Received: 31 July 2024 | Accepted: 17 December 2024

DOI: 10.1002/hem3.70079

HemaSphere eha

LETTER

Prevalence of type I Gaucher disease in patients with smoldering or multiple myeloma: Results from the prospective, observational CHAGAL study

Sonia Morè[1] | Irene Federici[1] | Alessandra Bossi[1] | Serena Rupoli[1] | Erika Morsia[1] | Valentina M. Manieri[1] | Attilio Olivieri[1] | Maria T. Petrucci[2] | Francesca Fazio[2] | Chiara Lisi[2] | Silvia Sorella[2] | Adele D. Paoli[2] | Francesca Farina[3] | Anna Mele[4] | Rossella De Francesco[4] | Antonino Greco[5] | Francesca Fioritoni[6] | Carmine Liberatore[6] | Tommaso Caravita di Toritto[7] | Attilio Tordi[7] | Angela Rago[7] | Agostina Siniscalchi[7] | Marino Brunori[8] | Nicola Sgherza[9] | Pellegrino Musto[10] | Angela Amendola[11] | Angelo Vacca[12] | Antonio G. Solimando[12] | Assunta Melaccio[12] | Antonio Palma[12] | Lorella M. A. Melillo[13] | Lucia Ciuffreda[13] | Silvia Gentili[14] | Gabriele Buda[15] | Maria L. Del Giudice[15] | Antonietta P. Falcone[16] | Patrizia Tosi[17] | Simona Tomassetti[17] | Francesco Rotondo[17] | Alessandro Gozzetti[18] | Piero Galieni[19] | Miriana Ruggieri[19] | Ferdinando Frigeri[20] | Rosario Bianco[20] | Alessandra Lombardo[21] | Fabio Trastulli[22] | Laura Corvatta[23] | Carmela Zizzo[24] | Giovanni Duro[24] | Massimo Offidani[1]

Correspondence: Massimo Offidani (massimo.offidani@ospedaliriuniti.marche.it)

[1]Hematology Unit, AOU delle Marche, Ancona, Italy
[2]Hematology, Department of Translational and Precision Medicine, Azienda Ospedaliera Policlinico Umberto I, Sapienza University of Rome, Rome, Italy
[3]IRCCS Ospedale San Raffaele, Milan, Italy
[4]Haematology, Ospedale Cardinale Panico, Tricase (Lecce), Italy
[5]UOSD Oncoematologia ARNAS Ospedale Civico, Palermo, Italy
[6]Hematology Unit, Department of Oncology and Hematology, Ospedale Santo Spirito, Pescara, Italy
[7]Haematology Unit, ASL Roma 1, Rome, Italy
[8]Internal Medicine, Ospedale Santa Croce, Fano, Italy
[9]Hematology and Bone Marrow Transplantation Unit, AOUC Policlinico, Bari, Italy
[10]Department of Precision and Regenerative Medicine and Ionian Area, Aldo Moro University School of Medicine, Bari, Italy
[11]Hematology Unit, Azienda Ospedaliera Regionale "San Carlo", Potenza, Italy
[12]Department of Precision and Regenerative Medicine and Ionian Area, UOC Medicina Interna "Guido Baccelli", University of Bari Aldo Moro, Policlinico, Bari, Italy
[13]U.O.C. Ematologia e Trapianto di Cellule Staminali Emopoietiche, Policlinico Foggia Ospedaliero-Universitario, Foggia, Italy
[14]Internal Medicine, Ospedale Civitanova Marche, Civitanova Marche, Italy
[15]Hematology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[16]Department of Hematology and Bone Marrow Transplant, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy
[17]Hematology, Ospedale di Rimini, Rimini, Italy
[18]Hematology, Department of Medical Science, Surgery and Neuroscience, University of Siena, Siena, Italy
[19]Department of Haematology and Stem Cell Transplantation Unit, C. e G. Mazzoni Hospital, Ascoli Piceno, Italy
[20]UOC Ematologia Indirizzo Oncologico AORN S. Anna e S. Sebastiano, Caserta, Italy
[21]AO Santa Maria, Università di Perugia, Terni, Italy
[22]Hematology, Hospital "Antonio Cardarelli", Napoli, Italy
[23]Internal Medicine, Ospedale Profili, Fabriano, Italy
[24]Institute for Biomedical Research and Innovation (IRIB), National Research Council (CNR), Palermo, Italy

[Correction added on 15 April 2025, after first online publication: The name of co-author Tommaso Caravita di Toritto has been corrected and Angela Rago has been added as a co-author in this version.]

