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REVIEW

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Neuromonitoring in Rare Disorders of Metabolism

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Inborn errors of metabolism (IEM) are a unique class of genetic diseases due to mutations in genes involved in key metabolic pathways. The combined incidence of IEM has been estimated to be as high as 1:1000. Urea Cycle disorders (UCD), one class of IEM, can present with cerebral edema and represent a possible target to explore the utility of different neuromonitoring techniques during an hyperammonemic crisis. The last two decades have brought advances in the early identification and comprehensive management of UCD, including further understanding of neuroimaging patterns associated with neurocognitive function. Nonetheless, very important questions remain about the potential acute neurotoxic effects of hyperammonemia to better understand how to treat and prevent secondary brain injury. In this review, we describe existing neuromonitoring techniques that have been used in rare metabolic disorders to assess and allow amelioration of ongoing brain injury. Directions of future research should be focused on identifying new diagnostic approaches in the management of metabolic crises to optimize care and reduce long term morbidity and mortality in patients with IEM.

INTRODUCTION

Inborn errors of metabolism (IEM) are a unique class of genetic diseases caused by mutations in genes involved in key metabolic pathways. There are more than 1000 IEM described to date and different taxonomical approaches have been used to categorize them [1,2]. Partial or complete defect in a specific enzyme or transport protein or co-factor leads to manifestations of the disease by one of the following mechanisms – a. accumulation of a toxic metabolite (eg, urea cycle disorders, galactosemia, maple syrup urine disease, etc.), b. failure of energy machinery (eg, fatty acid oxidation disorders, glycogen storage disorders, mitochondrial diseases, etc.) and c. abnormal breakdown of complex storage substances (eg, lysosomal and peroxisomal storage disorders) [3]. Clinical presentation is often non-specific and multi-systemic affecting the central and peripheral nervous system, skeletal muscle, heart, and liver. Disorders mediated by build-up of noxious metabolite and failure of energy production typically present in the neonatal period or infancy, but partial enzyme deficiency can lead to later and atypical presentations in childhood or even adulthood in the presence of a trigger [4]. "Triggers" could be any event or endogenous substances which induce catabolic phenomena such as fasting, infections, trauma, surgery,

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Abbreviations: CA, cerebral autoregulation; CMD, cerebral microdialysis; CT, computed tomography; EEG, electroencephalogram; ICP, intracranial pressure; HA, hyperammonemia; IEM, inborn errors of metabolism; MRI, magnetic resonance imaging; MM, metabolic myopathy; MRS, magnetic resonance spectroscopy; NBS, newborn screening; NIRS, near-infrared spectroscopy; OTD, ornithine transcarbamylase deficiency; UCD, urea cycle defects; US, ultrasound; TBI, traumatic brain injury.

Keywords: neuromonitoring, acute brain injury, inborn errors of metabolism, urea cycle disorders

