

# Spongiform leukoencephalopathy: A unique case of biopsy confirmed leukoencephalopathy secondary to toxic, non-inflammatory exposure

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## Abstract

Toxin-induced leukoencephalopathy is a rare neurological condition that has been previously associated with intracranial radiation, chemotherapy, drugs of abuse, and environmental exposures. Herein, we present a patient with brain-biopsy proven toxin-induced leukoencephalopathy, likely secondary to multiple environmental offenders including insecticides and non-Food and Drug Administration approved anabolic steroids, opioids, and benzodiazepines. A 60-year-old man presented to our service as a direct transfer from an outside facility for evaluation of a rapidly progressive neuropsychiatric decline. Extensive workup with blood work, cerebrospinal fluid analysis, paraneoplastic panel, serial magnetic resonance imaging brain with and without contrast, and electroencephalograms were unrevealing. Magnetic resonance imaging brain showed diffuse confluent white matter disease, which was non-specific. The patient was treated with high-dose methylprednisolone and trials of intravenous immunoglobulin without any significant improvement. Finally, a brain biopsy was performed, and pathology confirmed a spongiform leukoencephalopathy, favoring a toxin-related etiology. The diagnosis of toxin-induced leukoencephalopathy should be considered in patients with steep neuropsychiatric decline and associated diffuse white matter disease. Diagnosis relies heavily on history of exposure, clinical presentation, imaging findings, and ultimately, histopathology from brain biopsy. The recognition of the clinical presentation is important to pursue the appropriate diagnostic workup and treatment.

## Keywords

Neurology, pathology, toxicology

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## Introduction

The concept of toxin-induced leukoencephalopathy has long been described in the literature with a myriad of known offenders since the 1980s. These include, but are not limited to, intracranial radiation, chemotherapy, drugs of abuse (i.e. classically inhaled heroin, but also other opioids and cocaine), and environmental exposures.<sup>1,2</sup> However, environmental exposures can change over time, including exposure to intentionally and unintentionally chemical exposure. As these environmental factors change over time, it is imperative to identify new etiologies for previously well-described disorders.

In this article, we describe a case an interesting case of a patient who developed a rapidly progressive encephalopathy of unknown etiology, and brain biopsy confirmed non-inflammatory spongiform leukoencephalopathy, which was

attributed to toxin-induced due to history of several prior environmental exposures including insecticides and non-Food and Drug Administration (FDA) approved anabolic steroids, opioids, and benzodiazepines.

