MYELODYSPLASIA IN CHILDHOOD
Shantaraman. K

Abstract:
Myelodysplasia is a heterogenous group of disorders that was earlier described as preleukemia, refractory anemia with excess of blasts, subacute myeloid leukemia, oligoleukemia and odoleukemia (1). This disorder is predominately an ineffective marrow due to a stem cell disorder characterized by progressive cytopenia(s), associated with a hypercellular, normocellular or hypocellular marrow and associated dysmorphism of myeloid, erythroid and/or megakaryocyte cell lineages (2). Myelodysplasia is associated with a greater predilection to evolve into acute myeloid leukemias (AML), though not in all patients. MDS is considered to be rare in childhood but the implications of such diagnosis in a child has more implications than in the adult.

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Introduction: Myelodysplasia is a clonal stem cell dysfunction that involves one or more of the three marrow cell lines with a predilection to evolve into acute myeloid leukemias (AML). The 2001 World Health Organization (WHO) classification incorporated cytogenetics into the FAB classification system for adult myelo-dysplastic syndrome (MDS) (2). The FAB system, which is based on a correlative peripheral blood and marrow evaluation, has five types based on a transition from myelo-dysplastic syndrome to AML (3). The clinical and morphological presentation in this disorder in childhood is similar to that seen in the adult, but certain unique differences are to be mentioned, especially when the child does not show blasts in the peripheral blood or bone marrow. The 2008 World Health Organization (WHO) classification system recognized childhood MDS as a distinct entity named refractory cytopenia of childhood (RCC) (ICD-O 9985/3) (4). Down syndrome-associated MDS is also categorized as “Myeloid Proliferations related to Down Syndrome”.

Etiopathogenesis: The pluripotent hematopoietic stem cell have extensive regenerative and differentiating capacity and generate lymphoid and myeloid precursors, which then produce lymphocytes, neutrophils, monocytes, eosinophils, basophils, erythrocytes, and platelets. In MDS, a disorder occurs in this process of differentiation due to a dysregulation of cellular mechanisms of growth & differentiation, which varies with the genetic defect. This primarily results in a clone of sick cells which end up activating its own cellular damage control mechanisms and result in apoptosis and hence ineffective hematopoiesis and marrow failure. This presents as either isolated anemia, neutropenia, or thrombocytopenia, or as bi or tri phenotypic cytopenias and progressive pancytopenia over a period of weeks to months (5). The mechanisms involved include genomic instability, epigenetic changes, abnormal apoptosis, abnormal signal-transduction pathways, immune dysregulation, and the marrow microenvironment. Chromosomal abnormalities frequently found in MDS, involve chromosomes 5, 7, and 8; especially monosomy 7 or deletion of 7 (del7q) in de novo, secondary or constitutional forms of MDS has been implicated as a secondary genetic event in leukemogenesis. Cytogenetic studies indicate loss or dysfunction of tumor suppressor genes within deleted chromosome 7 segments which may occur as germline mutation or acquired due to prior cytotoxic injury. Favorable cytogenetic aberrations in adults namely - chromosome Y and chromosome 20q- and 5q- are rare in children. The risk of both MDS and AML is increased in preexisting genetic syndromes especially the Shwachman-Diamond syndrome, Diamond-Blackfan syndrome, dyskeratosis congenita, Fanconi anemia, neurofibromatosis (NF), and severe congenital neutropenia (Kostmann syndrome) (5-6). Mutations in the ras proto-oncogene are observed in 20-30% of childhood myelodysplasia syndrome cases. Increasing evidence suggests that, even in absence of a mutation in Ras, the dysfunction of certain upstream regulators could contribute to the development of MDS eg: In neurofibromatosis, NF-1 gene product loss leads to loss of negative feedback via guanosine 5’triphosphate (GTP) of oncogenic N-ras resulting in unregulated proliferation of the abnormal clone. This is one major mechanism hypothesized as responsible for the increased incidence of MDS in children with NF1 defect (7,8). Mutations in the telomerase component seen in patients with dyskeratosis congenita, are occasionally seen in pediatric myelodysplasia syndrome without the typical phenotypic features. Aberrant methylation of genes has also been reported in pediatric myelodysplasia syndrome and is under continued investigation (9,10,11).

