Predicting hepatic encephalopathy

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Introduction

One of the main functions of the liver is to remove waste products from the blood. In patients with scarring of the liver (cirrhosis) as a result of chronic liver disease this process can be impaired and patients are at risk of developing hepatic encephalopathy (HE), a spectrum of neuropsychiatric abnormalities, which can affect the quality of the patient's life and is also a poor prognostic factor.

Under normal circumstance blood from the gut, containing harmful substances (toxins), travels via the portal vein to the liver, where it is detoxified (see Figure 1). However, when the liver is scarred, portosystemic shunts may develop: abnormal connections between the blood supply from the gut and the blood supply going to the heart (and thereon to the brain), thus bypassing the liver. Because of this bypass (or shunt), the liver does not filter the blood, and nitrogenous waste products from the intestine, in particular ammonia (NH_3), gain access to the systemic circulation and the brain, where they can lead to swelling, resulting in clinical symptoms (see Figure 2).

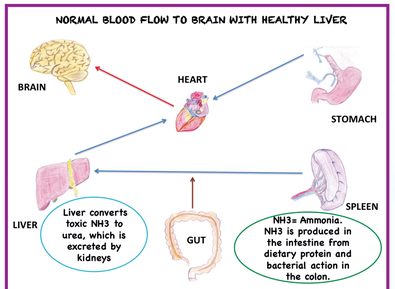


Figure 1 shows the normal blood flow to the brain with a healthy liver.

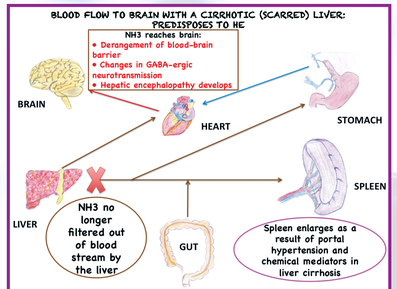
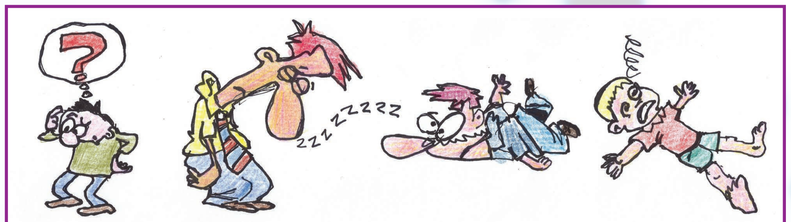


Figure 2 shows the blood flow to the brain with a cirrhotic liver and portosystemic shunts, putting the patient at risk of HE.

HE can be episodic or persistent and can lead to coma (see Figure 3). It is difficult to predict and in the early stages, hard to detect. Most patients with cirrhosis will develop some degree of HE during the course of their disease. Up to 45% develop overt HE (grades II - IV) and up to 80% develop minimal HE (grade I). In 2008



Grade I - Shortened attention span

Grade II - Lethargy with slight disorientation

Grade III - Somnolence with gross disorientation

Grade IV - Coma

Figure 3 West Haven criteria for grading hepatic encephalopathy: clinical presentation

prevalence of HE was 1.4 per 100 000 in the UK.

Overt HE (grades II - IV) affects the quality of life of patients with liver cirrhosis and is a poor prognostic indicator: from the onset of HE, patients with liver cirrhosis have a 3 year survival of only 23%. There is currently no accepted system for early recognition or risk stratification for HE in patients with chronic liver disease. It is a clinical diagnosis and patients can present with subtle cognitive defects that may not be detected early. Crucially, if HE is diagnosed, there are treatments, which can improve both length and quality of life.

What are we interested in?

The objective of this project was to derive a risk score, based on

a) routine imaging data performed in patients with chronic liver disease: an ultrasound (USS) and computed tomography scan (CT) of the abdomen, which allow us to measure the size of the spleen. This functions as a proxy indicator that the blood from the gut is bypassing the liver due to scarring, as this process frequently leads to enlargement of the spleen;

b) the UKELD score, which is routinely calculated to predict the prognosis of patients with chronic liver disease, from the results of simple blood tests; and

c) basic patient data, such as weight.

It was hoped that the result of the project would provide a method to enable non-specialists (such as GPs) to identify those patients at higher risk of encephalopathy, to enable treatment to be initiated before the development of this life-threatening complication.

What does this mean?

