CHILDHOOD MYELODYSPLASIA

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ABSTRACT

The clinical data and hematological features of 29 children, under the age of 12 years, with primary myelodysplasia are presented. The diagnosis was made using the FAB (French-American-British) Cooperative Group criteria. There were 24 males and 5 females aged 4 months to 12 years (median 2.5 years) with marked male preponderance. Childhood myelodysplasia constituted 16% of all hematological maligenancies and 36.7% of acute myeloid leukemias. The median duration of symptoms prior to diagnosis was 3 months. There were 15 cases of refractory anemia, one of refractory anemia with excess blasts, 3 of refractory anemia with excess blasts in transformation and 10 cases of chronic myelomonocytic leukemia. Five patients evolved to acute myeloid and 4 to acute lymphatic leukemia. The median duration of preleukemic phase in these patients was 7 months (range 4-29 months). The overall mean survival was short (5-9 months) in all the subgroups. Besides supportive therapy in most patients, two patients were treated with etoposide, one with alfa interferon 2b and one with high dose methylprednisolone. Our results show that myelodysplasia is not infrequent in children. The disease has an aggressive clinical course and may evolve into acute leukemia.

Key words: *Myelodysplasia, Preleukemia, Acute leukemia.*

Preleukemia might be thought of as a recognizable syndrome of hematopoietic dysfunction, which often but not invariably precedes the development of acute leukemia(l). Hallmarks of preleukemia include ineffective hematopoiesis, peripheral blood cytopenias, and hypercellular bone marrow. In children, this is true in pre-AML (acute myeloid leukemia) patients, but in pre-ALL (acute lymphoid leukemia) the bone marrow may be hypocellular(2). A French-American-British group in 1982 subclassified preleukemia into five myelodysplastic syndromes (MDS, *Table I*)(3).

Subsequently, refinements have been suggested based on trephine biopsies and cytogenetic information. However, the adequate diagnosis of primary myelodysplasia (preleukemia) in childhood has been complicated by both its rarity and a confusing nomenclature^). Hence, a majority of preleukemic cases in children may remain undiagnosed and unpublished(5). We have reviewed the clinical and hematological characteristics in 29 consecutive patients with primary myelodysplasia diagnosed at Our centre over the past 8 years.

Material and Methods

During November 1984 to October 1992, 29 patients under the age of 12 years with primary myelodysplasia, as defined by the FAB diagnostic criteria *(Table I),* were

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TABLE I-*FAB Classification of the Myelodysplastic Syndromes (3)*

Subtype	Features	
	Blood	Bone marrow
Refractory anemia	Cytopenia	Blasts < 5%
	Monocytes < 1 x 10^9/L	Sideroblasts <15%
Refractory anemia	Cytopenia	Blasts <5%
with ring sideroblasts	Monocytes < 1 x 10^9/L	Sideroblasts 15%
Refractory anemia	Cytopenia	Blasts >5% - <20%
with excess of .	Monocytes < 1 x 10^9/L	
blasts	Blasts >1% - <5%	
Refractory anemia	Cytopenia	Blasts <20% - <30%
with excess of	Blasts >5% or	or Auer rods
blasts in trans-	Auer rods	
formation		
Chronic myelomonocytic	Monocytes > 1 x 10^9/1	Blasts up to 20%
leukemia	Blasts <5%	Promonocytes ++

seen at B.J. Wadia Hospital for Children. In the same period 150 patients with acute leukemia were diagnosed. None of the patients had known prior exposure to cytotoxic drugs, radiation or other known mutagens. No geographical clustering of cases was noted. There was no family history of hematopoietic malignancy or other solid malignancy. Patients with major constitutional abnormalities, *e.g.,* Down's syndrome were excluded.

The diagnosis of myelodysplasia was based on peripheral blood and bone marrow findings, using standard cytochemical stains in all cases. Staining for sideroblasts was done in the last 5 cases. Bone marrow and lymph node histology was examined in 15 and 3 cases, respectively. Bone marrow karyotype was determined by GTG (G banding with trypsin and Giemsa) banded metaphases analysis in three cases. Granulopoietic (CFU-GM) colonies were evaluated after incubation of marrow buffy coat or light density peripheral blood mononuclear cells in cultures in two cases(6). Hemoglobin F was estimated using a standard method. Patients were also assessed using the Bournemouth score(7).

