Cerebral Blood Flow and Metabolism in Hepatic Encephalopathy—A Meta-Analysis

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Hepatic Encephalopathy (HE) is associated with abnormalities in brain metabolism of glucose, oxygen and amino acids. In patients with acute liver failure, cortical lactate to pyruvate ratio is increased, which is indicative of a compromised cerebral oxidative metabolism. In this meta-analysis we have reviewed the published data on cerebral blood flow and metabolic rates from clinical studies of patients with HE. We found that hepatic encephalopathy was associated with reduced cerebral metabolic rate of oxygen, glucose, and blood flow. One exemption was in HE type B (shunt/by-pass) where a tendency towards increased cerebral blood flow was seen. We speculate that HE is associated with a disturbed metabolism—cytopathic hypoxia—and that type specific differences of brain metabolism is due to differences in pathogenesis of HE. (J CLIN EXP HEPATOL 2018;8:286–293)

During Hepatic Encephalopathy (HE) the deterioration of brain function is accompanied by alterations in brain perfusion and energetics. Over several decades, several studies have focused on this pathophysiological aspect. The regulation of cerebral perfusion is essential in supporting the metabolic requirements for normal brain function. Under normal physiological conditions the global Cerebral Blood Flow (CBF) is kept almost constant during variations in systemic blood pressure—the cerebral autoregulation.¹ Furthermore, during normal brain function the regional changes in neuronal activity are matched with a tight regulation of the regional CBF in the so called neurovascular unit.² Several mechanisms are involved in this, including the myogenic response (the Bayliss effect)³ that couples hydrostatic pressure with vascular wall tone as well as the neurovascular coupling of metabolic supply and demand that acts through numerous and redundant mediators.⁴ Given the multifactorial pathophysiology of HE and the involvement several mechanisms that are directly or indirectly associated with perfusion and energy utilization, it is not surprising that patients with HE suffer from dysmetabolism and dysperfusion of the brain. For example, cerebral ammonium

toxicity has experimentally been shown to affect extracellular potassium buffering,⁵ adenosine tone,⁶ glutamate signaling,⁷ lactate homeostasis,⁸ and microglia activation,⁹ which all represent potential points of interference with normal CBF regulation. With this literature review we summarize the published data on CBF and brain metabolism in patients with HE with special focus on: (1) the effect of HE on the global absolute CBF (mL of blood/100 g brain tissue * min) and (2) the cerebral metabolic rates of oxygen (CMR_{O2} (mL of oxygen/100 g brain tissue * min)) and glucose (CMR_{glc} (μmol of glucose/100 g brain tissue * min)).

METHODS

We performed our literature search using the terms “hepatic encephalopathy” and “cerebral blood flow”, “brain blood flow”, “fulminant liver failure”, or “cerebral metabolic rate”. The final search was completed in January 2018, using the following search engines: MEDLINE, Scopus, Web of Science, and Embase. From the publications, we extracted estimates of CBF and cerebral metabolic rates. Our inclusion criteria were: human data on absolute measurements of CBF in patients with HE. Analyses were done in the statistical software R ver. 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria) using the package ‘metafor’. We calculated standardised mean differences of CBF and metabolic rates and fitted random-effects models as a conservative effect measure. I^2 was used as a marker of heterogeneity. We undertook subgroup analyses based on the aetiology of HE and the method of CBF measurements. The majority of the studies reported results expressed in means ± standard deviation. Where median (range) values were used we accepted the median as an approximation of the sample mean and estimated the standard deviation as (maximum–minimum)/4.

Keywords: hepatic encephalopathy, liver failure, cerebral blood flow, cerebral metabolism

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Abbreviations: ALF: Acute Liver Failure; CBF: Cerebral Blood Flow; CMR: Cerebral Metabolic Rate; HE: Hepatic Encephalopathy; ICH: Intracranial Hypertension; MHE: Minimal Hepatic Encephalopathy; MRI: Magnetic Resonance Imaging; OHE: Overt Hepatic Encephalopathy; pcMRI: Phase-Contrast MRI; PCS: Portocaval Shunt

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RESULTS

Our literature search resulted in 345 individual publications. Of these, 80 papers contained human original data. After exclusion of publications with case reports or only relative changes in CBF, we finally included 27 papers with absolute measurements of CBF in patients with HE. Of these, 16 described comparisons between patients with HE (minimal and/or overt) and controls (healthy subjects and/or cirrhotic patients without HE) allowing us to estimate the standardized mean differences. 14 studies also reported data on CMR_{O_2} and CMR_{glc} . The 27 included studies are listed in Table 1 and the CBF data from each study in Table 2.

Our meta-analysis revealed a large degree of variation in CBF results across studies (Table 2). By limiting our analysis to the 16 studies that included comparisons between groups we found no clear difference between patients with HE compared with controls (Figure 1).

