A MULTICENTER OBSERVATIONAL STUDY FOR EARLY DIAGNOSIS OF GAUCHER DISEASE IN PATIENTS WITH SPLENOMEGALY AND/OR THROMBOCYTOPENIA

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BACKGROUND

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder resulting from deficiency of beta-glucosidase and the accumulation of glucocerebroside in the reticuloendothelial cells. Prevalence of GD is elevated in Ashkenazi Jewish population (1/450-1/1000), and rare in the non-Ashkenazi (1/40000-1/60000). GD is a multisystemic disease; cytopenias and splenomegaly are frequently the presenting symptoms leading to hematological evaluation. Data from the Gaucher Registry 2008 show that splenomegaly and thrombocytopenia are present at diagnosis in more than 5000 patients (respectively 86% and 60%). Because of the non-specific presenting symptoms, diagnostic delays are frequent, leading to severe complications including hematological malignancies. Enzyme replacement therapy is available and effective in reversing or preventing many manifestations, including hepatosplenomegaly, marrow infiltration, cytopenias and osteopenia (Weinreb 2002). A global survey among 406 Hematology-Oncology specialists demonstrated that only 20% consider GD in the differential diagnosis of cytopenia, hepatosplenomegaly, and bone pain (Mistry 2007). It is clear that a different approach based on a specific diagnostic algorithm is necessary to avoid under-diagnosis (Mistry PK 2010).

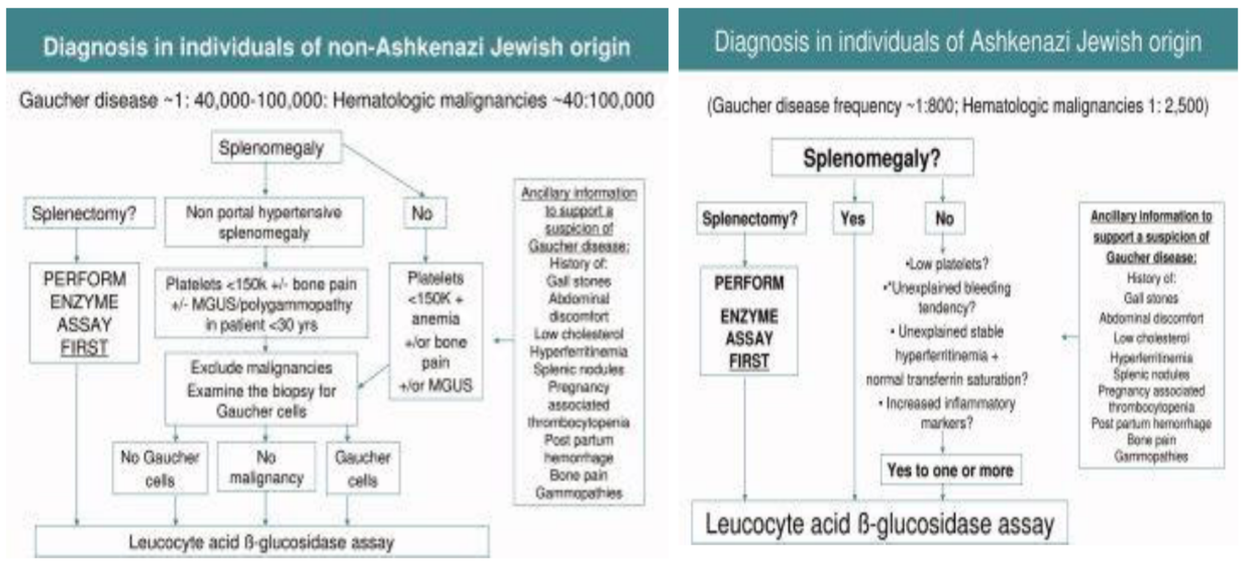

Figure 1. Diagnostic algorithm fo Ashkenazi and non-Ashkenazi population

AIMS and METHODS

Aims: The aim of this multicenter observational study is to evaluate the prevalence of GD in a selected population presenting to hematological clinic with at least one of the two including criteria: 1) splenomegaly, 2) thrombocytopenia associated to at least one of the following symptoms: anemia (Hb <11 g/dl for women, and Hb <12 g/dl for men), MGUS, policlonal gammopathy in patient younger than 30 y.o., splenectomy or history of bone pain. Exclusion criteria include: a) splenomegaly due to portal hypertension in cirrhosis, b) hematological malignancy, c) hemoglobinopathies or other hemolitic anemias.

INCLUDING CRITERIA	EXCLUDING CRITERIA
1. SPLENOMEGALY (palpable spleen or demonstrated with abdominal US, >12 cm)	1. DIAGNOSIS OF HEMATOLOGICAL MALIGNANCY
2. THROMBOCYTOPENIA + 1 of the following criteria - Anemia (Hb<12 g/dl in women, <13 g/dl in men) - MGUS - Policlonal gammopathty in under 30 y.o. - Splenectomy - History of bone pain	2. DIAGNOSIS OF HEMOGLOBINOPATHY/ HEMOLITIC ANEMIA
	3. DIAGNOSIS OF CIRRHOSIS

Table 1. Including and excluding creteria.

