The Polymorphonuclear Neutrophil FcγRIIb Deficiency Is More Frequent Than Hitherto Assumed

To the Editor:

Human Fcγ receptor III (FcγRIII; CD16) is a high-affinity Fc receptor for complexed IgG. Two very homologous genes code for this receptor and are expressed in a cell-type-specific way. The FcγRIIIA gene is expressed as a transmembrane protein by natural killer cells and macrophages, whereas the polymorphic FcγRIIIB gene is constitutively expressed only by neutrophils as a phosphoinositol-linked protein. A polymorphism of FcγRIIIB gene is responsible for the biallelic, codominant, neutrophil-specific antigen (NA) system located on FcγRIIIB. Population studies have shown that there is a difference in the NA phenotype distribution between white and Japanese populations. The phenotype frequency of NA2 is higher in whites, whereas NA1 is more frequent in Japanese. Furthermore, a neutrophil-FcγRIIIB gene deficiency, which gives rise to an NA-null phenotype, has been reported in a small number of patients.

On the basis of the NA-phenotyping results of French donors, the frequency of FcγRIIIB deficiency in whites has been estimated to be 1 in 1,000. Surprisingly, during routine neutrophil NA-typing of 500 healthy Spanish blood donors, we identified 4 individuals with a neutrophil FcγRIII deficiency, corresponding with a frequency close to 1%. The neutrophils were phenotyped with the granulocyte immunofluorescence test (GIFT) using specific monoclonal antibodies (MoAbs) for NA1 (CLB-Fcγr 11; CLB, Amsterdam, The Netherlands) and NA2 (GRM1; kindly provided by Dr F. Garrido, Granada, Spain). When the NA-null phenotype was detected, the results were confirmed using two CD16 MoAbs (CLB-Fcγr 1 [CLB] and 3G8 [Medarex, Annandale, NJ]). Additionally, the anti-FcγRIIIB antiserum from a Spanish mother with FcγRIII deficiency who delivered a child with neonatal isoimmune neutropenia was tested against the cells of the deficient donors and no reactivity was obtained. The gene frequencies found for NA1 (0.306) and NA2 (0.614) are comparable to the frequencies established in other white populations. On the contrary, the frequency of the NA null allele in the Spanish population is considerably higher (0.8%) than hitherto assumed for whites (Table 1). In the French study, neutrophils were typed with the GIFT and/or the granulocyte agglutination test using polyclonal antibodies and only when the NA-null phenotype was suggested were MoAbs used. We hypothesize that this approach may have led to a false-positive result; the exclusive use, as in our study, of specific MoAbs and the GIFT could prevent this. Nevertheless, the possibility of a higher prevalence of this polymorphism in the Spanish population should be considered and will be explored in the near future.

Table 1. NA Genotype Frequencies in Different Populations

<table>
<thead>
<tr>
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<th>NA1</th>
<th>NA2</th>
<th>NA Null</th>
</tr>
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<tbody>
<tr>
<td>France</td>
<td>0.332</td>
<td>0.640</td>
<td>0.028</td>
</tr>
<tr>
<td>Spain</td>
<td>0.306</td>
<td>0.614</td>
<td>0.080</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>0.374</td>
<td>0.625</td>
<td>0.001</td>
</tr>
<tr>
<td>United States</td>
<td>0.337</td>
<td>0.663</td>
<td>0.0</td>
</tr>
<tr>
<td>Japan</td>
<td>0.651</td>
<td>0.302</td>
<td>0.047</td>
</tr>
</tbody>
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The four donors (2 women and 2 men) were healthy, having neither a history of repeated or protracted infections nor any clinical features indicating autoimmune or immune-complex pathology. No anti-FcγRIIb antibodies were found in the sera of the two women, although both had been pregnant. The molecular analysis of the genomic defect in these donors and their relatives is currently in progress. In summary, in contrast to the findings of the French study, we suggest that the neutrophil FcγRIIIB deficiency is not such a rare phenomenon. Whether this high frequency is valid for whites in general or is restricted to the Spanish population should be evaluated by studies in other populations.

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