

This study again confirms the results of previous smaller studies that prevalence of carcinoma at diagnosis is high in IPMN-M, ranging from 57% to 92% (Arch Surg 1999;134:1131–1136, Am J Surg Pathol 2000;24:1372–1377, Br J Surg 2003;90:1244–1249). In the present study, of the resected IPMN-M, 60% had carcinoma and 46% had invasive carcinoma. The findings of this study that asymptomatic patients with IPMN-M frequently harbor malignancy shows that there are no reliable clinical features that predict malignancy in IPMN-M. This is in contrast to IPMN-Br, in which most patients are asymptomatic and risk of malignancy in small tumors is low in cystic lesions <30 mm in size (Br J Surg 2003;90:1244–1249, J Clin Gastroenterol 2003;36:261–265).

Thus, it is quite clear that identification of main duct involvement is an indication for resection. In practice, patients classified as IPMN-Br based on preoperative imaging studies sometimes show microscopic involvement of the main duct not detectable preoperatively. It is unclear if such subjects with “predominantly” side-branch IPMN with microscopic main duct involvement have a higher prevalence of malignancy compared with those with dysplasia confined solely to the side-branch.

The present study and other studies have shown that resection of noninvasive IPMN (Ann Surg 2004;239:788–797, Gastroenterology 2002;123:1500–1507) and MCN (Ann Surg 2000;231:205–212, Am J Surg Pathol 1999;23:1320–1327) is curative in the vast majority of patients. Whereas in MCN no recurrence has been reported after resection of noninvasive tumor, at least 3 studies, including the present one, have reported a small but definite risk of recurrence after complete resection (with negative margins) of noninvasive IPMN (Ann Surg 2004;239:788–797, Gastroenterology 2002;123:1500–1507). This may reflect the presence of undetected synchronous lesions or development of metachronous lesions in a disease known to be multifocal in up to 30% of patients (Surgery 2001;129:55–65, J Jpn Pancreatol Soc 1996;11:344–352).

Survival after resection of invasive IPMN seems to be better than that for invasive ductal adenocarcinoma. In the present study, the actuarial survival of subjects with invasive carcinoma was 60% at 5 years and 50% at 10 years. However, these data are calculated survival based on median follow-up of only 2.5 years. It is quite likely that, as in other studies (Ann Surg 2004;239:788–797, Gastroenterology 2002;123:1500–1507), longer follow-up might show a greater number of patients with invasive cancer dying from recurrence of cancer. However, there is a subset of IPMN, especially those with colloid carcinoma (Ann Surg 2004;239:788–797), who seem to have a less aggressive course despite having metastatic disease, suggesting differences in biology of adenocarcinoma arising in IPMN compared with that of ductal adenocarcinoma.

Rapid progress has been made in a disease discovered just over 2 decades ago. However, there are still a number of unanswered questions regarding IPMN. To make further progress, extent of main duct involvement in subjects with predominantly branch duct disease should be carefully delineated prospectively. Also, criteria for diagnosis of MCN need consensus. Until specific molecular or immunohistochemical markers to differentiate MCN from IPMN-Br can be identified, ovarian stroma should be used as a necessary criterion to diagnose MCN (Clin Gastroenterol Hepatol 2004;2:1026–1031).

After careful separation among MCN, IPMN-M, and IPMN-Br, one will have better understanding of the natural history and biology of the various mucinous neoplasms of the pancreas. The present and previous studies have relied heavily on resected neoplasms. Ability to accurately categorize unresected tumors will be a major step in delineating the natural history of small tumors and providing mean-

ingful advice to the ever-increasing number of patients with incidentally discovered cystic lesions of the pancreas.

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MINIMAL HEPATIC ENCEPHALOPATHY: SHOULD WE START TREATING IT?

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Minimal hepatic encephalopathy (MHE) has generated a lot of interest in recent years. There is increasing evidence to show that MHE is an important disorder that could seriously impair daily living and health-related quality of life (HRQOL) in patients with cirrhosis. Treatment with lactulose is of benefit as it decreases ammonia production and absorption by modulating the gut microecology. Treatment with synbiotics (probiotics and fermentable fiber) has been suggested but not assessed in controlled studies. The investigators of this study have attempted to confirm the usefulness of synbiotics in the treatment of MHE. They screened 97 consecutive cirrhotic patients without overt hepatic encephalopathy (HE) for MHE using the number connection test (NCT) and measurement of brainstem auditory evoked potentials (BAEP). The cause of cirrhosis was hepatitis virus B or C in 75 (77%) patients, alcohol in 19 (20%), and other in 3 (3%). Patients with alcoholic hepatitis were carefully excluded. MHE, defined by abnormality of at least one test modality, was seen in 58 (60%) patients. In 55 patients, MHE were randomized to receive a synbiotic preparation, ie, a probiotic plus fermentable fiber (n = 20), fermentable fiber (n = 20), or placebo (n = 15) for 30 days. Probiotic compound consisted of 4 freeze-dried, non-urease-producing bacteria, namely *Pediococcus pentoseceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *Lactobacillus paracasei* subspecies *paracasei* 19, and *Lactobacillus plantarum* 2592, each at dose of 10¹⁰ colony forming units per sachet. Fermentable fiber consisted of beta glucan, 2.5 g, inulin 2.5 g, pectin 2.5 g, and resistant starch 2.5 g. Placebo consisted of wheat-based nonfermentable fiber. Patients were evaluated with NCT and BAEP, serum ammonia and endotoxin levels, and stool quantitative bacteriological analysis at study entry, after 1 month of treatment and again after 14 days.