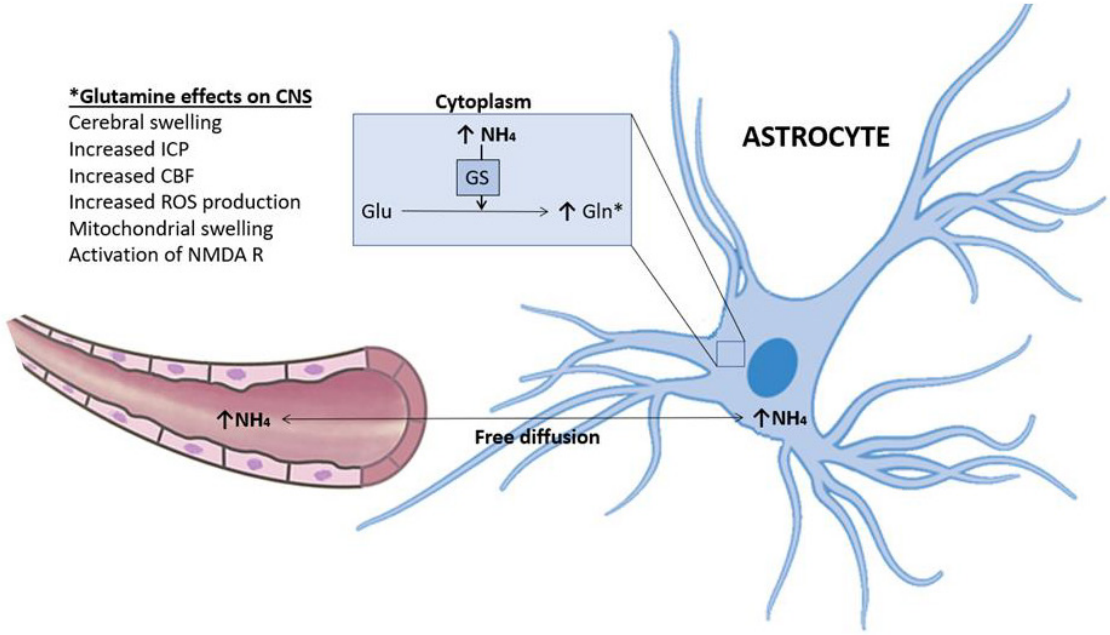

Figure 1. **Glutamine effects on CNS**.

and certain medications (eg, valproate in mitochondrial diseases, steroids in urea cycle disorders).

The combined incidence of IEM has been estimated to be as high as 1:1000 [2]. However, individually these disorders are exceedingly rare and can present as diagnostic dilemmas if a high index of suspicion is not maintained. The expansion of newborn screening (NBS) programs has changed the landscape for many of these disorders as early recognition and initiation of specific diet and treatment can lead to reduction in mortality and morbidity [5]. However, certain IEM such as proximal urea cycle disorders (UCD) and mitochondrial disorders, do not have a reliable biomarker to be detected by NBS and therefore, present as acute neurometabolic emergencies [6,7]. A metabolic emergency encompasses one or a combination of the following laboratory abnormalities which is peculiar to each class of disorders – hypoglycemia, hyperammonemia (HA), metabolic acidosis, transaminitis, rhabdomyolysis, and coagulopathy. These metabolic aberrations are the harbinger of sinister neurological sequelae including altered sensorium, status epilepticus, cerebral edema, persistent emesis, respiratory failure, and stroke-like episodes. Animal models and non-invasive *in vivo* studies using magnetic resonance spectroscopy have helped to elucidate the mechanisms of acute brain injury [8]. For example, we now know that HA exerts toxic effects on the brain by increased glutamine levels which in turn causes raised intracranial pressure, loss of NMDA receptors, excitotoxic cell injury, and over-production of reactive oxygen species (Figure 1). Management of acute decompensation in IEM is focused on common themes which consist of providing additional caloric support (in the form of intravenous dextrose or intralipids), temporary cessation of exogenous protein in some class of disorders (such as organic acidemias, urea cycle disorders) and elimination of offending molecules with special drugs (eg, sodium phenylbutyrate and sodium benzoate for HA) [9,10]. Due to significant morbidity and mortality associated with these episodes, management is often pursued in critical care units and meticulous neuromonitoring becomes key to prevent secondary brain injury.

For the last two decades, the Urea Cycle Disorders Consortium (UCDC) has conducted a longitudinal study including almost 700 children with UCD to further understand the natural history of UCD. The data accumulated by this consortium has revealed important information related to outcome, focusing primarily on neuroimaging findings and neurocognitive function [11,12]. However, very important questions remain about the potential acute neurotoxic effects of HA to further understand how to treat and prevent secondary brain injury during an acute crisis. In this review, we describe existing neuromonitoring techniques that have been used in rare metabolic disorders to rapidly detect and prevent secondary brain injury. It is noteworthy to recognize that we present low-quality evidence which is not intended to change current clinical practice; nonetheless, exploring new diagnostic approaches in the management of metabolic crises is crucial to optimize care for patients with IEM.

