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Sedation Failure in a Patient with Fahr Syndrome in the Intensive Care Unit

Fahr Sendromu Olan Bir Hastada Yoğun Bakımdaki Sedasyon Problemi

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ABSTRACT

Fahr Syndrome, which is a rare neurologic syndrome, is characterized by sporadic or genetically inherited basal ganglion calcification. There are some hypotheses about the pathophysiology of Fahr Syndrome related to a defect in calcium metabolism, metastatic calcium deposits and increased free radical production. Although patients are usually diagnosed with extrapyramidal symptoms, they may also present with cerebellar dysfunction, speech disorders, dementia and neuropsychiatric symptoms. We aimed to discuss sedation failure with dexmedetomidine and midazolam in a 49-year-old female patient with Fahr Syndrome who was admitted to our intensive care unit after suicidal carbamazepine overdose in this case report. Adequate sedation levels could not be reached although infusion of 1.5 μg kg^{-1} h^{-1} dexmedetomidine and bolus injections of 1.5 mg midazolam were administered. This may be due to the tolerance to sedatives developed by long-term use of antidepressant and antiepileptic agents. On the other hand; the unique sedative agent dexmedetomidine is a specific and selective α2 agonist and the widespread intracerebral calcification in our patient may have impaired α2 receptor activity. Besides, calcium metabolism disorder, one of the probable causes of Fahr Syndrome, may affect calcium-mediated inhibition of neurotransmitter release through α2 adrenoreceptors and reduced the effectiveness of dexmedetomidine.

Keywords: *Dexmedetomidine, critical care, sedatives, failure treatment*

ÖZ

Nadir görülen nörolojik bir sendrom olan Fahr Sendromu, sporadik ya da genetik geçişli bazal ganglion kalsifikasyonuyla karakterizedir. Fahr Sendromu'nun patofizyolojisiyle ilgili olarak; kalsiyum metabolizma bozukluğu, metastatik kalsiyum depozitleri ve artmış serbest radikal üretimi gibi bazı hipotezler mevcuttur. Hastalar genellikle ekstrapiramidal semptomlarla tanı alsa da, serebellar disfonksiyon, konuşma bozuklukları, demans ve nöropsikiyatrik semptomlarla da başvurabilirler. Bu olgu sunumunda amacımız, intihar amaçlı karbamazepin alımı sonrası yoğun bakımımıza kabul edilen 49 yaşındaki kadın hastadaki sedasyon yetersizliğinden bahsetmektir. Hastaya 1.5 mcg kg^{-1} sa^{-1} deksmedetomidin infuzyonu ve 1.5 mg midazolam bolusları uygulandığı halde yeterli sedasyon düzeyine ulaşılamamıştır. Bu durum uzun süreli antiepileptik ve antidepresan kullanımına bağlı olabilir. Diğer yandan da, benzersiz bir sedatif ajan olan deksmedetomidin spesifik ve selektif bir α2 agonistidir. Hastamızdaki yaygın serebral kalsifikasyon, α2 reseptör aktivitesini bozmuş olabilir. Bunun yanında Fahr Sendromu'nun muhtemel nedenlerinden biri olan kalsiyum metabolizma bozukluğu da α2 adrenoreseptör aracılıklı kalsiyum ilişkili nörotransmitter salınımını etkilemiş ve böylece deksmedetomidinin etkinliğini azaltmış olabilir.

Anahtar kelimeler: *Deksmedetomidin, yoğun bakım, sedatifler, tedavi yetersizliği*

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INTRODUCTION

Fahr Syndrome which is a rare neurological syndrome (with an incidence of < 1/1000000) was first described by Theodor Fahr in 1930 and characterized by sporadic or genetically inherited basal ganglion calcification [(1)]. Although patients are usually diagnosed with extrapyramidal symptoms, they may also present with cerebellar dysfunction, speech disorders, dementia, and neuropsychiatric symptoms [(2)]. We aimed to discuss the intensive care unit process and the usage of dexmedetomidine and midazolam in a patient with Fahr Syndrome, particularly in this rare case. There have been several articles in the literature about Fahr Syndrome while none of them have reported on the sedation process of the patients with Fahr Syndrome during the intensive care unit (ICU) stay.

