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Ureaplasma parvum causes hyperammonemia presenting as refractory status epilepticus after kidney transplant

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ABSTRACT

Purpose: Alert intensivists about the diagnostic pitfalls arising from hyperammonemia due to *Ureaplasma* infections in post-transplant patients.
Materials and methods: Clinical observation of one patient.
Case report: A 65-year-old female with a medical history of semi-recent kidney transplant was admitted to the Intensive Care Unit for refractory status epilepticus. There were no lesions on brain imaging. Bacterial cultures and viral PCR of cerebrospinal fluid were negative. The first blood ammonia level measured on day 2 was 13 times the normal level, but biological liver tests were normal. The persistence of elevated ammonia levels led to the initiation of symptomatic ammonia lowering-treatments and continuous renal replacement therapy, which led to its decrease without normalization. An *Ureaplasma spp* infection was then diagnosed. Levofloxacin and doxycyline were administered resulting in normalization of ammonia levels within 48 h. However repeat MRI showed diffuse cortical cytotoxic edema and the patient remained in a minimally conscious state. She eventually died 4 months later from a recurrent infection.
Conclusion: Ureaplasma infection must be suspected in cases of neurological symptoms associated with hyperammonemia without liver failure, following an organ transplant. Only urgent treatment could improve the prognosis and prevent severe neurological damage or death.

1. Introduction

Neurological complications after solid organ transplantation are frequent, but only a few can be attributed to the surgery itself. The others can be classified in several core groups: infection, drug toxicity, brain lesions, and metabolic abnormalities [1,2]. After excluding central nervous system infection, and in the absence of any structural abnormalities on brain imaging, it is recommended to perform electroencephalogram (EEG) and check the ammonia blood level for seizure activity and hepatic encephalopathy. Recently, several studies reported a relationship between hyperammonemia and *Ureaplasma* spp. infection in immunosuppressed patients, including patients with solid organ transplants such as lung or kidney [3-6]. Indeed, *Ureaplasma* spp. infection in immunosuppressed patients can lead to a rise in serum ammonia causing dramatic brain damage such as seizures and cerebral edema [5,7]. We describe a case of hyperammonemia following a kidney transplant associated with *Ureaplasma parvum* revealed by severe neurological impairment. Although initiation of symptomatic ammonia lowering-treatments and appropriate antibiotic therapy resulted in a temporary resolution of hyperammonemia and eradication of the causative pathogen, the patient unfortunately died.

2. Case report

A 65-year-old female with a medical history of end-stage renal failure underwent a kidney transplant. She did not suffer from immediate post-operative complications and was weaned from chronic dialysis (usual plasmatic creatinine concentration around 70 μmol/l), but her surgical wound had never healed despite repeated care. Three months later, she presented with acute change in mental state, with a Glasgow Coma Scale of 6, afebrile and without metabolic disorder. She was

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admitted to the Neuro-Intensive Care Unit where she was intubated on arrival for airway protection, mechanically ventilated and sedated intravenously (IV) with midazolam and sufentanil. On arrival plasma creatinine, calcium and magnesium levels were respectively 136 μmol/l, 2.35 mmol/l, 0.84 mmol/. Cerebral magnetic resonance images (MRI) were unremarkable and EEG showed triphasic waves evocative of a metabolic encephalopathy. On Day 2, despite the IV administration of midazolam (3 to 10 mg/h), she developed a refractory status epilepticus requiring levetiracetam (15 mg/kg), then phenytoin (15 mg/kg), propofol (50 to 100 mg/h) and then ketamine (50 mg/h). After cessation of clinical convulsions, continuous EEG revealed posterior seizure with bilateral periodic epileptiform discharges in frontal lobes (Fig. 1. A), therefore lacosamide was added and hypnotic drugs were increased, which resulted in a burst-suppression pattern. No seizure activity was then observed on successive EEGs in the following days. A lumbar puncture was performed and IV acyclovir 10 mg/kg/8 h and cefotaxime 2gx3/24 h started, whereas tacrolimus was discontinued in anticipation of neurotoxicity and septic risk. Bacterial cultures and viral PCR of

