The Use of Statistical Methods for Predicting the Status of Patients with Acute Cerebral and Coronary Ischemia

I. I. Eremin, N. A. Konstantinova, V. I. Skvortsova, A. N. Komarov, and E. V. Konstantinova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 142, No. 11, pp. 594-597, November, 2006
Original article submitted April 4, 2006

The most significant informative clinical laboratory parameters were determined and the exceptional value of cryoglobulin concentrations for predicting the clinical status was demonstrated. The efficiency of the proposed protocol of selective plasmapheresis for patients with atherothrombotic variant of stroke is confirmed, mathematical models describing and predicting the patient status are plotted.

Key Words: *cryoglobulins; stroke; infarction; plasmapheresis*

Cerebrovascular and cardiovascular diseases are the main causes of death in the world. The study of the etiology, pathogenesis, and factors essential for the progress and prognosis of these diseases is important and attracts much attention. The involvement of autoimmune mechanisms in the development of ischemia associated with the appearance of cryoglobulins (CG) in the blood was demonstrated [1,3,7-10]. However, the role of these proteins and their prognostic and diagnostic significance in this process remain unclear.

Using statistical methods, we determined the most informative clinical laboratory values (including CG concentrations) essential for predicting the severity of clinical status during the acute period of disease and created a mathematical model for prediction of the severity of patient's status.

MATERIALS AND METHODS

The study is based on retrospective analysis of examinations of 50 patients aged 42-84 years (25 men, 25 women) during the acute period of the first carotid ischemic stroke, hospitalized during the first 24 h of the disease [7]. The group included no subjects with hereditary degenerative, autoimmune and infectious diseases, diseases of the peripheral nervous system, or patients with a history of cerebrovascular episodes, or patients with disputable type and location of stroke.

The study group consisted of 26 patients with atherothrombotic and 24 patients with cardioembolic variants of stroke. Some patients in addition to standard therapy received sessions of selective plasmapheresis (PP) for elimination of cryoglobulins by a previously proposed protocol [7] on days 2, 4, and 6 of the disease. All patients were divided into 4 groups depending on the type of stroke and use of PP: 1) atherothrombotic stroke without PP; 2) atherothrombotic stroke+PP; 3) cardioembolic stroke without PP; and 4) cardioembolic stroke+PP. The reference group consisted of 30 patients with acute transmural myocardial infarction.

The status of patients with ischemic stroke was evaluated using Orgogozo score, the degree of functional recovery of patients was evaluated using Bartel's index on days 21-30 [1]. Neurological status was evaluated on days 1, 3, 7, and 21 of the disease. On days 1 and 7 the hemostasis system was studied: coagulation (activated partial thromboplastin time, prothrombin time, fibrinogen), fibrinolytic (XIIa euglobulin fibrinolysis), and cellular (spontaneous and ADP-induced platelet aggrega-

Russian State Medical University, Moscow. ***Address for correspondence:*** cryoglobulin@mail.ru. I. I. Yeryomin

tion) components by standard methods [2,4,5]). The level of CG in the peripheral blood was measured on a Cary 50 spectrophotometer at λ=280 nm on days 1, 2, 3, 7, and 21 of stroke [3]. The method of multiple step-by-step linear regression [6] was used for predicting the severity of clinical status and determining the most significant parameters. It was hypothesized that the dependent sign Y (severity of clinical status or functional recovery) was in linear relationship with independent prognostic signs X_1, X_2, X_n (laboratory and clinical parameters):

$$Y=a+b_1X_1+b_2X_2+...+b_nX_n,$$

where a, b_1, b_2, b_n are constant coefficients and n is the number of independent prognostic signs. A total of 30 clinical laboratory parameters were evaluated. The algorithm of direct step-by-step procedure was used. The independent sign most essential for dependent sign Y was included at each step [7]. Prognostic signs (X_i) were placed in the order of their informative value. Regression equations were plotted for each of the 4 groups of patients on days 1, 3, 7, and 21 of disease and the effects of each variable on the clinical status was evaluated. Standard laboratory values measured over the course of the disease, case history data, and CG concentrations measured over the course of the disease served as the independent variables. The self-service score was additionally determined on day 21 for verifying the prognosis of clinical status. Hence, a total of 20 mathematical models predicting the severity of clinical status on days 1, 3, 7, and 21 of the acute period were plotted for all groups of patients. The efficiency of the model was verified by the "sliding" examination and examination in a control sample. Control sample consisted of two patients with the same disease, not included in the study group (training sample).

The "sliding" examination method is a multistep procedure, when one case (patient) is excluded from the initial sample at each step; a regression equation is plotted for the remaining patients and the prognosis of clinical status for the excluded patient is verified. The procedure is repeated at the next step. The mean square deviations between the known (determined by the doctor) score (A) and predicted score, derived on the training sample, is evaluated. The second mean square deviation (B) is the deviation of the score deduced from the equation with the excluded patient from the known score (determined by the doctor). If the difference between the mean square deviations A and B is low, the prognostic model can be used for other patients with similar disease.

RESULTS

No more than 5 informative variables were selected for plotting each model for predicting the clinical status. Based on the derived regression equations, the most informative signs were determined, using which the severity of clinical status could be predicted for each group receiving treatment by various protocols with and without PP (Tables 1, 2).

