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Estimation of plasma concentrations of hepatocyte growth factor in acute leukemia in Upper Egypt

Ahmed E. Ahmed *, Khalid A. Abd El-Baser, Sameh S. Zytoun, Mohammed A. Alsenbesy, Abd-Elrahman A. Elsaid

Qena Faculty of Medicine, South Valley University, Egypt

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KEYWORDS

Angiogenesis;
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Abstract *Background:* Angiogenesis is a fundamental element during malignant transformation, the induction of angiogenesis has been proposed to be through angiogenic factors such as the hepatocyte growth factor (HGF).

Aim: The aim of the study was to assess plasma concentrations of HGF in acute leukemia in Upper Egypt.

Methods: We performed a cross-sectional study of 90 subjects and divided them into three groups, group I consisted of 30 newly diagnosed acute lymphatic leukemia (ALL) cases, group II consisted of 30 patients with newly diagnosed acute myeloid leukemia (AML) cases and group III consisted of 30 apparently healthy persons as control subjects. Plasma HGF was measured using the ELISA technique.

Results: Statistical comparison between the mean values of plasma HGF in the three studied groups using the *F*-test followed by the least significant difference showed a significant difference ($F = 77$, $P = 0.001$) between ALL cases and the control group and between AML cases and the control group.

Conclusion: The results of the present study suggest that high plasma HGF may play a significant role in the leukemia process and contribute to the leukemic cell dissemination. The clinical significance of the increased level of HGF in acute leukemia needs further investigation and may suggest a novel therapeutic approach in this disease.

Introduction

Acute leukemia is a heterogeneous group of malignant disorders arising from the hematopoietic progenitor cell at different stages of maturation. It is characterized by the appearance of immature cells (blasts) in the bone marrow cells, resulting in anemia, thrombocytopenia and an outpouring of the neoplastic blasts into the peripheral blood. They may infiltrate other

* Corresponding author at: Pediatric Department, Qena Faculty of Medicine, South Valley University, Egypt. Mobile: +20 1003329944, +20 1223215223.
E-mail address: Yasen112010@gmail.com (A.E. Ahmed).

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parenchymatous organs such as the liver, spleen and lymph nodes. The blasts have common characteristics which include rapid proliferation, immaturity and poor responsiveness to regulatory mechanisms.[1,2] There are two types of leukemia: Acute lymphoblastic Leukemia (All) and Acute myeloid leukemia (AML). All is a proliferation of lymphoblasts originating in lymphocyte progenitor cells of the bone marrow[2] while AML originates from myeloid hematopoeitic cells which include myeloblasts, monoblasts, erythroid precursors and megakaryoblasts.[3]

Acute myeloid leukemia is a relatively rare cancer. There are approximately 10,500 new cases each year in the United States, and the incidence rate has remained stable from 1995 through 2005. AML accounts for 1.2% of all cancer deaths in the United States.[4]

The incidence of AML increases with age; the median age at diagnosis is 63 years. AML accounts for about 90% of all acute leukemia in adults, but is rare in children.[1] The rate of therapy-related AML (that is, AML caused by previous chemotherapy) is rising; therapy-related disease currently accounts for about 10–20% of all cases of AML. AML is slightly more common in men, with a male-to-female ratio of 1.3:1.[5]

There are many risk factors for acute leukemias; I- Environmental Factors: Three well documented environmental factors are established causal agents increasing the risk of AML; exposure to high dose of external radiation, chronic benzene exposure and chemotherapeutic agents as alkylating agents,[5] while pesticide exposure (occupational or home use) and parental cigarette smoking before or during pregnancy have been suggested as causes of childhood ALL. Other proposed causes of childhood ALL include neonatal administration of vitamin K and maternal alcohol consumption during pregnancy.[6] II- Acquired disease (Evolution from a chronic clonal hemopathy); AML may develop from progression of other clonal disorders of hematopoietic stem cells including chronic myeloid leukemia CML, polycythemia vera, idiopathic myelofibrosis and primary thrombocythemia.[7] III- Inherited conditions; Down's syndrome: children with down's syndrome have a 10–30-fold increased risk of leukemia AML predominates in patients younger than 3 years and ALL in the older age group,[8] Fanconi syndrome[9] and Bloom syndrome.[9]

