Assessment of appropriate laboratory measurements to supplement the Crohn's disease activity index

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SUMMARY The ability of 11 laboratory parameters to reflect the degree of activity of Crohn's disease, using a clinical index as reference point was compared by means of multiple stepwise regression analysis. Activity was best defined in decreasing order by orosomucoid, sedimentation rate, C reactive protein, alpha-1-antitrypsin, albumin, haematocrit, IgM, circulating immune complexes, serum iron, IgG, and IgA. The haematocrit, the only laboratory measurement in the Crohn's disease activity index developed by the National Cooperative Study Group in the USA, is less discriminant than acute phase reactants. Only three parameters—namely, orosomucoid, sedimentation rate, and C reactive protein—have a significant weight and should be complementary to a simple clinical index.

It is generally accepted that a need exists for a numerical index of the activity of Crohn's disease at a given moment in time. Such an index would help to define the course of the disease in any individual patient, but would also be an important tool for assessing the efficacy of different therapeutic approaches, particularly in the case of multicentre trials.

Several indices have been proposed,^{1,2} but that established by the National Cooperative Study Group in the USA—CDAI—has received most attention. Although this index has been shown to be adequate in reflecting disease activity in most circumstances,^{3,4} it has been criticised because of its complexity and the fact that it depends almost exclusively on clinical features—for example, well-being and pain—which are often subjective.⁵⁻⁷ The only laboratory measurement used is the haematocrit.

More recently a completely objective index has been developed by Van Hees *et al.*⁸ Their evaluation of the index demonstrated convincingly that it is superior to the CDAI, and that it correlates well with a simple index of disease activity as assessed by one physician. Calculation of this index is complex and depends on measurement of various objective para-

meters. It is therefore unsuitable for routine clinical use and cannot, by definition, be superior to the simple four-point clinical index.

It has, however, been suggested that the simple clinical index should be supplemented by laboratory findings, especially those measuring inflammatory activity.^{9,10} The aim of the present study was to compare the ability of 11 laboratory parameters to reflect the degree of activity of Crohn's disease, using a clinical index as reference point and making comparison by means of multiple stepwise regression analysis.

Methods

PATIENTS

The study comprised 54 patients, 19 females and 35 males, aged between 16 and 66 years, in whom the diagnosis of Crohn's disease of the ileum, colon, or both had been confirmed according to the classical clinical, radiological, endoscopic, and histological criteria. The clinical activity of the disease was graded according to a formula which did not include any laboratory parameters. Grade 1 corresponded to a state of quiescence indicated by a complete absence of signs and symptoms. Grade 2 indicated mild activity, grade 3 a moderately severe relapse, and grade 4 severe disease necessitating hospitalisation or surgery. These grades were determined by the

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presence and severity of the usual symptoms experienced by patients with Crohn's disease—that is, abdominal pain, number and consistency of stools per day, number of anti-diarrhoeal tablets taken per day, and by the presence or absence of physical signs, whether general—for example, asthenia, fever, weight loss—or more specific for the disease—perineal lesions, abdominal mass, extra-abdominal complications. The patients were also classified according to the CDAI of the National Cooperative Group¹ and to the Dutch AI,⁸ using the corrections recommended for measurement of serum albumin using radial immunodiffusion.

Using the above clinical grading the disease was considered to be quiescent in 14 patients (CDAI range 5–97, AI range 45–90), mild in 14 (CDAI range 90–154, AI range 94–145), moderate in 12 (CDAI range 138–254, AI range 130–213), and severe in 14 (CDAI range 210–508, AI range 190–290).

At the same time as the clinical grade was determined blood was taken for the following laboratory tests: ESR, serum iron and haematocrit using standard techniques and serum albumin, IgA, IgG, IgM, orosomucoid, alpha-1-antitrypsin, and C-reactive protein by radial immunodiffusion using Partigen plates and the standards of Behringwerke A G (Marburg-Lahn, Germany). The titre of circulating immune complexes was also measured by Ouchterlony immunodiffusion after precipitation by polyethylene glycol.¹¹

Stepwise multiple regression analysis was used in an attempt to assess the relationship between these 11 laboratory parameters and the clinical activity of Crohn's disease. The mathematical model used was linear and of the following form:

$$yR = \alpha + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_n x_n + \epsilon$$

where ϵ is the error, β_i the regression coefficient and α a constant.

The activity scale was the dependent variable—that is to say, the variable to be defined. The laboratory parameters were the independent variables or in other words the defined variables. The scale of disease activity was graded from 1 to 4, as already described. The calculations were performed at the Centre de Calcul, Hôpital Universitaire de la Pitié Salpêtrière (Pr Gremy) Paris.

Results

Table 1 shows the mean and standard error of each of the 11 laboratory parameters. A correlation matrix showed no important intercorrelation between the different parameters (r was always inferior to 0.65).

