Published in final edited form as:

Clin Gastroenterol Hepatol. 2008 September ; 6(9): 988–992. doi:10.1016/j.cgh.2008.04.009.

Serological Profiles Aiding the Diagnosis of Autoimmune Gastrointestinal Dysmotility

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Abstract

Background and Aims—Autoimmune gastrointestinal dysmotility is a limited autoimmune dysautonomia occurring idiopathically or in the context of an anatomically remote neoplasm, previously documented or unsuspected. Here we report 24 Mayo Clinic patients in whom the profile of serum autoantibodies aided this diagnosis.

Methods—All patients were ascertained serologically in the course of service evaluation for autoantibodies consistent with neurological autoimmunity. Review of their histories, motility studies and laboratory findings revealed that all had presented with subacute gastrointestinal dysmotility.

Results—Recorded motility abnormalities included: esophageal dysmotility 8 (6 had achalasia), delayed gastric emptying 12, slow small intestinal transit 7, slow colonic transit 4, and pelvic floor dyssynergia 4. Four patients underwent abdominal surgery; 2 commenced total parenteral nutrition. Plasma membrane cation channel autoantibodies were detected in 23 patients: neuronal voltage-gated calcium channel (5 N-type and 1 P/Q-type), acetylcholine receptor (11 ganglionic-type and 4 muscle-type) and neuronal voltage-gated potassium channel autoantibodies (4). Two patients had anti-neuronal nuclear autoantibody, type 1. Approximately half of the patients had other antibody markers of organ-specific autoimmunity (including skeletal muscle, striational, GAD65, thyroid or gastric parietal cell specificities). Neoplasia was diagnosed in 11 patients (9 recent, 2 remote): lung, breast and endometrial, gastrointestinal and thymoma. Moderate to dramatic improvement in gastrointestinal symptoms was reported following immunotherapy in 4 of 4 patients treated, and following pyridostigmine in 2 of 2 patients treated.

Conclusions—Autoimmune serology aids the diagnosis of autoimmune gastrointestinal dysmotility, both paraneoplastic and idiopathic, and may guide management.

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Conflict of Interest: The authors have no conflict of interest to disclose.

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INTRODUCTION

Autoimmune gastrointestinal (GI) dysmotility (AGID) is a limited form of autoimmune dysautonomia that can occur idiopathically or in the context of an anatomically remote cancer. Onset is typically subacute, with symptoms reflecting GI hypermotility or hypomotility. However, by the time a gastroenterologist is formally consulted the onset may appear historically to have been insidious. Signs may be focal or generalized. The most striking presentation of AGID is intestinal pseudo-obstruction,^{1–4} but more commonly the presentation is regionally restricted, with manifestations of achalasia, gastroparesis, pyloric stenosis, slow intestinal transit and rarely anal spasm.^{5–8} Symptoms include dysphagia, odynophagia, vague postprandial epigastric discomfort, early satiety, recurrent nausea with or without postprandial vomiting, unexplained weight loss with malnutrition, abdominal pain and intractable constipation or diarrhea.

Autoantibodies targeting postsynaptic ganglionic neuronal acetylcholine receptors (AChRs) containing $\alpha 3$ subunits have potential to cause widespread autonomic dysfunction, i.e., pandysautonomia.^{9, 10} GI dysmotility in those patients is commonly prominent and sometimes profound.^{7, 9, 11} Mice injected systemically with IgG prepared from serum containing ganglionic-type AChR antibodies develop slowed GI transit, urinary retention, dilated pupils, reduced heart rate variability, and impaired catecholamine response to stress.¹² Gastrointestinal dysmotilities and other manifestations of dysautonomia also have been described in patients with anti-neuronal nuclear autoantibody, type 1 (ANNA-1, sometimes called “anti-Hu”) and neuronal voltage-gated cation channel antibodies.^{5, 6, 13} Here we report, from recent clinical-serological correlative experience, a profile of organ-specific serum autoantibodies that aids the diagnosis of AGID.