Results

Of the 29 patients with myelodysplasia, 24 were boys; the age ranged between 4 months and 12 years (medium 2.5 years). Twenty patients were below four years at diagnosis *(Table II).* No seasonal predilection was noted. During the period under study 100 cases of acute lymphatic leukemia, 50 cases of acute myeloid and 2 cases of chronic myeloid leukemia were diagnosed. Myelodysplasia thus constituted 16% of all hematological malignancies, and 36.7% of acute myeloid leukemias (AML).

The duration of symptoms prior to diagnosis ranged from 11 days to 24 months,

TABLE II - *Clinical Data at Diagnosis*

Patient No.	Sex	Age (yr)	Symptoms	Lymphadeno-pathy	Liver (cm)	Spleen (cm)
1	M	9	Pallor, fever abscesses	Cervical	2	3
2	M	11	Fleeting joint pains, bruising, bleeding, fever	-	2	2
3	M	8	Fever, bleeding	Right hilar	0	0
4	M	12	Fever, bleeding	Hilar and mediastinal	0	0
5	M	0.7	Fever, pallor	Generalized	5	8
6	F	0.6	Fever, recurrent	-	4	9
7	F	4	Fever, joint pains, pallor, cough	-	0	1
8	M	0.8	Pallor, bleeding fever	-	2	1
9	M	1.3	Fever, cough	-	2	10
10	M	4	Fever, pallor	-	0	0
11	M	4	Fever, pallor	Axilla	2	0
12	M	1	Fever, irritability	-	4	10
13	M	10	Pallor, recurrent infections	-	4	12
14	M	7	Pallor, recurrent infections	-	3	8
15	F	1.5	Fever, pallor	Generalized	6	8
16	F	10	Fever, abdominal pain, bleeding	Hilar	1	0
17	M	8	Fever, bleeding	-	2	2
18	M	10	Fever, bleeding anasarca	Generalized	8	3
19	M	3.5	Fever, limbs pains, pallor	Cervical	4	,3
20	M	3.5	Fever, stomatitis	Inguinal	1	0
21	M	0.5	Pallor, irritability	-	5	5
22	M	2	Fever, recurrent infections	-	1	0

(Contd.)

TABLE II *(Contd.)*

Patient No.	Sex	Age (yr)	Symptoms	Lymphadeno-pathy	Liver (cm)	Spleen (cm)
23	F	0.3	Pallor	-	4	3
24	M	2	Pallor, fever	-	6	10
25	M	1.5	Pallor, fever, cough	-	5	2
26	M	2.5	Fever, epistaxis	Generalized	3	5
27	M	0.3	Loose motions	-	6	8
28	M	2	Fever, abdominal distension	Generalized	3	3
29	M	1	Fever. cough	Cervical	5	1

with a median of 3 months. Typically, patients presented with symptoms related to anemia, neutropenia and thrombocytopenia. Three patients had history of jaundice 6 to 8 months prior to onset of symptoms. Two patients had tuberculosis and one had infectious monoriucleosis 6 months prior to diagnosis of myelodysplasia. Three cases had associated recurrent, fleeting joint pains. Hepatosplenomegaly was prominent in all but seven patients; half the patients had lymphadenopathy. Unusual presentations included multiple recurrent lymph node abscesses (Case 1), generalized anasarca (Case 13), serositis (Case 1) and Mickulick's syndrome (Cases 2 and 5).

At presentation all patients had functional or numerical deficits in at least two of three myeloid stem cell derivatives *(Table III)*. Hemoglobin levels ranged from 3.1 g/dl to 9.7 g/dl (median 5.4 g/dl); leucocyte count ranged from 1.7 x 10^9/L to 68.4 x 10^9/L (median 13.2 x 10^9/L), and the platelet count varied from 8 x 10^9/L to 265 x 10^9/L (median 54 x 10^9/L). Seven patients had blasts on the peripheral smear; 2 of them also showed Auer rods. Only four patients did not have circulating nucleated red blood cells. Twenty three patients showed morphological changes in red blood cells. Fetal hemoglobin was measured during the preleukemic phase in 15 patients. It was normal in seven cases, ranging in the others between 2.2% and 18.8%. Six cases had clinical and laboratory features suggestive of juvenile chronic myeloid leukemia.

