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Reye Syndrome with Severe Hyperammonemia and a Good Neurological Outcome

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Statistical Analysis C
Data Interpretation D
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Patient: Male, 4-year-old
Final Diagnosis: Reye syndrome
Symptoms: Hypoglycemia • disturbance of consciousness • diarrhoea • signs of respiratory infection • vomiting and nausea
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine • Endocrinology and Metabolic • Pediatrics and Neonatology

Objective: Rare disease
Background: Reye syndrome (RS) is a rare life-threatening condition combining acute noninflammatory encephalopathy and acute liver failure with an absence of defined etiology. We present a case of fulminant RS that had a good neurological outcome.
Case Report: A 4-year-old previously healthy boy had no history of acetylsalicylic acid (ASA) use, nor had he been diagnosed with any inborn errors of metabolism. RS was preceded by a mild viral infection, possibly caused by human bocavirus, which has not been previously implicated in RS. He presented with a combination of a very high concentration of ammonia but only mildly elevated aminotransferases and mild hypoglycemia. Computed tomography (CT) of the head additionally showed diffuse cerebral edema with tentorial herniation. The extensive metabolic evaluation did not confirm any inborn errors of metabolism to explain the etiology. We provided optimal treatment of severe hyperammonemia (>500 µmol/L) and cerebral edema, including high doses of arginine chloride, sodium benzoate, hemodialysis, mild hypothermia, and supportive care. He has been followed up for over 4 years. The patient recovered completely, with no long-term psycho-cognitive or neurological sequelae.
Conclusions: Although extremely rare, hyperammonemia and RS should be considered in cases of an acute encephalopathy to be treated as soon and as decisively as possible to enable a good outcome.

Keywords: Bocavirus • Brain Edema • Case Reports • Hyperammonemia • Metabolism, Inborn Errors • Reye Syndrome

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Background

Reye syndrome (RS) is a rare life-threatening condition in children [1]. Three mandatory criteria have been proposed to establish its diagnosis: acute noninflammatory encephalopathy; acute liver failure (at least 3-fold increase of transaminases or/and ammonia); and absence of defined etiology [2]. Clinically, RS manifests with fever, nausea, and vomiting, followed by unconsciousness, convulsions, and coma, as hyperammonemia causes astrocyte edema and thus increased intracranial pressure [2,3].

RS typically develops in the course of an infectious disease or in the days just after recovery, with concomitant acetylsalicylic acid (ASA) administration. Hall et al found that 80% of patients had received ASA within 3 weeks of onset, but only 0.1% of children receiving ASA developed RS [4].

Cases with typical features of RS that have been etiologically explained are defined as Reye-like syndromes (RLS). Cases of RLS have an etiology of latent inborn errors of metabolism (IEM), including fatty acid oxidation disorders or urea cycle disorders that manifest during infectious disease or other illness; however, the IEMs could also be triggered by taking specific medicines, including ASA [4-6]. The course is unpredictable, and brain edema usually causes permanent neurological consequences [2].

We report a case of RS in a patient who presented with severe hyperammonemia but had a good neurological outcome.

Case Report

A 4-year-old boy who had no significant medical or family history was admitted to our Emergency Department because of impaired consciousness and vomiting. He had a high fever (40.5°C), mild signs of respiratory infection, and diarrhea for 5 days, and his condition was already improving 1 day before admission. His parents denied giving him ASA. On day 4 of illness, he started to vomit frequently (up to 10 times/day). He was first admitted to the Infectious Disease Department, where laboratory tests were unremarkable, with the exception of borderline-low blood glucose concentration (2.7 mmol/L; 48 mg/dL); the C-reactive protein (CRP) level was low and the white blood cell count (WBC) was within the reference range; he was discharged with a diagnosis of viral gastroenterocolitis. One hour after discharge he became agitated and ceased talking. At readmission to the hospital, he was somnolent and soporous, withdrawing to pain, cardio-circulatory compensated, and had spontaneous breathing. His pupils were dilated but symmetrical and reactive, and his plantar responses were in extension. The meningeal signs were negative and with no signs of lateralization. He had no signs of acute infection. The liver was palpable 3 cm below the right rib arch. The first blood glucose measurement in the ambulance was low (2.2 mmol/L; 39 mg/dL), so while in transit he was given a parenteral glucose bolus (3 g/kg) followed by infusion of 10% glucose at a rate of around 8 mg/kg/min, which by arrival, corrected the blood glucose to normal (8.0 mmol/L) but had no effect on the patient's clinical state.