NEUROMONITORING TECHNIQUES IN ACUTE BRAIN INJURY

Secondary brain injury develops when mismatch exists between cerebral metabolic demand and energy substrate leading to cell damage and death [13]. These techniques provide unique variables to monitor pathophysiologic mechanisms to ameliorate and prevent secondary brain injury and have been previously applied in the adult neuro-intensive care unit for traumatic brain injury (TBI) [14-16], subarachnoid hemorrhage [16,17], intracerebral hemorrhage [18,19], and acute ischemic stroke [16].

Understanding cerebral physiology is paramount in the management of patients with acute brain injury regardless of the etiology. Cerebral autoregulation (CA) is a cerebral compensatory mechanism to ensure stable and regulated blood flow in the brain despite changes of cerebral perfusion pressure [20-22]. With intact CA, a rise in cerebral perfusion pressure produces vasoconstriction, a decrease in cerebral blood volume, and a fall in intracranial pressure (ICP). With impaired CA, changes in cerebral perfusion result in a passive pressure effect intracranially, producing either ischemia when the blood pressure is too low or increased ICP when the pressure is too high. The correlation between hemodynamic variables such as the median arterial pressure and any indirect or direct measure of cerebral blood flow can provide an overall assessment of CA. Monitoring of continuous CA at the bedside is feasible and has the potential to be used to direct blood pressure management in acutely ill patients with IEM.

NEUROIMAGING

As neuroimaging technologies have become more accessible, the current research has focused on the use of non-invasive neuroimaging technology to understand the long-term consequences and risk of neurodevelopmental disabilities in patients with IEMs. For instance, altered brain networks in the frontal lobes, abnormal white matter microstructure, and damage of corticospinal tracts are often present in structural and functional MRI and Diffusion Tensor Imaging in patients with UCD [23]. Not surprisingly, these patients often have deficit in executive functioning, including working memory. This section will cover multimodal neuroimaging techniques that can be considered during a metabolic crisis, recognizing that the role of these techniques during acute brain injury is less clear and currently there are no formal prospective studies evaluating its impact on short- and long-term neurological outcomes.

Head Ultrasound/Computed Tomography

Cranial US is a reliable, first line modality performed at bedside used to evaluate the neonatal brain morphology given it has no risk of radiation. As cerebral edema is a severe complication that often accompanies an acute metabolic crisis, a cranial US is an acceptable screening tool in neonates with suspected IEM and encephalopathy or/and focal deficits [24]. Findings suggestive of cerebral edema include effacement of the cerebral sulci, flattening of the corpus callosum, compressed slit-like ventricles, and narrowing of the intrahemispheric fissure and basal cisterns [25]. It is important to note that since cerebral edema occurs usually 24-48 h after an insult, a cranial US may be negative in the acute phase of the disease [25]; or if the metabolic crisis occurred remotely from the time of delivery. In this case, serial ultrasounds are usually performed to evaluate the full evolution of the disease. In the absence of acute findings, other findings suggestive of a metabolic disorder include ventricular dilation, abnormal cortical folding, germinolytic cysts, abnormal white matter, lenticulostriate vasculopathy and absent or thin corpus callosum [26]. Computed tomography (CT) also allows the identification of cerebral edema and is especially useful to detect cerebral hemorrhage, a finding that can be seen in certain IEMs, such as glutaric aciduria type 1, Menkes disease, and disorders of collagen [27].

