



COVID 19 and myoclonus, do hemodialysis patients have more risk?

Mioclonías y COVID19: ¿mayor susceptibilidad en pacientes en hemodiálisis?

Dear Editor,

We present two cases of patients with GSD chronic kidney disease in a renal replacement therapy (RRT) programme with regular haemodialysis (HD) and SARS-CoV-2 infection. They both suffered movement disorders whose onset coincided chronologically with the haemodialysis sessions.

The first case was a 78-year-old woman on HD, without previous neurological clinical history of neurologic abnormalities who was brought to the Emergency Room having developed behavioural and language abnormalities within a few hours after her scheduled haemodialysis session. She had developed a cough and fever 48 h before, so a SARS-CoV-2 Polymerase Chain Reaction test was performed, which resulted to be positive. On neurological examination, the patient was disconnected from the environment with generalised myoclonus, most evident in the orofacial muscles and right upper limb, and she had spontaneous horizontal saccadic eye movements, negative meningeal signs and unaltered deep tendon reflexes. Lab tests and brain computed tomography were performed, without findings that could help to explain the symptoms. She was started on anticonvulsant therapy, but 24 h later she continued to be disconnected, with a tendency to adopt a lateral decubitus position and persistence of the myoclonus. A lumbar puncture was performed, obtaining cerebrospinal fluid with protein, explained by prolonged status epilepticus, and microbiology was negative. The neurophysiological study was consistent with severe metabolic encephalopathy with a large amount of epileptogenic activity. Given the lack of response to the combination of lacosamide and levetiracetam, valproic acid was added, achieving complete remission of the neurological symptoms.

The next case was a 46-year-old male on HD, positive for COVID-19 after close contact, but without respiratory symptoms. Day +10 after the positive PCR, the patient began to suffer from involuntary clonic movements in the upper limbs during the HD sessions. Initially, slight hypocalcaemia was detected, but, despite its correction, the symptoms reappeared coinciding with the HD sessions. After assessment by Neurology, he was diagnosed as having myoclonus and was started on treatment with valproic acid.

Neither of these cases had undergone any recent changes in medication or in the usual haemodialysis schedule.

SARS-CoV-2 infection is a disease whose full range of symptoms has yet to be completely defined. In the neurological setting, involvement has been described at various levels: central nervous system (CNS) (for example, dizziness, reduced level of consciousness, headache, acute cerebrovascular disease, ataxia, seizures), peripheral nervous system (for example, alteration of taste and/or smell, loss of vision, neuropathic pain, post-infectious polyneuropathy) and musculoskeletal manifestations (for example, myalgia).¹ Cases have also been reported of post-infectious symptoms in COVID-19: acute post-infectious myelitis; Guillain-Barré; Miller-Fisher syndrome; acute disseminated encephalomyelitis; and several cases of myoclonus.² In a series of cases, Cuhna et al. describe late-onset movement disorders (23 ± 7 days) associated with severe COVID-19 disease; and they hypothesise the possibility of a combined post-hypoxic, cortico-subcortical (post-infectious) and metabolic origin of the myoclonus secondary to kidney damage (with the need for renal replacement therapy) in one of the patients.³ In a review by Maury et al. on neurological manifestations associated with SARS-CoV-2, that analysed five cohorts, a greater risk of encephalopathy is described in patients with higher serum urea levels, and with regard to the development of generalised myoclonus, the authors believe that is possible related with immune-mediated mechanism.⁴ Anand et al. published a multicentre case series of eight patients with COVID-19 disease who developed myoclonus between days 2 and 9 of illness; all of them also had metabolic abnormalities: hypo- or hyperglycaemia, hypo- or hypernatraemia and uraemia, three of them required renal replacement therapy and in four of them, severe hypoxia was observed in the 72 h prior to the onset of myoclonus.⁵ Ros-Castelló et al. describe a case of the development of myoclonus in a female patient who required admission to the Intensive Care Unit a month after the onset of symptoms which, after various tests, was attributed to CNS hypoxia. The authors hypothesise that the endothelial damage caused by the systemic inflammatory response can lead to neuroinflammation that reduces the hypoxic threshold required for the development of post-hypoxic myoclonus. This would suggest that it is not necessarily linked to prolonged or severe hypoxia as usually occurs in Lance Adams syndrome.⁶ Latorre et al. analysed cases of myoclonus reported after

the resolution of acute respiratory infection by SARS-CoV-2, and emphasise the late appearance of this symptom, which would more strongly suggest an immune-mediated cause secondary to a cross-reaction between ganglioside epitopes, carriers of COVID-19 spike proteins, and glycolipid remains on the surface of peripheral nerves, similar to the pathogenic mechanism in Guillain-Barré syndrome. However, they also state that in the post-hypoxic mechanism, onset could be late as a consequence of the abnormal reorganisation that occurs in neuronal networks after brain injury.⁷