A head CT was urgently performed 30 min after admission and revealed no cerebral edema. Lumbar puncture results were normal. Initial laboratory results showed significant hyperammonemia (in the range of >500 µmol/L [the exact figure was not available]; reference range 9-33 µmol/L), lactic acidosis with pH 7.25 (reference range 7.35-7.45), lactate 6.8 mmol/L (reference range 0.6-2.4 mmol/L), and borderline raised aspartate transaminase (AST) 49.1 U/L (reference range <34.8 U/L), but a normal alanine transaminase (ALT) level. Coagulation tests were within the reference range. WBC was within normal range, CRP was low, and procalcitonin was high at 16 µg/L, which rose to 23 µg/L during day 1 (reference range <0.5 µg/L).

We immediately started treatment with a high-glucose infusion (10 mg/kg/min) with parallel infusion of insulin 0.1 IE/kg/h because of iatrogenic hyperglycemia, arginine chloride (225 mg/kg in short infusion, then continuous infusion of 10 mg/kg/h), sodium benzoate (250 mg/kg in short infusion, then continuous infusion of 10 mg/kg/h), which, after 21 h, was substituted with combined sodium benzoate/sodium-phenyl-acetate infusion 10 mg/10 mg/kg/h. Intensive hemodialysis was introduced 3 h after admission. Until we received negative results of the lumbar puncture, he also had 1 dose of acyclovir, and until negative hemoculture results were received, he was given 10 doses of cefotaxime (150 mg/kg/day, divided into 4 doses/day). After 24 h of intensive treatment, the concentration of ammonia decreased to normal; therefore, hemodialysis was discontinued after 16 h, followed by no post-dialysis rebound hyperammonemia (**Figure 1**).

He was vitally stable but he hyperventilated while compensating for metabolic acidosis; therefore, he was intubated on day 2. On day 2, his pupils were asymmetrical. A CT scan was repeated at 36 h after arrival in the hospital and showed diffuse cerebral edema with signs of tentorial herniation. Mild therapeutic hypothermia was initiated (35°C for 62 h), combined with dexamethasone, mannitol, furosemide, and vasopressors. Another CT scan was performed 11 h later, showing no additional deterioration. On day 3, we introduced parenteral nutrition, in which the proportion of amino acids was gradually raised, starting with 0.5 g/kg/day and reaching the final amount of 1 g/kg/day on day 6. During the first week, AST and ALT levels rose, reaching the highest concentrations on day 14 (AST 281 U/L; ALT 246 U/L), then gradually declining

