SAGE Open Medical Case Reports
Volume 12: 1–4

DOI: 10.1177/2050313X241243148
journals.sagepub.com/home/sco
Sage

Tau and delirium superimposed on dementia: A case report

Po-Chung Yu[1], Ching-Min Kuo[1] and I-Chun Chen[1,2,3]

Abstract

We present a case involving a 60-year-old man with subacute delirium characterized by challenging attention shifts and obstinate behavior, contrasting with his usual mild-mannered personality. The patient developed pneumonia and a urinary tract infection following the onset of subacute delirium. Despite exhaustive investigations, the cause remained elusive until cerebrospinal fluid analysis revealed Tau positivity. Our overview suggests neurodegenerative diseases as the primary cause, rather than infectious or autoimmune factors. The case underscores a significant association between Tau and delirium superimposed on dementia, offering guidance to clinicians managing such patients.

Keywords

Tau, delirium superimposed on dementia, postoperative delirium, subacute delirium

Date received: 13 October 2023; accepted: 13 March 2024

Background

When addressing a patient with rapid changes in consciousness, it is crucial to rule out delirium first and identify potential causes,[1] including metabolic encephalopathy, electrolyte imbalance, malnutrition, dehydration, and underlying infections.[2] If no apparent cause for altered consciousness is found, delirium superimposed on dementia should be considered.[3] Objective evidence of dementia can be obtained through Tau positron emission tomography imaging tests and Tau levels in cerebrospinal fluid (CSF).[4] Studies on Alzheimer's disease (AD) provided evidence that β-amyloid becomes abnormal first, before cognitive symptoms, and Tau becomes abnormal later.[5,6] Elevated Tau in CSF has been associated with delirium, even in individuals without dementia.[7]

This case report highlights delirium superimposed on dementia in a patient with Tau positivity.

Case presentation

In March 2022, a 60-year-old veteran male presented in our psychiatric outpatient department with restlessness. He insisted his wife to walk back and forth with him. He exhibited difficult-to-shift attention. He behaved with apparent obstinacy, which was notably distinct from his typically mild-mannered personality. Over the last 3 months, he displayed rapid cognitive decline, worsening ability of daily living. He could not recall how to use a mobile phone and required assistance with bathing and eating. Over the last 1 year, he had been investigated by a psychiatrist for anxious mood, poor memory, delusions of persecution, delusions of being theft, and episodes of violent behavior, suspected to be due to dementia. In August 2021, the severity of dementia had been moderate, as indicated by a score of 18 on the Mini-Mental State Examination scale (cutoff score: 24–25), and a score of 55 on the Cognitive Abilities Screening Instrument (cutoff score: 79–80).[8]

The patient had no history of hypertension, cardiovascular disease, cerebrovascular disease, or diabetes mellitus. He had no psychiatric illness in the past. He had a 9-year schooling period. He served in the military, concluded his military career, and retired as a veteran. In his late 50s, he worked as a driver and resigned from the position following the initial onset of an anxious mood and poor memory.

[1]Department of Psychiatry, Taichung Veterans General Hospital, Taichung City, Taiwan
[2]School of Medicine, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[3]Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung City, Taiwan

Corresponding Author:
I-Chun Chen, Department of Psychiatry, Taichung Veterans General Hospital, No. 450, Section 1, Dongda Road, Xitun District, Taichung City 407, Taiwan.
Email: i-chun.chen@vghtc.gov.tw

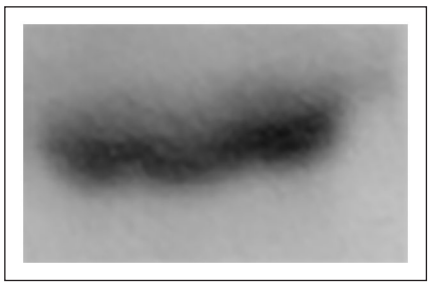

Figure 1. Western blotting of the patient's CSF indicated Tau positivity. The bands corresponding to molecular sizes of 45–70 kDa were consistent with Tau detected using anti-Tau antibodies.
CSF: cerebrospinal fluid.

Investigations

The patient was arranged for psychiatric inpatient treatment, initially thought to be due to behavioral and psychological symptoms of dementia. Upon admission, physical examination showed no focal neurological sign, and motor function was normal. Brain computed tomography showed no prominent atrophy of the frontal or temporal lobe, no subdural hemorrhage, no subarachnoid hemorrhage, no intracranial hemorrhage, no enlarged ventricles, and no specific finding. Due to the patient's restlessness and poor response to sedation medication, brain magnetic resonance imaging could not be conducted successfully. The laboratory survey for delirium and dementia revealed normal results, ruling out metabolic encephalopathy, electrolyte imbalance, malnutrition, dehydration, and underlying infections. Considering the 3-month rapid cognitive decline in this patient, a neurologist was consulted. The neurologist suggested a diagnosis of frontotemporal dementia.

On day 14 of inpatient treatment, the patient was observed confuse consciousness, worsened restlessness, and episodes of violent behavior, such as kicking people. On day 18 of inpatient treatment, a lumbar puncture was performed. CSF analysis revealed a mildly elevated protein level of 65.7 mg/dL and an antinuclear antibody (ANA) titer of 1:160 (cutoff value: 1:80). Upon consultation with a rheumatologist, autoimmune encephalitis seemed unlikely to be the diagnosis. The patient's CSF tested positive for Tau protein (Figure 1).

