Liver Update

A publication of the Center for Liver Diseases and the Inova Transplant Center

Partnership for a Higher Quality of Life

Having a medical illness does not mean surrendering one's dignity, respect and honor. Life has many challenges for all of us. There are challenges that come at different times in our lives and are measured in many degrees of seriousness and difficulty. We take many of our daily comforts for granted as we go through life. Not intentionally, but because they just do not seem to be threatened when all is well.

We are brought up to appreciate many comforts that life has to offer the warmth of a family's love; later in life, the companionship of a spouse or partner. The respect and deference given by others; caring and nurturing the gift of children. Probably the most important and most taken for granted is the internal peace that we enjoy by having a full and healthy life.

A challenge that many of us unfortunately will encounter is unforeseen health and medical problems that arrive unannounced on our doorstep. When we have lived a healthy life and all of a sudden we find ourselves not in control of our own daily existence, and even of our destiny, it throws our balance off. It not only becomes earth shattering, but it truly does reveal our innermost fears of inadequacy.

To be plunged into a whole new world, the world of "medicine," is not only shocking but also debilitating in far reaching ways that are hard to comprehend. To wake up one day and realize that your whole life from that moment on will be determined in many ways by outside factors that will guide your internal well-being is about the most horrific feeling of helplessness in the world.

Is there anything we can do if confronted with the dilemma of a long-term illness or condition that would lessen the emotional and physical impact?

The answer is *yes.*

When thrown into a medical illness or condition, we become newly inducted members of the 'medical profession'. I use the term 'profession' deliberately because we truly become an integral part of the team that will medically and emotionally treat our ailments. Patients will become so familiar with their conditions and treatments that they can and must feel essential to the team of doctors and health care professionals that treats them. This I believe is not a new concept but one that is and must be welcomed and truly accepted without reservations and anxieties by doctors and hospitals.

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We all suffer without this conscious effort by the medical institutions to bring the patients in as equal partners in their own care. Without the honest, forthcoming, deliberate effort, the care, treatment and well-being of the patient and their illness will ultimately fail. This is a very strong statement, but one that can be documented with long-term studies on the quality of life of those who receive such consideration.

To receive respect, inclusion and treatment makes a huge difference in the quality of life one lives, opposed to those who are discounted and dealt with as though they merely do not exit. Or only exist through the illnesses in the countless and faceless medical charts that become the person (patient).

How to achieve the most effective medical care from caregivers is hard work. The burden falls squarely on the shoulders of *both* the caregivers and the patient. Mutual respect and a cunning ability to feel the needs and obligations of the other is the pin that holds the relationship together. This is like a pin holding a broken limb that needs time to mend and heal (mature). Caregivers and patients need time to bond and mature with mutual appreciation for the other's intentions, needs and abilities. This is not easy. We are all humans and we bring our daily feelings and moods to the table everyday. This is not to say that a doctor or a patient is being less than professional - it is just a fact of life. We need to appreciate the personality of people and to accommodate for their attributes with extreme flexibility and patience. To do any less will only lead to misunderstandings, ill feelings and heartache. Once a relationship is established where both parties are equally accepting of the other, only then will there be positive progress to a higher quality of life given the medical condition.

We need to make time to listen when we do not have time. We need to understand when we think we know the answer but are questioned. We need to be compassionate when short tempers flare and words are uttered without proper thought given to how those words are received. We need to follow up on the small things and not just the big things. Small things add up and become big problems. Nip them early and confront the unlikely and ridiculous, for they may sound off the wall to you, but mean the world to the other person.

Respect, dignity, honor, compassion and professionalism are the keys to a healthy relationship between the medical professional and the patient. The quality of life of a person is at stake if these attributes are infringed upon. Be ever vigilant. No one can be perfect all the time, but with a sense of constant awareness we can deliver and receive the best care possible.

I have experienced this medical phenomenon. I can tell you from my experience of living under the microscope for nine years and having the ever-present medical fluctuations that accompany a liver transplant. Life can and does proceed with a high degree of quality if we take the time to participate equally in the medical care given.

At times it may not just be that a given clinical approach is not working. It could just mean that a smile and a moment of respect, reflection and compassion are needed.

Take a deep breath and enjoy life's bounties to the fullest. We are all in this together. Having an illness should not be a requisite for a total surrender of one's ability to control their destiny. As partners, we can make life's quality beautiful and full for everyone in our care and for those who deliver the care.

Publications and Presentations

Publications

- Younossi, A M Diehl, J Ong. Nonalcoholic Fatty Liver Disease: An Agenda for Clinical Research. Hepatology 2002, 35(4): 746-752.

