Invited Review

Epstein-Barr virus infection and gastrointestinal diseases

E. Paraskevas, D. Dimitroulopoulos

SUMMARY

Epstein-Barr is a member of the herpesvirus family that infects more than 90% of the world's population. Although primary infection typically occurs within the first few years of life or in adolescence and is generally asymptomatic or results in infectious mononucleosis respectively, in some cases the virus is implicated with the development of a large spectrum of gastrointestinal malignant and benign diseases.

Thus, Epstein-Barr virus is strongly involved in the pathogenesis of non-Hodgkin's lymphomas and is associated also with some cases of Hodgkin's disease, Burkitt's lymphoma, gastric and esophageal cancer and rarely with some benign gastrointestinal diseases.

Key words: Epstein-Barr virus, non-Hodgkin's lymphomas, Hodgkin's disease, Burkitt's lymphoma, gastric cancer, esophageal cancer, esophagitis, gastritis, inflammatory bowel disease.

INTRODUCTION

Epstein-Barr (EBV) is a member of the herpesvirus family with a 184-kbp long, double-stranded DNA genome that encodes more than 85 genes.[1] As with other herpesviruses, EBV is an enveloped virus that contains a DNA core surrounded by an icosahedral nucleocapsid and a tegument.

It is known that EBV infects more than 90% of the world's adult population. Upon infection, the individual remains a life-long carrier of the virus.[2] EBV is transmitted by salivary contact. During acute infection, EBV primarily infects and replicates in the stratified squamous epithelium of the oropharynx.[3,4] This is followed by a latent infection of the B lymphocytes (although the sequence of epithelial versus lymphoid infection is a matter of debate). EBV infection of B lymphocytes is thought to occur in the oropharyngeal lymphoid organs, and in normal carriers, the virus persists in circulating memory B cells.[5-7] The B-lymphotropic nature of EBV is evidenced by the ability of the virus to immortalize normal resting B lymphocytes in vitro, converting them into permanently growing lymphoblastoid cell lines.[8] Of interest, once the virus has colonized the B-lymphoid compartment, reactivation from latency can occur at any mucosal site where B cells reside.

Primary infection with EBV typically occurs within the first few years of life and is generally asymptomatic in most undeveloped countries. In more developed areas, primary infection can be delayed until late adolescence or adulthood and results in infectious mononucleosis in some cases.[9] Long-term EBV coexists with most human hosts without overt serious consequences. However, in some individuals, the virus is implicated in the development of malignancy.

Gastrointestinal lymphomas

1. Non-Hodgkin's Lymphomas (NHLs): NHLs were originally defined as neoplastic equivalents of reactions usually occurring in lymphoid tissue after antigenic stimulation.[10] Several studies have shown that tissue-restricted lymphocytes from gut, skin and lymph nodes show preferential homing to their site of origin.[11-13] Thus, lymphocytes from the gut preferentially home to gut.[14]

Although organ-specific homing receptors play a role in organ-specific homing, the molecular basis of these differential homing patterns is not yet completely understood. Extending the concept of NHLs with this aspect of tissue restriction of lymphocytes, extranodal lymphomas can be considered as neoplastic equivalents of im-

Gastroenterology Unit, "Saint Savvas" Cancer Hospital, Athens, Greece

Author for correspondence:

D. Dimitroulopoulos, Parnassou 35, GR 152 34 Halandri, Athens-Greece, Tel. 003010-6892460, e-mail: dimdim@otenet.gr

munological reactions involving tissue restricted lymphocytes.

Three populations of tissue restricted T lymphocytes have been recognized: mucosa-associated, cutaneous and nodal T lymphocytes.

T-cell lymphomas of nodal origin have been associated with the presence of EBV.[15-17] A possible involvement of the virus in the pathogenesis of extranodal T-cell lymphomas is still under investigation.

T-cell extranodal lymphoma cases from different sites, i.e., the nasal cavity, gastrointestinal tract, lung and skin were investigated using several methods (polymerase chain reaction, RNA in situ hybridization, immunohistochemistry, etc) for the presence of EBV, but the results are controversial.

EBV-associated primary gastrointestinal T-cell lymphomas seem to be rare in nonimmunocompromised patients.

In the body of literature there are some case reports[18-24] and few studies[25-32] that report detection of EBV genome with a rate ranging between 6% and 14%.