Cirrhotic patients with MHE had substantial derangements in the gut microecology, with significant fecal overgrowth of potentially pathogenic *Escherichia coli* and *Staphylococcal* species. Synbiotic treatment significantly increased the fecal content of non-urease-producing *Lactobacillus* species at the expense of

these other bacterial species. The effect persisted at reassessment 14 days after cessation of supplementation. Such modulation of gut flora was associated with a significant reduction in blood ammonia levels and reversal of MHE in 50% of patients. Synbiotic treatment was also associated with a significant reduction in endotoxemia. The Child–Turcotte–Pugh functional class improved in nearly half of patients. Similar benefit was observed with fermentable fiber alone in a substantial proportion of patients. The authors concluded that treatment with synbiotics or fermentable fiber is an alternative to lactulose for management of MHE in patients with cirrhosis.

Comment. Hepatic encephalopathy (HE) reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain disease. Working Party at the 11th World Congress of Gastroenterology, Vienna, under the Organisation Mondiale de Gastroentérologie, proposed a multiaxial definition of HE that defines both the type of hepatic abnormality (type A, B, or C) and the duration/characteristics of neurological manifestations (episodic, persistent, or minimal HE) in chronic liver disease (Hepatology 2002;35:716–721). HE has been considered a continuous dimension that could be measured with one index to summarize several neurological domains, such as cognition, emotion, behavior, or biologic rhythms. MHE would represent a portion of this dimension, would be the mildest form of HE, and would be diagnosed on the basis of a cut-off score. To perform such a study, a large sample is required, and until this is carried out, the best characterization of MHE can be done by psychometric and neurophysiologic methods (Indian J Gastroenterol 2003;22:[Suppl 2]:S37–S41, Hepatology 2002;35:716–721). Whereas patients with HE have impaired intellectual functioning, personality changes, altered level of consciousness, and neuromuscular dysfunction, patients with MHE have no recognizable clinical symptoms of HE but have mild cognitive and psychomotor deficits. Standard neurological examination is not sufficient to recognize subtle cognitive function abnormalities, which mainly affects attention, speed of information processing, and motor abilities and coordination.

Various tools have been evaluated for the correct diagnosis of MHE and include the psychological tests, neurophysiological tests, regional cerebral blood flow changes, and magnetic resonance spectroscopy. However, in the absence of a “gold standard,” psychometric and neurophysiological methods have been the most trusted and widely used tests. Combination of at least 2 psychometric (trailmaking tests, block design, or digit symbol test) and 1 neurophysiological test (P300 BAEP or electroencephalography with mean dominant frequency) seems to be optimal in detecting MHE (Indian J Gastroenterol 2003;22:[Suppl 2]:S37–S41, Hepatology 2002;35:716–721).

Is MHE clinically significant? To address this question, we need to discuss at least 3 issues: (1) Does MHE impair daily functioning or HRQOL? (2) What is its natural history? and (3) Is it associated with poor prognosis? First, increasing evidence suggests that MHE is an important disorder that impairs patients' daily functioning and HRQOL (Hepatology 1998;28:45–49, Metab Brain Dis 2001;16:37–41, J Gastroenterol Hepatol 1998;13:752–760). Although the basic activities of daily life, such as shopping, dressing, personal hygiene, etc, are largely preserved, complex activities involving attention, information processing, and psychomotor skills such as driving a car, planning a trip, etc, are mainly affected. Blue-collar workers suffering from cirrhosis with MHE are less likely to earn their wages than the white-collar workers (Metab Brain Dis 2001;16:37–41). In

addition, psychometric studies have shown that patients with MHE may be unfit to drive a car (Metab Brain Dis 1995;10:239–248, Dig Dis Sci 1981;26:622–630). In a landmark study, using a standardized 90-minute on-the-road driving test, Wein and colleagues reported that fitness to drive a car is impaired in cirrhotic patients with MHE; the ratings were worst in patients with MHE, whereas patients without MHE scored similar to controls. More importantly, the instructor had to intervene more frequently during the test to avoid accidents in patients with MHE (36%) than in those patients without MHE (6%) and controls (8%) (Hepatology 2004;39:739–745). The results of Wein et al's study suggest that MHE should be considered a medical condition that warrants treatment to improve psychomotor impairment. Second, natural history of MHE in cirrhotic patients is not widely studied. However, our and other observations indicate that MHE predicts the occurrence of overt HE (J Gastroenterol Hepatol 2001;16:531–535, Am J Gastroenterol 2001;96:2718–2723, Liver 2002;22:190–197). Finally, the prognosis of MHE is also not clearly established. Although Hartmann et al did not find any prognostic significance of MHE (Am J Gastroenterol 2000;95:2029–2034), Amodio et al found that computerized psychometric tests and quantifiable alterations in EEG predict poor prognosis (Hepatology 1999;29:1662–1667). A pathological oral glutamine challenge response in patients with MHE also seems to be associated with the development of overt HE and poor survival (J Hepatol 2002;37:781–787, Hepatology 2004;39:939–943). MHE, therefore, is a clinically significant disorder that impairs HRQOL, predicts the development of overt encephalopathy, and is probably associated with poor prognosis.

