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Neonatal manifestations of inherited bone marrow failure syndromes

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SUMMARY

The inherited bone marrow failure syndromes (IBMFS) are a rare yet clinically important cause of neonatal hematological and non-hematological manifestations. Many of these syndromes, such as Fanconi anemia, dyskeratosis congenita and Diamond–Blackfan anemia, confer risks of multiple medical complications later in life, including an increased risk of cancer. Some IBMFS may present with cytopenias in the neonatal period whereas others may present only with congenital physical abnormalities and progress to pancytopenia later in life. A thorough family history and detailed physical examination are integral to the work-up of any neonate in whom there is a high index of suspicion for an IBMFS. Correct detection and diagnosis of these disorders is important for appropriate long-term medical surveillance and counseling not only for the patient but also for appropriate genetic counselling of their families regarding recurrence risks in future children and generations.

Keywords

Neonate; Cytopenia; Cancer; Bone marrow failure; Fanconi anemia; Dyskeratosis congenita

1. Introduction

The inherited bone marrow failure syndromes (IBMFS) are a group of biologically distinct yet clinically related cancer-prone syndromes that may present with significant cytopenias in at least one hematopoietic cell lineage. Some of these disorders may present with hematologic manifestations in the neonatal period, such as thrombocytopenia absent radii (TAR) syndrome or severe congenital neutropenia (SCN), whereas other IBMFS, including Fanconi anemia (FA) and dyskeratosis congenita (DC), rarely manifest with neonatal-onset cytopenias but may present with congenital abnormalities or dysmorphic features [1]. The

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differential diagnosis of neonatal cytopenias is complex and includes physiologic or iatrogenic causes, congenital or acquired infection, non-IBMFS genetic diseases, as well as maternal causes such as pregnancy-induced hypertension/pre-eclampsia. Early diagnosis of an IBMFS is important to optimize clinical management, anticipate possible complications that may develop later in life, and provide appropriate genetic counseling for the family. Many of these syndromes require multi-disciplinary, multi-specialty medical care for appropriate surveillance and management. In this review, we discuss the most prevalent IBMFS, possible neonatal presentations, current understanding of underlying molecular basis for disease, and medical problems associated with each syndrome that may present later in life.

1.1. General evaluation of IBMFS in neonates

The evaluation of any neonate for an underlying IBMFS should include a thorough family history for presence of hematologic and non-hematologic problems in the family (such as cancer or pulmonary fibrosis for DC, or anemia for DBA), a complete physical exam with a specific focus on evaluation for dysmorphic features, a complete blood count with differential, reticulocyte count, and peripheral blood smear for evidence of hematologic disease. Many of the IBMFS are associated with elevated fetal hemoglobin (HbF) and elevated mean corpuscular volume (MCV). HbF and the MCV are postulated to be markers of stress erythropoiesis in older patients, but these parameters are not necessarily useful in the neonatal evaluation due to normally elevated levels in the first few months of life. Surrogate peripheral markers for decreased erythrocyte and platelet production in the marrow include a low reticulocyte count for age and a low immature platelet fraction, respectively [1]. A bone marrow aspirate and biopsy may be required to aid in diagnosis. Specific diagnostics are further discussed under each syndrome.

2. Fanconi anemia

2.1. Clinical features

Fanconi anemia is a chromosomal instability disorder caused by genetic defects in DNA repair. Bone marrow failure (BMF) in FA is rarely present in infancy. Many patients with FA have congenital anomalies that may affect almost any organ system (Table 1). The most prevalent congenital anomalies are short stature in about 40% of patients, skin abnormalities such as café-au-lait and hyper- or hypopigmented spots in about 40%, upper limb abnormalities in 35% including absent, hypoplastic, bifid, duplicated or rudimentary thumb, absent or hypoplastic radius (with abnormal thumbs), flat thenar eminence, clinodactyly or polydactyly [2,3]. Other frequent anomalies in about 20–25% of patients include microcephaly, facial features such as triangular “Fanconi” face, micrognathia, mid-face hypoplasia and epicanthal folds; renal anomalies such as horseshoe kidney, ectopic or pelvic kidney, absent kidney and hypogonadism. Physical features of FA may overlap significantly with those of the VACTERL-H association; VACTERL-H is the acronym for vertebral anomalies, anal atresia, cardiac anomalies, trachea–esophageal fistula, esophageal atresia or duodenal atresia, renal structural anomalies, limb abnormalities – particularly radii and thumbs and hydrocephalus [4]. It has been suggested that 5–10% of babies reported to have VACTERL-H may indeed have FA, with FA VACTERL babies having renal abnormalities,

radial ray defects and cardiac anomalies more frequently than classic VACTERL [4]. FA patients with VACTERL may have worse prognosis with shorter median survival and earlier onset of malignancy compared with other FA patients [4]. FA testing should be considered in neonates with VACTERL-H. It is important to note that up to two-thirds of patients do not present with the physical features of FA and may initially present with later complications such as bone marrow failure or cancer [5,6]. A physically normal-appearing baby does not rule out the disease, especially in a family with known history of FA.