Presentations

- HCV and Steatosis and New Insights into NASH Sessions, Schering Hepatitis Investigator's Network (SHINE), Orlando, FL.
- Current Treatment and Research Protocols in the Treatment of Hepatitis C, UNOS Region 2 Clinical Forum, Bethesda, MD.
- Natural History of NASH; Clinical Symposium, Digestive Diseases Week, San Francisco, CA

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Hepatic Encephalopathy

Hepatic encephalopathy (HE) comprises a spectrum of neuropsychiatric conditions seen in patients with liver disease after exclusion of other causes of brain dysfunction. These conditions have in common reversibility with correction of underlying liver dysfunction and range from subtle neuropsychiatric changes to severe coma.

DEFINITION

A recent report by the Working Party assembled by the World Organization of Gastroenterology (OMDE) classified HE into three types —Type A is encephalopathy associated with acute liver failure, Type B is encephalopathy associated with portal-systemic bypass without intrinsic liver disease, and Type C is encephalopathy associated with cirrhosis and portal hypertension. They further divided Type C into Episodic HE, Persistent HE, and Minimal HE. Episodic HE can be precipitated, spontaneous or recurrent. Persistent HE can be mild, severe or treatment-dependent. Minimal HE is the term that the Working Party proposed to replace the older term "Subclinical Hepatic Encephalopathy" to detract from the potential misconceptions that this condition has a different pathogenesis or that it lacks clinical significance. This update will concentrate on Type C HE – its pathogenesis, clinical manifestations and diagnosis, and treatment.

PATHOGENESIS

The study of the pathogenesis of HE has been difficult, primarily due to our inability to study the brains of humans with HE. Additionally, although there are several animal models that are in use today, there is not one that is widely acceptable and the results from animal studies may not adequately reflect the condition in humans.

There have been many theories put forward to describe the pathogenesis of HE in patients with HE. HE can be the result of alterations in the blood brain barrier, alterations in cerebral energy metabolism, or the result of neurotoxins. Several potential neurotoxins have been evaluated over the last few decades. The list includes ammonia, GABA/benzodiazepine, false neurotransmitters, serotonin, manganese and endogenous opioids.

Ammonia is the best characterized neurotoxin in HE. The implication of ammonia in the pathogenesis of HE stems from studies that showed elevated ammonia levels in patients with HE. Additionally many of the classic precipitating factors of HE such as gastrointestinal bleed, constipation, or ingestion of a protein load can result in elevated ammonia levels, and the available therapeutic agents for HE are thought to work by reducing ammonia levels. Studies on the correlation between blood ammonia levels and HE, however, have been conflicting, which can be accounted for by the design of the studies and by the manner in which blood ammonia measurement was performed.

The GABA/benzodiazepine neurotransmitter system has also been implicated with the finding of increased benzodiazepine receptors in the brains of patients with HE. Moreover, endogenous benzodiazepines have been identified in patients with HE. The exact origin of these substances in humans is not clear, although they could come from the gut from natural benzodiazepines in the diet or manufactured by gut bacteria.

Activation of the GABA/benzodiazepine neurotransmitter system can be augmented by ammonia, indicating possible interaction between these two putative neurotoxins. Amino acid imbalance has been postulated to lead to the production of false neurotransmitters that replace true neurotransmitters, resulting in HE, although this has not been borne-out in more recent studies. Serotonin levels have been found to be elevated in blood, cerebrospinal fluid, and brain tissue of patients with HE; however, there is evidence both for an excess and a deficiency of serotonin in studies of HE.

Endogenous opioids have recently been implicated in the pathogenesis of HE based on increased levels in cirrhotics with HE, compared to those without HE. Other studies have not confirmed these results and more work needs to be done regarding the role of endogenous opioids in HE.

Manganese has been shown to be deposited in the basal ganglia of patients with cirrhosis; however, the exact role of manganese in HE remains to be defined.

CLINICAL MANIFESTATIONS

Patients with Type C HE or encephalopathy associated with cirrhosis will have other clinical manifestations of chronic liver disease. Alterations in mental status ranges from disturbances in sleep-wake patterns to more severe alterations in consciousness such as stupor or coma. Patients may present with subtle personality changes that are obvious only to close family members. Neurologic findings may include hyperactive deep tendon reflexes, hypertonia, asterixis and even transient decerebrate posturing.

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Focal neurologic findings such as hemiplegia are not common but can occur and are often reversible.