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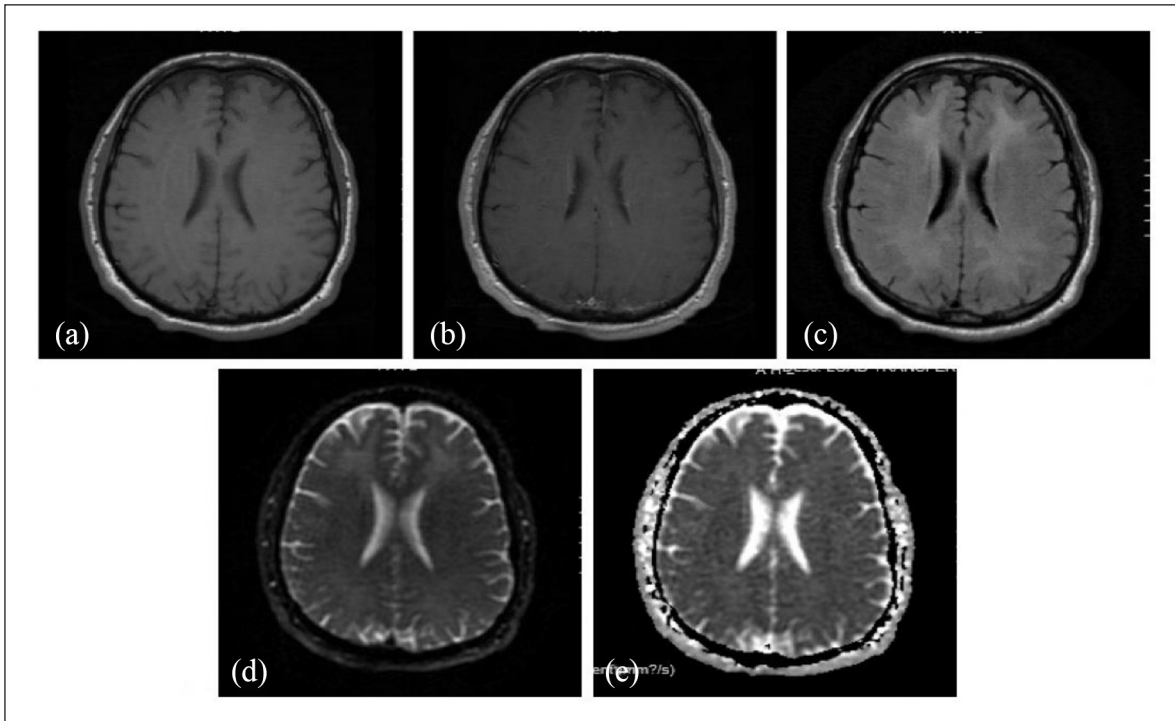
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**Figure 1.** Initial MRI of the brain from outside hospital. It showed T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence hyperintensities in the bilateral basal ganglia and diffuse increased signal in the white matter in the bilateral cerebral hemispheres (c), with no structural abnormality, mass effect, hemorrhage, restricted diffusion, or enhancement. (a) T1-weighted, (b) T1-weighted post-contrast, (d) diffusion-weighted imaging, and (e) apparent diffusion coefficient.

## Case presentation

A 60-year-old man with a past medical history of hypothyroidism and alcohol abuse was initially admitted to an outside hospital on 11 June 2018 after being found unresponsive by his wife. The preceding month, he had a 1-month history of a subacute, rapidly progressive cognitive decline. He was treated for sepsis and presumed aspiration pneumonia in the setting of suspected accidental opioid and benzodiazepine overdose. His hospital course was complicated by acute respiratory failure, requiring intubation and 4 days in the intensive care unit (ICU). The patient improved clinically from his acute respiratory failure, completed rehabilitation, and was discharged home. However, his mental status was not back to baseline.

One week following discharge, he was noted to have behavioral changes (e.g. leaving water running, walking around naked, and defecating in the closet). He was readmitted to the outside hospital 24 days after his prior admission. During this hospitalization, he continued to have a progressive neuropsychiatric decline with a decrease in awareness and engagement with his surroundings to near akinetic mutism.

An extensive workup was unremarkable, including laboratory testing (i.e. ammonia, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody (AB), striated muscle AB, acetylcholine receptor (AChR) binding

AB, and *N*-methyl-D-aspartate (NMDA) receptor AB), a paraneoplastic panel (i.e. myeloperoxidase AB IgG, proteinase 3 AB IgG, amphiphysin AB, Purkinje cell cytoplasmic AB type 1, 2, Tr, antiglial AB type 1, collapsin response-mediator protein-5 (CRMP-5)—immunoglobulin G (IgG), P/Q type and N type calcium channel AB, antineuronal Nu type 1, 2, 3 AB, and neuronal (V-G) K channel AB), and lumbar puncture with normal opening pressure (OP) and cerebrospinal fluid (CSF) analyses (i.e. glucose, encephalitis panel, VDRL, cytology, West Nile virus, and protein 14-3-3), except for elevated protein at 86 mg/dL. A computed tomography (CT) of the head, magnetic resonance imaging (MRI) of the brain with and without gadolinium, magnetic resonance angiogram (MRA) of the head and neck, and cerebral angiogram were also performed and were negative, except for T2-weighted image hyperintensities in the bilateral basal ganglia and increased T2-weighted image signal of the white matter in the bilateral cerebral hemispheres (Figure 1). Initial electroencephalogram (EEG) showed intermittent left-sided fronto-temporal slowing and sharp waves, and a subsequent one a week later showed diffuse slowing.