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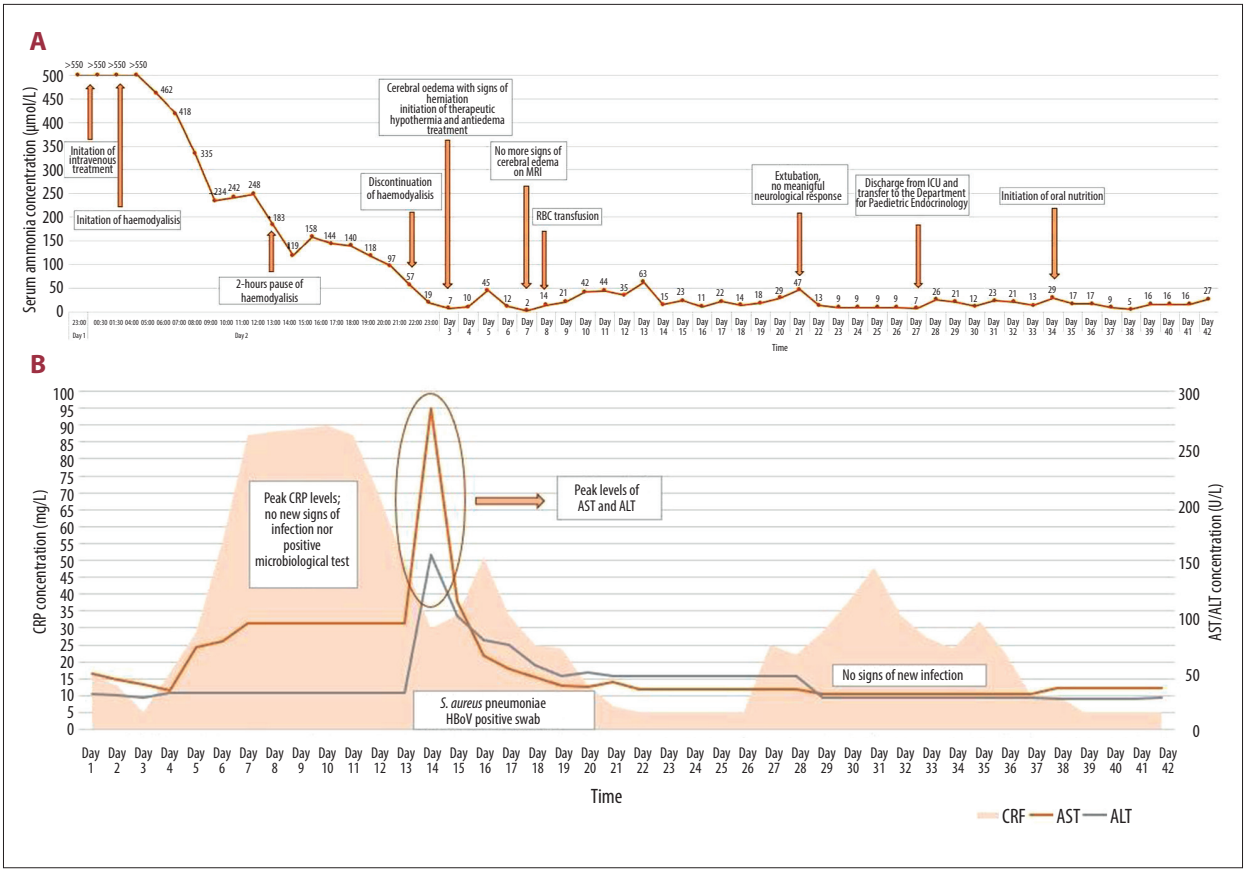

Figure 1. (**A**) Ammonia concentration and important turning points in clinical state and treatment over time of hospitalization. (**B**) Aspartate transaminase (AST), alanine transaminase (ALT), and C-reactive protein concentrations over time of hospitalization.

to within the reference range by day 27. At the time of highest AST and ALT levels, coagulation and ammonia measures were in the reference range (**Figure 1**).

On day 7, magnetic resonance imaging showed mild signs of cerebral edema but suspected hypoxic lesions in both thalami. He was showing significant neurological impairment, which was probably combined with withdrawal symptoms. An electroencephalogram showed no clear epileptic activity. He additionally presented with pneumonia (*S. aureus* tracheal aspirate culture) on day 13, and was treated with penicillin. At that time, the presence of the human bocavirus was also confirmed in the nasopharynx by a polymerase chain reaction (PCR) swab test, without any new upper respiratory symptoms, most likely showing prior infection, as the swab was done for the first time. Among the multiple microbiological tests performed (multiple hemocultures, lumbar and urine culture, nasopharyngeal swab for pathogenic bacteria), only these 2 were positive.

On day 21, the patient was extubated. Parenteral nutrition was still needed because he was not tolerating oral intake well. On day 27, he was transferred from an intensive care unit (ICU) to the Department for Pediatric Endocrinology, where he gradually regained full consciousness. Neurologically, he was improving rapidly. We started with oral nutrition on day 34, when parenteral nutrition was finally stopped. Oral intake of proteins was kept low at 1 g/kg/day. He was receiving arginine chloride and sodium benzoate regularly until being discharged from the hospital on day 42 because we suspected possible IEM, which could not be excluded at that point. He also continued taking both medicines regularly for 1 year, and then we cancelled the therapy as we gathered results of all the procedures, which did not reveal any IEM. Protein intake after discharge was also kept low at 1 g/kg/day, then during the first year it was gradually increased to 1.5 g/kg/day (protein intake just above the age-specific WHO recommendations' lower threshold of 1-1.5 g/kg/day). Finally, the low-protein diet was finished at 14 months after discharge.

One month after hospitalization, psychological evaluation was performed using the Wechsler Preschool and Primary Scale of Intelligence, Third Edition, showing general intellectual ability, with the Full-Scale IQ (FSIQ) and Verbal IQ (VIQ) in the average range (FSIQ=90; percentile rank [PR; percentage of children in

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the normative sample scoring below that score]=25; VIQ=90, PR=25) and Performance IQ (PIQ) in the low-average range (PIQ=84, PR=14). The Processing Speed Quotient (PSQ) was in the borderline range, significantly lower than most of his peers (PSQ=71; PR=3), revealing his difficulties with focusing and staying on task. During clinical observation, he displayed oppositional behavior and was distracted very easily.