MATERIALS AND METHODS

We tested sera stored from 24 Mayo Clinic patients (none previously published) who were identified consecutively as having one or more autoantibodies consistent with neurological autoimmunity in the course of service serological evaluation in the Mayo Neuroimmunology Laboratory. The test had been ordered by a consulting neurologist in 9 cases and a consulting gastroenterologist in 15 cases. In reviewing each patient’s history to formulate clinical interpretive comments, the laboratory-based consultant noted that the major presenting problem in each case was a subacute disorder of gastrointestinal dysmotility, with onset of GI symptoms recorded as acute (< 2 weeks) or subacute (< 6 months). All patients had objective abnormalities on GI motility studies and all case histories were reviewed by a motility disorders specialist to confirm the diagnosis of GI dysmotility. Service serological testing had included: 1) radioimmunoprecipitation assays for cation channel autoantibodies (muscle-type and ganglionic neuronal ($\alpha 3$)-type AChR,^{14, 15} voltage-gated calcium channels [VGCC, P/Q-type and N-type]^{14, 16} complexed with ¹²⁵I-ligand [alpha-bungarotoxin, epibatidine or omega-conopeptide M_{VII}C or G_{VI}A]), 2) an indirect immunofluorescence screening assay for well-characterized neuronal or glial nuclear and cytoplasmic autoantibodies, using as substrate a 4 μ m thick composite frozen tissue section comprising adult mouse cerebellum/midbrain, gut and kidney, postfixes with 10% formalin,¹⁷ and 3) ELISA assay for skeletal muscle striational antibodies.^{14, 18} Assays performed retrospectively included radioimmunoprecipitations to detect antibodies reactive with neuronal voltage-gated potassium channels (VGKC) complexed with ¹²⁵I-alpha-dendrotoxin,¹⁵ GAD65,^{17, 19} IA-2 and insulin (both employing ¹²⁵I-labeled recombinant human islet cell antigens obtained from Kronus, Inc.), latex agglutination tests for thyroid microsomal (peroxidase) and thyroglobulin antibodies,^{17, 19} immunofluorescence for gastric parietal cell autoantibody¹⁷ and recombinant Western blot for CRMP-5-IgG.²⁰

RESULTS

Sixteen of the 24 patients of this report were female (67%), 7 were smokers, and median age was 59 years (range, 17–87). GI dysmotility was confirmed in all patients by gastric, small intestinal or colonic nuclear transit studies and/or esophageal, gastroduodenal or colonic manometry or anorectal manometry with balloon expulsion. The median duration of follow-up from symptom onset was 25 months (range, 2–127 months).

Documented GI dysmotilities for the 24 patients were: esophageal dysmotility 8 (of whom 6 had achalasia), delayed gastric emptying 12, slow small intestinal transit 7, slow colonic transit 4, and pelvic floor dyssynergia 4 (Table 1). In 7 patients dysmotility was confirmed to involve more than one level of the GI tract. Four patients reported antecedent events immediately preceding GI symptom onset: 2 were post-partum (#21 and #22), 1 followed abdominal surgery (#8), and 1 followed an upper respiratory tract infection (#12). Four patients underwent abdominal surgery for treatment of GI symptoms, 3 reported no benefit (2 cholecystectomy, 1 colectomy with ileostomy) and 1 reported symptomatic relief (ileostomy in a patient with severely slowed colonic transit). Two patients required initiation of total parenteral nutrition.

Twelve patients had co-existing neurological diagnoses: 5 had orthostatism (3 orthostatic hypotension and 2 orthostatic intolerance, all documented by tilt-table testing and not attributable to hypovolemia or medication effect), and 3 had peripheral sensory neuropathy (1 small-fiber, 1 large-fiber sensory, 1 mixed small- and large-fiber; all displayed a length-dependent pattern with predominant lower extremity involvement). Five patients had co-existing psychiatric diagnoses (anxiety, depression) and 2 had chronic pain syndromes (one characterized as fibromyalgia).

In 22 patients the index autoantibodies detected (Table 2) were neuronal or muscle cation channel autoantibodies: acetylcholine receptor (11 ganglionic-type and 4 muscle-type), neuronal voltage-gated calcium channel (5 N-type and 1 P/Q-type) and neuronal voltage-gated potassium channel autoantibody (3). ANNA-1 was detected in the remaining 2 patients; algorithmic reflexive testing revealed one had co-existing VGKC autoantibody. AGID manifestations in the patients without ANNA-1 included esophageal dysmotility 8 (6 had achalasia), delayed gastric emptying 11, slow small intestinal transit 5, slow colonic transit 4, and pelvic floor dyssynergia 4.

