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The current pediatric perspective on type B and C hepatic encephalopathy

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ABSTRACT

That children present with hepatic encephalopathy (HE) in the setting of acute liver failure (ALF) is accepted and a recognized prognostic factor for survival [1,2]. What is less understood is the impact of chronic liver disease (CLD) on the neuro-cognitive and –psychiatric development and outcomes of children with chronic liver disease early in life. Much is extrapolated from the adult literature or from work in experimental models. But what distinguishes children is that central nervous system development, characterized by massive brain growth, is ongoing at the time of liver disease, arguably exposing them to unique risks, something which cannot be extrapolated from adults. The purpose of this brief review is to summarize what is distinctive about the neurocognition of children with CLD or having presented CLD or portosystemic bypass in childhood.

1. Definition and classification of hepatic encephalopathy in adults and children\

1.1. Definition

Hepatic encephalopathy (HE) is be defined as brain dysfunction caused by liver insufficiency and/or portal-systemic shunting, that manifests as a wide spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma [3]. There is no clear definition of HE in children, although in practice, extrapolation from evidence in adults is common.

1.2. Classification

HE is classified in adults and children according to underlying disease and severity of clinical manifestations. Pathophysiology varies between acute and chronic liver disease. Table 1 summarizes a classification considering type, severity, trend, precipitating factors and response to treatment. The focus of the present paper is type B and C HE in children.

2. Prevalence and diagnosis in children

Although still underestimated, chronic hepatic encephalopathy in children is detectable much as it is in adults: covert or minimal encephalopathy requires imaging or neuropsychological testing for diagnosis, while overt encephalopathy can be identified on clinical exam or by taking a thorough history. In the chronic setting, children can present with either type B (due to portosystemic shunting) or C (chronic liver disease) encephalopathy, similar to what has been described in adults-it is these chronic forms of HE which will be the focus of the present discussion. Type B encephalopathy refers to portosystemic encephalopathy in the context of congenital portosystemic shunts (CPSS) or extrahepatic portal vein thrombosis (EHPVT) and secondary portosystemic collaterals [4]. In pediatrics, the most common cause of cirrhosis and therefore type C HE is biliary cirrhosis. Akin to adults, the challenge is identifying those patients with covert or minimal HE (MHE), as it is commonly held that they could benefit from early intervention to optimize long-term outcomes whether with native liver or following liver transplantation.

2.1. Burden of disease

Historically, HE was considered completely reversible. Recent observations in adult patients have put this into question by showing that some deficits in working memory and learning , unlikely to be ascribable to other transplantation-related causes, may persist after liver transplantation [5]. Whether this holds true in children who experienced type

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Table 1
Classification, grading and clinical features of hepatic encephalopathy.

1. Type	2. Severity grading	3. Trend	4. Precipitating factors	5. Response to treatment
Type A: associated with acute liver failure	Covert: -Minimal or latent -West Haven grade 1	Episodic (<2 episodes in 6 months)	-Gastrointestinal bleeding -Bacterial infections -Electrolytes imbalance	-Correction of fluids and electrolytes -Lactulose -Oral antibiotics (rifaximin)
Type B: associated with porto-systemic shunting without liver disease	Overt: -West Haven grade 2 -West Haven grade 3 -West Haven grade 4 (coma)	Recurrent (≥2 episodes in 6 months)	-Constipation -Overtreatment with diuretics	-Systemic antibiotics
Type C: associated with cirrhosis		Persistent (dementia-like)		

B or C hepatic encephalopathy early in life, is not well established, but there is compelling evidence that children after LT experience a higher need of learning support that the general population which may be a surrogate for irreversible sequalae [6–8].