We did an extensive metabolic evaluation. Acylcarnitine analysis excluded disorders of fatty acid oxidation. Amino acids in plasma revealed normal concentrations of glutamine and alanine as well as other amino acids. Dicarboxylic aciduria or diagnostic compounds of organic acidurias were not present in the urine. Slightly increased urinary excretion of orotic acid (4.2 µmol/mmol creatinine; reference value, 0.68-2.24 µmol/mmol creatinine) and lactaciduria were present; however, the urine sample was taken 6 h after initiation of intensive treatment.

To exclude urea cycle disorders, genetic testing was performed but did not reveal any urea cycle disorders (sequence analysis of ARG1, ASL, ASS1, CPS1, NAGS, OTC genes; multiplex ligation-dependent probe amplification was additionally performed for the OTC gene). Also, his family history was without specificity, and the parents were not related.

He was followed up for 56 months. In subsequent episodes of infectious diseases, including a severe episode of bacteriemia, he never again presented with hyperammonemia. Further testing (eg, allopurinol challenge test or enzyme analysis) was not performed since all the follow-up tests and genetic testing results were negative and he remained asymptomatic during several infections afterward. At the age of 8 years and 7 months, the boy was examined by a pediatric neurologist and a psychologist. The parents reported no problems. The neurological examination was completely normal in all domains.

The psychological reevaluation showed mild improvement in all evaluated areas of the Wechsler Intelligence Scale for Children, Fifth Edition. His general intellectual ability was estimated to be in the average range (FSIQ=93, PR=32). More precisely, the Verbal Comprehension Index (VCI), Fluid Reasoning Index (FRI), and Working Memory Index (WMI) were in the average range (VCI=103, PR=58; FRI=91, PR=27; WMI=91, PR=27), while the Visual-Spatial Index (VSI) and Processing Speed Index (PSI) were in the low-average range (VSI=86, PR=18; PSI=83, PR=13). There was no deviation in his cooperation during the evaluation. He had been attending the third grade of primary school, where he was thriving.

Discussion

The incidence of RS has been extremely low since 1986, when ASA was contraindicated in children up to 12 years of age [2]. In the United States, RS occurs in 1: 100 000 children under 18 years of age, and in the United Kingdom, in 1: 300 000 [7]. With the decline in ASA use and, consequently, RS incidence, any diagnosis of acute encephalopathy accompanied by hepatopathy requires ruling out possible IEM [8]. However, the decline in RS is also due to improved diagnosis of IEM that could cause RLS [5]. With hypoglycemia accompanied by hyperammonemia, IEMs were highly suspected working diagnoses owing to a combination of hyperammonemia with hypoglycemia and lactacidemia, and especially primary carnitine deficiency and the organic acidemia, methylmalonic acidemia. The combination of hyperammonemia and hypoglycemia is also described in a spectrum of fatty acid oxidation disorders, which results in a clinical picture of RLS [9-12]. In the present case, despite the extensive diagnostic evaluation, we did not confirm any IEM, so we concluded that our patient had RS. He also did not present with hyperammonemia ever again. However, despite the 417 disease-causing mutations known so far, only 85% to 90% of all patients with clinical and biochemical aspects of ornithine transcarbamylase deficiency have confirmed mutation in the OTC gene, and the remaining 15% of symptomatic patients remain without an explained molecular cause. On the other hand, large phenotypic heterogeneity is observed among individuals with known OTC sequence variants, making it possible to remain asymptomatic throughout life or present with severe hyperammonemia at the time of specific triggers. This is probably due to modifiers of genes from the environment, but still, whole-genome sequencing uncovers new disease-causing mutations, especially in OTC gene regulatory regions and introns, and widens the understanding of genotype-phenotype correlations. However, our patient later had several infections during the follow-up, with ammonium levels remaining stable [13,14].