The family of the patient reviewed this case report and gave written permission for the authors to publish this report.

CASE

A 49-year-old female patient who was admitted to the emergency department with ingestion of carbamazepine overdose with suicidal intent and seizures was intubated and referred to our ICU. On ICU admission she was confused and agitated with verbal and painful stimuli. The hemodynamic parameters were stable but arterial blood gas analysis revealed metabolic acidosis (Ph: 7.1). Multiple intracerebral calcifications were detected on computed tomography (CT) (Figure 1).

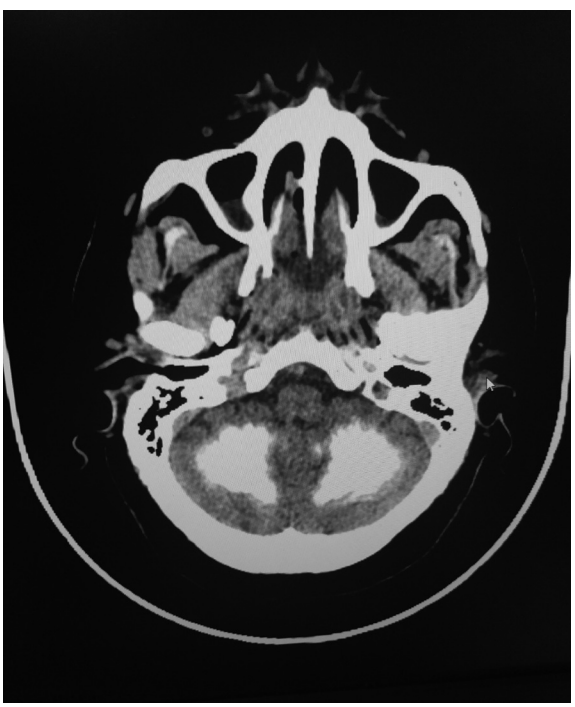

Figure 1. Cranial tomography image of patient

Blood test analysis were normal except hypocalcemia (8 mg dL^{-1}) and hyperphosphatemia (5.6 mg dL^{-1}). Her medical history revealed that she was diagnosed with epilepsy since age 11, depression and hypoparathyroidism since age 30, and Fahr's Syndrome since age 45. She had been medicated with carbamazepine (1x200 mg), quetiapine (1x200 mg), oral calcium and vitamin D.

After admission to our ICU unit (at the third hour of suicidal intake); gastric lavage, administration of active charcoal, calcium replacement, and dialysis were performed with close hemodynamic monitoring. The patient was sedated with bolus injection of 2 mg midazolam and dexmedetomidine infusion at a dose of 0.2 mcg^{-1} kg^{-1} h due to agitation and ventilator incompatibility. Muscle relaxation was not achieved for a possible plan of weaning from mechanical ventilation. While hypocalcemia and metabolic acidosis were normalized with medications; she remained in asynchrony with mechanical ventilation because of ongoing confusion and agitation. So dexmedetomidine dose was increased to 1.5 mcg^{-1} kg^{-1} h and bolus injections of 1.5 mg midazolam were added at 30-minute intervals.

Despite the increased bolus doses of dexmedetomidine and midazolam, adequate sedation levels could not be achieved and the patient extubated herself. She was re-intubated, and sedation was continued in the same manner with dexmedetomidine, midazolam, and movement restriction. The patient could not be weaned from the mechanical ventilatory support and she developed sepsis after ARDS despite all supportive and preventive treatments. The patient died on the 29th day of her admission to the intensive care unit.

