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ACUTE MYELOID LEUKEMIA IN ADOLESCENT AND ADULT IRAQI PATIENTS CLINICAL AND HAEMATOLOGICAL STUDY

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الخلاصه

عنوان الدراسه

مرض ابيضاض الدم النخاعي الحاد لدى المرضى العراقيين من اليافعين والبالغين دراسة سريريه و تحليله

هدف الدراسه

الهدف من هذه الدراسه هو لتقييم الخصائص السريريه والتحليلية وتوزيع الأنواع المختلفة لمرضى ابيضاض الدم النخاعي الحاد.تم استخدام الطرق الاحصائيه لتقييم فيما إذا كان لأنواع التقسيم الفرنسي الأمريكي البريطاني خصائص مميزه في ما بينها.

المرضى و الطرق

تم شمول مائة و ستة و عشرون مريضا بمرض ابيضاض الدم النخاعي الحاد ممن تجاوزوا سن الثالثة عشر عاما. تم إجراء الفحص السريري الشامل لكل المرضى إضافة إلى فحوص الدم و فحص نخاع العظم و قد تم تقييم النتائج بعناية ومقارنتها إحصائيا بين الأنواع المختلفة لمرض ابيضاض الدم النخاعي الحاد.

النتائج

من بين 126مريضا تمت دراستهم خلال مدة 5سنوات كان توزيع الأنواع المختلفة لمرض ابيضاض الدم النخاعي الحاد كما يلي :م 1 (19%)،م2 (22.2%)،م 3 (26.9%) ،م 4 (14.2%) ، م5 (15.8%) و م 6(1.5%).
سريرا ، الحمى ، الشحوب والتعرق كانت شائعة في كل أنواع المرض و كذلك فقر الدم ووجود الخلايا غير الناضجة في الدم .كان هنالك بعض الخصائص المميزة لبعض أنواع المرض ، نوع م 3 تميز بقصر فترة الأعراض ، الميل للنزف الدموي، اقل تضخم الغدد اللمفاويه،اقل تضخم الطحال، اكثر نقص الصفائح الدموية، اكثر نقص كريات الدم البيضاء واكثر نقص كريات الدم البيضاء معتدلة الصبغه.تميز نوع م 4و نوع م5 بتضخم اللثة في حين لم يكن للنوعين م 1 و م 2 خصائص مميزه.

الاستنتاج

استنتجنا من هذه الدراسه إن النوع م 3 هو الأكثر شيوعا بين أنواع مرض ابيضاض الدم النخاعي الحاد وان العديد من أنواع هذا المرض كان لها صفات مميزه سريريه وتحليليه عند التقديم الطبي .

SUMMARY

Aim of the study

Aim of this study is to evaluate the clinical and hematological presenting features and distribution of different subtypes of acute myeloid leukemia (AML) and to

evaluate with statistical methods whether the different French-American - British classification (FAB) categories have distinctive features in relation to each other.

PATIENTS AND METHODS

126 patients older than 13 year with diagnosis AML were included, thorough history and examination performed for every patient, peripheral blood and bone marrow findings were evaluated carefully and compared statistically between different subtypes of AML

RESULTS

Among 126 patients recruited during 5 years period, the distribution of different subtypes of AML was as follow: M1: 19%, M2: 22.2%, M3: 26.9,M4: 14.2%, M5: 15.8%, M6: 1.5.

Clinically fever, pallor, sweating were common to all subtypes of AML, also the presence of blasts cells in peripheral blood and anemia. There were some distinctive features of some subtypes of AML such M3 is characterized by shorter duration of symptoms, bleeding tendency, less lymphadenopathy and less splenomegaly, more thrombocytopenia, more leukopenia and neutropenia. M4 and M5 by gingival enlargement, while M1 and M2 had no distinctive features. We concluded from this that the M3 is commonest subtype of AML, many subtypes of AML defined by FAB criteria had characteristic clinical and haematological distinctive features at medical presentation.