Bone marrow failure in FA may present at any age and has been reported in neonates but occurs most frequently in the first decade of life. It may present as a single cytopenia or pancytopenia [3,7,8]. FA is a cancer-prone IBMFS with increased risk of myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and solid tumors, particularly squamous cell carcinoma of the head, neck, gastrointestinal (GI) tract, skin, and genitourinary tract. Competing risk analyses have shown the cumulative incidence of AML to be 10% by age 24 years, and that of solid tumors to be 29% by age 48 years [9]. Patients with mutations in *FANCD1/BRCA2* have a very high risk for developing brain tumors, AML or Wilm's tumor at an early age [10].

2.2. Pathogenesis, genetics, and diagnosis

Fanconi anemia is caused by germline mutations in DNA repair genes. Inheritance is autosomal recessive (AR), except FA subtype B, which is X-linked recessive (XLR). Whereas the first genetic mutation causing FA was discovered more than 20 years ago, recent advances in genomic technology, including next generation sequencing and whole exome analysis, have accelerated gene discovery efforts. There are currently 16 known genes causative of FA, which account for ~95% of FA patients [5] (Table 2).

The diagnosis of FA in neonates requires a thorough physical examination with a detailed dysmorphology exam. Prenatal ultrasound may be helpful in identifying pathognomonic physical features of FA, including thumb abnormalities or VACTERL features.

Fanconi anemia is diagnosed by the presence of elevated chromosomal breakage in lymphocytes after exposure to a DNA cross-linking agent such as di-epoxybutane or mitomycin C [2,11]. In 10–30% of FA patients, this test may be inconclusive due to somatic mosaicism, which occurs when there are two populations of lymphocytes in a patient's blood – one with increased sensitivity to DNA cross-linking agents and another with normal sensitivity. In patients with negative or inconclusive chromosomal breakage of lymphocytes, skin fibroblasts should be tested for chromosome breakage as these cells are not known to be affected by mosaicism [2,12].

2.3. Management

The management of infants with FA requires a multi-disciplinary team approach that adapts to the patient's changing needs. The Fanconi Anemia Research Fund publishes clinical care guidelines focused on all FA-associated medical problems [13]. Surgery is often required for life-threatening congenital anomalies, such as congenital heart disease or anal atresia.

Absent thumbs are often surgically corrected with pollicization to create a functional thumb from an existing finger [13,14].

Hematopoietic cell transplant (HCT) is currently the only curative treatment for the hematological manifestations of FA; however, this does not diminish the increased risk of malignancy – indeed, the risk of solid tumors after successful HCT has been shown to be further increased [15,16]. Due to their exquisite sensitivity to DNA-damaging agents, non-myeloablative HCT may be indicated in FA patients with severe BMF in the absence of malignancy, and survival rates have been reported to be better in patients who underwent HCT from a related donor [17]. In patients who choose not to or who are unable to undergo HCT, androgens such as oxymetholone have been successful in treating BMF in about 50% patients [2]. Patients on androgens must undergo regular testing for blood counts, lipid panel testing, liver function tests, and abdominal ultrasound to monitor for liver tumors. Treatment of malignancies is particularly challenging due to sensitivity to chemotherapy and radiation, making surgery the mainstay of treatment for solid tumors in FA [3].

3. Dyskeratosis congenita

3.1. Clinical features

The mucocutaneous triad of lacy skin pigmentation, oral leukoplakia, and nail dystrophy is diagnostic of DC. It is typically not present in the neonatal period but, instead, develops at different rates in different patients [18]. Patients with DC rarely develop hematological manifestations as infants. The neonatal presentation of DC is non-specific but may include low birth weight, urethral stenosis, hypoplastic gonads, blocked lacrimal ducts, and esophageal stenosis [1,19,20] (Table 1). Hoyeraal–Hreidarsson syndrome (HH) and Revesz syndrome (RS) are clinical variants of DC with complications that may be present in neonates or in early infancy. Patients with HH have cerebellar hypoplasia, intrauterine growth retardation (IUGR), developmental delay, immunodeficiency, and non-specific enteropathy. The immunodeficiency in HH is non-specific and may be clinically significant in infancy. Revesz syndrome (RS), another variant of DC, presents with IUGR, intracranial calcifications, and bilateral exudative retinopathy in addition to features of DC [3,19]. Patients with ‘Coats plus syndrome’, a related telomere biology disorder, develop vascular ectasias in the eye, GI tract, and lungs, in addition to intracranial calcifications.