It is important to emphasize that children following liver transplantation display a high rate of mental retardation, learning disability, and among those who go to school, an increasing need for additional support over time [6]. This need for support is out of range with what is reported in pediatric recipients of other solid organs [9], suggesting a unique vulnerability of patients with liver disease. We understand from patients who present early in life with hyperammonemia due to urea cycle disorders that the neurocognitive consequences are life-long [10]. Although children with CLD do not have the same degree of hyperammonemia, they are exposed to low-grade elevation of plasma ammonia as well as to other neurotoxins owing to impaired hepatic first pass, during a critical window of brain development and growth. Duration of disease does appear to increase the likelihood of globus pallidus hyperintensity of T1 weighted magnetic resonance imaging [11]. However, one should not rule out the potential role of numerous other factors on cerebral functioning and development in the setting of chronic liver disease (Fig. 1). The relative contribution of these factors to the final neurocognitive outcomes of patients with CLD or PS shunting in childhood is difficult to quantify.

3. Functional domains impacted

Unlike what has been reported in this issue in adult patients with CLD [12], depression and mood disorders have not been reported in detail in children with CLD. Rather, the following functional domains seem to be impacted by the consequences of CLD or portosystemic bypass, resembling what has been reported in adults: attention span, executive functioning, occasional memory loss, and language acquisition, all in all pointing to pre-frontal functioning [13–15]. The real-life difference with adults however, is that these changes arise in a developing brain. As such, they are unlikely to be temporary, but rather associated with life-long consequences. Of concern is the fact that some of these deficits have been identified in infants with cholestatic liver disease being evaluated for liver transplantation, with all infants scoring below the norm for gross motor, fine motor, visual reception, receptive language, and expressive language. Importantly, gross motor skills and expressive language skills were well below 2 standard deviations [16].

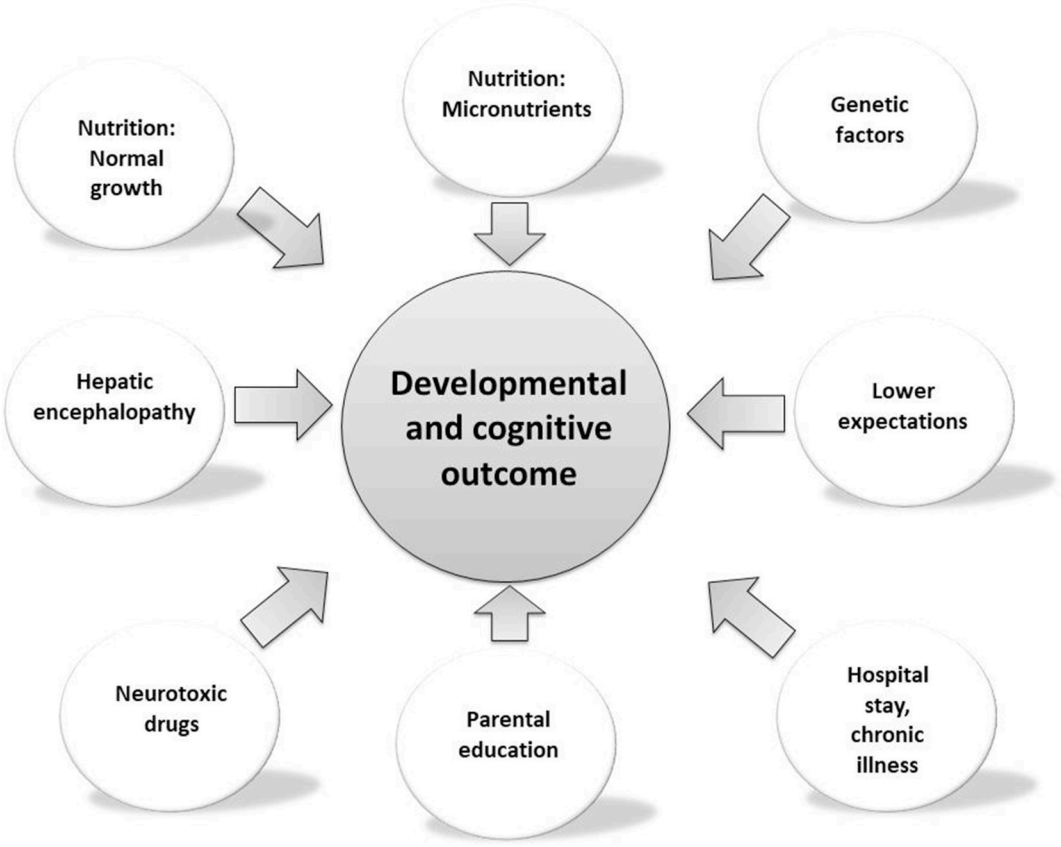

Fig. 1. Potential variables contributing to neurological outcomes in children with chronic liver disease or portosystemic shunting.

