CORRESPONDENCE

Significance of Abnormal Neutrophil Chemotaxis in Gaucher’s Disease

To the Editor:

In their interesting study of monocyte and granulocyte function in patients with Gaucher’s disease, Liel et al.1 used several methodologies to infer impaired function of monocytes. They found suppression of superoxide generation, staphylococcal killing, and phagocytosis in monocytes, but not in neutrophils; mean chemotaxis rates were normal in both types of cells, though “decreased chemotaxis rates were observed in some patients.” In fact, two of seven patients (29%) had some decrease in neutrophil migration and two of four patients (50%) had some decrease in monocyte migration. The authors apparently disregarded these findings as significant, possibly because of the small sample size. However, these studies of granulocyte function actually confirm our original observations of impaired neutrophil migration in approximately one third of our patients (9 of 29 patients),2 which is actually the same percentage of granulocyte dysfunction as found by Liel et al.

Moreover, they did not appreciate the prominent role of repeated and life-threatening bacterial infections in patients with severe Gaucher’s disease, whose expression was underscored by the defect of granulocyte chemotaxis in some of our patients. Pyogenic infections are recognized as one of the three major causes of death in Gaucher’s disease patients;3 and in our opinion, based on our experience with more than 200 active patients, it is a crucial factor in patient morbidity, especially in the pediatric population. Liel et al.’s study also failed to find any correlation between severity of disease and degree of dysfunction in either granulocytes or monocytes. This is in contrast to our findings of neutrophil function, where there was a direct relationship between genotypic and phenotypic expression (i.e., early age of onset, severity score index, and tendency to bacterial infections) and chemotaxis defect.

Of interest to clinicians as well as scientists is correction of the chemotactic defect and the decreased predilection for bacterial infections after enzyme replacement therapy.4 We have currently treated four patients with the neutrophil chemotactic defect; two patients had severe pyogenic infections and one suffered recurring urinary tract infections. Neutrophil chemotaxis defect was corrected in all the patients; the three suffering from infections were clinically markedly improved as well. These observations highlight the inherent connection between this laboratory abnormality and the tendency toward bacterial infections in Gaucher’s disease patients. It would be important to know what, if any, changes occur in monocyte function upon the advent of enzyme therapy.

We are currently studying two hypothetical constructs for the mechanism whereby the neutrophil chemotactic defect may occur. First, the defect may be the result of the physical accumulation of even a minute amount of glucocerebroside in the neutrophil, which is not classically considered to be a site of sphingolipid storage. This study may prove to be difficult because of the small differences expected. Secondly, we are studying the hypothesis whereby neutrophil motility, and hence the chemotactic response, is the result of secretory products of mononuclear phagocytes, e.g., tumor necrosis factor and interleukin-2. In vitro studies supporting this theory show stimulation of this secretory capacity to be dose dependent5 that parallels the conclusions by Liel et al regarding the dose-dependent nature of the response of monocytes to accumulation of glucocerebroside.

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Response

We have carefully considered the comments by Zimran et al referring to our recent article on phagocytic dysfunction in Gaucher’s disease patients. All our patients were type 1 and none of them suffered from recurrent infections. Among the various mononuclear and granulocyte functions that we performed, suppressed superoxide production by monocytes was by far the dominant abnormality, irrespective of the clinical severity of the disease, observed in eight of nine patients. Thus, reduced superoxide production by peripheral blood monocytes seems to be one of the most sensitive metabolic markers yet described in Gaucher’s disease.

As mentioned by Zimran et al, only three of their nine patients with abnormal granulocyte chemotactic activity and type 3 or severe type 1 Gaucher’s disease patients suffered from predisposition toward infection. The fact that not all their patients with abnormal chemotactic activity suffered from recurrent infection questions the pathogenetic relevance of this abnormality.

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Whereas predisposition for severe infection is a known risk in Gaucher’s disease patients, it is adequately documented only in previously splenectomized Gaucher’s disease patients. We are not aware of any documentation of such predisposition in nonsplenectomized patients, which would be most desirable.

We have recently obtained experience regarding peripheral blood monocyte superoxide production in 2 glucocerebrosidase (Ceredase; Genzyme, Cambridge, MA)-treated patients. Both showed normal superoxide production while on treatment. One of those (patient no. 4) was examined both before and after 8 weeks of enzyme therapy, showing complete correction of his initially reduced monocyte superoxide production after enzyme therapy (Liel Y and Levy R, unpublished observations). This correction of monocyte superoxide production was significantly faster than the 6-month to 1-year lag until response to therapy of abnormal chemotaxis observed by Zimran et al. Although the beneficial effect of enzyme therapy on improvement in the tendency to infection observed by Zimran et al seems evident, the temporal pathogenetic role of the chemotactic abnormality is again questioned in view of the impression that improvement in the tendency to become infected in their patients preceded the improvement in granulocyte chemotactic activity. We wonder what role could recurrent infection and granulocyte auto-oxidation associated with it, have on the granulocyte chemotactic dysfunction in their patients.

Regarding the mechanism of action, the hypothesis brought up by Zimran et al, assuming accumulation of glucocerebroside as the cause of cellular disturbance, is in agreement with our published in vitro observations that showed a negative correlation between the duration of exposure to glucocerebroside in the medium and monocyte superoxide production. Moreover, we assume that the lower rate of functional abnormalities observed in granulocytes, as compared with peripheral blood monocytes, represents less exposure and less accumulation of glucocerebroside, which results from a shorter life span in the circulation of granulocytes. This hypothesis gains further support from another recent observation indicating normal peripheral blood monocyte superoxide production in a Gaucher’s disease patient during the acute phase of osteomyelitis, which evidently involves accelerated turnover of those cells (Y. Liel and R. Levy, unpublished observation, 1993). Thus, we suggest: (1) that the monocyte abnormalities observed in our study reflects a similar abnormality of the reticuloendothelial system, the functional elements of that are transformed into Gaucher’s cells, and thus, infections in Gaucher’s disease patients would most likely reflect failure of local defense, such as in osteomyelitis or sinopulmonary infections; (2) that predisposition toward infection in most Gaucher’s disease patients is probably less marked than expected from the severity of monocyte abnormality in our study because of the relative integrity of granulocyte function in the majority of patients; and (3) that predisposition toward recurrent infection may occur in the most severely affected patients, who suffer of significant granulocyte dysfunction, such as in the severe phenotype Gaucher’s disease patients described by Aker et al. The ability to revert monocyte and granulocyte abnormalities and the clinical predisposition toward infection by enzyme replacement is of distinctive practical importance in this respect.

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[letter; comment]

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