DC patients are at high risk of developing BMF at varying ages, with cumulative incidence of 50% by the age of 50 years across all genotypes [20,21]. BMF in HH usually develops in early childhood [19]. DC patients are also at high risk of developing pulmonary fibrosis, non-alcoholic liver disease/cirrhosis, avascular necrosis of femoral head and osteoporosis, among other problems such as premature loss or graying of hair and dental problems [1,19,22]. DC is a cancer-predisposition syndrome with increased risk of cancers similar to those in FA, namely squamous cell carcinoma of head, neck, anogenital regions; and MDS/leukemia. It confers an 1100-fold increased risk of tongue cancer and 2500-fold increased risk for MDS [9,23].

3.2. Pathogenesis, genetics, and diagnosis

The central component in the molecular pathogenesis of DC is defective telomere biology. Inheritance is complex and can be AR, XLR, autosomal dominant (AD), or due to denovo mutations [19]. There are currently eleven known genetic causes of DC, all of which are genes involved in telomere lengthening, or protection. Together they account for disease in ~70% DC patients (Table 2) [5,24,25]. The carrier frequency of specific mutations may be higher in founder populations such as mutations in *RTEL1* in Ashkenazi Jewish individuals [26].

The clinical diagnosis of DC, in the absence of the classic triad, is challenging given its phenotypic heterogeneity. Telomere length <1st percentile for age in lymphocyte subsets measured by flow cytometry with fluorescence in-situ hybridization is a highly sensitive and specific diagnostic test [27,28].

3.3. Management

Patients with DC may have multiple, difficult-to-diagnose medical problems. Esophageal or urethral stenosis may require dilation. Lacrimal duct stenosis has been managed with stents. Exudative retinopathy in RS requires pediatric consultation with retinal specialists.

BMF in DC does not respond to immunosuppressive therapy. Between 50% and 70% of patients with BMF show a response to androgen treatment, but co-treatment with granulocyte colony-stimulating factor (G-CSF) must be avoided due to the risk of splenic peliosis [29]. Patients on androgens for BMF were reported to have increased occurrence of lipid panel abnormalities and liver tumors compared with those who were not [21,29]. HCT with a non-myeloablative conditioning regimen is curative for the non-malignant hematologic manifestations of DC. However, HCT-associated chemotherapy and immunosuppressive medications may further compound the risk of pulmonary fibrosis, liver disease and veno-occlusive disease. Late graft failure is another complication seen in post-HCT DC [3,30].

4. Diamond–Blackfan anemia

4.1. Clinical features

Diamond–Blackfan anemia (DBA) frequently presents with isolated anemia due to pure red blood cell (RBC) aplasia in the neonatal period or infancy [1,31]. Congenital anomalies have been reported in 40–50% patients (Table 1) [1,32]. Craniofacial dysmorphism includes widely separated eyes, ‘snub’ nose, thick upperlip, and rarely cleft lip/palate; upper limb deformities include triphalangeal, bifid or subluxed thumbs with subtle thenar eminence flattening and normal radius [33]. The thumb abnormalities are important to differentiate from FA. Other reported congenital anomalies include genitourinary defects, cardiac abnormalities, webbed neck, Klippel–Feil anomaly (fusion of cervical vertebrae), and Sprengel deformity (congenital asymmetric high scapula) [1,5,31,34]. Growth retardation is seen in about 30% of neonates with DBA [32]. There is a broad phenotypic spectrum even within families with DBA, the molecular basis of which is not clearly understood, with some

mutation-positive members being clinically unaffected and some with severe anemia requiring treatment [35].

Anemia in DBA may occasionally lead to aplastic anemia, though not typically as severe as that of FA or DC [3]. Patients with DBA are also at a 5-fold increased risk of developing cancer compared to the general population, with highest risk observed for MDS, followed by colon carcinoma, osteosarcoma, AML and genitourinary cancers [36].