Primary small intestine T-cell lymphomas account for about 5% of all primary gastrointestinal lymphomas and are mostly associated with celiac disease.[22] A considerable number (36%) of enteropathy-associated T-cell lymphoma cases were reported to be EBV-positive (33). EBV genome was detected also in some cases of colorectal T-cell lymphomas[19,28] and in some cases of gastric B-cell lymphomas.[28,30]

The major presenting symptoms in the cases reported above included fever, weight loss, malabsorption, coffee-ground vomitus, diarrhea, tarry stool, gastrointestinal bleeding and intestinal perforation.[18,20,24]

Although no data were given about race or geographical origin of the patients, the vast majority of these studies are from Korea, Japan and Netherlands.[27,27-32]

Based on these data, the presence of EBV in only a subpopulation of cells suggests that the infection is secondary to malignancy or that the viral genome has been lost from the malignant cell. Additionally, the presence of EBV-positive B-cells in peripheral T-cell lymphomas[34] raises questions about the possible activation of EBV in latently infected B cells by neoplastic T cells and/or the role of the EBV-positive B cells in maintaining the malignant T cell process.[35,36]

2. Hodgkin's Disease (H.D.): Although EBV positivity in HD is extremely high in some geographical areas the role that the virus plays in their pathogenesis is still not fully understood.[37]

On the other hand, gastrointestinal involvement is an extremely rare event in HD and might occur as infiltration from mesenteric lymph nodes.[38] Initial symptoms limited to extranodal tissue are more rare in HD than in NHLs, and only few cases have been described with EBV positive primary gastrointestinal HD. All these cases were associated also with Crohn's disease and immunosuppression.[39,40]

3. Burkitt's Lymphoma: Burkitt's lymphoma is a B cell lymphoma composed of monomorphic, medium-sized cells with basophilic cytoplasm and a high proliferation fraction, characterized by translocation and deregulation of the c-myc gene on chromosome 8, which is often extranodal and occurs most often in children and immunocompromised hosts.

Three distinct clinical forms of Burkitt's lymphoma can be recognized: endemic, sporadic and immunodeficiency associated.[41] In sporadic form the distal ileum, cecum, mesentery or both cecum and mesentery are often involved.

Patients typically present with rapidly growing tumor masses and often have a high serum LDH. Burkitt's lymphoma is highly aggressive but potentially curable with aggressive therapy.[42]

Gastrointestinal cancer

1. Gastric adenocarcinoma: EBV presence varies from more than 90% in lymphoepigastric adenocarcinomas (44-55). Whether EBV plays a pathogenic role in either of these two tumors is still unclear.[45-52]

Given the morphological similarities between lymphoepithelioma-like gastric carcinoma and undifferentiated nasopharyngeal carcinomas, it has been proposed that in lymphoepithelioma-like gastric carcinoma, EBV spreads from the nasopharynx to the stomach.[54,55] In regard to gastric adenocarcinomas, EBV may enter the gastric epithelium without the use of a receptor. It has been suggested that this is accomplished by the binding of IgA antibody with EBV particles derived from B lymphocytes and the uptake of these particles by gastric epithelial cells.[59] Alternatively, EBV may enter the gastric epithelial cells via a receptor other than the CD21 receptor.[56]

EBV exhibits a novel latency pattern in gastric adenocarcinomas that includes the production of BARF-1, a

homologue to human colony-stimulating factor 1 receptor and intracellular adhesion molecule 1, and the absence of LMP-1.[57-60] Although any mechanism relating EBV to tumorigenesis in gastric malignancies remains highly speculative, it has been demonstrated that there is a delay in apoptosis in EBV-positive gastric carcinomas and a decrease in cellular differentiation.[55,60]

2. Esophageal cancer: The etiology and pathogenesis of esophageal cancer (adenocarcinoma and squamous cell carcinoma) is thought to involve a combination of genetic and environmental events which lead to epithelial cell transformation.

A possible association of EBV with undifferentiated esophageal cancer with a lymphoid stroma, just as it is associated with nasopharyngeal lymphoepithelioma, has been proposed.[61] However, reports concerning a possible relationship between EBV and esophageal cancer are few. Although in some studies a possible association is reported with a detection rate ranging between 6% and 36%, further studies are required to establish the implication or not of EBV in esophageal carcinogenesis.[61-66]

Other Gastrointestinal Diseases

Although EBV is associated with esophagitis and esophageal ulcers, in some cases with AIDS or AIDS-related complex,[67,68] there are no reports for a possible association of EBV with esophageal diseases in non-immunocompromised individuals.

