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Enteric Autoantibodies and Gut Motility Disorders

Purna Kashyap, M.B.B.S^{a,b,d} and Gianrico Farrugia, M.D.^{a,b,c,d}

a Enteric NeuroScience Program, Mayo Clinic, Rochester, MN

b Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN

c Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN

d Miles and Shirley Fiterman Center for Digestive Diseases, Mayo Clinic, Rochester, MN

Abstract

There is increasing evidence that a subset of gastrointestinal motility disorders is associated with the presence of circulating antibodies. These antibodies are directed against various molecular targets, the best known being anti-neuronal nuclear antibody (ANNA-1, aka anti-Hu) associated with paraneoplastic motility disorders. There is also evidence that the presence of distinct auto-antibody profiles is associated with non-paraneoplastic motility disorders. This review will focus on the types of antibodies associated with gastrointestinal motility disorders and the significance of these antibodies. The review will also suggest algorithms for the work up and treatment of patients with circulating antibodies associated with gastrointestinal motility disorders

Keywords

Enteric autoantibodies; paraneoplastic; pseudoobstruction; achalasia; ganglionitis; ANNA-1

Antibodies associated with paraneoplastic and idiopathic dysmotility

ANNA-1 (anti-Hu)

A small proportion of patients with occult or established neoplasms develop a gastrointestinal motility disorder, referred to as paraneoplastic dysmotility. The diagnosis of a paraneoplastic dysmotility requires the onset of gastrointestinal dysmotility associated with the presence of a tumor and presence of specific serum antibodies. In patients with paraneoplastic gastrointestinal dysmotility, a humoral immune response involving circulating anti-neuronal antibodies is commonly seen. The exact mechanism by which these antibodies are generated is unclear. They are known to target onconeural antigens shared by enteric neurons and tumor cells suggesting that the antibody was generated against the tumor antigen with the enteric neuron as the 'innocent' bystander [1]. The antigens for these antibodies may be localized to the nucleus, plasma membrane or the cytoplasm. The most common neuronal autoantibody associated with a paraneoplastic dysmotility is the type 1 antineuronal nuclear antibody (ANNA-1) [1,2]. ANNA-1 recognizes the nuclear protein Hu which belongs to a family of conserved RNA binding proteins that includes HuC, HuD, HuR and Hel-N1. These proteins

Corresponding Author: Gianrico Farrugia, M.D., Mayo Clinic, 200 First St. SW, Rochester, MN 55905, phone: (507) 284-4695, fax: (507) 284-0266, email: farrugia.gianrico@mayo.edu.

Co-authors addresses: Purna Kashyap M.B.B.S, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, Phone: (507)266-4347, Fax: 507-266-0266, Email: kashyap.purna@mayo.edu

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are expressed in the neurons of the central, peripheral and enteric nervous system, with the exception of HuR which is ubiquitously expressed in proliferating cells [3]. The tumor that most commonly expresses ANNA-1 is small cell lung cancer [4]. Other tumors that may express ANNA-1 include breast, prostate, ovarian carcinomas and lymphomas [5]. Antibodies to ANNA-1 are consequently, most commonly found in patients with small cell lung cancer with associated paraneoplastic gastrointestinal dysmotility. Although there is a very strong association between the presence of ANNA-1 in the setting of a gastrointestinal motility disorder and the presence of an occult or manifest tumor, the exact mechanism by which ANNA-1 antibodies cause enteric neuronal dysfunction is still unclear as the proteins to which the antibody is directed are not expressed on the cell membrane. However, there is some evidence that the antibodies may directly influence motility. A preliminary study in guinea pig ileum suggested that anti-Hu antibodies impair the ascending excitatory reflex and therefore peristalsis. Enteric neuronal degeneration has also been reported in patients with paraneoplastic dysmotility as a possible pathogenetic mechanism [7]. Anti HuD positive sera from patients with paraneoplastic gut dysmotility disorder as well as commercial Anti HuD antibodies were shown to induce apoptosis in a human neuroblastoma cell line (SH-Sy5Y) as well as guinea pig cultured myenteric neurons. The authors further demonstrated that the apoptosis was dependent on mitochondria as evidenced by the specific activation of effector caspase 3 and the cytochrome c-dependent proapoptotic messenger apaf-1 [8]. Mitochondrial dysfunction leading to subsequent neuronal injury is well described and has also been implicated in dorsal root ganglion apoptosis in streptozocin- induced diabetes in rats [9]. Pardi et al described a patient with sudden onset of gastroparesis and small bowel dysfunction and the presence of high circulating levels of ANNA-1 [6]. This patient was subsequently found to have decreased and disorganized interstitial cells of Cajal networks and a small cell lung cancer expressing c-Kit, also expressed on interstitial cells of Cajal.