A trial of lacosamide and a 3-day course of intravenous methylprednisolone (IVMP) 1 gr/day was provided as a therapeutic approach, without any clinical improvement. He was subsequently transferred to Tampa General Hospital (TGH) for further management few days after second admission to

outside hospital. Some results from the workup at the outside hospital, including the autoimmune panel, paraneoplastic, and protein 14-3-3 were pending at the time of transfer, but later resulted negative.

On arrival to TGH, patient was awake and alert with eyes wide opened, but was non-verbal, and unable to follow or mimic any commands. He required assistance with all activities of daily living including feeding and bathing. Meaningful movements were limited, but he lacked any focal or asymmetric weakness. Given the patient's significant and rapidly progressive decline of an unknown etiology and unrevealing prior workup, a very extensive workup was initiated. Serum laboratory testing was unrevealing, including complete blood count (CBC), complete metabolic panel (CMP), urinalysis, thyroid studies (i.e. thyroid-stimulating hormone (TSH) and free T4), folate, vitamin levels (i.e. B<sub>12</sub>, 1,25-dihydroxyvitamin D, B<sub>1</sub>, and B<sub>6</sub>), homocysteine, ammonia, ceruloplasmin, methylmalonic acid, hemoglobin electrophoresis, serum and urine electrophoresis, heavy metal panel, autoimmune workup (i.e. antinuclear AB (ANA), double-stranded DNA (ds DNA), rheumatoid arthritis, thyroglobulin AB, thyroid microsomal AB, creatine phosphokinase, complement C3/C4, scleroderma-70 AB, Sjogren's ABs (SSA/SSB), and lupus anticoagulant), infectious workup (i.e. hepatitis A, B, and C, human immunodeficiency virus (HIV), rapid plasma reagin (RPR), BK JC virus, procalcitonin, lactic acid, Epstein-Barr virus (EBV), and cytomegalovirus (CMV)), and paraneoplastic panel (i.e. ABs to Yo, Hu, Ri, CV2/CRMP-5, amphiphysin, NMDA, and VGKC). voltage-gated potassium channel [VGKC]. Serum inflammatory markers with CRP 0.79 mg/L and ESR 23 mm/h were mildly elevated. Serum concentrations of specific toxins were not obtained.

A repeat lumbar puncture showed an OP of 22 cmH<sub>2</sub>O and CSF analyses were unrevealing (i.e. meningitis panel, cryptococcal, lyme, West Nile virus, arbovirus, CMV, Herpes simplex virus (HSV), VDRL, gram stain, cultures, IgG index, myelin basic protein, angiotensin-converting enzyme, and oligoclonal bands), except for a mildly elevated protein of 70 mg/dL (similar to prior results at the outside hospital).

MRI brain with and without contrast again demonstrated extensive white matter changes without abnormal enhancement (Figure 2). A continuous video EEG for 24 h revealed a slow background with intermittent generalized and rhythmic slow, consistent with a mild to moderate diffuse encephalopathy, and with no evidence of epileptogenic activity. CT of the chest, abdomen, and pelvis with and without contrast was negative for any underlying malignancy, mass, or lymphadenopathy.

Steroid responsive encephalopathy with thyroiditis (SREAT) was considered in the differential and the patient was treated with a 5-day course of IVMP 1 gr/day. However, he demonstrated no clinical improvement. He continued to be mostly awake and alert, sometimes making eye contact, but without purposeful movement and persistent inattention to his surroundings. While SREAT remained a possibility, a

brain biopsy was pursued to evaluate for primary central nervous system (CNS) lymphoma or adult-onset versus toxin-induced leukodystrophy/encephalopathy.