The concentration of CG is of exceptional prognostic significance for patients with atherothrombotic CG. This parameter is used for predicting the clinical status of patients with atherothrombosis receiving standard therapy without PP on days 1-21 and remains the most significant parameter during the entire study (Table 1). In patients treated by PP the prognostic significance of CG concentration is lost by day 7 of disease (by the moment of an appreciable reduction of CG level as a result of PP). This fact also indicates the efficiency of eliminating CG by this treatment protocol.

The distribution of cryoprotein levels by significance was determined for the reference group of patients with acute transmural myocardial infarction, similar to the distribution for patients with atherothrombotic variant of stroke receiving no PP.

The prognostic significance of CG concentration for patients with cardioembolic stroke (Table 2) was lower than for patients with atherothrombosis and infarction. The blood level of CG in this group of patients is significant for predicting the clinical status only on days 3 and 21 of the disease irrespective of the treatment strategy. It seems to be due to different mechanisms of stroke development. Vascular wall damage (atherosclerosis, hypertensive crisis, *etc.*) precedes the atherothrombotic stroke and transmural infarction. In the former case this leads to destruction of the blood-brain barrier, release of neurospecific proteins into the blood, persisting there for a long time, and development of autosensitization [7]. This latter phenomenon can cause the production of abnormal immunoglobulins (cryoproteins) formation of cryoimmune complexes, and autoimmune sensitization.

The onset of brain ischemia in cardioembolic variant of stroke is sudden (without preliminary autostimulation). The autoimmune mechanisms were not yet fully triggered during the first days after the debut of ischemia, while therapeutic PP procedures were completed within the first 7 days of observation. Our results suggest that for patients with the cardioembolic variant of stroke PP sessions are more effective, if performed later.

Hence, blood concentration of CG is the most prognostically significant parameter for patients

TABLE 1. Distribution of Prognostically Significant Clinical Laboratory Parameters in Patients with Atherothrombotic Variant of Stroke

Day of evaluation of patient's status; group		Orgogozo scale	Barthel scale
1	no PP	Age, CG1, Creat1, FG1, INR1	
3	PP	CG1, TP1	
	no PP	CG2, Chol1, ESR1, INR1, TP1	
7	PP	TP7, Chol7, FG1, APTT1, Hem1	
	no PP	CG7, FG1, CG2, ESR7, Hem1	
21	PP	TP7, Chol7, age, FG1, APTT7	TP7, Hem7, TP1, ESR7, INR7
	no PP	CG1, CG3, FG7, Creat1, Creat7	CG3, Chol1, Hem1, ESR7, age

Note. Here and in Table 2: no PP: patients receiving treatment by standard protocol; CG: cryoglobulin concentration; TP: total protein; ESR: erythrocyte sedimentation rate; INR: International normalized ratio; Creat: creatinin; APTT: activated partial thromboplastin time; FG: fibrinogen; Hem: hematocrit; Chol: cholesterol. The figure after the code indicates the day on which the parameter was determined. The parameters are listed in the order of decreasing significance.

TABLE 2. Distribution of Prognostically Significant Clinical Laboratory Parameters in Patients with Cardioembolic Variant of Stroke

Day of evaluation of patient's status; group		Orgogozo scale	Barthel scale
1	no PP	Creat1, Hem1, INR1	
3	PP	Age, Creat1, CG1	
	no PP	CG3, Creat1, APTT1, ESR1	
7	PP	FG7, ESR7, Chol1	
	no PP	Creat7, Chol7, INR7, Hem1, ESR7	
21	PP	FG7, CG21, Creat1	TP1, Hem1, FG7, FG1, APTT1
	no PP	INR7, Creat1, CG1, APTT1, INR1	FG7, CG7, age

with atherothrombotic stroke and transmural myocardial infarction. The method of step-by-step linear regression can be used for predicting the clinical status of patients with ischemic stroke. Selective PP according to the recommended protocol (on days 2, 4, and 6 of disease) effectively removes CG in atherothrombotic stroke. The mathematical models describing the clinical status were verified on a control sample and can serve as the mathematical base for subsequent creation of applied programs for practitioners.

REFERENCES

1. E. I. Gusev and V. I. Skvortsova, *Cerebral Ischemia* [in Russian], Moscow (2001), pp. 13-210.
2. F. I. Komarov, B. F. Korovkin, and V. V. Men'shikov, *Biochemical Studies in Clinical Practice* [in Russian], Moscow (2001), P. 216.
3. N. A. Konstantinova, *Cryoglobulins and Disease* [in Russian], Moscow (1999), pp. 3-39.
4. V. M. Lifshits and V. I. Sidel'nikova, *Medical Laboratory Analyses* [in Russian], Moscow (2000).
5. S. A. Lugovskaya, V. T. Morozova, M. E. Pochtar', and V. V. Dolgov, *Laboratory Hematology* [in Russian], Moscow (2002).
6. O. Yu. Rebrova, *Statistical Analysis of Medical Data* [in Russian], Moscow (2003), pp. 213-221.
7. V. I. Skvortsova, N. A. Konstantinova, L. I. Zelyonkina, *et al.*, *Konsilium*, Special Issue, 33-35 (2005).
8. V. Agnello, *Scand. J. Immunol.*, **42**, No. 2, 179-184 (1995).
9. A. Ghinoi, M. T. Mascia, R. Puccini, and C. Ferri, *G. Ital. Nefrol.*, **21**, No. 3, 225-237 (2004).
10. M. Trendelenburg and J. Schifferli, *Ann. Rheum. Dis.*, **57**, No. 1, 3-5 (1998).