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LETTER TO THE EDITOR

Uremia presented as acute cranial neuropathy

Wook Hur[1] · Ji Yeon Chung[1] · Pahn Kyu Choi[1] · Hyun Goo Kang[2,3]

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Dear Sir,

A 61-year-old patient who had been receiving hemodialysis three times per week due to end-stage renal disease (ESRD) for 10 years visited a nearby hospital due to upper respiratory tract infection symptoms 4 days before visiting our hospital. The patient was diagnosed with pneumonia and started treatment with 3rd-generation cephalosporin administration while hemodialysis was discontinued. On the third day of antibiotic treatment, dysphagia and dysarthria occurred, and consequently, the patient was transferred to our hospital.

In the neurologic examination, the patient was not able to swallow and drooled because of partial lower facial diplegia and paralysis of the soft palate and pharynx (Fig. 1a). All other neurologic examinations were normal, except for decreased bilateral ankle jerk. Left vocal cord palsy was confirmed by laryngoscopy (Fig. 1b). Abnormal findings were not observed on contrast-enhanced brain magnetic resonance imaging (MRI) and a diffusion-weighted image. In laboratory tests, the electrolyte levels were normal and blood urea nitrogen (BUN) (60 mg/dL), creatinine (13.29 mg/dL), and ammonia (75 μg/dL) were increased. The glomerular filtration rate (GFR) was 4.7 ml/min. The results of the cerebrospinal fluid (CSF) test showed clear color, pressure of 150 mmH_2O, white blood cells (WBC) count 2/mm^3, glucose concentration 63 mg/dL, and protein concentration 69 mg/dL. The results of facial nerve conduction studies (NCS) revealed bilateral facial nerve abnormalities. NCS in the upper and lower limbs did not show abnormal findings.

Hemodialysis was performed daily from the day of admission. From the third day of admission, the dysphagia of the patient had partially improved. Therefore, the patient was able to eat a liquid diet, and the number of hemodialysis sessions was reduced to three times per week. We could not exclude the possibility of multiple cranial nerve palsy caused by viral infection, and as a result, the patient began to take valacyclovir from the third day of admission. However, dysphagia began to worsen from the 7th day of admission, and the patient showed drowsy mentation from the 8th day. The results of the laboratory test had worsened again (BUN = 73.1 mg/dL, creatinine = 9.84 mg/dL, and GFR = 5.99 ml/min). Hemodialysis was again conducted daily, immediately after stopping the administration of valacyclovir. The patient was recovered to alert mentation from the 10th day of admission. After that, the facial palsy and dysphagia were gradually resolved, and the patient was able to carry out independent activities. Viral markers, blood and CSF cultures, and autoimmune and demyelinating markers were all negative (Fig. 2). Therefore, the patient was discharged.

The presented case reports a patient who, under hemodialysis due to ESRD, suddenly developed facial, glossopharyngeal, and vagal neuropathy during discontinuation of hemodialysis. The possibility of various diseases that could show acute neurological symptoms had to be excluded, but no test showed abnormal findings. The patient symptoms were improved by hemodialysis alone. Therefore, the subject was diagnosed with uremic cranial neuropathy (CNP).

Neurologic complications of CKD are classified as central/cortical neurologic complications, neuropathy, myopathy, and

Wook Hur and Ji Yeon Chung contributed equally to this work.

✉ Hyun Goo Kang
hgkang@jbnu.ac.kr

Wook Hur
ieb002@hanmail.net

Ji Yeon Chung
time4peace@hanmail.net

Pahn Kyu Choi
naanana@hanmail.net

[1] Department of Neurology, Chosun University Hospital, Gwang-ju 61453, South Korea

[2] Department of Neurology, Chonbuk National University Medical School, Jeonju 54907, South Korea

[3] Department of Neurology, Research Institute of Clinical Medicine of Chonbuk National University - Biomedical Research Institute of Chonbuk National University Hospital, Jeonju 54907, South Korea

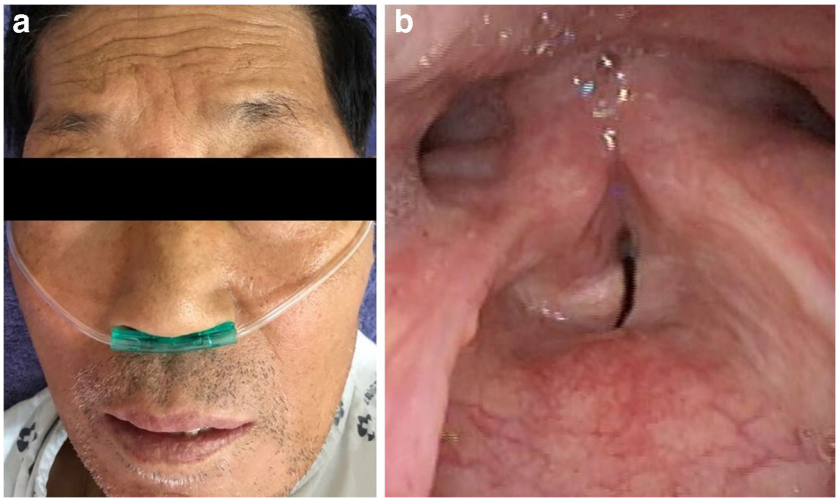

Fig. 1 **a** Neurological examination revealed a lower facial diplegia (left > right side). **b** Laryngoscopy assessment shows left vocal cord palsy, glottic gap, and right cord compensation

cranial neuropathy, depending on the invasion site. When the complication invades the central nervous system (CNS), it may cause cognition dysfunction, seizures, delirium, and encephalopathy. It has also been reported that approximately 16.4–60% of CKD patients have peripheral neuropathy of the limbs. One known mechanism of nerve injury is excessive axonal depolarization and axonal damage induced by intracellular accumulation of calcium secondary to hyperkalemia in CKD [1]. In addition, there are some reports that an increase of neurotoxic molecules and parathyroid hormone, which are accumulated in CKD, can cause nerve damage.