During discussions with family regarding these more invasive procedures, the patient's wife reported additional information including multiple environmental exposures. These included the administration of non-prescription opioids and benzodiazepines for worsening anxiety 1–2 months leading to the suspected accidental overdose; the use of injectable anabolic steroids (i.e. testosterone enanthate and dianabol) obtained off of the street for 4 years for muscle bulking, which were discarded by his wife in an attempt to make them unavailable to the patient, and formulary information was unavailable; and the application of insecticides and rodent-repellents inside and outside his tent every time he went hunting about once a month, which were also thrown away by his wife during the same general time frame.

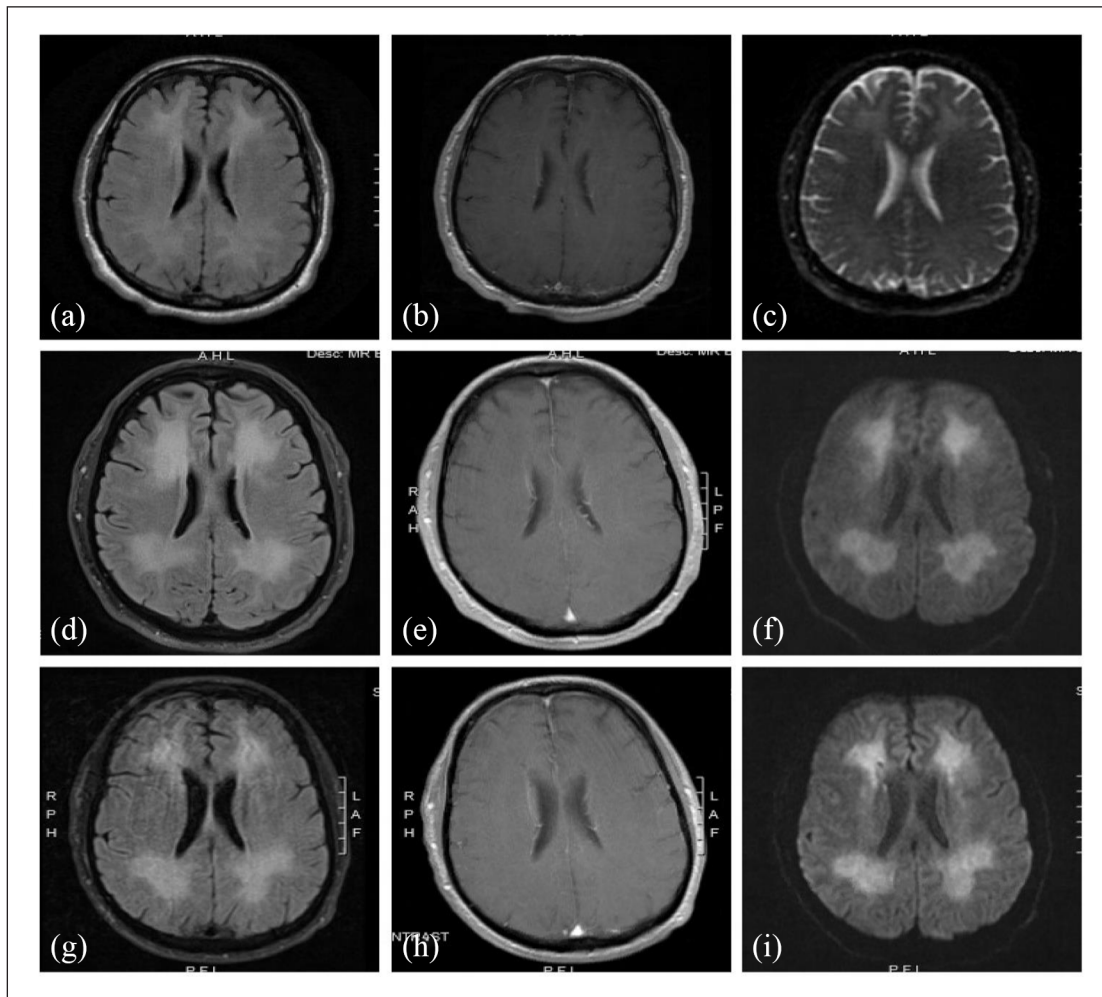
While awaiting family decision regarding a brain biopsy, he was treated as a trial with intravenous immunoglobulin (IVIG) 2 gm total, to be administered over a 4-day course. A few days later, the patient's clinical status remained the same. A right frontal brain biopsy was performed and pathology revealed white matter spongiform changes, with reactive gliosis, and absence of any signs of inflammation (Figure 3), suggestive of toxin exposure. A sample was sent to Case Western for an in-depth evaluation for suspected leukodystrophy, and final pathology confirmed a spongiform/vacuolar degeneration with focal areas of myelin pallor and breakdown, favoring a toxin-related leukoencephalopathy.