The random-effects analysis showed substantial heterogeneity ($I^2 = 90.88\%$). We therefore undertook subgroup analyses based on the type of HE and modality of CBF measurement. These analyses showed that MRI and N_2O based methods resulted in higher CBF during HE (Figure 2A) and that HE type B in contrast to type A and C was more likely to result in increased CBF (Figure 2B).

The metabolic rates of oxygen were significantly lower in patients with HE (Figure 3), but the analysis demonstrated substantial heterogeneity. The metabolic rate of glucose tended to be lower during HE, but only three studies were available for this comparison.

DISCUSSION

Our findings support the current understanding of HE as a metabolic encephalopathy with reduced neuronal

Table 1 The 27 Included Studies in the Meta-Analysis.

Author	Year	Journal	HE type	Method
Zheng ¹⁸	2017	European Journal of Radiology	Cirrhosis OHE	pcMRI
Zheng ¹⁹	2013	European Journal of Radiology	MHE	MRI Arterial Spin
Strauss ²⁰	2001	Gastroenterology	ALF	Kety-Schmidt 133-Xe
Almdal ²¹	1989	Scand J Gastroenterology	ALF	Kety-Schmidt 133-Xe
Aggarwal ²²	1991	Transpl Proc	ALF	Kety-Schmidt 133-Xe
Wendon ²³	1994	Hepatology	ALF	Kety-Schmidt 133-Xe
Durham ²⁴	1995	JCBF	ALF	Kety-Schmidt 133-Xe
Jalan ²⁵	2001	Hepatology	ALF-ICH	N_2O
Jalan ²⁶	2004	Gastroenterology	ALF-ICH	N_2O
Dam ²⁷	2013	Hepatology	Cirrhosis OHE	PET 15-O
Iversen ²⁸	2009	Gastroenterology	Cirrhosis OHE	PET 15-O
Porro ²⁹	1969	Gut	PCS	N_2O
Zheng ³⁰	2012	European Journal of Radiology	After TIPS	MRI Arterial Spin
Jalan ³¹	2010	Journal of Hepatology	1 h after TIPS	N_2O
Ahl ³²	2004	Hepatology	MHE	PET 15-O
Larsen ³³	2000	Critical Care Medicine	ALF	Kety-Schmidt 133-Xe
Larsen ³⁴	2000	Critical Care Medicine	ALF	Kety-Schmidt 133-Xe
Larsen ³⁵	1999	Transplantation	ALF	Kety-Schmidt 133-Xe
Philips ³⁶	1998	Hepatology	Cirrhosis OHE	N_2O
Larsen ³⁷	1996	Livertransplantation Surgical	ALF	Kety-Schmidt 133-Xe
Larsen ³⁸	1995	Hepatology	Cirrhosis OHE	Kety-Schmidt 133-Xe
Lockwood ³⁹	1991	JCBF	Liver disease	PET 15-O
Testa ⁴⁰	1989	Ital J Neu Sci	MHE	Kety-Schmidt 133-Xe
Rodriguez ⁴¹	1987	JCBFM	MHE	Kety-Schmidt 133-Xe
James ⁴²	1971	Gut	Cirrhosis OHE	Kety-Schmidt 133-Xe
Posner ⁴³	1960	J Clin Invest	Cirrhosis OHE	Kety-Schmidt
Fazekas ⁴⁴	1956	American Journal of Medicine	Cirrhosis OHE	Kety-Schmidt

ALF: Acute Liver Failure; ICH: Intracranial Hypertension; MHE: Minimal Hepatic Encephalopathy; MRI: Magnetic Resonance Imaging; OHE: Overt Hepatic Encephalopathy; pcMRI: Phase-Contrast MRI; PCS: Portocaval Shunt.

Table 2 Cerebral Blood Flow Estimates From the Included Studies.

