Case Report

Cerebellar talcosis following posterior reversible encephalopathy syndrome in an intravenous methamphetamine abuser

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ABSTRACT

Background: Intravenous (IV) methamphetamine abuse is associated with a variety of short- and long-term effects on the nervous system, some of which have yet to be fully elucidated. One known systemic complication that has not been described in nervous system tissues is the deposition of substrate crystals contained in injectable drugs.

Case Description: An unusual case is presented of a 35-year-old active IV methamphetamine abuser with posterior reversible encephalopathy syndrome (PRES) who subsequently developed multifocal bilateral cerebellar enhancing lesions and leptomeningeal enhancement due to biopsy-proven crystalline deposits.

Conclusion: Although large crystalline substances will not normally penetrate the blood–brain barrier (BBB), during a state of BBB compromise such as with PRES, talc deposition may occur in the central nervous system.

Keywords: Intravenous drug abuse, Methamphetamine, Positively birefringent crystals, Posterior reversible encephalopathy syndrome, Talc, Talcosis

INTRODUCTION

Intravenous (IV) drug abuse is a broad entity well known to perpetrate both acute and chronic insults that are deleterious to the complex physiology of the central nervous system (CNS). Psychostimulant drugs such as methamphetamines are recreationally abused through oral, inhalational, and IV routes. The latter often involves contamination with cutting or bulking substances including cornstarch and talcum powder (talc). In examination under polarized light, positively birefringent talc crystals have been demonstrated in systemic tissues of IV drug abusers, particularly in the pulmonary perivascular regions. These crystals would not be expected to traverse an intact blood–brain barrier (BBB) and have never been described in CNS tissues. The case of a patient with a history of IV methamphetamine abuse, who was initially treated for posterior reversible encephalopathy syndrome (PRES) and subsequently presented with diffuse bilateral cerebellar enhancing lesions and leptomeningeal enhancement, with demonstration of positively birefringent crystals in the leptomeninges and cerebellum on biopsy, is presented. CARE guidelines for case reporting are implemented.
CASE DESCRIPTION

A 35-year-old right-handed male with Type II diabetes mellitus, alcoholism, polysubstance abuse, posttraumatic stress disorder, and bipolar disorder presented to the emergency department (ED) with a 3-week history of progressive headaches, visual decline, and bilateral hand numbness. He admitted to using IV methamphetamines 3 weeks prior and to smoking cannabis nightly as a sleep aid. His vital signs and examination were noted to be normal except for the ED physician’s report that he “would not participate in visual fields examination.” His urine drug screen was positive only for cannabinoids. He underwent noncontrasted computed tomography (CT) as well as magnetic resonance imaging (MRI) of the brain demonstrating no abnormality, and he was subsequently discharged.

The patient represented to the ED 2 ½ weeks later with complaints of worsening headaches and visual loss along with nausea and photophobia. His vital signs were again noted to be normal and he was again noted to be uncooperative with a visual examination. CT on this occasion demonstrated bilateral occipital lobe hypodensities, and subsequent MRI imaging demonstrated bilateral occipital fluid-attenuated inversion recovery (FLAIR) changes with patchy diffusion restriction [Figure 1].

A consensus of the likely diagnosis of PRES was entertained. He was managed with headache control and repletion of mild hypomagnesemia. He was never found to have hypertension or require antihypertensive treatment. He continued to have difficult to control headaches, although he did report marginal subjective improvement in visual acuity. Given uncertainty regarding the etiology of his condition, digital subtraction angiography was performed and demonstrated no evidence of vasculitis or other cerebrovascular pathology. Ophthalmologic evaluation demonstrated no evidence of papilledema and visual acuity of 20/800 bilaterally. He underwent a lumbar puncture (LP) with an opening pressure of 28 cm H₂O and cerebrospinal fluid (CSF) studies demonstrating a relative neutrophilia [Table 1].

On the basis of these results and concern for meningitis, he was empirically started on broad-spectrum antimicrobial therapy which was later discontinued. CSF was sent for additional bacterial, viral, fungal, inflammatory, and autoimmune assays. Repeat MRI demonstrated only mild increase in the bilateral occipital lobe FLAIR changes but new extensive leptomeningeal enhancement [Figure 2].

