MESENTERIC AND MEDIASTINAL LYMPHADENOPATHY IN EGYPTIAN CHILDREN WITH GAUCHER DISEASE: A STUDY OF 6 PATIENTS... CAN ENZYME REPLACEMENT THERAPY (ERT) PLAY A ROLE IN IMPROVING THEIR CONDITION?

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INTRODUCTION

- In Gaucher disease (GD), lipid laden macrophages (*Gaucher cells*) are deposited in liver, spleen, bone marrow and lymph nodes.

- Reports of mesenteric and mediastinal lymphadenopathy (LN) in GD in the literature are very few and usually sporadic case reports of children with type 3 GD

  [Lim, 2002; Burrow, 2007]

- Since the start of enzyme replacement therapy (ERT), selected tissues as *lungs* and *lymph nodes* were reported to have diminished/absent responses implying that certain organs are poorly accessible to intravenously administered enzyme therapy products.

  [Altarescu, 2001, Grabowski, 1998]
INTRODUCTION

- *However*, other studies reported that the relation between ERT and lymphadenopathy development is unclear [*Yagci et al, 2009]*

- Moreover, patients with GD usually adults have an increased risk for development of malignancy possibly due to chronic immune stimulation [*de Fost et al, 2006*] with first report in 2 children by Burstein et al, 1985.
AIM OF THE WORK

- To report six Egyptian children with Gaucher disease who developed mesenteric and mediastinal lymphadenopathy.............

  As well as assess the response of this lymphadenopathy to replacement therapy.
PATIENTS

- Patients were diagnosed by decreased leukocyte $\beta$–glucocerebrosidase activity and molecular study was done with full sequencing of the glucocerebrosidase gene.

- All patients were started on Imiglucerase at an initial dose of 60 IU/kg/2 weeks.

- None were splenectomized.
PATIENTS

- The 6 children, 3 males and 3 females were from 4 families of consanguineous marriage including

  - 3 with *GD type 1*
  - 3 with *GD type 3*

- Four were symptomatic and 2 discovered accidentally on routine screening in view of affected siblings.

- Patients were on regular ERT for a mean period of 4 years before developing lymphadenopathy.
PATIENT1 (GD TYPE 1, R359Q/R359Q)

- A 12 year old male who presented initially at age of 6 months with loss of weight, recurrent chest infections, delayed motor development and organomegaly. Patient was diagnosed and started on ERT showing marked improvement in growth and hematological parameters, general well being with regression of organomegaly after 6 months of treatment and maintained thereafter.

- After 5 years on ERT, patient developed multiple abdominal masses associated with abdominal pain and constipation.
PATIENT 1

- Patient did CT scan abdomen, misdiagnosed as intestinal lymphoma and was referred to Oncology institute where he did bone marrow aspirate, multiple biopsies and took 3 doses of chemotherapy.

- However, after one month, LN biopsy did not show any malignant cells and then another biopsy was done showing infiltration with Gaucher cells.

- At that point dose was increased to 120IU/kg/2wks
CT scan abdomen of Patient 1 presenting with abdominal masses showing improvement and regression in relation to ERT dosing.

A Initial study showing pelviabdominal soft tissue mass 6x10 cm of mixed solid and cystic components due to mesenteric Lymphadenopathy.

B Follow up shows reduced size of the mass 5x8cm in response to increased drug dose to 120IU/kg/dose.

C The second follow up shows increased size of the pelviabdominal mass 6x10 cm predominantly involves the solid component due to decrease of dose not just to 60 IU/kg/2wks but to ≤ 20 IU/kg/2wks.
Initial study showed several mediastinal lymphadenopathy that remained stationary on 120IU/kg/2wks BUT deteriorated on dose reduction

Serum Chitotriosidase assay level: 2960 µmol/L/hr initially and reached 9190 µmol/L/hr
PATIENT 2 AND 3 (2 SIBLINGS WITH GD TYPE 1, GENOTYPE UNKNOWN)

- The youngest, a 7 year 2 months old girl (pt 2) who presented initially at the age of 1 year with abdominal enlargement and delayed physical milestones. She was started on ERT after diagnosis.
- She showed improvement of her visceral, hematological and growth parameters till she started to complain of abdominal distension 3 years ago after being on ERT for 2.5 years.
- This was associated with pallor but no manifestations of gastrointestinal or hepatic affection. Liver function tests were normal but abdominal U/S showed huge HSM and mild free ascites.
**PATIENT 2 AND 3 (SIBLINGS)**

- **CT abdomen** was done and on preparing patient for biopsy, to exclude lymphoma, **coagulation profile was impaired**; prolonged PT, PTT and decreased PC though other liver function tests were normal.