Much more subtle neuropsychiatric abnormalities can only be detected with the use of psychometric testing. This condition has often been referred to as subclinical HE or minimal HE. The severity of HE has traditionally been described using the West Haven Criteria which is shown in Table 1.

Table 1. West Haven Criteria for Grading of HE

Grade 0	No alteration in consciousness, intellectual function, personality, or behavior.
Grade 1	Trivial lack of awareness, euphoria or anxiety, shortened attention span, or impaired performance of addition.
Grade 2	Lethargy or apathy, disorientation to time or place, impaired performance of subtraction.
Grade 3	Somnolence, gross disorientation.
Grade 4	Coma (unresponsive to verbal or noxious stimuli).

TIPS AND HE

Transjugular intrahepatic portosystemic shunts (TIPS) were introduced more than a decade ago and have been increasingly used in the management of the complications of portal hypertension in cirrhotics. Aside from stenosis and TIPS malfunction, one of the major drawbacks of TIPS has been the development of new or worsening HE. The exact incidence of HE after TIPS placement is not certain because of the heterogeneity of studies, but estimates range from 14 to 55 percent.

The pathogenesis of post-TIPS HE is a result of a combination of decreased portal blood flow and increased bioavailability of gut-derived toxins. Possible predictors of the development of post-TIPS HE include pre-TIPS HE, Child-Pugh class, advanced age, low albumin, and low post-TIPS portosystemic gradient. The treatment of post-TIPS is similar to other forms of HE except consideration should be made to give prophylactic treatment to those with risk factors for post-TIPS HE, especially those with pre-TIPS HE.

DIAGNOSIS

The evaluation of a patient suspected of having HE should include a careful history and physical examination. A systematic neurologic examination, including a mini-mental status examination, must be performed. Clinical evidence or stigmata of cirrhosis must be looked for. One has to bear in mind that the diagnosis of HE is a clinical diagnosis after exclusion of other causes of altered mental status such as intracranial hemorrhage, hypoglycemia or drug overdose.

There are no specific diagnostic tests for HE. Many clinicians order blood ammonia levels in patients suspected of having hepatic encephalopathy, while others obtain serial levels to follow the clinical course with treatment. It is therefore surprising that there has not been a study that evaluated the clinical utility of blood ammonia levels in the diagnosis of HE. Some believe that arterial ammonia may be more useful than venous ammonia.

Another issue with blood ammonia levels in HE are the cutoff values used as normal. The main organ involved in the metabolism of ammonia in the body is the liver. In cirrhotic patients, the ammonia level may be elevated by virtue of their liver disease alone in spite of the absence of symptoms of HE because most clinical laboratories use cut off values derived from normal volunteers. A possible use of blood ammonia levels is in the evaluation of a patient with altered mental status who does not have a known history of hepatic dysfunction, as an elevated ammonia level may point to HE as the cause of altered mental status in that situation.

Electrophysiological tests such as EEG and evoked responses have been considered useful in the diagnosis of HE but often require patient cooperation, expensive equipment and highly trained operators which preclude their widespread use in the clinical setting. The use of computed tomography (CT) scans of the head in HE is limited to excluding intracranial disorders such as subdural hematomas, intracranial abscess or other cerebrovascular disorders.

Recently, magnetic resonance imaging (MRI) has been found to show hyperintense basal ganglia in cirrhotic patients with HE. This hyperintensity on MRI has been linked to deposition of manganese in the basal ganglia. Although these MRI findings have been found to correlate with severity of liver disease, they have not been found to correlate with severity of HE and probably have limited utility in the diagnosis of HE. Magnetic resonance spectroscopy (MRS) allows us to study the *in vivo* cerebral metabolic balance in patients with or without HE. Patients

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with HE have increased glutamine concentration. These results are preliminary and this modality remains experimental at this time.

TREATMENT

Once the diagnosis of HE has been made, a search for precipitating factors for HE must be made and measures taken to reverse the identified precipitating factor(s). Precipitating factors include gastrointestinal bleeding, sepsis, hypokalemia from diarrhea or diuretics, dehydration, azotemia, inadvertent administration of benzodiazepines or narcotics, constipation and dietary indiscretion with increased dietary protein load. It must be noted that multiple precipitating factors may co-exist in one patient and they must all be addressed in the management of HE.

Specific therapeutic agents used in HE can best be discussed by dividing them into those agents directed towards the ammonia hypothesis, those agents directed towards the GABA/benzodiazepine hypothesis, and other agents. Protein restriction as a therapeutic modality aims to decrease the ammonia generated in the gut by the action of bacteria. Severe protein restriction below 70 grams a day appears unnecessary in cirrhotics and is not recommended. Levels below 40 grams a day may result in negative nitrogen balance.

