Utility of a laboratory score in the prediction of altered autonomic nervous system function in autoimmune gastritis

Çağdaş Kalkan, İrfan Soykan

Division of Gastroenterology, Department of Internal Diseases, Ankara University School of Medicine, Ibni Sina Hospital, Ankara, Turkey

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ABSTRACT

Background/Aims: *Autoimmune gastritis patients may have autonomic nerve dysfunction. The goal of our study was to explore the predictive value of two scoring systems in the differentiation of altered autonomic nerve function in autoimmune gastritis patients.*

Materials and Methods: *Seventy-five patients with autoimmune gastritis were evaluated by using cardiovascular reflex tests in order to delineate autonomic nerve function. Data were analyzed by using two laboratory-based scoring systems: "global score" (hemoglobin, mean corpuscular volume, gastrin, vitamin B_{12}, and chromogranin A) and "simple score" (hemoglobin, mean corpuscular volume, gastrin) in order to discriminate deranged and normal autonomic nerve function.*

Results: *Mean "simple" and "global" scores were significantly higher in subjects with altered autonomic dysfunction than in subjects with normal autonomic function (3.55±1.88 vs. 0.908±0.409, p<0.001 and 5.95±2.07 vs 2.46±1.28, p<0.001, respectively). Receiver operator characteristic (ROC) analysis revealed that the optimum "simple score" cutoff point was 0.75 with a sensitivity of 86.7% and specificity of 92.3% for discriminating autoimmune gastritis patients with autonomic nerve dysfunction from patients with normal autonomic nerve function [area under the curve (AUC): 88.3, positive predictive value (PPV): 97.5% and negative predictive value (NPV): 66.6%; 95% confidence interval (CI), 88.4-99.7].*

Conclusion: *Simple score and global score have a high predictive value in the assessment of autoimmune gastritis patients with autonomic nerve dysfunction. These scoring systems may help physicians while evaluating autoimmune gastritis patients for the existence of autonomic nerve dysfunction instead of complex cardiovascular reflex tests.*

Keywords: *Autoimmune gastritis, autonomic nerve function, global score, simple score*

INTRODUCTION

Autoimmune gastritis (AIG) is a chronic, inflammatory disease of the gastric mucosa. It is marked by the destruction and loss of the gastric parietal cells replaced by connective tissue or glandular structures. Development of autoantibodies against H+/K+-ATPase and intrinsic factor results in hypochlorhydria, hypergastrinemia, and neuroendocrine cell hyperplasia (1). This condition interferes with the absorption of vitamin B_{12} and iron, which leads to vitamin B_{12} and iron deficiency. Continuous hypergastrinemia due to hypochlorhydria stimulates the proliferation of endocrine cells of the corpus, which might give rise to gastric neuroendocrine tumor and gastric cancer (2,3). Symptoms of AIG are non-specific and patients undergo investigations because of vitamin B_{12} and/or iron deficiency, commonly reporting vague symptoms which are not specific enough to reach a diagnosis (4).

Autonomic nervous system dysfunction is common in subjects with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and scleroderma. The presence of autonomic nervous dysfunction affects the clinical progress of these kinds of diseases (5). There is enough evidence that AIG involves autonomic nervous system and the vagus nerve has a significant role in the control of gastric motility (6,7). Furthermore, gastric emptying is also controlled by vagal and sphlanchnic nerves and intrinsic innervation via the enteric nervous system. Although the enteric nervous system runs autonomously, it also interacts with the vagus nerve, and the enteric nervous system links directly with the vagal fibers (8). Recently, Miceli et al. developed a laboratory score for the diagnosis of AIG without using endoscopic and histopathologic examination (9). They prospectively investigated some serum biomarkers including vitamin B_{12}, mean corpuscular volume (MCV), hemoglobin, gastrin, and chromogranin A (CgA) levels and created two biochemical scores: global score (GS) and simple score (SS). They concluded that these two scoring systems are dependable. From their results, these scoring systems

Address for Correspondence: ***İrfan Soykan*** *E-mail:* ***isoykan@medicine.ankara.edu.tr***

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Table 1. Codes used for "simple" and "global" score calculations

1	Hb<g/dL	MCV>98 fL	Gastrin>20 pg/mL	VitaminB12<240 pg/mL	Chromogranin A>100 ng/mL
0	Hb≥g/dL	MCV ≤98 fL	Gastrin≤120 pg/mL	VitaminB12≥240 pg/mL	Chromogranin A<100 ng/mL

Hb: hemoglobin; MCV: mean corpuscular volume

are suitable for use in widespread screening programs to choose prospect subjects who need gastroscopy in order to diagnose AIG. They suggested that SS is particularly important and cost-effective, and endoscopy should be recommended in cases of AIG identified by the proposed scoring systems to detect AIG. In this study, we hypothesized that the GS and SS scoring systems may be helpful in differentiating AIG patients with autonomic neuropathy from patients with normal autonomic nervous system function.

