990s, expanding opportunities to tailor treatment for each patient. However, they have not substantially altered the overall seizure-free outcomes (Salomon et al., 2012). Antiepileptic drugs lead to weight gain and cause obesity but don't affect growth in prepubertal children (Babacan et al., 2009). Epilepsy surgery is the most effective treatment for drug-resistant focal epilepsy and should be considered as soon as appropriate trials of two AEDs have failed. The success of epilepsy surgery is influenced by different factors, including epilepsy syndrome, presence and type of epileptogenic lesion, and duration of post-operative follow-up. For patients who are not eligible for epilepsy surgery or for whom surgery has failed, trials of alternative AEDs or other non-pharmacological therapies, such as the ketogenic diet and neurostimulation, may improve seizure control. Ongoing research into novel antiepileptic agents, improved techniques to optimise epilepsy surgery, and other nonpharmacological therapies fuel hope to reduce the proportion of

individuals with uncontrolled seizures. With the plethora of gene discoveries in the epilepsies, “precision therapies” specifically targeting the molecular underpinnings are beginning to emerge and hold great promise for future therapeutic approaches (Salomon et al., 2012). Epilepsy can result from various types of brain tumors, but is most common in patients with low grade intrinsic lesions. Across all brain tumors, glioneuronal tumors, including gangliogliomas and dysembryoplastic neuroepithelial tumors (DNETs), are most likely to have seizure as the presenting symptom (Englot et al., 2016). Long-term epilepsy associated tumors (LEAT) represent a frequent cause of focal epilepsies, particularly in children and young adults. Epilepsy associated with LEAT is generally poorly controlled by antiepileptic drugs while it is extremely responsive to surgical treatment. Epilepsy associated with brain tumours can be divided into two groups: tumors without other symptoms (usually low-grade tumors affecting children or young patients) or tumors together with neurological deficits (more frequently high-grade tumours in middle-aged and older patients) (Giulioni et al., 2014).

### 4. Conclusions

Molecular characterization has the potential to advance the management of pediatric cancer and high-risk hematologic disease. The clinical integration of genome sequencing into standard clinical practice has been limited. Central nervous system complications are among the most common, devastating sequelae of sickle cell disease occurring throughout the lifespan. Shared genetic susceptibility to breast cancer, brain tumors, and Fanconi anemia was reported in past. Anemia is a common finding in children presenting with malignancy. Central nervous system complications are among the most common, devastating sequelae of sickle cell disease occurring throughout the lifespan. Bleeding episodes due to von Willebrand syndrome have been reported in patients affected by

lymphoproliferative, myeloproliferative, cardiovascular, neoplasia, and autoimmune disorders. Venous thromboembolism result in significant morbidity and mortality in children with cancer.

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