Sindromes de Fallo Medular hereditario

Inherited bone marrow failure syndromes

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Introduction

The inherited BM failure syndromes are a diverse group of life threatening disorders[1]. The features of the recognized inherited BM syndromes are summarized in **Table 1**. An outline of the syndromes frequently associated with trilineage hematopoietic defect is given below; this short review has not focused on the disorders typically associated with a single lineage defect such as Diamond-Blackfan anemia.

Fanconi anemia (FA)

FA was first described by Fanconi in 1927[2]. It is usually inherited as an autosomal recessive (AR) trait but in a small subset of patients it can be an X-linked recessive (XLR) disorder. FA patients are clinically heterogeneous[3]. Characteristic features include the progressive development of BM failure and an increased predisposition to malignancy (hematological and non-hematological). Affected individuals may also have one or more developmental/somatic abnormality including skin (e.g. cafe au lait spots), skeletal (e.g. radial hypoplasia), genitourinary (e.g. single kidney), gastrointestinal (e.g. duodenal atresia) and neurological abnormalities. Approximately 30% of FA patients have no overt somatic abnormalities. The majority of patients present towards the end of the first decade of life. However, increasingly some patients are being diagnosed in adulthood and many patients diagnosed in childhood are surviving into adulthood.

FA cells display a high frequency of spontaneous chromosomal breakage and hypersensitivity to DNA cross-linking agents such as diepoxybutane and mi-

tomycin-C. This "FA cell hallmark" led to the development of a diagnostic test over three decades ago and has facilitated many advances, including elucidation of the genetics with 18 subtypes/complementation groups currently characterized[4-19]. The proteins encoded by the FA genes participate in a complicated network important in DNA repair[20-22]. Specifically, eight of the FA proteins (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL and FANCM) interact with each other and form a nuclear complex called the "FA core complex". The FA core complex is required for the activation of the FANCI-FANCD2 protein complex to a monoubiquitinated form (FANCI-FANCD2-Ub). FANCI-FANCD2-Ub then interacts with DNA repair proteins (including BRCA2, BRCA1 and RAD51) leading to repair of the DNA damage. FA-D1 patients have biallelic mutations in BRCA2. These observations have linked the FA proteins with BRCA1 and BRCA2 (FANCD1) in a DNA damage response pathway "The FA/BRCA pathway". The BRCA2 protein is important in the repair of DNA damage by homologous recombination. Cells lacking BRCA2 inaccurately repair damaged DNA and are hypersensitive to DNA cross-linking agents. It has been established that FANCJ is BRIP1 (partner of BRCA1), FANCN is PALB2 (partner of BRCA2) and that SLX4 is also a FA protein. These findings further strengthen the connection between FA and DNA repair; specifically it appears that the FA pathway orchestrates incisions at sites of cross linked DNA[21]. Recent studies suggest the FA proteins may be important in counteracting aldehyde induced genotoxicity in hematopoietic stem cells[23-24]. In addition to their role in DNA repair they also have other functions. For example, there is evidence of mitochondrial dysfunction and impaired ROS (reactive oxygen species) detoxifying machinery in FA cells[25].

Table 1: Characteristics of the inherited bone marrow failure syndromes

	FA	DC	SDS	DBA	CDA	CAMT	SCN	Other
Inheritance pattern	AR, XLR	XLR, AR AD	AR	AD XLR	AR AD	AR	AD AR	AR, AD
Somatic abnormalities	Yes	Yes	Yes	Yes	Rare	Rare	Rare	Rare
Bone marrow failure	AA (90%)	AA (80%)	AA (20%)	RCA[a]	Dysery	Meg[b]	Neut[c]	AA
Short telomeres	Yes	Yes[d]	Yes	No	No	No	?	?
Cancer	Yes	Yes	Yes	Yes	No	Yes	Yes	?Yes
Chromosome instability	Yes	Yes	Yes	?	?	No	?	?
Genes identified	18	12	1	14	4	1	5	4

FA = Fanconi anemia; DC = dyskeratosis congenita; SDS = Shwachman-Diamond syndrome. DBA = Diamond-Blackfan anemia; CDA = congenital dyserythropoietic anemia; CAMT = congenital amegakaryocytic thrombocytopenia; SCN = Severe Congenital Neutropenia; AD = autosomal dominant; AR = autosomal recessive; XLR = X-linked recessive.

RCA[a] = Red cell aplasia although some patients can develop global BM failure. Dysery= Usually dyserythropoiesis. Meg[b] = low megakaryocytes which can progress to global BM failure. Neut[c] = usually low neutrophils. Yes[d] = Usually very short.