Bone Marrow Features

Bone marrow aspirates were obtained in all cases and were hypercellular in 15 cases, normocellular in 8 cases and hypocellular in 6 cases. All the cases showed dysplastic changes in at least two cell lineages in the marrow. Dysgranulopoiesis with abnormalities of maturation was seen in all but one patient. Dyserythropoiesis and dysmegakaryopoiesis was present in 22 and 18 patients, respectively. Only 2 patients had more than 20% blasts (Case no. 15 and 17) and 17 patients had none. There were 15 cases of refractory anemia (51.7%), one case of refractory anemia with excess blasts (3.5%), 3 cases of refractory anemia with excess blasts in transformation (10.3%) and

TABLE III - *Hematological Features at Diagnosis*

Patient No.	Hb (g)	WBC ($x10^9$/L)	MCV (FL)	ESR	Monocytes (%)	Blasts (%)	Platelets ($x10^9$/L)	HbF (%)	Circulating # NR(+/-)	RBC abn (+/-)
1	4.6	20.5	NR*	142	41	5	42	ND***	+	-
2	9.7	5.9	NR	30	15	4	45	ND	+	+
3	6.3	12.4	NR	78	0	2	35	ND	+	-
4	7.3	16.0	NR	133	2	1**	15	ND	-	+
5	4.4	46.2	82	115	12	0	54	6.8	+	+
6	3.6	37.4	76	82	18	0	36	18.8	+	+
7	6.3	2.2	NR	152	6	0	70	ND	+	-
8	3.1	10.4	80	27	51	0	210	ND	-	-
9	8.9	48.1	64	45	30	0	32	1.2	+	+
10	8.4	2.6	NR	58	0	0	242	ND	-	-
11	3.3	1.7	80	78	0	0	265	ND	-	+
12	5.8	68.4	78	26	24	0	28	11.1	+	+
13	3.6	2.1	74	110	3	0	110	2.4	+	+
14	5.8	3.3	78	96	4	0	132	2.8	+	+
15	3.5	16.0	80	74	6	6	8	2.2	+	+
16	6.1	19.7	90	128	9	7**	10	ND	+	-
17	5.4	13.2	92	98	12	0	18	ND	+	+
18	4.6	13.5	78	140	16	0	28	ND	+	+
19	5.8	7.4	86	117	13	0	208	0.7	+	+
20	3.3	3.2	115	54	6	0	8	ND	+	+
21	7.0	14.6	99	44	23	0	244	ND	+	+
22	7.2	9.1	81	22	3	0	132	3.0	+	+
23	3.2	11.3	95	67	5	0	90	1.1	+	+
24	5.0	23.3	94	41	2	0	54	0.8	+	+
25	3.5	13.5	78	42	8	0	215	ND	+	+
26	4.1	3.6	90	43	9	0	115	1.1	+	+
27	9.7	65.4	81	18	11	2	12	17.8	+	+
28	5.4	33.9	80	82	29	0	88	1.4	+	+
29	3.2	8.2	96	78	10	0	24	1.7	+	+

* NR = Not recorded; ** Auer rods seen;