4.2. Pathogenesis, genetics, and diagnosis

DBA is caused by AD mutations in key components of the small or large ribosomal subunits (Table 2) [5]. *RPS19*, the first known gene to cause DBA, was discovered more than 15 years ago and accounts for about 25% of DBA patients. Since then mutations in 13 ribosomal genes have been identified in many patients. However, approximately half of DBA patients still have an unknown genetic cause [5,37]. X-linked mutations in *GATA1* were found in two families with DBA, expanding the understanding of the disease outside the ribosomal pathways and linking it to X-linked dyserythropoietic anemia and thrombocytopenia [5,38,39].

It is not clear why these mutations affect erythropoietic development specifically. It is speculated that defective ribosomal protein function may result in activation of cellular stress-signaling pathways such as p53 [40].

The classic anemia diagnostic of DBA is isolated normochromic macrocytic anemia with reticulocytopenia occurring in the first year of life, with normal or increased platelet counts, and decreased erythroid precursors in the bone marrow [32,41]. With the heterogeneity of disease, diagnosis may not be as straightforward. Elevated levels of HbF, erythropoietin and erythrocyte adenosine deaminase (eADA) are supporting criteria for diagnosis, but their absence does not rule out the diagnosis of DBA. A recent study showed that whereas elevated eADA has good predictive value, up to 16% of DBA patients have a normal eADA [32,42]. Markers such as eADA and erythropoietin may be helpful in distinguishing DBA from transient erythroblastopenia of childhood, which may present at an overlapping age as DBA (although typically after one year of age) and usually remits spontaneously [1,3].

4.3. Management

Anemia is the major clinical complication in children with DBA. RBC transfusions are the mainstay of treatment until the diagnosis of DBA has been established. Corticosteroid therapy is a viable treatment option in older children and has shown response rates of up to 80% of treated DBA patients. However, caution must be exercised and regular surveillance performed for steroid-related complications such as diabetes mellitus, infections, and growth retardation [3,32]. Transfusions may be continued in patients who are medically unable to take, tolerate or are unresponsive to steroids. The most prevalent secondary and potentially life-threatening complication of chronic RBC transfusions is iron overload of the liver, heart, and endocrine organs. Iron chelation is recommended after 10–15 transfusions and compliance is of utmost importance in preventing free iron build-up in the body. Studies have shown that ferritin correlates poorly with amount of solid organ overload, and

magnetic resonance R2/T2* imaging is now recommended to evaluate solid organ iron load and damage [3,41,43]. HCT may be considered for patients with treatment for steroid-unresponsive anemia but is a difficult decision to make in a disease that typically presents with a single cytopenia. Furthermore, 20–25% of affected DBA patients undergo spontaneous remission at no specific age. These patients may, however, relapse with anemia requiring treatment again [3,41].

5. Shwachman–Diamond syndrome

5.1. Clinical features

Shwachman–Diamond syndrome (SDS) usually presents with a single cytopenia – neutropenia – that may progress to BMF. SDS is characterized by exocrine pancreatic insufficiency leading to malabsorption and steatorrhea in the first few months of life, in addition to growth retardation and bone marrow dysfunction [1,3]. In a small series of SDS patients, the skeletal phenotype in infancy has been characterized to include delayed appearance of secondary ossification centers, metaphyseal widening and dysostosis, osteopenia, and wormian bones of the skull (Table 1) [44].

Patients with SDS develop infantile growth retardation, frequent bacterial infections secondary to intermittent severe neutropenia, and failure to thrive resulting from recurrent infections and malabsorption due to pancreatic dysfunction. It is second to only cystic fibrosis in leading causes of inherited pancreatic dysfunction [45]. The hematological features of SDS vary but typically intermittent severe neutropenia with absolute counts $<0.5 \times 10^9/L$ is the initial finding and may be followed by bilineage or trilineage cytopenia in ~20% patients [3].

5.2. Pathogenesis, genetics, and diagnosis

Shwachman–Diamond syndrome is inherited in an AR fashion, with germline mutations in the *SBDS* gene being the only known disease-causing gene and accounting for about 95% of patients (Table 2). The SBDS protein interacts with the 60S ribosomal precursor and moves between the nucleus and cytoplasm of the cell based on the cell cycle [46,47]. The involvement of multiple organ systems including skeletal system, hematopoietic system and exocrine pancreas may be due to the biological link between SBDS and ribosome biology [1].

