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APPENDIX 1

Mental Status : Details of Operational Definition for Clinical Stage of Hepatic encephalopathy

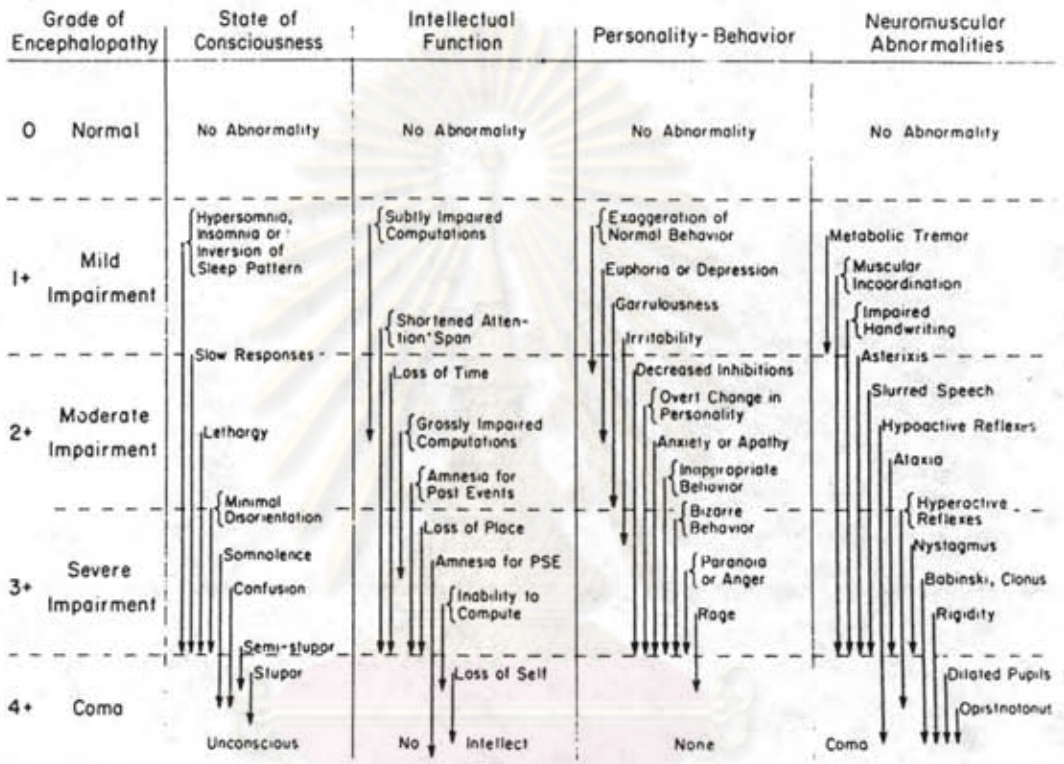

Figure A-1. Spectrum of disordered mental status in HE. The grade of HE is indicated on the left. Each of the three components of mental state plus neuromuscular abnormalities are shown in the other columns. Within each column the grade at which specific abnormalities usually appear is shown by the tail of the arrow. The length of the arrow indicates the range of grades through which each abnormality may be observed.

Disturbances of mental state is the major manifestation of HE and is the basis of clinically grading HE stage.

In this figure the various components of mental state are presented as individual spectra in terms of the conventional criteria for grading mental state. These components may all appear and advance together or some may appear late and progress independently. The criteria of Conn et al have been used extensively in clinical evaluation.

Mental state can be divided into 3 component parts -- **the state of consciousness, intellectual function, and personality behavior.** These aspects will be considered individually in increasing order of abnormality. Each of these components is depicted diagrammatically in relationship to each other, to conventional grading of mental state,and to neuromuscular abnormalities (Figure A-1). Some aspects of mental state do not progress in linear fashion throughout the four grade of HE. Indeed, they cannot. Impairment of intellectual function, for example, is detectable in Grade 1, and by Grade 3 is grossly abnormal. In Grade 4, however, it is impossible to test intellectual function. Similarly, asterixis appears at Grade 2 but the stuporous patient is unable to cooperate enough to test for the flap. Furthermore, each of these disturbances may make assessment of the others difficult, or even impossible. It is impossible, for example, to assess the ability to do simple calculations in a patient who is too sleepy to pay attention to the questions. It is difficult to have a patient write or draw if his asterixis prevents him from holding a pen.

