Intracranial Pressure Monitoring Demonstrates that Cerebral Edema Is Not Correlated to Hyperammonemia in a Child with Ornithine Transcarbamylase Deficiency

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Abstract Background: Ornithine transcarbamylase deficiency (OTCD) is an inborn error of urea cycle resulting in increased plasma levels of ammonia and glutamine and cerebral edema. However, the underlying mechanism of brain cytotoxicity remains controversial. Our objective is to present an unusual acute hyperammonemic crisis suggesting a key role of brain glutamine to mediate ammonia neurotoxicity and the interest of intracerebral pressure (ICP) monitoring to maintain adequate cerebral perfusion pressure and to prevent neurological damages.

Patient: A 6-year-old boy with OTCD was admitted for an acute hyperammonemic encephalopathy following viral infection. At admission, he presented vomiting, confusion, lethargy (Glasgow scale 7/15), and bilateral papilledema,

suggesting cerebral edema. Plasma ammonia level was slightly increased (194 $\mu\text{mol/L}$, rr 25–50 $\mu\text{mol/L}$), contrasting with the severity of neurological deterioration and with high levels of glutamine in plasma (1,949 $\mu\text{mol/L}$, rr 335–666 $\mu\text{mol/L}$) and the brain (10-fold increase on in vivo MR spectroscopy). The patient was placed on neuroprotective treatments and respiratory support.

Main Results: With a hypercaloric protein-free diet and nitrogen scavenger drugs, plasma levels of ammonia and glutamine rapidly decreased without neurological improvement. Continuous ICP monitoring showed repetitive peaks of pressure up to 60 mmHg in the first four days and was helpful to manage neuroprotective treatments. After several days, the patient progressively recovered without cognitive or motor disability.

Conclusion: This case report highlights the discrepancy between the severity of neurological impairment, presumably related to high level of brain glutamine, and plasma levels of ammonia or glutamine in a child with acute hyperammonemic encephalopathy related to OTCD. In this situation, continuous ICP monitoring was helpful to manage neuroprotective treatments and prevent brain damages.

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Abbreviations

CPP Cerebral perfusion pressure

ICP Intracranial pressure

OTCD Ornithine transcarbamylase deficiency

rr Reference range

Introduction

Ornithine transcarbamylase deficiency (OTCD, MIM#311250) is an X-linked inborn error of metabolism of the urea cycle,

which converts ornithine and carbamoyl phosphate into citrulline in the hepatic mitochondria (Lichter-Konecki 2008). Enzyme dysfunction results in an increase of plasma levels of ammonia and its metabolites, glutamine and glutamate. Hyperammonemia may cause astrocyte swelling, cytotoxic edema, and increased intracranial pressure (ICP) with a high risk of irreversible damage to the brain (Albrecht et al. 2010; Braissant et al. 2013). In fact, cerebral ammonia is metabolized to glutamine by astrocytes, a process that is the principal means of ammonia detoxification into the brain. Glutamine is an essential precursor of the neuronal synthesis of the neurotransmitters glutamate and GABA, as well as an important energy metabolite in the brain (Albrecht et al. 2010). However, brain glutamine synthesis in excess has been recently reported to mediate key aspects of ammonia neurotoxicity (Albrecht et al. 2010; Braissant et al. 2013). Increased brain glutamine levels have a huge toxicity for astrocytes and other cerebral cells, inducing cellular swelling, cerebral edema, and neuronal cell death due to increased excitotoxicity (Pichili et al. 2007; Lichter-Konecki 2008). In contrast, the inhibition of glutamine synthesis by methionine sulfoximine reverses a spectrum of manifestations of ammonia toxicity, including brain edema and increased intracranial pressure (see Ref (Albrecht et al. 2010) for review). Therefore, brain glutamine metabolism may be viewed as the principal mediator of ammonia neurotoxicity (Albrecht et al. 2010; Braissant et al. 2013). Classically in children with urea cycle disorders (UCD), hyperammonemic encephalopathy is associated with severe hyperammonemia, and its management is based on the follow-up of plasma ammonia level (Haberle et al. 2012). However, ammonia level is not a reliable tool to predict raised ICP, and severe neurological crises have been reported in some patients with only mild increase in plasma ammonia level, suggesting that brain glutamine level will be a better marker of cerebral dysfunction than blood ammonia or glutamine levels (Kojic et al. 2005; Mak et al. 2007; Gropman et al. 2008). Brain glutamine level may be estimated by analysis of cerebrospinal fluid obtained by lumbar puncture or by brain magnetic resonance spectroscopy. These two methods can be performed punctually but do not allow a follow-up of brain glutamine level during acute crises. Therefore, monitoring ICP may be helpful to manage acute hyperammonemic encephalopathy and to prevent neurological damages (Wendell et al. 2010). We report the case of a 6-year-old OTCD boy who presented a severe and acute hyperammonemic encephalopathy that was managed with ICP monitoring to prevent decline of cerebral perfusion pressure (CPP) and neurological damages.