*** ND = Not done; # +/– = present/absent.

TABLE IV-*Marrow Morphology in Patients with MDS*

Patient No.	Cellularity	Myeloid: erythroid ratio	Dys-eryth#	Dys-granulo#	Dys-mega karyo#	Blasts (%)	Monocytes (%)	FAB diagnosis	Bournemouth score (0-4)
1	I	D	-	+	++	4	63	CMML	3
2	D	I	-	++	+	19	0	RAEB	3
3	N	I	Aplasia	++	++	0	0	RA	2
4	N	I	Aplasia	+	+	0	I	RA	2
5	I	I	+	+	+	0	I	CMML	3
6	I	I	-	.+	+	0	I	CMML	3
7	N	D	+	-	-	0	2	RA	2
8	I	D	+	+	-	0	I	CMML	
9	I	I	-	+	-	0	I	CMML	3
10	D	D	+	+	-	0	0	RA	3
11	D	D	+	+	+	0	I	RA	3
12	I	I	+	+	-	0	I	CMML	3
13	I	D	+	+	-	2	0	RA	2
14	I	D	+	+	-	1	1	RA	1
15	I	I	+	++	++	22	4	RAEBT	3
16	I	I	+	++	++	10	4	RAEBT	3
17	I	I	+	+	+	21	12	RAEBT	3
18	I	I	+	+	+	16	39	CMML	4
19	I	I	+	+	-	0	0	RA	1
20	D	D	+	+	+	2	12	RA	2
21	N	D	+	+	-	5	5	RA	2
22	N	D	+	+	+	1	2	RA	1
23	N	D	+	+	-	0	1	RA	2
24	D	D	+	.+	+	0	11	RA	2
25	N	D	+	+	-	0	0	RA	1
26	D	D	+	+	+	0	0	RA	1
27	I	I	-	+	+	0	0	CMML	3
28	I	P	+	+	+	1	12	CMML	3
29	N	D	+	+	+	0	1	CMML	2

+ = Mild; ++ = Moderate.

10 cases of chronic myelomonocytic leukemia (34.5%). There were no cases of refractory anemia with ring sideroblasts. Cytogenetic analysis carried out in three patients proved to be normal with no chromosomal aberrations. Cases 22 and 23 underwent the assessment of hematopoietic progenitors (CFU-GM) in blood and bone marrow. Case 22 showed increased number of granulopoetic colonies primarily of macrophage type with a clearly evident spontaneous growth of progenitors of all types. On evaluation of the Bournemouth score, 5 patients scored 1, 10 patients scored 2, 13 patients scored 3, and only one scored 4. It did not correlate with survival. More than half of the patients whose bone marrow histology was examined showed moderate marrow fibrosis and abnormal localization of immature precursors. The lymph node histology in 3 cases revealed nonspecific changes.

Treatment and Outcome

The latency period from the first symptoms to the diagnosis of acute leukemia in Cases 1 to 8 and 12 ranged from 4-29 months (median 7 months). Five patients evolved into acute myeloid and 4 to acute lymphatic leukemia. Three were classified as having AML-M_2 and two each as AML-M_5, ALL-L_1 and ALL-L_2. All these nine patients have died from hemorrhage or infection during the cytopenic phase of acute myeloid or acute lymphatic leukemia therapy, respectively. Of the remaining 20 cases, 7 are dead in the preleukemic phase, 11 are lost to follow up, and only two remain alive. In the refractory anemia group 5 patients have died with median survival of 4 months and 8 cases were lost to follow up. Case 2 with refractory anemia with excess blasts transformed to acute leukemia after 14 months. All the three patients with refractory anemia with excess blasts in transformation died 11 days, 4 months and 1 month after diagnosis, respectively. In the 10 cases with chronic myelomonocytic leukemia, 7 are dead and 3 were lost to follow up. Twenty four cases received supportive therapy alone involving blood products and antibiotic therapy when needed. Case 1 received one course of 3 days of daunomycin (30 mg/m^2/d) and 7 days of cytosine arabinoside (100 mg/m^2/d). After an aplastic phase, the marrow did show a partial response. In two patients (Cases 25 and 29), etoposide (100 mg/m^2/d) for 5 days was tried with no success. Case 22 was administered alfa-interferon 2b (1.5 million units subcutaneously/day) for 3 weeks with clinical and hematological response, but the baby died from intercurrent gastroenteritis. Only one patients of refractory anemia and myelofibrosis (Case 17) has responded to a high dose methylprednisolone (20 mg/kg/d) course, but remains steroid dependent on follow up.

Discussion

Myelodysplasia is one of the "Cinderella" subjects of Pediatric Hematology and Oncology(8). The myelodysplastic syndromes are a heterogenous group of acquired multipotent stem cell disorders characterized by ineffective and dysplastic hemopoiesis with peripheral blood cytopenia, seen often in elderly. The basic defect is a genetic alteration of a multipotent stem cell as shown by cytogenetic and G-6-PD isoenzyme studies and by molecular biology investigation on RAS oncogenes(9). Only **a** limited number of pediatric cases with primary myelodysplastic syndromes classified using FAB criteria have been reported. Many of these have been single case reports with some literature reviews(10-15). Recently, a few series with large numbers of

cases have been published(5,16,23). The incidence of myelodysplasia in a population based study was 3.4/1,000,000 in children below the age of 15. Myelodysplasia represented 8.7% of all malignant hematological disorders(23). A previous study from Philadelphia found that 17% of children with acute myeloid or 2.9% of all children with acute leukemia had a preleukemic presentation^). The incidence in this series is significantly higher with myelodysplasia constituting 16% of all hematological malignancies and 36.7% of acute myeloid, leukemias with a remarkable male preponderance.