Gaucher disease (GD) represents a lysosomal storage disease caused by a genetic defect of the enzyme β-glucocerebrosidase (GBA) involved in the breakdown of complex glycosphingolipids, which are important components of cell membranes. Deficient GBA enzyme activity causes the accumulation of substrate glucosylceramide in lysosomes of cells of the reticuloendothelial system and the characteristic macrophages loaded with glucosylceramide defined as "Gaucher cells."[1] Type 1 GD (GD1), affecting more than 90% of patients with GD from Europe and North America, can be diagnosed at any age since initial symptoms (fatigue, asthenia, bone pain) are nonspecific. The subsequent main clinical findings, such as bone disease, hepatosplenomegaly, anemia, thrombocytopenia, and coagulation abnormalities can be misdiagnosed, due to the rarity of the disease and heterogeneity of the clinical picture. Being inherited in an autosomal recessive manner, identification of biallelic pathogenic variants in *GBA1* on molecular genetic test is required to confirm the diagnosis of GD1, besides glucocerebrosidase activity measurement in peripheral blood leukocytes. The incidence is associated with particular populations such as those of Ashkenazi Jewish descent among whom GD1 was estimated at 1 in 450 births. In contrast, in a recent review, the incidence was estimated at 0.45–22.9/100,000 live births in Europe and North America (4.5/100,000 live births in Italy). Estimated prevalence per 100,000 population was 0.26–0.63 in Europe.[2]

Evidence has accumulated over time for a risk for multiple myeloma (MM) occurrence from 5.9 to 51.1 times greater in patients with GD1 compared to the general population.[3–5] However, no studies explored the concurrent GD1 in patients diagnosed with MM except a small retrospective study.[5] Herein, we reported the results of a multicentre, observational, cross-sectional study, designed to evaluate the prevalence of GD1 in patients with smoldering MM (SMM) and newly diagnosed MM (NDMM) or relapsed/refractory MM (RRMM),[6] aged >18 years giving written informed consent. The study was approved by the competent Ethics Committee for each center, and it was conducted in accordance with the Good Clinical Practice (ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996 Directive 91/507/EEC; D.M. 15.7.1997).

The primary aim of the study was the prevalence of unrecognized GD1 in a selected adult population with a confirmed diagnosis of SMM or MM. The secondary endpoint was to assess if, in patients with a final diagnosis of GD1, distinctive features could be identified to draw a diagnostic algorithm for early identification of genetic disease.

Peripheral blood of enrolled patients was drawn using EDTA as an anticoagulant, and it was applied to a specific adsorbent paper spot (dried blood spot, DBS) which was air dried for 4 h. The dried samples were sent to the Centre for Research and Diagnosis of Lysosomal Storage Disorders of CNR in Palermo for evaluating the presence and the quantity of glucocerebrosidase enzyme. In case of abnormal results, determination of the biomarker glucosylsphingosine (lyso-Gb1) and assessment of GBA gene mutational status according to previously described method[7] were performed.

Given the lack of data, the sample size has been determined considering clinically relevant prevalence of the condition when >0.5% for defining the selected population as "high risk." To test this hypothesis with an error alpha level of 5% and a statistical power of 95%, approximately 1000 patients were enrolled in this study. Categorical variables were summarized by number of observations and percentage. Continuous variables were described by median and range. Distinctive factors of MM patients associated with GD1 were eventually searched by appropriate analysis. All analyses were conducted using the SPSS statistical package (version 31).

