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The Association of Gaucher's Disease and Dysproteinemias

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The first communication of the existence of polyclonal (diffuse) hypergammaglobulinemia in Gaucher's disease was reported by Goldfarb et al. [4] in 1950 in a group of patients under the age of 30 years. 13 years later, the first report of a patient with Gaucher's disease and monoclonal gammopathy was published [8], followed by another report [17]. Later on, the coexistence of multiple myeloma and Gaucher's disease was described [2, 13]. Pratt et al. [15] described 16 patients with Gaucher's disease of whom 6 had diffuse hypergammaglobulinemia and four monoclonal proteins, all of them of the IgG type with 'K' light chains with a concentration of the monoclonal protein of between 2,500 and 3,600 mg/dl. Except for 1 patient, none had decreased concentrations of the polyclonal protein.

The monoclonal proteins tend to appear in splenomegalic patients with Gaucher's disease above the age of 50 [15], while they are not prevalent in splenectomized patients, a fact that may be associated with the participation of the spleen in the production of these proteins.

Pratt et al. [15] suggested that patients with Gaucher's disease have continuous antigenic stimulation which brings about the development of diffuse hyperglobulinemia and later on, in elderly patients, the appearance of monoclonal proteins and even multiple myeloma [19].

Despite the small number of cases reported concerning the coexistence of multiple myeloma and Gaucher's disease, an association exists between multiple myeloma and diseases caused by other distorted lipid metabolism [1, 14, 18]. Possibly, these lipids may be the antigen which induces the immunoglobulin synthesis. In effect, the repeated intraperitoneal injection of fat in BALB/c mice brought about increased production of gammaglobulins and eventually the appearance of overt multiple myeloma [9, 14].

In Gaucher's disease, there are at least three substances which may possibly serve as antigens:

- (1) Glucocerebroside, a lipid which accumulates in the reticuloendothelial system.
- (2) Glucocerebrosidase, which in patients with Gaucher's disease has a decreased activity in spite of its relatively high levels [10]. Moreover, in patients with Gaucher's disease this enzyme differs quantitatively [7] as well as structurally [10] from the enzyme present in healthy subjects.
- (3)

Acid phosphatase, which 'leaks' into the serum following destruction of the Gaucher cells. Therefore, its concentrations is rela-

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tively high in patients with Gaucher's disease, thus serving as a diagnostic tool as well.

In 1963, *Joffe et al.* [6] found that in contrast to galactocerebroside, glucocerebroside is not antigenically functional. Later on, *Hanash and Rucknagel* [5] could not demonstrate absorption of the monoclonal protein on glucocerebroside. The above-mentioned data support the assumption that none of these substances can serve as antigens.

The identification of the antigen stimulating the production of the monoclonal component in patients with Gaucher's disease is important in light of the experimental therapy of intravenous infusion of the enzyme and its entrapment in the reticuloendothelial system [3] in these patients. The presence of monoclonal protein directed against this enzyme may interfere with the possible benefits of this enzyme.

The appearance of monoclonal gammopathy in patients with Gaucher's disease raises the question of its benign or malignant character, mostly because osteolytic lesions and even pathological fractures may appear in patients with Gaucher's disease per se, with or without multiple myeloma. This problem becomes more accentuated by the recent report about pseudo-Gaucher cells in multiple myeloma [16]. Thus, the diagnosis of multiple myeloma in patients with Gaucher's disease must be based upon the combination of several criteria, mainly the appearance of monoclonal gammopathy and decreased levels of polyclonal immunoglobulins [11, 12], the presence of osteolytic lesions characteristic of myeloma, the presence of more than 15% plasma cells in the bone marrow, most of them being immature cells, the ultrastructural characterization of these plasma cells by electron microscopy, and the presence of laboratory and clinical parameters typical of myeloma and not of Gaucher's disease such as hypercalcemia, hyperuricemia or kidney damage [12].

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