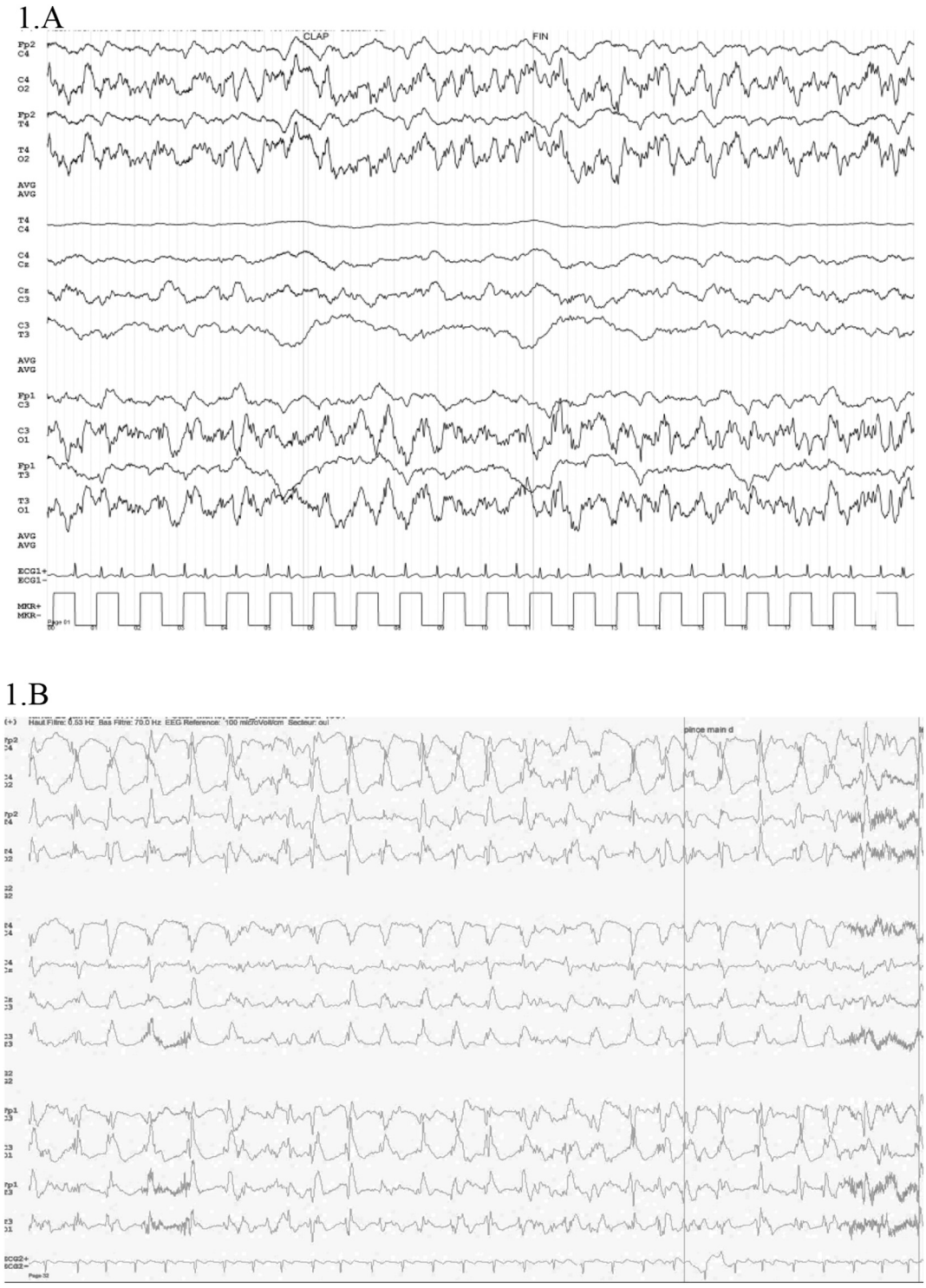

Fig. 1. EEG trace. **1.A** Day 2: posterior delta activity interspersed with peaks with a rhythmic aspect, not reactive to nociception. **1.B** Day 7: continuous short, generalized periodic activity of ample di and triphasic slow waves, without epileptic pattern. Reactivity to nociception was absent.

