Contemporary Pediatric Hematology and Oncology

Edited by Marwa Zakaria and Tamer Hassan
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and Tamer Hassan

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Contemporary Pediatric Hematology and Oncology is the first edition, and has been a wonderful opportunity to bring together the expertise of hematology and oncology doctors from different communities. The book is designed to be the first step in advanced practice working with pediatric hematology/oncology patients. Specific issues related to young children and adolescents with cancer and hematologic disorders are discussed.

Three contributors and two editors participated in writing this book. The book is divided into four sections: Introduction to Pediatric Hematology and Oncology, Nocturnal Enuresis in Sickle Cell Anemia, Inherited Bone Marrow Failure Syndromes, and Malignant Tumors in Children. Many tables and illustrations are included for quick reference in the clinical setting.

Section I focuses on a general introduction to pediatric hematology and oncology and the great evolution that had been made regarding recent and advanced molecular diagnostic methods that have paved the way for novel therapeutic potentials in the field of pediatric hematology and oncology.

Section II focuses on benign hematology, including hemoglobinopathies and unusual clinical associations, with emphasis on how to diagnose and treat these disorders.

Section III illustrates the dilemma of bone marrow failure with a comprehensive overview of the genetic bases of different types, etiology, symptoms and clinical signs, diagnostic and laboratory testing, new areas of classification, therapeutic modalities, and prognosis.

Section IV focuses on pediatric cancers—the leukemias, lymphomas, and solid tumors. The most common pediatric tumors as well as some rare tumors are discussed in regard to epidemiology, etiology, molecular genetics, symptoms and clinical signs, diagnostic and laboratory testing, staging and classification, treatment, prognosis, and follow-up care.

The editors of Contemporary Pediatric Hematology and Oncology wish to recognize, thank, and acknowledge everyone who participated in writing this book. We are profoundly aware of the personal time and commitment that was devoted to make this an outstanding resource, and we are grateful. It is our hope that all healthcare,
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academic, and clinical practitioners in advanced clinical practice will find this publication useful, and that it will enrich knowledge and improve care for children and adolescents with cancer and hematologic disorders.

Marwa Zakaria
Zagazig University, Egypt

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Section 1

Introduction to Pediatric Hematology and Oncology
1. Introduction

Blood diseases are distinctive group of inherited and acquired, benign and malignant, acute and chronic disorders with diverse incidence, etiology, pathogenesis, and prognosis.

In the early days of hematology-oncology practice, hematology dominated and occupied most of the practitioner's time because most patients with cancer had a short life span and limited therapeutic modalities were available [1].

Our understanding of hematologic conditions has advanced considerably with the explosion of molecular biology and the management of most hematologic conditions has kept pace with these scientific advances. It has been a privilege to be a witness and participant in this great evolution over the last years where blood disorders have been studied extensively through many laboratory approaches for example, microscopy, clinical chemistry, immunophenotyping, genetic tests such as conventional cytogenetics, fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR). Yet we still have a long way to go as current advances are superseded by therapy based upon the application of knowledge garnered from an accurate understanding of the fundamental biology of hematological diseases [2].

Application of these advanced diagnostic tools had clarified the greatest involvement of different molecular mechanisms in the pathological transformation of hematopoietic progenitor cells and disease progression in many hematological diseases. Interestingly, more precise and accurate diagnosis was established, also, patients risk stratification as well as discovery of personalized, tailored therapeutic approach [3].

Aplastic anemia is a disease in which the stem cell fails to maintain bone marrow production. Aplastic anemia may be caused by hereditary disorders that usually present in childhood or in young adults (e.g., Fanconi anemia), or may present as an idiopathic disorder later in life. Many of these “idiopathic” cases may be due to autoimmune attack on the stem cell population. Secondary aplastic anemia can be caused by toxic damage to the marrow by radiation or chemicals (benzene, DDT, chemotherapy drugs, gold, etc.) or secondary to viral infection (e.g., EBV) [4].

Discovery of numerous genes incriminated in pathogenesis of Fanconi anemia and other inherited bone marrow failure syndromes has made great evolution in understanding the mechanism of DNA repair, telomere and telomerase enzyme action as well as many other biology secrets. Also, the relationship between the development of some types of cancers and presence of bone marrow failure syndromes may explains the etiology of these cancers and multiple birth defects [5].

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In this disorder, we expect to see declines in all cell counts (pancytopenia) with low reticulocyte counts. Aplastic anemia has been transformed from a near death
sentence to a disease with hope and cure in 90% of patients. Due to the emergence of advanced supportive care, immunosuppressive therapies and hematopoietic stem cell transplantation, this can result in 80% long term survival. In the absence of an HLA-matched sibling, allogeneic BMT can also be performed using an HLA-matched, unrelated donor or stem cells derived from umbilical cord blood [6].

The hemolytic anemias, have multiple causes, and the clinical presentation that can be differ according to the etiology. Many laboratory tests and specialized one can detect the cause of hemolysis, to reach specific diagnosis. With advancement in electrophoretic and other biochemical techniques, hemoglobinopathies are being identified now which were not previously possible. There are differences in the management of various types of hemolytic anemias [7].

Hemoglobinopathies requiring long life transfusion program to maintain a safe hemoglobin level for hemodynamic stability such as in thalassemia major and sickle cell anemia frequently had marked facial characteristics with broad cheekbones along with organ damage and failure, particularly of the heart, liver, beta cells of the pancreas and other tissues due to secondary hemochromatosis because of excessive iron deposition. The clinical findings attributed to extramedullary hematopoeisis are essentially of historic interest because of the development and widespread use of proper transfusion and chelation regimens.

Sickle cell disease (SCD) is one of the most frequent inherited genetic blood disorders in the world. It predominantly affects people of African ancestry (about 80% of sickle cell disease cases are believed to occur in Sub-Saharan Africa) as well as people with Hispanic background and individuals from the Middle East, India, and Mediterranean regions [8]. The disease was first described in the medical literature by the American physician James B. Herrick in 1910 [9]. Sickle cell disease is an autosomal-recessive disease caused by a point mutation in the hemoglobin beta gene found on chromosome 11p15.5. Several subtypes exist, depending on the exact mutation in each hemoglobin gene, and results in a number of health problems, for example, attacks of pain “sickle cell crisis,” feet, anemia, bacterial infection, acute chest syndrome, pulmonary hypertension, stroke, cardiac, CNS, gastrointestinal involvement and nephropathy which is not only a chronic comorbidity but is also one of the leading causes of mortality. Significant advances in prophylactics and therapy achieved improved survival among children with sickle cell disease, with the majority of children attaining adulthood [10]. However, The average life expectancy in the developed world is 40–60 years with only 35.0% surviving beyond age 35 years was reported by the Centers for Disease Control (CDC).

Problems in sickle cell disease typically begin around 5–6 months of age. Knowledge of the natural progression of the disease, as well as identification of persons at risk, allows for timely intervention and improved outcomes. The search for biomarkers for the early diagnosis of the disorder and its outcomes is an area of intense contemporary research [11]. Our understanding of the basic science of molecular biology, oncology, genetics, and the management of several oncologic conditions made a huge evolution in the field of pediatric oncology. The previous decade was almost associated with fatal outcomes have changed a lot and replaced by an era in which most childhood cancers are cured.

This has been made possible not only because of advances in chemotherapeutic regimen but also, because of the parallel development of radiodiagnosis, radiotherapy, surgery as well as supportive care such as the pre-emptive use of antibiotics and blood product therapy.

There is greatest variation in childhood cancer incidence internationally, when comparing developed countries to developing ones. It is estimated that childhood cancer has an incidence of more than 175,000 per year, and a mortality rate of approximately 96,000 per year. In developed countries, childhood cancer has a
cancer has an incidence of more than 175,000 per year, and a mortality rate of comparing developed countries to developing ones. It is estimated that childhood regimen but also, because of the parallel development of radiodiagnosis, radio-

mortality of approximately 20% of cases. In low income countries, on the other hand, mortality ranges from 80–90%. This may attributed to different modalities in cancer diagnosis, differences in risk factors among different ethnic population subgroups as well as differences in reporting. In children aged 0–14 years incidence rates range from less than 100 per million in areas of sub-Saharan Africa and India to more than 150 per million in some populations of North America and Europe [12].

Familial and genetic factors are identified in 5–15% of childhood cancer cases. Many epidemiological studies have reported the effects of cancer genetics, family pedigrees and penetrance, and identified subtypes of certain cancers and their implications for treatment and prognosis. In addition, the study of certain genetic diseases that increase the risk of malignancy in childhood has led to understanding the genetics of cancer [13].

Survival from childhood cancer is no longer rare, and people who have been cured of cancer during childhood should be accepted as normal members of society. The overall survival rate for children’s cancer has increased from 10% to nearly 80% today, and it is considered one of the major success stories of medicine in the twenty-first century. Improvements in the survival rates of leukemias, Hodgkin lymphoma, gonadal, and renal tumors have been notable successes. On the other hand, Overall mortality has decreased by 50% between 1975 and 2010 [14, 15].

Improvements in survival rate has led to the new challenge of caring for a growing number of cancer survivors. The most ominous late effect of pediatric cancer treatment is a second malignancy, for example, the risk of a second malignancy appears 15–20 years after an initial diagnosis of acute lymphoblastic leukemia is approximately 10% [16]. Many risk factors such as environmental factors, treatment and hereditary factors have been incriminated in second cancer. For example, the risk of acute myeloid leukemia in subject with the 9:11 translocation is approximately 3–6% within 5 years of chemotherapy that includes alkylating agent therapy or high-dose etoposide according to the dose and type of in addition to exposure to diagnostic radiation in utero has been associated with an increased risk of childhood cancer [17].

Contemporary Pediatric Hematology and Oncology covers many aspects of research and patient management within the area of blood disorders and malignant diseases in children. Of interest are clinical studies as well as basic and translational research reports regarding pathogenesis, genetics, molecular diagnostics, pharmacology, molecular targeting, standard and novel therapies for the most common blood disorders and childhood cancer. This book intends to provide the reader with a comprehensive overview on today’s practices and tomorrow possibilities about the most important pediatric hematological and oncological diseases.

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References


the American Medical Association. 2007;297(11):1207-1215

Section 2
Nocturnal Enuresis in Sickle Cell Anemia
Section 2

Nocturnal Enuresis in Sickle Cell Anemia
Chapter 2
Nocturnal Enuresis in Children with Sickle Cell Anemia
Samuel N. Uwaezuoke, Chizoma I. Eneh, Osita U. Ezenwosu and Ikenna K. Ndu

Abstract
Sickle cell anemia (SCA) is the commonest hemoglobin disorder among the black population worldwide. Children with SCA may eventually end up with end-organ complications: the kidneys being one of the most frequently affected organs. The renal complications arise from medullary ischemia and infarction leading to features of tubular dysfunction such as hyposthenuria and renal tubular acidosis. Early in life, children with SCA may present with hyposthenuria: one of the earliest renal defects in the disease which results in an obligatory urine output of more than 2 l in a day. The symptomatic manifestation as nocturnal polyuria is thought to be the reason for nocturnal enuresis observed in these children. In spite of the more prevalent occurrence of nocturnal enuresis in children with SCA than in their non-SCA colleagues, its precise underlying mechanisms still remain controversial, with divergent conclusions regarding its pathogenesis. However, the consensus is now tilting towards a multifactorial etiopathogenesis in affected children. This book chapter aims to discuss the epidemiologic perspectives of nocturnal enuresis in SCA, as well as the current hypotheses on the etiopathogenesis of this complication.

Keywords: sickle cell anemia, nocturnal enuresis, hyposthenuria, multifactorial etiopathogenesis

1. Introduction
Sickle cell anemia (SCA) is the commonest hemoglobin disorder among the black population worldwide [1, 2]. As a genetic defect with the Mendelian autosomal-recessive inheritance, children with the sickle cell hemoglobin genes in the homozygous form have reversibly sickled and irreversibly sickled red blood cells. These abnormal red cells, which become rigid having lost their deformability, consequently block the microvasculature resulting in vasoocclusion. They are also prone to damage which leads to chronic hemolysis. Most of the clinical features of SCA are essentially related to these two events.

Children with SCA may eventually end up with end-organ complications: the kidneys being one of the most frequently affected organs. The renal complications arise from medullary ischemia and infarction leading to features of tubular dysfunction such as hyposthenuria and renal tubular acidosis [3]. As early as 3 years of age, children with SCA may present with hyposthenuria: one of the earliest renal defects in the disease which results in an obligatory urine output of more than 2 l in a day [4]. The symptomatic manifestation as nocturnal polyuria is thought to...
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be the reason for the observed nocturnal enuresis in these children. In spite of the more prevalent occurrence of nocturnal enuresis in children with SCA than in their normal colleagues, the precise underlying mechanisms have not yet been resolved. Research on the subject has led to divergent conclusions about the pathogenesis; one report had earlier suggested that hyposthenuria was a major determinant of enuresis in the disease [5], while other authors not only controverted this observation but had reported disparate etiopathogenic factors [6–8]. In fact, a recent review of published evidence on the subject indicates similar determinants of nocturnal enuresis for both SCA and non-SCA patients [9]. Thus, the role of hyposthenuria as the exclusive determinant of nocturnal enuresis in children with SCA remains debatable although the consensus is now tilting towards a multifactorial etiopathogenesis in affected children.

This book chapter aims to discuss the epidemiologic perspectives of nocturnal enuresis in SCA, as well as the current hypotheses on the etiopathogenesis of this complication.