The diagnosis of SDS is made based on clinical phenotype with involvement of the exocrine pancreas, skeletal abnormalities, and bone marrow dysfunction. An update on 37 SDS patients in the North American SDS registry reported a wide phenotypic spectrum with only about half the patients having the classic phenotypic criteria. Notably, about 65% of patients had congenital abnormalities, as described above [45,48]. Genetic testing for mutations in the *SBDS* gene is diagnostic of the majority of patients despite heterogeneity of clinical presentation. Exocrine pancreatic insufficiency may be evidenced by low levels of serum trypsinogen in children aged <3 years, low serum isoamylase levels in children aged >3 years, or elevated fecal fat excretion over a 72 h period. However, normal values of any of these do not preclude diagnosis [49]. Bone marrow clonality has been known to occur in SDS, with the most common molecular changes being abnormalities in i(7q) and del(20q)

[48]. SDS patients also have hepatomegaly with or without elevation of serum transaminases, and these may also resolve with age [45].

5.3. Management

Clinical management of SDS is based on the affected organ systems and requires multidisciplinary team coordination with hematology, gastroenterology, and immunology. G-CSF is used to treat patients with severe and recurrent infections and/or severe neutropenia, along with appropriate antimicrobial treatment. There has been no strong evidence to suggest malignancies associated with G-CSF treatment in this cohort [50]. Pancreatic insufficiency is managed with supplementation of vitamins A, D, E, K, and with replacement of pancreatic enzymes which also aids in treating growth failure due to malabsorption [45]. SDS patients may be at increased risk of AML; however, data for association between SDS and MDS have been inconclusive. Bone marrow examination can aid in the diagnosis and evolution of clonal bone marrow disease [9,48]. Some SDS patients have cognitive/intellectual disabilities and thus neuropsychological evaluation may be a valuable component of long-term management [45]. Data on HCT are limited due to small numbers and reporting in small case series or reports. HCT may be indicated in patients with multiple severe cytopenias or with evidence of leukemia, although it has been suggested that SDS patients are at increased risk of transplant-related mortality [50]. Identifying patients at risk of MDS may be challenging due to observations of persistent clonal bone marrow changes without malignant transformation. SDS patients have shown better results with reduced intensity conditioning regimens for transplant [45,50].

6. Thrombocytopenia absent radii

6.1. Clinical features

Patients with TAR are typically diagnosed in the neonatal period because of thrombocytopenia and absence of radii with presence of both thumbs (Table 1). Prenatal ultrasound may identify absent radii prior to birth. The radial absence is almost always bilateral (about 98% cases). The thumbs are present but may not appear normal. The presence of thumbs helps in differentiating TAR from FA; in FA the thumbs are absent and radii may or may not be present or deformed [1,51,52]. TAR-associated thrombocytopenia is often congenital or occurs in the first few months of life. In one review, ~60% affected babies developed thrombocytopenia in the first few weeks of life [53]. The thrombocytopenia is often severe in infancy and early childhood, with platelet counts $<50 \times 10^9/L$, but it tends to improve over time, although not quite reaching normal levels. The risk of spontaneous hemorrhage also follows this pattern [51].

Other physical abnormalities in TAR have been reported such as ulnar and humeral deformities, rib and cervical anomalies, cardiac lesions (usually septal defects), GI and genitourinary abnormalities that are non-specific but known to occur [51,53]. Cow's milk allergy is highly prevalent in patients with TAR. Some patients develop a transient leukemoid reaction with white blood counts $>35 \times 10^9/L$ that can be misdiagnosed as congenital leukemia [52]. Whereas aplastic anemia or multilineage cytopenias do not frequently occur in TAR, there have been reports of leukemia in four patients [9,54,55].

6.2. Pathophysiology, genetics, and diagnosis

It is important to distinguish TAR from the other IBMFS such as FA since the clinical course and risks are very different. The pathophysiology and genetics of TAR were unknown until recently. A combination of comparative genomic hybridization and next generation sequencing revealed that TAR patients inherit a deletion of chromosome band 1q21.1 from one parent and a single nucleotide variant in the *RBM8A* gene in the non-deleted allele from the other parent, thus following AR pattern of inheritance (Table 2) [56,57]. The *RBM8A* gene encodes for a subunit of the exon-junction complex that is integral to RNA processing. It is expressed in hematopoietic lineages, thus suggesting that this is a plausible mechanism for the thrombocytopenia in TAR. Inheritance of two hypomorphic variants in *RBM8A* has also been reported to cause TAR [56,57].

Genetic testing for the 200 kb minimally deleted chromosomal band and *RBM8A* variant may aid in diagnosis [51]. Bone marrow examination in TAR shows small hypoplastic megakaryocytes with normal erythroid and myeloid lineages [51,52].