It is known that CNP can also occur to patients with CKD. However, the mechanism is still unclear. Olfactory [2] and cochlear neuropathies [3] have been studied, because they are relatively common. Although rare, uremic optic neuropathy was also studied [4]. It has been reported that olfactory nerve abnormalities are found in 56% of patients with CKD. These are known to be caused by the retained uremic toxin, not adequately cleared with dialysis, which undermines the integrity of the olfactory epithelium and olfactory bulb and impairs central olfactory processing [2]. And cochlear neuropathy commonly co-occurs with CKD. It is believed that the cochlea and the kidney can be damaged by the same mechanisms because they share many physiological and structural similarities. Indeed, the two organs can be damaged at the same time by a single gene abnormality [3]. Several hypotheses are suggested for uremic optic neuropathy. Among them, the conductivity of the optic nerve is recovered by hemodialysis, so it is believed that a toxic metabolite is the cause [4].

It is very rare to see the invasion of uremia into the facial, glossopharyngeal, and vagal nerve. Only one previous study reported this phenomenon [5]. The previous study reported that a young male patient with Alport syndrome showed acute left oculomotor neuropathy, facial diplegia, and dysphagia. At the same time, the brain MRI of the patient showed diffusion restriction on the corona radiata and centrum semiovale,

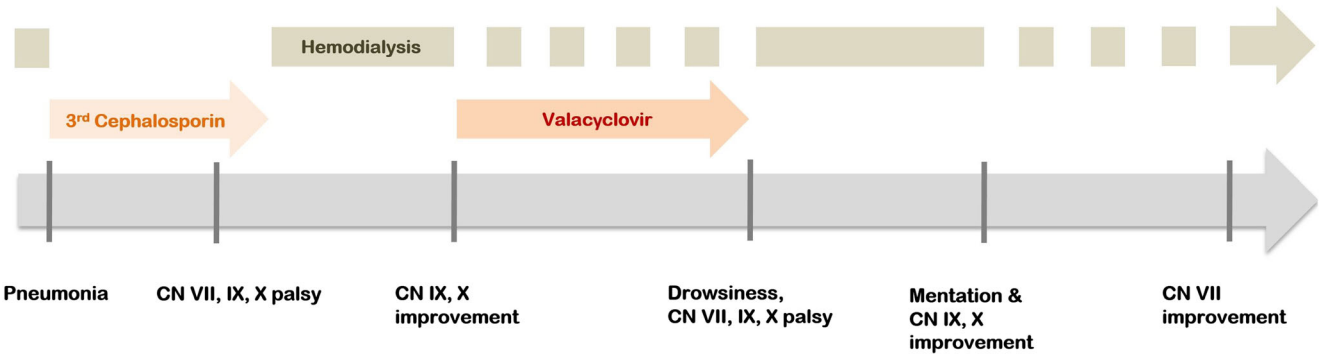

Fig. 2 Timeline of neurologic symptoms and treatments of the patient. The initial cranial nerve palsies occurred after 3rd-generation cephalosporin administration with dialysis discontinuation. Symptoms improved slowly by daily hemodialysis, but worsened again after the administration of valacyclovir. Complete recovery was achieved by hemodialysis with discontinuation of valacyclovir. The solid line means dialysis every day and the dotted line means dialysis 3 times a week

suggesting metabolic encephalopathy. In this patient, all symptoms were improved by hemodialysis. This study was thus very similar to ours in that acute cranial neuropathy, other than olfactory, optic, and cochlear neuropathies, occurred and the symptoms were improved by hemodialysis alone. In our case, acute cranial neuropathy was induced by stopping hemodialysis in the CKD patient. The symptom was improved as soon as hemodialysis was resumed. However, the symptoms were aggravated after administrating valacyclovir, which can induce renal function impairment. Therefore, the administration of valacyclovir was stopped, and the frequency of hemodialysis increased, to recover from CNP. In this case, we could observe dynamic changes in symptoms due to the improvement and deterioration of uremia. These two cases suggest that acute CNP due to uremia is reversible, and imply that uremic toxins and toxic metabolites, which are the known common mechanisms of CN injury [2, 4], are also the main mechanism of acute CNP.

This case study revealed that CKD may cause facial, glossopharyngeal, and vagal neuropathy in addition to that of the olfactory, optic, and cochlear nerves. It was suspected that the mechanism was associated with uremic toxin because this case study, just like the previous report, showed acute neurological symptoms that were recovered by hemodialysis. This case study thus confirms that symptoms due to uremia should be considered when treating acute CNP in CKD patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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