Thorough oncological evaluation was undertaken in all but 3 of the 24 patients. Neoplasia was diagnosed in 11 (including 4 of 6 smokers), and was confirmed histologically in 8. In 2 patients, the tumor was in remission for more than 2 years before GI symptoms began. In 6 patients, neoplasia was unsuspected at initial presentation, but was diagnosed as a consequence of workup prompted by the serum autoantibody profile. Two patients had breast carcinomas (1 with co-existing endometrial carcinoma), 2 had lung carcinomas (1 small-cell type and 1 non small cell type), 1 had remote esophageal carcinoma (with recent gastroparesis presentation), 1 had thymoma, 1 had prostatic adenocarcinoma with mediastinal metastases and concurrent chronic B lymphocytic leukemia, and 1 had cervical intraepithelial neoplasia, grade 2. In another 3 patients mass lesions were identified by CT imaging: a presumed pancreatic carcinoma, a lung nodule, and mediastinal and retroperitoneal lymphadenopathy.

In 11 patients we found organ-specific autoantibodies that are recognized associations of type 1 diabetes, thyroiditis or pernicious anemia: GAD65, IA-2, gastric parietal cell, muscle striational, thyroid peroxidase or thyroglobulin autoantibodies. These markers of “thyrogastric autoimmunity” are commonly identified in patients with neurological autoimmunity.^{17, 19, 21, 22} Co-existing autoimmune diseases were identified in 10 of these patients, of whom 7 had multiple organ-specific autoantibodies. Four had hypothyroidism, 5 had hyperglycemia (4 confirmed diabetes mellitus, 1 impaired fasting glucose), 2 had Raynaud’s phenomenon, 1 had

discoid lupus, 1 had pernicious anemia, and 1 had myasthenia gravis. Three patients had multiple co-existing organ-specific autoimmune disorders.

GI symptoms were reported to be moderately relieved in each of 2 patients who received oral pyridostigmine as therapy:

The first, a man aged 78 years (#3, Table 1), with several years' history of essential tremor, presented with 3 months of dysphagia and 15 pounds weight loss (10% of body weight). Esophageal manometry was consistent with achalasia. He had muscle-type AChR autoantibodies (0.11 nmol/L; normal, 0.02 nmol/L or less), but no evidence of myasthenia gravis by detailed electromyographic evaluation. Treatment with oral pyridostigmine (60 mg, 3 times daily) was elected rather than botulinum toxin, and was followed by moderate improvement in swallowing. Optimal dosing was achieved by starting at 0.5–1.0 mL on day one, (60mg/5 ml), and advancing to the final tolerated dose over 3–5 days.

The second, a woman aged 20 years (#23, Table 1), presented with subacute abdominal cramping, diarrhea followed by constipation, and 25 pounds weight loss over 6 months (20% of body weight). She had N-type voltage-gated calcium channel autoantibodies (0.04 nmol/L; normal, 0.03 nmol/L or less). Symptoms were almost completely alleviated following initiation of oral pyridostigmine (same schedule and dosage as the first patient). She gained 15 pounds in the first 4 months, and had regained her baseline weight 13 months after starting pyridostigmine.

GI symptoms were reported to be markedly improved in each of 4 patients who received immunomodulatory therapy:

The first, a woman aged 55 years (#15, Table 1), presented with acute epigastric pain which continued unabated following cholecystectomy for presumed cholecystitis. Severe nausea, vomiting and early satiety ensued. Over the next 5 years symptoms of more generalized autonomic dysfunction developed, namely, dry eyes and mouth, orthostatic intolerance, urinary hesitancy, and global anhidrosis. Serological evaluation, performed more than 6 years after GI symptom onset, revealed ganglionic AChR autoantibody (0.04 nmol/L; normal value 0.02 nmol/L or less). Following treatment with intravenous immune globulin, GI dysmotility and sicca symptoms resolved completely and moderate improvement was noted in other autonomic function tests.

The second, a man aged 76 years (#16, Table 1), presented with 18 months of anorexia, nausea, vomiting, alternating diarrhea and constipation, and 50 pounds weight loss (30% of body weight). ANNA-1 was positive at a serum dilution of 1:7,680; normal is negative at 1:240. Using currently optimized testing conditions, all of a total 960 ANNA-1 seropositive patients identified in this laboratory in the past 2 decades are positive at dilutions of 1:240 or greater, and with extended follow-up, cancer is confirmed in >80% of cases. Subsequent investigation revealed a limited-stage small-cell lung carcinoma. Following intravenous immune globulin and subsequent chemotherapy (delayed due to poor nutrition), he experienced dramatic improvement in GI symptoms, and regained 35 pounds of weight over the next 4 months.