INTRODUCTION

- **The acute leukemias are characterized by sudden uncontrolled growth of malignantly transformed hematopoietic progenitor cells. These cells accumulate within bone marrow leads to suppression of the growth and differentiation of normal blood cells. Symptoms results from varying degree of anemia, neutropenia and thrombocytopenia and from tissues infiltration The underlying pathophysiology consists of a maturational arrest of bone marrow cells in the earliest stages of development. The mechanism of this arrest is under study, but in many cases, it involves the activation of abnormal genes through chromosomal translocations and other genetic abnormalities (1,2,3).**
- **AML is heterogeneous disease. Therefore parameters are needed to classify this disease into biologic entities to understand its pathogenesis and develop specific treatment approaches (4,5).**
- **As therapeutic advances were made, distinguishing the subtypes of acute myeloid leukemia became increasingly important (6).**
- **Identification of AML subtypes is important because several new drugs have more activity against some varieties than against others. Prognosis and some clinical features may differ considerably among the various AML subtypes (7).**

Acute leukemias are classified on the basis of the presumed cell of origin. The modern era for classification of acute leukemia dates back to 1976, when international group of investigators from France, America and Britain developed

a uniform classification system designated as French-American-British (FAB) classification (8), which was subsequently revised in 1985 (9,10,11)
The FAB classification of AML divides cases into eight major groups, M0 through M8. The classification criteria are based on morphologic and cytochemical features, however for some of the categories, immunophenotyping is necessary(10,12).FAB classification designate a proportion of 30% or more blast cells as essential for diagnosis of AML. It is lineage-based morphological classification that categorizes cases according to the degree of maturation of the leukemic cells and their lineage differentiation. The major advantage of the FAB classification system is its ease of use. The cytological criteria are well defined; they do not require high technology and can be applied in most laboratories through out the world (13). Keeping in view these advantages, the FAB proposal was adopted internationally. It provided long needed standard terminology and was quickly accepted by most of the multi-institutional study groups for management plans and comparison of treatment results between morphologic subtypes for their prognostic significance.
Present study was done to determine the frequency of AML subtypes in our population and whether these subtypes have distinctive clinical and hematological features. As the patients were from all over Iraq , our study thus well represents AML subtypes of the entire country.

Table 1. FAB classification of AML. (13)

Myeloblastic leukemia minimally differentiated	**MO**
Myeloblastic leukemia without maturation	**M1**
Myeloblastic leukemia with maturation	**M2**
Hypergranular promyelocytic leukemia	**M3**
Microgranular variant	
Myelomonocytic leukemia	**M4**
With bone marrow eosinophilia (M4EO)	
Monocytic leukemia	**M5**
Poorly differentiated (M5A)	
Differentiated (M5B)	
Erythroleukemia	**M6**
Megakaryoblastic leukemia	**M7**

PATIENTS AND METHODS

One hundred twenty six patients of 13 year and older (70 males and 56 females) admitted to Baghdad teaching hospital, nursing home hospital and Baquba general hospital from October 1997 to October 2002 with a new diagnosis of AML based on clinical, peripheral blood and bone marrow (BM) examination were included in this prospective study. Patients with previous hematological malignancy of any type and patients who had received chemotherapy were excluded from this study.
Patients recruited subjected to detailed history, physical examination and hematological investigations including complete blood picture (CBP) and morphological examination of BM aspirate samples through iliac or sternal

approach under strict aseptic technique and local anesthesia with use of cytochemical stains (Sudan black and periodic acid schiff) to differentiate different subtypes of AML.For statistical analysis the chi-square (X2), student-t-test and fisher extract probability test were used to compare between the results of different subtypes of AML.In the following tables any statement greater or lesser than another means that this statement is statistically different at P value <0.05 significance level.

RESULTS

The distribution of 126 cases of AML is shown in table (2).

Table 2:Main features of studied group.

Main type	AML
Number	126
Male/Female ratio No.	1.2:1 (70/56)
Ranges of ages(yrs)	13-75
Mean age(yrs)+SD	34.2+17

The distribution of subtypes of AML with their relative incidence is shown in table 3.