Magnetic Resonance Imaging (MRI)

MRI is the modality of choice for evaluating IEM as characteristic patterns of brain involvement have been described for several metabolic brain disorders [24,28-31]. Most importantly, performing an MRI in the acute, or more often, the subacute stages of injury may provide information on the severity and extent of injury, allowing the clinician to continue aggressive management or withdraw life-sustaining measures depending on the projected neurodevelopmental outcome. For example, two patterns of acute brain injury that have been reported in patients with UCD vary depending upon the severity and duration of the HA. A diffuse pattern, commonly associated with high glutamine levels and worse developmental outcomes [32], includes extensive involvement of the posterior cerebral cortex and deep structures including basal ganglia, thalami, and brainstem; whereas, a central pattern affects mainly the rolandic region, basal ganglia, and internal capsule [32,33]. Unfortunately, the diagnostic yield of a structural MRI alone in the acute period is limited as findings are often non-specific [24] and a variety of IEM have overlapping neuroimaging findings.

^{1H} Magnetic Resonance Spectroscopy (MRS)

The management strategies in IEMs vary greatly and rapid confirmation is critical to start immediate treatment

Table 1. MRS Findings in Select Inborn Errors of Metabolism

	NAA	Cho	MI	Glx	lac	Other peaks	Treatable
Zellweger	↓	↑	↓	↑	↑	Lipid	
Neonatal ALD	↓	↑				Lipid	
Infantile Refsum	↓	↑	↑			Lipid	
RCDP		↓	↑			Lipid, acetate	
PDH	↓				↑	Acetate	Yes
NKH						Glycine	Yes
S-L-O		↑				Lipid	
Salla	↑	↓					
CDG	↓	↓	↑	↑			
CPS1, OTCD		↓	↓	↓	↔		Yes
GA type 1	↓	↑	↑	↑			Yes
GA type 2		↑					Yes
Mucolipidoses	↓						
Krabbe	↓	↑	↑	↑	↑		
MPS	↓	↑	↑				
MMA	↓				↑	methylmalonic acid	Yes
ALD		↓					
Arginase deficiency		↔	↓	↑			

The arrows indicate the direction of the change. ↓: decreased; ↑: increased; ↔: no change. ALD: adrenoleukodystrophy; RCDP: rhizomelic chondrodysplasia punctate; PDH: pyruvate dehydrogenase deficiency; KNH: nonketotic hyperglycinemia; SLO: Smith Lemli Opitz; CDG: congenital disorders of glycosylation; CPS1: carbomyl phosphate synthetase deficiency; OTCD: ornithine transcarbamylase deficiency; GA: glutaric acidemia; MPS: mucopolysacharoidosis; MMA: methylmalonic acidemia; nl: normal. Adapted from Gropman, Andrea L., and Afrouz Anderson. "Novel imaging technologies for genetic diagnoses in the inborn errors of metabolism." *Journal of Translational Genetics and Genomics* 4.4 (2020): 429-445.

and mitigate ongoing acute brain injury. Unfortunately, the typical biochemical testing turnaround time is between 3-4 days and molecular analysis confirmation can take up to several weeks [34]. While biochemical and molecular testing is mainstay for accurate diagnosis, ^{1}H MRS is a non-invasive diagnostic tool that can aid in diagnosis even within 6 hours of presentation [30,34,35]. By analyzing the presence of peak areas corresponding to the extracellular concentration of certain metabolites, ^{1}H MRS can provide useful information about the biochemistry of the central nervous system. Table 1 [36,37] shows different MRS patterns that have been described in a variety of IEMs, many of them treatable.

Often, one single imaging modality is not sufficient to serve as a diagnostic or prognostic biomarker, so a protocol promoting a multimodal approach is often utilized in clinical practice.

Continuous Electroencephalogram (EEG)

EEG measures the difference in voltage, or potential, between two electrodes (Figure 2). It provides significant advantages when compared to other diagnostic methods since it is inexpensive, feasible, and safe. The value of long-term continuous video EEG has been identified mostly in neonates with hypoxic ischemic encephalopathy to detect subclinical seizures and assist with long term prognosis [38,39]. Given that in UCD, acute seizures have been identified in 26-87% of the patients during the acute phase [40-42], EEG might be a valuable tool to screen for and prevent secondary injury during a metabolic crisis.