- Patient was corrected with plasma and vitamin k for about 2 months without improvement and biopsy was postponed. Interestingly, her coagulation profile corrected spontaneously.
CT abdomen showing multiple enlarged poorly enhancing mesenteric LN, especially para-aortic, cirrhotic liver with wide irregular ill defined poorly enhancing hepatic mass, showing internal scarring and splenomegaly of 15 cm.

Serum chitotriosidase: 1240 µmol/L/hr.
PATIENT 2 AND 3 (SIBLINGS)

- Abdominal U/S was repeated after 3 months showing markedly enlarged liver with irregular borders, multiple nodules, hugely enlarged spleen with minimal free ascites. Patient was negative for Hepatitis C virus infection as well as other infections.

- **CT chest** showed tiny mediastinal LN, 1cm.

- **Her older sister** was screened and CT scan abdomen showed multiple large mesenteric LN, the largest, 1.5 cm.
PATIENT 4 (TYPE 3 GD, L444P/L444P)

- A 9.5 year old male presented initially at the age of 1 year by abdominal distension, delayed physical milestones and bulbar symptoms. Patient was diagnosed and started on ERT showing improvement.

- Bulbar symptoms regressed on ERT but patient has apraxia and moderate mental deficit.

- After 3.5 years on ERT, severe abdominal enlargement was noted with change in bowel habits.
**Patient 4**

- Abdominal U/S revealed multiple abdominal masses confirmed by CT abdomen and showing **no evidence of cirrhosis**.

- Patient was **negative** for infection screen.

- **CT guided biopsy** was done to confirm nature of mass and exclude malignancy which showed **infiltration with Gaucher cells**.
Initial study showing pelviabominal mass, 9x 12 cm with areas of cystic breakdown and extensive flecks of calcifications.

Several mediastinal lymph node with a large posterior one is noted.

Serum chitotriosidase: 4932 µmol/l/hr.
Biopsy of retroperitoneal lymph node (HXE) showing fibrohyaline stroma entangling aggregates of histiocytic cells, some simulating Gaucher cells (arrow) with cytoplasmic inclusions.
The 9 year old younger male sibling (pt 5) presented at the age of 1 year by abdominal distension, was screened, diagnosed and ERT started.

After 5 years on ERT, patient complained of severe abdominal distension and abdominal pain.

CT chest showed mediastinal and hilar lymphadenopathy.

Neurologically, patient has apraxia and moderate mental affection.
Initial study showed pelviabdominal mass of mixed density 6 x 12 cm

PATIENT 5 WITH TYPE 3 GD
His older sister (pt 6) showed multiple innumerable discrete mesenteric lymphadenopathy, the largest is 1cm
**IMPORTANT ISSUES**

- 5th report worldwide (Lim et al, 2002; Fowler et al, 2006; Burrow et al, 2007; Yagaci et al, 2009)

- 3 patients had a stationary course and one regressed on increasing ERT to 120 IU/kg/2 weeks whereas 2 newly diagnosed.

- None required surgical excision
A lot of questions raise themselves
QUESTIONS

- Is mediastinal and mesenteric lymphadenopathy in Gaucher disease age and type related and what about gender?

- On presentation, what should be the diagnostic work up and management protocol in those patients?

- What is their chance of turning to malignancy, is it a life long risk?

- Does ERT has an effect on these lymph nodes and in what dose?
Questions

- Is development of lymphadenopathy related to duration of ERT, illness or both or is it simply *MULTIFACTORIAL*......

  *Many questions that need answers through collaboration in view of rarity of the condition........*

  *A field open for research as many others in Gaucher disease*
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