cerebrospinal fluid were negative, while a second MRI performed on day 2 showed frontal bilateral and diffuse cortical restricted diffusion. Notably, the first blood ammonia level measured on day 2 was at 671μMol/L (normal range 10–50) and follow-up ammonia measurements are shown in Fig. 2. The patient was not known to have chronic liver disease or acute hepatocellular insufficiency. Abdominal CT and echography ruled out any clues in favor of chronic liver disease or portosystemic shunt. No medication known to increase ammonia levels, especially sodium valproate, had been previously given. Blood lactate levels were normal. Repeated elevated ammonia levels led to the immediate initiation of lactulose, temporary protein eviction together with an enriched carbohydrate and lipid diet, IV ammonia lowering agents (sodium benzoate 13 g/24 h, sodium phenylbutyrate 4gx4/24 h), vitamin B1, B6, PP, B9, B12 and continuous renal replacement therapy from day 3 to day 8. Ammonia levels subsequently decreased (Fig. 2) but did not normalize. Plasma amino acids and urine organic acids profiles were not suggestive of urea cycle disorder. *Ureaplasma spp* infection investigations were sent from the surgical wound, urine and blood on day 10. From day 11, levofloxacin 500 mg twice a day and doxycycline 200 mg a day were administered intravenously, allowing ammonia levels to normalize within 48 h (Fig. 2). The serum and urine PCR for *Ureaplasma parvum* turned out positive on day 16 (in-house real-time Taqman PCR assay) [8].

The sedative drugs were stopped at day 8. At this time, the EEG showed a continuous generalized periodic activity without epileptic pattern or reactivity (Fig. 1.B). In the following months, the patient's neurological status did not improve to more than a minimally conscious state. Repeat MRI showed a diffuse cortical cytotoxic edema on day 13 (Fig. 3). Unfortunately, she died 4 months later from a recurrent infection fostered by her chronic immunosuppression.

3. Discussion

In our case, a chronic scar infection caused by *Ureaplasma parvum* occurring following kidney transplantation, led to a major hyperammonemia and severe brain lesions. Plasma antibiotics levels were not measured, but it is likely that these were effective because the ammonia level quickly decreased after their introduction and the abdominal wound healed. Usually, hyperammonemia is related to liver diseases and portosystemic shunts. However, a hepatocellular insufficiency is not always present. Inborn errors of metabolism can also be responsible for hyperammonemic encephalopathy such as urea cycle disorders [7]. In the same way, hyperammonemia can be induced by drugs (sodium valproate, L-asparaginase, 5-fluoro-uracile, barbiturates, sunitinib, regorafenib), or by surgical procedures such as ureterosigmoidostomy and transurethral resection of prostate with use of Glycine gel [9].

A few studies have demonstrated the responsibility of *Ureaplasma* spp. as a causal agent of hyperammonemia but its pathophysiology is still poorly understood. Wang et al. have established an immunocompromised experimental mouse model and have showed that *U. urealyticum* and *U. parvum* can cause hyperammonemia [10]. *U. urealyticum* and *U. parvum* produce large amounts of urease, which hydrolyses urea to produce ATP, generating ammonia in the process. Moreover, the liver metabolizes ammonia into urea. Beside the liver, ammonia can be metabolized into glutamine by the glutamine synthase in muscle cells and in central nervous system's astrocytes. Glutamine is osmotically active and high glutamine levels are responsible for astrocyte swelling [11]. Virulence of *Ureaplasma* spp. has been showed since 1991, when Ligon et al. observed progressive twitching, hyper reactivity, coma and then convulsion resulting in a rapid death after

