COAGULATION ABNORMALITIES IN ACUTE CHILDHOOD LEUKEMIA

THESIS

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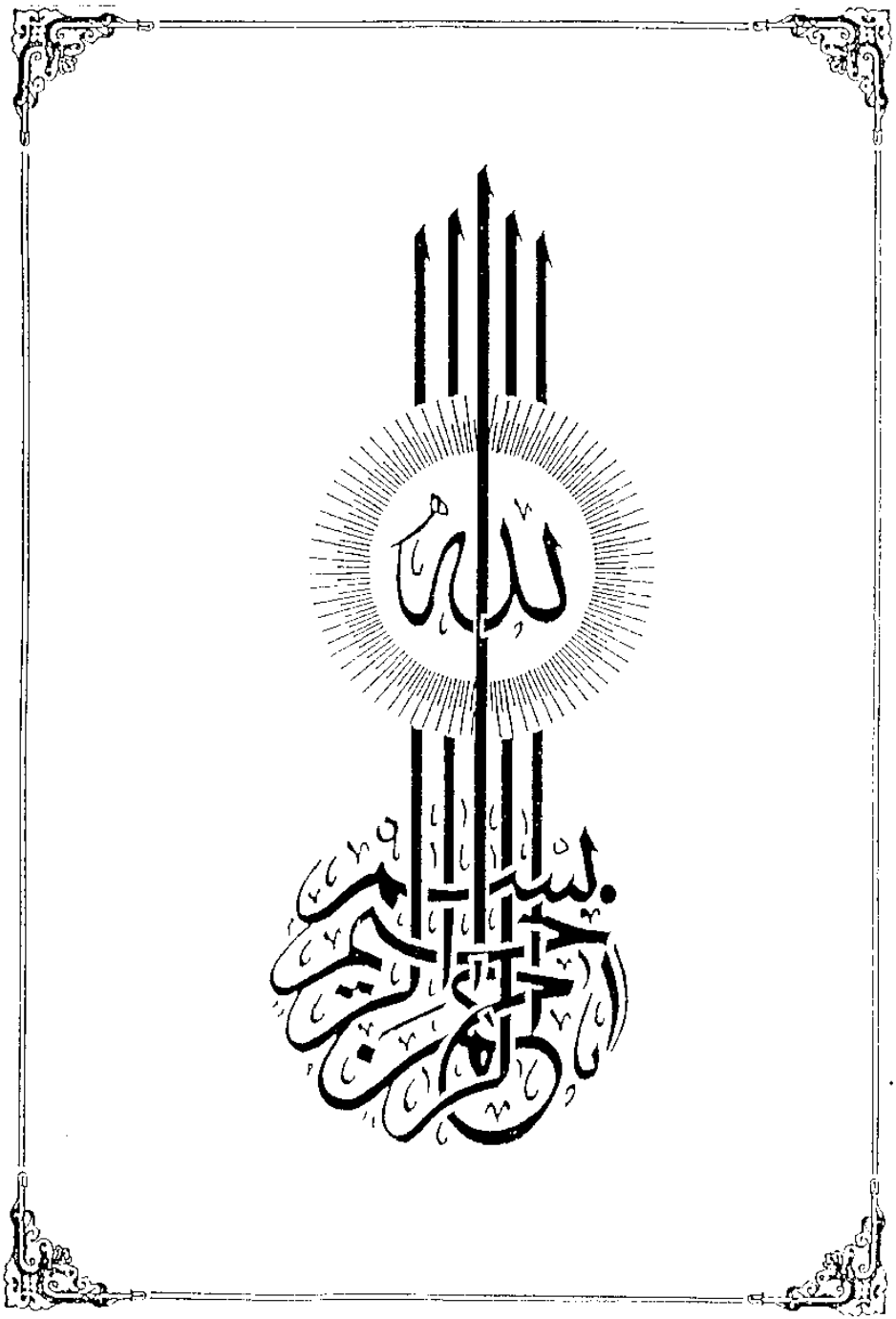