4. Pathophysiology

Much of what is understood about the pathophysiology of HE in children is either derived from adult studies or from studies in children with urea cycle defects. Both of these models are imperfect to understand type B and C HE for the reasons mentioned above: the adult brain is not undergoing development at the time of exposure to ammonia and other neurotoxins, and patients with urea cycle defects are exposed to extremely high plasma ammonia levels, often in the newborn period, well beyond what is seen in children or adults with CLD [17,18]. Further, patients with UCD have an otherwise normal liver, without cirrhosis, portal hypertension, and the ensuing inflammation. The reader is referred to other papers in this issue for details on the pathophysiology of HE, the role of ammonia and glutamine, the role of inflammation, and ensuing edema.

Therefore, animal models have proven paramount in apprehending the consequences of CLD on the developing central nervous system (CNS) [19]. Most relevant to the problem of biliary cirrhosis in children, is the recent study using high field ^{1}H-MRS to analyze 15 brain metabolites in young rats longitudinally after BDL, modeling human ages 8 months to 8 years. Although this study confirmed the findings in adult animals [20], it did show that brain Gln is related to plasma ammonia, and that the correlation between the two is much stronger than in adult animals, suggesting an age-dependent vulnerability [21]. What more, the response to the osmotic stress induced by Gln was followed by significant changes in osmolytes, together with modifications in oxidative and metabolic stress were all stronger than what was observed in adult animals [20]. Novel findings included significant fluctuations in aspartate, GABA, lactate, and glutathione not previously observed in adult animals. In addition, brain total creatine (tCr) decreased significantly over the course of the study [21]. Finally, it is important to highlight that while osmotic stress is associated with some degree of low-grade brain edema in this model [20] and in adults with CLD [22], there is only preliminary evidence in children with CLD or PSS [23].

Although ammonia is most likely not the only driver of biochemical and signaling abnormalities in the CNS of children or young animals with CLD, organotypic brain cultures of pup rats exposed to ammonia have taught us that ammonia does impair axonal growth and that creatine is protective [24]. It is intriguing to consider this report together with findings of Cr decrease in the *in vivo* longitudinal model above [21].

Finally, the role of bile acids in HE has been queried, certainly in the case of type A HE [25–27]. The G-protein-coupled bile acid receptor 1 (TGR5; Gpbar1) is expressed in astrocytes and neurons, and its expression downregulated in the presence of ammonia [28]. It was recently reported that in organotypic cultures of rat hippocampus, exposure to a mix of bile acids impacted dendritic spine turnover, pointing to altered synapse formation [29]. In sum, while evidence in favor of a role for bile acids in the pathogenesis of type B and C HE is mounting, much is still unknown.

5. Diagnostic tools

5.1. Magnetic resonance imaging and spectroscopy

The challenge of studying children is two-fold: imaging often requires sedation in children aged 5 and below, although new techniques are being developed to overcome this obstacle [30–32]. In addition, neuropsychological (or psychometric) testing may be onerous in sick children who are also highly likely to under-perform owing to illness or context [33]. Nonetheless, several studies have reported the hallmark imaging feature of HE in children with liver disease or porto-systemic bypass, namely a hyperintense signal of the *globus pallidus* on T1 weighted magnetic resonance imaging (MRI) [11,23,34–37]. There are several reports suggesting that upward of fifty percent (50%) of children with CLD or portosystemic bypass suffer by some kind of neuro-cognitive involvement [11,23].