The results of the stepwise regression analysis appear in Table 2, where the dependent variable was the clinical scale graded from 1 to 4 according to the clinical activity of the disease. The computation was stopped at the 10th step when the F test was insufficient to proceed further. The F value was significant ($P < 0.01$) for only three parameters—namely, orosomucoid, sedimentation rate, and C reactive protein. The increment of the square of the multiple regression coefficient was respectively 0.593, 0.050, and 0.046. The equation of the multiple regression analysis for these variable was

$$yR = 0.9317 + 0.0062 x_5 + 0.0006 x_6 + 0.0200 x_8$$

where x_5 is the orosomucoid, x_6 the C reactive protein and x_8 the sedimentation rate. The standard deviation of the regression coefficient were respectively 0.0021, 0.0002, 0.0067. To appreciate and compare the relative contributions of the three parameters all the vari-

Table 1 Mean and standard error of 11 laboratory parameters measured in 54 patients

Variables	Disease activity							
	Grade 1		Grade 2		Grade 3		Grade 4	
	Mean	Standard error	Mean	Standard error	Mean	Standard error	Mean	Standard error
x_1 Immunoglobulin A (2.10 g/l)*	2.51	0.89	2.39	1.10	2.81	1.90	3.23	1.55
x_2 Immunoglobulin M (1.40 g/l)*	1.36	0.64	1.56	0.82	1.54	0.85	1.38	0.61
x_3 Immunoglobulin G (12.50 g/l)*	11.95	2.33	12.30	4.07	13.31	5.23	13.81	4.41
x_4 Alpha-1-antitrypsin (2.90 g/l)*	3.09	1.14	3.44	0.65	4.45	1.06	4.74	0.78
x_5 Orosomucoid (0.90 g/l)*	0.70	0.15	0.97	0.43	1.47	0.55	2.07	0.52
x_6 C reactive protein (<1 mg/dl)*	0.08	0.24	1.36	2.19	3.30	2.43	8.88	6.52
x_7 Albumin (44.00 g/l)*	42.93	3.00	39.54	4.86	32.65	5.50	30.87	8.08
x_8 Sedimentation rate (<20 mm/h)*	12.57	9.61	12.50	5.10	40.75	13.50	39.64	16.55
x_9 Serum iron (19 micromol/l)*	18.96	5.97	16.81	6.71	11.07	4.11	8.15	3.32
x_{10} Antigen-antibody complex (titre reciprocal: 0)*	0.29	0.73	0.50	0.76	0.17	0.39	0.93	1.14
x_{11} Haematocrit								
42 units, women	38.84	2.04	43.06	3.07	38.15	3.42	35.63	1.52
47 units, men*	44.72	2.60	44.54	3.72	40.90	2.65	36.78	5.70

*Normal values

Table 2 Stepwise multiple regression analysis with clinical scale as dependent variable

Steps (no.)	Variables	MRC* (R)	Square of MRC (R ²)	Increment of R ²	F value
1	Orosomucoid (x ₁)	0.770	0.593	0.593	75.76†
2	Sedimentation rate (x ₂)	0.802	0.643	0.050	7.20†
3	C Reactive protein (x ₃)	0.830	0.689	0.046	7.40†
4	Alpha-1-antitrypsin (x ₄)	0.840	0.706	0.017	2.89
5	Albumin (x ₅)	0.848	0.720	0.013	2.33
6	Haematocrit (x ₁₁)	0.851	0.725	0.004	0.83
7	Immunoglobulin M (x ₂)	0.854	0.729	0.004	0.76
8	Antigen-antibody complex (x ₁₀)	0.858	0.736	0.007	1.23
9	Serum Iron (x ₆)	0.859	0.739	0.002	0.42
10	Immunoglobulin G (x ₁)	0.860	0.741	0.001	0.25

*Multiple regression coefficient.

†Significant at 1% level.

ables were normalised. The regression coefficient in the equation became respectively 0.428, 0.322, and 0.361. Thus the orosomucoid exerted the best correlation with the activity scale, followed by the sedimentation rate and by the C reactive protein.

A similar computation was performed with the CDAI as dependent variable. The orosomucoid, the sedimentation rate, and the C reactive protein exerted the same qualities as in the first computation. Neither in the first computation nor in the second did the haematocrit appear significant.

Discussion

The main objection which can be raised to the CDAI is that about 40% of the index is derived from subjective criteria such as pain and well-being, while it takes no account of objective measurements of inflammation in a disease which is by definition inflammatory in nature. These difficulties have been overcome in the index developed by Van Hees *et al.*,⁸ but their entirely objective index is cumbersome and its development depended on the comparison of the subjective impression of the significance of a combination of objective data with a simple clinical index. For everyday purposes, it cannot therefore be considered to be more useful than the physician's simple clinical index. The aim of the present study was different, in that we sought the laboratory parameter(s) which correlated best with the simple clinical index, and would therefore provide useful, simple, and objective corroboration of the simple index. The need for such a supplement to the latter has already been emphasised.¹⁰ Whereas the Dutch workers assessed a cumulative correlation of laboratory parameters, we have assessed each parameter individually against the simple clinical index and the CDAI.

The results obtained indicate that the activity of Crohn's disease is accurately reflected by the level of the acute phase proteins and that of all the parameters studied only orosomucoid, ESR, and C reactive protein correlated significantly with clinical

status. These parameters are, of course, no more specific for Crohn's disease than the clinical index, but they are easy and cheap to measure. Because of their nonspecificity a case can be made for measuring all three, particularly as they may not behave identically—C reactive protein, for example, possibly being useful in predicting relapse.¹² The superiority of these parameters over haematocrit, the only laboratory measurement included in the CDAI, seems clear. Unlike Van Hees *et al.*,⁸ we did not find that, when taken alone, the serum albumin correlated well with clinical activity. A further point worthy of note is that the activity of Crohn's disease seems to be indicated equally well by a simple 15 point index as by the complex CDAI⁸ or by the Dutch AI, or, indeed, by our own simple classification into four subgroups, resembling Truelove's classification of ulcerative colitis.¹³ Of all these indices, it now seems clear that the CDAI is the least useful.

The criticism that the CDAI has received has led to the suggestion that it should be replaced by a more workable clinical index supplemented by at least one laboratory measure of inflammatory activity.¹⁰ We suggest that, in view of their strong correlation with clinical disease activity, orosomucoid, ESR, and C reactive protein are the most suitable laboratory measurements to add to a practical clinical index of Crohn's disease activity.

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