MATERIAL AND METHODS

Patients

Autoimmune gastritis diagnosis was established according to the pathological features in biopsy specimens, which was obtained during gastroscopic examination. Histopathologically, AIG is marked by chronic infiltration of inflammatory cells, disappearance of oxyntic glands, parietal and zymogenic cells predominantly influencing the fundus and corpus of the stomach (10). We also investigated serum gastrin and antiparietal cell antibodies as supporting parameters of AIG depicted by Vargas et al. (11). Seventy-five patients diagnosed as having AIG who had undergone autonomic nervous function tests previously and whose data were available for the calculation of simple and GSs were included in the study. All patients gave informed consent prior to study, and this study was approved by the institutional review board of the related institution.

Tests

Calculation of "Global" and "Simple" scores

We used global and simple laboratory scores developed by Miceli et al. (9). In brief, we used the below-mentioned laboratory parameters: hemoglobin (Hb, abnormal if <12 g/dL), MCV (abnormal if >98 fL), vitamin B_{12} (abnormal if <240 pg/mL), basal 17-gastrin (abnormal if >120 pg/mL), and serum CgA (abnormal if >100 ng/mL). Serum CgA was determined by using available kits (CGA-ELISA CT; CIS bio international, Gifsur-Yvette Cedex, France). Serum gastrin level was assessed by DRG human gastrin 17-enzyme immunoassay kit (DRG International Inc., Mountainside, NJ, USA).

Formulas related to the calculation of GS and SS are shown below (9):

Global Score=1.5×Hb+0.5×MCV+3.5×Gastrin+2×Vitamin B_{12}+1.5×CgA

Simple Score=1.5×Hb+1×MCV+4×Gastrin

Codes to be used for score calculation are illustrated in Table 1. The total sum of GS ranged from 0 to 9: if all laboratory values are found to be within normal ranges, patient then would have a score of 0, whereas if all laboratory values are outside the normal ranges, then the patient would have a score of 9. However, the total sum of SS ranged from 0 to 6.5 (9).

Autonomic nerve function tests

Seventy-five patients diagnosed as having AIG were evaluated by using autonomic nerve function tests in order to delineate autonomic nerve function. Patients with accompanying conditions, which might influence autonomic nerve function, were not included in the study (12). Patients who were receiving drugs, which might influence these tests, were also not included in the study (13). We conducted autonomic nerve function tests by using cardiovascular reflex tests described by Ewing and was accepted to occur if at least two tests were positive (14). Valsalva maneuver, postural index, and heart rate response to deep breathing were used in order to assess parasympathetic function and blood pressure response to standing and handgrip test for sympathetic function and performed appropriately as described elsewhere (14).

Each test is depicted as normal (0), borderline (1), or abnormal (2), as demonstrated in reference values by Ewing et al. (13). In this computation, maximal possible cumulative score is 10 (i.e., if all five tests were considered to be abnormal). A cumulative score of 0 or 1 was interpreted as normal, a score of 2 or 3 was accepted as mild, a score between 4 and 6 was accepted as moderate dysfunction,

and a score of 7 or higher was accepted as severe autonomic dysfunction (12). Some data included in this study were used in previous studies (7).

Statistical Analysis

SPSS 16.0 (Chicago, IL, USA) for Windows version 10 was used for statistical analysis. Results were expressed as percentage of patients and mean±SD, where appropriate. The Shapiro-Wilk test was used to test of normality. Receiver operator characteristic (ROC) curves were used to describe and compare the performance of diagnostic values of GS and SS on predicting altered autonomic nerve function. A p-value less than 0.05 was accepted as significant.

