Sarcouncil Journal of Medicine and Surgery

ISSN(Online): 2945-3534

Volume- 03| Issue- 03| 2024

Letter to the Editor **Received:** 05-02-2024 | **Accepted:** 26-02-2024 | **Published:** 10-03-2024

Do Not Diagnose Creutzfeldt - Jakob disease Based Solely on Clinical Exam, Imaging, and Elevated 14-3-3 in Times of COVID-19

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Keywords: Creutzfeldt-Jakob disease, immune encephalitis, epilepsy, SARS-CoV-2, neuromuscular disorder, malignant hyperthermia, rhabdomyolysis, critically ill.

LETTER TO THE EDITOR

We read with interest Pandey *et al*'s. article on a 61 year-old male with Alice in Wonderland syndrome attributed to Creutzfeldt-Jacob disease (CJD) [Pandey, S. *et al*., 2023]. The patient initially suffered from micropsia, macropsia, hyperchromatopsia, and difficulty assessing depth while walking. Workup revealed hemianopsia to the left, gait disturbance, short-term memory loss, stereotyped, abnormal right upper extremity movements (repetitive combing movements), diffusion-weighted imaging (DWI) hyperintensity along the fronto-parieto-occipital cortex, sharp waves at irregular intervals with background slowing, and elevated 14-3-3 in the cerebrospinal fluid (CSF) [Pandey, S. *et al*., 2023]. Probable CJD was diagnosed. Within two weeks, disorientation, behavioural changes, myoclonus, and akinetic mutism also occurred, and the patient died 45 after admission [Pandey, S. *et al*., 2023]. The study is impressive, but some points require discussion.

The major limitation of the study is that the patient did not undergo brain biopsy or autopsy to document abnormal prion protein and exclude differential diagnoses such as immune encephalitis, infectious encephalitis, minimal convulsive status epilepticus, tuberculosis, cerebral vasculitis, lymphoma, or mitochondrial disorder. The patient was diagnosed with probable CJD, but real-time quaking-induced conversion (rt-QuIC) assay was not performed and tau-protein was not determined. Positron-emission tomography (PET) examination is also not mentioned. The 14-3-3 is a non-specific parameter that can be increased in all central nervous system diseases with loss of neurons or glial cells [Foote, M. *et al*., 2012]. Elevation of 14-3-3 in CSF has been reported in ischemic stroke, infectious encephalitis (e.g. Japan encephalitis, SARS-CoV-2 associated encephalitis), Parkinson's disease, Alzheimer's disease, neurodevelopmental disorders (e.g. lissencephaly), and psychiatric disease (e.g. schizophrenia, bipolar disorder [Foote, M. *et al*., 2012].

A second limitation is that the patient appeared to have focal seizures (repetitive combing movements of right upper extremity) and myoclonus, which were noted at follow-up clinical neurologic exam [Pandey, S. *et al*., 2023]. However, no anti-seizure drug treatment has been reported [Pandey, S. *et al*., 2023]. Were anti-seizure drugs given? Did the myocloni have a correlation to the EEG? Was lactate in the CSF elevated?

A third limitation is that cerebral imaging was performed without contrast agent application. Because autoimmune encephalitis can occur in about half of patients without the presence of immune encephalitis-related antibodies and without pleocytosis, it is imperative to assess whether there is an enhancing lesion on cerebral imaging. Apparent diffusion coefficient (ADC) maps are also missing to assess whether diffusion restriction corresponds to cytotoxic or vasogenic edema.

A fourth limitation is that no PCR results for SARS-CoV-2 have been reported [Pandey, S. *et al*., 2023]. The exclusion of SARS-CoV-2-associated immune encephalitis is particularly important because the patient became ill during the SARS-CoV-2 pandemic and SARS-CoV-2-associated immune-encephalitis mimicking CJD has already been reported [Beretta, S. *et al*., 2021].

There are several discrepancies. How to explain that colour vision was normal on ophthalmologic examination, but the patient reported hyperchromatopsia? How to explain that the ophthalmologic examination revealed hemianopsia

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DOI- https://doi.org/10.5281/zenodo.10802045

to the left, but the neurological examination revealed only memory impairment, dyscalculia, combing movements, and abnormal tandem gait?

In summary, the interesting study has limitations that put the results and their interpretation into perspective. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Before suspecting probable CJD, all suspected differential diagnoses, including SARS-CoV-2-related and immune encephalitis, should be thoroughly ruled out. Diagnosing CJD requires confirmation of an abnormal prion protein at autopsy. Vision problems as the beginning of CJD are not uncommon.

ACKNOWLEDGEMENTS

Statement of Ethics: a) The study was approved by the institutional review board. b) Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

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Source of support: Nil; **Conflict of interest:** Nil.

Cite this article as:
Finsterer, J. and Scorza, F.A. "Do Not Diagnose Creutzfeldt - Jakob disease Based Solely on Clinical Exam, Imaging, and Elevated 14-3-3 in Times of COVID-19." *Sarcouncil Journal of Medicine and Surgery* 3.3 (2024): pp 1-2.

Publisher: SARC Publisher