POSTCHEMOTHERAPY BRAIN CHANGES IN CHILDHOOD LEUKEMIA, EVALUATION BY MRI

THESIS
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Dedication

To my lovely family, because of you I am the person who I am today

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List of Abbreviations

ADC: apparent diffusion coefficient.

ALL: acute lymphoblastic leukemia.

AML: acute myeloid leukemia.

APL: acute promyelocytic leukemia.

CLL: chronic lymphoblastic leukemia.

CML: chronic myeloid leukemia.

CNS: central nervous system.

CR: complete remission.

CSF: cerebrospinal fluid.

CT: computed tomography.

DWI: diffusion weighted imaging.

FAB: French American British.

FLAIR: fluid attenuation inversion recovery.

FOV: field of view.

G-CSF: granulocyte colony stimulating factor.

GM-CSF: granulocyte macrophage colony stimulating factor.

IT: intrathecal.

LE: leucoencephalopathy.

MPRAGE: magnetization prepared rapid gradient echo.

MR: magnetic resonance.

MRD: minimal residual disease.

MRV: magnetic resonance venography.

PRES: posterior reversible encephalopathy syndrome.

SSS: superior sagittal sinus.

TE: thromboembolism.

TE: time to echo.

TOF: time of flight.

TR: time to repeat.

VTE: venous thromboembolism.

WBCs: white blood cells.

Abstract

Introdution: Leukemia is the most common pediatric malignancy. Acute lymphoblastic leukemia accounts for about one-fourth of all childhood cancers and about 75% of all childhood leukemias. Recent advances in therapy such as aggressive polychemotherapy, intrathecal cytostatic prophylaxis for pediatric leukemia have greatly improved the prognosis but have resulted in an increased incidence of associated complications and toxic effects. The main neuro-imaging features in pediatric patients with leukemia treated with chemotherapy were prospectively studied.

Patients and methods: 20 pediatric patients their age range 1-16 years receiving or have received chemotherapy for acute leukemia have undergone MR examination of the brain for evaluation of neurological symptoms related to treatment at the national cancer institute from April to August 2013.

Conclusion: Chemotherapy is associated with certain side effects that can be evaluated by utilization of MRI. An elevated degree of suspicion is needed to recognize the radiologic features of CNS complications of chemotherapy and familiarity with the imaging findings is essential for proper diagnosis and further treatment of neurologic symptoms in pediatric patients with leukemia.

Key words: Childhood. Leukemia.Chemotherapy.Neurotoxicity. Brain MRI.

INTRODUCTION

Leukemia is the most common malignancy in children. Acute lymphoblastic leukemia accounts for one-fourth of all childhood cancers and approximately 75% of all childhood leukemia. The peak of it occurs between 2-5 years***(Greenlee et al., 2000).***

The etiology of leukemia is unknown, but some factors predispose to it as ionizing radiation, chemicals, and drugs. Genetic factors also may predispose to it as increased incidence in siblings of leukemia, trisomy 21, Fanconi anemia, congenital Agamma-globulinemia, and neurofibromatosis ***(Dordelmann et al.,1998).***

Diagnosis depends on blood count which shows blast cells, that is confirmed by bone marrow aspiration containing more than 55 blasts/ mm^3***(Lanzkowsky., 2000).***

Modern treatment protocols have dramatically improved the prognosis. Therapeutic approaches consist of multimodal chemotherapy and radiotherapy. Prognostic factors include age, sex, race, nutritional status, the immunologic subtype, platelet count, rapidity of cytoreduction, and the presence of organomegaly or lymphadenopathy ***(Lanzkowsky , 2000).***

As advances in cancer therapy improve the prognosis of patients with childhood malignancies, awareness of the consequences of treatment methods assumes increasing importance ***(Parisi et al., 1999).***

Some types of chemotherapy can leave young patients with short-term or long-term neurological side effects. Methotrexate can cause neurotoxicity & cognition impairment within 3 days of administration ***(Dorfman, 2011).***

Up to 2% of patients treated with l-asparaginase develop hemorrhagic or nonhemorrhagic infarcts, usually secondary to sinovenous occlusion ***(Fleischhach et al., 1994).***

Agents, particularly methotrexate, cisplatin, arabinosylcytosine, carmustine, and thiotepa, occasionally cause cerebral white matter anomalies **(*Ball et al., 1992*).**

Central nervous system prophylactic treatment as well as other disease complications may produce many abnormalities seen on the cranial MRI . Cortical atrophy, ventricular dilatation and white matter hyperintensities are documented***(Surtrees et al., 1998).***

Both the underlying malignancy and the anti-neoplastic therapy can cause immunosuppression, leading to infection. Fungi are the most frequent causal microorganisms and typically affect patients having absolute granulocytic counts of less than 100/mm3 for more than 2 weeks ***(Chen et al., 1996).***

MRI is known for its superior soft tissue imaging. The use of MRI in the early detection of chemotherapy side effects on pediatrics brain prompts early management & avoidance or at least minimizing long term side effects ***(Yağmurlu et al., 2008).***

AIM OF THE WORK

The aim of this study is to evaluate the role of MRI in the detection of the side effects of chemotherapy on the brain in leukemic children presenting with clinically related symptoms.

EPIDEMIOLOGY AND PATHOGENSIS OF LEUKEMIA

Epidemiology:

Lymphoreticular malignancies account for about 40% of all malignant disorders in children. Leukemia represents nearly 30% of all malignancies. ALL accounts for 80% of all leukemias in children and adolescents; the median age at diagnosis is 4 years, and most children are between 4 and 6 years of age at diagnosis. AML accounts for 15% to 20% of new leukemias and presents throughout the pediatric age range**.** ***(Laningham, et al., 2007)***

Chronic leukemia is not common in childhood. The most common type is the chronic myelocytic leukemia (CML), accounts for less than 5% of all childhood leukemias. Other types include chronic lymphocytic leukemia (CLL), Juvenile myelomonocytic and chronic myelomonocytic leukemias, all are very rare in childhood.***(Pizzo and Poplak., 2002).***

Pathogenesis of leukemia

The etiology of leukemia is unknown but certain factors may predispose to it including:

(A)- Environmental factors:

Exposure to ionizing radiation is a known predisposing factor, especially for acute leukemias. It is the only environmental factor implicated in the etiology of CML.***(Pizzo and Poplak, 2002).***

Chronic exposure to some chemicals (e.g. benzene) and alkalyting agents has been associated with the development of AML. Other less important factors studied for possible association with acute leukemias include; parentral cigarette smoking, exposure to pesticides, and maternal use of alcohol and contraceptive pills. ***(Wen et al., 2000).***

Approximately 20% of patients with aplastic anemia treated with immuno-suppressive drugs may eventually develop AML. Paroxysmal noctural hemoglobinuria and myelodysplastic syndromes are also considered predisposing factors for AML. ***(Imashuku et al., 1994).***

It has been suggested that there is an increased risk for ALL in children born to mothers recently infected with viruses. The Epstein-Barr virus (EBV) and the human immunodeficiency virus (HIV) have been linked to some cases of all ***(Smith et al., 1999).***

(B)- Genetic factors:

Genetic factors are presumed to play a significant role in the development of acute leukemias. Evidence of this is based on several observations, including the association between various chromosomal abnormalities and childhood leukemia, the occurrence