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PRACTICAL PEARL

An Uncommon Case of Hyperammonemic Encephalopathy

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Hyperammonemic encephalopathy (HE) associated with urinary tract infections represents a rare but severe neurologic condition [1, 2]. Increased production of ammonia and uptake in the bloodstream upon urinary infections is considered the result of the metabolic activity of urea-splitting bacteria like the Proteus and Corynebacterium strains [2]. However, hyperammonemia has also been rarely reported to occur upon urinary infections sustained by bacteria such as the *Providencia rettgeri*. HEs associated with *P. rettgeri* have been described in children presenting massively dilated upper urinary tracts, such as in the prune-belly syndrome [3].

Case

A 64-year-old woman, with a long history of schizophrenia, was admitted to the emergency room (ER) and showed the signs of subacute and progressive orientation and vigilance deficits along with behavioral changes.

The women had a history of an attempted suicide that was carried out 18 years before by throwing herself out of the window and led to the development of chronic mild paraparesis, sensory disturbances in the lower limbs, and a neurogenic bladder. In the past years, she has suffered from relapsing urinary infections that required the use of intermittent catheterism and several cycles of antibiotic administration.

The woman was on a daily regimen of quetiapine 200 mg twice a day plus long-acting injections of 25 mg of risperidone every fortnight. She was free of major behavioral symptoms and reported to maintain full autonomy in daily living activities. She was able to walk with the use of orthopedic aids.

On admission, relatives reported that in the past 2 weeks she had progressively reduced food intake and presented several episodes of vomiting. In the evening before ER admission, the patient was found to be lying in bed, confused, and disoriented. That deteriorating condition led the relative to opt for admission to the ER of our hospital. On admission, the brain computed tomography (CT) scan and standard chest x-ray were normal. Electrocardiogram showed sinus tachycardia (heart rate at 146 pulses/min). Laboratory work showed a condition of hypernatremic dehydration and mild hyperglycemia. Liver, kidney, and the coagulation status were normal.

The women showed no meningeal signs or evidence of focal neurologic deficits. Arterial blood pressure, oxygen, and carbon dioxide saturation were in the physiological range. Physical examination was normal except for signs indicative of bladder over-distension and urine retention. After catheterization, 500 cc of purulent urine was drained. Within few hours, the woman becomes comatose.

Follow up blood work showed the presence of hypernatremic dehydration and increased creatinine levels. Body temperature was normal, but the laboratory work gave clear indication of an ongoing infection with increased erythrocyte sedimentation rate values, neutrophil count, and a slight increase in fibrinogen levels. Hepatic, pancreatic, and coagulation parameters were still normal. The urinary analysis showed increased pH

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values, proteinuria, increased erythrocyte, and leukocyte counts. Cerebrospinal fluid values were normal and excluded the presence of encephalitis. Next morning, an electroencephalogram (EEG) recording showed the presence of a diffuse slowing of background activity that was associated with large amplitude, generalized pseudo-periodic discharges (GPDs) with triphasic morphology that occurred symmetrically but with an anterior predominance (Fig. 1a). These anomalies were reactive to acoustic stimuli. As the pattern is strongly suggestive of an ongoing metabolic/toxic encephalopathy, serum ammonia was investigated and elevated serum levels were discovered (291 µg/dL; n.v < 75). Biochemical markers of liver damage remained negative. The urine culture test showed the presence of *P. rettgeri* infection. An abdomenal CT revealed a severe thickening of the bladder walls along with signs of marked bilateral hydroureteronephrosis (Fig. 1c). Following the antibiogram indications, intravenous ciprofloxacin was therefore introduced. In the following 3 days, the patient conditions rapidly improved and serum ammonia and sodium values returned in the physiological range. A control EEG performed 1 week after the introduction of ciprofloxacin showed the normalization of the brain electrical activity (Fig. 1b). At this point, serum ammonia levels were at 34 µg/dL and sodium levels were in range.

