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Correlation of neuropsychiatric signs with modified west haven scale on hepatic encephalopathy in children

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ABSTRACT

The hepatic encephalopathy (HE) is defined as wide spectrum neuropsychiatric alterations potentially reversible. *Objectives:* to know applicability of the modified West-Haven Scale (WHS), to correlate with neuropsychiatric signs in HE. *Materials and methods:* thirty three cases of HE were selected; the variables were: age, sex, type of hepatopathy, signs and symptoms (jaundice, fever, abdominal pain, vomiting, nausea and headache). Neurological signs were classified with WHS. *Results:* pre school children (45%). Etiology, non specific hepatitis and hepatitis A virus were predominant the neurological sign was asterixis. While correlating neurological signs and WHS, the Pearson's X^2 test was P=0.0006, the coefficient of determination R^2 0.5382, equivalent to a correlation coefficient > 72%. While comparing WHS and mortality, it was associated to higher grades of the scale, Fisher's test P=0.495. The mortality was 71.8%. *Conclusion:* the WHS has adequate correlation with the neurological signs in children and grades of the scale are also related to mortality.

Key words: hepatic encephalopathy, viral hepatitis, hepatitis A, neuropsychiatric signs.

Aplicabilidad de la escala de West-Heaven modificada y su correlación con signos neuropsiquiátricos

RESUMEN

La encefalopatía hepática (EH) se define como un espectro amplio de alteraciones neuropsquiátricas, potencialmente reversibles. *Objetivos:* conocer la aplicabilidad de la Escala de West- Haven modificada y su correlación con signos neuropsiquiátricos en EH. *Material y métodos:* se seleccionaron 33 casos de EH; las variables fueron: edad, sexo, tipo de hepatopatía, signos y síntomas (ictericia fiebre, dolor abdominal, vómito, náusea y cefalea). Los signos neurológicos se clasificaron con la EWH. *Resultados:* el grupo mayor fue preescolares 45%; en etiología. Predominaron las hepatitis no determinadas y hepatitis por virus A. Los signos neurológicos fueron asterixis. Cuando se correlacionaron signos neurológicos y EWH, la prueba X^2 de Pearson fue P= 0.0006, el coeficiente de determinación R^2 = 0.5382, equivalente a un coeficiente de correlación > 72%; al comparar EWH y mortalidad, esta se asocio a los grados mas altos de la escala, prueba exacta de Fisher P =0.495. La mortalidad fue 71.8 %. *Conclusiones:* la EWH tiene adecuada correlación, con los signos neurológicos en niños y las grados de la escala se relacionan adecuadamente con la severidad y mortalidad de EH .

Palabras clave: encefalopatía hepática, hepatitis virales, hepatitis A, signos neuropsiquiátricos.

Hepatic encephalopathy constitutes a set of progressive, potentially reversible clinical and neuropsychiatric manifestation that appear in patients who present with hepatic involvement of diverse nature (metabolic, viral infection, drugs, immunological congestive, idiopathic, toxins) which lead onto hepatic insufficiency of different grades of severity. According to the

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time of evolution of encephalopathy, it is possible to classify into three phases: the hyperacute phase presents within one week, the acute phase presents between 1 to 4 weeks and the subacute between 4 to 12 weeks. This classification considers that longer the time of evolution of HE, worse the prognosis. In the pathogenesis of HE, had existed controversies about the origin, having discussed, the role of ammonia, synergistic toxin gamma amino butyric acid (GABA) and endogenous benzodiazepines, false neurotransmitters, opiate and serotonin. Until now, it is known that deficiencies in metabolism of ammonia happens by the affected liver, which favor the arrival of this substances to the brain through the circulation; the ammonia is detoxified by the conversion of glutamate to glutamine by the enzyme glutamino synthetase. This conversion occurs near the astrocytes, producing a significant amount of glutamine that acts as idiogenic osmol and leads to swelling of astrocytes and cytotoxic edema facilitating vasogenic edema, producing deficient communication between astrocytes and other cells; also changes in the cerebral vasculature presents with arteriolar dilatation to elevate the cerebral blood flow, in addition to that, altered cerebral auto-regulation is encountered. As a result of these alterations, the astrocytes synthesize neurosteroids which activate GABA receptors and receptors of endogenous benzodiazepines, whose effect in neurotransmission are not well understood.

Finally, the HE is consequence of hepatocellular damage induced accumulation of the toxins, development of port systemic shunts which are precipitated by accumulation of ammonia, an increase in the production of false neurotransmitters, neuronal sensitization to GABA, increase of endogenous benzodiazepines and other metabolic enzymatic changes like changes in urea cycle, deficiency of and accumulation of maganese in basal ganglia. All the previous one has clinical manifestation, that ranges from euphoria to depression to the state of coma that of not reverting with the available therapeutic procedures (N- Acetylcysteine, lactulose, rifaximine, ornitines, membranes, bioartificial liver, hepatic transplant) and leading on to death.