Another nuclear autoantigen associated with disease is Ri, expressed in neurons of the central nervous system, small cell lung cancer and some breast cancer cells [10]. Formation of type 2 anti neuronal nuclear antibodies (ANNA-2 or anti-Ri) is far less common than anti Hu and is usually associated with neurological symptoms from midbrain, brain stem, cerebellar or spinal cord dysfunction [11]. ANNA-2 has not been associated with gastrointestinal dysmotility.

Calcium channel antibodies

The second most commonly reported antibodies in patients with paraneoplastic dysmotility target voltage-activated calcium channels. Calcium channels were originally classified based on pharmacology as L, N, P/Q, R, and T channels, a classification still used today. This nomenclature corresponds to the current accepted nomenclature that classifies voltage-gated Ca^{2+} channels into $\text{Ca}_v1.1$ - $\text{Ca}_v1.4$ (L-type Ca^{2+} channels), $\text{Ca}_v2.1$ (P/Q), $\text{Ca}_v2.2$ (N), $\text{Ca}_v2.3$ (R), and $\text{Ca}_v3.1$ - $\text{Ca}_v3.3$ (T) based on the amino acid sequence of the alpha 1 subunit (the pore forming subunit) of the channel. P or Q type calcium ion channels regulate acetylcholine release at the neuromuscular junction as well as central neurotransmission. N type calcium channels are particularly involved in cerebrocortical, cerebellar, spinal and autonomic neurotransmission. Both channel types are expressed in small cell lung cancer and are common targets of autoantibodies in such patients. These antibodies are predominantly seen in patients with Lambert Eaton myasthenic syndrome in association with small cell lung cancer [12]. Antibodies to P/Q and N type calcium channels are found in some patients with paraneoplastic dysmotility and their presence should trigger a targeted search for an occult malignancy (see below). However, these antibodies are less frequently found compared to ANNA-1 antibodies and their association with the eventual finding of a malignancy in the setting of a gastrointestinal motility disorder is not as strong as ANNA-1. These antibodies may coexist with ANNA-1

Nicotinic acetylcholine receptors

Another class of autoantibodies associated with gastrointestinal dysmotility is antibodies against neuronal nicotinic acetylcholine receptors. Antibodies directed towards the extracellular segment of acetylcholine receptor protein in the post synaptic membrane of skeletal muscle are found in patients with myasthenia gravis associated with thymic epithelial tumors [13]. Neuronal nicotinic acetylcholine receptors are also present on neurons in the sympathetic and parasympathetic nervous systems as well as the enteric nervous system. Antibodies targeting this protein can disrupt cholinergic synaptic transmission leading to autonomic failure. These antibodies are seen in both idiopathic and paraneoplastic forms of autonomic neuropathy resulting in autoimmune autonomic neuropathy [14]. Patients with ganglionic receptor blocking antibodies often manifest with symptoms of gastrointestinal dysmotility, abnormal pupillary response and subacute onset of autonomic neuropathy [15]. This antibody is of use to differentiate autoimmune autonomic neuropathy from degenerative autonomic neuropathy which is often more insidious and not usually associated with gastrointestinal manifestations. It is important to make this distinction as the diagnosis affects both prognosis and therapy. Degenerative autonomic neuropathy is a slowly progressive disorder while autoimmune autonomic neuropathy can be life threatening and often responds to therapy such as immunomodulators [15]. Neuronal nicotinic acetylcholine receptor antibodies are likely directly pathogenic as their levels correspond to the severity of autonomic dysfunction and decrease in their level is accompanied by clinical improvement [15]. Also, symptoms of autonomic failure can be induced experimentally by passive transfer of antibodies. Mice injected with rabbit IgG containing ganglionic acetylcholine receptor antibodies develop gastrointestinal dysmotility and autonomic dysfunction. Similar results are obtained by injecting mice with sera from patients with ganglionic acetylcholine receptor antibody [16].

