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ESPS Peer-review Report
Name of Journal: World Journal of Gastroenterology
ESPS Manuscript NO: 5467
Title: The Pathophysiology of Cerebral Oedema in Acute Liver Failure
Reviewer code: 00004296
Science editor: Cui, Xue-Mei
Date sent for review: 2013-09-11 17:34
Date reviewed: 2013-10-01 00:12

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[Y] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[Y] Major revision

COMMENTS TO AUTHORS

This article provides a general overview of the current knowledge on the mechanisms contributing to cerebral edema in ALF. However, there are several relevant aspects of the field which are not properly covered. The manuscript must be modified taking into account the following points: 1. Role of lactate. A relevant contributor to cerebral edema in ALF seems to be lactate. Several articles support this role. For example: Zwingmann et al (2003) show that increased brain lactate synthesis and impaired glucose oxidative pathways rather than intracellular glutamine accumulation are the major cause of brain edema in ALF. A role for lactate is also suported by Rose et al (2007) and Bernal (2010). The role of lactate must be discussed and (at least) the above studies must be mentioned. Zwingmann C, Chatauret N, Leibfritz D, Butterworth RF. Selective increase of brain lactate synthesis in experimental acute liver failure: results of a [H-C] nuclear magnetic resonance study. Hepatology. 2003 Feb;37(2):420-8. Rose C, Ytreb? LM, Davies NA, Sen S, Nedredal GI, Belanger M, Revhaug A, Jalan R. Association of reduced extracellular brain ammonia, lactate, and intracranial pressure in pigs with acute liver failure. Hepatology. 2007 Dec;46(6):1883-92. Bernal W. Lactate is important in determining prognosis in acute liver failure. J Hepatol. 2010 Jul;53(1):209-10. 2. Brain region differences of the effects and mechanisms and in their temporal progression. It has been clearly shown by Cauli et al (2011) in rats with ALF that the type of edema (vasogenic or cytotoxic) and the mechanisms involved in their induction are different in different brain areas, specially between cerebellum and cortex. Cerebellum shows vasogenic edema while cortex shows cytotoxic edema. Moreover, the time course of the appearance and progression of edema is also different in different brain areas. These aspects are very relevant and must be discussed and (at least) the above study must be mentioned. Cauli O, López-Larrubia P, Rodrigo R, Agusti A, Boix J, Nieto-Charques L,

Cerdán S, Felipo V. Brain region-selective mechanisms contribute to the progression of cerebral alterations in acute liver failure in rats. Gastroenterology. 2011 Feb;140(2):638-45 3. Another aspect which should be mentioned is that "The persistence of hyperammonemia, rather than its level determines brain glutamine levels, which correlate with IP" (Tofteng et al, 2006) Tofteng F, Hauerberg J, Hansen BA, Pedersen CB, J?rgensen L, Larsen FS. Persistent arterial hyperammonemia increases the concentration of glutamine and alanine in the brain and correlates with intracranial pressure in patients with fulminant hepatic failure. J Cereb Blood Flow Metab. 2006 Jan;26(1):21-7. 4. In several parts the references provided for some statements are not appropriate. Works confirming data from previous studies are cited to support the ideas. The original articles showing the idea must be cited (instead or in addition). For example: 4.1. Page 6: "Neuroinflammation is now widely considered to result from a direct interaction between microglia and ammonia". The article showing that hyperammonemia activates microglia is: Rodrigo R, Cauli O, Gomez-Pinedo U, Agusti A, Hernandez-Rabaza V, Garcia-Verdugo JM, Felipo V. Hyperammonemia induces neuroinflammation that contributes to cognitive impairment in rats with hepatic encephalopathy. Gastroenterology. 2010 Aug;139(2):675-84. 4.2. Page 10 (end) and 11 (beginnig): "Free radicals such as NO and superoxide can be categorised into reactive nitrogen and oxygen species (RNOS), respectively. In cultured astrocytes and in rat brain in vivo, ammonia triggers their formation through N-methyl-D-aspartate (NMDA)-receptor and calcium (Ca2+)-dependent mechanisms". The original article showing that NMDA receptors mediate oxidative stress induced by hyperammonemia in rats in vivo is: Kosenko E, Kaminski Y, Lopata O, Muravyov N, Felipo V. Blocking NMDA rec