Case Report

A 6-year-old boy with OTCD was admitted to pediatric intensive care unit for an acute hyperammonemic encephalopathy following viral infection. He had a familial history of severe neonatal OTCD confirmed by genotyping (mutation C584G in the exon 6). Despite prenatal diagnosis of OTCD and very low protein diet supplemented with essential amino acid mixture, citrulline, L-arginine, and sodium benzoate, he experienced previously more than ten acute episodes of hyperammonemia (maximal ammonia level between 70 and 170 $\mu\text{mol/L}$, reference range rr 25–50 $\mu\text{mol/L}$) rapidly resolving with stopping protein intake and nitrogen scavenger drugs and never requiring admission in intensive care unit. Apart from these acute crises, his metabolic status was relatively acceptable, with normal ammonemia and slightly increased plasma levels of glutamine (827 ± 143 $\mu\text{mol/L}$, rr 335–666 $\mu\text{mol/L}$), alanine (659 ± 268 $\mu\text{mol/L}$, rr 134–502 $\mu\text{mol/L}$), glycine (350 ± 126 $\mu\text{mol/L}$, rr 149–301 $\mu\text{mol/L}$), and citrulline (47 ± 54 $\mu\text{mol/L}$, rr 16–40 $\mu\text{mol/L}$) during the two previous years. For this new acute episode, this boy was asymptomatic the day before, presenting only a rhinitis without fever or neurological symptom. Upon waking, he remained sleepy and presented three hours later at admission vomiting, confusion, and lethargy with a Glasgow scale 7/15 and bilateral papilledema on fundus examination, suggesting cerebral edema. Biochemical investigations revealed compensated metabolic acidosis (pH 7.39, Pco_2 29 mmHg [3.9 kPa], HCO_3^- 17 mmol/L [2.3 kPa]) with hyperlactatemia (4.9 mmol/L, rr <2.2 mmol/L). Initial plasma levels of ammonia (194 $\mu\text{mol/L}$, rr 25–50 $\mu\text{mol/L}$) and glutamine (1,949 $\mu\text{mol/L}$, rr 335–666 $\mu\text{mol/L}$) were increased, contrasting with normal values of transaminases, gamma-glutamyl transferase, bilirubin, and prothrombin time test (80% initially, controlled to 25% few hours later, rr 70–100%). Other plasma levels of amino acids related to urea cycle were in normal range (alanine 295 $\mu\text{mol/L}$, glycine 297 $\mu\text{mol/L}$) except those of citrulline that was near undetectable (3 $\mu\text{mol/L}$). The electroencephalogram showed slow delta waves at one Hertz and reactivity to stimulation without seizures. Brain MRI revealed small ventricles and a slightly restricted diffusion in the occipital lobes suggesting cerebral edema with a huge peak of glutamine on MR spectroscopy performed at the level of the occipital white matter, whereas glutamate level remained normal (Fig. 1a). It was concluded to a severe acute metabolic crisis with hyperammonemia and cerebral edema.