2. Nocturnal enuresis in SCA: epidemiologic perspectives

Nocturnal enuresis has been defined as the persistence of urination in the bed (bedwetting) at night, two or more times per week after the age of 5 years, for a period of at least 3 months [10]. It can present as a primary form (no previous dry period) or a secondary form (previous dry period), and as monosymptomatic (absence of daytime symptoms) or non-monosymptomatic (presence of daytime symptoms) [9]. Studies which show that children with SCA have a tendency for nocturnal enuresis more than children with normal hemoglobin however reported different prevalence rates and epidemiologic patterns, depending on study methods and definition criteria (Table 1).

2.1 Presumed risk factors for nocturnal enuresis

For instance, the possible effect of sex and socioeconomic status on enuresis in children has been well documented in several studies [7, 11–16]. Firstly, male predominance was noted among children with SCA in some of the studies [7, 11, 13–15], whereas a female predominance was reported in one study [12]. Although the disparity could be due to study selection bias, a similar trend of male predominance has also been reported among non-SCA children [15, 17]. This gender bias suggests that contributory factors to nocturnal enuresis in non-SCA children such as slower maturation and reduced responsiveness to toilet training in boys [18], and more frequent developmental delays [19], may also apply to children with SCA. Secondly, there appears to be no significant impact of socioeconomic status on the prevalence of nocturnal enuresis in both SCA children [7, 14], and their non-SCA counterparts [16]. However, a previous report indicates that enuresis in non-SCA children was more frequent in those from lower socioeconomic classes [17], whereas another study noted a higher prevalence among non-SCA children from higher socioeconomic classes [20].

2.2 Global prevalence rates of nocturnal enuresis

There is a wide variation in the global prevalence rates of nocturnal enuresis among children with SCA (Table 1). Prevalence rates vary from 25–51% depending on methodology and definition of nocturnal enuresis adopted in each study. In the West African sub-region, prevalence rates of 41.6, 31.4 and 47.1% were reported in south-west [11], south-east [14], and north-west [15] regions of Nigeria respectively.

<table>
<thead>
<tr>
<th>Study Method</th>
<th>Age Bracket</th>
<th>NE Definition Prevalence</th>
<th>Sex</th>
<th>Socioeconomic Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective interview</td>
<td>6–40 years</td>
<td>Bed wetting at night &gt;1/week</td>
<td>Male</td>
<td>Not significant</td>
</tr>
<tr>
<td>Prospective interview</td>
<td>4–20 years</td>
<td>Recurrent bed wetting incontinence</td>
<td>Male</td>
<td>Not reported</td>
</tr>
<tr>
<td>Prospective interview</td>
<td>6–21 years</td>
<td>Bed wetting at night &gt;1/month</td>
<td>Male</td>
<td>Not significant</td>
</tr>
<tr>
<td>Prospective interview</td>
<td>6–21 years</td>
<td>Urinary passage of urine during sleep&gt;1/month</td>
<td>Male</td>
<td>Not reported</td>
</tr>
<tr>
<td>Prospective interview</td>
<td>5–22 years</td>
<td>Involuntary nocturnal micturition</td>
<td>Male</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Table 1. Global prevalence rates of nocturnal enuresis.
2. Nocturnal enuresis in SCA: epidemiologic perspectives

The presence of nocturnal enuresis (NE) in children with sickle cell anemia (SCA) has been reported in various studies, with reported rates ranging from 19.4% to 81.1% [2, 3]. The etiopathogenesis of NE in SCA is multifactorial, involving both physiological and psychological factors. Studies on the prevalence of NE in SCA have shown a higher occurrence compared to the general population [4].

2.1 Presumed risk factors for nocturnal enuresis

The risk factors for NE can be divided into medical and psychosocial factors. Medical factors include urological and neurological conditions, whereas psychosocial factors include socioeconomic factors and psychological stressors. A significant gender bias has been reported in the prevalence of NE, with boys exhibiting higher rates compared to girls, even in SCA patients [5].

2.2 Global prevalence rates of nocturnal enuresis

The global prevalence rates of NE among children with SCA range from 56.6% to 88.8%. A recent study conducted in the USA found a prevalence of 81.1% in a group of SCA patients [6].

Table 1: Nocturnal enuresis (NE) in children with sickle cell anemia: epidemiologic perspectives.

<table>
<thead>
<tr>
<th>Study authors (Country)</th>
<th>Study method (age bracket)</th>
<th>NE definition</th>
<th>Prevalence rates (N)</th>
<th>Sex predominance</th>
<th>Effect of socioeconomic status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eneh et al. (Nigeria)</td>
<td>Prospective parental interview (5–11 years)</td>
<td>DSM-IV criteria</td>
<td>31.4% (70)</td>
<td>Male</td>
<td>Not significant</td>
</tr>
<tr>
<td>Akinyanju et al. (Nigeria)</td>
<td>Prospective parental interview (4–20 years)</td>
<td>Involuntary passage of urine during sleep &gt;1/month</td>
<td>41.6% (209)</td>
<td>Male</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ogunrinde et al. (Nigeria)</td>
<td>Prospective parental interview (5–16 years)</td>
<td>≥3 bedwetting episodes/month (5–6 year old) or 1 episode/month (&gt;6 year old)</td>
<td>47.1% (360)</td>
<td>Male</td>
<td>Not significant</td>
</tr>
<tr>
<td>Mahiala Babela et al. (Congo Brazzaville)</td>
<td>Cross-sectional study (5–20 years)</td>
<td>Micturition during sleep in a child aged &gt;5 years</td>
<td>51% (456)</td>
<td>Female</td>
<td>Not reported</td>
</tr>
<tr>
<td>Portocarrero et al. (Brazil)</td>
<td>Prospective questionnaire (5–17 years)</td>
<td>Not stated</td>
<td>32% (155)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Barakat et al. (USA)</td>
<td>Prospective phone interview (5–22 years)</td>
<td>Nocturnal urinary incontinence &gt;5 years of age (&gt;2/week for 3 months)</td>
<td>39.2% (217)</td>
<td>Male</td>
<td>Not reported</td>
</tr>
<tr>
<td>Jordan et al. (USA)</td>
<td>Prospective interview (5–17 years)</td>
<td>Urinary incontinence &gt;5 years of age (&gt;2/week for 3 months)</td>
<td>25% (126)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Figueroa et al. (USA)</td>
<td>Prospective screening questionnaire (6–21 years)</td>
<td>Bed wetting at least 2/week</td>
<td>30% (91)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Field et al. (USA)</td>
<td>Prospective questionnaire (6–20 years)</td>
<td>Recurrent bed wetting</td>
<td>33% (213)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Lehmann et al. (USA)</td>
<td>Prospective questionnaire (4–19 years)</td>
<td>Pre-sleep bed wetting/month</td>
<td>39% (221)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Readett et al. (Jamaica)</td>
<td>Prospective interview (8 years)</td>
<td>Bed wetting 2 nights/week</td>
<td>45% (175)</td>
<td>Male</td>
<td>Not significant</td>
</tr>
<tr>
<td>Ekinçi et al. (Turkey)</td>
<td>Prospective questionnaire (6–40 years)</td>
<td>Bed wetting at night &gt;1/week for 3 months</td>
<td>26.4% (55)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

N = study population, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, USA = United States of America, †South East Nigeria, ‡South West Nigeria.

References:


Table 1. Nocturnal enuresis (NE) in children with sickle cell anemia: epidemiologic perspectives.
The study in south-east of the country prospectively interviewed parents of SCA subjects aged 5–11 years and parents of age- and sex-matched non-SCA controls; using the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria to define nocturnal enuresis [14]. In South West Nigeria, the authors also used prospective parental interview for subjects and controls aged 4–20 years, but defined nocturnal enuresis as ‘involuntary micturition during sleep which occurred more often than once in a month’ [11]. Conversely, the study in North West Nigeria used a structured questionnaire to obtain information from parents of enrolled 5- to 16-year-old subjects and controls; defining nocturnal enuresis as ‘3 or more episodes of bedwetting per month in a child aged 5 to 6 years and at least, once monthly in an older child’ [15]. In Central Africa, a prevalence rate of 51% was reported in a cross-sectional study of 5- to 20-year-old SCA patients (with age- and sex-matched controls) in Congo-Brazzaville which used the defining criteria for nocturnal enuresis as ‘complete act of urination most often during sleep in a child over 5 years’ [12]. Elsewhere in South America, a Brazilian study which was conducted on 5- to 17-year-old Negroid children and adolescents with SCA reported a prevalence rate of 32% [21]. The authors prospectively administered a questionnaire on the caregivers of these subjects and their age-matched controls. In North America, studies in the United States conducted among African-Americans documented prevalence rates of 39% [6], 39.2% [13], 25% [22], 30% [23], and 33% [24]. In these studies, there was disparity in the age bracket of the study population and the definition adopted for nocturnal enuresis. A prospective phone interview was used in one study, which defined nocturnal enuresis as ‘incontinence of urine at night after 5 years of age, more than twice a week for at least 3 months,’ while the study population were aged 5–22 years [13]. Another study employed a prospective interview of parents whose children were aged 5–17 years, and defined nocturnal enuresis as ‘incontinence of urine at night after 5 years of age, more than twice a week for at least 3 months’ [22]. Two of the studies utilized prospective questionnaires [6, 24], but interviewed primary caregivers of subjects who were aged 6–20 years [6], and 4–19 years [24]; defining nocturnal enuresis as ‘recurrent problem with bedwetting’ [6], and ‘wet bed in 1 month before sleep study’ [24]. In the last of the studies, nocturnal enuresis was defined ‘as wetting bed at least twice per week’ [23]; primary nocturnal enuresis was studied among subjects aged 6–21 years with a prospective screening questionnaire. In the Caribbean, a Jamaican study which used the prospective interview method reported a prevalence rate of 45% among 8-year-old SCA patients [7]. The authors’ definition of nocturnal enuresis was ‘being wet for at least 2 nights per week.’ A study in Turkey which adopted the definition criterion of nocturnal enuresis as ‘wet bed at night more than once a week for at least 3 months,’ reported a prevalence rate of 26.4% [25]. The investigators conducted semi-structured interviews with caregivers of pediatric and adult patients. Perhaps, the combination of SCA and thalassemia patients in the study population (with preponderance of the latter) as well as the wide age-bracket of 6–40 years accounted for this comparatively lower prevalence rate. Furthermore, it has been established that the prevalence of nocturnal enuresis decreases with advancing age, although this finding was essentially noted among non-SCA subjects [26, 27].

3. Nocturnal enuresis in SCA: hypotheses on etiopathogenesis

There are now several hypotheses on the etiopathogenesis of enuresis in children [9, 28, 29]. In fact, it is believed that children with SCA may have a tendency to develop nocturnal enuresis because of the common general etiopathogenic factors in childhood, SCA-related etiopathogenic factors or a combination of both [9]. Specifically, the unresolved questions include the following: What is the exact
role of hyposthenuria in SCA-related nocturnal enuresis? What are the contribu-
tory bladder-specific factors? Is there any relationship between sleep disordered
breathing (SDB) and nocturnal enuresis in SCA? and Is there a difference in arous-
ability threshold in normal subjects with nocturnal enuresis and those with SCA?
[9]. Interestingly, the current hypotheses on the etiopathogenesis of SCA-related
nocturnal enuresis revolve around these posers.

Firstly, the nocturnal polyuria resulting from hyposthenuria has long been
suggested as the cause of nocturnal enuresis in SCA patients [5]. This hypothesis
is supported by the fact that hyposthenuria is one of the commonest and earliest
infarction-related renal complications, as intravascular sickling occurs more readily in
the kidneys than in any other organs [30]. The microvasculature of the renal medulla
is particularly susceptible to hypoxia induced by sickling and vasoocclusion [31].
Medullary ischemia and infarction result in the impairment of the urine-concentrating
ability of the vasa recta and juxtedudillary nephrons, as failure of this function is
thought to manifest as polyuria and enuresis [32, 33]. Although the ‘hyposthenuria
hypothesis’ has been disputed by some authors who failed to establish a causal link
between SCA and enuresis [7, 34], it has later been observed that both urine osmol-
ality and overnight urine volume after fluid restriction were similar in enuretic and
non-enuretic children with SCA; making the authors to conclude that low maximum
functional bladder capacity and high overnight urine volume to maximum functional
bladder capacity ratio were the determinants of nocturnal enuresis in affected children
rather than low urine osmolality and high overnight urine volume [8].

Secondly, another hypothesis on nocturnal enuresis in the general population is
that it results from an interaction of detrusor instability, delayed arousal from sleep
and nocturnal polyuria [28]. Other authors also observed that in enuretic children,
the nocturnal bladder capacity during sleep was significantly smaller than the
diurnal functional capacity; thus highlighting the role of the inability to hold urine
during sleep as an important etiopathogenic mechanism for nocturnal enuresis [29].
Nocturnal polyuria, nocturnal detrusor over-activity and high arousal thresholds
are now regarded as crucial factors in the pathogenesis of enuresis, with an under-
lying mechanism on the brainstem level probably common to these pathogenic
mechanisms [35]. In a review which appraised the possible etiopathogenic factors of
primary nocturnal enuresis, the partly proven mechanisms were listed as matura-
tional delay of the central nervous system, genetic factors, sleep disorders and SDB,
and low levels of nocturnal anti-diuretic hormone (ADH) secretion [36]. Among
these hypotheses, delayed functional maturation of the central nervous system is
thought to be the most plausible mechanism for nocturnal enuresis as it reduces the
child’s ability to inhibit nocturnal bladder emptying [36]. This theory is supported
by the observation of spontaneous improvement in enuresis which occurs with
advancing age [26]. Despite bladder filling, the non-perception of the sensory out-
put emanating from its stretching removes the cortical control on the contraction
of the urethral sphincter. Failure of the sleep arousal mechanism due to high arousal
thresholds may also contribute to this inability to inhibit nocturnal bladder empty-
ing. Presumably, these hypotheses on etiopathogenesis also apply to nocturnal
enuresis in children with SCA. For instance, in these children a strong link between
nocturnal enuresis and urinary bladder dysfunction has been reported by several
authors [8, 37, 38]. Another recent postulation is that SCA-related enuresis may be
due to atonic detrusor muscle which results in an underactive bladder with defective
emptying mechanism. This abnormality is thought to be a consequence of chronic
bladder ischemia caused by recurrent cycles of ischemia-perfusion injury triggered
by vasoocclusion [39]. Evidence for this hypothesis was reported by some authors
who studied the urinary bladder function in a transgenic sickle cell disease murine
model and found these pathophysiologic changes: reduced urine output, inability
to produce the typical bladder contraction and emptying, lower detrusor muscle, small bladder contraction and reduced urethral contraction [40].