Identifying neonates who are at increased risk of seizures is crucial as symptomatic seizures increase cerebral metabolism, oxygen consumption [43,44], oxidative stress, and further mitochondrial dysfunction [44-46]. A lack of state changes, defined as no recognizable sleep or awake states, might be a useful marker to identify this population. In a small series of eight patients, a lack of state changes was present in all the patients who eventually developed clinical or electrographic seizures [40]. Interestingly, seizures were found to occur even with normal plasma levels of ammonia and glutamine, indicating that the serum levels are not necessarily correlated with the severity of brain injury [40]. A prolonged hyperammonemic state can have other residual effects on the brain including astrocytic swelling, an increase in blood brain barrier permeability, and disruption of energy through de-

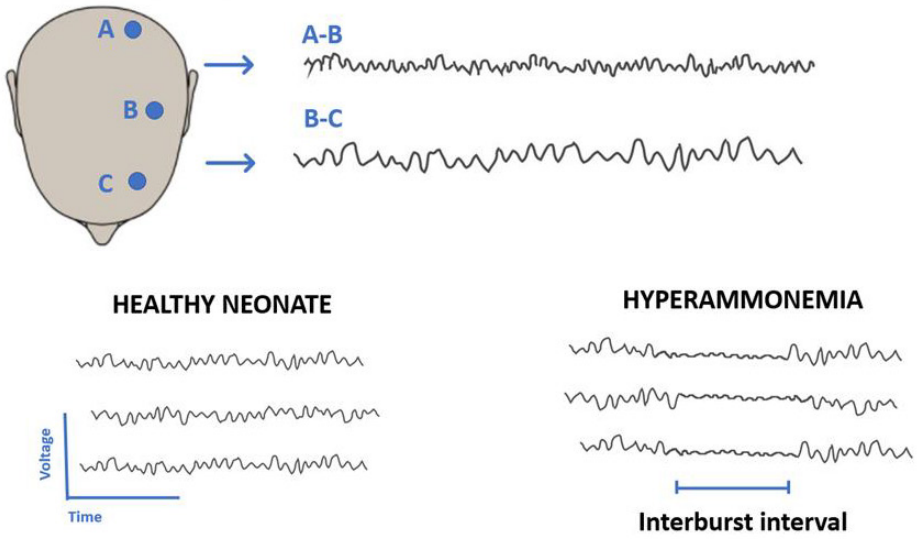

Figure 2. EEG allows to measure the difference in voltage between two different electrodes (blue circles). This signal is then amplified and converted into a digital signal that is processed by the computer. The type of brain activity—amplitude and frequency of these waves—depends on the area of the brain, level of arousal, medications, presence of seizures, and age. In neonates with HA there are periods of brain activity attenuation (interburst intervals) between periods of higher amplitude brain activity (bursts). The duration of interburst intervals may be correlated to a high serum ammonia level.

pletion of intermediaries of metabolism including altered amino acid and neurotransmitter levels [47-50].

High serum ammonia level might be associated with a shorter burst of cerebral activity and longer background suppression [40,42]. Another study that included 38 neonates with UCD (31% with argininosuccinate synthetase deficiency, 26% with ornithine transcarbamylase deficiency, 18% with adenylosuccinate lyase deficiency, 18% with carbamoyl phosphate synthetase 1 deficiency, 3% with N-acetylglutamate synthetase deficiency, and 3% with arginase deficiency) demonstrated an EEG with severe features, defined as absence of physiological features, non-reactive background activity, and/or presence of seizures or status epilepticus, which was present in 26% of the patients. Patients with "moderate" or "severe" EEG had higher levels of ammonia [42]. In clinical practice, a change of the EEG background and longer duration of interburst intervals (Figure 2) may indicate worsening HA and should prompt the clinician to perform more frequent serum levels.

Continuous EEG may also play a role in prognostication. The severity of EEG pattern and presence of status epilepticus were also associated to higher mortality and poor long-term developmental outcomes [42]. It has been suggested also that better neurodevelopmental outcomes could be associated with improvement of EEG background within 4 days [40].

