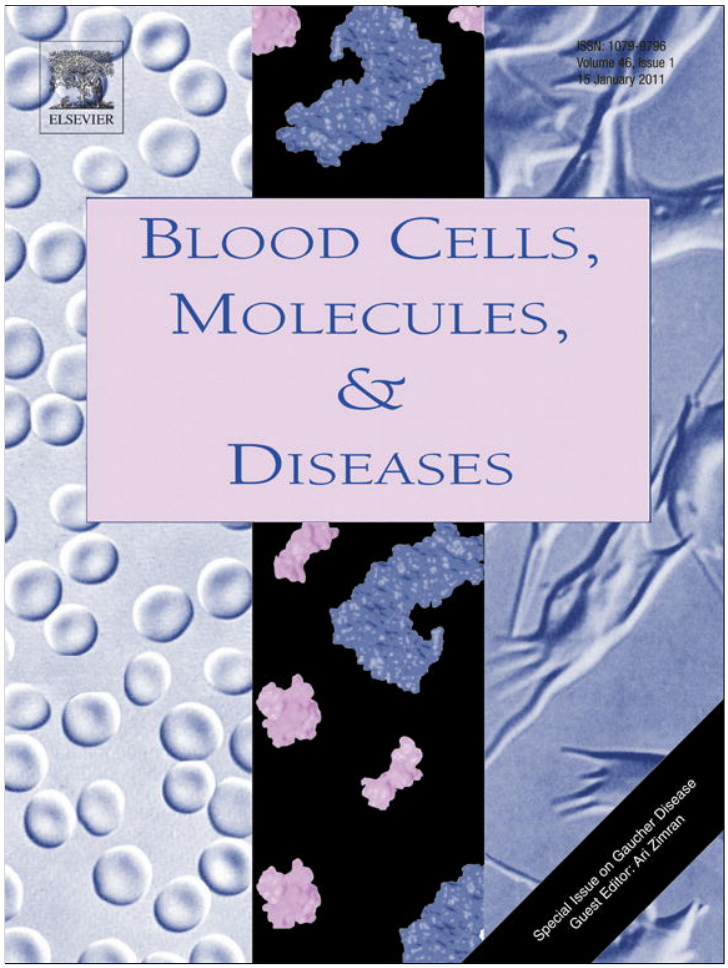

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Letter to the Editor

## Gaucher disease and dysgammaglobulinemia: A report of 61 patients, including 18 with GD type III

*To the Editor,*

According to the currently available literature, the adult form of Gaucher disease (GD type I), which accounts for 99% of the Gaucher cases, is associated with a high prevalence of hypergammaglobulinemia and monoclonal gammopathy of undetermined significance (MGUS) [1]. Thus far, there have not been any publications addressing the prevalence of these changes in GD type III (subacute neuronopathic).

We performed a study to assess the prevalence of dysgammaglobulinemia in a cohort of patients with GD in which 30% of patients had type III GD. The patients included in the study represent all Polish patients with GD and are registered in the national referral center for GD at the Children's Memorial Health Institute (CMHI), Warsaw, Poland. The patients were required to provide oral consent for their data to be computerized. Total serum concentrations of IgG, IgA and IgM were determined by nephelometry (BN ProSpec, Siemens Healthcare, Marburg, Germany). The presence of monoclonal proteins was determined by immunoelectrophoresis (SPE) performed in agarose gels, with amido-black staining (Sebia, Issy-les-Moulineaux, France). To confirm and characterize monoclonal proteins (M proteins), immunofixation (IF) was performed by the Sebia agarose gel method (Hydragel Double K20) using antisera against human IgG, IgA, IgM, IgD and κ and λ light-chain determinants (bound and free), according to the manufacturer's instructions. Because early monoclonal bands would have been missed in some of our patients if electrophoresis had been used alone, immunofixation was included as an obligatory method. Results are expressed as medians (range) for continuous variables and as numbers (percentages) for binary and categorical variables.

A total of 61 patients, 43 with type I GD (including 1 patient with SAP C deficiency) and 18 with type III GD, were recruited. The median age was 29.66 years (range 0.66–77.33), 25 (41%) were male and 36 (59%) were female (Table 1).