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LIST OF ABBREVIATIONS

AIC	Accelerated intravascular coagulation
AL	Acute leukemia
ALL	Acute lymphoblastic leukemia
AML	Acute myeloblastic leukemia
ANLL	Acute non lymphoblastic leukemia
APL	Acute promyelocytic leukemia
AT III	Antithrombin III
AUL	Acute undifferentiated leukemia
CML	Chronic myeloid leukemia
DIC	Disseminated intravascular coagulation
ELP	Elastase-like protease
FAB	French-American-British classification
FDPs	Fibrin/Fibrinogen degradation products
FPA	Fibrinopeptide A
FSPs	Fibrin split products
PCA	Procoagulant activity
PTT	Partial thromboplastin time
QPT	Quick prothrombin time
S.K.	Streptokinase
TPA	12-O-tetradecanoylphorbol-13-acetate
TT	Thrombin time
U.K.	Urokinase

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Introduction
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Aim Of The Work

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The hemorrhagic manifestations of AL were attributed to several causes, namely: Thrombocytopenia, disturbances of platelet function as well as clotting defects [Laursen, 1976].

Several studies of coagulation factors and fibrinolysis in AL have demonstrated that the patient with acute leukemia has a different set of coagulation values than healthy individuals [Gralnick, 1983].

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ACUTE LEUKEMIA

DEFINITION:

Acute Leukemia is a primary malignancy of bone marrow, leading to replacement of normal bone marrow and blood elements by immature or undifferentiated blast cells, and their accumulation in other tissues (lymph nodes, liver, spleen, kidneys, brain and meninges, testes and ovaries, lungs, and subcutaneous tissues). [Baehner, 1978].

It is often associated with abnormal white blood cell counts and an abnormal increase in leukocytic mass, and leads to anemia, thrombocytopenia, an - in the absence of successful treatment - death. [Henderson, 1983].

CLASSIFICATION:

In general, the childhood leukemias can be classified as acute, chronic or congenital.

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II. Immunologic Classification of acute leukemia:

* ALL

While the FAB classification of ALL is subjective and liable to observer variation, the immunological classification of ALL has been more widely accepted, and has clarified the relationship of ALL to other lymphoproliferative disorders. [Chessells, 1982].

Such classification divides the ALL into the following subtypes: [Riemenschneider, 1983].

1- T-cell ALL:

This subtype comprises about 25% of patients with ALL. It is characterized by spontaneous rosette formation of the blast cells with sheep erythrocytes, due to the presence of a specific cell membrane surface marker on the surface of the blast cells.

2- B-cell ALL:

It is the rarest major ALL subtype, and comprises no more than 5% of the total ALL cases. Blast cells possess cell surface immunoglobulins which can be identified by immunofluorescent techniques.

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* ANLL:
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Antibodies that uniquely characterize the surface of malignant myeloblasts are not available. However, hetero antisera to human myeloblastic leukemia - associated antigens have been used to detect imminent bone marrow relapse in patients with remission [Sallan and Weinstein, 1981].

Still, the FAB classification of the acute myeloid leukemia is more readily reproducible and has some clinico-pathological correlations [Chessells, 1982].

Table " 1 " shows the classification of the acute childhood leukemias [Bennett, 1983].

Morphologic type	AL
Lymphoid	ALL cALL (L_1-L_2) T-cell ALL (L_1-L_2) B-cell ALL (L_3) AUL (L_1-L_2)
Myeloid	AML FAB M_1 (no maturation) FAB M_2 (with maturation) FAB M_3 (Hypergranular) = APL
Myelo-monocytic	ANML FAB M_4
Monocytic	AMoL FAB $M_5{}^A$ FAB $M_5{}^B$
Erythroid	AEL FAB M_6
Mast cell	Acute mast cell leukemia
Megakaryocytic	Acute myelosclerosis (or megakaryocytic myelosis)

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CLINICAL MANIFESTATIONS:

Acute leukemia may present insidiously or acutely, as an incidental finding on a routine blood count of an a symptomatic child, or as a life-threatening hemorrhage, infection, or episode of respiratory distress. [Sallan and Weinstein, 1981].

The presenting foetures of the acute leukemias arise from the effects of bone-marrow failure and from the consequences of accumulation of leukemic cells [Chessells, 1982].

The following Table (Table 2) shows the different signs, symptoms and physical findings of patients suffering from ALL and compares them with the complaints of patients suffering from ANLL - Both types of patients being presented at the time of diagnosis [Wintrobe, 1981].