Intracranial Pressure Monitoring

Cerebral edema is a life-threatening complication in patients with severe HA and has been described in adults with hepatic encephalopathy [50-54] and children with organic acidemias and UCD (Figure 1) [12,55-58]. Classically, the management of HA is based on frequent plasma ammonia levels [41] which reflect an increased nitrogen load in the organism. Even though a serum ammonia level > 150-200 µmol per liter is a risk factor for increased intracranial pressure in adults [59], severe neurological crises have been reported even in the absence of severe HA [35,60-62]. The management of increased intracranial pressure is urgent as soon as HA progresses to cerebral edema to ameliorate secondary brain injury.

The utility of ICP monitoring in HA-induced cerebral edema has been described previously in children and adults with IEM [62-65]. Measuring ICP is routinely used in the neurointensive care unit, especially in TBI [66], as it allows to adjust hemodynamic variables that can affect cerebral physiology. Spikes of increased ICP in IEM can be as high as 60 mmHg [62] (normal value < 20 mmHg) and prior experience with hyperosmolar therapy [50,53,54,62-65,67] and decompressive craniectomy in refractory cases [63] have been reported.

Transcranial Doppler Ultrasound (TCD)

Transcranial Doppler Ultrasound provides a rela-

tively inexpensive, non-invasive, and rapid measures of cerebral physiology that can be used to estimate blood flow velocities (FV) within the intracerebral vessels. A Doppler probe emits ultrasound waves through the skull that are reflected by moving red blood cells (Figure 3). The "Doppler shift frequency" or the difference in the frequency between emitted and reflected waves is proportional to the blood FV and used as an indirect measure to determine cerebral blood flow [54]. Factors that can affect the blood flow velocities include age, gender, hematocrit, viscosity, carbon dioxide, temperature, blood pressure, and mental or motor activity [68].

The disease model of acute brain injury in IEM is poorly understood and likely to be complex and specific to each disease. For instance, Strauss et al. detailed the evolution of acute striatal injury in an Amish patient with glutaric aciduria type 1. A CT perfusion scan performed 10 hours after the child developed acute opisthotonus showed global low cerebral BF, low cerebral blood volume and transit time within the striatal nuclei. MRI and CT scans 90 h later showed a more evident metabolic stroke with cytoxic edema in the same region [69]. Considering that flow velocity and transit time are correlated in cerebral regions with impaired CA [70], TCD may be useful to detect hemodynamic changes during acute strokes in these patients. On the other hand, the utility of TCD in patients with cerebral edema due to HA is controversial. A prospective cohort study including 87 adult patients admitted to the ICU in a tertiary center in Brazil with non-hepatic HA, did not find any correlation between ammonia levels and cerebral blood flow measured by TCD, even in patients with cerebral edema [71]. The authors of this study hypothesized that the mechanisms associated to cerebral edema in patients with non-hepatic hyperammonemia may not be necessarily related to an increased blood flow as previously demonstrated in patients with hepatic HA [72,73]. Nonetheless, these results should be interpreted with caution as the cause of HA was not correlated and metabolic/genetic testing to diagnose IEM was not performed [71]. Despite this, some centers suggest the use of TCD to guide clinical management in patients with acute HA and organic acidemias [65,74].

The advantage of TCD to measure cerebral BF compared to other techniques is the potential to provide continuous information about CA, at the bedside and in real-time, allowing a wide range of new applications in IEM. This was shown by Kodaka et al. in 13 patients with mitochondrial disorders (including six with Mitochondrial myopathy, Encephalopathy, Lactic acidosis, and Stroke-like episodes) [75]. Under conditions of normocapnia, hypercapnia, or hypocapnia, mean FV was obtained from the right and left middle cerebral arteries and correlated with CO_2 levels to calculate the parameter K, an index of CO_2 reactivity. Lower K values were found in all six MELAS patients and most of the other patients with mitochondrial disorders, suggesting a high incidence of impaired CO_2 reactivity in these patients.