Epidemiology
Incidence: The annual incidence of MDS in children is 0.5-4 per million population and accounts for approximately 3-9% of hematologic malignancies in children (12,13,14). The exact incidence of MDS in childhood is difficult to estimate due to unclear classification, heterogeneity of presentation and risk factors. Refractory cytopenia of childhood (RCC) is the most common subtype of MDS in childhood, accounting for approximately 50% of the cases (15,16).

Mortality/Morbidity: Mortality in MDS results from significant bleeds, recurrent infection, and leukemic transformation and hence in the absence of timely intervention, MDS can be rapidly fatal, with or without the transformation to AML. An
estimated 20-40% develop leukemia, and 30-40% experience infection, bleeding, or both. Treatment-related morbidity and mortality in childhood myelodysplasia syndrome are usually related to complications of bone marrow transplant therapy - graft failure with subsequent aplasia, transfusion-related diseases, infection, iatrogenic immunosuppression, graft versus host disease, and graft rejection.

**Racial:** No racial predilection has been observed in MDS.

**Sex:** The male-to-female ratio varies from 1.7-4.8:1 in different series. The male predominance is attributed to increased prevalence of juvenile myelomonocytic leukemia (JMML), (Syn: juvenile chronic myelogenous leukemia (JCM), and monosomy 7 syndrome in males.

**Age:** Of the patients with MDS, 50% are older than 60 years. MDS though uncommon in childhood-Monosomy 7 syndrome and JMML occur exclusively in children younger than 4 years especially in children treated with radiation or intensive chemotherapy for another malignancy are more likely to develop MDS secondary to the adverse event.

**Medical History:** Adults with MDS may present with symptoms of hematopoietic failure, including infection, bleeding, bruising, fatigue, weight loss, and dyspnea upon exertion. However, no specific clinical symptoms are reported in up to 20% of children with RCC. In children cytopenia(s) or isolated splenomegaly is discovered during evaluation for unrelated symptoms. The interval between onset of symptoms and diagnosis ranges from 0-23 months, with a median of 2 months. A history of malignancy or cytotoxic therapy is important to distinguish between primary vs secondary MDS, especially exposure to alkylating agent chemotherapy, epothilone, radiation therapy, or hematopoietic stem cell transplant are risk factors for therapy-related MDS in children as in adults. Therapy-related myelodysplasia syndrome following cytotoxic chemotherapy is concern in the pediatric population. The risk of myelodysplasia syndrome peaks 5-7 years after treatment. In addition the syndromes involving bone marrow failure e.g., Fanconi syndrome, Diamond-Blackfan anemia, Kostmann syndrome, Shwachman-Diamond syndrome, or aplastic anemia can precede secondary MDS. Familial cases of MDS have also been reported in first-degree relative with myelodysplasia syndrome, AML, or both.

**Clinical Features:** The physical examination often reveals the intensity of cytopenia e.g., pallor, bruising, petechiae, Splenomegaly and hepatomegaly are more common in childhood MDS and predominate in JMML. In children with RCC; 65-70% have platelet count below 150,000, 50% have hemoglobin concentrations of less than 10 g/dl, 40-50% have Macrocytosis in peripheral blood films, 25-30% have leucopenia and 25% have severe neutropenia. A pathognomonic erythematous maculopapular rash is seen in one third of children with JMML. Congenital anomalies and syndromic features are significant because of the association of Primary MDS with several constitutional syndromes, especially in about 25% of children. The classification systems for myelodysplasia syndrome have also includes Down syndrome–related diseases (e.g., transient myeloproliferative disorder, myeloid leukemia of Down syndrome) as unique forms of MDS.

**Differential Diagnosis:** The differential diagnosis of MDS in children include -
1. Acute Lymphoblastic Leukemia
2. Acute Myelocytic Leukemia
3. Amegakaryocytic Thrombocytopenia
4. Aplastic Anemia
5. Autoimmune Lymphoproliferative Syndrome
6. Chemical and medication exposure (cytotoxic chemotherapy, antibiotics, benzene, anticonvulsants etc.
8. Chromosomal deletion syndromes (eg: velocardiofacial syndrome)
9. Dyserkeratosis Congenita
10. Gaucher Disease
11. Histiocytosis
12. Infections (eg, parvovirus B19, EBV, Herpes viruses, CMV, HIV, Visceral leishmaniasis)
13. Kostmann Disease
14. Lymphohistiocytosis (Hemophagocytic Lymphohistiocytosis)
15. Metastatic carcinoma
16. Nutritional deficiencies (eg, vitamin B12 deficiency, folate deficiency, pyridoxine-dependent anemia, vitamin E deficiency, copper deficiency)
17. Osteopetrosis
18. Paroxysmal Nocturnal Hemoglobinuria
19. Pearson Syndrome
20. Rheumatic disease and other chronic inflammation
21. Shwachman-Diamond Syndrome
22. Transient Erythroblastopenia of Childhood