The third, a woman aged 52 years (#19, Table 1), had a history of hypothyroidism, pernicious anemia, and Raynaud's phenomenon. She developed subacute constipation, postprandial fullness, nausea and vomiting and 35 pounds weight loss (25% of body weight). Serological evaluation identified ganglionic AChR autoantibody (0.26 nmol/L; normal value 0.02 nmol/L or less). Prokinetic medications (metoclopramide and erythromycin) yielded minimal improvement. Following commencement of oral prednisone and 6-mercaptopurine, she reported marked improvement in GI symptoms and quality of life, and her weight stabilized

over the next few months. GI symptoms of slow transit constipation worsened each time corticosteroid therapy was tapered.

The fourth, a woman aged 22 years (#21, Table 1), reported onset of severe constipation during her second pregnancy. Four days after vaginal delivery she experienced idiopathic rupture of the transverse colon. Laparotomy revealed an ulcerative lesion with transmural necrosis. Following subtotal colectomy and ileostomy, symptoms of constipation continued, with increasing abdominal distention and bloating. Progressive, unintentional weight loss of 50 pounds over 2 years (35% of body weight) necessitated total parenteral nutrition. Serological evaluation revealed ANNA-1 (at 1:15,360 dilution) and neuronal voltage-gated potassium channel autoantibody (0.10 nmol/L; normal value 0.02 nmol/L or less). Thorough oncological evaluation revealed cervical intraepithelial neoplasia, grade 2. Progressive difficulty walking was attributed to a large-fiber sensory neuropathy (confirmed by electromyography). Two months after commencing monthly intravenous pulsed cyclophosphamide, she reported marked improvement in GI symptoms, was able to walk and weight was maintained by oral nutrition alone.

DISCUSSION

Serological evaluation is a valuable adjunct to the diagnosis and management of autoimmune GI dysmotility. This newly recognized gastroenterological entity encompasses both paraneoplastic and idiopathic disorders.^{1–3, 5–7, 10} The defining autoantibody profile recognized to date comprises neuronal, endocrine and muscle-specific autoantibodies (Table 2). Nuclear transit, manometric and scintigraphic studies are essential to confirm the diagnosis. In common with most organ-specific autoimmune disorders, a majority (67%) of affected patients are female.

Factors that raise the clinical suspicion of AGID were noted in several patients of this report: an antecedent event, subacute onset, evidence of multi-level GI dysmotility, co-existing organ-specific autoimmune disorder (including subtle autonomic/neurological abnormalities, such as postural orthostatism or somatic neuropathy) or neoplasm. However 8% of the patients had no recognizable risk factors. More than 50% of the neoplasms identified were diagnosed in the course of oncological evaluation prompted by the autoantibody profile.

It is noteworthy that 4 patients with documented slow small intestinal transit carried an additional diagnosis of pelvic floor dyssynergia. Three of those patients had ganglionic AChR autoantibody (one with coexisting neuronal voltage-gated potassium channel autoantibody) and the fourth had neuronal N-type voltage-gated calcium channel autoantibody. This observation raises the possibility that at least some cases of pelvic floor dyssynergia may have an autoimmune neurological pathogenesis. These cases may reflect peripheral sphincteric neuromuscular hyperexcitability or impairment of central inhibitory interactions between sacral preganglionic neurons innervating the rectum and Onuf nucleus motor neurons innervating the pelvic floor. In normal conditions these circuits act in a coordinated fashion to control defecation.²³

The type 1 anti-neuronal nuclear autoantibody (ANNA-1, also known as “anti-Hu”) was the first serum autoantibody recognized as a marker of AGID.¹ Approximately 30% of patients with ANNA-1 autoimmunity have symptoms of GI dysmotility, as do approximately 20% of patients with the neuronal and glial cytoplasmic autoantibody, CRMP-5-IgG.²⁰ GI dysmotility is sometimes the sole manifestation of neurological paraneoplastic autoimmunity. Detection of ANNA-1 or CRMP-5-IgG mandates thorough cancer evaluation and long-term cancer surveillance because both are highly predictive of occult neoplasia (usually small-cell lung carcinoma; less often thymoma, Table 2).^{1, 5, 10, 20} Although first described in patients with

paraneoplastic pseudo-obstruction,¹ the most common GI presentation of ANNA-1 autoimmunity is one of subtle gastroparesis or slow transit constipation.⁵ Seropositive patients of young age often lack evidence of neoplasm,² however the finding of cervical intraepithelial neoplasia in our patient #21, and her remarkable response to pulse cyclophosphamide therapy, emphasizes the value of thorough oncological evaluation. We previously encountered an extrapulmonary small-cell carcinoma of the cervix in a young woman presenting with Lambert-Eaton syndrome.²⁴