Patients with chronic kidney disease have a great susceptibility to neurological alterations of multifactorial origin including accumulation of uraemic toxins, metabolic and haemodynamic abnormalities, oxidative and osmotic stress, and inflammation and alteration of the blood-brain barrier. This causes a damage that can occur at multiple levels: peripheral (neuropathy, myopathy); cortical (cognitive disorders, encephalopathy, stroke, movement disorders including myoclonus and seizures, sleep disorders such as restless leg syndrome); and cortico-subcortical (multifocal ischaemia, subcortical infarcts and movement disorders such as dystonia, chorea or myoclonus, whether reticular or cortico-subcortical).⁸ In patients on long-term haemodialysis, the development of neurocognitive disorders is three to five times more common than in the general population, with vascular dementia being more prevalent than Alzheimer's type dementia,⁹ and it also seems to be more common in patients on renal replacement therapy with haemodialysis compared to peritoneal dialysis.¹⁰ This phenomenon has led to a number of studies being carried out to determine and quantify the different factors that may cause vascular damage. Haemodialysis patients appear to have a microvascular vulnerability beyond traditional atherothrombotic mechanisms.¹¹ Moreover, functional myocardial perfusion studies have shown that during haemodialysis an environment of microvascular ischaemic damage is created, even when macroscopic arteriopathy is not detected,¹² which could be extrapolated to the brain. Another factor that can influence brain damage is brain hypoxia, both acute and chronic. Using non-invasive methods of cerebral oxygen saturation during haemodialysis sessions, it has been described an acute drop during the first 30 min of de HD session. Although no specific cause has been demonstrated, there are multiple hypotheses (results have been inconsistent regarding the possible relationship with changes in blood pressure, ultrafiltration rate, alteration of the oxygen dissociation curve due to changes in blood pCO₂ and pH and osmotic changes). After this initial drop, oxygen saturation return to their baseline level, which is also lower than in the population not on haemodialysis.^{13–15} Recently, the possibility has been raised that patients receiving long-term haemodialysis and suffering from COVID-19 disease may suffer intradialysis hypoxia, even before exhibiting the rest of the classic symptoms of the disease and being diagnosed.¹⁶

Therefore, it seems conceivable that haemodialysis patients, who routinely suffer from oxygen imbalances and damage to the central nervous system, could also be more susceptible to the development of myoclonus in COVID-19 disease, and even that these abnormalities are chronologically related to the haemodialysis sessions.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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<https://doi.org/10.1016/j.nefro.2024.03.015>

Prognostic implication of thyroid hormones among patients with acute kidney injury

Implicación pronóstica de las hormonas tiroideas en pacientes con insuficiencia renal aguda



Dear Editor,

A recent prospective study of thyroid functions among 35 patients with AKI found that 80% of them had thyroid dysfunction. The presence of thyroid dysfunction was not associated with prognostic implications among these patients.¹ We attempted to prospectively assess thyroid functions at the time of diagnosis of AKI in a larger cohort and try to assess if initial thyroid dysfunction had any prognostic implications on outcomes.

Adult patients admitted with renal injury or those who developed AKI during hospitalization were prospectively recruited for this observational study after informed consent for over a period of one year. The study was approved by the Institutional Research and Ethics committee of Christian Medical College and Hospital, Ludhiana. The diagnosis of AKI was made as per AKIN working group.² Pregnant women, patients with pre-existing thyroid disease including those on thyroxine supplements or anti-thyroid drugs, patients who received iodine contrast agents prior to recognition with AKI and patients on drugs which interfere with thyroid function were excluded.

Baseline clinical information was collected from the patient and from the charts. The type of AKI-pre-renal, renal, post renal-was then noted. Serum sample was taken for testing free T3(FT3), free T4(FT4) and TSH levels which were determined using the electrochemiluminescence immunoassay on Cobas e411/601 immunoassay analyzer. All recruited patients were first classified as having normal thyroid functions (euthyroid) or having thyroid dysfunction. Patients with thyroid dysfunction were classified into six different types; primary hyperthyroidism, subclinical hyperthyroidism, primary hypothyroidism, subclinical hypothyroidism, non-thyroidal

illness and central hypothyroidism. After baseline investigations, the patients were followed up till discharge from the hospital or in-hospital death.

One hundred and forty-seven patients with a mean age of 57.8 ± 16.8 (range 20–95) years were consented. There were 93 males (63.27%) males and 54 females (36.73%). 49 patients (33.33%) were with stage 1 AKI, 8 patients (5.44%) with stage 2 AKI, 90 patients (61.22%) with stage 3 AKI as per AKIN classification.⁶ Of 147 enrolled patients, pre-renal causes of AKI were seen in 35(25.80%) patients, renal causes in 13(8.84%) patients, a combination of pre-renal and renal causes in 98(66.67%) patients and combination of post-renal and renal causes in 1(0.68%) patient.

Thyroid dysfunction was seen in 114 (77.5%) patients with acute kidney injury. The spectrum of thyroid dysfunction is given in Fig. 1. Baseline characteristics in the patients with AKI with and without thyroid dysfunction were comparable.

Regarding outcome, 47 (31.97%) patients died in hospital. No significant association was found between the presence of thyroid dysfunction and mortality among patients with AKI (p -value=0.84). However, when we studied the association of type of thyroid dysfunction and in-hospital mortality, it was found that there was trend of increased in-hospital mortality in patients with AKI having primary hyperthyroidism, subclinical hyperthyroidism and non-thyroidal illness as compared to those having euthyroidism, primary hypothyroidism and subclinical hypothyroidism. Patients with AKI having TSH value < 2 mIU/L were found to have higher mortality as compared to those having TSH value ≥ 2 mIU/L (40.70% vs 19.67%) (p -value=0.007). Using a receiver operator curve (ROC) determination, we found that using a TSH cut off of < 1.92 mIU/L provided the best sensitivity and specificity for in hospital mortality estimation in patients admitted with AKI and this maybe a cut off useful for prognostication in patients with AKI (Fig. 2). No significant association was found between thy-