DISCUSSION

Fahr Syndrome is a general term used for more than

30 conditions with basal ganglion calcification, regardless of etiology. It may be idiopathic or familial or related to inflammatory (CMV infection, neurocysticercosis, toxoplasmosis, neurobrucellosis, tuberculosis, HIV infections), tumoral (astrocytoma), hypoxic vascular (arteriovenous malformation, calcified infarction, ischemic encephalopathy), and endocrine problems (hypoparathyroidism) or in some cases it can also be seen completely without any cause [3]. It is usually associated with low serum calcium levels [4]. Although the pathophysiology of Fahr Syndrome is poorly understood, there are some hypotheses such as the initiation of intracerebral calcifications by defective ion transfer or increased free radical production and its association with a defect in calcium metabolism and metastatic calcium deposits [5,6].

Although most intracranial calcifications occur bilaterally and symmetrically, a few occur unilaterally. In a review of 4219 cranial tomographies including cerebral calcification, such examples were shown. Globus pallidus is the most common site of calcification [7]. The age of onset of clinical symptoms is usually 40-60 years, though occasional cases have been reported in children [8,9]. Patients may present with neurological findings such as parkinsonism, chorea, tremor, paresis, dystonia, speech disorders, stroke, seizure, syncope, or psychiatric problems such as psychosis and dementia [5,6]. The diagnosis is based on clinical examination and radiological investigations that determine intracerebral calcifications. Treatment is symptomatic with antipsychotic, antidepressant, antiepileptic and procognitive agents. Hypocalcemia, which often accompanies intracranial calcifications, should be considered [10].

Dexmedetomidine is a specific and selective α2 agonist agent. Alfa-2 adrenoceptors inhibit the induction of neuronal firing in the brain and spinal cord via the regulation of noradrenaline and adenosine triphosphate (ATP) release and cause hypotension, bradycardia, sedation, anxiolysis and analgesia. Another prominent physiological feature of these receptors is prevention of neurotransmitter release with the inhibition entry of calcium into the neuronal endings. As a result, dexmedetomidine inhibits neuronal firing, calcium transfer to cells and neurotransmitter release, thereby impairing transfer of signals to neighboring neurons and produces sedation, analgesia and anxiolysis in this way [11]. In clinical trials about ICU sedation; the maximum dose of dexmedetomidine used is 1.5 μg^{-1} kg^{-1} hr. Rescue sedation can be provided with bolus infusion of 1-3 mg midazolam or 30-50 mg propofol repeated as necessary [12].

When the past medical history of our case was questioned extensively; the first seizure at age 11 was presumed to be a hypocalcemia- induced tetany. The patient had been medicated with antidepressant and antiepileptic agents for a long time due to the diagnosis of epilepsy and depression. Extensive intracerebral calcifications were first noted on CT only 4 years ago. Despite the infusion of extremely high dose of dexmedetomidine and intermittent midazolam boluses; we could not relieve the agitation and achieve adequate sedation in our patient which may be due to the tolerance to sedatives developed by long-term use of antidepressant and antiepileptic agents.

From another point of view; α2 adrenoceptors are widely distributed in the human brain [13]. The calcifications in Fahr Syndrome is most commonly located in the caudate nucleus, globus pallidus, putamen, lateral thalamus, dentate nucleus, cerebral cortex, internal capsule, cerebellar film [14,15]. The widespread intracerebral calcification in our patient may have impaired α2 receptor activity and reduced the effectiveness of dexmedetomidine. Besides, calcium metabolism disorder, one of the probable causes of Fahr Syndrome, may have affected calcium-mediated inhibition of neurotransmitter release through α2 adrenoreceptors.

In conclusion; the management of patients with Fahr Syndrome in the intensive care unit consists of the correction of electrolyte disorders such as hypocalcemia and supportive treatment and it may present a therapeutic challenge in attempting to provide adequate sedation due to the tolerance to sedatives and varied response because of intracranial calcifications. Further postmortem and experimental studies can be useful in understanding this issue.

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