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Leading Article

Is Myelodysplastic Syndrome a Rarity in Childhood? Or are We Failing to Diagnose?

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Introduction:

The Myelodysplastic Syndrome (MDS) were historically characterized by a cellular marrow with peripheral cytopenias. They were described as smouldering leukaemia or pre-leukaemia. These disorders were predominantly of late adult life and have since been well classified in the extensive adult literature[1].The Myelodysplastic Syndrome in children have been poorly defined, characterized, studied and reported. Previously it was variously called chronic monocytic leukaemia, preleukaemia and some called this even haematopoitic dysplasia[2]. It has been a dilemma for the paediatric haematologists as regards MDS to be understood properly. This lack of understanding has been further complicated by the rarity of this disorder, lack of uniform diagnostic criteria, and confusing nomenclature and poor understanding of the biologic mechanisms of this disorder[3]. It has further been complicated in children by the use of classification and prognostic system for adult patients in the MDS. The adult classification has little utility for children with MDS[4].

Definition: MDS are a heterogenous group of disorder of haematopoisis of acquired clonality of pluripotent or multipotent hematopoitic progenitor cells-typically resulting in bone marrow containing blasts between more than 1% and less than 20%[2].

Morphologically these disorders are characterized by dysplastic feature of the peripheral blood and bone marrow.The dysplasia could be in the granulocytic, megakaryocytic, monocytic and erythrocytic lineage occuring in single or multiple lineages.Dysplastic features in the granulocytic lineage of the bone marrow include dysgranulopoisis with hypogranulation, nuclear hypofragmentation, megaloblastoid maturation and left shift with a increase number of monocytes. The peripheral blood may show dygranulopoisis with circulating myeloblast, hypogranulation of neutrophils and eosinophils. Greater than 50% of children with de novo MDS will have a detectable chromosomal abnormality.The karyotypic abnormality most commonly seen in denovo MDS in children include -7, 7q- and +8. Of importance is the findings that certain chromosomal abnormalities commonly present in de novo MDS in adults, including -5, 5q- and -y are not present in paediatric MDS except in patients with DNA repair defects such as Fanconi's Anaemia.

Therefore the minimal diagnostic criteria in MDS would include the common de-novo MDS, AML cytogenetic translocation and at least two of the following

a) Sustained unexplained anaemia, neutropenia or thrombocytopenia
b) Dyplastic morphology in erythroid, granulocytic and megakaryotic lineage (at least Bilineage)
c) Acquired sustained clonal cytogenetic abnormalities.
d) >5% marrow blast[2].

Incidence and Epidemiology:

Despite an increasing number of case reports, the true incidence of paediatric MDS is unknown but generally is estimated to account for approximately 3% to 7% of childhood haematological malignancies. And only four actual population based studies have been reported. In the study based in Denmark, an annual incidence of 4 cases per million was detected representing 9% of all paediatric hematologic malignancies in that country[5]. This was consistent with the report in British Columbia where the actual incidence of MDS was determined to be a 3.1 per million, representing 6% of haematologic malignancies in British columbia. This is in contrast to a third study representing to be 0.5 case per million and more recently in United Kingdom 1.35 cases per million MDS and JMML case at 0.66 case per million[6-7]. The reasons for this differences are not clear, possibilites could be due to diagnostic, inclusion and classification system, incomplete ascertainment of cases and a true variation in incidence.

A number of environmental exposure and genetic disorders may predispose patients to the development

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of MDS. Exposure to alkylating agents (eg:- Cyclophosphamide, nitrogen mustard), Topoisomerase-II inhibibitors (etoposide) and ionozing radiation may lead to the development of MDS and AML[2].

Morphologic Classification

FAB cooperative group defined five categories for the adult myelodysplasic and myeloproliferative syndromes-refractory anaemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RA with excess blasts in transformation (RAEB-T) and chronic myelomonogenic leukaemia (CML)[8]. On the contrary, classification of childhood MDS into distinct FAB categories is not always easy[9].

The FAB classification has a number of limitation, especially in childhood MDS. Many children with MDS have monocytosis which automaticlly classes them as having JMML.In any such cases, there may be >5% blasts in the blood without any excess of blast in the marrow.This finding thereby may be reclassified as RAEB (Refractory anaemia with excess of blasts in transformation) and in most Paediatric studies these are termed as JMML. There are a number of patients where there is eosinophilia and dysplatic blood and bone marrow for which it is impossible to assign in a FAB system[10].

