Multiple myeloma and Gaucher genes

To the Editor:

Gaucher disease (GD), the most prevalent lysosomal storage disease, is caused by an inherited deficiency of glucocerebrosidase with resultant intracellular accumulation of its glycosphingolipid substrate, glucosylceremide. Its heterogeneous clinical manifestations and autosomal recessive transmission are well described.[1] An association between GD and multiple myeloma was reported in 1968[2] and in multiple later case reports. Recently, myeloma in adult patients with type 1 GD has been estimated as occurring 6–50 times more often than expected.[3,4] There is no proven explanation for the increased risk of myeloma in patients with GD1. Suggested hypotheses have focused on the sphingolipid storage process itself as contributory to chronic antigenic stimulation or on an autocrine and/or paracrine stimulus to the production of cytokines and cellular growth factors. For example, serum concentrations of IL-6, one of the putative agents suspected as contributing to the development and progression of myeloma,[5] is sometime elevated in patients with GD1.[6]

As an additional pathogenic mechanism, attention has now been directed at mutant glucocerebroside molecules that fail to traffic to the lysosome because of posttranslational misfolding.[7] Retention in the endoplasmic reticulum may lead to the formation of potentially harmful protein aggregates if normal quality control degradation mechanisms are overwhelmed. In theory, such a mechanism might even be operative in clinically unaffected carriers who possess a single missense mutation. Indeed, a disproportionately large number of heterozygous Gaucher (GBA) mutations are now reported in both Ashkenazi Jewish (17–30%) and non-Jewish (8%) patients with Parkinsonian syndromes[8,9] although, as with the GD1 myeloma association, the cause is still unknown. With institutional review board approval and with the "Parkinson model" in mind, we looked for the presence of GBA mutations in 95 consecutive patients with multiple myeloma. All 95 patients had bone marrow confirmation of the diagnosis of multiple myeloma. Ages varied from 43 to 92 years. Sixty-three were male, 18 of Ashkenzi Jewish descent, five of African American, four Asian, three Hispanic, and the remainder white descent. Sixty-five patients had IgG myeloma, 12 IgA myeloma, 17 light chain type, and one null type. GBA mutations were assayed from peripheral blood leukocytes by the Genzyme Corp., which in part, supported this study. Only two patients (both Ashkenazi Jewish) carried a GBA mutation, both being heterozygous for the N370S mutation. One had IgG myeloma and the other light chain type. Among Ashkenazi Jews screened at random, the likelihood of finding at least one GBA mutation is approximately 1 in 15.[1] Thus, in our analysis, GBA mutations were neither significantly increased among Ashkenazi Jews (2/18) nor among non-Jews (0/77). Therefore, unlike the Parkinsonian syndromes, in our sample there was no apparent relationship between heterozygosity for a Gaucher mutation and the presence of multiple myeloma.

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