Following initial evaluation, he was intubated, ventilated, and sedated with midazolam (50 $\mu\text{g/kg/h}$) and sufentanil

Fig. 1 MR spectroscopy during and after an acute episode of hyperammonemic encephalopathy in a 6-year-old boy with ornithine

transcarbamylase deficiency. Brain glutamine (Gln) and glutamate (Glu) levels were estimated by in vivo MR spectroscopy (1.5T)

Fig. 2 Plasma ammonia (**a**) and glutamine (**b**) levels during an acute episode of hyperammonemic encephalopathy in a 6-year-old boy with ornithine transcarbamylase deficiency. Normal range is in gray

(0.2 μg/kg/h) to protect upper airways and to manage cerebral edema and intracranial hypertension. Hypercaloric protein-free diet was started by total parenteral nutrition, and intravenous treatment by sodium phenyl acetate and sodium benzoate (Ammonul®) was initiated 3 h after admission (loading dose infusion of 250 mg/kg administered over 90 min, followed by an equivalent maintenance dose infusion administered over 24 h). With these treatments, plasma levels of ammonia and glutamine progressively decreased to normal range since the fifth day (Fig. 2a, b). Proteins were reintroduced in the diet from the third day (0.2 g/kg/day) and gradually increased up to 0.8 g/kg/day at day 6, with a progressive switch from parenteral to continuous enteral nutrition. Intravenously treatment with sodium phenyl acetate and sodium benzoate was switched to enteral sodium phenylbutyrate (250 mg/kg/day in four doses) and intravenous sodium benzoate (continuous infusion of 250 mg/kg/day) from day 4. Due to neurological deteriora-

tion, an ICP monitoring (Codman® MicroSensor basic kit, Johnson & Johnson Professional Inc, MA, USA) was set in the first 24 h after correction of coagulation disorders. The monitoring of ICP showed repetitive peaks of pressure up to 60 mmHg in the first four days and was helpful to manage and adapt the neuroprotective treatments in the aim to maintain an adequate CPP (Fig. 3). Continuous neuroprotective treatments with midazolam and sufentanil were rapidly increased up to 1,200 μg/kg/h and 0.5 μg/kg/h, respectively, associated with bolus of both treatments and atracurium besylate (0.5 mg/kg/dose) at the time of ICP peaks. Vasoactive support (norepinephrine up to 0.12 μg/kg/min) was associated from day 2 to maintain arterial pressure and CPP. The frequency of ICP peaks decreased after few days, boluses of neuroprotective treatments were progressively spaced, and continuous treatments with midazolam, sufentanil, and norepinephrine were discontinued after eight days. Due to favorable outcome, ventilation support can be

Fig. 1 (continued) performed at the level of the occipital white matter during (**a**, day 1) and after (**b**, day 16) an acute episode of hyperammonemic encephalopathy. Data were analyzed using LCMo-del, 6.3-1H version, and concentrations were expressed related to Cr

+PCr (standard deviation expressed in percentage, %SD). Cho, choline; Cr+PCr, creatine + phosphocreatine; Glx, Glu+Gln; mI, myoinositol; NAA, *n*-acetyl-aspartic acid

Fig. 3 Evolution of intracranial pressure and cerebral perfusion pressure during an acute episode of hyperammonemic encephalopathy in a 6-year-old boy with ornithine transcarbamylase deficiency. Intracranial pressure (**a**) was monitored invasively and cerebral

perfusion pressure (**b**) was calculated from the difference between mean arterial pressure and intracranial pressure. Normal range is in gray. Bolus of neuroprotective treatments (midazolam, sufentanil, and atracurium besylate) are represented as bars at the top of the graph

stopped on day 8 and the boy was discharged from intensive care unit at day 12 without apparent severe damage.

He progressively recovered and a second brain MRI realized four days after discharge was considered as normal, with a reduced peak of glutamine on MR spectroscopy (Fig. 1b). At the same time, plasma levels of ammonia and glutamine were normal (21 and 534 $\mu\text{mol/L}$, respectively). A clinical evaluation 6 months later found no cognitive or motor disability.