	ALL	ANLL
	178 patients (%)of patients	144 patients (%)of patients
Symptoms		
1. Fever	71	74
probably due to infection	17	26
2. Purpura	51	30
3. Other hemorrhages	27	44
4. Bone or joint pain	79	20
5. Weight loss	66	47
6. Abnormal masses	62	11
Physical findings		
1. Splenomegaly	86	60
2. Hepatomegaly	74	54
3. Lymphadenopathy	76	47
4. Sternal tenderness	69	65
5. Petechiae and/or ecchymoses	50	46
6. Fundic hemorrhage	14	16

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Although hemorrhagic manifestations are present in both types of leukemia, yet they are more predominant in the ANLL group, especially in the FAB type M_3 (Acute promyelocytic leukemia) [Gralnick and Sultan, 1975; Olweny, 1981; Khalifa et al, 1982; Gralnick, 1983; Riemenschneider, 1983].

COMPLICATIONS OF ACUTE LEUKEMIAS

1- Hemorrhage:

Effective hemostasis requires adequate numbers of functional platelets, adequate levels of plasma coagulation factors, and vascular integrity. In patient with leukemia, a hemorrhagic diathesis may develop as a result of compromise of any or all of these mechanisms, either by the malignancy, by products of the malignant cells, or by complications of therapy [Allegratta et al, 1985].

Such hemorrhagic diathesis may be manifested in the form of petechiae, ecchymoses, epistaxis, hematuria, or mucous membrane or venipuncture bleeding. These are usually not of major consequence, while intracranial, intrapulmonic, or gastrointestinal hemorrhage with or without a generalized bleeding diathesis quite often results in death [Gralnick, 1983].

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Severe hemorrhagic symptoms appear more commonly in AML than in ALL. Acute promyelocytic leukemia characteristically presents with hemorrhagic manifestations secondary to acquired fibrinolysis or disseminated intravascular coagulation (DIC). The abnormal granules of the promyelocytes contain and release either fibrinolysins or collagenases that destroy clots or initiate intravascular clotting [Gralnick and Abrell, 1973].

Effective control of bleeding in leukemic children depends on an appropriate treatment of the underlying cause. When thrombocytopenia is present, with a platelet count of $<30,000/mm^3$, platelet transfusions are given in a dose of 6 U/m^2 or 0.2 U/kg. This will raise the count by approximately $75,000/mm^3$. Aspirin administration is also avoided in such patients, as well as intramuscular injections and deep venipunctures [Allegretta et al, 1985].

On the other hand, if bleeding is due to DIC, as in cases of acute promyelocytic leukemia (APL), the initial and most effective treatment involves treatment of the underlying condition that activates the cascade [Sallan and Weinstein, 1981]. In addition, replacement of depleted factors may be required to arrest or prevent bleeding. The serum fibrinogen level should be maintained above 100 mg/dl by transfusion of cryoprecipitate or fresh frozen plasma (FFP). Vitamin K may also help in raising levels of factors II,

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VII, IX and X. Infants should receive 5 mg and older children 10 mg once or twice weekly [Allegretta et al, 1985]. Heparin can also be given either as a continuous infusion or as an IV bolus. The dose of IV bolus therapy usually starts at 50 U/kg. In either continuous or bolus therapy, patients should be started at lower doses of heparin than in other conditions requiring anticoagulation, since most of these patients are hemostatically deficient at the initiation of therapy [Gralnick, 1983].

2- Infection:

Infection due to granulocytopenia is an important early complication of leukemia [Sallan and Weinstein, 1981].

Most early infections are presumably bacterial, but specific etiologic agents are usually uot found [Hughes, 1973].

Therefore, any febrile patient with an absolute granulocyte count of less than 500 cells per mm^3 must be considered septic. Cultures must be obtained promptly, and the patient begun immediately on broad-spectrum antibiotics with activity against bowel and respiratory organisms [Sallan and Weinstein, 1981].

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kidney infiltration can lead to renal failure. In addition, infiltration of the mediastinal structures may cause life-threatening tracheobronchial or cardiovascular compression. Prompt application of systemic chemotherapy or local irradiation is necessary to deal with such emergencies [Sallan and Weinstein, 1981].

5- Leukemic infiltration of the central nervous system (CNS):

The major consequences of CNS invasion include leukostasis (especially noted in patients with AML), leptomeningeal infiltration, optic nerve and/or retinal invasion, and spinal cord compression [Sallan and Weinstein, 1981].

Lumbar puncture is indicated for diagnostic and therapeutic purposes when CNS symptoms are present. At the time of the procedure, intrathecal methotrexate or cytosine arabinoside should be administered [Hyman and Boule, 1965].

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