The term angiogenesis, first used by Hertig in 1935 to describe the growth of blood vessels in the placenta, was re-introduced by Folkman in 1972 to describe neovascularization accompanying solid tumor growth.[10] Angiogenesis is the process by which new capillaries sprout and differentiate from pre existing blood vessels. This process results in newly developed microvessels, most of which resemble capillaries (diameter of 5–8 μm). This process is distinct from vasculogenesis, which occurs during embryonic development and involves the formation of larger blood vessels from stem cells of mesenchymal origin called angioblasts.[11] In normal mature adults, angiogenesis is a rare event that occurs only in certain specialized situations such as during the female reproductive and menstrual cycle. Micro vascular blood vessels are extremely long lived. The endothelial cells that line the microvasculature have a half-life of months to years.[12] Abnormal or pathologic angiogenesis can be seen in diseases such as rheumatoid arthritis, diabetic retinopathy, infantile hemangiomas, psoriasis and cancer.[11] Hepatocyte growth factor/scatter factor was initially identified in 1984[13] and molecularly cloned as a potent mitogen of primary cultured hepatocytes.[14] It has multiple activities (multifunctional cytokine) in a variety of tissues during the course of development and also in various disease states. It is named scatter factor as it affects the increase in local motility and a scattering of contiguous sheets of cells. This factor might be involved in epithelial migration such as that which occurs in embryogenesis and wound healing.[15] Molecular cloning revealed that HGF is a heterodimeric molecule composed of a 69 kDa α chain and 34 kDa β chain. The α chain contains an N-terminal hairpin domain and subsequent four-kringle domains. The β chain contains a serine protease like domain with no enzymatic activity.[16] The α subunit and the β subunit have a length of 440 and 234 amino acids respectively.[17] HGF is synthesized and secreted as a biologically inactive single chain precursor form, and further processing by the Serine protease into the two chain form. Serine proteases responsible for the activation of HGF include HGF activator or HGF converting enzyme and urokinase type plasminogen activator (UPA).[18] The receptor for HGF was identified as c-Met proto-oncogene product. The c-Met receptor is composed of a 50 kDa α chain and 145 kDa β-chain. The α chain is exposed extracellularly, while the β-chain is a transmembrane subunit containing an intracellular tyrosine kinase domain.[19] Binding of HGF to the c-Met receptor induces activation of tyrosine kinase, an event that results in subsequent phosphorylation of c-terminally cultured tyrosine residues. Although HGF was initially identified as a potent mitogen for hepatocytes, considerable evidence indicates that intracellular signaling pathways driven by HGF and c-Met receptor coupling leading to multiple biological responses in a variety of cells including mitogenic, motogenic (enhancement of cell motility), morphogenic, neurite extension, anti-apoptotic activity and enhancement of hematopoiesis. HGF has also an organotrophic role in the regeneration and protection of various organs including the liver, lung, stomach, pancreas, heart, brain and kidney. Cells shown to express HGF mRNA include megakaryocytes, monocytes, platelets, fibroblasts, smooth muscle cells, mast cells and endothelial cells but not epithelial cells. Various types of human leukemia cells also secrete HGF. Expression of HGF receptor in vitro and in vivo in epithelial cells suggests that HGF acts in a paracrine fashion to mediate interactions between epithelial and stromal cells during development and in normal tissue maintenance.[19,20] HGF is a potent inducer of angiogenesis, a process necessary for the continued growth of tumors. In vitro, HGF stimulates endothelial cell proliferation, chemotaxis and chemokinesis, it promotes migration of endothelial cell from carrier beads to flat surfaces and it induces capillary like tube formation. It has also been reported that HGF induces endothelial cell expression of plasminogen activators. In vivo studies also indicated that HGF induced neovascularization exceeds that achieved with VEGF. HGF has been shown to be induced in Skeletal muscle after ischemic injury and it has been implicated in capillary endothelial cell regeneration in ischemically injured myocardium. The receptor for HGF the c-Met proto-oncogene product is expressed by endothelial cells and pericytes of blood vessel walls, because HGF is apparently produced by stromal cells located outside the vessel wall, it has been suggested that it may act as a paracrine mediator in the angiogenic cascade.[20,21]

Bone marrow stromal cells which include macrophages, fibroblasts, endothelial cells, and adipocytes have been shown