Discussion

Acute hyperammonemic encephalopathy is a medical emergency for which the aim of treatment is to prevent irreversible brain damage by timely action (Haberle et al. 2012). This case report highlights the key role of brain glutamine to mediate ammonia neurotoxicity and the interest of monitoring ICP to maintain adequate CPP and to prevent neurological damages. The first hallmark of this case report is the discrepancy between the level of plasma ammonia, only moderately

increased, and the severity of neurological impairment. This boy has previously experienced recurrent episodes of acute hyperammonemic crises but without the same degree of neurologic impairment. The absence of intoxication symptom the day before suggested a very acute and sudden crisis. Lactic acidosis at admission is unusual in OTCD crises but may be explained in the present case by either an initial vasomotor instability related to brain edema or by transient ischemic brain damage, in accordance with the severity of this episode. The presence of a coma at admission was reported to be associated with a lower survival rate, particularly in OTCD patients (Enns et al. 2007), and neurological symptoms persisted even after decreasing ammonemia levels under 100 $\mu\text{mol/L}$. In UCD, the function of excretion of nitrogen as urea is impaired and leads to accumulate ammonia and glutamine, two toxic molecules for the brain. The severity of neurologic impairment and survival are classically related to age and peak ammonia level (Enns et al. 2007). Acute hyperammonemic crises in the neonatal period are typically most severe, with a peak ammonia level >500 $\mu\text{mol/L}$. In older children, peak

ammonia levels are generally lower but remains $>200 \mu\text{mol/L}$ in most of the patients during acute crises (Enns et al. 2007). However, severe neurological crises have been reported even in the absence of severe hyperammonemia (Kojic et al. 2005; Mak et al. 2007; Gropman et al. 2008). This apparent discrepancy between neurological impairment and plasma ammonia level may be explained in part by the mechanisms of hyperammonemia neurotoxicity. Following its uptake by the brain, ammonia is mainly metabolized to glutamine by astrocytes, leading to high levels of cerebral glutamine that may be viewed as the principal mediator of ammonia neurotoxicity (Albrecht et al. 2010; Braissant et al. 2013). Glutamine is osmotically active and its concentration increase leads to cytotoxic edema by astrocyte swelling possibly related to glutamine transport into mitochondria, thereby increasing ammonia synthesis from glutamine into mitochondria, inducing apoptosis and producing reactive oxygen species. A significant proportion of newly synthesized glutamine will also exit astrocytes and enter neurons to give rise to glutamate into the intercellular space which is excitotoxic, essentially through NMDA receptor activation, altering neurotransmission and NO synthesis and inducing neuronal cell death. Finally, glutamine efflux across the blood-brain barrier would favor the removal of brain glutamine and decrease its toxic effect. Brain concentrations of ammonia and glutamine are not strictly related to plasma levels, possibly due to variations of brain ammonia uptake and glutamine synthesis and transport (Pichili et al. 2007; Lichter-Konecki 2008; Zwimer et al. 2010). In our case, brain glutamine estimated by MR spectroscopy appeared to be largely increased (about tenfold, compared to 2 weeks later), contrasting with the moderate increase of ammonemia, then possibly explaining the discrepancy between neurological impairment and plasma concentrations of ammonia.

Classically, the management of hyperammonemic encephalopathy is based on the follow-up of plasma ammonia level (Haberle et al. 2012). In fact, increased plasma levels of ammonia and glutamine are indicators of the increased nitrogen load of the organism and must be closely monitored for optimal treatment (Enns et al. 2007). However, their plasma concentrations are not a predictor of their brain concentrations and are not a reliable guide to manage cerebral edema (Haberle et al. 2012). The clinical situation of the patient should guide clinical decisions and the rather low ammonia levels should never prevent from aggressive intervention in such comatose patient. Clearly, there is a need to identify predictors of cerebral injury. As in our case, brain glutamine level can be appreciated by MR spectroscopy, a simple and reliable method to assess in vivo the cerebral concentration of several brain metabolites. The acquisition of spectroscopy measurements takes only about ten additional minutes during a conventional structural MRI. This gives a