The limitation of most of these studies is the lack of correlation between imaging and neurocognitive assessment, something in part overcome by Srivastava and colleagues in 2017 [23]. Using MRI, MR spectroscopy, and diffusion tensor imaging (DTI), they showed that performance on neuropsychological testing (NPT) was related to neurometabolic profile and that mean diffusivity in frontal white matter was the best discriminator of MHE. Of note, while plasma ammonia was not outside the normal range in patients with MHE, it was significantly higher than in patients without MHE. Interestingly, the proportion of patients with autoimmune liver disease was greater than in typical cohorts. These two points will be discussed below in regards to pathophysiology.

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a tool of interest to non-invasively measure neurometabolites in the brain of children with CLD. The higher the magnetic field, the higher the spectral resolution, which confers an advantage to study brain metabolites non-invasively. Arguably, ^{1}H-MRS could also serve to follow patients with type B or C HE longitudinally, for example to assess response to treatment, although the exact protocol and area of interest still need to be identified [12]. Still, we can learn from studies performed to date. Table 2 summarizes the findings of a few relevant studies using ^{1}H-MRS conducted in animals and humans. In summary, there are two main messages to be extrapolated from these data. The first is that the hallmark glutamine (Gln) elevation does suggest some low grade response to an increased ammonium load even if minimal; it is tempting to consider that chronic exposure does cause osmotic stress in astrocytes, not just absolute numbers. Second is the finding that some degree of brain edema is indeed observed in chronic HE [38], although this needs confirmation in children.

Finally, using conventional MRI, a decrease in brain volume has been described in adults, something which was just recently reported in a child with biliary cirrhosis, and which corrected following liver transplantation [39]. While some degree of brain atrophy was previously reported in adults [40], this finding in a child highlights the probable impact of CLD and its many variables on brain growth and development.

5.2. Neurocognitive or psychometric testing

Psychometric testing has been developed extensively in adults. Although a wide range of tools have been used and reported, there is still some debate about a standardized battery of tests. It follows that in children, there is also no standard approach, an area clearly ripe for investigation. Compared to adults, there are several additional challenges in the neurocognitive assessment of children. First, tests should be age-appropriate to test developmentally correct milestones. Second, defining which domains are affected by HE and consequently should be screened for is another area which needs further research. Third, the testing method needs to be reliable and reproducible.

Several tests designed to explore cognitive functions in children and meeting the above criteria have been developed and validated in several languages. In order to reliably test a child's abilities, the battery of tests should be administered by an expert pediatric neuropsychologist ideally during a single session. A previous study reported that selective attention, executive functioning, and short-term visual memory were the domains more frequently altered in children with CLD or PSS. The psychometric testing protocol assessed the following domains: abstract reasoning, school learning, memory, perception and praxis, attention, and executive functioning [13].

5.3. Neurophysiological studies

Children with extrahepatic portal hypertension and MHE have altered EEG patterns. Quantified electroencephalogram (EEG) may be an interesting tool to detect MHE, given that its result is independent of patient performance or education [13], and that it is less cumbersome than MRI [41]. Unfortunately, to date, EEG measures have not been

Table 2
Summary of proton spectroscopy and MRI findings in animals and human Gln: glutamine, GP: globus pallidus, mI: myoinositol, Lac: lactate, tCr: total creatine, Glx: combined glutamate and glutamine.

	Author (reference)	Liver disease	Magnet	MRI findings*	Metabolite	Comment
Rat						
Adul	Braissant [19]	BDL	9.4T	n/a	↑Gln, ↓ osmolytes	
Pup	Rackayova [20]	BDL	9.4T	n/a	↑ Gln, ↑Lac, ↓osmolytes and tCr	
Human						
Adult						
	Chavarria [35]	Mixed	1.5T	Edema ↑ T1 signal GP ↓ brain volume	↑Gln, ↓mI and choline	
Child						
	Hanquinet [11]	Mixed	1.5T	↑ T1 signal GP	↓mI/Cr	
	Foerster [28]	Mixed	1.5T	↑ T1 signal GP		
	Yadav [30]	EHPVO	1.5T		↑Glx/Cr ratio	Gln vs Glu discrimination not possible at 1.5T
	Srivastava [29]	CLD	1.5T	↑ T1 signal in GP + frontal white matter diffusivity	↑ Gln **	

shown to be related to performance on NPT or school performance.