This figure, nevertheless, serves merely as a diagrammatic guide that help to grade the various stages of HE according to the criteria.

State of Consciousness

Grade 1	Hypersomnia, insomnia or inversion of sleep pattern.
Grade 2	Slow thinking and sluggish and delayed responsiveness. Lethargy and/or apathy. Early disorientation for time (the date, the day of the week, or the month, the season, before or after some time markers). Next disorientation for the sphere of present place but retaining basic information about where he was born or lives.
Grade 3	Somnolence but can be aroused. Confusion and loud delirium (may thrash, mutter, moan, or scream, but completely unaware of their senseless actions and amnesia for these events if the recovers). Developed disorientation to persons (to his family's and his own identity at last).
Grade 4	First semi-stupor to stupor that responds can only be elicited by progressively more rigorous and noxious stimuli, until unconsciousness.

Intellectual Function

Grade 1	Unable to do serial sevens or to present a sequence of numbers in reverse order. Less-well and less-rapidly doing simple intellectual tasks (Number connection test). Very slowly writing a dictated sentence and with unexpected errors.
Grade 2	Difficult to do all computations and unable to repeat in order a short series of numbers. Irregular, slanted and sloppy handwriting. Much slower to do NCT. Obvious constructing apraxia (reproducing a simple figure, or constructing a star of matches). Later, some degree of forgetfulness for recent or remote events.
Grade 3	Grossly impaired intellectual function measured. Illegible handwriting, caricatural signature. Unable to compute at all. Lost in sphere of persons and usually retrospective amnesia for HE period.
Grade 4	Lost himself. No meaningful mental function.

Personality-Behavior

Grade 1	Early changes only recognized by the family (exaggerations of normal moods, attitudes, or behavior). Subsequent changes sensed by physicians (euphoria or depression or irritability).
Grade 2	Obvious changes, such as wandering aimlessly or endlessly rearranging bedclothes or house contents, lose of inhibitions, inappropriate behavior (washing windows, singing loudly at night).
Grade 3	More bizarre behavior (urinating or defecating in hallways, bedrooms, or shoes). Anxiousness, paranoia and/or apathetic. May pose a danger to himself and to their associates.
Grade 4	None can be assessed.

Appendix 2

PSE Sum & Index

In order to conduct investigation of various forms of therapy of PSE, it is necessary to develop an objective overall index which will permit comparison of the severity of PSE in different times. For this purpose, an arbitrary index of the intensity of PSE based on the degree of abnormality of each of the various components measured -- **mental status, number connection test (NCT) time, asterixis, electroencephalography (EEG), and venous ammonia concentration** -- has been devised to grade the severity of the syndrome. Each component is expressed on a 0 to 4 scale.

- **Mental status** is assessed using the West Haven criteria for grading PSE.

Grade	Contents
Grade 0	No abnormality detected;
Grade 1	Trivial loss of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction;
Grade 2	Lethargy, disorientation for time, obvious personality change, inappropriate behavior;
Grade 3	Somnolence to semistupor, responsive to stimuli, confusion, gross disorientation, bizarre behavior;
Grade 4	Coma, tests of mental function not possible.

- The **Number-Connection Tests (NCT)** are employed to assess one or another aspect of mental performance. The subject is given the NCT sheet and asked to connect the numbered circles in consecutive order as quickly as possible. The score is the time it takes to complete the task measured in seconds, arbitrarily converted to a 0 to 4 scale:

Grade 0	< 30 seconds
Grade 1	31-50 seconds
Grade 2	51-80 seconds
Grade 3	81-120 seconds
Grade 4	120 seconds.

- The presence or absence of **asterixis** is determined by extending the patients arms and forearms, with the wrists dorsiflexed for at least 30 seconds:

Grade 0	No flapping motions;
Grade 1	Rare flapping motions;
Grade 2	Occasional irregular flaps;
Grade 3	Frequent flaps;
Grade 4	Almost continuous flapping motions.

If unable to cooperate, the patient will be asked to squeeze two fingers steadily and the number of involuntary relaxations of grip is quantified in a similar manner.