Purkinje Cell Cytoplasmic Autoantibody, type 1 (PCA1)

This autoantibody (sometimes called “anti-Yo”) targets a neuronal signal transduction protein Cdr. The antibody was originally defined as a marker of paraneoplastic cerebellar degeneration related to ovarian or breast carcinoma with remarkably limited metastasis [17,18]. In vitro, its Cdr antigen, a prominent cytoplasmic component of large neurons in the central and autonomic/enteric nervous systems [19], has been shown to promote neuronal apoptosis and degeneration by inhibiting c-myc transcriptional activity [20]. Paraneoplastic gastrointestinal dysmotility has been documented in a minority of PCA-1 seropositive patients (with and without cerebellar ataxia) in association with gynecological or breast carcinoma [21].

Other autoantibodies

Antibodies have also been detected against other cytoplasmic antigens such as amphiphysin, present on the cytoplasmic side of the synaptic vesicle membrane [22]. Antistriational autoantibody targets the skeletal muscle proteins actinin, alpha actin, myosin, titin and ryanodine receptor [23,24]. They may be seen in patients with myasthenia gravis associated with thymoma [25] and paraneoplastic neurologic disorders with primary lung cancer but are usually not associated with gastrointestinal dysmotility [13]. Voltage-gated potassium channel autoantibodies have been reported in rare patients with slow transit constipation [26] and in a patient with diarrhea predominant irritable bowel syndrome [27]. Their significance is currently unknown. Likewise, glutamic acid decarboxylase-65 (GAD) antibodies have been reported in a significant percentage of patients with achalasia but again this finding is currently of uncertain pathogenetic significance [28].

Clinical presentation of a paraneoplastic dysmotility syndrome

Paraneoplastic dysmotility of the gastrointestinal tract is often manifested as esophageal dysmotility (pseudoachalasia), gastroparesis, intestinal pseudoobstruction or constipation. Patients frequently present with a dominant symptom but often have pan-gut involvement. In patients who have had a full thickness biopsy, all have an inflammatory lymphocytic and plasma cell infiltrate of the myenteric plexus as well as loss of ganglion cells. The smooth muscle layers are often spared [29–31].

Pseudoachalasia

Pseudoachalasia accounts for about 2–4% of all cases that have the manometric criteria of incomplete or absent relaxation of the lower esophageal sphincter seen in true achalasia. The majority of the patients with pseudoachalasia have a primary tumor at the gastroesophageal junction [32,33]. This form of pseudoachalasia is not a form of paraneoplastic dysmotility as it is usually due to obstruction of the lower esophageal sphincter by the tumor or direct involvement of myenteric plexus with the neoplastic cells. However, depletion of ganglion cells in the dorsal nucleus of the vagus nerve as a consequence of neuronal degeneration distant to primary tumor can also occur [34]. In a small proportion of patients there is no evidence of neoplastic involvement of the gastroesophageal junction but they demonstrate antineuronal antibodies, most often ANNA 1 [35,36]. Liu et al described a case series of 13 patients with pseudoachalasia in which 8 patients had direct infiltration of the esophageal wall and involvement of the myenteric plexus. The total number of ganglion cells was normal and it is unclear how the neoplastic cells altered ganglion cell function. In the same series they described a patient with small cell lung cancer and lymph node metastasis with achalasia-like symptoms but no radiographic or histological involvement of the esophagogastric junction. The patient had ANNA-1 antibodies suggesting a paraneoplastic dysmotility. Histologically there was complete absence of myenteric ganglion cells and both perineural and intraneural lymphocytic infiltration [36]. Lee et al published a series of 12 cases of which esophageal dysmotility was seen in 4 patients with small cell lung cancer. Two patients had pseudoachalasia, one had a non specific esophageal motility disorder and one patient had abnormal manometry but no esophageal symptoms [21].

