

Immunodeficiency and other clinical immunology

Suppression of plasma neutrophil elastase- α 1-anti-proteinase complex by adequate replacement therapy in a patient with acquired hypogammaglobulinemia

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Periodic intravenous immunoglobulin infusion is the established treatment for patients with hypogammaglobulinemia. The treatment is generally well tolerated and considerably improves the health of such patients, with significant reduction in the rate of recurrent infections.

We have previously reported on a 59-year-old woman who had recurrent attacks of acute bronchitis and episodes of purulent endometritis.¹ After the diagnosis of hypogammaglobulinemia was made, she was treated successfully with immunoglobulin infusions (Sandozglobulin, Sandoz Pharmaceuticals). At the time of diagnosis she was taking part in a prospective study of the pattern of inflammatory marker changes in patients with recurrent respiratory tract infections. Stored specimens from that study have now been analyzed. We report here the effect of immunoglobulin replacement on the plasma level of neutrophil elastase- α 1-anti-proteinase complex (NEAPC) in this patient.

METHOD

The patient's clinical details have been reported elsewhere.¹ As part of the study protocol, venous blood samples were collected during regular monthly visits and also at the onset of symptoms suggesting infection. Serum and plasma aliquots were prepared and stored at -70°C . All the samples were analyzed during the same laboratory "run" at the end of a 12-month period of follow-up.

Extracellular immunoreactive plasma neutrophil elastase was measured in complex with α 1-anti-proteinase by a modified double-sandwich ELISA comprising a capture antibody to human neutrophil elastase and a detector antibody to human α 1-anti-proteinase.² Serum C-reactive protein was measured by a quantitative ELISA technique by using a double antibody

Abbreviations used

CI:	Confidence interval
NEAPC:	Neutrophil elastase- α 1-anti-proteinase complex

method.³ Both assays were developed at the research laboratory of the Respiratory Section of the University of Wales College of Medicine in Cardiff.

Control values for inflammatory markers in the study were obtained from analysis of blood samples of 45 healthy, age-matched volunteers.

RESULTS

The median control value of NEAPC was 22.4 ng/ml, and the upper 95% confidence interval (CI) was 48.5 ng/ml. The patient's serial results are given in Table I and graphically plotted in Fig. 1.

Despite the almost continuous use of antibiotics for treatment of infective episodes, plasma NEAPC concentrations generally tended toward the upper 95% CI, which they often exceeded. Within days of the first infusion of immunoglobulin, the NEAPC concentration dropped toward the median, closely following the patient's clinical improvement. A symptomatic relapse a few months later (Oct. 20), at a time when the IgG level was at the lower limit of the normal range, was associated with a rise in plasma NEAPC level, which again subsided when infusions of immunoglobulin were given every 3 weeks instead of every 4 weeks. Comparison of NEAPC levels before and after the introduction of immunoglobulin therapy (excluding defined episodes of infection) showed a significant decrease with treatment (mean [SD]: 45.2 [6.2] ng/ml vs 25.5 [4.3] ng/ml; $p < 0.01$). The C-reactive protein was not consistently increased with NEAPC on all occasions, though during two episodes of infection high values were recorded (upper 95% CI for normal control subjects: 9.5 mg/L).

DISCUSSION

Patients with immunoglobulin deficiency experience frequent infections with pyogenic bacteria and may have

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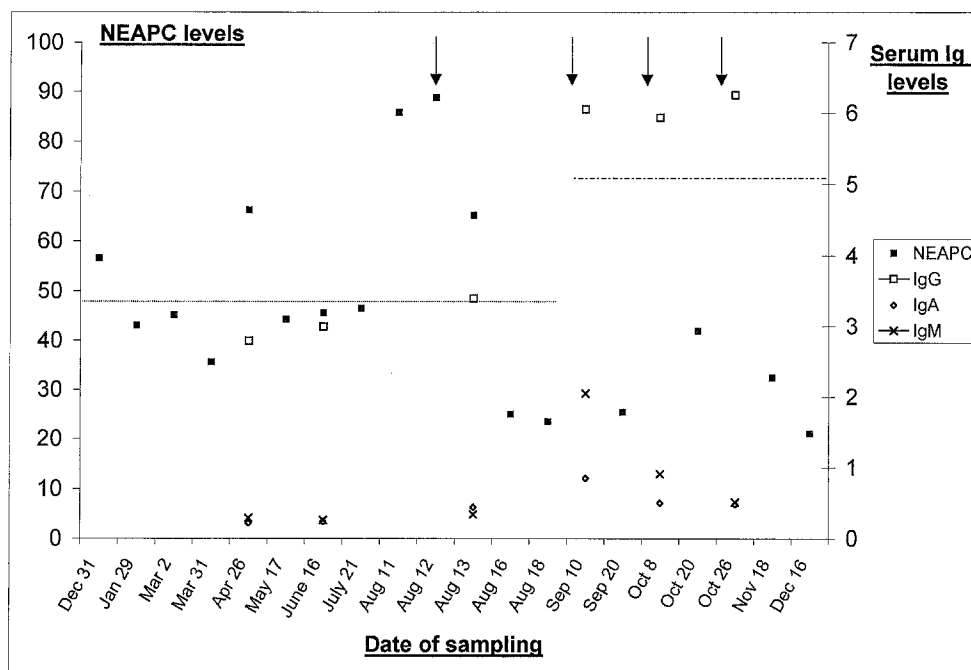