Author	Year	OHE			ALF			Shunt (TIPS/PCS)			MHE			Cirrhotic controls			Healthy controls			
		N	CBF mean ± s.d.	N	CBF mean ± s.d.	N	CBF mean ± s.d.	N	CBF mean ± s.d.	N	CBF mean ± s.d.	N	CBF mean ± s.d.							
Zheng	2017	8	45.3	±16.0							11	55.6	±7.9							
Zheng	2013				16	39.0	±8.0				16	67.4	±11.5		20	52.2	±12.0	25	48.8	±8.9
Strauss	2001				16	39.0	±8.0								5	62.0	±11.0	8	63.0	±9.0
Almdal	1989				12	31.0	±4.0													
Aggarwal	1991				33	42.0	±19.8													
Wendon	1994				30	30.0	±14.3													
Durham	1995				24	42.0	±13.0											24	55.0	±10.0
Jalan	2001				9	111.0	±16.3													
Jalan	2004				14	78.0	±9.7													
Dam	2013	10	29.1	±9.4											9	44.7	±6.2			
Iversen	2009	6	30.2	±2.5											6	48.9	±5.1	7	51.0	±7.6
Porro	1969							8	97.6	±26.8					8	63.8	±22.1	12	54.3	±9.1
Zheng	2012							9	65.5	±17.9					9	60.0	±11.0			
Jalan	2010							9	67.2	±9.6					9	53.2	±7.2			
Ahl	2004										5	42.4	±6.2		3	52.8	±11.1			
Larsen	2000				8	34.0	±16.3													
Larsen	2000				12	30.0	±9.8													
Larsen	1999				13	43.8	±10.4													
Philips	1998	14	44.0	±16.3																
Larsen	1996				6	34.0	±10.8													
Larsen	1995	6	60.8	±11.9														6	67.5	±13.3
Lockwood	1991														11	51.0	±24.0	11	54.0	±20.0
Testa	1989										20	42.3	±6.9		10	47.5	±5.4			
Rodriguez	1987										18	42.0	±7.0					18	50.0	±6.0
James	1971	6	56.0	±18.4																
Posner	1960	18	39.3	±10.9														11	53.0	±8.0
Fazekas	1956	16	39.6	±8.0											20	47.1	±8.1			

Data expressed as means $\pm$ standard deviation in the unit of mL blood/100 g*min. ALF: Acute sLiver Failure; MHE: Minimal Hepatic Encephalopathy; OHE: Overt Hepatic Encephalopathy; PCS: Portocaval Shunt; TIPS: Transjugular Intrahepatic Portosystemic Shunt.

Figure 1 Random-effects meta-analysis of studies with estimates of standardized mean differences (SMD). Insert: funnel plot. ALF: Acute Liver Failure; Minimal HE: Minimal Hepatic Encephalopathy; OHE: Overt Hepatic Encephalopathy; PCS: Portocaval Shunt; TIPS: Transjugular Intrahepatic Portosystemic Shunt.

activity and hence a reduced CBF and delivery of oxygen and glucose. Generally, we found that the results were characterised by a rather large degree of variation and substantial heterogeneity between studies. Of interest we found that HE due portacaval shunting (type B) was associated to an increased CBF, in contrast to studies of patients with HE of type A and C. This could indicate that the pathogenesis in HE is type specific and that the isolated hyperammonia that is often seen in type B HE leads to vasodilation and hyperperfusion, which also has been observed in animal studies.¹⁰ It is also noteworthy that the cerebral metabolic rates tended to be unaltered in type B HE in contrast to the reduced metabolic rates that were seen in type A and C. Since type A and C HE often is seen in patients with multi-organ failure, infections and electrolyte disturbances it is likely that the brain metabolism and blood flow is affected in a multi-factorial fashion that leads to reduced neuronal activity and hence reduced blood flow. It is important to stress

the fact that we found substantial heterogeneity in our meta-analysis and that most of the studies were done with rather small sample sizes and at different time-points in the disease course. It should also be noted that we were not able to account for the individual arterial partial pressures of carbon dioxide, haemoglobin levels or the type and depth of sedation, which all could represent potential confounding factors.

One interesting aspect observed in several experimental and clinical studies is cerebral accumulation of lactate^{8,11-16} and we have previously proposed that the brain is suffering from some kind of cytopathic hypoxia¹³—e.g. a condition with anaerobic metabolism in spite of sufficient delivery of oxygen. This is based on the circumstance that the metabolic abnormalities seem too extensive to simply reflect reduced neuronal activity. Conditions associated with hypoxic metabolism include: (1) ischemia hypoxia due to low perfusion pressure, (2) low oxygen extraction due to low pO_2 , anaemia, or increased

Figure 2 Random-effects subgroup analysis based on the modality of cerebral blood flow measurement (A) and aetiology of hepatic encephalopathy (B).

Figure 3 Random-effects meta-analysis of cerebral metabolic rates of oxygen (A) and glucose (B).

haemoglobin oxygen affinity, (3) arteriovenous shunting, (4) increased diffusion distance or reduced endothelial diffusion area, (5) impaired mitochondrial function, and (6) hypermetabolism. Most of these types of hypoxia can be excluded in HE based on published experimental and clinical data cited above. However dysperfusion in the cerebral microcirculation—for example due to shunting—might be a possible explanation, that to our knowledge has not been thoroughly studied although the hypothesis is far from new.¹⁷

In conclusion, we have found substantial heterogeneity in the published results on CBF and metabolic rates for oxygen and glucose in patients with HE. However, a general tendency towards reduced flow and metabolism was found.

CONFLICTS OF INTEREST

The authors have none to declare.

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