Thirdly, the role of sleep disorders and SDB in the etiopathogenesis of nocturnal enuresis has also been advanced as a sleep-related study show that patients with nocturnal enuresis have difficulties in waking, and are thus considered as ‘deep sleepers’ [41]. In addition, nocturnal enuresis is associated with SDB as a result of upper airway obstruction in children; surgical relief by tonsillectomy, adenoidectomy or both was reported to have reduced nocturnal enuresis in up to 76% of patients [42]. In a recent study, enuresis has not only been linked to SDB in children with SCA but the severity of SDB has been observed to have a strong correlation with frequency of nocturnal enuresis [6]. Notably, SDB is a common sleep disorder comprising a spectrum from snoring to obstructive sleep apnea syndrome (OSAS) which may worsen nocturnal enuresis through disrupted sleep and neurologic dysregulation [9]. While the finding of a study suggests that SDB is more prevalent in children with SCA than in the general population [43], overwhelming evidence also shows that a significant relationship exists between SDB and nocturnal enuresis among non-SCA children [44–46].

Furthermore, the role of low levels of some vitamins in the etiopathogenesis of nocturnal enuresis has been highlighted in recent studies. For instance, enuretic children were observed to have lower serum vitamin B₁₂ and folate levels than their non-enuretic counterparts [47, 48]. The reduced vitamin levels are believed to be associated with slow cortical maturation which has been linked to enuresis. Interestingly, significantly lower or deficient vitamin B₁₂ levels have equally been reported in children with SCA compared to non-SCA controls [49, 50]. In addition, increased risk of nocturnal enuresis has been observed in vitamin D-deficient children as this vitamin deficiency directly correlated with severity of enuresis [51]. In a recent systematic review, the prevalence of vitamin D deficiency was reported to vary from 56.4% to 96.4% in children with SCA [52]. This link between vitamin D deficiency and nocturnal enuresis can be explained partly by its influence on SDB and nocturnal polyuria. Reports indicate that low level of serum 25 (OH) D was associated with increased risk of developing OSAS [53], as well as primary snoring [54]. The association of low vitamin levels with OSAS is reportedly mediated through promotion of adenotonsillar hypertrophy, chronic rhinitis and/or myopathy of airway muscle [55]. Better still, low vitamin D levels may result in nocturnal enuresis through obstructive sleep apnea, sleep fragmentation and nocturnal polyuria, which all occur in children with SCA [39].

Another etiologic consideration for nocturnal enuresis seen in SCA is its association with some involuntary movements such as periodic limb movement syndrome and restless leg syndrome. The prevalence of periodic limb movement syndrome in SCA has been documented as 20.5–29% [56–58], which was significantly higher than the rates of 1.2–8% reported for non-SCA children [59, 60]. Similarly, a prevalence rate of 11.1% has been observed for children with restless leg syndrome [56]. Notably, both involuntary movements are associated with sleep disruption [60]. Given that enuretic children have higher incidence of periodic limb movement and sleep fragmentation [59] and the higher rate of periodic limb movement syndrome associated nocturnal enuresis and sleep disruption in SCA patients, it is therefore not surprising to observe a high prevalence rate of nocturnal enuresis in them. To underscore the nexus between these aforementioned etiologic factors (low serum vitamin D level and restless leg syndrome), it has been observed that Vitamin D supplementation also improved the severity of this involuntary movement [61].

In summary, the etiopathogenic mechanisms involved in nocturnal enuresis among SCA and non-SCA children are multifactorial and not mutually exclusive, and they include hyposthenuria-related nocturnal polyuria, decreased bladder capacity or nocturnal bladder over-activity, high sleep arousal thresholds and SDB [9] (Figure 1).
Children were observed to have lower serum vitamin B12 and folate levels than their non-enuretic counterparts [47, 48]. The reduced vitamin levels are believed to produce the typical bladder contraction and emptying, lower detrusor muscle, nocturnal bladder over-activity, high sleep arousal thresholds and SDB [9] (Figure 1).

The proposed etiopathogenic mechanisms for nocturnal enuresis. SDB, sleep-disordered breathing; nocturnal polyuria, induced by hyposthenuria. Concept and design: by SNU (one of the authors).

4. Conclusion

Although nocturnal enuresis appears more prevalent in children with SCA than in their non-SCA counterparts, the exact etiopathogenesis of enuresis is not completely understood. In fact, the suggested mechanisms for nocturnal enuresis in SCA children are also applicable to their non-SCA counterparts. Moreover, the multiregional variations in prevalence rates may be due to differences in definition criteria and study methods. Male predominance in enuretic children has been somewhat established, but there is no unanimity yet on the influence of socioeconomic status on prevalence rates. Perhaps, adopting standardized definitions and study methods may in future minimize the disparities in the reported prevalence rates. More importantly, further research is still required to establish the precise etiopathogenesis of nocturnal enuresis in children with SCA.

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Disclosure

The authors declare that there are no conflicts of interest.
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Section 3

Inherited Bone Marrow Failure Syndromes
Chapter 3

Inherited Bone Marrow Failure

and Chromosome Instability

Syndromes and their Cancer

Predisposition

Zhan He Wu

Abstract

Inherited bone marrow failure syndromes (IBMFS) and chromosome instability syndromes (CIS) are the most classic and representative genetic syndromes. They are classified as genetic rare diseases, typically with complex medical complications in the delay of mental and physical development. Commonly, these syndromes present with different degrees of dysmorphics; organs/systems dysfunction generally and these syndromes have higher risk of inherited solid cancer and leukemia predisposition due to the similar pathway of DNA defects. These syndromes are often hard to diagnose and they overlap with their phenotypes clinically. Very importantly cancers from the germ line mutation of these syndromes require different treatment strategies with the sporadic malignancies. The significance of recognition of such diseases is not only beneficial to patients phenotypically affected but also to individuals phenotypically unaffected and members/relatives of the family. Remarkable advances have been made in the definition and classification of these genetic syndromes. Identification of the IBMFS and CIS has led to important advances in the understanding of the genotypes, guiding the clinical practice of the phenotypes. Interestingly, such studies provided insights into the function of the various DNA repair pathways. Fanconi anemia studies are an example in IBMFS and CIS is named as the paradigm of the studies of cancer and aging.

Keywords: inherited bone marrow failure syndromes, chromosomal instability syndromes, genetic rare syndromes, cancer predisposition, cancer prone human syndromes

1. Introduction

Bone marrow failure is the term for the activity or function in the bone marrow production of blood cells from the hematopoietic cells. Studies demonstrated that there are more than 80 causative genes identified from bone marrow failure disorders but still about 40% of the disease cause is unidentified. Bone marrow failure disorders are classified into idiopathic (acquired) and inherited-(IBMFS) due to the inherited conditions transmitted in autosomal recessive pattern [1, 2].
Chapter 3

Inherited Bone Marrow Failure and Chromosome Instability Syndromes and their Cancer Predisposition

Zhan He Wu

Abstract

Inherited bone marrow failure syndromes (IBMFS) and chromosome instability syndromes (CIS) are the most classic and representative genetic syndromes. They are classified as genetic rare diseases, typically with complex medical complications in the delay of mental and physical development. Commonly, these syndromes present with different degrees of dysmorphics; organs/systems dysfunction generally and these syndromes have higher risk of inherited solid cancer and leukemia predisposition due to the similar pathway of DNA defects. These syndromes are often hard to diagnose and they overlap with their phenotypes clinically. Very importantly cancers from the germ line mutation of these syndromes require different treatment strategies with the sporadic malignancies. The significance of recognition of such diseases is not only beneficial to patients phenotypically affected but also to individuals phenotypically unaffected and members/relatives of the family. Remarkable advances have been made in the definition and classification of these genetic syndromes. Identification of the IBMFS and CIS has led to important advances in the understanding of the genotypes, guiding the clinical practice of the phenotypes. Interestingly, such studies provided insights into the function of the various DNA repair pathways. Fanconi anemia studies are an example in IBMFS and CIS is named as the paradigm of the studies of cancer and aging.

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There are more than 30 different types of disorders, classified into inherited bone marrow failure syndromes. The common types are Fanconi anemia, dyskeratosis congenita, Swachman-Diamond syndrome, Diamond-Blackfan anemia, Congenital amegakaryocytic thrombocytopenia, Severe congenital neutropenia and thrombocytopenia absent radii [3, 4].

There is another group of syndromes named as chromosomal instability syndromes (CIS), are also known as chromosomal breakage syndromes, typically transmitted in an autosomal recessive pattern of inheritance defined on the basis of cell culture in vitro. The affected individuals exhibit elevated rates of chromosomal breakage or instability, leading to chromosomal rearrangements. CIS often lead to an increased tendency to develop certain types of malignancies as well [5, 6]. Individuals with IBMFS and CIS are commonly in children and these disorders are often lethal.

Relatively high rates of some types of IBMFS and CIS can occur in certain ethnic groups. Diagnosis is usually complicated because the symptoms presented from individuals with IBMFS and CIS may be varied and are often very complex. So practically the differential diagnosis of these two groups of syndromes clinically can be very difficult because they share some characteristics of overlapping phenotypes.

Studies on IBMFS and CIS for better therapies have achieved exciting successes, not only beneficial to IBMFS and CIS studies self but also beneficial to other diseases. One of the IBMFS and CIS, Fanconi anemia, is the disease which achieved a success in stem cell transplantation used umbilical blood in 1988 [7]. This revolutionary treatment has been using as an effective therapy for many different types of diseases, commonly in malignancies in clinical application since then. Studies found that the majority of IBMFS and CIS are associated with cancers from the germ line mutation and such studies have explored many mysteries in cancer research. For example, Fanconi anemia is found to associate with many different types of cancers from those mutated genes [8].

Recent advances in molecular-based studies on the identification of responsible genes and defects in their pathways of IBMFS and CIS have provided more understanding in the pathophysiological mechanisms. Such advances also provided the link between IBMFS/CIS and some types of cancers in the genetic defective pathways. Results obtained from research showed that human cancer is caused of genetic and environmental factors and their interactions in general. Cancers fall into the genetic disease category due to two genetic factors: (1) acquired somatic mutations produced by genomic instability and (2) inherited gene mutations. The important difference between familial/inherited and sporadic cancer is due to the form of germ line mutation in a DNA caretaker gene facilitating the accumulation of oncogenic DNA changes, which can result in a high susceptibility to cancer. Both IBMFS and CIS have cancer predisposition commonly in AML and MDS, often diagnosed at a young age. These types of malignancies require different treatment strategies due to the underlying gene defects.

To increase the recognition of myeloid leukemia/MDS associated with inherited or germ line mutations, a major change has been made by adding the germ line mutation in the classification of myeloid neoplasms and acute leukemia in the new version of classification of tumors of the hematopoietic and lymphoid tissues published by the World Health organization (WHO) in 2016 including (1) myeloid neoplasms with germ line predisposition without a pre-existing disorder or organ dysfunction, (2) myeloid neoplasms with germ line predisposition and pre-existing platelet disorder and (3) myeloid neoplasms with germ line predisposition and other organ abnormalities.
dysfunction. Similarly, studies demonstrated that hereditary predisposition has a higher risk of development of acute lymphoblastic leukemia (ALL) as reported in TP53 [9].

Recently, studies on genetic disease by the modern technologies, particularly by the next generation sequencing dramatically increased the understanding of the etiology and classification of IBMFS. So more and more mutated genes have been identified and these studies demonstrated that genomic instability, defects in DNA repair and telomere biology are the genetic causes. Such discoveries have provided insights into several biological pathways, correlation between phenotype and genotype, and clinical therapeutically strategies.

In this chapter, the aim is to review and discuss IBMFS and CIS, together with comparison of their phenotypes and genotypes. It is hoped that review will increase understanding in further translation of research to clinical practice, so as to raise awareness of these genetic-based diseases and the impact on patients’ lives as well as improvement of the therapies.

2. The common types of IBMFS

IBMFS are a heterogeneous group of complex genetic disorders characterized by bone marrow failure, commonly associated with one or more somatic abnormalities and increased cancer risks in childhood but also in adulthood.

The common and representative types of IBMFS are Fanconi anemia, Dyskeratosis congenita, Shwachman-Diamond syndrome, Diamond-Blackfan anemia, Congenital Amegakaryocytic thrombocytopenia, Severe congenital neutropenia and thrombocytopenia absent radii. The phenotype and genotype of IBMFS and their association are summarized in Table 1.

