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Review

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.

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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 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 prevalenty 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.

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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

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–Fiel 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	
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, esophaeal 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.