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ملاحظات: ....

Hepatic Manifestations of Pediatric Hemophagocytic Lymphohistocytosis

Thesis

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Fatma Mohamed Azazy Elshorbagy

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List of Abbreviations

Abb.	Full term
BIR2	Baculovirus IAP repeat
CBC	Complete blood counts
CNS	Central nervous system
CTL	Cytotoxic T lymphocyte
DIC	Disseminated intravascular coagulation
EBV	Epstein-Barr virus
EBV	Epstein–Barr virus
FH	Family history
FHL2	Familial hemophagocytic lymphohistiocytosis type 2
GS2	Griscelli syndrome type 2
HCT	Hematopoietic cell transplantation
HLH	Emophagocytic lymphohistiocytosis
HPS2	Hermansky–Pudlak type 2
ICUs	Intensive care units
IQR	Interquartile range
LDH	Lactate dehydrogenase
MOD	Multi organ dysfunction
MRI	Magnetic resonance imaging
NK	Natural killer
NOD	Nucleotide-binding oligomerization domain containing
PID	Primary immune deficiency
PT	Prothrombin time
PTT	Partial thromboplastin time
SD	Standard deviation
SLAM	Signaling lymphocyte activation molecule
UCBT	Unrelated donor cord blood transplantation
XIAP	Xlinked inhibitor of apoptosis protein
XLP-1	X-linked lymphoproliferative disease 1
XLP-2	X-linked lymphoproliferative syndrome type 2

ABSTRACT

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare hyper-inflammatory disorder caused by benign systemic overgrowth of macrophages in the reticulo-endothelial system leading to cytokine storm. The main features of HLH are; fever, splenomegaly, bi/pancytopenia; hyper-ferritinemia, hyper-triglyceridemia and hypofibrinogenemia; which if not diagnosed and early treated progresses to disseminated intravascular coagulation (DIC), multi-organ dysfunction with dismal outcome. Hepatic manifestations are not well recognized primary presentation in pediatric patients with HLH. This presentation mandates high levels of suspicious for early diagnosis.

Aim of the Work: To study the hepatic involvement clinical, laboratory, and pathological in patients clinically diagnosed or genetically confirmed Familial/primary (1ry) HLH and in patients with secondary (2ry) acquired HLH.

Patients and Methods: A 6 month retrospective cohort study included 35 patients with genetically confirmed HLH divided into familial HLH by its types, X linked lymphoproliferative syndrome and HLH with partial albinism; following at pediatric hematology/oncology clinic, Ain Shams University. In the studied patients, detailed review of patient's clinical, laboratory data of HLH, hepatic transaminases and synthetic liver functions were done at time of presentation, at week 2, 8 from treatment start and at time of reactivation; Liver biopsy results and genetic analysis were recorded. Biochemical liver involvement was considered when alanine aminotransferase was 3 more the upper level of normal at presentation. Overall and reactivation free survival were analyzed according to liver involvement.

Results: Thirty five patients with HLH were recruited with age range of 2-108 months, 62.9% of patients with HLH were genetically confirmed and 34.3% of them had MUNC13D mutations, 8.6% had STXBP2 mutation and 14.3% had RAB27A mutation while 11.4% had secondary HLH.; 82.9%) had liver enlargement at diagnosis with hepatic reactivation in 51.4%. 22.8% of patients had biochemical liver involvement; there was no significant difference in their demographic data or their clinical presentation, their final outcome or the type of mutant gene according to liver involvement.

Conclusion: Variable transaminitis and synthetic liver dysfunction might be the presenting manifestation of HLH and upon reactivation. Significant biochemical liver involvement is an under recognized presentation of HLH. Hepatic involvement did not impact response to treatment and disease outcome.

Keywords: Hemophagocytic Lymphohistiocytosis, Disseminated Intravascular Coagulation.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH); is a potentially catastrophic rare hyperinflammatory syndrome occurring due to hyperactive immune system responses ***(Rosado and Kim, 2013).*** First cases were described as "histiocytic medullary reticulocytosis" by Scott Robin and Smith in 1939, following which several changes in the disease nomenclature took place ***(Hayden et al., 2016).***

Classically, HLH has been divided into two types: (i) primary HLH which is attributed to germline mutations implicated in the cytotoxic dysfunction of the NK cell/CTL presenting mainly in infancy and early childhood; and (ii) acquired HLH which occurs in elder population ***(Janka and Lehmberg, 2016).***

The clinical findings of pediatric HLH are usually non-specific. The important criteria to diagnose initially as HLH that was proposed by the HLH-2004 study include persistent fever that is resistant to antibiotics and splenomegaly with or without hepatomegaly ***(Henter et al., 2007)***

Since 2004 HLH diagnostic criteria, diagnosis of pediatric HLH incorporated the mutational/genetic analysis as a "major criterion" for primary HLH diagnosis ***(Hayden et al., 2016).***

While HLH Hepatobiliary disorder is being increasingly described in both pediatric and adults; the characteristics of

hepatic affection still yet poorly understood (***Ost et al., 1998).*** Organomegaly with elevated liver enzymes, biphasic hyperblirubinemia and coagulopathy can occur early in the disease, presenting a challenging diagnosis of hepatobiliary HLH ***(Fardet et al., 2014).***

In rare instances acute hepatic failure may dominate the clinical picture, which in combination with hyperferritinemia, may mimic neonatal hemochromatosis ***(Chen et al., 2010).***

Cytokine mediated hepatic damage includes wide range of biochemical changes such as hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, coagulopathy, disseminated intravascular coagulation (DIC) and multi organ dysfunction (MOD); which if not treated early, may lead to death in virtually all the patients ***(Rosado and Kim, 2013).***

The histopathology of hepatic biopsies in hepatobiliary HLH is not well established owing to rarity of cases with insufficient biopsy data, delayed diagnosis with dismal outcome, sampling bias (needle biopsy vs. wedge biopsy); and associated triggering factors such as virus associated histological alterations; especially in acquired cases ***(Padhi et al., 2019).***

AIM OF THE WORK

- **Primary objective:**

Study the hepatic involvement clinical, laboratory, and pathological in patients clinically diagnosed or genetically confirmed 1ry HLH and in patients with 2ry acquired HLH.

- **Secondary objective:**

- Study the frequency of hepatic affection in relation to genetic subtypes, viral induced HLH or other potential trigger.
- Explore the repetition of hepatic affection in sibs affected by HLH.
- Study the hepatic flares in relation to disease reactivation.
- Study the histologic changes in genetically confirmed HLHL.
- Find the relation of final outcome to the severity of hepatic affection.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Introduction:

Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome is a potentially catastrophic hyper inflammatory syndrome occurring in genetically susceptible individuals which results due to hyperactive, inappropriate, excessive immune system activation ***(Rosado et al., 2013).***

That results due to impaired cytotoxic T lymphocyte (CTL)/natural killer (NK) cell activity producing uncontrolled proliferation of benign macrophages in all reticuloendothelial organs such as bone marrow, spleen, liver, and lymph nodes.

Hemophagocytic histiocytosis, unexplained peripheral blood cytopenia (s), cytokine storm, cytokine mediated hepatic injury/ dysfunction producing spectrum of biochemical alteration such as hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, coagulopathy, disseminated intravascular coagulation (DIC), multi organ dysfunction (MOD); and if not diagnosed and treated early, may lead to death in virtually all case ***(Janka et al., 2012).***

Since the first description of cases coined as “histiocytic medullary reticulocytosis” by Scott Robin and Smith in 1939, there has been a sequential change in nomenclature of this entity ***(Hayden et al., 2016).***