- The **Electroenphalography (EEG)** mean cycle frequencies are graded semiquantitatively:

Grade 0	Normal alpha rhythm > 9.0 cycles per sec (cps);
Grade 1	7-8.9 cps;
Grade 2	5-6.9 cps;
Grade 3	3-4.9 cps;
Grade 4	2.9 cps or less.

- **Venous ammonia concentrations** are assessed and converted to:

Grade 0	< 60 mmoles per liter;
Grade 1	61-100;
Grade 2	101-150;
Grade 3	151-200;
Grade 4	>201.

Each of these five components are arbitrarily weighted in proportion to its importance. Mental status is weighted by a factor of 3, and each of the others a factor of 1. The **PSE Sum** is the total of the weighted scores, its maximum possible value is 28. PSE Sums are not always comparable, since asterixis and the NCT cannot be tested in comatose patients and other components may not be available at any time. The **PSE Index** takes such missing data into account. The PSE Index is expressed as the ratio of the estimated PSE Sum to the maximal possible PSE Sum.

If the total 5 components are assessed,

PSE Index = Total scores (of 5 components) / 28

If one component (e.g., EEG) is missing,

PSE Index = Total scores (of 4 components) / 24

If two components (e.g., EEG, ammonia) are missing,

PSE Index = Total scores (of 3 components) / 20

Comparison of PSE Indices permit changes in the severity of HE to be monitored before and after treatment.

The PSE Index is a useful clinical tool. It allows the physician to express the severity of HE as an integrated number, rather than as a series of individual components. It is weighted so that the mental status, the most important of the components, contributes most of the index.

Appendix 3

CONSENT FORM

I have been informed that Department of Medicine, Zhong Shan Hospital, Shanghai Medical University is conducting a study of cirrhotic patients with hepatic encephalopathy ("hepatic coma"). The purpose of this study is to evaluate the therapeutic effect of flumazenil on improving the clinical stage of mental status of these encephalopathical patients.

I, being the guardian of _____ (the patient's name), agree this patient to participate in this study, understanding that it involves:

1. General clinical examination and clinical grading for the patient;
2. Proposed treatment [flumazenil or placebo (normal saline)]for the patient with the conventional therapies, for about 150 minutes in the intensive observation period;
3. Routine and conventional therapies for HE and other related diseased after procedure "2";
4. Review of the previous medical records;
5. All information about the specific treatment will be kept confidential. No one will be identified individually in any publish reports. Only the researchers will have assess to the study.

I also have been informed the adverse effects that may occur and the possibly unfavorable therapeutic outcomes of my patient.

I understand that my agreement of my patient's participation in this study is entirely voluntary and that I may withdraw my consent to participate at ant time without penalty and without in any way affecting the health my patient receives.

I have been an opportunity to ask questions about this study and if I have further questions about this study, I may contact the researchers in this hospital on Tel. ext. 2940.

Subject's (Patient's) name _____

Subject's guardian's signature _____ (relation: _____)

Physician's name _____

Date of participation _____

VITAE

Dr. Chouwen Zhu was born on July 26, 1966 in Shanghai, P. R. China. He graduated from Peking Union Medical College (PUMC), Beijing in 1992 after accomplishment of an eight-year course and earned the degree of Doctor of Medicine (M.D.). As a medical student, he was an active participant in all student affairs and was elected the president of student union of PUMC. In 1991, as a part of medical student exchange program, he visited United States of America for two months. He completed one-year internship in PUMC Hospital, Beijing, and two-year residency in Department of Internal Medicine, Zhong Shan Hospital, Shanghai Medical University, Shanghai. Since June, 1994, he has been admitted in the Master Degree Program of Health Development in Faculty of Medicine of Chulalongkorn University, Bangkok, Thailand. He was selected and supported in this course by Thai CERTC (Clinical Epidemiology Regional Training Center) Consortium of INCLEN (International Clinical Epidemiology Network), principally sponsored by the Rockefeller Foundation, New York, USA.

His principal interest in medical field is research in gastroenterology and hepatology. During this course, he has conducted a clinical controlled trial on the effect of a new drug on the restoration of mental status of patients in different stages of hepatic encephalopathy.

Presently, his duty engages him to work as the consultant of Division of Gastroenterology, Zhong Shan Hospital, Shanghai Medical University, and additionally, his interest in clinical epidemiology has enabled him to perform as the acting secretary of the CEU (Clinical Epidemiology Unit) of Shanghai Medical University, Shanghai.