FIG. 1. Serial changes in NEAPC levels (in nanograms per milliliter) and serum immunoglobulin levels (in grams per liter). Arrows indicate dates of intravenous immunoglobulin infusion. The horizontal line to the left side of the y axis represents the upper 95% CI for NEAPC in normal control subjects, and the dotted-and-dashed line to the right side of the y axis indicates the lower normal level for serum IgG.

TABLE I. Marker and serum immunoglobulin levels, and infused immunoglobulin doses

Date	CRP	NEAPC	IgG	IgA	IgM	Ig Infusion	Comments
Dec. 31	3.6	56.54					Receiving antibiotics
Jan. 29	2.6	42.92					Receiving antibiotics
Mar. 2	2.4	45.03					Receiving antibiotics
Mar. 31	2.1	35.54					Receiving antibiotics
Apr. 26	3.2	66.2	2.79	0.22	0.29		Infection
May 17	2.4	44.16					Receiving antibiotics
June 16	1.9	45.53	2.99	0.24	0.26		Routine
July 21	2.8	46.45					Routine
Aug. 11	44.1	85.74					Infection
Aug. 12		88.7				30 gm	(First dose)
Aug. 13		65.24	3.39	0.44	0.34		
Aug. 16		25.04					
Aug. 18	3.6	23.52					
Sept. 10			6.05	0.85	2.05	30 gm	
Sept. 20	3.8	25.47					
Oct. 8			5.93	0.5	0.91	30 gm	
Oct. 20	18.2	41.87					(Relapse)
Oct. 26			6.25	0.48	0.51	30 gm	
Nov. 18	2.7	32.49					
Dec. 16	7.1	21.08					

CRP values are given in milligrams per liter, NEAPC values in nanograms per milliliter, immunoglobulin values are in grams per liter.

Bold type denotes marker values above upper 95% CI for healthy control subjects.

CRP, C-reactive protein.

continuous activation of their neutrophils, the primary function of which is not impaired, though the absence of opsonizing antibodies reduces the efficiency of phagocytosis and bacterial killing.

Increased plasma concentrations of NEAPC have

been taken to indicate increased neutrophil activity. In episodes of localized infection, the site of the release of neutrophil elastase is unknown. It has been postulated that this represents minor degranulation occurring in the vascular compartment as neutrophils marginate and

start migrating across the vascular endothelium.⁴ This concept is supported by the finding of increased concentrations of other neutrophil granule products in plasma.^{2, 5, 6}

Evidence of continuous neutrophil degranulation, even at times of apparent clinical stability, has been reported in patients with the adult respiratory distress syndrome⁵ and in patients with cystic fibrosis,^{2, 6} in whom immunoglobulin function is considered to be intact, though there are IgG subclass adaptations to chronic infection.⁷ In cystic fibrosis the concentration of such inflammatory markers was significantly decreased after parenteral antibiotic treatment, though persistent bacterial colonization prevented it from returning to a normal level. Our patient showed transient clinical improvement with antibiotics, sometimes for long periods, only to relapse again. Even during clinical remissions, her plasma NEAPC concentrations were statistically higher than the levels achieved when her circulating immunoglobulins were restored to near normal.

It is usual practice in immunoglobulin replacement therapy to monitor serum IgG levels at "trough" time (i.e., just before the next infusion) and to increase the infused dose until the IgG is in the low-normal range. The findings in our patient suggest that the plasma level of NEAPC might be a surrogate marker for physiologically adequate replacement (i.e., sufficient to protect from infection). A persistently increased NEAPC level may mean that immunoglobulin replacement is inadequate. On the other hand, if NEAPC is suppressed and

the patient has no clinical evidence of infection, there may be no need to increase the dose of infused immunoglobulin, even though the serum level might not yet be in the normal range. This might allow the patient to be treated with lower doses of immunoglobulin, with a reduction in the infusion time and also in the cost of treatment. The value of monitoring plasma NEAPC levels during immunoglobulin replacement therapy may merit further investigation.

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