The pathogenesis of acute brain injury in IEM is complex and multifactorial that results from a dynamic interaction between different cerebral processes including CA, metabolic demand, cerebral blood flow, and flow-metabolism coupling [72,76]. As cerebral hemodynamics play a primary role in acute brain injury, TCD remains a useful tool to provide insight on possible pathophysiologic mechanisms to prevent further brain injury and improve outcomes in these patients.

Near-infrared Spectroscopy (NIRS)

NIRS is a non-invasive technology that provide a continuous measure of regional tissue oxygenation, with potential applications in a wide range of clinical scenarios with acute brain injury (Figure 3). A tight coupling between oxygen supply and oxygen demand is present in the brain and muscles, and the relationship between these two variables produces a specific regional oxygen saturation. Specifically, an increase in oxygen consumption or a decreased in oxygen delivery can precipitate episodes of regional tissue hypoxia and lower levels of oxygen saturation in that specific organ.

The utility of NIRS to screen for metabolic diseases was previously reported by Cellie et al. [77]. In primary or secondary mitochondrial disorders, there is an inherent limited capacity to increase microvascular oxygen extraction during metabolic stress, leading to an increased regional tissue oxygenation. For example, in patients with mitochondrial myopathy (MM), a lower increase in deoxyhemoglobin and deoxymyoglobinin (a measure of oxygen extraction) was observed during an incremental handgrip exercise in affected patients when compared to healthy controls [77]. Celie et al. showed that among 12 patients with unexplained chronic fatigue, four patients had an abnormal regional oxygenation level suggesting a possible MM. When these patients underwent tissue muscle and skin biopsies and massive parallel sequencing of the entire mitochondrial genome, a genetic diagnosis was achieved in 100% of the patients [76].

This technology could also provide beneficial information on cerebral tissue oxygenation during an acute metabolic crisis. A single center study that included four neonates with metabolic disorders (three with primary mitochondrial disorders and one with methylmalonic acidemia) revealed that all the patients had abnormally high cerebral oxygen saturations (>90%) [78] due to poor oxygen utilization and mitochondrial dysfunction, leading to ineffective oxidative phosphorylation and anaerobic glycolysis and lactic acidosis [79].

Another potential utility of NIRS is the ability to provide information about CA. Prior studies have shown