Dyskeratosis congenita (DC)

Classical DC, first described in 1910, is an inherited BM failure syndrome characterized by the muco-cutaneous triad of abnormal skin pigmentation, nail dystrophy and mucosal leucoplakia[26-27]. A variety of other [dental (e.g. severe caries), gastrointestinal (e.g. esophageal stenosis), genitourinary (e.g. phimosis), neurological (e.g. cerebellar hypoplasia), ophthalmic (e.g. naso-lacrymal duct narrowing), pulmonary (e.g. fibrosis) and skeletal (e.g. osteoporosis)] abnormalities have also been reported. BM failure is the major cause of mortality with an additional predisposition to malignancy (hematological and non-hematological) and fatal pulmonary complications. XLR, autosomal dominant (AD) and AR subtypes of DC are recognized. Twelve DC genes (*DKC1*, *TERC*, *TERT*, *NOP10*, *NHP*2, *TINF2*,

TCAB1, *USB1*, *CTC1, RTEL1, TPP1* and *PARN*)[28-41] have been identified to date.

The gene mutated in X-linked DC (*DKC1*) encodes a highly conserved nucleolar protein called dyskerin. Dyskerin associates with the H/ACA class of small nucleolar RNAs in small nucleolar ribonucleoprotein particles (snoRNPs), which are important in guiding the conversion of uracil to pseudouracil during the maturation of ribosomal RNA. Dyskerin also associates with the RNA component of telomerase (TERC) where it is important in stabilizing the telomerase complex, which is critical in the maintenance of telomeres[42-44]. Heterozygous mutations in *TERC* and *TERT* (telomerase reverse transcriptase) have been found in patients with AD-DC[29-31] and in some patients with aplastic anemia (AA), myelodysplasia (MDS), acute myeloid leukemia, pulmonary and liver fibrosis[45-50]. A subset of patients with the multi-system disorder Hoyeraal-Hreidarsson (HH) syndrome, have been found to have *DKC1* mutations[51]. It has also been established that AR-DC is genetically heterogeneous with nine subtypes due to biallelic mutations in *NHP2*, *NOP10*, *TERC, TCAB1*, *USB1*, *CTC1, RTEL1*, *TPP1* and *PARN)* One AD-DC subtype was found to be due to mutations in *TINF2* which encodes a component of the shelterin complex that protects telomeres and controls access of telomerase to the telomere. Collectively, these findings have demonstrated that classical DC, HH, a subset of AA and MDS/AML are principally due to a defect in telomere maintenance and cells from these patients have very short/and or abnormal telomeres[42, 52]. The multi-system abnormalities seen in these patients, including the increased incidence of malignancy, have highlighted the critical role of telomeres and led to the recognition of a new category of human diseases – "the telomeropathies".

Shwachman-Diamond syndrome (SDS)

SDS, first described in 1964, is an AR disorder characterized by exocrine pancreatic insufficiency, BM failure and other somatic abnormalities (particularly metaphyseal dysostosis)[53-54]. Features of pancreatic insufficiency are apparent early in infancy. The spectrum of hematological abnormalities includes neutropenia, pancytopenia (~20%), MDS and leukemia (~25%). The majority (>90%) of SDS patients have biallelic mutations in the *SBDS* gene[55]. The *SBDS* gene product (SBDS) has an important role in the maturation of the 60S ribosomal subunit and therefore ribosome biogenesis[56]. SDS is thus principally a disorder of defective ribosome biogenesis.

Other subtypes of inherited bone marrow failure syndromes

There are cases of BM failure where they are familial and/or have one or more extra-hematopoietic abnormality but which do not fit into the recognized entities listed above. The recent availability of next generation sequencing technology is making it possible to elucidate the genetic basis and pathophysiology of these cases. Examples of such cases that have been recently characterized include the familial aplastic anemia associated with constitutional thrombopoietin receptor (MPL), thrombopoietin ligand, *SRP72* and *ERCC6L2* mutations[57-60]. It is likely more such cases of familial/constitutional BM failure will be characterized in the near future; they are also likely to provide new insights on hematopoiesis and how this might be disrupted in BM failure.

General principles of diagnosis and management

A diagnosis of an inherited BM failure should be considered when there is one or more extra-hematopoietic feature associated with the BM failure. In the context of children presenting upfront with aplastic anemia (global trilineage BM failure) a diagnosis of an inherited BM failure also needs to be on the differential list. The specific extra-hematopoietic abnormalities help in making diagnosis of a recognized syndrome; however this is not always possible on clinical features alone.