He was started on IV Solumedrol due to concern for the possibility of an inflammatory process, which led to mild improvement in the patient’s headaches but not vision. Subsequent MRI was unchanged. Repeat LP revealed an opening pressure of 50 cm H₂O and CSF with a lymphocytic predominance [Table 1]. He was started on acetazolamide and neurosurgery was consulted for intracranial pressure (ICP) management. A right frontal ventriculostomy was placed with an opening pressure of 11 cm H₂O. The patient never had any significant elevations in ICP and tolerated wean of his ventriculostomy, with eventual removal. All infectious studies were negative as were serum and CSF inflammatory workup. He remained clinically stable and was discharged on a steroid taper.

Two weeks after discharge, his headaches had improved as did his visual acuity to 20/70 on the left and 20/100 on the right. A noncontrasted head CT showed stable occipital hypodensities.

At 4-week follow-up, the patient complained of recurrent headaches and visual decline, nausea, and excessive sleepiness. His visual acuity was noted to be stable at 20/70 on the left and improved at 20/50 on the right. Contrast MRI that had been ordered as part of the routine follow-up demonstrated stable occipital FLAIR changes with residual occipital and cerebellar leptomeningeal enhancement, but more strikingly, the development of extensive tiny bilateral cerebellar enhancing lesions associated with edema, fourth
ventricular compression, and early obstructive hydrocephalus [Figure 3].

He was admitted and underwent placement of a right frontal ventriculostomy with an opening pressure of 6 cm H2O and a xanthochromic appearance to the CSF [Table 1]. CSF drainage at 5 cm H2O was initiated and he was started on IV dexamethasone. The neurology and infectious diseases teams were consulted and CSF studies were sent for analysis. Given the cryptogenic posterior fossa lesions, the patient underwent transthoracic echocardiography (TTE) with a bubble study that did not reveal any septal defect or valvular pathology. The patient remained clinically stable, and repeat MRI was roughly stable. Laboratory workup remained unrevealing. Therefore, the patient underwent a suboccipital craniotomy for cerebellar and meningeal biopsy to establish a definitive diagnosis. Subsequent clinical course was unremarkable, and he eventually underwent placement of a right frontal ventriculoperitoneal shunt. Subsequent MRI confirmed adequate shunting of the ventricular system with no other changes. He was eventually discharged on a steroid taper.

Final pathology from the posterior fossa biopsy revealed multiple elongated, diamond-shaped, avidly polarizable crystals in both the leptomeninges and cerebellar cortex [Figures 4 and 5]. There was no evidence of ischemia, vasculitis, infection, necrosis, or other findings to suggest an inflammatory or neoplastic process.

MRI imaging 2 months after biopsy demonstrated significant improvement in occipital FLAIR changes and cerebellar enhancing lesions/edema. At last follow-up 2 years after his initial presentation, he had ongoing headaches and visual difficulties and imaging demonstrating residual bilateral occipital cortical encephalomalacia with resolution of the enhancement and edema [Figure 6].

DISCUSSION

Methamphetamines have long been implicated in the development of strokes in young people due to acute induction of hypertension as well as their chronic effects on blood pressure and their potential to cause vascular changes including vasculitis. Vasculitis is theorized to result from chronic direct toxicity to vessel walls and fibrinoid necrosis of the intima and media. In addition to multiple other illicit substances, methamphetamines may be implicated in some cases of reversible cerebral vasoconstriction syndrome (RCVS) or PRES through acute elevation of blood pressure. Only a few cases in the literature specifically suggest a correlation between amphetamine use and these syndromes, and in each case, acute hypertension is a prominent feature of the clinical picture. One case report implicated methamphetamine use in the development of PRES in a 32-year-old female who presented with hypertension and right cerebral hemispheric edema that ultimately required management with a hemicraniectomy, where brain/leptomeningeal biopsy did not demonstrate any neuropathologic features. Another report described primarily cerebellar PRES in a 17-year-old male who overdosed on both prescription clonidine and dextroamphetamine, resulting in profound hypertension that was successfully managed with phentolamine and then nicardipine. A third case described a 45-year-old male with

| Table 1: CSF studies. |
|-----------------------|
| **First LP on initial admission** | **Repeat LP on initial admission** | **Ventricular CSF studies on second admission** |
| Protein (mg/dL) | 117 | 57 | 68 |
| Glucose (mg/dL) | 167 | 73 | 143 |
| RBC (cells/cmm) | 0 | 8 | 1880 |
| WBC (cells/cmm) | 56 (94% polymorphonuclear cells) | 39 (91% lymphocytes) | 50 (60% lymphocytes) |
| Gram stain/culture | Negative | Negative | Negative |