The patient remained clinically stable, and was discharged to a rehabilitation facility few days following the brain biopsy. On post-discharge follow-up, he showed a slowly significant clinical improvement over a course of 6–8 months. Approximately a year after his initial presentation, he was alert and attentive, with a non-dysarthric speech, normal speech content, following commands, and with a mild expressive aphasia. He was also fully ambulatory. Mini-Mental State Examination (MMSE) examination revealed a score of 23/30 with deficits in delayed recall and visuospatial/executive function.

A follow-up MRI of the brain with and without contrast demonstrated moderately extensive chronic deep white matter changes, which were improved from MRI obtained only a few months before. A genetic evaluation for a possible underlying adult-onset leukodystrophy was also performed and results were not consistent with an inheritable metabolic defect. The patient has continued to follow up in clinic and appears to continue to have a slow, but steady and significant clinical improvement.

## Discussion

Toxin-induced leukoencephalopathy was first well described in the literature in the 1980s following the introduction of the MRI, which allowed clinicians to visualize brain parenchyma in real time.<sup>3</sup> While there are numerous causes of leukoencephalopathy, the vacuolization (termed "spongiform") is specific to



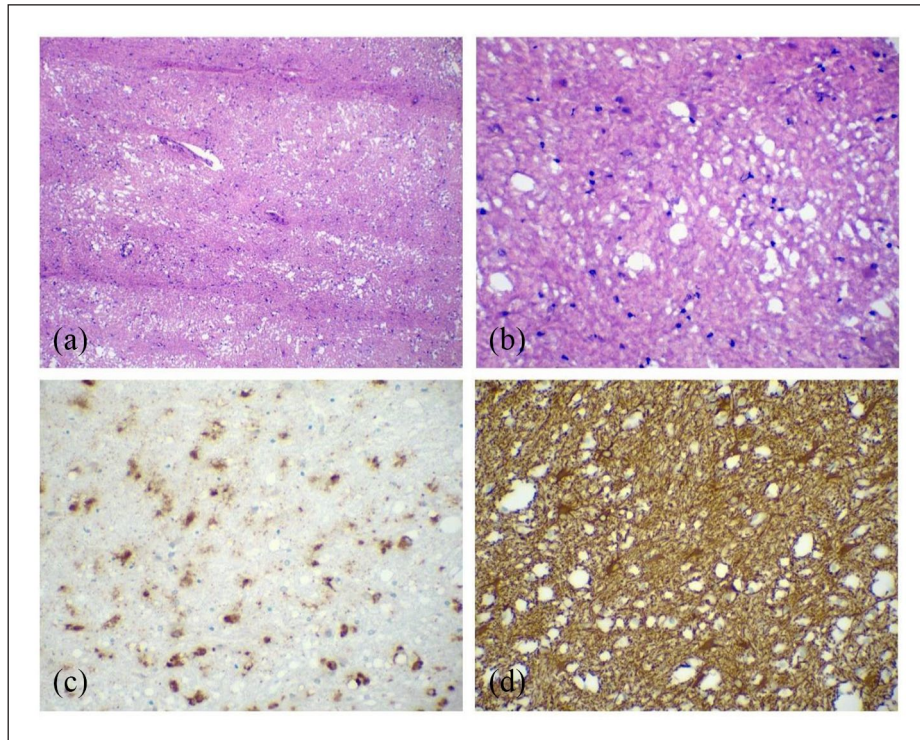
**Figure 2.** Temporal sequence MR imaging of the brain comparing initial MRI from outside hospital to those obtained at our institution. (a)–(c) Initial MRI from the outside hospital obtained on 9 July 2018. Serial MRIs are shown from our institution obtained on 18 July 2018 (d)–(f) and 2 August 2018 (g)–(i). (a), (d), and (g) show temporal T2-weighted FLAIR sequences at the different dates above. (b), (e), and (h) show T1-weighted post-contrast images. (c) shows apparent diffusion coefficient image. (f) and (i) show diffusion-weighted imaging. Images again demonstrate the temporal history of the T2-weighted FLAIR sequence hyperintensities in the white matter in the bilateral cerebral hemispheres ((a), (d), and (g)).