**Laboratory Findings:** CBC count (differential and peripheral blood smear) in the earliest investigation that can reveal indications of an MDS. Peripheral blood count reveals anemia, neutropenia, and/or thrombocytopenia. The anemia is often macrocytic. Cytopenias can evolve and progress over a period of weeks to months. The blood smear commonly reveals macrocytosis, hypogranular granulocytes, Pseudo–Pelger-Huet anomaly (hypogranular and hypolobulated granulocytes), and giant platelets. Reticulocyte counts are low despite normal numbers of erythroid progenitors in the marrow. In JMML, marked monocytosis may be present. Bone marrow aspiration and biopsy are essential to establish the diagnosis and to classify the myelodysplasia syndrome. Biopsy findings are needed to ascertain cellular architecture, cellularity, percentage of blasts, and the presence of fibrosis. As myelodysplasia has a varied temporal course, these procedures may need to be repeated at different time points if initial studies are not confirmatory and there is no alternate explanation for clinical/laboratory findings.

**Marrow Cytology / Histology:** The minimal morphologic criteria for the diagnosis of myelodysplasia syndrome remains similar in the most recent WHO classification system: In the appropriate clinical setting, at least 10% of the cells of at least 1 myeloid bone marrow lineage
(erythroid, granulocytic, megakaryocytic) must show unequivocal dysplasia for the lineage to be considered dysplastic. Bone marrow biopsy should also be performed to assess cellularity and architecture because fibrosis can be a component of disease. The bone marrow of patients with myelodysplasia syndrome can be hypercellular, normocellular or hypocellular. Hypocellularity of the bone marrow is more commonly observed in childhood myelodysplasia syndrome than in older patients. The diagnosis of MDS relies heavily on marrow morphology, hence observer differences complicate disease classification & diagnosis. The current FAB system is based on morphology and does not account for the cytogenetics or predisposing abnormalities, thus limits its use in children. The classification schemes have changed rapidly in the last 10 years and hence underscore the fact that the understanding of myelodysplasia is evolving.

The WHO classification system published in 2008 devotes a section to childhood cases of myelodysplasia. The category of RCC is reserved for childhood cases (RCC) is introduced in the classification for the first time. Children with myelodysplasia syndrome and 2-19% blasts in peripheral blood and/or 5-19% blasts in the bone marrow are categorized using the same criteria as adults with myelodysplasia syndrome. In contrast to adults, isolated refractory anemia is uncommon in children with myelodysplasia syndrome, who more commonly present with thrombocytopenia and/or neutropenia, often accompanied by a hypocellular bone marrow. The changes are tabulated below in table1.

The WHO classification includes some cytogenetic information; the most recently proposed WHO classification scheme for myelodysplasia syndrome is as follows:

- Refractory cytopenia with unilineage dysplasia - Refractory anemia, refractory neutropenia, refractory thrombocytopenia
- Refractory anemia with ringed sideroblasts
- Refractory anemia with multiple dysplasia
- Refractory anemia with excess blasts
- Myelodysplastic syndrome with isolated del(5q)
- Myelodysplastic syndrome, unclassifiable

JMML is unique to the pediatric age group and hence categorized separately from myelodysplasia syndrome. JMML is characterized by an absence of t(9;22), an absolute peripheral monocyte count of more than 450/mcL, elevated fetal hemoglobin levels, selective in vitro hypersensitivity to granulocyte-macrophage colony-stimulating factor (GM-CSF), and excessive proliferation of monocyte-macrophage colonies in clonogenic cultures. JMML, in nearly 75% of patients, expresses mutually exclusive mutations of PTPN11, NRAS or KRAS, or NF1.

**Quantitative hemoglobin electrophoresis**: This may reveal elevated fetal hemoglobin levels, indicating reversal of fetal erythropoiesis due to bone marrow stress and arrest of maturation.