The association of EBV with a proportion of gastric carcinomas is well established. The role of EBV in conditions predisposing to carcinoma such as chronic gastritis has remained undefined, however. The vast majority of the performed studies argue against a direct involvement of EBV in the pathogenesis of chronic gastritis.[69-71]

Little is known about EBV infection of colon mucosa, particularly in inflammatory bowel diseases. Crohn's disease and ulcerative colitis are though to differ in T-helper lymphocyte composition and cytokine secretion patterns. Some of the implicated cytokines are growth factors for EBV-infected cells.

A high detection rate of EBV-encoded small RNA1 (EBER-1) and EBV-DNA in inflammatory bowel disease tissue specimens have been reported[72,73] with the EBV positive lymphocytes accumulated under and within the epithelium.[74]

A possible association of EBV with some cases of gastroparesis and intestinal pseudo-obstruction has also been reported.[75-77]

REFERENCES

1. Kieff E, Rickinson AB. Epstein-Barr virus and its replication. In: B.N.Fields, D.M. Knipe, P.M.Howley (Eds), Fields Virology, Ed 4, Vol. 2, pp 2511-2575. Philadelphia, PA: Lippincott-Raven, 2001.
2. Henle G, Henle W. Seroepidemiology of the virus. In: M.A.Epstein and B.G.Achong (Eds), The Epstein-Barr Virus, pp 297-320. Berlin, Springer-Verlag, 1979.
3. Murray PG, Young LS. The role of the Epstein-Barr virus in human disease. Front Biosci 2002; 7d:519-540.
4. Sixbey JW, Nedrdud JG, Raab-Traub N et al. Epstein-Barr virus replication in oropharyngeal epithelial cells. N Engl J Med 1984; 310: 1225-1230.
5. Babcock GJ, Decker LL, Volk M et al. EBV persistence in memory B cells in vivo. Immunity 1998; 395-404.
6. Farrell PJ. Epstein-Barr virus immortalizing genes. Trends Microbiol 1995; 3: 105-109.
7. Gerber P, Lucas S, Nonoyama M et al. Oral excretion of Epstein-Barr viruses by healthy subjects and patients with infectious mononucleosis. Lancet 1972; 2:988-989.
8. Nilsson K. Human B-lymphoid cell lines. Human Cell 1992; 5: 25-41.
9. Henle G, Henle W, Diehl V. Relation of Burkitt's tumor-associated herpers-type virus to infectious mononucleosis. Proc Natl Acad Sci USA 1968; 59: 94-101.
10. Mann RB, Jaffe ES, Berard CW. Malignant lymphomas-A conceptual understanding of morphologic diversity. Am J Pathol 1979; 94: 105-191.
11. Cerf-Benussan N, Jarry A, Brousse N et al. A monoclonal antibody (HML-1) defining a novel membrane molecule present on human intestinal lymphocytes. Eur J Immunol 1987; 17: 1279-1285.
12. Picker LJ, Michie SA, Rott LS et al. A unique phenotype of skin-associated lymphocytes in human: Preferential expression of the HECA-452 epitope by benign and malignant T cells at cutaneous sites. Am J Pathol 1990; 136: 1053-1068.
13. Kishimoto TK, Jutila MA, Butcher EC. Identification of a human peripheral lymph node homing receptor: A rapidly down-regulated adhesion molecule. Proc Natl Acad Sci USA 1990; 87: 2244-2248.
14. Stein H, Dienemann D, Dallenbach F, et al. Peripheral T-cell lymphomas. Ann Oncol 1991; 2: 163-169.
15. Noorduyn LA, Beljaards RC, Pals ST, et al. Differential expression of the HECR-452 antigen (cutaneous lymphocyte associated antigen, CLA) in cutaneous and non-cutaneous T-cell lymphomas. Histopathology 1992; 21: 59-64.
16. de Bruin PC, Beljaard RC, vaan Heerde P, et al. Differences in clinical behavior and immunophenotype between primary cutaneous and primary nodal large cell anaplastic lymphoma of T cell of null cell phenotype. Histopathology 1993; 23: 127-135.
17. Herbst H, Dallenbach F, Hummel M, et al. Epstein-Barr virus DNA and latent gene products in Ki-1 (CD30)-positive anaplastic large cell lymphoma. Blood 1991; 98: 2666-2673.