2.1 Fanconi anemia

Fanconi anemia (FA) is a hereditary disorder with defects in DNA repair and is usually inherited as an autosomal recessive trait but it can be X-linked (FA

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Inheritance</th>
<th>Somatic abnormalities</th>
<th>Bone marrow failure</th>
<th>Short telomeres</th>
<th>Cancer risk</th>
<th>Identified gene numbers</th>
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<td>Yes</td>
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**Table 1.**
Common types of inherited bone marrow failure syndromes.
complementation group B). Cells from patients with FA are more sensitive to chemotherapy than those from patients without FA, which can cause severe consequences from the normal dose of chemotherapies. So far, 22 genes responsible for FA have been identified [10]. In the general population, the complementation A occurs in about 60–70%, while complementation-C occurs in about 15% and the complementation-G occurs in about 10% of the total 22 FA responsible genes mutated with a vary of their subgroups in some geographical regions (Table 2 and Figure 1).

Patients with FA are characterized with congenital abnormalities but progressive bone marrow failure is the most common characteristic, so it is named as IBMFS. FA also increases susceptibility to malignancies and individuals with FA also can suffer one or more types of cancers.

FA also has with variable congenital malformations and a predisposition to develop hematological or solid tumors, commonly in MDS, AML, and solid tumors, commonly carcinoma of the oropharynx and skin. Studies found the association of FA with a pattern of recurrent chromosomal abnormalities including monosomy chromosome 7, deletion of the long arm of chromosome 7, gain of the long arms of chromosome 3 and 1 and the RUNX1 gene mutations in about 20% of the combined MDS cases. Chromosome abnormalities with 7 and 3 had a poor prognostic indication value [11].

<table>
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<td>16q22.3</td>
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</table>

Data extracted from the Rockefeller University » Fanconi Anemia Mutation. Database at www.rockefeller.edu/fanconi. Ref. [10].

Table 2.
Fanconi anemia genes and locations on chromosomes.
The FA pathways are defined from the encoded proteins work in concert in a distinct genomic maintenance. The FA pathways in normal cells are not constitutionally active but they are turned on during the S phase of the cell cycle in the presence of DNA damage to coordinate distinct repair functions in nucleotide excision, translesion synthesis and homologous recombination to remove the cross links [12].

The 22 FA gene products make up the FA pathways in the maintenance of genomic stability and the FA pathways can be activated by DNA damage and replication. The number of FA proteins reflects the complicated nature of the FA pathways. Mutation in any of the 22 FA genes causes defects in the response to DNA damage and repair results in disease of FA by the loss of DNA interstrand cross-links repair [13]. The FA pathways are the key event with the complex pathological mechanisms in DNA repair and cancer suppression in both inherited and sporadic cancers.

The proteins involved in FA consist of several classes of enzymes and structural proteins, including ubiquitin ligase, monoubiquitinated proteins and helicase [14]. FA nuclear core protein complex consists of eight proteins, encoded by FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL and FANCM, with ubiquitin ligase activity. This protein complex is required for the critical monoubiquitination of FANCD2 and FANCI in response to DNA damage during replication. The biological functions of this protein complex are to maintain DNA stability and repair DNA damage protein-protein interactions are required for core complex protein stability form the stable core protein complex in function that is required for the modification of FANCD2 and FANCI by monoubiquitination.

E3 ubiquitin-protein ligase FANCL belongs to the multi-subunit FA complex and is a ligase protein that mediates monoubiquitination of FANCD2, a key step in the repair of ICLs in the FA pathways [15]. FANCL is associated with hypersensitivity to DNA-damaging agents, chromosomal instability (increased chromosome breakage) and defective DNA repair [16]. The monoubiquitination process of FANCD2 and FANCI recruits DNA repair machinery in order to maintain genomic integrity during cellular proliferation within certain tissues. Mutation in any member
of a core protein complex results in the loss of the monoubiquitination of the FANCI/FANCD2 complex step [17]. FANCD2 and FANCI proteins are substrates for ubiquitination with the two being similar in size and domain structure. This monoubiquitination is the crucial event of the FA pathways, and the monoubiquitination isoform of FANCD2 associates with the repair protein BRCA1 in DNA damage-induced nuclear foci. This foci formation is induced by both cross-linking agents and DNA-damaging agents and this process is regulated by the nuclear core protein complex [18].

The genetic association between cancers with FA and without FA gene mutation clinically has been intensively investigated and a close connection has been discovered between FA and tumorigenesis observed from both clinical and cellular phenotypes. Inherited homozygous (bi-allelic) mutations from germ line can cause FA phenotype and increase susceptibility to both hematologic and non-hematologic malignancies [19]. The first case of FA was recognized as a cause of Juvenile leukemia in 1967 [20]. Cancers with FA gene mutations are difficult to be treated (except surgically) because cells from patients with FA are more sensitive to chemotherapy and radiation comparing with non-FA cancers [21]. The relative risk of non-hematologic malignancies in patients with FA is increased commonly for squamous cell carcinomas (700 times greater than in normal population) including the head and neck, vulva, esophagus, gastric osteogenic sarcoma, cervix and skin. Many other types of cancers including breast cancer, lung cancer, colon cancer and brain tumor were found from patients with FA as well, with the median onset age of cancers being 16 years old in FA patients compared with 68 years in the non-FA population [22]. In addition, FA patients could develop different types of cancers.

The risk of developing to acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) has been reported to increase by 785-fold [23, 24]. It is estimated that acute myeloid leukemia from the germ line mutation associated cause is about 10–15% and it could be higher. Inherited germ line mutations are present in an increasing proportion of children, predisposing them to leukemia. Several genetic syndromes have been found to associate with leukemia/cancers and the best examples are IBMFS and CIS. The risk of leukemia/cancers and the outcome of these syndromes particularly in these with substantial proportion of patients with therapy related leukemia/cancer harbor germ line mutations in DNA damage and response genes such as BRCA1/2 and TP53.

To deal with germ line mutated leukemia, not only requires an increase in awareness of germ line mutations but also taking family history from patients and offering genetic counseling for the relevant to malignant diagnosis, it also requires an understanding of the developments of the genetic landscapes because the treatment strategy for IBMFS and CIS associated malignancies is different from the malignancies in the sporadic manner. The differential diagnosis on malignancies such as MDS, acute leukemia and solid tumors is imperative.

Studies showed that there was no increase of cancer risk from FA carriers in overall but there was evidence that these carriers from FANCC type mutation increase breast cancer risk, so it was suggested that carries of relatives of FANCC should carefully follow the recommendations for breast cancer screening [25].

However, an early and accurate diagnosis for FA is often difficult because FA is a genetically and phenotypically heterogeneous disease lacking specific and typical clinical features. Diagnosis in more or less cases can be delayed until bone marrow failure or cancer/leukemia occurs. As a result, Delayed or misdiagnosis or even wrong treatment received for patients with FA are not uncommon events clinically in some regions or countries due to the lack of recognition of FA from the clinicians and the limitation in testing resource in laboratory.
2.2 Dyskeratosis congenita

Dyskeratosis congenita (DC or DKC) is an inherited disease in autosomal dominant, autosomal recessive and X-linked patterns which is defined as one of the IBMFS characterized by the presence of bone marrow failure and the mucocutaneous triad of abnormal skin pigmentation, nail dystrophy, and mucosal leukoplakia [26]. Patients with DC increases the risk of MDS, AML and other types of cancers (carcinomas of the upper gastro-intestinal tract). Aplastic anemia, MDS and AML from patient with DC could be the early or first signs to be seen clinically. DC is the most typical representative type in IBMFS in telomere abnormality causing genomic instability due to the accelerated telomere shortening to result in cell loss or dysfunction and nine genes responsible for DC (DKC1, TERT, TERC, TINF2, RTEL1, NOP10, NHP2, WRAP53 and CTC1) the functioning and maintenance of telomeres have been identified so far [27].

2.3 Shwachman-Diamond syndrome

Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder characterized by early onset exocrine pancreatic insufficiency, bone marrow failure and other genetic abnormalities. About 20% of SDS patients will develop MDS and 25% of patients with SDS will develop leukemia [28]. Deletion 5q, monosomy/ deletion of chromosomal 7q and 20q are the most frequent abnormalities in patients with SDS presenting with MDS but such types of chromosomal abnormalities do not contribute to leukemia transformation. Molecular studies showed about 90% of SDS patients have SBDS gene mutation and its product has an important role in the maturation of the 60S ribosomal subunit [29].

2.4 Diamond-Blackfan anemia

Diamond-Blackfan anemia (DBA) is a rare, dominantly inherited syndrome characterized by bone marrow failure, birth defects, and a significant predisposition to cancer. The main clinical characteristics of DBA are the early infant anemia selectively in erythroid lineage (pure red cell aplasia) with some somatic abnormalities such as craniofacial thumb, cardiac and urogenital malformations [30] commonly develop to an increased predisposition to MDS, AML and other types of tumors has been reported [31]. DBA gene (RPS19) was identified in 1999 [32].

Subsequent studies found the heterozygous mutations in other encoding genes for ribosomal proteins of the small (RPS24, RPS17, RPS7, RPS10, RPS26) and large (RPL5, RPL11, RPL35) ribosomal subunits have also found to associated with DBA and RPS5 gene was found tend to have multiple physical abnormalities [33]. RPS19 mutations causing DBA showed ethnic difference in phenotype expression [34]. Recent studies using aCGH identified deletion of RPL15 as a novel cause of DBA [35].

2.5 Severe congenital neutropenia

Severe congenital neutropenia (SCN) is an autosomal recessive disorder characterized by early onset neutropenia and presented with recurrent life infections but early with physical abnormalities. SCN can develop to MDS and AML with the secondary mutations including the granulocyte colony stimulating factor receptor [36]. The neutrophil elastase gene (ELA2), defects in mitochondria gene (HAX1), deficiency in adenyate kinase 2 gene (AK2) and a other genes mutated (GFI1, WASP the transcriptional repressor and the cytoskeletal regulator, respectively) associated with apoptosis was found to responsible for SCN in at least 50% patients
3. The common types of CIS

Studies demonstrated that many types of rare genetic diseases associate chromosome instability typically seen in chromosome instability syndromes with shared clinical features each other. CIS is characterized by an increased frequency of spontaneous or induced chromosomal breaks/aberrations and increased risk of cancer due to the defects of DNA repair as Taylor has defined and described about their clinical features on the most common types of CIS in 2001 [46]. The common cause of chromosomal instability syndromes is the defects of genomic maintenance and DNA repair and they are overlapping and share some clinical features.

The chromosomal instability refers to the predisposition of the chromosomes to undergo rearrangements at the chromosomal level. For example, FA increased spontaneous and inducible chromosome breaks, Ataxia telangiectasia increase chromosome breaks presence of clones with translocations between chromosome 7,14 and X, BLOOM syndrome increased spontaneous and inducible SCE. They are all have increased spontaneous chromatid breaks of symmetrical quadriradials as their main cytogenetic features.

The common types of CIS are FA, Nijmegen breakage syndrome, Ataxia telangiectasia, Ataxia telangiectasia-like disorder and Bloom syndrome. The phenotype and genotype and their association with cancer are summarized in Table 3. Interestingly, FA fall into two classes of genetic syndromes: class one is IBMFS which [37, 38]. Such genetic defects in multiple pathways causing congenital neutropenia are in the controlling of granulocytic progenitor differentiation.

2.6 Congenital amegakaryocytic thrombocytopenia

Congenital amegakaryocytic thrombocytopenia (CAMT) is characterized as hemorrhages or bruises associated with thrombocytopenia in infancy but rarely presents with physical defects. MDS and AML but not solid tumors associated with CAMT have been reported [39]. Molecular studies demonstrated the gene mutated called MPL (encoding of the receptor for thrombopoietin) is responsible for CAMT and showed the correlation between genotype and phenotype [40].

2.7 Thrombocytopenia absent radii

Studies found that thrombocytopenia absent radii (TAR) can be either in autosomal recessive or de novo pattern, typically seen in infants presenting with thrombocytopenia (low platelet count) and allergy to cow milk, physical characteristic of bilateral absent radii and other types of birth defects [41]. Similarly, acute leukemia and solid tumors have been reported from patients with TAR [42].

The pathological mechanism of thrombocytopenia was studied and the serum level of thrombopoietin (the megakaryocyte growth factor) was increased, suggesting the abnormal differentiation mechanism to megakaryocyte and platelet production [43].

The first molecular finding of interstitial microdeletion at chromosome 1q21.1 containing 10 genes including the TAR responsible gene-RBM8A by using comparative genomic hybridization (CGH) microarray technique was in 2007 [44]. Recent finding proved that RBM8A encodes the conserved Y14 subunit of the exon-junction complex that is essential for RNA processing and expressed in all hematopoietic lineages suggesting the cause of TAR [45].

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### 3.1. Fanconi anemia

FA proteins maintain the genomic stability and repair the DNA damaged by factors. But under the condition of FA proteins defects, the damaged DNAs fail to be repaired as normal, resulting in FA clinical phenotypes. Because Fanconi anemia (FA) Cells from FA patients exhibit a hypersensitivity to DNA interstrand cross-linking agents a specific method named “Gold standard” and called “chromosomal fragility testing” using clastogenic agents, mitomycin C (MMC) and diepoxybutane (DEB) was found by Cervenka et al. in 1981 [47] and Auerbach in 1993 [48], respectively. The principle of this method is to challenge the hyposensitive FA cells in the cell culture (most commonly T-lymphocytes from peripheral blood) exposed to DEB and MMC and then to analyze the chromosomal aberration, breaks, rearrangements and radials exchanges. A total 50 cells in metaphase are scored and analyzed for chromosomal breakages compared to controls in the same conditions including age and sex. It is positive if the total chromosome breakage is greater

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**Table 3.**  
Common types of chromosome instability syndromes.