Most commonly, RS is related to influenza A or B, or varicella-zoster virus infection, and more rarely with coxsackie, parainfluenza, Epstein-Barr virus, cytomegalovirus, adenovirus, or bacterial (*Chlamydia, Bordetella pertussis, Mycoplasma, Shigella*) infection [1,15]. Gastroenteritis precedes RS in 14% of RS cases [1]. We confirmed human bocavirus in the nasopharynx, which has not previously been described in relation to RS. According to the literature, bocavirus is detectable from nasopharyngeal aspirates for up to a few months, and it was the only virus that was positive on multiple tests by PCR swab [16].

Viruses have many strategies to target the mitochondrial machinery through induction of mitophagy, suppression of mtDNA copy number, inhibition of interferon production, and regulation of apoptotic processes [15]. Mitochondria play important roles in antiviral immunity and can regulate the activation of the inflammasome, glycolysis, and other metabolic processes, which indicate a complex molecular interplay between inflammation and metabolism [17]. Dysfunctional mitochondria

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after a viral infection can lead to RS, with sharply and transiently decreased activities of urea-cycle mitochondrial enzymes and mitochondrial changes in hepatocytes, as seen by electron microscopy [18,19]. The regulatory urea-cycle enzymes are in the mitochondria and maintain blood ammonia levels in the normal range. Our patient had no acute liver failure by definition (no coagulation abnormality), and the clinical course indicated mitochondrial dysfunction as a leading mechanism for the reduced hepatic capacity for ammonia removal. Hyperammonemia has a direct effect on the brain through brain edema, brainstem herniation, astrocytic swelling, and white-matter damage, as was presented in our patient [20,21]. The extended knowledge about mitochondrial dynamics is helping to clarify the historical pathogenetic hypotheses of RS encephalopathy, but further studies are needed to understand whether the mitochondrial dysfunction in each instance is primary or secondary [19].

At admission, the diagnosis was questionable since our patient did not present with elevated liver enzymes, and acute liver failure is one of the diagnostic criteria for diagnosis of RS. However, we found there have been RS cases described with normal or just slightly elevated activity of AST and ALT and cases with extremely high values. It is estimated that around 25% of patients with RS have normal AST at admission, and the likelihood of normal ALT activity is even greater. Furthermore, increasing AST activity has been described to occur coincidentally with clinical recovery (as was the case in our patient), pointing rather to increased synthesis than to simple enzyme leakage from damaged liver cells, as happens in most of the other hepatopathies [22].

Owing to the unclear diagnosis at the beginning, with the highest suspicion for IEMs, and to the normal activities of liver enzymes, we did not decide to perform a liver biopsy, although coagulation tests were in the normal range. Although liver biopsy is a useful criterion for diagnosing RS owing to the typical pathohistological features, approximately 25% of RS cases have no pathohistological changes on biopsy [23]. Therefore, biopsy is still only optional, and hepatopathy as an obligate part of the clinical course in RS can be confirmed either by liver biopsy or laboratory tests, including at least a 3-fold increase of serum AST and ALT activity or increase in serum ammonia [1].

The progression of RS can stop at any stage spontaneously, with subsequent recovery in 5 to 10 days; however, 30% to 70% of cases are fatal [7]. To some degree, serum ammonia, severity of the neurologic disorder, and degree of liver failure determine the final neurological outcome; however, there is no prognostic threshold of hyperammonemia, and rapid decline in ammonia and also of intracranial pressure are more important [7,24]. Our patient was treated with hemodialysis, which is considered if serum ammonia is >500 µmol/L [1]. Intensive control of intracranial pressure was enhanced by hypothermia, which extends survival time, prevents further cerebral edema, and decreases ammonia in cerebrospinal liquor by limiting the transfer through the brain-blood barrier [1,24]. Such an intensive approach resulted in a very good final neurological outcome. Therefore, considering hyperammonemia in a patient with vomiting and/or impaired consciousness is the key step, as hyperammonemia needs prompt and proper management without delays, consisting of stopping protein intake, providing enough calories with glucose infusion, starting nitrogen scavenging drugs, and, of course, hemodialysis if serum values are higher than 500 µmol/L. To define IEM among differential diagnoses, samples for urgent metabolic workup should be collected before starting any therapy [25].

Conclusions

Treatment with ASA is not the only cause of RS, as several different viruses have been implicated as its possible cause. Even though RS is a rare cause of hyperammonemia, RS should be considered in cases of acute encephalopathy because early and intensive treatment can not only increase the chances of survival but can also enable normal neurological outcomes, as was the case in our patient.

Department and Institution Where Work Was Done

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Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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