What more, imaging, plasma ammonia, or EEG have not been analyzed in association with school performance, which is the most commonly reported complaint by parents of children with CLD or portosystemic bypass.

5.4. Laboratory tests

Remarkably, ammonia is the most important biochemical marker in patients suspected to have HE, and is almost invariably increased, usually slightly (<2 ULN). In fact, although the degree of increase in blood ammonia levels is not linearly correlated to the severity of HE, normal ammoniemia should put the diagnosis of HE in question [42].

6. History and clinical exam

Neurological exam is of limited value in assessing the child with chronic liver disease and possible HE. The only recognized clinical assessment scale is for Wilson's disease [43], which comes with its own set of neurological symptoms, and therefore cannot be generalized to the child with CLD. Therefore, the finer tool is probably a thorough history. Clinical signs associated with HE are summarized in Table 3. Symptoms reported by families of children with CLD and MHE include daytime sleepiness, seizures, irritability, aggressive behavior, attention deficit, and executive functioning difficulties [13,34]. It is particularly important to assess if the child has repeated any grades and if he/she is in the right level for his/her age. The simple question 'how is she doing in school' is insufficient, because in the setting of chronic disease parents often omit to share that she has repeated a grade, needs special assistance, or has changed school to benefit from specialized support [44].

Table 3
West haven criteria for the diagnosis of hepatic encephalopathy.

Stage	Distinguishing Features
0	No abnormality detected
I	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impairment of addition or subtraction
II	Lethargy or apathy
	Disorientation for time
	Obvious personality change
	Inappropriate behavior
III	Somnolence to semi-stupor
	Responsive to stimuli
	Confused
	Gross disorientation
	Bizarre behavior
IV	Coma, unable to test mental state

7. Treatment

Management of MHE depends in large part on underlying liver disease. Cirrhosis and portal hypertension will likely indicate liver transplantation, which may ultimately protect from further neurometabolic disturbances hindering ultimate neurocognitive outcomes. In case of EHPVO, however, the risk of progression of cognitive impairment may be greater as these patients typically do not have liver dysfunction, and as such are not candidates for liver transplantation. When portal perfusion can be restored such as through the use of Meso-Rex bypass, it has been shown that cognitive fluency is restored [15]. In the case of CPSS, there is now mounting evidence in the literature that school performance improves following shunt closure [4,45].

There is no satisfactory medical treatment for pediatric HE at the present time. Anecdotal experience using lactulose, L-ornithine L-aspartate, rifaximin and nitrogen scavengers is not sufficient to make firm recommendations. In rodent models, the use of rifaximin and/or probiotics does suggest that they may attenuate the neurometabolic response to Gln [46,47].

Other exciting candidate molecules are emerging from animal studies that could be tested quite easily in humans and in particular children: creatine has been used in other pediatric neuro-metabolic conditions [48], and antioxydants such as ascorbic acid seem like low hanging fruit [20]. The challenge will be to measure the outcome of any intervention in such a complex, multifactorial clinical condition.

8. Future directions and unmet needs

Clearly, much is still unknown about the impact of CLD or portosystemic bypass on the developing brain of children. At this juncture, the priority should be on identifying subclinical disease and recognizing modifiable factors amenable to intervention. What holds true for UCD may not hold true for type B and C HE. In other words, some domains may be amenable to medical or behavioral therapies. Therefore early diagnosis and prevention should be a goal of the community working with children at risk. Understanding the determinants of neurocognitive outcomes in patients who suffered from CLD or PSS early in life is a clear, unmet need.

Well-designed studies on screening tests, biomarkers of HE, and other variables such as environmental and genetic contributors are strongly needed. Neurometabolic studies may help identify molecular methods of prevention or treatment. How the outcome of such an intervention is measured also remains to be determined, but all efforts

should be made to recognize the factors impacting long term neurocognitive development of patients with childhood liver diseases.

Declaration of competing interest

The authors have no conflict of interest to disclose.

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