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# Association of rare disease and acute intoxication – case report

**Radu A. Macovei[1,2], Radu C. Ţincu[1], Mihail S. Tudosie[2]**

**Abstract:** *Benzodiazepine overdose has various clinical manifestation, mainly regarding the central nervous system (CNS), cardiac and respiratory side effects, but rarely results in significant morbidity and mortality. Acute benzodiazepine poisoning results in dizziness, ataxia, nystagmus, dysarthria, hypoxia, hypothermia, bradycardia, hypotension, apnea, pulmonary aspiration, respiratory depression, coma, cardiopulmonary arrest and death. Anyway, deep nonresponsive coma should be investigated for additional etiologies. On the other hand, human transmissible prion disease has a fatal outcome with no specific treatment.*

**Keywords:** *prion disease, benzodiazepine intoxication, opisthotonus*

[1] Intensive Care Unit, Clinical Emergency Hospital Bucharest, Bucharest, Romania

[2] Carol Davila University of Medicine and Pharmacy, Bucharest

Human transmissible prion diseases are neurodegenerative disorders characterized by infectious pathogens accumulation with a long incubation period and devastating outcomes. A prion is defined as a small infectious agent lacking of nucleic acid, but containing protein [1]. It has an important feature regarding resistance to a number of decontamination procedures including processes affecting nucleic acids such as hydrolysis [2]. Up to present, human pathology recognize five related entities: Creutzfeldt-Jakob disease (CJD), Kuru, variant Creutzfeldt-Jakob disease (vCJD also known as new variant CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI) [3].

Prionopathies result from abnormal isoforms accumulation in the brain that leads to neuron apoptosis and important brain damage. Infective prion is a product resulting from defective folding of the normal prion, having the gene located on the short arm of the chromosome 20 [4]. Unfortunately, the prognosis is very poor in these patients, despite all efforts and sustained interventions.

Benzodiazepines are commonly used against various disorders such as insomnia and anxiety. They also are preferred agents for drug overdose, although their acute toxicity is low. Oral benzodiazepine intoxication rarely results in

significant morbidity and mortality. The body develops tolerance against such effects in the course of time and most common side effects are sedation and ataxia. Anxiolytic effects is rarely implicated in tolerance development. Acute benzodiazepine poisoning may result in dizziness, ataxia, nystagmus, dysarthria, hypoxia, hypothermia, hypotension, bradycardia, apnea, pulmonary aspiration, respiratory depression, coma, cardiopulmonary arrest and death.

## CASE PRESENTATION

We present the case of a young white female, aged 26, admitted in our Toxicology – Intensive Care Unit of Clinical Emergency Hospital Bucharest from Bucharest, the capital of Romania. She was referred to us after deliberate ingestion of 200 mg benzodiazepine associated with 500 mg metoprolol. Ten months before this event the patient experienced complaints such as mood disorders, memory loss, irritability, inability every day social behavior and insomnia; initially, the condition was assessed as depression but no certain treatment was recommended. We couldn't find any history of visual hallucinations or tremor. Interview emphasized multiple study visits in the United Kingdom and occasionally intravenous abuse substances dependence. Any other past medical data were unremarkable. The first medical examination revealed a conscious patient, mild agitated, stable vital signs, with unusual hyperosmia and visual impairment. Toxicology assessment was positive for benzodiazepine in the urine, detected with fluorescence polarization immunoassay method; toxicological screening was negative for other drugs. She had a rapid unfavorable evolution the following hours after admission experiencing degenerative progression of psychomotor and cognitive functions, lack of hand-eye and alternating hand coordination, left hand tremor and left lower extremity weakness and in the end, ten hours after ingestion, she developed impressive opisthotonus and deep coma that required mechanical ventilation. The evolution was unexplained by her toxicological status and occurred unexpectedly.

Brain tomography was in normal ranges (Figure 1). She was performed lumbar puncture and the cerebral fluid features included clear aspect, normotensive, with glucose and electrolyte levels within normal limits and no type of cell detection. Regarding highly suspicion of tetanus, due to her occasionally intravenous drug administration, the infectious disease evaluation indicated anti-tetanus serum therapy, but clinical evolution wasn't improving. After 48 hours of nonresponsive evolution a new brain CT scan identified massive cerebral edema. Cranial MRI showed marked cerebral atrophy in frontoparietal areas, DWI hyperintensities (cortical ribboning) in basal ganglia bilaterally and diffusion restriction in these areas suggesting progressive multifocal leukoencephalopathy, whereas putamen and caudate nucleus were free of signal intensity (Figure 3). Considering these aspect, we performed PCR for the detection of JC virus which was negative. A prionic disease was highly suspected and 14-3-3 protein immunoassay on CSF was positive. The patient died after 2 months in Critical Care Unit due to multiple dysfunctions, with the diagnostic of Creutzfeldt-Jakob disease.

## DISCUSSION

As a part of the prionic disease family, CJD evolution is characterized by rapid evolution and neurological deterioration. The majority of cases are represented by sporadic human prion diseases, while 1-2% of the remaining are infectious forms acquired from an established source with the prion disease and 5-15% is represented by the autosomal dominant type [1]. The presented case exhibits most of the sporadic CJD clinical features with rapid cognitive decline and mioclonus; MRI was an indispensable tool for differential diagnosis considering that DWI hyperintensities in the putamen, caudate and cortex have a high specificity for sporadic prion disease [6]. However, the short dramatic course of the disease and detection of protein 14-3-3 in CSF adds value to diagnostic criteria. The literature shows that the mean age of onset is around 65 years of age with a very short median survival time around four months [7], but we report an extreme age (eg. 26 years old).