On the basis of extracted information on 144 cases of pediatric myelodysplasia reported in the literature, 9% presented with refractory anemia, 48.6% with refractory anemia with excess blasts and refractory anemia with excess blasts in transformation, and 42.4% with chronic myelomonocytic leukemia(5). No cases of refractory anemia with ring sideroblasts were observed. In the present study, more patients compared to previous studies presented with refractory anemia (51%). The relatively higher number of refractory anemia with excess blasts and refractory anemia with excess blasts in transformation in previous larger studies is probably due to selection bias.

The clinical presentation of these cases with fever, infection, anemia and hemorrhage is similar to adults. Patients often have a different constellation of findings at different times in the course of their disease, and not all progress to AML(l). The blood count and peripheral blood smear findings should alert the clinician. The hematological changes of childhood preleukemia may simulate many other conditions including aplastic anemia, pure red cell aplasia, hemolysis, hypersplenism and viral infections(2). When the preleukemia in children is compared with the preleukemic condition in adults, there are both resemblences and differences. The peripheral cytopenias are similar, as are the highly nonspecific signs and symptoms. Childhood pre-AML type resembles adult preleukemia .(MDS) in many respects, both hematologically and morphologically. On the other hand childhood pre-acute lymphatic leukemia is a different entity. The pre-acute lymphatic leukemia patients usually have hypoplastic marrow *(e.g.,* Cases 1, 2 and 6). True hypoplasia of any of the three cell lines is more common in pre-acute lymphatic leukemia, whereas ineffective thrombopoiesis and normal or increased myelopoiesis are specific for pre-AML. Ineffective erythropoiesis occurs in both types(24).

Cytogenetics are often abnormal. Karyotype changes unfold with time(25). Culture studies of the hematopoetic progenitors may be useful in diagnosis and understanding the pathogenesis. Both hypo and hypergammaglobulinemia are frequently seen and abnormalities of B-cell, T-cell and NK-cell function have all been described in myelodysplasia, as observed in some of our patients.

The outcome in childhood myelodysplasia shows considerable varianee. Wegelius, in a review of 26 cases, observed the myelodysplasia phase to be 1 year (range 1-42 months) with a median survival of 15 months (range 2-75 months)(10). In the German-Italian series of 21 children, the rate of progression to myelodysplasia was 1 year (median time) and range of 1-21 months; the median survival time was 20 months (range 1-69 + months including those who received BMT)(17). Another group of 33 patients with childhood myelodysplasia overall mean survival was 9.9 ±

5.9 months, irrespective of treatment(5), marginally more than 5.9 months observed in our group but clearly highlighting the aggressiveness of the pediatric disease.

Treatment of myelodysplasia in children is not well defined. Standaru therapy is supportive care. Neither corticosteroids, methylprednisolone, androgens, nor differentiating agents such as low dose cytarabine, low dose etoposide, retinoids, vitamin D, hemarginate and interferon have shown consistent or durable responses(26). The most effective treatment so far has been bone marrow transplantation(12).

In conclusion, childhood myelodysplasia or preleukemic syndromes are worthy of more attention by pediatricians and hematologists, since its prevalence seems to be very high from our data. Secondly there are stark differences with adult MDS in presentation *(e.g.,* pre-acute lymphatic Jeukemia group), survival and approach to treatment. Hence more data and better methods for diagnosis, classification and treatment for pediatric myelodysplasia are obviously needed.