This study constitutes the **first step** in the attempt to build a successful model for the prediction of encephalopathy risk in patients with liver cirrhosis. Our predictive model using weight, UKELD score and spleen size measured by USS, **provides GPs with a tool to predict low risk of encephalopathy in patients with chronic liver disease**, and thereby rule out the necessity of an urgent referral for specialist assessment. Despite the good predictive power of this model, a margin of error nonetheless remains, hence, it should not to be used in isolation but as an adjunct to clinical judgement

Who are we?

I am a final year medical student at the University of Edinburgh. My supervisor was Mr Ian Currie, a consultant transplant surgeon at the Royal Infirmary of Edinburgh.

This work was done in the Scottish Liver Transplant Unit. I would like to acknowledge the University of Edinburgh for facilitating this research and Medical Research Scotland for funding my Vacation Scholarship. I would also like to offer thanks to the transplant coordinators and the data manager at the Royal Infirmary of Edinburgh, for their assistance. With many thanks to Saoud Al-Khuzaei, final year medical student at the University of Edinburgh who made the anatomical drawings in Figures 1 and 2.

What did we do and what did we find?

We used statistical analysis to investigate whether a combination of a patient's UKELD score, weight and spleen size on USS can enable us to predict the risk that they will develop HE. We obtained data from 76 patients with chronic liver disease awaiting transplant including the UKELD score, whether the patient developed encephalopathy or not, and patient weight.

Imaging data relating to the size of the spleen was obtained from abdominal CT scans and USS (see Figure 4). We found a significant correlation between spleen size on USS and on CT which would allow the use of USS measurements in a risk prediction model for encephalopathy (see Figure 5). In the clinical setting, USSs are quicker and cheaper to obtain than CT scans and abdominal CT scans are not conducted routinely in chronic liver disease patients who are not being assessed for transplant.

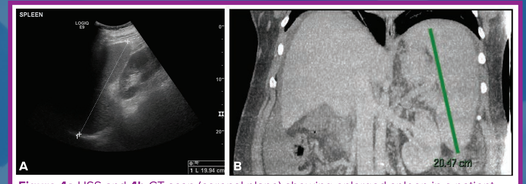


Figure 4a USS and **4b** CT scan (coronal plane) showing enlarged spleen in a patient with liver cirrhosis.

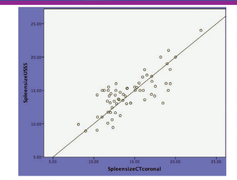


Figure 5 Plot of linear correlation between spleen size on USS and spleen size on CT scan.

A probabilistic statistical methodology, called binary logistic regression analysis, showed that UKELD score, weight and spleen size on USS have predictive value where the development of HE is concerned (see Figure 6)

This model has reasonable strong negative predictive value: it can predict low risk of developing HE correctly and did so in 90.2% of cases. However, we are currently working on including different factors to increase both negative predictive value, as well as positive predictive value: the ability to predict that a patient *will* develop HE (see Figure 7).

A model was developed with GPs in mind, to enable patient categorization into low and increased risk for encephalopathy. It has high negative predictive value (90.2%) and a good fit (p= 0.020). The followinng equation was derived in order to predict the probability that a patient will not develop encephalopathy:

	B (SE)	95% confidence intervals for odds ratio		
		Lower	Odds Ratio	Upper
UKELD score	0.144 (0.060)	1.026	1.155	1.300
Spleen length on USS	-0.038 (0.112)	0.773	0.962	1.198
Weight (kg)	-0.029 (0.018)	0.939	0.972	1.006
Constant	-5.892			

Figure 6 Regression coefficients and odds ratios for the regression model.

Classification table[a]

			Predicted		
			Encephalopathy yes or no		
	Observed		no	yes	Percentage correct
Step 1	Encephalopathy yes or no	no	37	4	90.2
		yes	15	6	28.6
	Overall percentage				69.4

a. The cut value is .500

Figure 7 Illustrates the ability of our model to correctly predict whether or not a patient will develop HE.

$$\text{Probability} = 1 - \left(\frac{e\{(0.144 \times \text{UKELD score}) + (-0.038 \times \text{spleen length on USS}) + (-0.029 \times \text{weight in kg}) - 5.892\}}{1 + e\{(0.144 \times \text{UKELD score}) + (-0.038 \times \text{spleen length on USS}) + (-0.029 \times \text{weight in kg}) - 5.892\}} \right)$$

Phoebe was supervised during her Vacation Scholarship project, *"Hepatic Encephalopathy in Liver Transplant Candidates"*, by Mr Ian Currie.