Paraneoplastic Gastroparesis

Gastroparesis is characterized by reduced emptying of gastric content, often associated with decreased gastric motility. The presentation of gastroparesis often includes nausea, vomiting of food consumed several hours earlier, bloating, epigastric fullness and the finding of retained gastric contents on endoscopy. Gastroparesis was reported to be the most common paraneoplastic syndrome associated with ANNA-1 antibodies by Lucchinetti et al. [5]. As other paraneoplastic gastrointestinal dysmotilities, paraneoplastic gastroparesis is commonly associated with small cell lung cancer [48]. However, paraneoplastic gastroparesis has also been reported in association with other tumors including pancreatic cancer with no other identifiable cause [49,50]. It has also been described in a patient with untreated breast cancer which improved with cisapride and chemotherapy and resulting tumor remission [51]. It is not possible to conclude whether the patient's symptoms improved with the prokinetic or treatment of the underlying tumor but it is more than likely that a paraneoplastic dysmotility responds to treatment of the underlying tumor. Gastroparesis has also been reported in a patient with retroperitoneal leiomyosarcoma with no evidence of local invasion or metastasis and resolved completely after resection of the tumor [52]. As described above, Pardi et al reported a patient with small cell lung cancer with both ANNA 1 and P/Q type calcium channel antibody with gastroparesis and a disrupted interstitial cell of Cajal (ICC) network suggesting that enteric neurons are not the only enteric neural target of the paraneoplastic autoimmunity [6]. Gastroparesis has also been associated with other auto antibodies including ganglionic

acetylcholine receptor antibodies. This finding was observed by Vernino et al in a patient with bladder cancer and also in cases with idiopathic gastroparesis with no known antecedent risk factors and no underlying cancer [15]. These observations also strongly suggest that the histological nature of the underlying malignancy does not always dictate a certain autoantibody formation or specific dysmotility syndromes.

Paraneoplastic chronic intestinal pseudoobstruction

Chronic intestinal pseudoobstruction is defined as recurrent episodes or persistent symptoms of bowel obstruction in the absence of mechanical obstruction. Most cases of chronic intestinal pseudoobstruction are due to primary defects in the contractile apparatus (nerves, interstitial cells of Cajal, smooth muscle cells) of the gut or secondary to an infiltrating disease such as amyloidosis or scleroderma [37–39]. Paraneoplastic intestinal pseudoobstruction is most often reported in cases with small cell lung cancer and thymoma and is usually associated with the presence of circulating ANNA-1 antibodies [40–44]. Though most often seen in the setting of either small cell lung cancer or thymoma, there have been several case reports of patients with pseudo-obstruction with other primary cancers. Chronic intestinal pseudoobstruction along with achalasia, gastroparesis and constipation was reported in a patient with metastasizing bronchial carcinoid [45]. Intestinal pseudoobstruction associated with lymphoplasmacytic infiltration of the myenteric plexus and presence of ANNA-1 antibodies was found in a patient about one and a half years after removal of paravertebral ganglioneuroblastoma [46]. Viallard et al reported a case of colonic dysmotility associated with antibodies against voltage gated potassium channels in a patient with invasive thymoma and acquired neuromyotonia, which improved after plasmapheresis [47].