Figure 3: Development of occipitocerebellar leptomeningeal enhancement with diffuse bilateral cerebellar enhancing lesions.
The mechanism by which amphetamines contribute to RCVS or PRES likely extends beyond their ability to generate hypertension. In addition to injury and suppression of serotonergic and dopaminergic systems with chronic use, methamphetamine are thought to disrupt BBB function as well as the tight junction and structural proteins necessary for BBB integrity. Murine studies have shown that even a single high dose of IV methamphetamine can induce acute transient changes in BBB proteins and permeability. It has been suggested that psychological or physiologic stress as well as ethanol use may potentiate the deleterious effects of methamphetamines on the BBB.

The patient in this case did not have evidence of vasculitis on DSA or any of the characteristic changes expected on biopsy. The relatively normal vascular and cytoarchitecture on the pathology specimen speak against chronic changes related to methamphetamine use. Although he was never recorded to be hypertensive in the hospital, it is plausible that the patient’s admitted use of IV methamphetamines 3 weeks before his initial presentation resulted in a transient hypertensive episode and/or a direct BBB insult that set in motion the cascade of cerebral dysautoregulation that culminated in the development of PRES. The patient unfortunately did not undergo a new urine drug screen on his subsequent admission with the bizarre cerebellar lesions, but we hypothesize that in the interim between admissions, he may have used IV methamphetamines again. As mentioned previously, TTE did not demonstrate evidence of a cardiac septal defect. While some relatively large particles are known to traverse the pulmonary circulation, an undetected route of paradoxical embolism is another plausible mechanism of crystalline delivery. In the setting of nonfully recovered PRES and a leaky BBB, a “one-two punch” of large crystals depositing in the vulnerable leptomeningeal and cerebellar parenchymal vessels may have generated the observed clinical and radiographic syndrome. However, that does not explain the predilection for the previously radiographically uninvolved cerebellar hemispheres rather than the occipital lobes.

Systemically, pulmonary talcosis has been described in the setting of inhalational use of illicit substances but also through IV use of crushed substances cut or combined with talc powder and other similar agents, leading to characteristic perivascular deposition of birefringent crystals termed “talc granulomas.” Larger crystals can potentially lead to gross embolic complications. Similar deposits have been described in hepatic, splenic, renal, and retinal tissues of chronic IV drug abusers. Experimental studies in rats involving talc pleurodesis have demonstrated embolic talc material in the CNS vasculature. One case report from 1980 described a 28-year-old female patient with a history of IV drug abuse who expired after bilateral...
medial medullary as well as the left frontal ischemic infarcts, with the finding of systemic talcosis on autopsy and a small amount of intravascular talc in the area of the medullary infarct, thought to be embolic. In our case, the patient did not have any evidence of diffusion restriction or suggestion of embolic infarcts but rather, what could be described as a true “CNS talcosis” involving the cerebellar hemispheres and leptomeninges during a state of BBB compromise. To the best of our knowledge, this is the first demonstration and report of this phenomenon.

CONCLUSION
The authors present what we believe to be the first documented case of CNS talcosis in a 35-year-old male IV methamphetamine abuser presenting with leptomeningeal enhancement, diffuse bilateral cerebellar enhancing lesions, vasogenic edema, and low pressure hydrocephalus while recovering from PRES. We hypothesize a mechanism of PRES resulting from aberrant autoregulation in the setting of a methamphetamine-related transient hypertensive episode and/or the direct effects of methamphetamine intoxication on the BBB, with the subsequent opportunistic deposition of talc crystals into susceptible CNS tissue. Further reports and studies are needed to better elucidate this rare pathology.

Declaration of patient consent
Patient’s consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest
There are no conflicts of interest.

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