6.3. Management

Clinical management is based on presentation, with platelet transfusions as required for thrombocytopenia and orthopedic intervention for functional optimization of upper limbs. In patients with cow's milk allergy, consultation with a GI specialist and avoidance of dairy products may help decrease severity of gastroenteritis and prevent potential exacerbation of thrombocytopenia [51,58].

7. Congenital amegakaryocytic thrombocytopenia

7.1. Clinical features

Of all the IBMFS, congenital amegakaryocytic thrombocytopenia (CAMT) is the most likely to present at birth or in the neonatal period (Table 1). Approximately 70% of patients present with severe thrombocytopenia in the neonatal period [59]. CAMT is a rare cause of neonatal thrombocytopenia and other causes must be ruled out including prenatal causes, such as vertical transmission of toxoplasma, rubella, cytomegalovirus, herpes, and other infections such as syphilis, varicella, parvovirus B19 (TORCH) infections, and neonatal alloimmune thrombocytopenia [59,60]. Neonates with CAMT usually have severe thrombocytopenia with petechiae at birth and may develop intracranial or intestinal mucus membrane bleeding. The median platelet counts in these neonates have been reported as low as $16 \times 10^9/L$ [59]. There are no characteristic congenital physical abnormalities associated with CAMT that differentiate it from other syndromes. Strabismus, cardiac defects, and intracranial abnormalities have been reported in patients with CAMT but may be coincidental [59,61]. Many children with CAMT develop pancytopenia. In some cases, multi-lineage cytopenias develop without the preceding thrombocytopenia. It has been suggested that patients with persistent severe thrombocytopenia in infancy, $<50 \times 10^9/L$, develop pancytopenia at an earlier age (group I; median age at pancytopenia: 22 months) compared with those whose platelet counts rise after infancy (group II; median age at pancytopenia: 48 months) [61]. There are reports of MDS and leukemia [9,62], as well as of bone marrow trisomy 8 and monosomy 7 after the development of pancytopenia [59,63].

A rare form of CAMT associated with fusion of the radius and ulna (radio-ulnar synostosis) has been described. Typically these patients have mutations in *HOXA11* that regulates megakaryocytic differentiation [1,64].

7.2. Pathogenesis, genetics, and diagnosis

The majority of CAMT patients have AR inherited biallelic mutations in *MPL*, the gene encoding the thrombopoietin receptor, an integral component of megakaryopoiesis (Table 2). These mutations have been divided into two groups. Group I CAMT has frameshift or nonsense mutations that cause more severe disease due to disruption or absence of TPO receptor function. Group II CAMT has missense *MPL* mutations that lead to reduced TPO receptor function and milder phenotypes [59,61]. Mouse models have shown that deletion in TPO or its receptor recapitulates the CAMT hematological phenotype and illustrates the role of MPL in hematopoiesis [1,60].

The diagnosis of CAMT may be made in newborns or infants with thrombocytopenia and/or hemorrhagic manifestations in absence of other causes, such as the lack of pathognomonic manifestations of other IBMFS, and morphologically normal platelets on peripheral smear. Genetic testing that finds mutation in *MPL* can be diagnostic of disease in cases of ambiguity [59]. If a bone marrow aspiration is performed, it may show absence or very low numbers of small-appearing megakaryocytes, with otherwise normal marrow cellularity unless done in presence of pancytopenia [60].

7.3. Management

Management of hematological manifestations is symptomatic, with platelet transfusions and antifibrinolytics for patients with bleeding caused by thrombocytopenia [60]. Currently the only curative treatment for CAMT and associated pancytopenia is HCT. Comparisons of patients with CAMT who have undergone HCT with standard chemotherapy conditioning versus those who have undergone HCT with reduced intensity conditioning have suggested higher rate of graft failure and transplant-related mortality in those who received standard chemotherapy. Outcomes have improved better with matched related donors, but further studies need to be carried out to characterize appropriate regimens [59,60,65].

8. Severe congenital neutropenia

8.1. Clinical features

Also known as Kostmann syndrome, severe congenital neutropenia (SCN) is a disease of severe neutropenia presenting in the neonatal period or early infancy, with neutrophil counts $<0.5 \times 10^9/L$ and recurrent bacterial infections such as skin and subcutaneous infections, abscesses, and pneumonia. Omphalitis is a typical neonatal presentation of SCN [1,52,66,67]. There are no other distinguishing physical features or congenital anomalies associated with SCN (Table 1). Hemoglobin levels and platelet counts are normal [68]. G-CSF is a mainstay of treatment of, or prophylaxis from, life-threatening bacterial infections. Patients with SCN were reported to be at increased risk of MDS and AML prior to the availability of G-CSF treatment and now G-CSF appears to add to that risk [69–72]. Notably, a prospective study on 374 patients on G-CSF treatment and overall risk of

MDS/AML was 15–25% by age 15 years. The risk was reported to be higher with increasing doses of G-CSF and is postulated to be due to changes in the stem cell, not directly to G-CSF [73,74].