toxic etiologies. Since that time, four main groups of associated toxins have been described in the literature, most notably—chemotherapeutic agents, cranial radiation, drugs of abuse, and environmental exposures.<sup>4</sup> While the exact pathophysiology of drug-induced leukoencephalopathy is not fully understood, current theories are based largely on post-mortem tissue samples mainly suggesting that axonal injury may be the initial hit with subsequent demyelination as a secondary process.<sup>5</sup> One current hypothesis is that the spongiform leukoencephalopathy is consistent with an incomplete infarct pattern, which may be the result of a partial hypoxic injury commonly seen with poly-drug abuse.<sup>5</sup> The white matter tracts themselves are thought to be exceedingly susceptible to such injury, largely due to their relatively high metabolic requirement and vastness.<sup>3</sup>

The prevalence and incidence of toxin-induced leukoencephalopathy are not readily available in the current literature. Current information at this time is confined to case

reports or small case series. This is likely due to the rarity of this condition, even with widespread abuse of known offenders, specifically heroin, although all opioids have been implicated. Overall, there does not appear to be an age or sex predilection.<sup>6</sup>

While exact etiology and predisposing factors remain elusive, the clinical presentation associated with such acquired leukoencephalopathies is better understood. The most prominent presentation is a change in mental status, with correlation between the degree of impairment and severity of the white matter affected in the brain.<sup>4</sup> Clinical presentation can widely vary along a well described and broad continuum, which can range from mild symptoms including restlessness, bradyphrenia, and apathy, to severe symptoms such as abulia, akinetic mutism, stupor, and coma.<sup>7,8</sup> The onset of symptoms is also exceptionally variable with decline starting hours to months after exposure, with some studies citing an



**Figure 3.** Pathology of frozen sections from brain biopsy. (a) Low power demonstrating white matter spongiform changes (40 $\times$ , H&E). (b) High power demonstrating white matter spongiform changes in a background of gliosis (400 $\times$ , H&E). (c) CD68 IHC stain highlighting macrophages (200 $\times$ , CD68). (d) GFAP IHC stain highlighting reactive gliosis (200 $\times$ , GFAP).

average latency of approximately 3 weeks.<sup>9</sup> As this presentation is exceptionally vague, intracranial imaging should be obtained in all cases of altered mentation of unknown etiology, with preference for MRI, if no contraindications exist, as CT imaging is often unremarkable and unrevealing. Without fail, in the cases of leukoencephalopathy, diffuse and symmetric hyperintensities on T2-weighted imaging, with a non-enhancing pattern on T1-weighted imaging with contrast, were noted in the white matter tracts of the brain. There appears to be some predilection for the cerebellum and posterior cerebral white matter and posterior limb of the internal capsule in heroin-induced leukoencephalopathy,<sup>7,10</sup> but the specific area of the brain targeted may vary depending on the toxin or offending agent itself. Case reports have not adequately defined specific lobes or regions of the brain targeted by one specific toxin compared to another.<sup>2</sup>

Involvement of the supratentorial white matter has also been noted in the literature.<sup>11</sup> Recommended clinical practice at this time is to confirm presence of drugs of abuse or toxic exposures in cases with clinical and neuroradiological evidence of leukoencephalopathy prior to making the diagnosis of toxin-induced leukoencephalopathy. However, even with the aforementioned picture, differential diagnosis remains vast, and patients and their families may be hesitant to report these drugs of abuse.