In this retrospective work, we try to establish that is there any relation exist between the neuropsychiatric signs described in pediatric patients with HE and the clinical scale of West Haven , modified for pediatrics, especially as this clinical evaluation for being within the reach of all centers of medical attention.

MATERIALS AND METHODS

237 clinical records of the patients with the diagnosis of hepatitis in different departments of Hospital Infantil del Estado de Sonora, (between the periods of january 1997 to december 2007) were reviewed retrospectively. 33 (13.9%) records were selected, based on the evolution of hepatic failure to HE. Neuropsychiatric signs were identified and the West-Haven scale modified for pediatrics was also used (grade 1- confusion, change of temperament, grade 2- somnolesence, inappropriate behavior, grade 3- stupor, lethargy, but obeys simple commands, grade 4A - comatose, but reacts to painful stimuli, grade 4 B - deep coma, does not respond to any stimuli).

Other variables were: age (1 month to 18 years), sex, Type of hepatopathy, signs and symptoms: Jaundice, fever, nausea, vomiting, headache. Laboratory alterations:taken into consideration were alanine aminotransferase (ALT), Aspartate amino transferase (AST), alkaline phospatase, bilirubins, amonia, Coagulation studies such as prothrombin time, partial thromboplastin time, platelets, urea, creatinine, uric acid and treatment used in all the patients. Statistical tests used were such as Central tendency measurements, pearson's X2 *tests,* coefficient determination and Fisher's exact tests by means of Software JMP version 7.0.7.

RESULTS

Thirty three medical records of the patients with HE were selected. The Age groups registered were: 13 cases between 1 month to 1 year 11 month(0.39), of the 2 to 5year 11 month were 15 (0.45), between 6 year to 17 year 5 patients (0.15). Among 33, 16 were masculine, 17 were feminine. The hepatic disease which progressed to hepatic insufficiency and HE due to nonspecific hepatitis (probably viral) in 14 cases (0.42) and 9 with hepatitis A virus (0.27) (table 1).

Table 1. Etiology of HE.

Type of Hepatopathy	No. Cases	Proportion
Non specific hepatitis	14*	0.42
Hepatitis A virus	9*	0.27
Cholestatic syndrome	2	0.06
Biliary atresia	2	0.06
Primary biliary cirrhosis	1	0.03
Dengue virus	1	0.03
Reye syndrome	1	0.03
Metastasis by lymphoma	1	0,03
Auto immune hepatitis	1	0.03
Paracetamol intoxication	1	0.3

***** Severe acute hepatic failure and HE
4 non specific Hepatitis
8 Hepatitis A viruses

The signs and symptoms regarding hepatic disease were: jaundice in 33 cases (1.00), fever more than 38ÚC in 26 (0.71), abdominal pain in 21 (0.68), vomiting in 19

(0.57), nausea in 9 (0.27), headache in 5 (0.15). The grade of encephalopathy according to the West–Haven scale was, grade 1 in 13 (0.14), Grade 2 in 7 (0.21), grade 3 in 4 (0.12), grade 4A in 4 (0.12), and grade 4B in 5 (0.15).

The neurological signs most frequently encountered were asterixis in 17 cases (0.51), difficulty to realize mental tasks such as drawing, correlating simple sentences in 16 cases (0.48), flaccidity in 11 cases (0.33), hyperreflexia, spasticity in 1 case (0.33). Other signs associated to hepatic insufficiency that appeared in addition to neurological signs were, fetor hepaticus in 5 cases (0.15) and urinary incontinence in 5 cases (0.15). These features were seen in children between 4 to 18 years.

While contrasting the neurological signs and others related to HE with mortality, we did not encounter significant difference in the frequency proportion between them , X2 P=0.2576 and R2 0.1046. Nevertheless, while comparing these neurological signs and West-Haven scale, the results of frequency proportion were similar for asterixis and difficulty to do mental tasks, while applying X2 test of Pearson, the results of percentage proportion were different, P=0.0006; emphazing that the Coefficient of determination R_2 0.5382 is equivalent to a correlation coefficient greater than 72% (table 2).

Table 2. Correlation of neurological signs and others in HE and West-Haven scale.

NEUROLOGIC SIGNS	Grade 1	Grade 2	Grade 3	Grade 4A	Grade 4B
Difficulty to draw, add and correlating sentences	12	3	1	0	0
Asterixis, urinary incontinence, fetor hepaticus	1	4	0	0	0
Asterixis, hyperreflexia, spasticity	0	0	1	0	0
Asterixis, flaccidity, hyporreflexia	0	0	2	4	5
Total	13	7	4	4	5

Pearson's X^2 statistical test P=0.0006. Coefficient of determination, R_2 0.5382.

When comparing the mortality with WHS, considering grade 1 and 2 as lower grades and Grade 3 to 4 B as higher grades, the patients who deceased were more related with higher grades of the scale, since 53% of the deceased were associated to Grade 3 - 4B and 48% to grade 1 and 2, Fisher's exact test P=0.0495.

Of the laboratory parameters considered, those altered at the time of admission and which related directly with HE, were compared with the Grades of WHS in search of an association between these alterations and higher grades of the scale, did not have significant difference (table 3).