As discussed above, Lee et al published a case series of 12 patients in which chronic intestinal dysmotility and acute colonic pseudoobstruction was observed in patients with cancer and either ANNA 1, PCA-1 or anti-N type calcium channel antibodies. All patients with small cell lung cancer had ANNA-1 antibodies, a patient with ovarian cancer was positive for PCA-1 antibody and a patient with lymphoma had N type calcium channel antibody. Histologically, the ANNA-1 antibodies in these patients were reactive with both nucleus and cytoplasm as opposed to cases of idiopathic colonic pseudoobstruction where a predominant cytoplasmic staining has been observed. Interestingly, in this study, the authors observed that the gastrointestinal dysmotility preceded the small cell lung cancer by a mean period of 8.7 months while in other malignancies antibodies were found after the tumor diagnosis. These data suggest that the diagnosis of new onset gut dysmotility accompanied by the presence of ANNA-1 antibodies should prompt a search for an occult small cell lung cancer. Even if the initial screen is negative vigilance should be maintained in the subsequent years. The authors also observed that the patients with colonic pseudoobstruction and small cell lung cancer often have additional disease, including peripheral, sensorimotor or autonomic neuropathies, cerebellar degeneration or encephalopathy [21].

Chronic constipation

Chronic constipation without accompanying pseudoobstruction is not a common presentation of a paraneoplastic syndrome. As described above, Vernino et al reported constipation in two patients with ganglionic acetylcholine receptor antibody associated with thymoma and small cell lung cancer [15].

Management algorithm for paraneoplastic dysmotility

There currently is insufficient evidence to recommend a paraneoplastic antibody profile on every patient with new onset of a gut motility disorder. However, the presence of significant weight loss, a rapid onset of the disease, a past or present smoking history should prompt the

physician to consider testing for the presence of autoantibodies associated with paraneoplastic dysmotility. Several laboratories offer a paraneoplastic autoantibody profile. In patients testing positive for ANNA-1, together with the appropriate gastrointestinal motility work up including a work up to exclude obstruction, investigations should be initiated to look for small cell lung cancer as paraneoplastic dysmotility may precede the diagnosis of the primary malignancy in patients testing positive for ANNA-1 [21]. A reasonable strategy is to start with a CT chest and if negative follow up with a PET scan and directed biopsies of any suspicious lymph nodes or masses if indicated. In a subset of patients with a very high suspicion of malignancy, if the workup is negative one may consider bronchoscopy followed by mediastinoscopy to increase the diagnostic yield. An alternative strategy is to repeat the CT chest at 6 month intervals for at least 1 year. Importantly, finding an alternate primary malignancy should not stop the search for possible small cell lung cancer as in nearly 13% patients an unrelated primary malignancy co-exists with small cell lung cancer, the most common being renal cell cancer[5].

The presence of other autoantibodies without concomitant ANNA-1 positivity is less likely to predict the presence of a malignancy. It is at present unclear what strategy to use in this situation. Our current management algorithm, not evidence based, is to obtain a CT of the chest and if negative to repeat once in 6 months.

Treatment of paraneoplastic dysmotility

The diagnosis of a paraneoplastic dysmotility is unfortunately associated with a bad outcome, death often occurring within 6 months of the diagnosis, usually from the underlying malignancy but accelerated by difficulties in maintaining nutrition. There are no effective treatments available for paraneoplastic dysmotility. Several treatments have been investigated including immunosuppressive therapy with steroids and cyclophosphamide, plasmapheresis and IV immunoglobulin but none have been convincingly shown to alter outcome [5,53]. The mainstay of treatment is treatment of the underlying primary malignancy. It is important to provide supportive care including nutritional support either enterally or parenterally, adequate hydration, use of prokinetics to promote motility and treatment of complications such as bacterial overgrowth. One additional management strategy is to use high dose IV steroids for 3 days and if there is a clinical response switch to 6-mercaptopurine or azathioprine, however this approach often needs to be aborted due to the need for chemotherapy.