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS

This is a comprehensive review of the current mechanisms and viewpoints towards cerebral edema in chronic liver failure. It summarizes major points in this regard and is helpful for researchers. However, there are some problems. 1) The author discussed the already well accepted knowledge like the astrocyte swelling, hyperammonemia too much. My suggestion is to slim the discussion on the already familiar results and focus on the controversy and new progress. 2) Studies of recent 3 years are not fully covered in this review. Some of them are very important. The author should complete this. For example (1) Bosoi, C. R.; Parent-Robitaille, C.; Anderson, K.; Tremblay, M.; Rose, C. F. AST-120 (spherical carbon adsorbent) lowers ammonia levels and attenuates brain edema in bile duct-ligated rats. Hepatology 53:1995-2002; 2011 (2) Bosoi, C. R.; Yang, X.; Huynh, J.; Parent-Robitaille, C.; Jiang, W.; Tremblay, M.; Rose, C. F. Systemic oxidative stress is implicated in the pathogenesis of brain edema in rats with chronic liver failure. Free radical biology & medicine 52:1228-1235; 2012. (3) Bosoi, C. R.; Rose, C. F. Oxidative stress: a systemic factor implicated in the pathogenesis of hepatic encephalopathy. Metabolic brain disease 28:175-178; 2013. (4) Montoliu, C.; Cauli, O.; Urios, A.; ElMlili, N.; Serra, M. A.; Giner-Duran, R.; Gonzalez-Lopez, O.; Del Olmo, J. A.; Wassel, A.; Rodrigo, J. M.; Felipo, V. 3-nitro-tyrosine as a peripheral biomarker of minimal hepatic encephalopathy in patients with liver cirrhosis. The American journal of gastroenterology 106:1629-1637; 2011. (5) Qu, J.; Lu, X. Hydrogen: a promising novel treatment for hepatic encephalopathy? Free radical biology & medicine 63:457-458; 2013.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[Y] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[Y] Accept
[ ] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	
[ ] Grade D (Fair)		BPG Search:	[ ]Rejection
[ ] Grade E (Poor)	[ ] Grade D: rejected	[ ] Existed	[ ] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The manuscript written by Scott et al. summarizes the current understanding of mechanism of cerebral edema and its treatment in acute liver failure. Their institute has been worldwide famous for various achievements for the advances in the understanding of pathophysiology of acute liver failure, and the present review comprehensively summarizes the mechanisms and treatments for brain edema in acute liver failure. Although there is some overlapping in the descriptions, the review provides important information for the management of brain edema in patients with acute liver failure.

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A (Excellent)	[Y] Grade A: Priority Publishing	Google Search:	[ ] Accept
[Y] Grade B (Very good)	[ ] Grade B: minor language polishing	[ ] Existed	[ ] High priority for publication
[ ] Grade C (Good)	[ ] Grade C: a great deal of language polishing	[ ] No records	[ ]Rejection
[ ] Grade D (Fair)	[ ] Grade D: rejected	BPG Search:	[Y] Minor revision
[ ] Grade E (Poor)		[ ] Existed	[ ] Major revision
		[ ] No records	

COMMENTS TO AUTHORS
Scott et al submitted an interesting review dealing with the pathophysiology of brain edema in acute hepatic failure. I found the manuscript very interesting and well-written. Their approach of the underlying pathophysiology of brain edema in this population is appealing. I have some minor concerns regarding their recommendations of monitoring and management that, hopefully, will be addressed by the authors: -Their comments on the role of transcranial sonography in this setting are scarce. Please, describe the patterns associated with high intracranial pressure. -Please, discuss the potential interest of cerebral microdialysis in these patients (mainly as an investigating tool) since it allows measuring different metabolites that can be involved in brain edema. - The recommendation of blood pressure and Cerebral perfusion pressure in these patients (diastolic blood pressure > 40 mmHg higher than ICP and CPP higher than 70 mmHg) can be very difficult to achieve in these patients. In addition, literature supporting these recommendations is poor. Please, support your recommendations. - Barbiturates can be used as a last resort therapy. However, not all the barbiturates are equal and, in addition, they have hepatic metabolism. Do the authors recommend thiopental or pentobarbital?. In TBI, thiopenthal was more effective in reducing high ICP. Please, discuss. Overall, a very interesting piece of work.