The chromosomal breakage analysis test on peripheral blood lymphocytes following exposure to diepoxybutane or mitomycin-C remains a very useful way of diagnosing FA. All children presenting with AA should be tested for FA. Genetic testing for the FA genes is possible but this is not straightforward and not always routinely available.

Telomere length, particularly using flow fluorescence in situ hybridization (Flow–FISH) can be a very useful initial screen[61] in the diagnosis of DC. Patients with DC frequently (but not always) have very short telomeres compared to age matched controls. Genetic testing for the DC genes (*DKC1*, *TERC*, *TERT*, *NOP10*, *NHP2*, *TINF2*, *USB1*, *TCAB1*, *CTC1*, *RTEL1*, *TPP1* and *PARN*) can be

helpful in substantiating the diagnosis. However as in FA this is not straight forward (as many patients will have private mutations and some of the genes are large) and in approximately a third of patients the genetic basis will remain unknown even after testing for all 12 DC genes.

In patients with global BM failure the other genetic tests to consider are those for the *MPL*, *SBDS, SRP72* and *ERCC6L2* genes. For patients presenting with an isolated neutropenia analysis for the *ELANE*, *GFI1* and *HAX1* may help substantiate the underlying diagnosis. For those with an isolated anemia testing for the DBA and CDA genes is indicated.

Once diagnosis of an inherited syndrome has been made (clinically and/or genetically) it is important to explain to the patient/family the chronic nature of these disorders. In general, patients need to be followed up throughout life and will need to be monitored for complications. The frequency of monitoring investigations (such as blood tests, BM examinations, pulmonary function tests) is difficult to define precisely in view of the considerable clinical heterogeneity. However regular (possibly on an annual basis) follow-up is advisable; with more frequent monitoring (and appropriate investigations) being implemented if there is a specific problem.

In view of the significant risk of cancer in many of these syndromes patients should be advised (according to age) to avoid active and passive smoking. They should also avoid sunbathing and keep alcohol intake to a minimum as they go through adolescence and adulthood. Treatment for cancer depends on the specific cancer but consideration has to be given to the underlying genetic defect (i.e. more supportive care, reduction of drug doses).

With regards to pulmonary disease in FA and DC, patients should be encouraged to avoid smoking. Medical treatment is usually difficult in severe lung disease; lung transplant may be an option in some cases. Advice on skin care (e.g. use of moisturising creams) and avoidance of sunlight is important. They should also avoid occupations that expose them to hazardous chemicals or repeated physical trauma. When doing domestic chores such as washing up use of protective gloves is advisable (particularly in DC). Avoidance of extremes of temperature, both hot and cold, is desirable as the skin is usually fragile compared to the normal population.

Liver disease is more common in FA and DC patients than the normal population. Alcohol consumption should therefore be kept to a minimum and all drug administrations require close monitoring.

Drugs also need to be used carefully as patients with inherited BM failure syndromes tend to be small and more sensitive to many drugs. This is particularly important in FA and DC patients undergoing allogeneic hematopoietic stem cell transplantation (SCT).

Management of the hematological complications

Major advances in supportive treatments[62] have led to considerable improvement in the outcome of these patients. Blood product support has been a key component of this effort. Packed red cell transfusions should be given to maintain the haemoglobin at a level which allows the patient to be asymptomatic (typically >8g/dl), platelets should be maintained above 10 x 10^9/l. It is reasonable to give prophylactic antimicrobials to patients with a neutrophil count consistently below 0.5 x 10^9/l. As a general rule all neutropenic patients need prompt therapy with broad-spectrum intravenous antibiotics if they develop an infection. Leuco-depleted and where appropriate CMV-negative, blood products should be chosen to prevent development of HLA-antibodies and reduce the risk of CMV disease.

Inherited BM failure syndromes do respond to specific interventions. In patients with FA and DC who have significant peripheral cytopenia (Hb < 8 g/dl, neutrophils < 0.5 x 10^9/l, platelets < 20 x 10^9/l) the first line medical therapy is usually with oxymetholone which should be started at a dose of 0.5-1.0 mg/kg/day and gradually increased, if necessary, to a maximal dose of 5mg/kg/day. DC patients are usually more sensitive to oxymetholone than FA. There is also increasing experience in the use of danazol in these patients[63-64]. Approximately 70% of patients with DC and FA will have a hematological response to anabolic steroids; this can be durable for years in some patients. Patients with severe BM failure and with HLA- compatible donors can be cured of their hematological complications. Over the years, it has been recognised that patients with inherited BM failure syndromes have greater efficacy and lower toxicity using low intensity fludarabine based protocols. There is now considerable experience using such protocols in both FA and DC patients[65-69]. This represents a major advance in outcome following SCT in FA and DC patients.

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