Clinical presentation of a non-paraneoplastic dysmotility syndrome associated with circulating antibodies

Achalasia

Idiopathic achalasia is a relatively common esophageal motility disorder (1:100,000) characterized by ineffective peristalsis and an abnormal relaxation of the lower esophageal sphincter [54]. A consistent finding in idiopathic achalasia is loss of nitrergic neurons with a relative preservation of cholinergic neurons [55–57]. As the disease progresses, the enteric neuronal loss becomes more generalized. Most studies that have reported on biopsy specimens taken from patients with relatively early disease have shown the presence of an inflammatory infiltrate in the myenteric plexus. This infiltrate is predominantly due to CD 3 positive T cells suggesting an underlying immune-mediated process [58–60]. The serum from patients with achalasia often contains anti-neuronal antibodies. However, studies on their role in causation of disease have been inconclusive as similar antibodies are also present in patients with gastroesophageal reflux disease. Moses et al collected sera from 45 patients with achalasia and 16 with gastroesophageal reflux disease as well as from healthy controls and demonstrated that the sera from both the achalasia patient and the GERD patient labeled myenteric neurons in the esophagus as well as the ileum and submucosal plexus neurons in guinea pig and mice with

rare labeling of the spinal neurons. Based on these findings the authors felt that the presence of anti-neuronal autoantibodies was likely secondary to tissue damage and not involved in the pathogenesis of achalasia [61]. A recent study, at present reported only in abstract form, suggests that the 60% of patients with primary idiopathic achalasia have circulating anti-GAD-65 antibodies. Like ANNA-1, GAD-65 is not a membrane protein and it is therefore unclear what role the antibodies play in the pathophysiology of the disease [28].

Chronic intestinal pseudoobstruction

As discussed above, chronic intestinal pseudoobstruction can be divided into primary chronic intestinal pseudoobstruction and secondary chronic intestinal pseudoobstruction, the latter a consequence of an underlying condition such as amyloidosis, scleroderma and a variety of other systemic disorders. Primary chronic intestinal pseudoobstruction may be due to genetic defects affecting the contractile apparatus but often it is idiopathic with no identifiable cause detected. Antineuronal antibodies are detected in some patients with idiopathic chronic intestinal pseudoobstruction suggesting a possible cause. Antibodies such as ANNA-1 usually indicate occult malignancy such as small cell carcinoma but some patients with autoantibodies do not have underlying malignancy. Intestinal dysmotility has been observed in patients with antibodies such as ganglionic acetylcholine receptor antibodies with no evidence of malignancy even on long term follow up [15]. They likely represent the idiopathic form of autoimmune autonomic neuropathy. Ganglionic acetylcholine receptor antibody has been associated with variable degree of autonomic failure and is one of the more common antibodies detected in patients with intestinal dysmotility. As described previously in a series of 25 patients with ganglionic receptor antibodies published by Vernino et al, at least 4 patients had constipation with no antecedent risk factors or malignancy [15]. Again as outlined previously, these antibodies are likely pathogenic as they cause disease when injected in animal models [16] and there was a positive correlation between antibody levels and degree of autonomic failure [15]. Smith et al described two patients with intestinal pseudoobstruction characterized histologically with acquired aganglionosis and a T cell infiltrate affecting the myenteric neurons. Their sera contained antineuronal IgG antibodies similar to anti Hu but demonstrated strong cytoplasmic staining rather than nuclear staining [31]. Neurogenic inflammatory chronic intestinal pseudoobstruction is being increasingly recognized in a small but distinct subset of patients with chronic intestinal pseudoobstruction who underwent a full thickness biopsy. The typical finding is a dense plasma cell and lymphocytic infiltrate in and around the ganglia. The identity of the lymphocytic infiltrate (CD3 positive and both CD4 and CD8 positive cells) suggests a T-cell mediated injury to the ganglionic cells, although B-cells have also been reported [37,38]. Myenteric ganglia are invariably involved however submucosal ganglia may also sometimes be involved.