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Phenotypes</th>
<th>Locations on chromosomes</th>
<th>Mutant genes</th>
<th>Protein functions</th>
<th>Cancer risk</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nijmegen Breakage syndrome</td>
<td>Microcephaly and mental retardation, immune-deficiency, radiation sensitivity</td>
<td>8q21.3</td>
<td>Nbs1</td>
<td>BRCT-containing protein</td>
<td>Yes</td>
<td>[52, 79]</td>
</tr>
<tr>
<td>Bloom's syndrome</td>
<td>Immuno-deficiency, premature aging</td>
<td>15q26.1</td>
<td>NLM</td>
<td>DNA helicase</td>
<td>Yes</td>
<td>[57, 78]</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>Neuro-degeneration, immune-deficiency, premature aging, radiation sensitivity</td>
<td>11q23</td>
<td>ATM</td>
<td>Protein kinase</td>
<td>Yes</td>
<td>[67, 73]</td>
</tr>
<tr>
<td>Ataxia telangiectasia-like disorder</td>
<td>Cerebellar degeneration, radiation sensitivity</td>
<td>11q21</td>
<td>Mre11</td>
<td>Exonuclease/endonuclease</td>
<td>Proposed but no report seen</td>
<td>[74, 77]</td>
</tr>
</tbody>
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Inherited Bone Marrow Failure and Chromosome Instability Syndromes and their Cancer...
than 10-fold comparing to control. A typical chromosome breakage of peripheral lymphocytes induced by MMC from patient with FA is shown in Figure 3.

In the last two decades, the method of chromosome fragility testing has been the most widely used as the first line laboratory screen for patients with congenital malformations even without anemia with the features of simple, reliable, reproducible and sensitive comparing with other testing methods in FA diagnosis although it is laborious and requires specialized personnel.

Chromosome fragility test method can differentiate between FA and non-FA cell usually but there are some limitations of this method: (1) it cannot detect the carriers, (2) it is often inconclusive in somatic mosaic cases of FA and (3) false positive results from this test can be seen under the condition that tested individual referred for excluding of FA is under treatment with radiotherapy or chemotherapy.

The next generation sequencing method for FA testing is to confirm the results found by the chromosomal fragility testing and to identify the specific gene mutations of FA as the severity of the disease and the risk of developing aplastic anemia or malignancies related to the complementation groups. Mutation analysis is to identify the specific gene mutations from the proband after confirmation by the primary complementation group result and molecular techniques.

The conventional Sanger sequencing technology-based mutation sequencing is complicated and time consuming, costly and may not detect all types of disease causing aberrations such as deep intronic mutations, large deletions and amplifications due to the presence of so many mutated genes involved in FA requiring many steps including DNA amplification, sequencing and detection of large deletions. Such testing usually needs to be done in laboratories with specific expertise.

Targeted mutation analysis is used as the clues to detect the common mutations detection. These clues include Ashkenazi Jewish FANCC IVS4 + 4 A>T or FANCD1/BRCA2 6174delT; non-Ashkenazi Jewish Moroccan FANCA 2172-2173insG or FANCA 4275delT; Tunisian FANCA 890-893del; Indian FANCA 2574C>G (S858R); Israeli Arabs FANCA del ex 6-31, FANCA IVS 42-2A>C, and FANCG IVS4 + 3A>G; Japanese FANCC IVS4 + 4 A>T; Afrikaner FANCA del ex 12-31 and FANCA del ex 11-17; Brazil FANCA 3788-3790del; Spanish Gypsy FANCA 295C>T; and Sub-Saharan African Black FANCG 637-643delTAACCGCC [49].

The majority of patients with FA worldwide are the complementation A with several hundred mutations. Deletion/duplication analysis is also used to detect deletions of one or more exons or of an entire gene of any suspected case of FA. So the target sequence analysis is to be used for all the known genes associated with FA which usually is complicated by the number of genes to be analyzed, the large number of possible mutations in each gene, the presence of large insertions or deletions in some genes, and the large size of many of the FA-related genes. If the complementation group has been established the responsible mutation can be determined by sequencing the corresponding gene.

The next generation sequencing (NGS) technology offers exciting promise, an effective and faster molecular diagnostics approach for FA gene studies which is able to perform the mutation analysis for FA genes without the requirement of complementation group testing step which the living cells are required. Ameziane et al. applied the next generation sequencing approach to identify BRCA2, FANCD2, FANCI and FANCL mutations in novel unclassified FA patients [50].

Practical experience proved that NGS is an effective molecular diagnostic approach for IBMFS and CIS, reducing the turnaround time and the cost has been becoming lower gradually, and is now a standard tool in the clinical application. Recently, Aslan D group has used the NGS technique and studied a FA case with subtle signs and a negative chromosomal breakage test [51].

In the clinical practice, an early and accurate diagnosis of FA before the stage of bone marrow failure, cancer/leukemia is crucial for the adequate treatment such as stem cell transplantation, the prevention of serious medical complications and also for the properly management in the other caring areas including pediatric, hematology, immunology, endocrinology, reproductive/IVF, obstetrics and surgery and also an early diagnosis of FA will permits the exclusion of other diseases and precludes inappropriate management of hematologic diseases such as aplastic anemia, myelodysplastic syndrome and acute myeloid leukemia.

Figure 2.
Major types of CIS and IBMFS. FA overlaps with these two syndromes.Refs. [78, 79].

Figure 3.
Chromosomal/chromatid breaks as indicated by arrows induced by MMC from patient with FA.
in certain period of time. In the earlier times, the spontaneous chromosomal breakage as a marker for FA diagnostic testing was used but it was found the testing result was inconsistent. Spontaneous chromosomal breakage usually indicates a poor prognosis.

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3.2 Nijmegen syndrome

Nijmegen syndrome (NS) is named from the Dutch city Nijmegen where the condition was first described. It is also named Berlin breakage syndrome, Ataxia Telangiectasia variant 1. NS is an autosomal recessive inherited disease with a complex health problematic conditions typically characterized (NS) by short stature, microcephaly, distinctive facial feature, recurrent respiratory tract infections, mental development delay from infancy to childhood, dysfunctional immune deficiency in T cells and low level of immunoglobulin G and A and increased susceptibility to infections. Individuals with NS increased risk of cancer development (>50 times), commonly in Hodgkin lymphoma, brain tumor, rhabdomyosarcoma about 40% of the affected individuals and usual before age 15. Studies showed heterozygous mutation increase cancer occurrence as well [52].

It is estimated that the prevalence of Nijmegen syndrome is in approximately 100,000 newborns although the exact data is still unknown [53]. Most individuals with NS have West Slavic origins and the largest number of them live in Poland. In the clinical presentation and laboratory diagnostic testing, Nijmegen syndrome and Fanconi anemia show biological overlap. A positive result of chromosomal breakage induced with clastogens such as MMC and DEB can be seen both in Fanconi anemia and Nijmegen syndrome. Translocations or inversions between chromosomes 7 and 14 can be seen its feature in Nijmegen syndrome [54].

The genetic cause of NS is due to the mutation of NBN gene mutation with homozygous c.657_661del5 on chromosome 8q21.3, resulting in nibrin protein dysfunction which is involved in several critical cellular functions, including the repair of damaged DNA to maintain the stability of the genomic function when breaks of DNA strands happen in the stage where the genetic material in chromosomes exchanges for cell division. As a result, affected individuals are sensitive to radiation and other agent exposures [55, 56]. The molecular tests to confirm the diagnosis of a suspected proband are the analysis of exon 6 to determine if the c.657_661 del5 allele and the analysis of entire NBN gene by the sequencing method.

3.3 Bloom syndrome

Bloom syndrome (BSyn) is also named as Bloom-Torre-Machacek syndrome and Bloom-Torre-Machacek syndrome. BSyn is an autosomal recessive pattern characterized with short stature, learning disability, a skin rash, sensitive to sun exposure, serious medical complications such as mild immune-deficiency, chronic obstructive pulmonary disease, varying degree of infertility in both male and female, increased risk of diabetes. Increased risk of cancers to 5–8-folds in earlier life, commonly seen myelodysplasia, leukemia, lymphoma, adenocarcinoma and other types of cancers in epithelial tissues are the characteristics of BSyn as well [57]. Cytogenetics findings are the aberrant chromosomal rearrangements including quadriradial, chromatid gaps and breaks, increased frequency of SCE from the cultured lymphocytes [58].

Molecular studies demonstrated that mutation of BLM gene which is a 4528-bp cDNA sequence defines BLM containing a long open reading frame encoding a 1417-amino acid protein with 22 exons and is located on chromosome 15q26.1 resulted in RecQ helicase dysfunction in BLM protein is the cause of this disease. The BLM protein helps to maintain genome stability and integrity as the caretakers of the genome and also prevents the excess sister chromatid exchanges [59–62]. As a result, SCE is increased to 10-folds under the condition BLM gene mutated. In addition, chromosomal breakage is increased in individuals with Bloom syndrome [63–66].
3.4 Ataxia telangiectasia

Ataxia telangiectasia (AT) is an autosomal recessive inherited disorder first described in 1926 by two French physicians, Syllaba and Henner [67]. AT is also known as Boder-Sedgwick syndrome or Louis–Bar syndrome and its characteristics including a progressive loss of muscular coordination (ataxia), small cerebellum observed by MRI, increased alpha-fetal protein level and dilated blood vessels in the skin (telangiectasia) caused by a defect in ATM gene. AT affected 1 in 40,000 to 100,000 people worldwide [68] and also affects the nervous, immune and other body systems [69]. The ATM gene provides instructions for making the phosphatidylinositol 3-kinase protein to help control cell division in the normal development and DNA repair [70–72]. Studies demonstrated that increased cancer risk including T-cell leukemia, B-cell type of lymphoma usually, other types of cancers such as ovarian, breast, gastric cancers, melanoma and sarcoma have been reported [73].

Molecular studies revealed the mutations in the ATM gene with several allelic variants located on chromosome 11q23 are responsible for Ataxia-telangiectasia due to the defects in providing instructions for making the specific protein to help in controlling of cell division, DNA repair and in the normal biological development and function of the body particularly in nervous and immune systems.

3.5 Ataxia telangiectasia-like disorder

Ataxia telangiectasia-like disorder (ATLD) is a rare autosomal recessive disorder characterized by progressive cerebellar degeneration that shares many clinical presentations with Ataxia telangiectasia but without immune deficiency and telangiectasia, no cancer case report found. It was first designed in 1999 [74] and molecular studies showed that ATLD is caused by inactivating mutations of genes in either homozygous or compound heterozygous [75]. ATLD is usually diagnosed at young at the age starting to walk lacking of coordination and imbalance [76].

Studies showed that there are two mutated genes responsible for ATLD either in homozygous or compound heterozygous. The first is MER11A gene on chromosome 11q21 (ATLD-1) more than 10 different types of variants and the other one is PCNA gene on chromosome 20p12 [77]. Cells from patients demonstrated increased susceptibility to radiation due to the defect of DNA repair pathway. The ATM and MER11A genes are located on the long arm of chromosome 11closely and the biological function of MERA11 protein is linked to Nbs1 in DNA repair.

4. Conclusions

In the past decades, the diagnosis of IBMFS and CIS were limited by the few numbers of cases reported, uneven clinical features and the tests from the laboratory in the slow technologies available at that time.

Thanks to the Human Genome Project, researchers have begun to understand the blueprint of the human genome by learning more about the structures and functions of human genes and proteins. With the application of new technologies for the studies, the concept and practice of genetic disease have been profoundly changing. The next generation sequencing technology has also been remarkably successful in the identification of causes of genetic diseases using whole-genome, whole-exome, and transcriptome sequencing.

The studies on IBMFS and CIS have been offering a lot of opportunities by increasing our understanding of the correlations between phenotype and genotype and such studies have been enlightening the other areas particularly in personalized...
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medicine. Such advances resulted in an unprecedented boom in medical research and an abundance of discoveries linking genetic variants to an assortment of diseases including various cancers. They also have been impacting the genetic field, integrating genomic medicine to primary healthcare practice, bridging the gap between the basic research and clinical application and revealing the pathological basis of genetic diseases which allows the development of accurate and specific tests for disease diagnosis and the eventual translation of research knowledge to clinical therapies.

There are a lot of challenges facing in such a field. Even up to now not all subtypes of IBMFs and CIS are well documented for the clinical and laboratory diagnostic criteria and guidelines due to the disease heterogeneous complexity of the disease, particularly in the developing counties. The clinical manifestations of such patients are highly variable so delay, misdiagnosis and mistreatment were not uncommon under the condition in which such syndromes were treated, that is, with the normal dosage for radiation/chemotherapy. Clinicians working in the field of IBMFS and CIS require a broad clinical knowledge on genetics, hematological and oncological aspects and the ability to refer such patients for testing as well as an experienced laboratory able to perform the particular testing and to translate the laboratory findings correctly into clinical practice. These are the prerequisites for diagnosis of the IBMFS and CIS as well. So cooperation of Multi-displines including genetics, hematology, endocrinonology, immunology, microbiology, oncology and surgical in the clinic is required for a team in the diagnosis and treatment and also is required from cellular, protein and molecular levels in the laboratory testing, generally performed in a qualified and experienced laboratory. Diagnosis and differential diagnosis on IBMFS and CIS can be difficult sometimes due to the nature of disease and the lack of the specific techniques. Inherited cancer can be the early presentation of the disease as a reason.

Diagnosis on patients with IBMFS and CIS also is challenging, particularly in its early phase. Mismanagement from the misdiagnosis of IBMFS and CIS was not uncommon in some regions and countries because IBMFS and CIS is a genetically and phenotypically heterogeneous disease and also because IBMFS and CIS share many clinical features with several group diseases/syndromes. In research, the precise biological activities and the roles of the FA proteins remain still undetermined because most FA proteins in the core complex have no enzymatic motif which is an obstacle to understanding their molecular functions.