## CONCLUSIONS

The case presented in this paper was meant to describe the clinical progression of a rapid evolving encephalopathy in a patient admitted for benzodiazepine ingestion. It also underlines the importance of keeping an open mind when dealing with unexpected and unusual evolution of acute intoxication.

**Figure 1**. The first CT scan within normal ranges

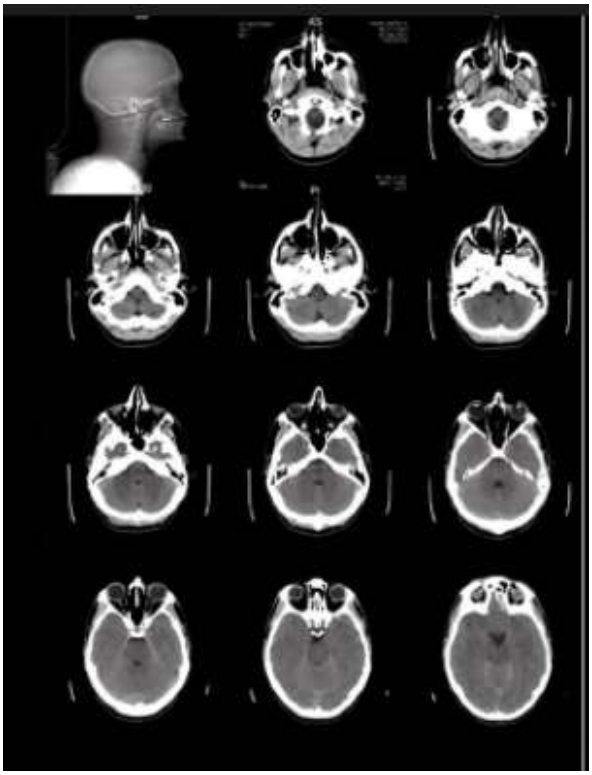
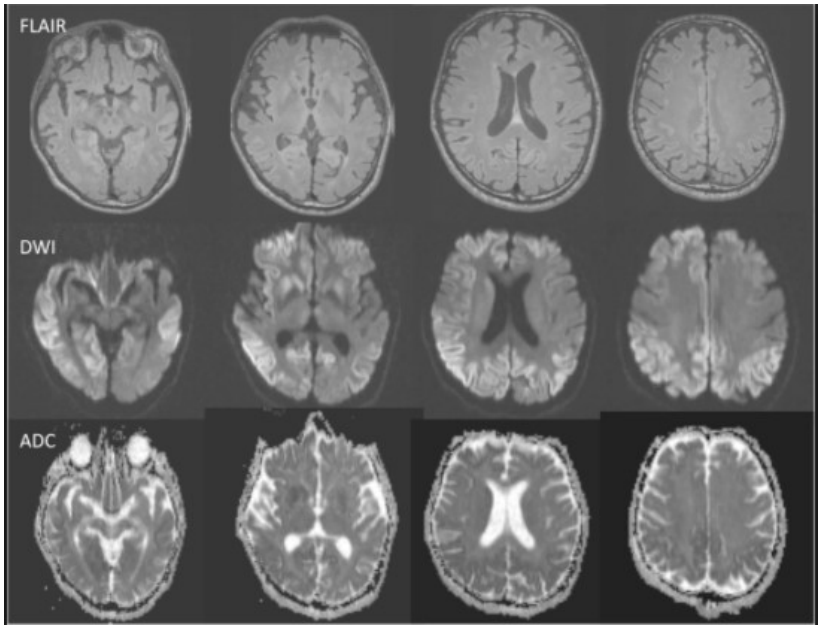


**Figure 2**. Cranial MRI showing cerebral atrophy, DWI hyperintensities (cortical ribboning) in basal ganglia bilaterally and diffusion restriction in these areas suggesting progressive multifocal leukoencephalopathy, whereas putamen and caudate nucleus were free of signal intensity



## References:

1. Prusiner SB. Novel protein aceous infectious particles cause scrapie. Science 1982; 216:136-144

2. McDonnell G, Burke P. The challenge of prion decontamination. Clin Infect Dis 2003;36:1152-1154

3. Marandi Y, Farahi N, Sadeghi A, Sadeghi-Hashjin G. Prion diseases - current theories and potential therapies: a brief review. Folia Neuropathol2012;50:46-44

4. Hill AF, et al. Molecular classification of sporadic Creutzfeldt-Jacob disease. Brain 2003;126:1333-1346

5. Zerr I, Pocchiari M, Collins S, et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. Neurology 2000;55:811-815

6. Sabrina D. Talbott, Brian M. Plato, Ronald J. Sattenberg, John Parker, Jens O. Heidenreich. Cortical restricted diffusion as the predominant MRI finding in sporadic Creutzfeldt-Jakob disease. Acta Radiologica 2011;52(3):336-339

7. Das K, Davis R, Dutoit B, et al. Sporadic Creutzfeldt-Jakob disease: a description of two cases. Int Psycho geriatr. 2012; 21:1-3