Histopathology remains the gold standard for diagnosis.<sup>6</sup> In patients with known heroin-induced leukoencephalopathy, spongiform degeneration of white matter with spared

subcortical U-fibers has been described.<sup>12</sup> Review of five case reports of patients with known poly-drug exposures showed post-mortem biopsies that were relatively similar, all showing widespread myelin pallor with numerous axonal spheroids and multifocal necrosis.<sup>5(1)</sup> A review of five cases with known poly-drug exposures showed post-mortem biopsies that were relatively similar, all of which demonstrated widespread myelin pallor with numerous axonal spheroids and multifocal necrosis. It is worth noting that spongiform leukoencephalopathy is distinctly different from hypoxic leukoencephalopathy on histopathology in that it results in intramyelinic vacuolar edema. In cases of hypoxic leukoencephalopathy, diffuse hemispheric demyelination is still seen, but vacuoles are not present.<sup>13</sup>

While there is no specific treatment for toxin-induced leukoencephalopathy, early identification, high-level supportive care, and abstinence from further toxic exposures have yielded the best outcomes for patients. Patient outcomes vary depending largely on the degree of impairment, but data on specific predictive factors are limited.<sup>14</sup>

Our case illustrates an archetypic clinical and radiological case of toxin-induced leukoencephalopathy. The patient's progressive neuropsychiatric abnormalities, with the development of bizarre behaviors and deterioration to prominent cognitive impairment, abulia, and complete inattention are a classic presentation for severe leukoencephalopathy. In our patient, after an extensive workup ruled out other etiologies, especially those that could be

rapidly reversed with acute treatment, open lines of communication with the patient's family led to admission of a history of drugs of abuse and ultimately, a concern for toxin-induced leukoencephalopathy. However, a single agent was not identified. Similar to other cases reported in the literature, our patient was exposed to several potentially damaging toxins, notably opioids, benzodiazepines,<sup>15</sup> insecticides,<sup>2</sup> rodent-repellents, and non-FDA approved anabolic steroids. Heroin is the most commonly described offender with data dating back to the 1980s. However, even with the significant rise in opioid misuse, abuse, and addiction, associated leukoencephalopathy remains rare suggesting our patient may have been exposed to a unique combination of agents that precipitated such a deleterious process. While we were unable to identify the specific insecticide our patient used, exposure to various pesticides has been implicated in toxic leukoencephalopathy, specifically Chlorfenapyr which may cause reversible white matter damage.<sup>1</sup>

The current case report has some shortcomings. As a case report, it lacks the potential to be generalized to a larger group of patients. Similarly, the specific toxin responsible for our patient's presentation was not identified, although several possible offenders were noted. Subsequently, a cause-effect relationship cannot be established. Moreover, we cannot conclude that the treatments used (i.e. high-dose IVMP and IVIG) aided in the subsequent clinical improvement of the patient. However, the description of this case raises awareness regarding this rare neurological disease and may aid in diagnosis and treatment for patients in the future.

## Conclusion

Although the diagnosis of toxin-induced leukoencephalopathy is rare, it is important to consider in patients with steep neuropsychiatric decline and associated diffuse white matter disease. Diagnosis relies both on histopathology, and typically on identification of a known offending agent. However, as poly-drug abuse is more and more common and access to the exact substances patients are exposed to is limited, recognizing the clinical presentation is key to pursuing the appropriate diagnostic workup, treatment, and support to both patients and their families.

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## Informed consent

Written informed consent was obtained from the subject for publication of his case report. The patient had full decisional capacity to provide written informed consent.

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