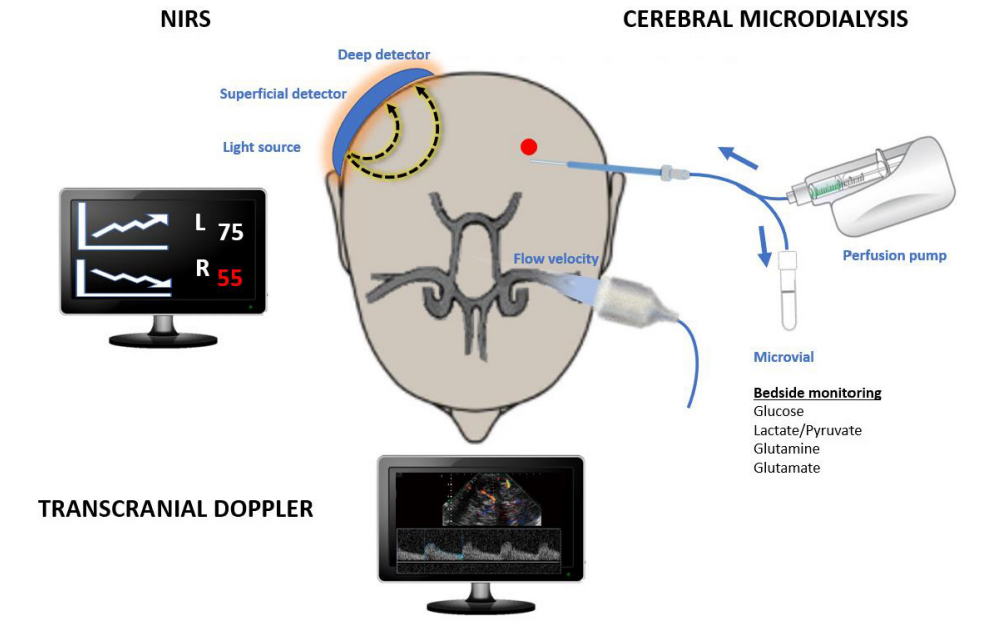

Figure 3. **NIRS (A) probes are placed in the scalp, and they transmit infrared light (light source) that passes through skin and bone to the tissue**. The detectors in the skin probe senses the light that has not been absorbed from oxy-hemoglobin and deoxy-hemoglobin and converts this data into a number which indicates the regional tissue oxygenation. The monitor shows that the right cerebral hemisphere has a lower oxygen saturation indicating either decreased perfusion or increased metabolic demand in that hemisphere. CMD (**B**) allows semi-continuous monitoring of extracellular metabolites. A pump allows constant perfusion of isotonic or colloid-enriched fluid to a tubular semi-permeable membrane on the tip of the catheter (red circle). All small molecules cross the membrane by diffusion. The perfuse or microdialysate is sampled and analyzed for brain extracellular concentrations of glucose, lactate, pyruvate, glutamine, and glutamate. A Doppler probe (**C**) emits ultrasound waves through the skull that are reflected by moving red blood cells. The "Doppler shift frequency" or the difference in the frequency between emitted and reflected waves is proportional to the blood flow velocity and used as an indirect measure of cerebral blood flow.

that impaired CA in preterm infants may be related to developmental delays, poor cognitive outcomes, and death [80-82]. HA affects cerebral blood flow by causing cerebral dilation [83] and impaired CA has been reported in hyperammonemic states [84,85]. A twin case study revealed possible impaired CA in a patient with ornithine transcarbamylase deficiency when compared to his healthy twin sibling [20]. However, further studies are needed to elucidate the pathogenesis of impaired CA in HA.

Cerebral Microdialysis

Another prospective candidate that can provide insight into cellular metabolism with potential application to guide clinical therapy is cerebral microdialysis (CMD) (Figure 3). Microdialysis allows to monitor the chemistry of the cerebral interstitial fluid continuously [86] and can specifically measure the extracellular levels of glutamate, glutamine, glucose, lactate, and pyruvate. The use of this technique in animal models have allowed a better understanding of the physiological alterations that underlie hepatic encephalopathy in the human and possible alternative therapies for this disease [87-93]. The use of CMD in pediatrics is sparse and limited only to TBI [94].

In adults with HA, the extracellular concentration of lactate is increased before the development of brain edema and surges of increased ICP [67]. Furthermore, one study using CMD showed that accumulation of glutamine in the brain caused by HA correlated with a higher lactate–pyruvate ratio in patients with liver failure, supporting that there is possibly secondary mitochondrial dysfunction with an energy deficit state [95,96]. As cerebral and peripheral levels of glutamine do not necessarily correlate [41,97], targeting cerebral glutamine remains an attractive strategy for the treatment of HA.

CONCLUSIONS AND OUTLOOK

This review highlights a critical knowledge gap in the management of acute brain injury in patients with

IEMs. Although there are no prospective studies validating the efficacy of these techniques in patients with IEM, advanced neuromonitoring could meaningfully impact the current practice in children with IEM in the future. We advocate for creating an international registry of patients with rare diseases that can cause acute brain injury that includes cerebral, cardiovascular and respiratory variables during a metabolic crisis and follow-up metrics during scheduled visits. Further research should focus on expanding the use of these neuromonitoring techniques to develop primary targeted goal-directed therapy against HA-induced energy metabolism failure and secondary brain injury.

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