Table 3:Distribution of subtypes of AML with their relative incidence

Subtype	M1	M2	M3	M4	M5	M6
No.	24	28	34	18	20	2
% Male/Female ratio No.	19 1:1 9:9	22.2 1.3:1 16/12	26.9 1.8:1 21/11	14.2 1:2 8:16	15.8 1:1 11/11	1.5 1:1 1/1
Range of ages(yrs)	16-70	16-58	13-53	21-75	16-51	40-44
Mean age(yrs)+SD	36.2+21.1	39.1+10.9	29.7+12.9	40.2+18	36.4+12	42

M3 was the commonest subtype of AML accounting for 26.9 % of total cases, only two cases of M6 identified so it was not included in statistical analysis and comparison.
From AML subtypes M3 was associated with mean age less than other subtypes. There was an increase in male: female ratio in all types as shown in table 3,although the ratio was equal for M5 and reversed in M4 subtype (1:2) which was statistically insignificant.

The historical features at presentation of different subtypes are shown in table 4.only those variables for which there were differences among different categories or symptoms of particular interest were included.

Table 4:The main presenting symptoms of patients with AML

Type	AML	M1	M2	M3	M4	M5
Number	126	24	28	34	18	20
Duration of Symptoms <1mo.	76(60)	14(58)	14(50)	28(82)	10(55)	10(50)
Pallor	74(58)	16(66)	20(71)	12(35)	10955)	16(80)
Fever	50(39)	12(50)	10(35)	14(41)	8(44)	6(30)
Bleeding	52(41)	4(16)	10(35)	30(88.2)	4(22)	4(20)
Bone pain	2(1.5)	2(8.3)	0	0	0	0
Sweating	50(39)	10(41)	14(50)	8(23)	8(44)	10(50)

Duration of symptoms, till diagnosis was confirmed, varied from few days to a maximum of three months .M3 patients had the shortest duration of symptoms, although statistically significant only in relation to M2.
Pallor, fever, and sweating were common symptoms and in many patients may occur in combination with no significant difference between the different subtypes.
Bleeding from gum, nose or as hematemesis and melena was common in AML, recorded in 41% of patients and in M3 patients occurred in majority of them (30 patients 88.2%), more than other subtypes, which was statistically significant, P<0.05.Two patients were pregnant at time of diagnosis, one case was M2 and the other was M3 subtype.
Findings on physical examination are shown in table 5

Table 5:Findings on physical examination.

Type	AML	M1	M2	M3	M4	M5
Number	126	24	28	34	18	20
Fever	52(41.2)	12(50)	12(42.8)	14(41.1)	6(33.3)	8(40)
Splenomegaly	32(25.3)	4(16.6)	14(50)	2(5.8)	6(33.3)	6(30)
Hepatomegaly	24(19.4)	6(25)	4(16.6)	2(5.8)	8(44.4)	4(20)
Lynphadenopathy	30(23.8)	6(25)	6(21.4)	2(5.8)	4(22.2)	12(60)
Purpura	38(30.1)	2(8.3)	12(42.8)	16(47)	2(11.1)	6(30)
Gingival enlargement	20(15.8)	2(8.3)	2(7.1)	4(11.7)	6(33.3)	6(30)

Fever was found in 41.2% of patients with AML with no significant difference among subtypes. Splenomegaly was found in 25.3% and it is significantly less in

M3 (5.8%). All cases with splenomegaly the enlarged spleen did not reach the level umbilicus i.e.was mild to moderate enlargement.
Lymph node enlargement was found in 23.8% and it is also significantly less in M3 subtype (5.8%). The cervical nodes group is most commonly involved. Purpura and ecchymosis found in M3 (47%) and M2 (42.8%) patients significantly more than other subtypes.
Gingival enlargement found in 20 cases (15.8%) of AML patients and it was significantly more in M4 and M5 than other subtypes.
Neurological findings were present only in two cases of AML-M3 presented with headache, blurring of vision and papillodema.
Pleural effusion occurred in four cases, two M3 and other two were M1. Skin lesions were found in only two cases one was M4 and other M5.

The main hematological values of peripheral blood are shown in table 6.