**Cytogenetic studies**: Conventional karyotype, fluorescence in situ hybridization (FISH), polymerase chain reaction etc reveal chromosomal abnormalities in 40-70% of pediatric cases of myelodysplasia syndrome (MDS). Acquired chromosomal abnormalities confirm the diagnosis. The most commonly known abnormalities include monosomy 7 or 7q, monosomy 5 or 5q, or trisomy 8. Myelodysplasia syndrome may also be associated with 20q, isochromosome 17, and abnormalities of 11q. Reciprocal translocations and inversions are uncommon. Children who present with a peripheral blood and/or bone marrow disorder associated with t(8;21)(q22;q22), inv(16)(p13.1q22) or t(16;16)(p13.1;q22) or t(15;17) (q22;q12) should be considered to have AML regardless of the blast count.

**Faunconi anemia test**: A Fanconi screen using diepoxynbutane (DEB) or mitomycin C stimulation reveals abnormal chromosome breakage if this syndrome is present.

**Paroxysmal nocturnal hemoglobinuria (PNH) test**: Measurement of 2 complement regulatory proteins, CD55 (decay accelerating factor [DAF]) and CD59 (membrane inhibitor of reactive lysis [MIRL]) aids in diagnosis of PNH. The clinical picture of PNH is rare in childhood, although PNH clones in the absence of hemolysis or thrombosis may be observed in children with refractory cytopenia of childhood (RCC).

**Human leukocyte antigen (HLA) typing**: Human leukocyte antigen (HLA) typing of patient and family members should be performed in anticipation of allogeneic hematopoietic stem cell transplantation (HSCT).

**Other Lab Studies**: Viral serologies, especially human immunodeficiency virus (HIV), cytomegalovirus (CMV), EBV, and parvovirus, can be used to exclude viral etiologies of altered hematopoiesis. The novo or primary form of myelodysplasia syndrome in children should be distinguished from cases of secondary myelodysplasia syndrome that follow congenital or acquired bone marrow...
failure syndromes\(^{[23]}\) and from therapy-related myelodysplasia syndrome that follows cytotoxic therapy for a previous neoplastic or nonneoplastic condition.

**Diagnostic Challenges:** Diagnostic problems arise when the clinical or laboratory findings suggest myelodysplasia syndrome but the morphologic findings are inconclusive; when secondary dysplasia is caused by nutritional deficiencies, medications, toxins, growth factor therapy, inflammation, or infection or when bone marrow hypocellularity or myelofibrosis obscures the underlying disease process.\(^{[30]}\)

A presumptive diagnosis of myelodysplasia syndrome can be made if only one or a specific clonal abnormality is present. Hypocellular MDS may be more common in children because of the relative prevalence of inherited marrow failure syndromes. Hence, if no MDS-related cytogenetic abnormalities are present, the distinction between childhood MDS and evolving aplastic anemia or congenital bone marrow failure syndrome can be very difficult. Therefore, at least 2 biopsies obtained at least 2 weeks apart are recommended to facilitate the detection of representative bone marrow spaces containing foci of erythropoiesis.\(^{[4]}\)

**Medical Care:** Once the diagnosis is established, management involves supportive care that includes transfusion, treatment of infections, and a search for an allogeneic stem cell donor. MDS is an incurable disease without hematopoietic stem cell transplantation (HSCT). Allogeneic HSCT regimens are associated with a 30% event-free survival rate at 3 years. Stem cell transplantation. Children with monosomy 7 cytogenetics or congenital bone marrow failure syndrome can be very difficult. Therefore, at least 2 biopsies obtained at least 2 weeks apart are recommended to facilitate the detection of representative bone marrow spaces containing foci of erythropoiesis.\(^{[4]}\)

**Surgical Care:** Splenectomy is restricted to patients with severe hypersplenism and disease that is unresponsive to other treatment modalities.

**Follow up:** Blood product and infectious disease support need to be managed aggressively at a tertiary care center where specialized blood banking procedures are available. All pediatric patients should be evaluated at an institution with expertise in pediatric stem cell transplantation. Children with monosomy 7 cytogenetics should have family members evaluated for familial monosomy 7.

**Diet:** Dietary restrictions pertain to periods of neutropenia and are similar to those used for immunocompromised patients with cancer. No clinical trials have demonstrated the benefit of these dietary modifications to prevent infection.

References:


