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Case Report

The Neurological Complication of Intradiscal Ozone Injection, A Case Report

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Abstract

Ozone therapy is a novel treatment methos using worldwide. Controlling disk herniation pain is one of its usages nowadays. The associated neurological complications are not known yet.

Herein, we are going to present two patients, one presenting with cortical blindness and focal to generalized bilateral seizure, and one with acute onset quadriplegia. Posterior reversible encephalopathy and maybe cord infarction are the probable occurred complications. We are going to discuss the likely scenarios that happened and highlight the neurological consideration in the ozone injection.

Keywords: ozone therapy; neurological complication; cord infarction; pres syndrome

Introduction

Ozone therapy (OT) is a novel treatment method based on the mixture of oxygen and ozone (O2 O3) that is used in many indications such as arthrosis, disk herniation, infections, especially in The COVID pandemic, cancer, autoimmune and neurodegenerative disorders.[1-4]

In recent years, one of the main areas of OT application is disk herniation treatment that has not responded to conservative management. There are two approaches for ozone injections: intradiscally (direct) and into the paravertebral muscles (indirect); which probably help to shrink the herniated disc size and have analgesic or anti-inflammatory effects.[1, 5]

Due to the novelty of this treatment method, its neurological complications are not known completely; therefore, we need more studies on the reliability and safety of this medical treatment.[6]

So, we herein report two cases that were complicated by posterior reversible encephalopathy syndrome (PRES) and spinal cord infarction after intradiscal ozone injection.

Case presentation

Case1

A 64-year-old diabetic and hypertensive female was admitted to our hospital emergency room with abrupt onset headache, nausea and vomiting, disorientation and bilateral painless visual loss immediately after 20 ml of an oxygen-ozone mixture (ozone concentration of 20 μg/ml) injection in cervical discs for her neck pain.

On admission, she was drowsy and confused. She was afebrile, with no neck stiffness or respiratory distress and had a blood pressure of 150/90 mmHg, Heart Rate (HR) of 82 beats per minute Detailed neurological examination revealed bilateral blindness with persevered pupillary reflex and pink and sharp optic disks. She had bilaterally extensor plantar reflexes, truncal ataxia with intact muscle forces. She had three episodes of focal to bilateral seizures.

The laboratory investigations were in normal range. Axial view fluid-attenuated inversion-recovery (FLAIR) sequence of the brain MRI (Magnetic resonance imaging) showed high signal intensity in bilateral cerebellar hemispheres (left more than right), cerebellar vermis and bilateral thalamus. The lesions had no restriction or gadolinium (GAD) enhancement (Figure 1.A-C). All findings were compatible with vasogenic edema.

The patient was admitted to intensive care unit and was managed with intravenous antiepileptic, fluids and blood pressure monitoring for 7 days. During admission, clinical neurologic exams improved. MRI showed relative remission of T2/FLAIR sequence lesions in 2 weeks follow up. (Figure 1.D)

According to improved clinical presentation and remission in MRI findings, the diagnosis of PRES (posterior reversible encephalopathy syndrome) due to ozone injection was confirmez

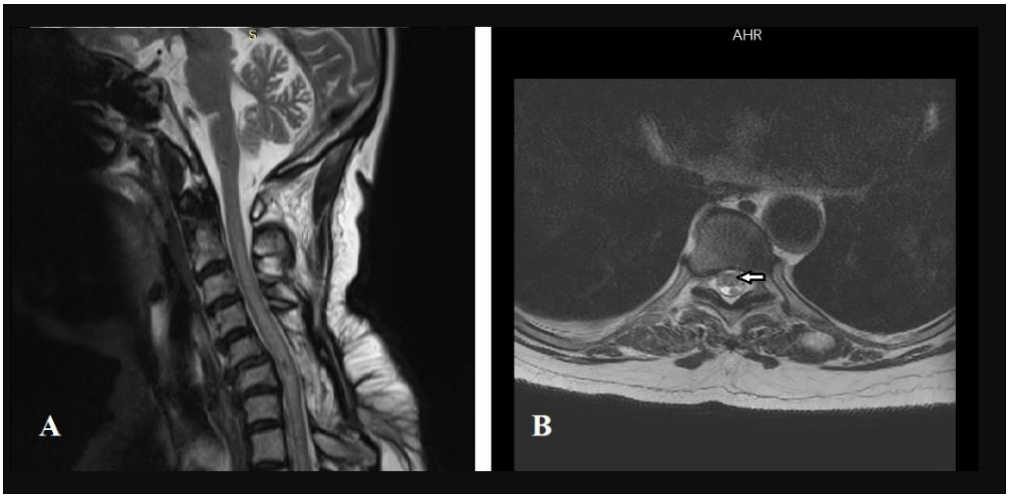

Figure 1: MRI findings at the onset (A-C) and follow up (D). (A) FLAIR sequence, shows edema within bilateral thalamus (white arrows) and (B) bilateral cerebellum hemisphere (Left more than right) and vermis, (C) Apparent diffusion coefficient (ADC) shows vasogenic edema (D) FLAIR MRI sequences showing a near complete resolution of the lesions at the 2weeks follow-up

Case 2

A 72 years-old female who was known case of diabetes mellitus and hypertension admitted to the university hospital neurology ward with hyper acute quadriparesis from 2 weeks prior to the admission. It occurred immediately after 15 ml of an oxygen-ozone mixture (ozone concentration of 15 µg/ml) injection in the third cervical disc. Her symptoms had not changed between the onset of paresis and admission. She suffered from a burn wound in the right side of her abdomen due to loss of temperature sensation. She also complained of urinary retention.

In the examination she was alert and oriented with stable vital signs and normal peripheral pulses. She was areflexic and had quadriparesis (more prominent in lower limbs and left sides), Normal position sense in all limbs along with a sensory deficit at the T2 level and bilateral positive Babinski sign. The cranial nerves examination were intact.

Whole cord Magnetic resonance imaging (MRI) was done to assess structural insults. It revealed a longitudinal T2/STIR hypersignal lesion of the cervical cord preferentially affecting anterolaterally elongated from C2 to C7 level. (Figure 2.A,B) There was no remarkable finding in brain MRI.

Considering hyper acute myelitis, we did number of paraclinical tests. The electrocardiogram (ECG) showed sinus rhythm with no abnormality. Trans-thoracic echocardiography (TTE) and trans-esophageal echocardiography (TEE) were done, no patent foramen oval (PFO) was seen.

Beside the post renal acute kidney injury, routine lab test including cell count, biochemistry studies were normal. Lumbar puncture was unremarkable and one oligoclonal band was detected. (WBC: 0-1, RBC: 190, Glucose: 68, Pro: 28). CSF Polymerase chain reaction (PCR) checked for HCV and CMV.

Serum Aquaporin-4 (NMO-IgG) and Myelin oligodendrocyte glycoprotein (MOG) antibodies were also negative. Serum Rheumatologic and viral markers were negative.

Due to normal lab tests, hyper acute onset of symptoms, cervical MRI findings, and no clinical improvement in one month follow up assessments, Ozone injection induced ischemic myelitis was the most probable diagnosis.

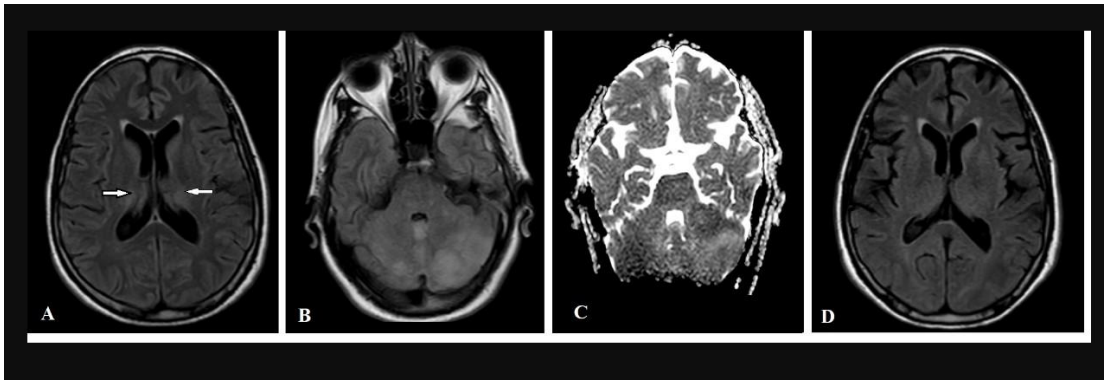

Figure 2: spinal cord infarct in the central territory of the anterior spinal artery. T2/STIR sequence (A) sagittal view, high intense longitudinally extensive lesion from C2-C7. (B) axial view, hyperintense signal at the center of cord, sparing posterior cord (white arrow).