8.2. Pathogenesis, genetics, and diagnosis

Severe congenital neutropenia results from the maturational arrest of neutrophil development at or before the promyelocyte stage in the bone marrow (Table 2). Originally described by Kostmann with AR inheritance, genetic discovery has broadened the spectrum of SCN inheritance. Mutations in the neutrophil elastase gene *ELA2* (*ELANE*) cause AD inherited and sporadic SCN in about 50% of patients. Elastase is a glycoprotein that is released from azurophilic granules during the promyelocyte–myelocyte maturation stage. There are two current hypotheses: (i) that *ELA2* mutations cause accumulation of neutrophil elastase on the cytoplasm, leading to neutrophil apoptosis; and (ii) that *ELA2* mutations cause amino-terminally deleted isoforms of the elastase rather than affecting the complete protein coding sequence [1,75–77]. AR inherited mutations in the mitochondrial gene *HAX1* cause SCN, likely by activating the apoptotic cascade in myeloid cells [78]. Other mutations that have been reported to cause SCN include mutations in *G6PC3*, *WAS*, *GS11* and *JAGN1* [78–81]. It has been seen that mutations in *CSF3R* that encodes G-CSF receptor are linked with leukemia progression in SCN [82].

The diagnosis of SCN is based upon the presence of recurrent bacterial infections and severe, persistent neutropenia. The differentiating factor between SCN and cyclic neutropenia (also caused by *ELA2* mutations) is the persistence of neutropenia in SCN. Neutropenia waxes and wanes in cyclic neutropenia. Bone marrow aspiration in SCN, if performed, shows normocellular marrow with arrest of myeloid maturation [83].

8.3. Management

Clinical management of SCN is based on infectious manifestations due to profound neutropenia. It requires careful surveillance and early antimicrobial treatment for infections. G-CSF became available in the late 1980s for treatment of severe neutropenia to maintain levels that greatly reduced the risk of bacterial infections in the majority of patients [1,82,83]. However, as described, caution must be exercised in patients needing higher than usual doses of G-CSF due to risk of malignant transformation. HCT is the only curative treatment [1].

9. Conclusion

Whereas the above-described syndromes are considered the ‘classic’ IBMFS, there are several other disorders that may have hematological manifestations along with involvement of other organ systems or diagnostic constellations of symptoms such as Wiskott–Aldrich syndrome, Chediak–Higashi syndrome and Griscelli syndrome, among others that have not been discussed here. The importance of correctly diagnosing the IBMFS lies not only in the ability to differentiate future medical and oncological risk factors for each syndrome but also in proper genetic counseling and testing of family members. It is necessary for families to have a basic understanding of the disease inheritance and biological process to interpret and

acknowledge risks for future children in the family and risks to first and second degree relatives based on inheritance patterns. Although the IBMFS remain a rare cause of hematologic abnormalities in neonates, they are without doubt a group of disorders that may cause a multitude of future morbidity, the knowledge of which allows for proper multi-disciplinary screening and appropriate treatment.

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Practice points

- A high index of suspicion for IBMFS should be maintained in neonates with cytopenia and/or congenital abnormalities for proper diagnosis.
- IBMFS may confer an increased risk of cancer.
- Treatment of specific syndromes often requires multidisciplinary team coordination.
- Genetic counseling is very important in families with IBMFS to aid in their understanding of disease etiology and risk to their children.

Research directions

- Optimizing early diagnosis of IBMFS through combining current approaches with next generation genomics.
- Advancing understanding of genotype–phenotype correlations in IBMFS.
- Optimize HCT conditioning regimens to improve clinical outcomes.
- Increase understanding of biological mechanisms involved in IBMFS.
- Identify the genetic causes of all IBMFS to improve patient diagnosis and understanding of underlying biology.

Table 1

Selected clinical manifestations of IBMFS in the neonate.