Discussion

Ammonia is the physiological bio-product of the metabolism of amino acids and other nitrogenous

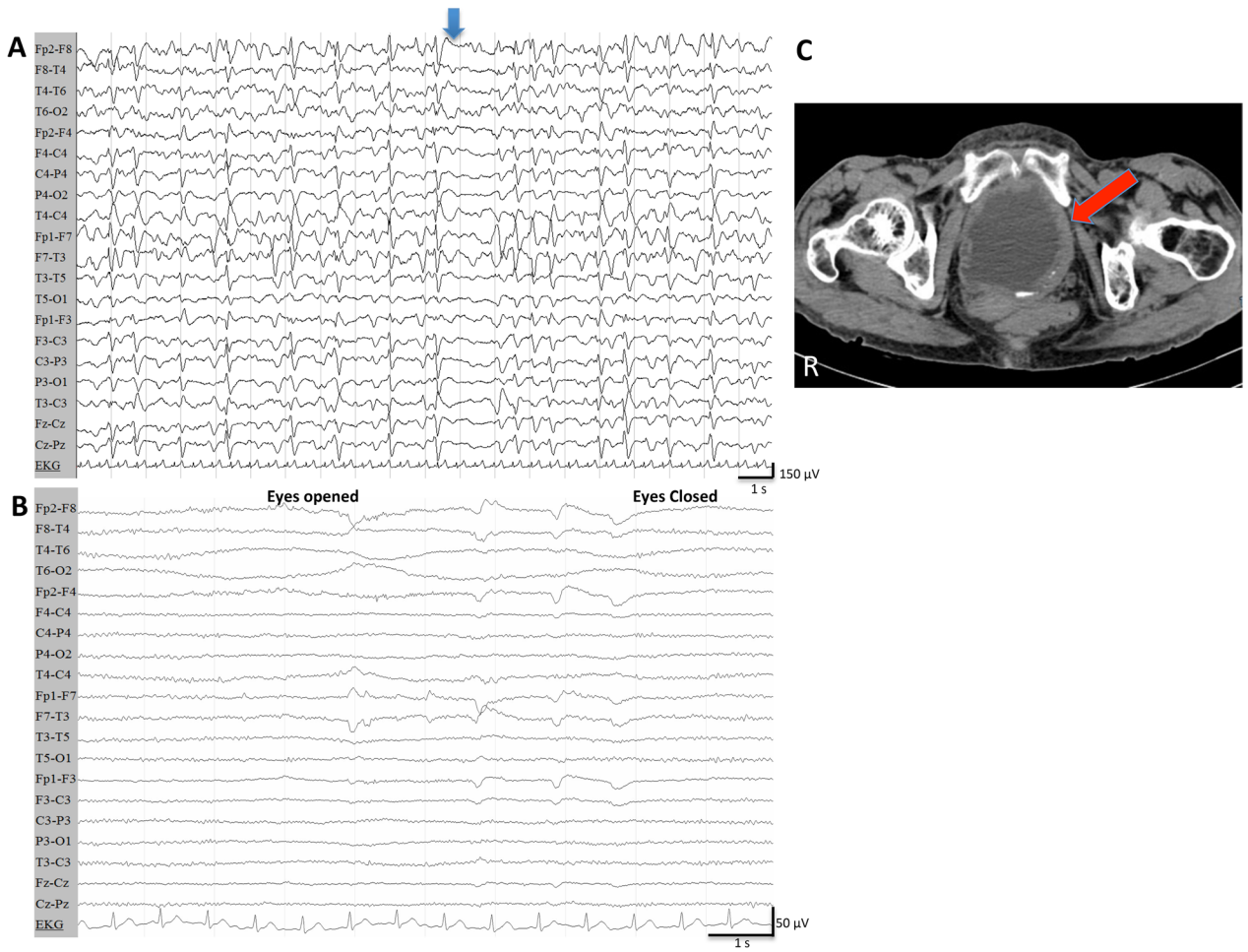

Fig. 1 EEG findings. **a** Severe disorganization of the background activity associated with pseudo-periodic short-interval generalized discharges (GPDs) with triphasic wave morphology repeating at a rate of 1–2 s. These complexes are prominent in frontocentral regions. Notice the reactivity to acoustic stimuli (arrow). During EEG recordings, the patient was comatose (GCS = 6) with high serum ammonia levels (294 µg/dL, 0–75). **b** EEG performed 7 days after the previous recording. Notice the reappearance of low-amplitude reactive posterior rhythmic activity at 10 Hz with superimposed pharmacological rhythms at 20–24 Hz more evident on anterior derivations. Clinically, the patient was alert and collaborative. Ammonia levels were in the normal range (34 µg/dL, 0–75). **c** An abdomen CT reveals the presence of hypertrophic neurogenic bladder (red arrow) (Color figure online)

substances. However, elevated blood levels of ammonia are toxic and associated with the development of metabolic encephalopathy. Hyperammonemia is commonly observed upon defective hepatic detoxification, as occurring in hepatic failure or severe cirrhosis with the portacaval shunt [4–6]. In general, hyperammonemia without liver failure is a rare condition occurring in a minority of critically ill patients. This condition can result from several and heterogeneous causes and has been associated with a poor prognosis [7]. The list of potential causes, other than liver failure, includes congenitally acquired deficits in the urea cycle metabolism [8], valproate, or other drugs intake [9]. Moreover, hematologic neoplasms, digestive system bleeding, and acute/chronic renal failure can independently promote serum hyperammonemia [7].