Methods: Thirty five Italian Hematologic Centers participate in this study. According to a preliminary survey, 18% of all hematologic first evaluations are positive for splenomegaly and/or thrombocytopenia, among them 11% did not received an appropriate diagnosis. According to these data 762 patients are expected to be tested every year (mean of 1100 first evaluations/year for each centre). Patients fulfilling including criteria who have given their informed consent are recruited into the study and tested for beta-glucosidase enzyme activity on Dried Blood Spot (DBS). All the analysis are centralized and performed by the Laboratory of Diagnosis of Metabolic Diseases Ospedale Gaslini, Genova - Italy. Results can show normal, decrease or borderline beta-glucosidase activity. In the last case, DBS must be repeated to confirm the result. Beta-glucosidase deficiency and GD diagnosis must be subsequently confirmed dosing the enzyme activity in the leukocytes from fresh blood and by DNA analysis. The expected duration of the study was 24 months, starting from September 2010, subsequently extended up to the enrollment of 500 patients (recruitment still active at present).

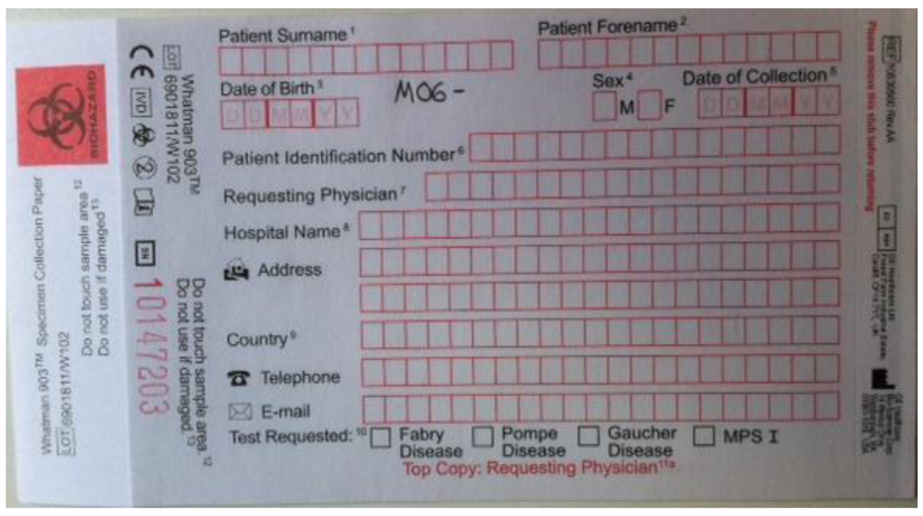

Figure 2. DBS.

RESULTS

Starting from September 2010 153 patients (45 female, 108 male) have been enrolled. All the patients are non-Ashkenazi, among them 61% had splenomegaly, 4% thrombocytopenia and 35% both of them. Six patients have been diagnosed with GD.

PARAMETERS	(n=123)
Hb (g/dl) mean±SD	13,3±2,3
PLATELETS (num/mm^3) mean±SD median (range)	 128±72 110 (8-356)
SPLEEN (cm) mean±SD	14,7±5,4
FERRITIN (ng/dl) mean±SD median (range)	 229±288 119 (5-1500)

Table 2. Hematological parameters so far available for 123 subjects.

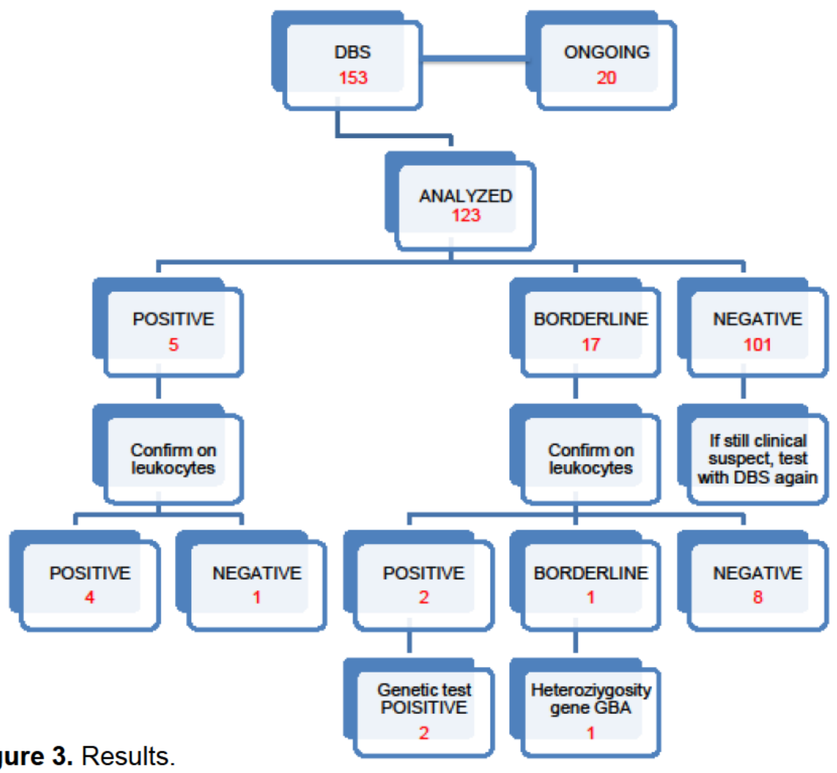

Figure 3. Results.

CONCLUSION

Our results are clinically relevant, showing that the use of a simple diagnostic algorithm helps to identify GD patients at an early stage presenting to hematologists with splenomegaly, leading to an appropriate and prompt therapy to prevent the development of complications.

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Platelets 2

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