Agents directed to the ammonia hypothesis. Lactulose is a synthetic disaccharide that is the mainstay in the treatment of HE. Lactulose is thought to exert its therapeutic benefit by several mechanisms, including lowering of colonic pH, thereby trapping ammonia in the gut catharsis and increased gastrointestinal transit leading to decreased ammonia absorption, and reduced formation of toxic, short chain fatty acids. The dose of Lactulose should be individualized and titrated to two to three soft bowel movements a day.

In a small proportion of patients, symptoms are not controlled by Lactulose or side effects preclude use of Lactulose, antibiotics such as Neomycin (two to eight grams in four divided doses) or Metronidazole (250 milligrams three times a day) can be added to or substituted for Lactulose in these patients. Other agents that affect ammonia metabolism that are currently being investigated in HE include L-ornithine L-aspartate (LOLA) and sodium benzoate.

Agents directed to the GABA/benzodiazepine hypothesis. Flumazenil is a benzodiazepine receptor antagonist that has been evaluated in more than 700 patients with HE. Its therapeutic effect is based on the theory that endogenous benzodiazepines or increased benzodiazepine receptors may be involved in the pathogenesis of HE. The use of Flumazenil was associated with a clinical response in 30 percent of those treated, compared with seven percent of those receiving a placebo. However, the response was short-lived and survival benefit could not be demonstrated.

Other agents. Branched chain amino acids, orally or intravenously, have been used in HE but the studies have been small and the results conflicting. Their use at the present time is probably reserved for patients who are protein-intolerant as a source of increased dietary protein intake. Because zinc deficiency is common in patients with cirrhosis and HE, zinc supplementation may therefore be beneficial for HE. However, results of studies on the use of zinc in HE have been inconsistent. Other agents that are in experimental stages include the serotonin antagonists and opioid antagonists.

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Research Protocols

The following is a list of the research protocols at the Center for Liver Diseases at Inova Fairfax Hospital:

- Pegylated Interferon Alfa 2b and Ribavirin for chronic hepatitis C.
- Triple regimen of Pegylated Interferon Alfa 2b, Ribavirin and Amantadine for treatment of chronic hepatitis C.
- Pegylated Interferon Alfa 2a alone or in combination with Ribavirin for chronic hepatitis C.
- Growth Factors for treatment of cytopenia in patients with hepatitis C on Ribavirin/PEG-IFN.
- The use of Interferon Gamma-1b as an anti-fibrotic agent in hepatitis C.
- Pegylated interferon Alpha 2a with or without Thymosin Alpha 1 for chronic hepatitis C.
- Lamivudine with or with out monoclonal HBV antibody for chronic hepatitis B.
- Adefovir Dipivoxil for the treatment of hepatitis B.
- Epidemiology for hepatitis B in the United States.
- Epidemiology of Hepatocellular carcinoma in the United States.
- Epidemiology of Non-Alcoholic Fatty Liver Disease.
- New agents for treatment of Non-Alcoholic Fatty Liver Disease.

For patient screening or additional information, please call the Center for Liver Diseases at **703-698-3182**, or fax **703-698-3481**.

American Liver Foundation Corner

Liver Foundation Sponsor *Bid for Life*

It is once again time to *Bid for Life*. On June 15, the Greater Washington, DC, Chapter of the American Liver Foundation will host the Second Annual Bid for Life Auction Against Liver Disease presented by Regional Contracting Services, L.L.P, at the La Maison Francaise, Embassy of France, from 5:30 to 8:30 p.m.

Join Virginia Hayes Williams, vice-chair; and Lesli Foster, WUSA-TV9, mistress of ceremonies, in support of the American Liver Foundation's mission — to prevent, treat, and cure hepatitis and other liver diseases.

To attend the event or obtain additional information, call 202-872-6000.

Support Groups

Inova Fairfax Hospital and the ALF sponsor a Hepatitis C Support Group in Northern Virginia. The group will meet May 14 at the hospital in conference rooms D, E and F, with a speaker on *Side Effect Management Tips for Antiviral Therapy*. On June 11, Janus Ong, MD, will speak on the role of *Liver Biopsy in Hepatitus C*.

Inova Health System is a not-for-profit health care system in Northern Virginia that consists of hospitals and other health services including home care, nursing homes, mental health services, physician practices, wellness classes, and emergency and urgent care centers. Governed by a voluntary board of community members, Inova's mission is to provide quality care and to improve the health of the diverse communities we serve.

www.inova.org

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