18. Chim CS, Au WY, Shek TW, et al. Primary CD56 positive lymphomas of the gastrointestinal tract. Cancer 2001; 91: 525-533.
19. Hsiao CH, Kao HL, Liu MC, et al. Ulcerative colon T-cell lymphoma: an unusual entity mimicking Crohn's disease and may be associated with fulminant hemophagocytosis. Hepatogastroenterology 2002; 49: 950-954.
20. Chuang SS; Jung YC. Natural killer cell lymphoma of small intestine with features of enteropathy but lack of association with celiac disease. Hum Pathol 2004; 35: 639-642.
21. Losco A, Gianelli U, Cassani B et al. Epstein-Barr virus-associated lymphoma in Crohn's disease. Inflamm Bowel Dis 2004; 10: 425-429.
22. Lavergne A, Brocheriou I, Delfau MH, et al. Primary intestinal gamma-delta T-cell lymphoma with evidence of Epstein-Barr virus. Histopathology 1998; 32: 271-276.
23. Carey MJ, Medeiros LJ, Roepke JE, et al. Primary anaplastic large cell lymphoma of the small intestine. Am J Clin Pathol 1999; 112: 696-701.
24. Abe Y, Muta K, Ohshima K, et al. Cytotoxic T-cell lymphoma diffusely involving the entire gastrointestinal tract associated with Epstein-Barr virus and tubercle bacilli infection. Int J Hematol 2000; 71: 379-384.
25. Katoh A, Ohshima K, Kanda M, et al. Gastrointestinal T cell lymphoma: predominant cytotoxic phenotypes, including alpha/beta, gamma/delta T cell and natural killer cells. Leuk Lymphoma 2000; 39: 97-111.
26. Mitarnun W, Saechan V, Pradutkanchana J, et al. Epstein-Barr virus-associated peripheral T cell lymphoma with gastrointestinal tract involvement. J Med Assoc Thai 2003; 86: 816-828.
27. de Bruin PC, Jiwa NM, Oudejans JJ, et al. Epstein-Barr virus in primary gastrointestinal T cell lymphomas. Association with gluten-sensitive enteropathy, pathological features and immunophenotype. Am J Pathol 1995; 146: 861-869.
28. Futamura N, Nakamura S, Koshikawa T, et al. Association of Epstein-Barr virus with primary malignant lymphomas of the digestive tract. Nippon Shokakibyo Gakkai Zasshi 1996; 93: 322-330.
29. Tomita Y, Ohsawa M, Hashimoto M, et al. Plasmacytoma o the gastrointestinal tract in Korea: higher incidence than in Japan and Epstein-Barr virus association. Oncology 1998; 55: 27-32.
30. Yang WI, Cho MS, Tomita Y, et al. Epstein-Barr virus and gastrointestinal lymphomas in Korea. Yonsei Med J 1998; 39: 268-272.
31. Brink AA, ten Berge RL, van den Brule AJ, et al. Epstein-Barr virus is present in neoplastic cytotoxic T cells in extranodal and predominantly in B cells in nodal T non-Hodgkin lymphomas. J Pathol 2000; 191: 400-406.
32. de Bruin PC, Jiwa M, Oudejans JJ, et al. Presence of Epstein-Barr virus in extranodal T cell lymphomas : differences in relation to site. Blood 1994; 83: 1612-1618.
33. Pan L, Diss TC, Peng H, et al. Epstein-Barr virus (EBV) in enteropathy associated T cell lymphoma (EATL). J Pathol 1993; 170: 137-143.