A total of 1004 SMM/MM patients with a median age of 68 years (range: 36–92) years were enrolled in 22 Italian hematology centers. Baseline general and laboratory characteristics are detailed in Supporting Information S1: Table 1. Out of 891 patients with evaluable disease status information, 54% were NDMM, 32% RRMM, and 3% SMM and their disease-related characteristics are listed in Table 1. As for typical GD1 clinical symptoms, we found bone pain in the majority of cases (40%), asthenia in 26%, and other symptoms in less than 5% each. Out of 1004 enrolled patients, 14 were positive for DBS test (1.3%), one with a compound heterozygous mutation of GBA gene (prevalence: 0.09%; 95% confidence interval [CI]: 0.022–0.36), one patient with a double heterozygous mutation of GBA gene, and 12 patients with a single heterozygous mutation of GBA gene (prevalence of double/single heterozygous status: 1.3%). The most frequently identified mutation was N370S (3 patients), followed by L444P (2 patients) and others.

The only compound heterozygous GBA-mutated patient had his mutation on L444P and R170C. He was 75 years old, had IgG kappa MM, presenting with anemia and bone disease. Platelet count, ferritin, and alkaline phosphatase values were normal and no organomegaly was documented. His GBA enzymatic activity was 2 nmol/h/mL (pathological range: 0.2–2.5 nmol/h/mL), and his LysoGb1 value was 14.6 ng/mL (normal value <6.8 ng/mL). After the identification of a compound heterozygous GBA mutation, he was diagnosed with GD1 and he started ERT along with daratumumab-based anti-MM therapy. The characteristics of mutated patients are detailed in Table 2.

Being only one MM patient affected by GD1, we were not able to analyze the factors associated with this disease. Considering all DBS-positive patients, we found no distinctive factors associated with this condition (Table 2).

Our multicentre study, including 1004 MM patients coming from Northern and Southern Italy, found one patient affected by GD1 and underwent ERT treatment along with antimyeloma therapy.[8] Therefore, in our study, the prevalence was 1 in every 1004 patients (0.09%), which was lower than the assumed 0.5% but similar to the highest prevalence found in a high-risk population of Ashkenazi Jewish descent in North America (0.14%)[2] and higher than that reported in Italy.[9] Really, according to the prevalence of GD1 in the general Italian population (0.009/1000), the prevalence in our study (0.9/1000 MM/SMM) resulted in 100 times higher. Moreover, median age of our SMM/MM patients was much higher than the median age GD1 that was diagnosed (68 years vs. 33 years); so hypothetically, we should have found an even lower prevalence. In a previous report of a screening approach in 285 patients with plasma cell dyscrasias, one patient was found to carry two heterozygous mutations for GD but no GD diagnosis was made so the authors decided to evaluate a larger population to better define this association.[10] In a recent prospective observational multicenter study conducted in southern Italy, GD1 was diagnosed in four patients among 600 MGUS-screened patients, with a prevalence of 1 every 150 patients.[7] Over time, evidence has accumulated that GD patients had an increased risk of developing cancers,[11] with three times higher risk of liver and renal cell malignancies and nine times risk of MM in patients with GD1.[12] Several hypotheses have been formulated to explain pathophysiological link between GD and MM. Increased levels of pro- and anti-inflammatory cytokines regulating B-cell proliferation, such as IL-1β, TNFα, IL-10, and IL-6, have been found in the plasma of patients with GD1;[13] in patients with GD and MGUS or MM, the clonal immunoglobulin was found to be reactive against lyso-glucosylceramide (LGL1) as well as clonal immunoglobulin was shown to react with a bioactive lysolipid in nearly one-third of patients with sporadic MGUS or MM, suggesting that chronic antigenic stimulation by lysolipids could induce development of these gammopathies and depletion of substrate can improve GD-associated gammopathy in mice.[14] A recently published paper[15] reported a significantly

TABLE 1 Baseline characteristics of the diseases.