Neonatal manifestations	FA	DC	DBA	SDS	TAR	CAMT	SCN
Hematological	Very rare, cytopenia	Very rare, cytopenia	Macrocytic, normochromic anemia with reticulocytopenia	Neutropenia	Thrombocytopenia	Thrombocytopenia	Neutropenia
General	LBW, VACTERL-H	LBW, IUGR (HH and RS)	LBW				
Skeletal	Absent or hypoplastic thumbs or radii, flat thenar eminence. Toe syndactyly, foot malformations	Sprengel deformity, Klippel–Feil anomaly, spina bifida, hemivertebrae, abnormal ribs, coccygeal aplasia	Webbed or short neck, Klippel–Feil anomaly, Sprengel deformity. Absent radial artery, flat thenar eminence, Triphalangeal, duplex, bifid, hypoplastic, or absent thumb	Metaphyseal dysostosis, epiphyseal dysplasia, abnormal ribs	Bilaterally absent radii with thumbs present, hypoplasia or absence of ulnae or humeri. Non-specific bony abnormalities	Valgus and varus deformities, vertebral anomalies	
Dermatological	Café au lait spots	Dysplastic nails					
Craniofacial	Microcephaly. Triangular bird-like facies, small eyes	Microcephaly. Exudative retinopathy (RS)	Microcephaly, hypertelorism. Broad, flat nasal bridge, microtia, cleft lip/palate, high arched palate, micrognathia, low anterior hairline, congenital glaucoma or cataract	Hearing loss		Cleft and high arched palate, optic atrophy, coloboma	
CNS		Cerebellar hypoplasia (HH), intracranial calcifications (RS)		Chiari type I malformation, cerebellar tonsil ectopia, hypotonia			
Cardiac	As part of VACTERL-H		VSD, ASD, coarctation of the aorta	VSD, ASD, PDA	VSD, ASD	VSD, ASD	
Gastrointestinal	As part of VACTERL-H	Esophageal stenosis		Exocrine pancreatic insufficiency, Hepatomegaly with abnormal serum transaminases, Malrotation, inguinal hernia, imperforate anus			
Renal	Structural renal anomalies	Structural renal anomalies	Structural renal anomalies		Structural renal anomalies	Structural renal anomalies	

Neonatal manifestations	FA	DC	DBA	SDS	TAR	CAMT	SCN
Genitourinary	Males, hypospadias, micropenis; undescended or absent testes. Females, bicornuate uterus, small ovaries. Both sexes, hydronephrosis or hydroureter	Urethral stenosis in males. Hypogonadism	Hypospadias	Hypogonadism	Rarely agenesis of uterus, cervix, upper vagina		
Immune		Immunodeficiency (HH)		Infection due to neutropenia			Infection due to neutropenia

FA, Fanconi anemia; DC, dyskeratosis congenita; DBA, Diamond-Blackfan anemia; SDS, Shwachman-Diamond syndrome; TAR, thrombocytopenia absent radii; CAMT, congenital amegakaryocytic thrombocytopenia; SCN, severe congenital neutropenia; LBW, low birth weight; VACTERL-H, vertebral anomalies, anal atresia, cardiac anomalies, tracheo-esophageal fistula, esophageal or duodenal atresia, renal structural anomalies, limb anomalies, hydrocephalus; IUGR, intrauterine growth retardation; HH, Hoyeraal-Hreidarrson syndrome; RS, Revesz syndrome; VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus.

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Molecular mechanisms, known genes, and modes of inheritance of inherited bone marrow failure syndromes.

	Biological pathway	Gene(s)	Inheritance
Fanconi anemia	DNA repair	<i>FANCA, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG/XRCC9, FANCI, FANCI/BA CH1/BRIP1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C, FANCP/SLX4, FANCP/ERCC4</i>	AR
Dyskeratosis congenita	Telomere biology	<i>FANCB</i> <i>NOPI0, NHP2, WRAP53, RTEL1, TERT, CTC1, ACD, PARN</i> <i>TERT, TERC, TINF2, RTEL1</i> <i>DKC1</i>	XLR AR AD XLR
Diamond-Blackfan anemia	Ribosomal biogenesis	<i>RPS19, RPS17, RPS24, RPL35A, RPL5, RPL11RPS7, RPL26, RPS26, RPS10, RPS29</i>	AD
Shwachman-Diamond syndrome	Ribosomal RNA processing	<i>GATA1</i>	XLR
Thrombocytopenia absent radii	Not yet elucidated	<i>SBD5</i>	AR
Congenital amegakaryocytic thrombocytopenia	Reduced or non-functional thrombopoietin receptor	1q21.1 deletion and <i>RBM8A</i>	AR
Severe congenital neutropenia	Maturation arrest of neutrophil development	<i>MPL</i> <i>ELANE (ELA2)</i> <i>HAX1, G6PC3, GSI1, JAGN1</i>	AR AD AR

AR, autosomal recessive; AD, autosomal dominant; XLR, X-linked recessive.