34. Ho J, Ho F, Chan A, et al. Frequent detection of Epstein-Barr virus infected B cell in peripheral T cell lymphomas. J Pathol 1998; 185: 79-85.
35. Hojo I, Takanishi M, Hirai K et al. Increased number of Epstein-Barr virus latency infected B cells in T cell non-Hodgkin's lymphoma tissues. Arch Virol 1995; 140: 1419-1426.
36. Ho J, Liang R, Srivastava G. Differential cytokine expression in EBV positive peripheral T cell lymphomas. J Clin Pathol (Lond) 1999; 52: 269-274.
37. Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. Clin Cancer Res 2004; 10: 803-821.
38. Diehl V, Maugh PM, Harris NL. Hodgki'ns disease. In: V.T. DeVita, S. Hellman, S.A. Rosenberg (Eds). Cancer, Principles and Practice of Oncology, pp 2339-2387. Philadelphia, PA: Lippincott, Williams and Wilkins, 2001.
39. Kumar S, Fend F, Quintanilla-Martinez L, et al. Epstein-Barr virus-positive primary gastrointestinal Hodgkin's disease: association with inflammatory bowel disease and immunosuppression. Am J Surg Pathol 2000; 24: 66-73.
40. Li S, Borowitz MJ. Primary Epstein-Barr virus-associated Hodgkin disease of the ileum complicating Crohn disease. Arch Pathol Lab Med 2001; 125: 424-427.
41. Wright DH. What is Burkitt's lymphoma? J Pathol 1997; 182: 125-127.
42. Armitage JO, Maugh PM, Harris NL, et al. Non-Hodgkin's lymphoma. In : V.T.DeVita, S.Hellman, S.A. Rosenberg (Eds). Cancer, Principles and Practice of Oncology, pp 2256-2316. Philadelphia, PA: Lippincott, Williams and Wilkins, 2001.
43. Niedobitek G, Herbst H, Young L, et al. Epstein-Barr virus and carcinomas: expression of the viral genome in an undifferentiated gastric carcinoma. Diagn Mol Pathol 1992; 1: 103-108.
44. Oda K, Tamaru J, Takenouchi T, et al. Association of Epstein-Barr virus with gastric carcinoma with lymphoid stroma. Am J Pathol 1993; 143: 1063-1071.
45. Pittaluga S, Loke S, So K, et al. Clonal Epstein-Barr virus in lymphoepithelioma-like carcinoma of the stomach: demonstration of viral genome by in situ hybridization and southern blot analysis. Mod Pathol 1992; 5: 661-664.
46. Shibata D, Tokunaga M, Uemura Y, et al. Association of Epstein-Barr virus with undifferentiated gastric carcinomas with intense lymphoid infiltration. Am J Pathol 1991; 139: 469-474.
47. Shibata D, Weiss L. Epstein-Barr virus-associated gastric adenocarcinoma. Am J Pathol 1992; 140: 769-774.
48. Tokunaga M, Land C, Uemura Y, et al. Epstein-Barr virus in gastric carcinoma. Am J Pathol 1993; 143:1250-1254.
49. Imai S, Koizumi S, Sugiura M et al. Gastric carcinoma: monoclonal epithelial malignant cells expressing Epstein-Barr virus latent infection protein. Proc Natl Acad Sci USA 1994; 91: 9131-9135.
50. Fukuyama M, Hayashi Y, Iwasaki Y, et al. Epstein-Barr virus associated gastric adenocarcinoma and Epstein-Barr virus infection of the stomach. Lab Invest 1994; 71: 73-81.
51. Harn H, Chang J, Wang M, et al. Epstein-Barr virus-associated gastric adenocarcinoma in Taiwan. Hum Pathol