Baseline MM features	*n* (%)
Type of Ig involved	
IgG k/L	372/198 (37/20)
IgA k/L	120/75 (12/7.5)
IgD k/L	3/8 (0.3/0.8)
FLC k/L	82/42 (8/4)
NS	6 (0.6)
Missing	98 (10)
Previous MGUS	
Yes	262 (26)
No	631 (63)
Missing	111 (11)
MM phase	
NDMM	541 (54)
RRMM	319 (32)
SMM	31 (3)
Missing	113 (11)
Clinical parameters	
Typical Gaucher symptoms	
Asthenia	263 (26)
Bone pain	400 (40)
Fracture	148 (15)
Impotence	9 (1)
Alvus alteration	32 (3)
Active infections	11 (1)
Orthostatic hypotension	24 (2)
Systemic manifestations	31 (3)
Weight loss	29 (3)
Hyperviscosity	5 (0.5)
Neurological symptoms	34 (3)
CRAB	
Anemia	405 (40)
Renal failure	153 (15)
Hypercalcemia	64 (6)
Bone disease	565 (56)
SLiM CRAB	
>1 MRI lesion	136 (13.5)
FLC ratio ≥100	109 (11)
Plasma cells ≥60%	277 (27.5)
Neuropathy (yes/no/NA)	104/761/139 (10/76/14)
Abdominal evaluation (pathological/normal/NA)	34/850/120 (3/85/12)
AL Amyloidosis (yes/no/NA)	25/664/315 (2/66/32)
Skeletal radiography (pathological/normal/NA)	116/66/822 (11.5/6.5/82)
MRI (pathological/normal/NA)	312/71/621 (31/7/62)
Skeletal CT (pathological/normal/NA)	437/154/413 (44/15/41)
Plasmocytoma	
Yes	95 (9)
No	773 (77)
Missing	136 (14)
Cytogenetic features	
1q21	134 (13)
Del13	90 (9)
Del17p	45 (4)
Hyperdiploid	59 (6)
Hypodiploid	13 (1)
t(11;14)	80 (8)
t(14;16)	8 (1)
t(4;14)	44 (4)
Normal	21 (82)
ISS	
I	314 (31)
II	270 (27)
III	226 (23)
Missing	194 (19)
R-ISS	
I	156 (15.5)
II	257 (25.5)
III	92 (9)
Missing	499 (50)

Abbreviations: CT, computed tomography; FLC, free light chains; ISS, International Staging System; MGUS, Monoclonal Gammopathy of Indetermined Significance; MM, multiple myeloma; MRI, magnetic resonance imaging; NDMM, newly diagnosed multiple myeloma; NS, not specified; R-ISS, Revised International Staging System; RRMM, relapsed refractory multiple myeloma; SMM, smoldering myeloma.

decreased SMM burden in two patients with SMM and GD1 receiving ERT therapy. The peculiar population of type II natural killer T (NKT) may also constitute a link between GD1 and monoclonal gammopathies since they are abundant in patients with GD1 and are able to regulate B-cell activity.[16,17]

Unfortunately, having found only one patient with GD1 diagnosis and not presenting particular clinical or disease characteristics, we were not able to define an algorithm to establish factors associated with GD1 in SMM/MM. In Giuffrida et al.'s study,[7] 3 out of 4 patients with MGUS and GD1 presented with typical features of GD1 as splenomegaly, thrombocytopenia, and high ferritin. Therefore, due to the high prevalence of GD1, we found, in the presence of any of these signs, a DBS screening should be considered in the SMM/MM population, thereby increasing the probability of early diagnosis of GD1, which is necessary given the availability of three different ERTs.

In our study, we also found 13 heterozygous GD1 mutations without any hematological disease or signs of GD1. Heterozygous GD1 mutations in *GBA1* are associated with an increased risk of Parkinson's disease (PD)[18] but it was 2.2% in matched healthy controls in a large Italian study.[19] Therefore, speculation about this particular population is difficult.

TABLE 2 Characteristics of GBA-mutated patients.