Management of dysmotility associated with antibodies of likely pathogenic importance

Treatment needs to be directed both towards managing the disorder as well as attempting to intervene in the immune-mediated process. Intestinal dysmotility is often associated with complications such as bacterial overgrowth and malabsorption. These need to be treated appropriately. The treatment of the primary disorder is often difficult and requires the judicious use of available medications including prokinetics. The most benefit among patients with idiopathic myenteric ganglionitis with intestinal dysmotility has been shown with use of immunosuppressive therapy such as steroids either alone or in conjunction with azathioprine or cyclophosphamide. Steroids that have been used in varying doses and tapers include prednisolone, methylprednisolone and beclomethasone. A female patient with chronic intestinal pseudoobstruction with underlying lymphoid infiltrate in the myenteric plexus showed mild improvement in symptoms with prednisone and cyclophosphamide [62]. A young

male with idiopathic myenteric ganglionitis and intractable vomiting failed therapy with prokinetics, but responded to a steroid taper starting at 60mg/day methylprednisolone with sustained response at one year [29]. As described above, Smith et al published a series of two patients with chronic pseudoobstruction and IgG autoantibodies directed against enteric neurons, one patient improved with a trial of prednisolone used in a dose of 10mg/day and relapsed on discontinuation of the steroid. The other was treated initially with prednisolone 2mg/kg for four weeks and reduced to 0.5mg/kg every other day allowing the introduction of enteral feeds [31]. This patient did poorly in the long term requiring intestinal transplantation. De Giorgio et al described a patient with intestinal subocclusion and the presence of anti Hu (ANNA-1) antibodies who responded well to pulse dose steroids (100mg IV methylprednisolone for 3 days) [63]. Schäpi et al described three patients with predominantly eosinophilic myenteric ganglionitis and good response to either oral beclomethasone, prednisolone 60mg/day with azathioprine or high dose intravenous prednisolone [64]. Treatment with steroids often has to be tailored to individuals. One approach is to either attempt a short course of pulse steroids such as intravenous methylprednisolone or start with oral steroids in a dose of 60mg/day and taper over the next 4–6 weeks. If symptoms relapse after discontinuation, steroids should be reinstituted and a slower taper attempted. At this time it would also be reasonable to consider immunomodulator therapy such as azathioprine starting at a dose of 2mg/kg. Plasmapheresis may be beneficial in patients with ganglionic receptor antibodies who often show improvement with decrease in titers of the antibodies. Acetylcholinesterase inhibitors such as neostigmine [65] and pyridostigmine have been used successfully to treat intestinal dysmotility. Pasha et al described a patient with idiopathic gastroparesis associated with N type calcium channel antibody and ganglionic acetylcholine receptor antibody who responded to treatment with pyridostigmine in spite of a 15 year history of gastrointestinal symptoms [66]. Gastrointestinal motility tests such as gastroduodenal manometry and colonic motility testing with combined with administration of neostigmine may help with making the decision to pursue pyridostigmine therapy.

A significant problem in the diagnosis and treatment of dysmotility attributed to an auto-immune cause is the lack of a well defined way to assess the degree of inflammatory infiltrate and the response to therapy. We are currently limited to surgery, be it open or laparoscopic to obtain full thickness gut wall biopsies. This requirement significantly limits our ability to repeatedly obtain tissue and make informed decisions on the need for immunosuppression as well as the duration of immunosuppression or of other therapeutic modalities. A significant advance in the field will be the introduction of endoscopic methodology to obtain full thickness biopsies. This will allow not only the determination of utility of current approaches but also studies to determine the potential role, inflammation and autoimmunity may play in the pathophysiology of a wide variety of gastrointestinal disorders currently not thought to be immune mediated.

Summary

There is increasing evidence for an immune-mediated role in the pathogenesis of a number of gastrointestinal motility disorders. The role of autoantibodies in paraneoplastic dysmotility is now well established and the role of autoantibodies in a subset of patients with non-paraneoplastic gastrointestinal dysmotility is being recognized and the antibodies characterized. It is hoped that a better understanding of the role of autoimmunity and the specific antibodies involved, coupled with the development of less invasive techniques to obtain tissue or the development of better biomarkers, will lead to earlier diagnosis and targeted treatment with appropriate immunosuppressant therapy.

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