Discussion

In our first case, initially posterior circulation acute ischemic stroke , was considered in the context of air gas emboli following ozone-oxygen intradiscal injection. The evolution of case 1 symptoms and the absence of infarction and the pattern of vasogenic edema distribution in the primary brain imaging ruled out the infarction and highlighted the "PRES central variant" diagnosis. There were two interesting findings in our case presentation. She experienced serial focal onset seizure with impaired awareness in the absence of cortical/subcortical gross pathology. So, there may be supratentorial microscopic abnormalities in central variant of PRES that needs quantitative MRI DWI sequence for detection.[7] our patient complaint of sudden painless bilateral vision loss with preserved pupillary response in favor of cortical blindness despite intact occipital lobe in brain imaging. We explain this phenomenon with role of lateral geniculate nucleus of the thalamus in relaying visual data from the retina to the primary visual cortex. Bilateral thalamic involvement explains her blindness.

cerebral autoregulation failure leading to hyper perfusion or an excessive vascular reactivity is the pathological explanation for all the

disorders that cause PRES. Regardless of the underlying cause, most common neurological deficit include cortical blindness, confusion, headache, nausea and vomiting, seizure and focal neurological deficit. In brain MRI, vasogenic edema is seen as white matter T2/FLAIR sequence hyperintensity mostly in occipitoparietal lobe; however, it can be superimposed with infarction. Atypical regional involvement may include thalamus, brainstem, deep gray matter and cerebellum which is called "central variant". The interesting phenomena of the central variant is that there is less cytotoxic insult and the DWI sequence may show no restriction as it was, in our patient. [8] A hallmark of the PRES syndrome is the improvement of clinical and radiological findings with the treatment of underlying cause.[9] there are a variety of underlying etiologies for PRES but ozone therapy role is a novel finding.

The probable explanation is the effect of the ozone on the vascular permeability via Nitrous Oxide(NO) production which leads to vasogenic edema. [10] Another possible mechanism may be the theory of "ozone-induced oxidative stress".[11] Free radical mediated oxidation of arachidonic acid, produce 8-Iso-prostaglandin (PG)E_2 and 8-iso-$PGF_{2\alpha}$ which are both potent vasoconstrictors.[12] In a study conducted on 2013, the urine level of 8-iso-$PGF_{2\alpha}$ was significantly higher in patients with reversible cerebral vasoconstriction syndrome (RCVS) and correlated with the severity of vasoconstrictions. [13] RCVS mimicking PRES radiologically, makes the differentiation even more challenging. [14]

Ischemic infarction of the spinal cord is rare and presenting about 1% of all strokes. It mostly involves the ventral two- third due to anterior spinal artery infarction. Infarction commonly result from systemic hypotension in the most vulnerable site, the thoracic region.[15]

Ozone-oxygen intradiscal injection has been reported to causes anterior spinal artery infarction in the presence of patent foramen oval (PFO) and paradoxical gas embolism, as the result of right to left shunt.[16] despite, the through workup conducted, there was no evidence of PFO in our patient. This was the interesting finding of our patient.

Spinal arteriovenous shunt normally present between arteries and veins in the epidural space.[17] If the injected ozone-oxygen could gain access to the spinal venous system, it may have retrograde travel in the venous route due to the increased intrathoracic pressure as the result of the patient Valsalva maneuver or injection pain.[18] Then, it can inter the spinal arterial system (probably anteriorly because of its dominancy) directly from arteriovenous shunt without crossing the pulmonary system. Another theory is the misplacement of the injection site. If the needle placed in the anterosuperior part of the foramen it may insult the radicular artery and cause cord infarction.[19]

By these 2 mechanisms, we explained that maybe local gas emboli has caused anterior spinal cord infarction. However; the exact mechanism is not clear.

Conclusion

ozone therapy has been utilized widely as medical treatment in the recent years. it is assumed as a safe method to ameliorate disk herniation pain. Our study highlights the detrimental neurological consequence of intradiscal ozone injection that may be irreversible. Further study is needed to prove its safety and clarify the associated complications.

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