The next question that needs to be answered is whether MHE improves with treatment. The pathogenesis of MHE is thought to be similar to that of overt HE, and ammonia plays a key role (Radiology 1994;193:457–463, J Hepatol 2001;35:598–604, J Cereb Blood Flow Metab 1991;11:337–341, J Hepatol 2004;41:49–54). Ammonia-induced alterations in cerebral blood flow and glucose metabolism have shown that there is a significant decrease of glucose utilization of various cortical regions that correlate with the patients cognitive functions (J Cereb Blood Flow Metab 1991;11:331–336).

Various treatment modalities have been tried to treat this condition, eg, dietary protein manipulation (Gut 1983;24:53–60), branched-chain amino acids (Gastroenterology 1985;88:887–895), L–ornithine L–aspartate (Hepatology 1997;25:1351–1360), and lactulose (Hepatology 1997;26:1410–1414, Dig Dis Sci 2000;45:1549–1552). Most of these therapies were aimed to reduce ammonia levels. Lactulose lowers ammonia levels by alteration in gut flora, resulting in decreased production and absorption of ammonia. Treatment with lactulose is of benefit in a majority of patients with MHE (Dig Dis Sci 2000;45:1549–1552, Hepatology 1997;26:1410–1414).

In the May 2004 issue of the *Hepatology*, Liu et al reported an alternative and novel approach of modulating the gut microecology and acidifying the gut lumen for therapeutic benefit in cirrhotic patients with MHE by treatment with synbiotics. The major strength of this study was a detailed quantitative bacteriological analysis and measurement of pH of fecal samples and careful exclusion of alcoholic hepatitis and other factors that might affect gut flora and other known precipitants of HE. The trial would have been strengthened by treatment crossover after washout and subsequent reevaluation of study end points (Hepatology 2004;39:1197–1200). Fermentable fiber, a prebiotic, demonstrated benefits similar to the synbiotic preparation. Because similar effects were seen with a synbiotic preparation (combination of probiotics and fermentable fiber) and with fermentable fiber alone, it is possible that effect was due to fermentable fiber and not because of probiotics. However, a direct comparison

between probiotics and fermentable fibers would be required to either substantiate or to refute this hypothesis. Even if probiotics are as effective as fermentable fibers, the effect does not seem to be an additive one. Therefore, fermentable fibers might be preferred over probiotics because of safety and regulatory concerns.

The selection of a psychometric test in this study for the diagnosis of MHE was not appropriate. The authors used a single psychometric test (NCT), which relies mainly on psychomotor speed, visuo-spatial orientation, and to some extent attention. MHE cannot be reliably diagnosed by the application of a single psychometric test (J Hepatol 2001;34:768–773).

The concept that gut flora therapy (manipulation of the endogenous gut bacterial flora by prebiotic, probiotics, or a combination of the two) in liver disease is not new. Treatments such as antibiotics and lactobacillus that inhibit production of endotoxin by the intestinal flora significantly inhibit the development of steatohepatitis in alcoholic (Gastroenterology 1995;108:218–224, Proc Soc Exp Bio Med 1994;206:243–247) and nonalcoholic (Hepatology 2003;37:343–350) fatty liver disease. In this study, modulation of gut flora not only resulted in improvement in MHE but also liver disease coupled with reduction in endotoxemia. Endotoxin-induced activation of macrophages plays a key role in the pathogenesis of tumor necrosis factor α over production and associated liver injury in patients with alcoholic and nonalcoholic liver disease (N Engl J Med 2000;343:1467–1476). Improvement in Child–Turcotte–Pugh functional class was also associated with improvement in necroinflammatory activity, as reflected by serial alanine aminotransferase

levels. These findings are interesting and relevant because a majority of patients (77%) in this study had a viral etiology of cirrhosis. Thus, further studies are required to elucidate the precise molecular mechanism(s) of improvement of liver disease due to gut flora–based therapy in patients who do not have fatty liver disease. The improvement in MHE was associated with decreasing ammonia levels, thus supporting its role in the pathogenesis of MHE.

Should we routinely screen cirrhotic patients for the presence and treatment of MHE?

When things are investigated, then true knowledge is achieved.

—Confucius

Recently published literature has just started unfolding true knowledge regarding MHE. It confirms that patients with MHE have impaired daily living and HRQOL; treatment not only results in improvement in cognitive and psychomotor deficits, but also liver disease. If the work by Liu et al is further corroborated by larger prospective studies, then failure to diagnose and treat MHE could be considered a medical error. Recent studies have also suggested that MHE predicts overt HE; whether treatment also prevents or delays progression to overt HE and improves HRQOL remains to be determined in prospective studies.

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