Out of 61 patients, 41 (67%) had normal levels of immunoglobulins, while 20 (33%) showed the presence of variable dysgammaglobulinemia and their demographic and clinical data are summarized in Table 2. The median age of these 20 patients was 32.5 years (range 9 months–78 years) and 4 of them were over 50.

Selective hypogammaglobuliemia was observed in 4 patients (1 IgG; 3 IgM), in one patient a deficiency of IgM was accompanied by elevated level of polyclonal IgA, and in 13 individuals polyclonal hypergammaglobulinemia was found (4 IgG; 5 IgA; 3 IgM; 1 IgG+IgM). Only 2 patients (3.3% of the study population) developed monoclonal gammopathy of unknown significance (MGUS) e.g. in one of them monoclonal protein of IgG λ type was present and in the other monoclonal band of free λ chain was detected. Among 20 patients with dysgammaglobulinemia, 5 were splenectomized, 15 were treated with enzyme replacement therapy (ERT) with imiglucerase (median 9 years, range 0.4–15), 1 with miglustat and 4 did not receive treatment for GD. During observation none of the patients had malignant gammopathy.

Patients with monoclonal gammopathies, aged 78 and 65 years old, were significantly older than the median age of patients without MG (29.245 years). Both patients with MG had type I GD, one was untreated and the other has been treated with ERT for 5 years at the time of assessment, neither was splenectomized.

With regard to 18 patients with type III GD, the median age was 19.665 years (range 9 months–51 years); 8 were male (44.4%%) and 10 were female (55.6%). Twelve (67%) of these patients had normal levels of immunoglobulins, while in the remaining 6 (33%) variable dysgammaglobulinemia was observed. Selective hypoglobulinemia was observed in 2 patients (1 IgG and 1 IgM), while polyclonal hypergammaglobulinemia was found in 4 patients (3 IgG and 1 IgG+IgM). Among 6 GD type III patients with dysgammaglobulinemia, 3 were splenectomized and all received ERT. During the assessment, none of GD type III patients had either monoclonal or malignant gammopathy.

It is estimated that approximately 6% of Gaucher patients have neuronopathic forms (NGD); with 5% having type III [2,3]. Like other GD variants, the neuronopathic forms, are pan-ethnic, although particularly high prevalence has been documented among patients from Northern Sweden [4], Poland [5] and in the Jenin Arab population [6]. Thus far, there have been several publications reporting incidence of polyclonal gammopathies and MGUS in GD patients. However, it has not been investigated whether prevalence of hypergammaglobulinemia and MG is increased in type III GD patients, a group that encompasses a very small part of the Gaucher population in Europe.

This study represents a cohort of patients with GD that includes the largest number of patients with type III reported up to now.

**Table 1**
Distribution of dysgammaglobulinemia in GD patients.

| Parameters | | Patients (all, $n=61$) | | Patients (type III, $n=18$) | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| Age | median range | 29.66 | 0.66–77.33 | 19.665 | 0.66–51.08 |
| Gender | male | 25 | 41 | 8 | 44.4 |
| | female | 36 | 59 | 10 | 55.6 |
| Normal levels of Ig's | total | 41/61 | 67 | 12/18 | 67 |
| dysgammaglobulinemia | total | 20/61 | 33 | 6/18 | 33 |
| hypogammaglobulinemia | total | 5/20 | 25 | 2/6 | 33 |
| | IgG | 1 | 20 | 1 | 50 |
| | IgM | 4 | 80 | 1 | 50 |
| hypergammaglobulinemia | total | 15/20 | 75 | 4/6 | 67 |
| | IgG | 5 | 33 | 3 | 75 |
| | IgA | 6 | 40 | 0 | 0 |
| | IgM | 3 | 20 | 0 | 0 |
| | IgG + IgM | 1 | 7 | 1 | 25 |
| Monoclonal component | total | 2/61 | 3.3 | 0 | 0 |
| | IgG L | 1/2 | 50 | 0 | 0 |
| | L | 1/2 | 50 | 0 | 0 |

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**Table 2**
Characteristics of 20 GD patients with dysgammaglobulinemia.