The enteric nervous system of patients with paraneoplastic pseudo-obstruction is characteristically infiltrated with mononuclear inflammatory cells, predominantly T lymphocytes.^{1, 25} It has not been convincingly demonstrated that circulating autoantibodies specific for intracellular autoantigens (e.g. ANNA-1, CRMP-5 or muscle sarcomeric antigens) can access intracellular antigens *in vivo*. However, in more than 25% of cases, autoantibodies targeting intracellular antigens are accompanied by autoantibodies targeting plasma membrane cation channels,²⁶ which are known to have pathogenic potential. The only autoantibodies demonstrated to be pathogenic in the context of AGID thus far are those reactive with the neuronal nicotinic AChR of ganglionic type.^{9, 12} Additional cation channel autoantibodies encountered as accompaniments of AGID include neuronal voltage-gated calcium channel antibodies of N-type and P/Q-type,^{3, 13} neuronal voltage-gated potassium channel autoantibody,^{6, 10} and muscle AChR autoantibody.¹³ Here we report that organ-specific autoantibodies long recognized as markers of “thyrogastric” and “neurological” cluster disorders are additionally valuable as markers of AGID. These include antibodies specific for GAD65, gastric parietal cells, thyroid peroxidase, thyroglobulin, and contractile proteins of striated muscle.^{19, 21, 22} Associations with thyroid and autoimmune disorders and autoantibodies were the earliest clues that myasthenia gravis and the Lambert-Eaton myasthenic syndrome had an autoimmune basis.^{21, 27, 28} Our laboratory recently recognized a 22% frequency of GAD65 autoantibodies in patients with idiopathic achalasia, compared with 2.3% among 171 age-matched control subjects.⁸ It is noteworthy that 9 of the 24 patients of this report had one or more coexisting autoimmune disorders. We currently consider the profile of antibodies listed in Table 2 as most pertinent in the serological evaluation of patients in whom AGID is suspected.

Acknowledgments

The authors thank Drs. Michael Camilleri and Gianrico Farrugia for critically reviewing the manuscript.

Grant Support: Funding provided by the National Institute of Diabetes and Digestive and Kidney Diseases (DK68055).

Abbreviations

AChR	nicotinic acetylcholine receptor
AGID	autoimmune gastrointestinal dysmotility
ANNA-1	anti-neuronal nuclear autoantibody, type 1
GAD65	glutamic acid decarboxylase, 65 kD isoform
IA2	islet cell antigen 512 (putative tyrosine phosphatase), SCLC, small-cell lung carcinoma

VGCC

voltage-gated calcium channel

VGKC

voltage-gated potassium channel

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Table 1
Clinical and Serological Attributes of 24 Patients with AGID