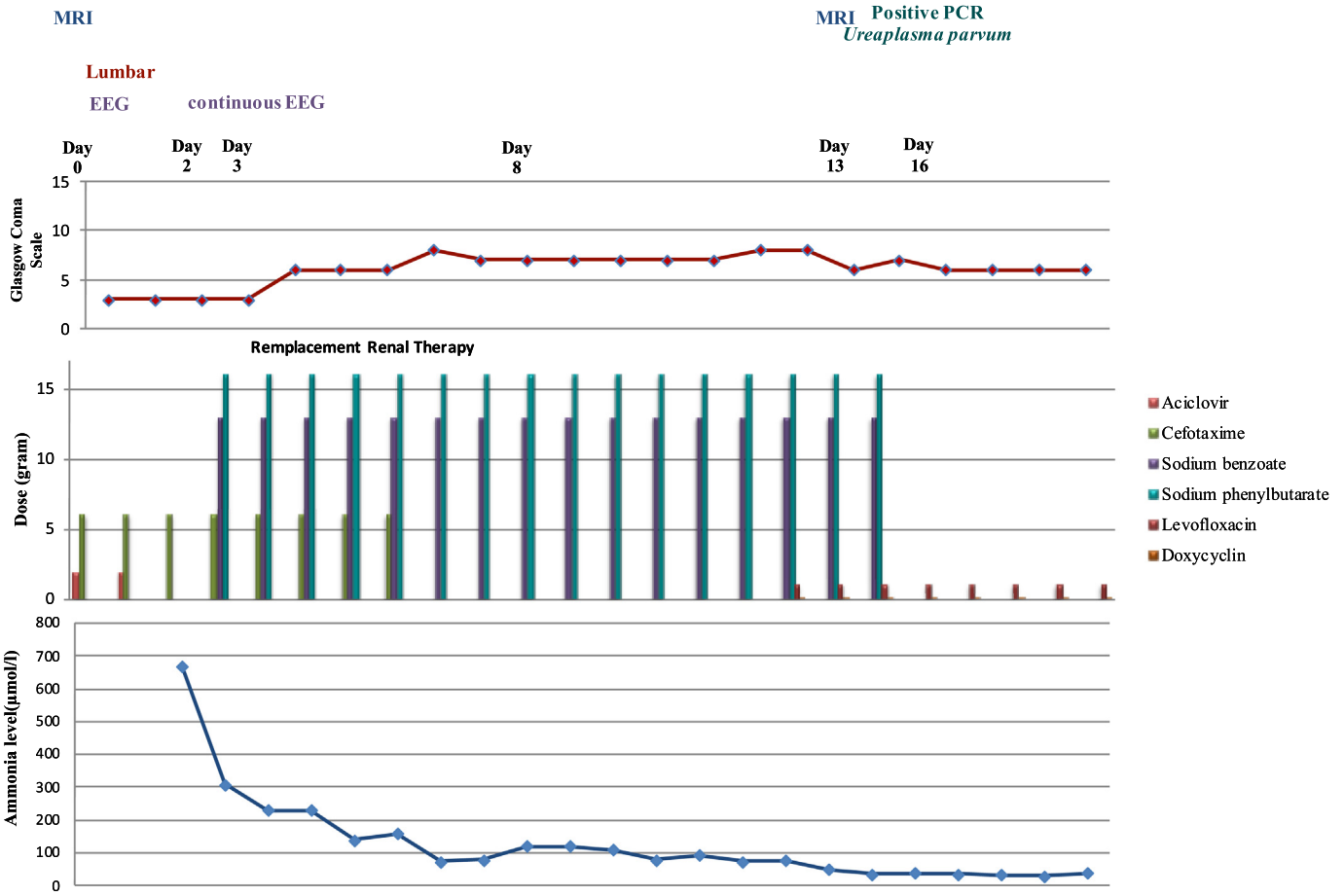

Fig. 2. Kinetics of ammonia according to therapeutic.