Also we tried to establish a correlation between abnormal laboratory values and mortality or survival, while applying X^2 test and coefficient of determination, no significant difference was encountered in any of them.

While revising the relation between mortality and therapeutic procedures (N-Acetylcysteine in twenty cases, lactulose, neomycin were also used, in addition ursodeoxycholic acid in minor proportion of cases), while applying Pearson X^2 test and coefficient of determination, no distinct difference was encountered when comparing with mortality or improvement.

Table 3. Abnormal laboratory parameters at admission and its relation with West-Haven scale.

Altered Parameter	Range	Pearson X^2	R_2	Significance
Alanine amino transferase	(>28 U->1000U)	P=0.5523	0.2249	NS
Aspartate amino transferase	(>10 U->1000 U)	P=0.1903	0.02747	NS
Direct Bilirubin	(0.4mg/dl ->3mg/dl)	P=0.4700	0.2324	NS
Prothrombin time	(<14seg -125seg)	P=0.4609	0.2396	NS
Partial Thromboplastin time	(>35 seg)	P=0.1127	0.4980	NS
Platelets	150,000xmm^3	P=0.5531	0.1165	NS
Ammonia serum	(>50mg/dl)	P=0.5882	0.2688	NS

DISCUSSION

HE is a complication that happens in 28% of the patients with cirrhosis or as a consequence of acute hepatic failure preceding viral infection or of another nature. In Mexico and Latin America, it has been considered that HE is most frequently related to infection by hepatitis A virus. In this series, that reports as infection with non specific hepatitis and hepatitis A virus are likely to be the principle cause of HE, unlike other countries where the main etiology of hepatic failure that evolves to HE is related to poisoning by medicines.

The hepatic insufficiency or chronic hepatitis happens in variable time period, which could go up to 12 weeks, in this report the average time was 4 days. The possibility of HE that can be reverted depends on many factors, among this, the important being low hepatic functional reserve as it can occur in children with chronic hepatic disease, in these cases, HE can manifest in episodic form or also in persistent manner with persistent neuropsychiatric signs, later type of evolution is more frequently observed in adults. In pediatric age groups, more acute form of evolution to HE is observed.

By etiologic factors, majority of that correspond to viral infection, like wise in this report also, three fourth of the registered cases happened due to the viral infection. Nevertheless, it is duty to take into consideration of some other precipitating factors in general, much more in chronic patients, like those who initiate suddenly, among these are, intestinal bleeding, constipation, protein rich diet, uremia, infection, electrolyte and acid base imbalance, use of opiates, diuretics, sedatives, acetaminophen, phenols and surgical events.

Until now, the true incidence of HE in pediatric ages is not known, still more the neuropsychiatric signs that are considered to be clinically oriented to establish this complication, especially in those children who evolve with

acute hepatic failure. The neurological signs that are encountered mostly in adults, like bradypsychia, asterixis, flaccidity, rigidity that can be combined with others like fetor hepaticus and urinary incontinence, it is not possible to identify some of these signs with clarity in the different pediatric age groups. In infants and children who do not express themselves, irritability, drowsiness, hypotonic, hyporeflexia, convulsive crisis and spasticity and of course jaundice and associated hepatomegaly are more frequent in children less than 2 years of age. Nevertheless, in half of the cases, it was possible to identify asterixis and altered mental functions that prevent the children from realizing simple mental tasks like drawing, correlating simple sentences and also flaccidity that are to be more persistent, associated with or without fetor hepaticus and urinary incontinence in older children.

While trying to relate the neuropsychistric signs to the parameters indicated in WHS, a good correlation could be appreciated between them with Pearson's X2 of P=0.0006 and coefficient of determination R^2 = 0.5382 which is equivalent to correlation coefficient greater than 72% as appear in table 2. Also, when comparing the mortality with WHS, by means of Fisher's exact test P = 0.495 was obtained.

The earlier results induces to think that the Modified WHS is an useful instrument for neurological evaluation in children since it contemplates identifiable signs by clinical exploration in any hospital; of course it did not claim to reduce the importance of laboratory studies with electroencephalogram those were considered in the evaluation, on the other hand they are not, within the reach of many centers of average level of attention in Mexico. In addition, we tried to establish relation between laboratory alterations and medical treatment provided, no significant difference was noted as expressed in table 3.

It deserves to specially mention the fact that, majority of the children received N-acetylcysteine, associated with lactulose and neomycin, based on the experience obtained in the patients with hepatic insufficiency and HE treated in this hospital, but no statistical support was encountered to value whether it influenced the evolution or not. It is reasonable to mention that this particular issue is motive for another specific study; without forgetting to mention that as per the reports from our country, some other treatments exist with other medicaments and novel procedures.

Even though this report constitutes a short series and that comes from a hospital of level 2 care of National Health System, we can not let it pass unnoticed the fact that, a good proportion of (27%) children with HE with high mortality had Hepatitis A, which forces us to seriously consider the systematic vaccination of all the children more than a year of age in Mexico and also in Latin America.

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