Table 6:Peripheral blood findings in AML (No./ %)

Type		AML	M1	M2	M3	M4	M5
Number		126	24	28	34	18	20
Hb<10gm/dl		106(84)	20(83.3)	24(85.7)	30(88.2)	16(88.8)	15(75)
WBC X 10^9/L	<4	40(31.7)	6(25)	6(21.4)	20(58.8)	4(22.2)	2(10)
	4-10	36(28.5)	8(33.3)	4(14.2)	10(29.4)	6(33.3)	8(40)
	10-50	50(39.6)	10(41.6)	18(64.2)	4(11.7)	8(44.4)	10(50)
	50-100	18(14.2)	6(25)	6(21.4)	0	4(22.2)	2(10)
	>100	4(3.1)	2(8.3)	0	0	0	2(10)
Neutrophis X 10^9 /L	<0.5	62(49.2)	12(50)	8(28.5)	30(88.2)	4(22.2)	8(40)
	0.5-2	34(26.9)	8(33.3)	10(35.7)	4(11.7)	8(44.2)	4(20)
	>2	96(76.1)	20(83.3)	18(64.2)	34(100)	12(66.6)	12(60)
Platelets<50000 $X10^9$		74(58.7)	10(41.6)	10(35.7)	32(94.1)	12(66.6)	10(50)
Presence of blast cells		120(95)	24(100)	26(92.8)	32(94.1)	18(100)	18(90)

Anemia was present in all cases with no significant difference.
56.9%of patients with AML had WBC count more than normal.
Absolute severe neutropenia (<0.5X10^9/L) was present in 49.2% of patients with AML with M3 more than other subtypes, which was statistically significant. Marked thrombocytopenia (<50.000 X10^9) found in more than one half of all patients with AML which was significantly seen in M3 patients than other subtypes.
Blast cells were seen in peripheral blood in most of our patients and were absent (Aleukemic leukemia) in 4.7% of AML cases
The degree of BM infiltration by blast cells and blast cell count in peripheral blood were not included in table 6,as there was no significant difference between different subtypes.

DISCUSSION

With the introduction during the late 1960s and 1970s of increasingly effective therapy for acute leukemias, it became necessary to determine subgroups, which might require different treatment approaches. FAB system provided structured criteria for the diagnosis of various subtypes of AML. The World Health Organization (WHO) classification of acute myeloid leukemia (AML) incorporates and interrelates morphology, cytogenetics, molecular genetics, and immunologic markers in an attempt to construct a classification that is universally applicable and prognostically valid (14,15).

This classification is not practiced widely because of financial constraints. Our study reported M3 as the most common subtype accounting for 26.9%of cases followed by M2 with 22.2% In table (7) below the our results are compared with other series. Arber et al reported M2 as the commonest subtype followed by M5 (15). Most published data indicate the predominance of M2 as a most common subtype. (16,17,18,19,20,21) .

D'Costa GG et al reported M1and M2 as the most common types followed by M4 with no reported cases from M5 and M7 subtypes (22)

Nakase et al showed AML-M4 as common subtype in Australian population compared to Japanese, where AML-M2 is common (23), Kakepoto et al (24) reported M4 to be the commonest followed by M2.

Al-Niami et al reported in local study that M2 is the commonest subtype followed by M3 (25)

Many of the differences in AML subtypes may be due to the subjectivity of morphologic diagnosis together with variable nature of acute myeloid leukemia subtypes, with no real demarcation. Some genetic factors may be responsible for a particular FAB subtypes distribution of AML in our population. The other reason for this discrepancy may be patients of different ethnic group and or geographical variation.