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REFERENCES

1. Koeffler HP. Myelodysplastic syndromes. Sem Hematol 1986, 23: 284-299.
2. Wegelius R. Bone marrow dysfunctions preceding acute leukemia in children: A clinical study. Leukemia Research 1992, 16:71-76.
3. Bennett JM, Catovsky D, Daniel MT, *et al.* FAB Cooperative group: Proposals for the classification of the myelodysplas tic syndromes. Br J Hematol 1982, 51: 189-199.
4. Chessels JM. Myelodysplasia. *In:* Pediatric Hematology, Eds Hann IM, Gibson BES. London, Bailliere-Tindall 1991, pp 459-482.
5. Tuncer MA, Pagliuca A, Hicsonmez S, *et al.* Primary myelodysplastic syndrome in children: the clinical experience in 33 cases. Br J Hematol 1992, 82: 347-353.
6. Conlombel L, Eaves AC, Eaves CJ. Enzymatic treatment of long term human marrow cultures reveals preferential location of primitive hemopoetic progenitors in the adherent layer. Blood 1983, 62: 291-297.
7. Mufti GJ, Stevens JR, Oscier DG, *et al.* Myelodysplastic syndromes: A scoring system with prognostic significance. Br J Hematol 1985, 59: 425-433.
8. Hann IM. Myelodysplastic syndromes. Arch Dis Child 1992, 67: 962-966.
9. Luzzatto L, Colonna F, Reilly I. The n-1 model for .tnyelodysplastic syndromes. Leuk Res 1992, 16: 57-60.
10. Wegelius R. Preleukemic states in children. Scand J Hematol 1986, 36: 133-139.
11. Belanger R, Gyger M, Pereault C, *et al.* Bone marrow transplantation of myelodysplastic syndromes. Br J Hematol 1988, 69: 29-33.
12. Guinan EC, Tarbell NJ, Tantravahi R, *et al.* Bone marrow transplantation for children with myelodysplastic syndromes. Blood 1989, 73: 619-622.
13. Van't Veer-Korthof ET, Vossen JM. Myelodysplastic syndrome in childhood. BrJ Hematol 1989, 71:37-41.
14. Baranger L, Barnchel A, Leverger G. Monosomy 7 in childhood hemopoietic disorders. Leukemia 1990, 4: 345-349.
15. Choudhry VP, Adhikari RK, Saraya AK. Aplastic anemia an early phase preceding

acute lymphocytic leukemia. Indian J Pediatr 1982, 49: 343-346.

16. Castro-Malaspina H, Schaison G, Passe S, *et al*. Subacute and chronic myelomonocytic leukemia in children (JCML). Clinical and hematological observatons and identification of prognostic factors. Cancer 1984, 54: 678-686.

17. Creutzig U, Cantu-Rajnoldi A, Ritter J, *et al*. Myelodysplastic syndromes in childhood. Report of 21 patients from Italy and West Germany. Am J Pediatr Hematol Oncol 1987, 9: 324-330.

18. Sanders JE, Buckner CD, Thomas ED, *et al*. Allogenic marrow transplant for children with JCML. Blood 1988, 71: 1144-1146.

19. Brandwein JM, Horsman DE, Eaves AC, *et al*. Childhood myelodysplasia: Suggest ed classification as myelodysplastic syndromes based on laboratory and clinical findings. Am J Pediatr Hematol Oncol 1990, 12: 63-70.

20. Passmore SJ, Hann IM, Chessells JM. Pediatric myelodysplasia. Med Ped Oncol 1992, 20: 373-376.

21. Nair R, Athale VA, Dole MG, *et al*. Childhood myelodysplastic syndromes: Clinical features, cytogenetics and prognosis in sixteen patients. Am J Pediatr Hematol Oncol 1991, 13; 109.

22. Blank J, Lange B. Preleukemia in children. J Pediatr 1981, 98: 565-568.

23. Hasle H, Jacobsen BB, Pedersen NT. Myelodysplastic syndromes in childhood: A population based study of nine cases. Br J Hematol 1992, 81: 495-498.

24. Nagler A, Hazani A, Etzioni A. Disturbances of T lymphocyte subsets preceding refractory anemia with excess blasts in transformation in a child. Acta Hematol 1988, 79: 103-106.

25. Mufti GJ. Chromosomal deletions in the myelodysplastic syndromes. Leuk Res 1992,16:35-42.

26. Hast R, Hellstrom E. Therapeutic aspects of myelodysplastic syndromes in chronic phase. Leuk Res 1992, 16: 95-100.