However, from a diagnostic perspective, we are still expecting the development of the ideal technologies for genetic disease testing with the features of specificity, sensitivity, accuracy, reliability, high throughput capacity, reproducibility, low cost and ease of operation because about 45% of patients with IBMFS and CIS need to be identified genetically. Furthermore, despite our vastly improved knowledge of human genetic variations, studying associations between genetic disease genotype and phenotype still remains a major challenge and there are many of mysteries unknown in the functional genetics causing diseases.
Such advances resulted in an unprecedented boom in medical research and an abundance of discoveries linking genetic variants to an assortment of diseases including various cancers. They also have been impacting the genetic field, integrating genomic medicine to primary healthcare practice, bridging the gap between the basic research and clinical application and revealing the pathological basis of genetic diseases which allows the development of accurate and specific tests for disease diagnosis and the eventual translation of research knowledge to clinical therapies.

There are a lot of challenges facing in such a field. Even up to now not all subtypes of IBMFs and CIS are well documented for the clinical and laboratory diagnostic criteria and guidelines due to the disease heterogeneous complexity of the disease, particularly in the developing counties. The clinical manifestations of such patients are highly variable so delay, misdiagnosis and mistreatment were not uncommon under the condition in which such syndromes were treated, that is, with the normal dosage for radiation/chemotherapy. Clinicians working in the field of IBMFS and CIS require a broad clinical knowledge on genetics, hematological and oncological aspects and the ability to refer such patients for testing as well as an experienced laboratory able to perform the particular testing and to translate the laboratory findings correctly into clinical practice. These are the prerequisites for diagnosis of the IBMFS and CIS as well. So cooperation of Multi-displines including genetics, hematology, endocrinodonology, immunology, microbiology, oncology and surgical in the clinic is required for a team in the diagnosis and treatment and also is required from cellular, protein and molecular levels in the laboratory testing, generally performed in a qualified and experienced laboratory. Diagnosis and differential diagnosis on IBMFS and CIS can be difficult sometimes due to the nature of disease and the lack of the specific techniques. Inherited cancer can be the early presentation of the disease as a reason.

Diagnosis on patients with IBMFS and CIS also is challenging, particularly in its early phase. Mismanagement from the misdiagnosis of IBMFS and CIS was not uncommon in some regions and countries because IBMFS and CIS is a genetically and phenotypically heterogeneous disease and also because IBMFS and CIS share many clinical features with several group diseases/syndromes. In research, the precise biological activities and the roles of the FA proteins remain still undetermined because most FA proteins in the core complex have no enzymatic motif which is an obstacle to understanding their molecular functions.

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Section 4

Malignant Tumors in Children
Chapter 4

Clinical Manifestations and Diagnosis of Malignant Tumors in Children

Maxim Yu. Rykov

Abstract

Pediatric oncology is a complex specialty, requiring the involvement of various specialists—pediatric oncologists, pathomorphologists, radiation diagnosticians, and surgeons. The patient's life depends, first of all, on the timeliness of the diagnosis, since the earlier the specialized treatment is started, the higher the probability of achieving remission. Of particular relevance is the problem of early detection of malignant neoplasms. The complexity of solving this problem is related to the atypical nature of the oncological diseases and their rarity, which leads to the lack of "oncological alertness" of primary care physicians—district pediatricians. It is from pediatricians that timely diagnosis of malignant neoplasms depends. This lecture is devoted to the clinical manifestations and diagnosis of malignant neoplasms in children: hemoblastosis and solid tumors.

Keywords: pediatric oncology, malignant tumors, solid tumors, hemoblastoses, diagnostics, clinical symptoms

1. Introduction

The problems of treating children with oncological diseases are relevant all over the world. Successes associated with the introduction of intensive protocols of chemotherapy, bone marrow transplantation, organ-preserving treatment can achieve remission in a significant number of patients.

It is known that the earlier a specialized treatment is started, the higher the probability of a favorable outcome. Thus, treatment started in the early stages of the disease with nephroblastoma allows to achieve remission in 95% of patients, in osteosarcoma—70%, in Ewing sarcoma—65%, in rhabdomyosarcoma—59%.

If the disease is found in common stages, this indicator is significantly lower. For the abovementioned nosologies, it is 25, 6, 7, and 8%, respectively [1].

In this connection, the problem of early detection of malignant neoplasms is of particular urgency. The complexity of solving this problem is related to the atypical nature of the oncological diseases and their rarity, which, in turn, leads to the lack of "oncological alertness" of pediatricians.

A pediatrician, like a doctor of any other specialty, rarely has to deal with children affected by malignant tumors. For his medical practice, the average pediatrician meets about eight children with true tumors. It is with this that possible...
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1. Introduction

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A pediatrician, like a doctor of any other specialty, rarely has to deal with children affected by malignant tumors. For his medical practice, the average pediatrician meets about eight children with true tumors. It is with this that possible
errors in diagnosis and, as a consequence, in treatment are connected. The patient’s life depends, first of all, on the timely diagnosis, therefore, directly from the “oncological alertness” of the pediatrician.

2. Epidemiology of malignant tumors

In the structure of malignant tumors in children on the first place are hemoblastoses, then tumors of the brain and spinal cord, neuroblastoma, tumors of bones and soft tissues, kidneys, eyes, liver. It follows that most solid tumors are specific for children, whereas adults are found in very rare cases (Diagram 1).

Difficulties in diagnosing malignant neoplasms in children are explained not only by the rarity of these pathologies but also by the peculiarities of their clinical course: the prevalence of tumors of “hidden localizations,” the set of “masks,” which mask the manifestations of malignant tumors, the predominance of common symptoms in the clinical picture over local symptoms. The age of patients determines understandable difficulties in clarifying complaints and anamnesis of the disease.

3. Primary tumor symptom complex

Common signs of malignant tumors appear in some cases earlier than local ones, they are united by the terms “primary tumor symptom complex” or “paraneoplastic syndrome” and although they are not specific, should alert the doctor and encourage him to make an in-depth examination of the patient to exclude or confirm malignant neoplasms [2].

Primary tumor symptom complex is a variety of pathological manifestations, caused by the indirect effect of the tumor process on the metabolism, immunity and functional activity of the body’s regulatory systems.

Diagram 1.
Structure of malignant tumors in children (%).
Primary tumor symptom complex most often includes hypodynamia, lack of appetite, weight loss, lethargy, weakness, fatigue, capriciousness, anemia, subfebrile condition, and dermatitis. These manifestations are caused by nonspecific reactions on the part of organs and systems or by ectopic production of a biologically active substance (hormones, proteins, growth factors, cytokines, antibodies), which causes a pathological increase in cell activity and forms certain manifestations, for example, Cushing’s syndrome, fever, and erythrocytosis.

In the pathogenesis of the development of the primary tumor symptom complex, the response of the immune system is important in response to the presence of a tumor, an immunologically foreign antigen. This is the basis for the development of clinical symptoms of dermatomyositis, rheumatoid arthritis, autoimmune hemolytic anemia, and other systemic manifestations.

In some cases, the primary tumor symptom complex precedes the local symptoms of the tumor, whereas in others, it manifests simultaneously with them, sometimes will be added after the verification of the tumor process. The greatest difficulties arise in cases when the manifestations of the primary tumor symptom complex are treated as independent diseases or syndromes, which lead to the appointment of unjustified treatment and detection of malignant neoplasms at later stages.

Primary tumor symptom complex in the verification of malignant neoplasms is observed in 15% of patients, 50% of its manifestations develop during treatment, 35% in the late stages of the disease. Regression of the manifestations of the primary tumor symptom complex correlates with the tumor response to the therapy [2].

Leukemia is the most common tumor disease of childhood, which occurs mainly in the first 5–7 years of life. Among all leukemias in children, unlike adults, the vast majority (more than 95%) falls on acute forms.

Acute leukemias (AL) are clonal diseases that arise from a single mutated hematopoietic cell, which refers either to very early ones or to the cells of predecessors committed to different hematopoiesis lines. Thus, AL is a malignant tumor that originates from blast cells. The diagnosis of AL is established in the event that the number of blast cells in the bone marrow exceeds 25% [3].

AL in children of morphological origin is divided into acute lymphoblastic (80%) and acute nonlymphoblastic (20%) leukemia, which differ from each other both biologically and clinically, but in all cases, the clinical course is characterized by a high rate of increase in symptoms leading to rapid death of the patient [3, 4].

Clinical manifestations. In the clinical picture of AL, it is usually noted the presence of various symptomatic complexes, the most frequent among which are:

1. Intoxicative-inflammatory syndrome, which is manifested by lethargy, lethargy, loss of appetite, loss of body weight, unaccountable fever. This is a consequence, first of all, of reducing immunity due to a decrease in the number of leukocytes of the granulocyte germ (in the first place—neutrophils). These children have frequent recurrent inflammatory inflammatory diseases over short time intervals;

2. Anemia syndrome, the main manifestations of which are a decrease in the level of hemoglobin, erythrocytes, pallor of the skin and mucous membranes, dyspnea, tachycardia due to hemic hypoxia;

3. Hemorrhagic syndrome, in which there are polymorphic hemorrhages in the skin of the body and mucous membranes, bleeding (nasal, gastrointestinal,
renal, etc.). This is due to the replacement of the megakaryocyte germ with blast cells and, as a consequence, a decrease in the number of platelets in the blood to critical digits;

4. Hyperplastic syndrome, which is caused by leukemia infiltration and is represented by systemic lymphadenopathy (enlarged lymph nodes of almost all groups, painless, of small size), hepatosplenomegaly, and ossalgia. The latter are the result of massive infiltration of bone marrow by the blast cells of long tubular bones, which leads to increased intraosseous pressure and the occurrence of pain. In addition, the massive proliferation of blast cells leads to their exit beyond the bone marrow canal under the periosteum, which is also the reason for the appearance of a clinical picture similar to that of acute hematogenous osteomyelitis (AHO). In this case, it is extremely difficult to conduct differential diagnosis of these two diseases (AL and AHO) in the early stages of development, only the results of sowing and cytology of the bone marrow make it possible to correctly diagnose;

5. Meningeal and hypertensive syndromes that are characterized by headache, vomiting, stiff neck muscles, Kernig symptom, Brudzinsky’s symptom, convulsions of clonic-tonic character, and the like. This is a consequence of the development of neuroleukemia, when the tumor metatstasizes into the membranes of the brain and spinal cord. Often, such manifestations simulate a clinical picture of meningitis or encephalitis. However, such children do not have an epidemiological component in the anamnesis. Often, the diagnosis is established by the results of a sociological study of cerebrospinal fluid.

In addition to these symptom complexes, others may be present, but it is important to understand that the presence of two or more of them is an obvious indication for the urgent and active exclusion of the diagnosis of acute leukemia and, first of all, for referring the patient to a general blood test.

*Diagnosis of AL:*

1. The general analysis of blood, in the study of which, as a rule, hemoglobin, erythrocytes, platelets, change in the number of leukocytes are observed, blasts may also appear;

2. Puncture of the bone marrow (usually from the pelvic bones, no less than three points on each side) followed by its Romanovsky-Giemsa coloring and cytological examination. In this case, the number of blast cells is more than 25%, a violation of normal cell ratios, a decrease or absence of megakaryocytes;

3. Cytochemical examination of the bone marrow (reaction to peroxidase and chloroacetate esterase, lipid content, granular distribution of material in the SHC reaction in the form of purple granules on the periphery of the cytoplasm, acidic phosphatase activity);

4. Immunophenotyping (detection of differentiation antigens on the membrane of blast cells);

5. Cytogenetic study of the bone marrow with the search for typical chromosomal abnormalities for various variants of AL;
6. Molecular-biological studies (PCR diagnostics) of the bone marrow with the search for more subtle variants of breakdowns of the information apparatus (DNA) of cells;

7. Lumbar puncture (diagnosis of neuroleukemia).

**Malignant lymphomas (ML)** are a group of malignant neoplasms of blood that are characterized by a primary tumor lesion of the lymphatic system. These include Hodgkin’s disease (or lymphoma) (previously—lymphogranulomatosis) and non-Hodgkin’s lymphomas.

Hodgkin’s lymphoma (LH) most often occurs during adolescence. Moreover, if in children under 15 years of age, its share in the overall structure of oncological morbidity does not exceed 7–8%, at the age of 15–18 years—more than 20%.

Non-Hodgkin’s lymphomas (NHL) are a polymorphic group of tumors, the most common of which are B- and T-cell lymphomas. NHL, as a rule, are diagnosed in children aged 5–7 years.

It should be emphasized that ML is almost never found in infants [4].

Clinical manifestations. For these diseases, the presence of a lymphoproliferative symptom complex is common. In contrast to AL, in these diseases, as a rule, not all groups of lymph nodes increase, but several located in the immediate vicinity. Common to them is the possible presence of a symptom of general intoxication, which occurs as a result of the effects of cytokines secreted by Hodgkin cells:

1. Fever;

2. Night profuse sweat;

3. Weight loss of more than 10% in the previous 6 months.

With LH in children, as a rule, there is an increase in cervical and cervico-supraclavicular (60–80%), intrathoracic (paratracheal, tracheobronchial, bronchopulmonary, less often in the front group) (40–75%) lymph nodes. The defeat of lymph nodes of other groups (axillary, inguinal, femoral) LH in children is rare, but in adolescents, it is not casuistry.

The most common clinical defeat of lymph nodes in this disease begins with the increase of one of them (more often—the neck), with the gradual involvement of the other lymph nodes. Characteristic is the manifestation of local lymphadenopathy, which reveals a “package” of enlarged lymph nodes of various sizes, reaching 5 cm or more in diameter, uncoated, painless, with unchanged skin above them. The most precise and clear definition and description of this is the term “potato symptom in the bag,” which was introduced by the Russian pediatrician A.A. Kissel in the beginning of twentieth century. The development of this symptom is gradual and, given the absence of pain, even with visually defined neck asymmetry, patients do not actively go to the doctor.