first spectrum that can estimate concentration of the different metabolites. A more precise estimation of each metabolite concentration needs to model the in vivo spectrum as a linear combination of adequately line-broadened individual metabolite spectra. This can be achieved using an analysis program such as “LCModel,” but this step needs most of the time the assistance of a specialist. The use and the accuracy of this method have been clearly validated to evaluate brain metabolism in OTCD patients (see Gropman et al. 2008) for details), but this investigation cannot be regularly repeated (Connelly et al. 1993). In contrast, continuous ICP monitoring was very useful to detect ICP peaks and to treat them immediately, in the aim to maintain adequate CPP and to prevent cerebral damages. High doses of neuroprotective therapies were used because of the recurrence of ICP peaks higher than 40 mmHg and were associated with treatment bolus at the time of ICP peaks (Rabinstein 2010). In the case of persistent intracranial hypertension refractory to maximal medical management, the next therapeutic step would have been to propose a decompressive craniectomy (Wendell et al. 2010). An associated hypothermia protocol has also been proposed in some cases. In contrast, ventricular drainage is the treatment of choice when intracranial hypertension is due to hydrocephaly; it has also been proposed to treat refractory cerebral edema after traumatic brain injury, but its use is not classical for cytotoxic cerebral edema, as occurred during hyperammonemia. Continuous ICP monitoring was also helpful to evaluate improvement of cerebral hypertension and to decide time to discontinue neuroprotective therapy. The use of ICP monitoring has not been frequently reported in comatose patients related to urea cycle disorders, excepted in a recent adult case report (Wendell et al. 2010), but its utilization is validated in other pediatric conditions as traumatic brain injury (Exo et al. 2011). Treatment of cerebral edema is more effective when it is based on direct monitoring of ICP, with evidence of improved outcomes (Barlow and Minns 1999). However, coagulopathy associated with acute liver failure is often considered a contraindication for invasive monitoring of ICP due to risk for intracranial bleeding (Vaquero et al. 2005). Correction of coagulopathy disorders prior to ICP monitor placement may decrease rate of complications (Kamat et al. 2012).

Since the main mechanism for brain toxicity seems to be high intracerebral levels of glutamine rather than hyperammonemia itself, the aims of the treatment would be to decrease plasma levels of ammonia, the precursor of glutamine synthesis into the brain, and of plasma glutamine to favor removal of brain glutamine. In addition to symptomatic and nutritional therapies, the use of nitrogen scavenger drugs is also recommended. Intravenous treatments with sodium phenyl acetate and sodium benzoate are the mainstay drugs

for bypassing the urea cycle, by conjugation of benzoate with glycine to generate hippurate or of phenyl acetate with glutamine to generate phenylacetylglutamine, both conjugates being excreted in the urine. Their use without delay results in survival in the majority of patients (Enns et al. 2007). Extracorporeal detoxification, most of the time by continuous venovenous hemodiafiltration, can also be associated in severe hyperammonemic crises. Its use is classically indicated for children who have ammonia levels upper than 500 $\mu\text{mol/L}$ or if there has been an inadequate response to initial medical treatment (Haberle et al. 2012). However, its utilization for children requires a solid expertise in the field of dialysis therapy to avoid technical problems and hypotension that should be deleterious in the context of cerebral edema (Picca et al. 2008). Furthermore, continuous hemodiafiltration is not really efficient to detoxify glutamine with plasma concentration remaining high, in contrast to the effects on ammonia level (Chen et al. 2007).

To summarize, this case report highlights the absence of correlation between the severity of neurological impairment and plasma levels of nitrogen metabolites in a child with acute decompensation of urea cycle disorder. In this situation, invasive ICP monitoring appeared to be feasible and very helpful to manage hyperammonemic encephalopathy and neuroprotective treatments, in the aim to maintain adequate CPP and to prevent brain injury. Nitrogen scavenger drugs were efficient to decrease plasma levels of ammonia and glutamine, without resorting to hemodiafiltration.

Conflicts of Interest

The authors declare no disclosure.

Take-Home Message

This case report highlights the key role of brain glutamine to mediate ammonia neurotoxicity in urea cycle disorders and the interest of monitoring intracranial pressure to maintain adequate cerebral perfusion pressure and to prevent neurological damages.

Compliance with Ethics Guidelines

All the authors declare no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki

Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

The following are the details of the contributions of individual authors: JC, GF, NF, NRR, TP, and ES for patient management in ICU; MT and FL for metabolic management; NT for surgical placement of intracranial pressure monitoring; and LB and BM for MRI analyses. JC and FL wrote the paper. All coauthors have read the manuscript and approved its submission to the JIMD Reports.

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