Therapy related MDS or MDS occuring in association with congenital bone marrow disorders may defy classification by this scheme, the class may have hypoplasia and or fibrosis in addition to dysplasia in the marrow. Despite limitation FAB classification has been sometimes appropriate for paediatric MDS[2].

The world health organization recently published recommendation for classification of MDS and these have been modified for paediatrics[11]. A third classification system is used in parallel with the FAB and WHO system, the IPSS scoring system[12]. The international prognostic system (IPSS) for MDS is based upon weighted data on bone marrow (BM) blast percentage, cytopenias and cytogenetics separating patients into four prognostic groups. The higher score is associated with poor prognosis[13]. The value of IPSS for paediatric MDS patients remain to be proven. So, the best methods for classifying paediatrics MDS remains uncertain and the subject of recent debate[14].

Pitfalls in the diagnosis of refractory cytopenias:

Refractory anemia need to be distinguished from congenital dyserythropoitic anaemias and megaloblastic anaemias and the presence of clonal cytogenetic abnormalities needed for confirmation of the disease. Refractory Anaemia with ringed sideroblast as a true MDS is exceptionally rare in Paediatrics. So, diagnosis of such entity should be cautiously considered[15].

MDS or AML is sometimes a difficult thing to assess. Refractory anaemia with excess of blasts with or without tranformation is arbitrary because patient may present with an abnormal blast and precursor of blast in the marrow and subsequent development of overt AML within weeks or even days[2].

Biology & Pathogenesis:

The molecular abnormalities that results in MDS are now better understood. Studies of variants of Glucose 6-phosphate dehydrogenase and other X linked restriction fragment length polymorphism confirm that MDS is a clonal disorder. Newer assay demonstrate that clonal involvement of granulocytes and erythrocytes are possible but still controversial involvement of B and T lymphocytes are there.However most of the studies shown are in adults where clonal and oligoclonal haematopoisis may occur even in normal individual[16-18].

It is generally thought that MDS involves an abnormality in an immature stem cell that leads to the proliferation of a myelodysplasic clone of cells along with normal haematopoitic elements. This mosaicism of normal and abnormal haematopoisis may coexist for prolong period[3]. However as additional injuries and molecular defects occur in this abnormal myelodysplastic clone, the abnormal clone appears to develop a competitive advantage over normal haematopoitic clones leading to supression of normal haematopoisis and eventually to only ineffective clonal haematopoisis[19].

A number of distinct cytogenetic abnormalities may occur as these abnormal clones evolve. The most common abnormalities include the complete loss of specific chromosome (e.g. chromosome 7), Partial chromosome losses e.g. long arm of 7 (7q-) or addition of extra chromosome (Trisomy 8). The biologic implications of these chromosomal abnormalities are also unclear[20]. It is known however that a number of genes presumed to be important in the control of haematopoisis are encoded on these large areas of DNA that are gained or lost during the evolution of myelodysplastic clone[2]. For e.g. chromosome 5q,

commonly seen in older adult female with 5q- syndrome rarely seen in Paediatric MDS containing genes encoding for granulocyte-macrophage colony stimulating factor (GM-CSF), macrophage colony stimulating factor (M-CSF), interleukin -3 (IL-3), interleukin-4 (IL-4) etc[21-24].

The search to identify crucial genetic change has been accompanied by many investigations of cellular biology and cell culture in MDS. The paradox of cytopenias in the blood despite a cellular bone marrow has been debated for many years. Also investigators have shown that white cell proliferation in the bone marrow in MDS is high with large number of cells entering S phase, then cells rapidly undergo programmed cell death and they never enter the circulation[25].

Conclusion:

Myelodysplastic syndrome in children are a rare and clinically challenging group of diseases. They frequently occur in association with other genetically determined disorders. The FAB classification which may be suitable for adults are not always applicable to children as in JMML. However Paediatric modification of WHO classification of myelodysplasic disorders will be used with some more interest. But the variable incidence, the morphologic diagnostic pitfalls and the rarity need involvement of a third eye of paediatric haematologist for careful apprehension. Moreover we should keep MDS in our mind with peripheral cytopenias with cellular marrow. Further international collaborative studies would be very much necessary for uniform diagnostic criteria.

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