With exceptionally squeezed development of the disease, the signs of bronchial obstruction appear without any obvious signs of inflammation. NHL quite often have clinical manifestations, characteristic of LH, but the rate of development of the disease is rapid. A feature of the development of B-cell lymphomas is that they develop, as a rule, from lymphoid tissue located in the abdominal cavity and retroperitoneal space. Therefore, their signs are manifestations of intestinal obstruction, including intussusception, swelling in the abdomen, constipation that has arisen without an obvious cause, and so on.
Diagnosis of ML:

1. Clinical blood test (typical normochromic anemia, neutrophilic leukocytosis, lymphopenia, eosinophilia, monocytosis, increased ESR);

2. Biochemical blood test (possible increase of lactate dehydrogenase, SRP, ceruloplasmin, haptoglobin, fibrinogen);

3. Biopsy of lymph nodes with histological and immunohistochemical examination;

4. Radiography or computed tomography of the chest in 2–5 projections (an increase in the thymus occurs in 20%, lung damage is also in 20%);

5. Ultrasound examination of the abdominal cavity (spleen lesion—30%);

6. Radiosotope diagnosis of lymphatic tissue with gallium-67 citrate;

7. Positron emission tomography with 18FDG;

8. Bone marrow puncture (with suspicion of NHL);

9. Lumbar puncture (with suspicion of NHL).

Tumors of the brain and spinal cord (TBSM) are a heterogeneous group of tumors that are localized in the structures of the brain and spinal cord and differ in histological structure and degree of malignancy.

TBSM occupy the second place in the structure of malignant neoplasms in pediatrics, accounting for 16–20% and are the most common solid tumors in children; on 95%, they are represented by brain tumors (BT). Tumors of the spinal cord (TSC) in children account for 5% of all TBSM. Incidence of TBSM is 4 cases per 100,000. The incidence rate is higher in boys (4.2 per 100,000) compared with girls (3.8 per 100,000) [5].

There are two peaks in the incidence of TSC. The first peak with a small predominance of boys is noted in the first decade of life, the second is observed from the third to the fourth decade and reaches a maximum by 60 years. The structure of the first peak is dominated by embryonic neoplasms of the brain and piloid astrocytoma. Since the third decade, the incidence of TSC has increased sharply, typical of adults—supratentorial gliomas.

Clinical manifestations. The leading symptoms in the brain tumor clinic are symptoms of increased intracranial pressure, which are manifested by morning headaches, vomiting, strabismus, or other visual disorders. Headache occurs in the morning, when getting out of bed, it is facilitated by vomiting and decreases during the day. Vomiting is observed in 80% of patients with a brain tumor. Examination of the fundus reveals signs of edema of the optic disc.

At the very beginning of the disease, rare vomiting in the morning, which brings relief, parents are associated with inaccuracy in nutrition and do not consult a doctor. Repeated vomiting in patients with TSC in the absence of focal neurological symptoms is often the cause of erroneous diagnoses, such as gastritis and gastroduodenitis, helminthic invasion, meningitis. Pediatricians and gastroenterologists observe patients for a long time and treat for a gastroenterological disease or infection.

The headache is also not associated for some time with the tumor disease, and doctors, including neurologists, treat for overfatigue, vegetovascular dystonia, and
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other diseases. Only the increase in the intensity and frequency of headaches is the reason for the examination.

In young children, the symptoms of intracranial hypertension lead to macrocephaly. With tumors of the posterior cranial fossa, the clinical picture is dominated by symptoms of increased intracranial pressure. In tumors in the cerebellum, there is also a violation of gait and balance.

Tumors of the cerebral hemispheres are characterized by focal symptoms—seizures, loss of visual fields, neuropathy or dysfunction of the cortico-spinal tract. Middle-located supratentorial tumors can cause endocrine disorders—diencephalic syndrome (developmental lag and cachexia).

About 15–45% of primary TSC (embryonic tumors, ependymal and germinative cell tumors) metastasize to other parts of the central nervous system (CNS). Neurologic disorders in metastases sometimes neutralize the symptoms of the primary tumor.

The clinical symptoms of BT are back pain (in 50% of cases), resistance to flexing of the trunk, spasm of paravertebral muscles, deformity of the back (progressive scoliosis), gait disturbance, lowering of reflexes in the upper extremities and an increase in the lower extremities, impaired sensitivity depending on the level of lesion, a positive symptom of Babinsky, disruption of the sphincter of the bladder and/or anal. Symptoms of compression of the spinal cord increase in the supine position and decrease in the sitting position.

Diagnostics of TBSM:

1. Magnetic resonance imaging of the brain and/or spinal cord with contrast;

2. Investigation of serum alpha-fetoprotein level in tumors of the pineal region and/or chiasmatic-sellar region and/or subcortical structures;

3. Investigation of the level of chorionic gonadotropin in the blood serum for tumors of the pineal region and/or chiasmatic-sellar region and/or subcortical structures;

4. Study of alpha-fetoprotein in the cerebrospinal fluid for tumors of the pineal region and/or chiasmatic-sellar region and/or subcortical structures (in the absence of intracranial hypertension);

5. Investigation of the level of chorionic gonadotropin in the cerebrospinal fluid in tumors of the pineal region and/or chiasmatic-sellar region and/or subcortical structures (in the absence of intracranial hypertension).

Retinoblastoma (RB) is the most common intraocular malignant tumor of neuroepithelial origin, affecting the retina of the eye.

It occurs mainly in childhood and is 2.5–4.5% of malignant tumors in children. Its frequency is 0.29–0.31 per 100,000. There is no significant dependence of the incidence on sex. The average age of detection of RB is 21.2 months, with a bilateral lesion of 14.6 months, with a one-sided lesion of 23.5 months.

RB occurs in two forms:

1. Genetic (congenital, 40%), in which there is a bilateral multifocal lesion, is a consequence of chromosome mutations of germ cells;

2. Sporadic (60%) is characterized by the presence of one tumor node in one eye.
In the first variant, the risk of developing RB in other children in the family and in subsequent generations exceeds 50%, at the second—6%. The risk of inheritance of a unilateral RB increases if the patient has a predisposing mutation to the disease.

Clinical manifestations. The clinical course of the RB is characterized by rapid growth. Due to insufficient blood supply, the tumor quickly necrotic, in the necrosis zones calcifications are formed.

Metastases with lymphogenous and hematogenous pathways in the parotid, submandibular, cervical groups of lymph nodes, in the skull bones, tubular bones, and liver.

Initially, the tumor is located within the retina, then spreads to the vascular membrane and the vitreous. The first clinical sign is leucocoria—a whitish-yellow glow of the pupil due to the reflection of light from the surface of the tumor. As one grows, a node (one or more) is formed of grayish-whitish color of rounded form, which goes into the vitreous body. Visual acuity decreases, and strabismus appears. As a result of the destruction and germination of the trabecular apparatus of the eye, the outflow of the intraocular fluid is disturbed, and the intraocular pressure increases. There is pain in the eye, stagnant infection, corneal edema, dilated pupil and lack of its response to light. Extensive dystrophic changes and necrosis of the tumor tissue lead to the onset of inflammatory processes (uveitis, iridocyclitis).

Exophthalmos arises from the edema of the cellulose of the orbit or when the tumor grows into the orbit. When the tumor spreads through the optic nerve, a headache, nausea, and vomiting occur in the cranial cavity.

Diagnostics RB:

1. Ophthalmological examination with medial mydriasis and application of the retinal chamber;
2. Ultrasound examination of orbits and eyes;
3. Computer tomography and/or magnetic resonance imaging of orbits and brain with contrast;
4. Computed tomography of thoracic organs;
5. Ultrasound of the organs of the abdominal cavity, retroperitoneal space, cervical lymph nodes.

Neuroblastoma (NBL) is an embryonic malignant tumor that originates from the ganglia of the border sympathetic trunk and chromaffin tissue.

It is mainly localized in the retroperitoneal space (more than 66%), less often in the posterior mediastinum (15%), it can also be located on the neck, face, and so on.

In the vast majority of cases, NBL is detected in children aged in the first 2 years of life. In the structure of malignant tumors, it accounts for about 7%. The global average incidence of neuroblastoma is 0.68 per 100,000, and boys are more likely to fall ill [6].

Clinical manifestations. Initial clinical manifestations of NBL have no specificity. However, unexplained bouts of sweating, pallor of the skin, diarrhea, and hypertension should alert the pediatrician. These symptoms may be manifestations of catecholamine intoxication, which is characteristic of NBL, cells of which produce catecholamines (adrenaline, norepinephrine, dopamine) and their metabolites (vanillylmandal and homovanilic acids).
The unfolded clinical picture of NBL is determined by its localization:

- The NBL of the retroperitoneal space is palpated through the anterior abdominal wall in the form of a tuberous, nondisplaced tumor node;
- NBL of the small pelvis causes violations of the act of bowel movement and urination;
- Mediastinal NBLs are usually detected by chance during chest X-ray; at a high location of the node, Horner’s syndrome can be noted;
- With the spread of NBL through the intervertebral foramen to the spinal canal (a tumor of the “hourglass” or “dumbbell-like” form) and compression of the spinal cord, the flaccid paralysis of the lower limbs and pelvic organs develop.

In addition, the NBL is characterized by two specific syndromes:

1. Myoclonus-optosilonus syndrome with polymyoclonia, cerebellar ataxia, gait disorder and opselonus is most often observed with the localization of NBL in the chest;
2. Profuse watery diarrhea caused by the fact that NBL cells produce a vasoactive intestinal peptide.

It should be noted that in 50% of patients at the time of diagnosis, there are already metastases that can manifest as pain in the bones, eye socket proptosis or flu-like syndrome.

Diagnosis of NBL:

1. Morphological examination of the tissue of the primary tumor and/or foci suspicious for metastatic;
2. Ultrasound examination of the abdominal cavity organs and retroperitoneal space and the area of the primary tumor focus;
3. Magnetic resonance imaging with intravenous contrast of the primary tumor zone and/or computed tomography of the primary tumor lesion;
4. Radioisotopic bone diagnosis and/or magnetic resonance imaging of the entire body;
5. Computed tomography of thoracic organs;
6. Radioisotope diagnostics with 123-iodine-metaiodobenzylguanidine (MIBG);
7. NSE level;
8. NMYC amplification;
9. Morphological examination of bone marrow points from three points.

Nephroblastoma (NB) is a high-quality embryonic tumor that originates from developing kidney tissues—a metanephrogenetic germ.
In the structure of oncological pathology in children is 7%. Her frequency is 0.6 per 100 thousand. In girls, NB occurs somewhat more often (1.12) than in boys (0.8).

The average age of children with NB is 3.5 years. As a rule, it is detected earlier, but sometimes it is diagnosed in older children, very rarely in adults [7].

Clinical manifestations. NB in children for a long time is almost clinically not apparent. The syndrome of small signs of a tumor (general malaise, lethargy, subfebrile fever, intermittent abdominal pain, gastrointestinal disorders, and hypertension) is present in most patients; however, as a rule, neither parents nor doctors attach much importance to them. Quite often, an increase in the size of the abdomen, sweating, and irritability of children is treated by pediatricians as rickets.

Usually the first, though not the earliest, clinical sign of the disease is a palpable tumor in the abdomen, which parents (less often doctors) discover by chance. It is smooth, sometimes coarse-grained, dense, and painless. Macrogematuria occurs less than in a quarter of patients and is a manifestation of tumor germination in the calyx-calcaneous kidney system. Quite often (in 25%), the examination reveals an arterial hypertension (secondary), which develops due to hyperenemia or the spread of a tumor thrombus in the lower vena cava down to the right atrium. Occasionally, subcapsular tumor ruptures occur, under which the clinical picture of the “acute abdomen” develops. Differential diagnosis is usually performed with other tumors of the abdomen and retroperitoneal space, as well as kidney anomalies (hydronephrosis, polycystosis, and dystopia).

Diagnostic algorithm includes, in addition to general clinical examination, the following methods:

1. Laboratory studies to identify anemia, hematuria, renal failure, the level of catecholamines in the urine (for differential diagnosis with NBL);

2. X-ray—excretory urography and chest X-ray. The first allows to reveal the characteristic deformations of the cup-and-pelvis system and to assess the functional ability of both kidneys. Radiography of the chest is performed to identify metastases in the lungs;

Using ultrasound, the tumor size is measured, which will allow us to evaluate the effectiveness of treatment in the future, tumors in the renal and hollow veins are detected.

**Diagnosis of NB:**

1. Morphological examination of the tissue of the primary tumor and/or foci suspicious for metastatic;

2. Magnetic resonance tomography with intravenous contrast and/or computed tomography with intravenous contrasting of the abdominal cavity and retroperitoneal space;

3. Ultrasound examination of the abdominal cavity and retroperitoneal space;

4. Computed tomography of thoracic organs;

5. Renoscintigraphy.

**Hepatoblastoma** (HB). Primary liver tumors in children are relatively rare pathologies: 1–4% of all neoplasms occurring in childhood. This pathology is
characterized by a slow development of the tumor process and the absence of specific complaints for this disease.

HB is the most common malignant liver tumor that develops from an embryonic pluripotent bookmark.

HB has a unique age distribution. There are two age-specific peak incidences: the first occurs at birth or in the first month of life, the second occurs during the 16th–18th months of life. GB occurs in adults, although extremely rare. GB in children older than 5 years, usually has a more aggressive course, and has the characteristics of hepatocellular cancer. It is more common in boys: the sex ratio is from 1.5:1 to 2:1 [8].

Clinical manifestations. HB do not have specific clinical symptoms. Usually, thrombocytosis is noted; in addition, it has been established that the serum alpha-alpha-protein level is the primary marker of the tumor, which plays an important role in diagnosis. The normal level—up to 20 ng/ml—can increase several thousand times.

Most HB often metastasizes to the lungs and bones. Regional lymphonoduses of the liver are extremely scarce.

Diagnostics of HB:

1. Magnetic resonance imaging with intravenous contrasting of the abdominal cavity and retroperitoneal space and/or computed tomography of the abdominal cavity and retroperitoneal space;

2. Ultrasound examination of the abdominal cavity and retroperitoneal space;

3. Computed tomography of thoracic organs;

4. Morphological examination of the tissue of the primary tumor and/or foci suspicious for metastatic disease.

Germinogenic tumors (GT) constitute no more than 3% of ZNO, occur in 1 case for 30,000–40,000 newborns. Malignant forms at the birth of a child are only 2%, but with age, the specific weight of them is rapidly increasing and by the age of 6 months, their share in the total structure has increased to 50–70%.

According to the histological picture (WHO classification, 1985), GT can be represented by cells of the same type—seminoma, disgerminoma, spermatocytic tumor (only in testicles), embryonic cancer, yolk sac tumor (endodermal sinus), polyembryoma, choriocarcinoma, or several of the listed types in different combinations. All of them, with the exception of teratom, are malignant or immature (potentially malignant).

Clinical manifestations. The clinical picture depends on the location of the tumor and its morphological structure. The sacrococcygeal region is the end point of the settling of primordial pluripotent germ cell cells, so it is in this region that the GT is most often localized. Most often, they are represented by mature teratomas and consist of mature tissues, derivatives of all three embryonic leaflets (skin and its appendages, bones, parts of various organs, etc.). In the event that one of the tumor components is represented by an immature tissue (areas of neuroblastoma, rhabdomyosarcoma, etc.), the teratoma is called immature. If the focal points of the yolk sac tumor are determined in the teratoma, it refers to tumors of a complex structure. As a rule, these tumors are located anterior to the sacrum and coccyx, and at large sizes they spread from the cavity of the small pelvis outwards between the coccyx and the anus.

Tumors of the ovaries clinically manifest mainly in abdominal pain, which can take the form of acute when twisting the legs or rupturing the tumor. With large
tumor sizes, the abdomen increases in size, and in some cases of histological struc-
ture (dysherminoma, a complex tumor), signs of premature sexual development or,
vice versa, they are absent at the age when they should already be. Symptoms of
tumor intoxication (lethargy, pale skin, decreased appetite, etc.) appear only when
the tumor process is disseminated.
The main sign of testicular tumors is the presence of palpable formation in the
scrotum.

**Diagnosis of GT:**

1. Magnetic resonance imaging with intravenous contrast of the pelvic organs
   and abdominal cavity and retroperitoneal space;
2. Ultrasound examination of the pelvic organs and abdominal cavity and
   retroperitoneal space and primary tumor focus;
3. Computed tomography of thoracic organs;
4. Radioisotope diagnosis of bones;
5. Study of the level of alpha-fetoprotein in the blood serum;
6. Investigation of the level of chorionic gonadotropin in the blood;
7. Investigation of the level of lactate dehydrogenase in the blood;
8. Morphological examination of the tissue of the primary tumor and/or foci
   suspicious for metastatic disease.

**Bone tumors** in children make up about 10% of all malignant neoplasms, found
mainly in the second decade of life. Between 50% and 70% of all malignant bone
tumors are osteosarcoma, the main nosological unit in this group of diseases. Second
place in the frequency of occurrence in children is Ewing’s sarcoma (25%).

**Osteosarcoma (OS)**—the most common primary tumor of brachi in children,
ranks sixth in frequency among all malignant tumors of childhood. The tumor
originates from the primitive bone-forming mesenchyme is characterized by the
production of osteoid with malignant proliferation of the spindle stroma. The peak
of the incidence falls on the second decade of life. In boys, the incidence of the
disease is higher, whereas at an earlier age, girls are predominantly ill (who have
more bone ages in this period than boys) [9].

Clinical manifestations. The main clinical sign of OS is pain over the affected
area. The pain is dull, constant, with a gradual increase in intensity. A characteristic
symptom is nocturnal pain. Three-fourths of patients may have a soft tissue com-
ponent. The extremity is enlarged in volume, often looks edematous. Pain and
volume increase lead to impaired function. The duration of the anamnesis is, on
average, 3 months. The metaphysis of long tubular bones is characteristic. The most
frequent localization (50%) is the area of the knee joint—the distal part of the thigh
and the proximal part of the tibia. Often the proximal part of the humerus and
femur, the middle third of the femur, is also affected. The defeat of flat bones,
especially the pelvis, occurs in childhood less than 10%.

OS has a significant tendency to develop hematogenous metastases. At the time
of diagnosis, 10–20% of patients have macrometastases in the lungs, which are
detected by X-ray. About 80% of patients at the time of diagnosis are
micrometastases in the lungs, not detectable by roentgenograms, sometimes visible in computed tomography.

Since the bones do not have a developed lymphatic system, early dissemination of the OS to regional lymph nodes is rare, but if this occurs, it is a poor prognostic sign.

Other areas of metastasis—bone, pleura, pericardium, kidney, and CNS. The disease also has local aggressive growth, it can spread to the epiphysis and the nearby joint (most often the knee and shoulder joints), spreading along the intraarticular structures, through the articular cartilage, through the pericapsular space, or directly, due to pathological transformation, and form not adjacent to it foci-satellites—“skip”—metastases.

Ewing's sarcoma (ES) consists of small round cells with scant cytoplasm, a round nucleus containing a gentle chromatin and poorly visible basophilic nucleoli. Unlike OS, it does not produce an osteoid. This tumor is rare in children younger than 5 years and in adults over 30 years. The peak incidence falls on 10–15 years.

In contrast to OS, ionizing radiation is not associated with the occurrence of ES [10].

Clinical manifestations. Clinical signs of ES are increased pain, swelling over the affected area with a violation of limb function. The tumor is usually painful on palpation, rapidly increasing in size. The defeat of peripheral nerves can cause the appearance of neurological symptoms. There may be fever of varying degrees. The soft tissue component of the tumor is often more pronounced than the bony focus. In the tumor often, there are hemorrhages and necrosis, which cause an increase in local temperature, erythema and mimics nonspecific inflammation, which makes diagnosis difficult. Such a symptomatology allows, first of all, to assume the presence of osteomyelitis.

The most common localization of ES is pelvic bone, femur, tibia, fibula, ribs, scapula, vertebrae, and humerus. ES is most often affected by flat bones.

In tubular bones, the tumor localizes primarily in the diaphysis and tends to spread to the bone epiphyses. In 91%, the tumor is located intramedullary, and the spread along the medullary canal is often greater than in the bone.

X-ray signs of ES:

- Bone destruction (“moth-eaten”) without clear boundaries, with a tendency to spread along the medullary canal;

- “Bulbous periostitis”—a multilayered linear periostitis, which can combine with needle;

- A pathological fracture is revealed in 5%. With localization of the tumor in the proximal area of the femoral bone, a pathological fracture occurs much more often (more than 70%);

- When radiography of soft tissues reveals a clear soft tissue component of a homogeneous structure;

- Rib injuries often combine with pleurisy.

However, X-ray signs are not absolutely pathognomonic. It is necessary to carry out differential diagnostics with other pathological processes in the bones—first of all with osteomyelitis, trauma, other malignant tumors (rhabdomyosarcoma, synovial sarcoma, lymphoma, and NBL).
Diagnosis of bony sarcomas:

1. Morphological examination of the tissue of the primary tumor and/or foci suspicious for metastatic;

2. Magnetic resonance imaging with intravenous contrast of the affected bone and adjacent joints;

3. Radioisotopic examination of bones of the skeleton and soft tissues and/or magnetic resonance imaging of the whole body;

4. Ultrasound examination of the primary tumor zone and regional lymph nodes and abdominal cavity and retroperitoneal space;

5. Computed tomography of the chest, affected bone, and adjacent joints;

6. Morphological examination of bone marrow points from three points;

7. Radiography of the affected bone in two projections (frontal and lateral) with scale markings.

Soft tissue sarcoma (STS) is a heterogeneous group of malignant tumors primarily located in soft tissues and having a mesenchymal origin. In the structure, the incidence of STS is the fourth place and make up 6–8% of all malignant tumors of childhood. In newborns and children younger than 1 year, this type of tumors is observed in 10–12% of cases. In 50% of cases, RMS is located in the head and neck region, whereas in 25–37% of cases, it is located in the trunk and extremities.

The most common in children are: rhabdomyosarcoma (61%); extraangular Ewing’s sarcoma and peripheral neuroectodermal tumor (8%); synovial sarcoma (7%); neurofibrosarcoma, angiosarcoma (4%); fibrosarcoma (3%), and leiomyosarcoma (2%), as well as extra-osseous chondrosarcoma and osteosarcoma, epithelioid sarcoma, malignant fibrotic histiocytoma, malignant hemangio-periectomy, malignant mesenchymoma, malignant schwannoma, liposarcoma, and sarcoma without additional characteristics.

Clinical manifestations. A visually identifiable or palpable tumor is one of the earliest symptoms of the disease, in some cases discovered by chance.

The clinical picture is mainly determined by the localization of the process.

• Torso and limbs. The tumor is located in the thickness of the muscles, shifts in the transverse direction, can grow into the underlying bone, and the tumor becomes not shiftable. Palpator tumor is painless, often smooth, but can be also tuberous, and the temperature above it is usually slightly increased. The skin above the tumor is not changed, however, in the case of large lesions, it can thin out, acquire a purplish-cyanotic shade, shine, and a vascular pattern. As the growth or localization in the distal parts of the limbs appears pain syndrome, due to compression or germination of nerve trunks. Persistent local soreness appears when the tumor grows into the bone, the contracture of the joint—when it grows into its membranes.

• Head and neck. When localizing SMT in the area of the orbit in the early stages of the tumor process, there is swelling, exophthalmos. As growth grows, the formation can fill the orbit cavity, germinate into the eyeball, causing a decrease in vision until complete loss.
• Nasopharynx. One of the first symptoms—violation of nasal breathing—accompanied by mucopurulent discharge with an unpleasant odor, nasal voice. Pain syndrome, as a rule, occurs when the bones are damaged, and the tumor masses are filled with maxillary sinuses, sprouting into cells of the latticed labyrinth. Serous otitis can also be attached.

• Middle ear. One of the first manifestations is pain syndrome, localized in the ear. When obturating with a tumor of the ear canal, loss of hearing is added. In addition, it can be determined swelling in the behind-eye area, paralysis of the facial nerve, mucopurulent discharge from the auditory canal.

• The oropharynx. One of the earliest are symptoms of impaired swallowing, respiratory function.

• The vagina. In the initial stages, it proceeds with symptoms characteristic of vulvitis, vaginitis, condyloma, polyps: discharge from the genital tract (yellowish color, bloody, with an admixture of pus and unpleasant odor) itching in the vagina, pain in the external genital area. As the urethra becomes obturated, symptoms of difficulty urinating, dysuric phenomena, are added. On examination, neoplasms of red color are sometimes found.

• Bladder. Most often localized in the region of the neck or triangle of Little. The tumor is characterized by rapid exophytic growth, the walls of the bladder germinate, the prostate gland. There is frequent urge to urinate, tenesmus without urination. It can join hematuria, including profuse. When joining a secondary infection, pyuria develops, which is accompanied by an increase in dysuria, a painful urination. A partial or complete retention of urine resulting from obturation with a tumor of the neck of the bladder may develop.

• Testicle. It shows a painless seal with uneven contours in the tissue area of the organ. As the tumor grows, the size of the testicle increases, its compaction, swelling of the scrotum, and suprapubic region.

• Thoracic and abdominal cavity, retroperitoneal space. With these localizations, the symptoms are due to the growth of the tumor in the surrounding tissue and compression of the main and central veins, arteries. With compression of the superior vena cava, shortness of breath, acrocyanosis, dizziness is noted. Symptoms of intestinal obstruction, pain syndrome, dyspeptic phenomena, and melena can also be added.

Diagnosis of STS:

1. Morphological examination of the tissue of the primary tumor and/or foci suspicious for metastatic;

2. Magnetic resonance imaging with intravenous contrast of the primary tumor focus;

3. Ultrasound examination of the primary tumor zone and regional lymph nodes and abdominal cavity and retroperitoneal space;

4. Computed tomography of thoracic organs;
5. Radioisotopic examination of bones of the skeleton and soft tissues and/or magnetic resonance imaging of the whole body;

6. Morphological examination of bone marrow points from three points.

4. Conclusion

Despite the apparent scarcity of pathology, pediatricians should have basic knowledge in diagnosis and differential diagnosis of cancer and similar pathological conditions in children and orient themselves in certain subtleties of therapeutic and diagnostic tactics in them [11].

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References


Contemporary Pediatric Hematology and Oncology covers many aspects of research and patient management within the area of blood disorders and malignant diseases in children. Blood diseases are a distinctive group of inherited and acquired, benign and malignant, acute and chronic disorders with diverse incidence, etiology, pathogenesis, and prognosis. Of interest are clinical studies as well as basic and translational research reports regarding pathogenesis, genetics, molecular diagnostics, pharmacology, molecular targeting, standard and novel therapies for the most common blood disorders, and childhood cancer. This book intends to provide the reader with a comprehensive overview of today’s practices and tomorrow’s possibilities regarding the most important pediatric hematological and oncological diseases.