Sex	Age	Enzymatic GBA activity (nmol/h/mL)	LysoGb1 value (ng/mL)	GBA mutation	Monoclonal component	PLT	Ferritin	Spleen	Liver	Cytogenetic
M	75	2	14.6	**L444P; R170C**	IgG k	280	NA	Normal	Normal	Hyperdiploid
M	60	3.4	NA	**N370S**	IgA k	128	610	Normal	Normal	Del17p
M	NA	3.9	NA	**L444P**	IgG k	206	368	Normal	Normal	Normal
F	72	2.7	NA	**G241R: G202R**	IgG λ	103	NA	Normal	Normal	Normal
M	75	3.3	5.4	**Q208R:Q169R; N370S**	IgG k	285	NA	Normal	Normal	Normal
F	73	2.6	3.6	**V53M: c.157G>A**	IgG k	235	NA	Abnormal	Abnormal	Normal
M	73	3.5	1.8	**K13R: c.38A>G**	IgA λ	197	206	Normal	Normal	t(11;14)
F	55	2.5	2.2	**N370S**	IgA λ	175	49	Normal	Normal	Normal
M	NA	3.7	4.6	**E365K**	IgG k	208	NA	Normal	Normal	Normal
F	46	2.9	4.5	**M369T**	FLC λ	298	NA	Normal	Normal	t(11;14)
F	72	2.4	2.8	**I441T**	IgG λ	373	NA	Normal	Normal	Normal
M	69	2.5	2.1	**L444P**	IgA k	107	363	Normal	Normal	Normal
M	61	3.4	2.8	**N370S**	IgA k	284	333	Normal	Normal	Normal
M	69	2.5	1.7	**L444P**	IgA k	355	NA	Normal	Normal	Normal

Note: Bold terms are different mutations of different patients, and shaded part identifies the only patient with double heterozygous mutation of GBA gene.

In conclusion, we found that the prevalence of GD1 in SMM/MM patients is so much higher than that of the general population as a similar study also found in MGUS. Therefore, we and others have demonstrated that GD1 should be considered a disease associated with plasma cell dyscrasias. Any signs of GD1, such as thrombocytopenia, splenomegaly, and high ferritin level, should be searched in MGUS/SMM/MM and, if present, a DBS screening should be included in the diagnostic work-up with the aim to recognize GD1 and, eventually, to avoid therapy delay.

AUTHOR CONTRIBUTIONS

Massimo Offidani, Sonia Morè, Serena Rupoli, Attilio Olivieri involved in study design. Sonia Morè, Irene Federici, Alessandra Bossi, Erika Morsia, Valentina M. Manieri, Maria T. Petrucci, Francesca Fazio, Chiara Lisi, Silvia Sorella, Adele D. Paoli, Francesca Farina, Anna Mele, Antonino Greco, Rossella De Francesco, Francesca Fioritoni, Carmine Liberatore, Tommaso Caravita di Toritto, Attilio Tordi, Angela Rago, Agostina Siniscalchi, Marino Brunori, Nicola Sgherza, Pellegrino Musto, Angela Amendola, Angelo Vacca, Antonio G. Solimando, Assunta Melaccio, Antonio Palma, Lorella M. A. Melillo, Lucia Ciuffreda, Silvia Sorella, Gabriele Buda, Maria L. Del Giudice, Antonietta P. Falcone, Patrizia Tosi, Simona Tomassetti, Francesco Rotondo, Alessandro Gozzetti, Piero Galieni, Miriana Ruggieri, Ferdinando Frigeri, Rosario Bianco, Alessandra Lombardo, Fabio Trastulli involved in patient enrollment and data collection. Carmela Zizzo and Giovanni Duro involved in laboratory tests. Massimo Offidani, Sonia Morè, Irene Federici, Alessandra Bossi, and Lucia Ciuffreda involved in data analysis. Laura Corvatta, Massimo Offidani, and Sonia Morè involved in paper writing. All authors involved in paper revision.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

FUNDING

This study is funded by Sanofi.

ORCID

Maria L. Del Giudice http://orcid.org/0000-0003-4291-8875

Massimo Offidani http://orcid.org/0000-0003-2749-7347

SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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