Male to female ratio in present study is 1.2:1, other studies reported 1.5:1.(19,20,26) The mean age (34.2 years) at presentation seems to be lower than the expected mean age reported in western countries where AML peaks in incidence after the 6th decade of life(27,28). However, this is similar to mean age reported in studies from Saudi Arabia (20) and Pakistan(22,29)

Table 7: Incidence of adult AML subtypes in various centers

Author/ Year/ No of Cases	M0%	M1%	M2%	M3%	M4%	M5%	M6%	M7%
Swirsky et al 1986 (U.K) n= 619	00	30	25	5	23	13	2.4	00
Spence et al 1988 (KSA) n= 121	1.7	1.7	14.9	8.3	57.8	13.2	1.7	00
Raina et al 1990 (Libya) n= 54	00	7	57	15	13	4	4	00
Hassan et al 1993 (Pak) n= 62	1.6	22.5	32.2	9.1	22.5	8.6	1.6	1.6
Chaudry et al 1993 (Pak) n=54	00	13	44.4	11.1	24	3.7	3.7	00
Harakati et al 1998 (KSA) n=52	00	2	4	17	40	33	00	04
Khalidi et al 1998 (USA) n=78	8.9	19.2	27.0	9.0	20.5	11.5	2.6	1.3
Kakepoto et al 2002 (Pak.) n=74	00	8.1	16	15	46	9.5	00	2.7
Arber et al 2003 (USA) n=255	7.0	19.2	28.67	8.7	26.7	4.8	2.5	2.4
Our Study 2003 (Iraq) n= 126	00	19	22.2	26.9	14.2	15.8	1.5	00

In this study of 126 patients with AML, some features of AML, as pallor, fever and sweating were present in different subtypes of AML with no statistical significant difference between them, this is in concordance with other studies (8,9).

The presence of lymphadenopathy, splenomegaly and bone pain in our in AML (23.8%, 25.3% and 1.5% respectively), similar incidence was reported by other studies (1,21,37). Whittaker JA, reported splenomegaly in10% of AML patients at presentation (30)

Leukocytosis (>10X 10^9/L) was found in AML patients (39.6%) same reported by other recent studies (31,32)

Gingival enlargement occurred in in 15.8% of AML,Savage DG, (33) reported the comparable results.

Neurological manifestations were reported in 1.5% of AML patients,other studies(34,35,36) reported <5% incidence

The higher incidence of bleeding 88.2% in our M3 patients which was statistically significant (P<0.05) in relation to other subtypes, was in agreement with results of other recent studies (37,38).

82.3 % of M3 patients had duration of symptoms of less than one month, which may be attributed to higher incidence of bleeding that make patient to counsel the doctor earlier than other patients who present with fever and pallor.

The incidence of lymphadenopathy (5.8%) and splenomegaly (5.8%) in our M3 was less than other subtypes with significant P value of <0.05, by McKenna et al (39) reported 18% &17% respectively .The significant association of leukopenia (58.8%) and marked thrombocytopenia (94.1%) in our M3 patients more than other subtypes was observed by Burns et al (40) as 56 %&78% respectively and by other studies (11,16). The significant association (P<0.05) of gingival enlargement with M4 (33.3%) and M5 (30%) than other subtypes was also observed by Brunning RD et al and Burns et al. Skin lesions were found in two patients with M4 subtype (11.1%), Burns et al reported 12%, this higher incidence of extramedullary involvement especially if gingiva and skin in M4 and M5 subtypes probably as result of monocytic differentiation which is a feature of both subtypes (41,42).

Lymphadenopathy was found in 60% of our patients with M5 subtype, Tobelem et al reported 63%(43) and Burns et al 38%, though it was statistically significant P<0.05 only in relation to M3.

M4 affected females more than males (2:1) in contrast to other subtypes. This found in other study (8).

M1 and M2 showed no characteristic significant different features from other subtypes, this was also mentioned by other studies (15,44).

COCLUSIONS

1-In AML patients M3 was the commonest subtype of AML, comprising 26.9% of the total cases, followed by M2.

2-Common presenting features of all subtypes of AML, include; fever, pallor, sweating, involvement of males more than females, presence of blast cells in peripheral blood and anemia.

3-M3 is characterized by a shorter duration of symptoms, bleeding tendency, less lymphadenopathy and splenomegaly, marked thrombocytopenia, leukopenia and neutropenia.
5-M4 and M5 characterized by gingival enlargement more than other subtypes.
6-M1 andM2 had no distinctive features.
These observations of the presenting features demonstrate the clinical and hematological distinctiveness of many of the various categories of FAB classification system.

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