RESULTS

Laboratory scores (simple and global) depicted in Table 1 were used in order to define whether autonomic dysfunction occurs in autoimmune gastritis patients. Thirteen patients showed normal autonomic nerve function (total autonomic test score=0–1), whereas 62 subjects had altered autonomic function. Mean SS was significantly higher in subjects with autonomic dysfunction than in subjects with normal autonomic function (3.55±1.88 vs. 0.908±0.409, p<0.001). ROC analysis suggested that the optimum SS cutoff point was 0.75 with a sensitivity of 86.7% and specificity of 92.3% for discriminating AIG patients with autonomic nerve dysfunction from patients with normal autonomic nerve function [area under the curve (AUC): 88.3, positive predictive value (PPV): 97.5% and negative predictive value (NPV): 66.6%; 95% confidence interval (CI), 88.4-99.7]. As for GS, the mean GS score was also significantly higher in patients with autonomic nerve dysfunction than in patients with normal autonomic nerve function (5.95±2.07 vs. 2.46±1.28, p<0.001). ROC analysis suggested that the optimum GS cutoff point was 3.75 with a sensitivity of 91.1% and specificity of 61.5% for discriminating AIG patients with autonomic nerve dysfunction from patients with normal autonomic nerve function (AUC: 82.8; PPV: 89.1% and NPV: 66.6%; 95 % CI, 52.6-78.4) (Figure 1).

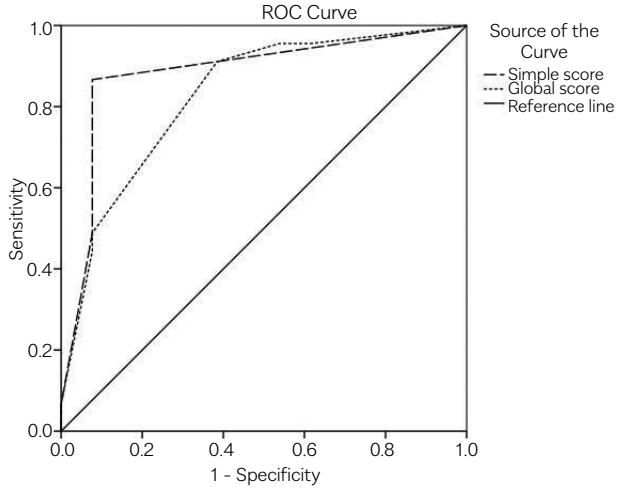

Figure 1. ROC curve for SS and GS in the prediction of deranged autonomic nerve function in AIG patients

DISCUSSION

Results of this study showed that SS, based on laboratory values, discriminates AIG patients with altered autonomic nervous system function from patients with normal autonomic nervous system function with a sensitivity of 86.7% and specificity of 92.3%. GS had a sensitivity of 91.1% and specificity of 61.5% for differentiating AIG patients with altered autonomic nervous system function from patients with normal autonomic nervous system function. The sensitivity was generally high (above 90%) for SS and GS. Miceli et al. recently described two inexpensive and reliable score models and concluded that especially the SS can be administered easily in routine clinical practice for recognizing patients potentially affected by AIG (9). We used the same models in order to diagnose altered autonomic function in subjects with AIG and confirmed the reliability and validity of SS and GS in our study. Furthermore, SS and GS are shown to have a role in predicting AIG patients with altered autonomic function. SS was significantly higher in subjects with altered autonomic function than in subjects with normal autonomic function. SS has a sensitivity of 86.7% and specificity of 92.3% with a selected cutoff point of 0.75 (AUC: 88.3; PPV: 97.5% and NPV: 66.6%). GS was also significantly higher in subjects with autonomic dysfunction than in subjects with normal autonomic function with a sensitivity of 91.1% and specificity of 61.5%, with a selected cutoff point of 3.75 for discriminating AIG patients with autonomic dysfunction from subjects with normal autonomic function (AUC: 82.8; PPV: 89.1% and NPV: 66.6%; 95% CI, 52.6-78.4) Therefore, both SS and GS are effective in predicting autonomic nerve dysfunction. However, specificity and PPV were lower for GS in predicting autonomic nerve dysfunction than for SS.

Data regarding autonomic nerve function may be valuable because gastric motor function is regulated by the central nervous system and the sympathetic and parasym-

pathetic nervous systems. The interactions of the central nervous system and the activity of the enteric nervous system and the interstitial cells of Cajal are also important parameters of this activity. These complex systems control the contractions and peristaltic waves and finally control the peristaltic activity of gastric smooth muscle (15). Although the enteric nervous system works autonomously, gastric motility is controlled by vagal and sphlanchnic networks and intrinsic innervation is mediated via the enteric nervous system (8).

In conclusion, our results showed that this model may help physicians while evaluating AIG patients, in whom there is autonomic nervous system dysfunction instead of performing cardiovascular reflex tests. Furthermore, these scoring systems also have a high sensitivity in predicting autonomic nerve dysfunction which may play a role in the symptoms and altered GI motility seen in patients with AIG. Altered autonomic nervous system function observed in these patients may shed light on the pathophysiology and may help explain a part of unexplained upper GI symptoms in patients with AIG.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ankara University Faculty of Medicine (Decision Date: August 31, 2015/ Decision No: 13-526-15)

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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