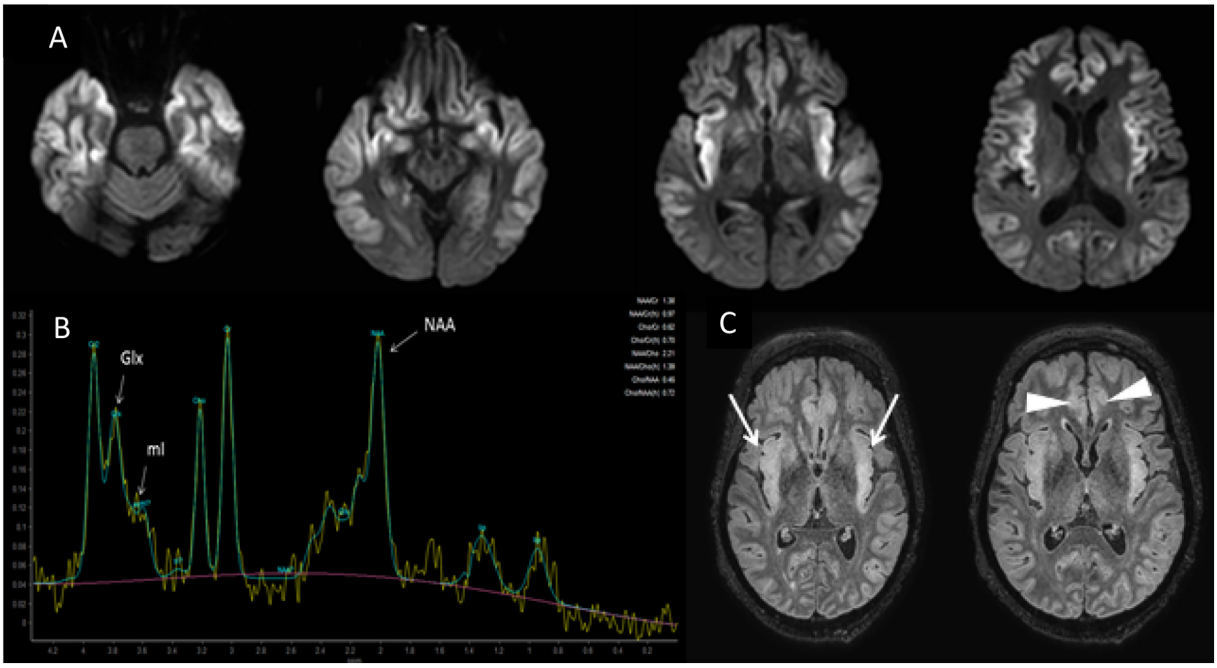

Fig. 3. MRI at D13. DWI (A) and FLAIR images (C) show symmetric abnormal signal intensity (corresponding to cytotoxic edema) involving preferentially the insular (arrows) and cingulate (arrowheads) cortices bilaterally and sparing the occipital lobes. MR Spectroscopy (B) shows elevated glutamine/glutamate (Glx) peak coupled with decreased myoinositol (mI) and N-Acetyl-Aspartate (NAA). **T**hese imaging and spectroscopy patterns are typical of ammonium overload.

injection of *Ureaplasma* spp. in mice [12]. In humans, Bharat et al. have found that hyperammonemia is an often-fatal complication of systemic immunosuppression, including in cases associated with lung and other solid organ transplantation except liver transplantation [13]. They also found evidence of systemic infection with either *U. urealyticum* or *U. parvum* in all 3 patients with hyperammonemia after lung transplantation and none in 20-control lung transplants patients with normal ammonia concentration. More recently, McLaughin et al. described a 65-year-old man who developed refractory status epilepticus secondary to hyperammonemia following lung transplant [5].

In all cases, the prognosis was poor without early treatment. However, two articles have reported, one case each, successful treatment of *Ureaplasma*-induced hyperammonemia, the former after lung transplantation [14] and the latter after hematopoietic cell transplantation [15]. As a result, in light of the severe neurotoxicity of hyperammonemia, the detection and treatment of *Ureaplasma* infection must be a priority. *Ureaplasma* infections should be systematically considered in antibiotic choices without waiting for the result of bacteria samples in patients with neurological symptoms and hyperammonemia, especially after kidney or lung transplantation. Particular attention should be brought to the ammonia blood sample, for which conservation and transport can be challenging (tube placed in ice, transported within 30 min to the lab). It is important to note that ammonia levels can be falsely increased in the case of delayed analysis but not falsely low.

4. Conclusion

Intensivists must be aware of the possibility of severe *Ureaplasma* infections in immunosuppressed patients, especially after an organ transplant. This complication should typically be suspected in cases with severe neurological signs and hyperammonemia but without liver disorder. Only urgent treatment could improve the prognosis and prevent severe neurological damage or death.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Consent for publication was obtained from the sister of the patient.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All the authors had a determining role in the clinical management of the patient.

CL and AH made substantial contributions to the conception, the design of the manuscript and drafted the manuscript.

FM gave essential advices for the case management and substantively revised the manuscript.

NW gave essential advices for the case management and made substantial contributions to the design of the work and revised the manuscript.

AC made contributions to the acquisition analysis and interpretation of data from MRI and revised the manuscript.

SP made biological diagnosis of Ureaplasma parvum, and revised the manuscript.

MP revised the manuscript.

NE made substantial contributions to the conception, the design, the acquisition analysis and drafted the manuscript.

All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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