Hyperammonemic encephalopathy associated with urinary tract infections represents a rare but severe condition that should not be overlooked [1–3, 9]. The first report of this condition was that of Drayna et al., describing the case of a 49-year-old woman who developed repetitive episodes of lethargy and stupor as result of intermittent serum ammonia increases provoking recurrent episodes of HEs [1]. Similarly to our case, the patient suffered of urinary retention as a result of bladder dysfunction. Urinary contamination by urea-producing organisms was the crucial etiologic factor for the appearance of HEs. As in our case, catheterization and drainage of contaminated urine were invariably associated with clinical improvement of the patient [1]. Increased production of ammonia and uptake in the bloodstream upon urinary infections is considered the result of the metabolic activity of urea-splitting bacteria like the Proteus, Corynebacterium, or Diphtheroid strains. However, hyperammonemia has also been reported to occur in children upon infections sustained by bacteria such as the *P. rettgeri*, a common pathogenic host found in neurogenic bladders [3]. Of note, in children, HE has been associated with the presence of massively dilated upper urinary tracts, such as in the prune-belly syndrome, in conjunction with urinary infections sustained by urea-splitting organisms [9, 10]. In these conditions, intravenous administration of antibiotics and use of a catheter have resulted in dramatic resolution of the encephalopathy. In our case, the choice of the antibiotic molecule was mainly made on the basis of the antibiogram results. Within the tested molecules, *P. rettgeri* bacteria resulted in highly sensitive to ciprofloxacin. Sufficient sensitivities were also detected for cefepime, cefotaxime, ceftazidime. However, although cephalosporin antibiotics are good candidates for the treatment of urinary infections, these molecules can promote neurotoxic effects [11]. Cefepime, in particular, is a well-known cause of toxic encephalopathies [12]. Therefore, considering the bacteria sensitivity profile, the different antibiotic features, and specific side effects, we decided to treat the patient with ciprofloxacin.

In our case, the negative laboratory work for liver dysfunction led to overlook for the presence of an ongoing HE, and the EEG was crucial to provide information to formulate the right diagnosis. Although EEG shows little specificity in differentiating etiology in metabolic and toxic encephalopathy, it still represents an invaluable tool when evaluating patients showing disorders of consciousness. For long time, the term “triphasic waves” has been widely used to describe EEG abnormalities associated with metabolic encephalopathy. However, over the past years, our understanding of these abnormalities has improved and new definitions have been introduced, leading to the elimination of several etiologic references [13–15]. For this reason, the term triphasic wave has been replaced by the term continuous (or subcontinuous) GPDs with triphasic wave morphology. GPDs represent a difficult pattern to interpret, as it can be associated with different pathological states, spanning from status epilepticus to metabolic/toxic and infectious encephalopathies [16, 17]. It is actually accepted that patients showing GPDs with triphasic wave morphology are associated with a low risk of seizures, mostly if GPDs show fluctuating features, an anteroposterior gradient, and occur at rates lower than 3–4 Hz [18, 19].

The case here described merits attention for several aspects. Despite *P. rettgeri* having been described as urea-splitting bacterium that promotes hyperammonemic encephalopathies in the pediatric population, to our knowledge, this is the first report of such condition in an adult patient.

In this case, the negative laboratory work for liver dysfunction led to overlook for the presence of an ongoing metabolic encephalopathy. Moreover, the patient psychiatric history represented a further confounding factor, leading to suspect a relapsing psychosis. In this case, EEG enabled a rapid and noninvasive bedside electrophysiological evaluation suggesting precious information; otherwise, we did not obtain with other instrumental examinations.

In summary, the case underlines the need always to include a check for ammonia levels in all patients showing signs of orientation and vigilance disturbances and that the presence of a neurogenic bladder or urinary infection should always raise a red flag in patients showing decreased level of arousal. Finally, this report also indicates the still ongoing importance of the EEG when evaluating acute or subacute conditions of fluctuating cognition.

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VF study concept, interpretation and revision of the clinical data, manuscript writing. MC analysis and interpretation of the clinical data. Critical revision of the manuscript. MO paper supervision. Critical revision of the manuscript.

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Conflict of interest
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