	Sex/Age	Smoker	Documented Motility Abnormalities	Neurological Diagnoses	Cation Channel Autoantibodies	Other Autoantibodies & Autoimmune Disorders	Neoplasms identified
1	M/79	Yes	Achalasia	-	VGCC, P/Q- type	-	-
2	M/70	Yes	Achalasia	-	AChR, muscle- type	-	Prostatic adenocarcinoma; Chronic lymphocytic leukemia
3	M/78	Yes	Achalasia	Essential tremor	AChR, muscle- type	-	-
4	F/59	No	Achalasia	Orthostatic intolerance	VGCC, N-type	TPO; Hypothyroidism	Breast carcinoma
5	M/58	Yes	Achalasia	Tardive dyskinesia	AChR, ganglionic-type	-	Lung carcinoma, non-small-cell type
6	F/42	Yes	Achalasia; Delayed gastric emptying	Depression	AChR, ganglionic-type	Diabetes mellitus	-
7	F/68	No	Diffuse esophageal spasm	Anxiety; Fibromyalgia	AChR, ganglionic-type	Hypothyroidism	Lung nodule
8	M/79	No	Non-specific esophageal dysmotility	Myasthenia gravis	AChR, muscle- type; VGKC	CRMP-5; striational; Diabetes mellitus	-
9	F/78	No	Delayed gastric emptying	-	VGCC, N-type	TPO; Tg	Endometrial carcinoma; * Breast carcinoma *
10	M/67	No	Delayed gastric emptying	-	AChR, ganglionic-type	GAD65	Esophageal carcinoma *
11	M/17	No	Delayed gastric emptying	-	AChR, ganglionic-type	-	-
12	F/71	No	Delayed gastric emptying	-	AChR, muscle- type	Striational; Tg; Hypothyroidism; Discoid lupus	Thymoma
13	F/42	No	Delayed gastric emptying	Migraine	VGCC, N-type	-	-
14	F/23	No	Delayed gastric emptying	Small- and large-fiber sensory neuropathy; Chronic pain syndrome	VGCC, N-type	GAD65; IA-2; Diabetes mellitus	-
15	F/55	No	Delayed gastric emptying; Reduced gastric accommodation	Orthostatic hypotension; Global anhidrosis; Migraine; Anxiety; depression	AChR, ganglionic-type	-	-
16	M/76	Yes	Delayed gastric emptying; Slow SI transit	Orthostatic hypotension	None	ANNA-1	Lung carcinoma, small-cell type (limited- stage)
17	F/23	No	Delayed gastric emptying; Slow SI transit; Slow colonic transit; Pelvic floor dyssynergia	Anxiety; depression	AChR, ganglionic-type	GAD65; IA-2; Diabetes mellitus	-
18	F/66	Yes	Delayed gastric emptying; Slow SI transit; Slow colonic transit	Depression	AChR, ganglionic-type	TPO; Tg	Mediastinal/retroperitoneal lymphadenopathy
19	F/52	No	Delayed gastric emptying; Slow SI transit; Pelvic floor dyssynergia	-	AChR, ganglionic-type	GPC; TPO; Hypothyroidism;	-

	Sex/Age	Smoker	Documented Motility Abnormalities	Neurological Diagnoses	Cation Channel Autoantibodies	Other Autoantibodies & Autoimmune Disorders	Neoplasms identified
						Pernicious anemia; Raynaud's	
20	F/87	No	Slow SI transit	Trigeminal neuralgia; Orthostatic hypotension	AChR, ganglionic-type	GAD65; Impaired fasting glucose	Pancreatic mass
21	F/22	No	Slow SI transit	Sensory neuropathy	VGKC	ANNA-1	Cervical intraepithelial neoplasia (grade 2)
22	F/26	No	Slow SI transit; Slow colonic transit; Pelvic floor dyssynergia	Orthostatic intolerance; Small-fiber neuropathy	AChR, ganglionic-type; VGKC	-	-
23	F/20	No	Slow SI transit; Pelvic floor dyssynergia	-	VGCC, N-type	Raynaud's	-
24	F/37	No	Slow colonic transit	Cerebellar degeneration	VGKC	TPO	-

SI = small intestinal; AChR = nicotinic acetylcholine receptor; VGCC = neuronal voltage-gated calcium channel; VGKC = neuronal voltage-gated potassium channel; TPO = thyroid peroxidase; Tg = thyroglobulin; GAD65 = glutamic acid decarboxylase, 65kD isoform; ANNA-1 = anti-neuronal nuclear autoantibody, type 1; CRMP-5 = collapsin response-mediator protein-5; IA2 = islet cell antigen 512 (putative tyrosine phosphatase).

* Indicates tumor in remission for more than 2 years before onset of gastrointestinal symptoms.

Table 2
Serum autoantibodies with heightened prevalence in AGID patients

Autoantibody	Frequency in healthy adults (%)	Normal value
ANNA-1 [*] 1:5	0	Titer < 240
CRMP-5-IgG [*] 20	0	Titer <240
Ganglionic AChR [†]	<1	0.02nmol/L or less
Muscle AChR [†] 13	<2	0.02nmol/L or less
Striational [†] 13	<2	Titer <60
Voltage-gated calcium channel, N- type [†] 3, 13, 16	<2	0.03nmol/L or less
Voltage-gated calcium channel, P/Q- type [†] 3, 13, 16	<2	0.02nmol/L or less
Voltage-gated potassium channel [†] 6	<2	0.02nmol/L or less
GAD65 ⁸	2.3	0.02nmol/L or less
Gastric parietal cell	<2	Titer <240
Thyroperoxidase, thyroglobulin ⁸	11	Titer <100

^{*} Most predictive of small-cell lung carcinoma or thymoma. 1, 5, 20

[†] Recognized with several organ-specific autoimmune disorders and with lung carcinomas (small-cell or non small-cell types) and other carcinomas (A. McKeon, D. Lachance, S.J. Pittock, V.A. Lennon, unpublished data).