| No. | Gender | GD Type | Molecular analysis | Splenectomy (age) | Current age | Therapy (number of years) | Gammopathy classification | Type of immunoglobulin |
|---|---|---|---|---|---|---|---|---|
| 1 | M | SAPC deficiency | | No | 40 | miglustat | hypo | IgM |
| 2 | M | I | N370S/IVS2+1 | Yes | 22 | ERT (10) | hypo | IgM |
| 3 | F | I | | | 60 | ERT (6) | hyper | IgG |
| 4 | F | I | 84GG/R120W | No | 39 | ERT (10) | hyper | IgA |
| 5 | M | I | N370S/L444P | No | 6 | No | hyper | IgM |
| 6 | M | III | L444P/L444P | No | 0.66 | ERT (7/12) | hypo | IgG |
| 7 | M | III | L444P/L444P | Yes | 33 | ERT (15) | hyper | IgG, IgM |
| 8 | M | III | L444P/L444P | No | 21 | ERT (15) | hyper | IgG |
| 9 | F | III | L444P/L444P | No | 5 | ERT (3) | hyper | IgG |
| 10 | F | III | L444P/L444P | Yes | 34 | ERT (10) | hyper | IgG |
| 11 | F | III | L444P/L444P | Yes | 30 | ERT (8) | hypo | IgM |
| 12 | M | I | N370S/L444P | Yes | 48 | ERT (9) | hyper | IgA, IgM |
| 13 | M | I | R463S/IVS2+1 | No | 12 | ERT (6) | hyper | IgA |
| 14 | F | I | N370S/N370S/L444P | No | 60 | no | hyper | IgA |
| 15 | M | I | N370S/L444P | No | 65 | ERT (5) | mono | IgG L |
| 16 | M | I | N370S/R120W | No | 20 | No | hyper | IgM |
| 17 | F | I | N370S/L444P | No | 32 | ERT (8) | hyper | IgM |
| 18 | M | I | N370S/not found | No | 78 | No | mono | L |
| 19 | M | I | N370S/R496H | No | 30 | ERT (10) | hyper | IgA |
| 20 | M | I | N370S/R496H | No | 34 | ERT (10) | hyper | IgA |

Dysgammaglobulinemia and MGUS occurred in 33% and 3.3% of our GD cohort. In patients with type III GD, the results were 33% and 0%, respectively. These results show relatively low prevalence of polyclonal gammopathies and MG when compared with the literature (14–64% and 1–35% of patients) [7–12]. Interestingly, higher percentages of monoclonal gammopathy have been reported in non-Jewish patients cohorts from the Netherlands than in Israeli Jewish population [13].

In the general population the risk of monoclonal gammopathy is about 1% and increases with advancing age reaching 3.2% of adults over the age of 50 and increasing to 7.5% at the age of 85 [14]. Only two patients from our study, aged 78 and 65, developed MGUS. One patient was untreated and the other treated with ERT for 5 years only. Since the second patient developed MGUS relatively shortly after start of ERT, one could postulate that irreversible changes had already taken place, and could not be corrected by ERT.

The annual risk of malignant transformation of MGUS in the general population is about 1% [14]. There are no data to evaluate if the rate of MGUS transformation in GD patients is similar to the general population or is increased.

The prevalence of multiple myeloma (MM) in GD I patients exceeds the general prevalence (0.02%) and has been reported as 0.4-4% [12,13,15,16]. None of our patients had malignant gammopathy.

Avaialble data regarding the effect of ERT on dysgammaglobulinemia and monoclonal gammopathy are controversial. Some reports suggested that ERT is more effective in polyclonal hypergammaglobulinemia than in monoclonal gammopathy [8]. However, De Fost et al., similarily to Martinez-Redondo et al., showed a benefical effect of ERT on the occurrence and severity of gammopathies in GD patients [12,17,18]. In our cohort, 67% of patients had normal levels of immunoglobulins and a majority of the patients have been receiving long-term ERT with disease stabilization.

In conclusion, our study shows a considerable variability of humoral immune response seen among different patients with GD, ranged from normal concentrations of total serum immunoglobulins (67%) to hypoglobulinemia (less than 1%), polyclonal gammopathy (25% for all patients, 22% for type III GD) and monoclonal gammopathy detected in 3.3% (0% in type III GD). Only two patients from our study, both with type I GD and aged 78 and 65, developed MGUS. The prevalence of dysgammaglobulinemia in type III does not seem to be higher that in type I. Similarly to other studies, we conclude that long-term ERT has positive effect on reducing both polyclonal gammopathy and MG in GD patients.

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