1995; 26:267-271.
52. Hsich LL, Lin PJ, Chen TC, et al. Frequency of Epstein-Barr virus-associated gastric adenocarcinomas in Taiwan. Cancer Lett 1998; 129: 125-129.
53. Galetsky S, Tsvetnov V, Land C, et al. Epstein-Barr virus-associated gastric cancer in Russia. Int J Cancer 1997; 73: 786-789.
54. Iezzoni J, Gaffey M, Weiss L. The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. Am J Clin Pathol 1995; 103: 308-315.
55. Wu MS, Shum CT, Wu CC, et al. Epstein-Barr virus-associated gastric carcinomas: relation to H.pylori infection and genetic alterations. Gastroenterology 2000; 118: 1031-1038.
56. Yoshiyama H, Imai S, Shimizu N, et al. Epstein-Barr virus infection of human gastric carcinoma cells: implication of the existence of a new virus receptor different from CD21. J Virol 1997; 71: 5688-5691.
57. Strockbine LD, Cohen JL, Farrah T, et al. The Epstein-Barr virus BARF1 gene encodes a novel, soluble colony-stimulating factor-1 receptor. J Virol 1998; 72: 4015-4021.
58. zur Hausen A, Brink A, Craanen M, et al. Unique transcription pattern of Epstein-Barr virus in EBV-carrying gastric adenocarcinomas: Expression of the transforming BARF1 gene. Cancer Res 2000; 60: 2745-2748.
59. Sapi E, Flick M, Gilmore-Herbert M, et al. Transcriptional regulation of the c-fms (CSF-1R) proto-oncogene in human breast carcinoma cells by glucocorticoids. Oncogene 1995; 10: 529-542.
60. Kume T, Oshima K, Shinohara T, et al. Low rate of apoptosis and overexpression of bcl-2 in Epstein-Barr virus-associated gastric carcinoma. Histopathology 1999; 34: 502-509.
61. Mori M, Watanabe M, Tanaka S, et al. Epstein-Barr virus-associated carcinomas of the esophagus and stomach. Arch Pathol Lab Med 1994; 118: 998-1001.
62. Wu MY, Wu XY, Zhuang CX. Detection of HSV and HBV in esophagel carcinomas from a high-incidence area in Shantou China. Dis Esophagus 2005; 18: 46-50.
63. Wang LS, Chow KC, Wu YC, et al. Detection of Epstein-Barr virus in esophageal squamous cell carcinoma in Taiwan. Am J Gastroenterol 1999; 94: 2834-2839.
64. Awerkiew S, Bollschweiler E, Metzger R, et al. Esophageal cancer in Germany is associated with Epstein-Barr-virus but not with papillomaviruses. Med Microbiol Immunol (Berl) 2002; 192: 137-140.
65. Khurshid A, Kazuya N, Hanae I, et al. Infection of human papillomavirus (HPV) and Epstein-Barr virus (EBV) and p53 expression in human esophageal carcinoma. J Pak Med Assoc 1998; 48: 138-142.
66. Hong T, Shimada Y, Kano M, et al. The Epstein-Barr virus is rarely associated with esophageal cancer. Int J Mol Med 2000; 5: 363-368.
67. Kitchen VS, Helbert M, Francis ND, et al. Epstein-Barr virus associated oesophageal ulcers in AIDS. Gut 1990; 31: 1223-1225.
68. Tilbe KS, Lloyd DA. A case of viral esophagitis. J Clin Gastroenterol 1986; 8: 494-495.
69. Hungermann D, Muller S, Spieker T, et al. Low prevalence of latently Epstein-Barr virus-infected cells in chronic gastritis. Microsc Res Tech 2001; 53: 409-413.
70. Yanai H, Takada K, Shimizu N, et al. Epstein-Barr virus infection in non-carcinomatous gastric epithelium. J Pathol 1997; 183: 293-298.
71. Hirano A, Yanai H, Shimizu N, et al. Evaluation of Epstein-Barr virus DNA load in gastric mucosa with chronic atrophic gastritis using real-time quantitative PCR assay. Int J Gastrointest Cancer 2003; 34: 87-94.
72. Yanai H, Shimizu N, Nagasaki S, et al. Epstein-Barr virus infection of the colon with inflammatory bowel disease. Am J Gastroenterol 1999; 94: 1582-1586.
73. Wakefield AJ, Fox JD, Sawyerr AM, et al. Detection of herpesvirus DNA in the large intestine of patients with ulcerative colitis and Crohn's disease using the nested polymerase chain reaction. J Med Virol 1992; 38:183-190.
74. Spieker T, Herbst H. Distribution and phenotype of Epstein-Barr virus-infected cells in inflammatory bowel disease. Am J Pathol 2000; 157: 51-57.
75. Debinski HS, Kamm MA, Talbot IC, et al. DNA viruses in the pathogenesis of sporadic chronic idiopathic intestinal pseudo-obstruction. Gut 1997; 41:100-106.
76. Oh JJ, Kim C. Gastroparesis after a presumed viral illness: Clinical and laboratory features and natural history. Mayo Clin Proc 1990; 65: 636-642.
77. Vassallo M, Camilleri M, Lynn Caron B, et al. Gastrointestinal motor dysfunction in acquired selective cholinergic dysautonomia associated with infectious mononucleosis. Gastroenterology 1991; 100: 252-258.