Informed consent

Informed consent was obtained from the legally authorized representative. A residual 1 mL of CSF collected from the patient during the lumbar puncture was used in this investigation. The study protocol was approved by the Ethics Review Committee in Taichung Veterans General Hospital (project number SF22141B).

Method of detecting Tau

Western blotting was performed to detect Tau in the patient's CSF. A CSF (1 mL) sample collected from the patient during the lumbar puncture was stored at 4°C. After 5 days of storage, the sample was centrifuged at 3000 rpm for 5 min at 4°C. The sample was then aliquoted and stored at −80°C. After 1 week, the sample was diluted to 1:500 and electrophoresed on a 10% polyacrylamide gel (70 V through the stacking gel and 100 V through the resolving gel). The obtained protein bands were transferred onto a polyvinylidene difluoride membrane. After blocking the membrane, it was incubated with primary anti-Tau antibodies (FineTest; catalog no: FNab08505; New Taipei City, Taiwan). The membrane was then washed and incubated with antirabbit secondary antibodies. The presence of Tau in the CSF sample was detected using high-performance chemiluminescence films.

Differential diagnosis

Our patient displayed restlessness, insisting his wife to walk back and forth with him. Transiently, difficult-to-shift attention led to obstinate behavior. These behavioral changes occurred within a brief period of 3 months. In this scenario, delirium becomes a primary consideration, suggesting that reversible causes may directly contribute to the behavioral changes observed. Although inapparent fluctuating consciousness with persisting behavioral changes were noted since admission, delirium was initially given less consideration. Subacute delirium should be considered as a differential diagnosis. The cognitive decline in our patient outpaced that reported in patients with AD. Consequently, frontotemporal dementia should also be considered in the differential diagnosis.

Treatment

Prescribed risperidone (2 mg) improved delusion. Escitalopram (20 mg) and Mesyrel (150 mg) for restlessness showed no improvement. We tapered the dose of escitalopram to 5 mg and increased valproic acid from 400 to 600 mg. The serum level of valproic acid was 43.04 µg/mL, which was normal. Fever (38.7°C) occurred on day 30 of inpatient treatment, approximately 2 weeks after the lumbar puncture was performed. The patient had dyspnea with SpO_2 desaturation and urine retention on the same day. Chest X-ray revealed a mild increase in infiltration over bilateral lung fields, and urine analysis indicated pyuria. Meningitis was not likely because no focal neurological signs occurred, nor neck stiffness. Thus, pneumonia and urine tract infection were suspected. After cefazolin 1000 mg Q12H was administered for 7 days, the infection was remitted. A complete recovery of difficult-to-shift attention, transiently obstinate behavior, restlessness, and violent behavior was observed, followed by the remission of infection. The patient's cognitive function returned to a moderate dementia baseline level. Subsequently, the patient was discharged from our hospital and continued treatment in a nursing home. Over the subsequent 2 months, the patient sustained emotional stability without displaying any signs of restlessness.

Discussion

In this patient, the most notable observation is the subacute delirium manifested in difficult-to-shift attention, transiently obstinate behavior, restlessness, and violent behavior. Exhaustive investigations failed to reveal the cause of subacute delirium. Tau is identified as a shared marker of CSF for both delirium and neurodegenerative cognitive decline.[9,10] Previous studies suggested delirium and dementia have shared markers involving neurodegeneration and neuronal injury, inflammation, disturbances in brain energy metabolism, disruption in neurotransmitter function, pharmacological effects, and failure of network connectivity.[11–13] Based on Tau positivity in CSF, we argue this patient is a case of delirium superimposed on dementia.

In this patient, the second most notable observation is the subacute delirium developed before pneumonia, and it subsided following the remission of pneumonia. Previous research indicated a strong association between delirium and sepsis in older patients.[14] Pneumonia might be less associated with delirium in patients without any critical illness.[15,16] Our patient had behavior change and cognitive decline much earlier than the onset of the infection. We argue infection was less likely to be the major etiology of delirium in this patient.

Besides, the titer of ANA in the patient's CSF was 1:160, which indicated a borderline finding.[17] Because his condition improved without any steroid and immunotherapy, we ruled out an autoimmune etiology.

In this patient, another notable observation is the early-onset dementia. Frontotemporal dementia, a subtype of neurocognitive disorder, could account for this occurrence. Early behavioral and executive deficiencies align with clinical features commonly associated with frontotemporal dementia.[18] Tau, which modulates the stability and assembly of microtubules in neurons,[19] is observed in patients undergoing frontotemporal dementia and AD.[5] Studies revealed gene mutations, such as MAPT(Tau) and C9orf72, in frontotemporal dementia cases, with mean ages of symptom onset at 49.5 years and 58.2 years, respectively.[20] Similar age was observed in the presented case.

In our patient, the presence of Tau was detected before the onset of the primary infection or potential delirium. However, both dementia and delirium can lead to an increased Tau in the CSF. In our case, we did not monitor the patient's Tau in the CSF after the infection, which might verify delirium superimposed on dementia. The trajectory of Tau—whether they would rise, decline, or if different Tau subtypes were present—remains unclear. On the other hand, Tau could be normal in AD patients and contrarily be increased in preclinical AD patients with minimal neurodegeneration. Further investigation may be required to ascertain this.

A study reported that <2% of the total amount of CSF phosphorylated Tau is found in serum.[21] The proportion is low, but blood-based evaluation of Tau is less intervensive.[22,23]

Conclusion

We presented subacute delirium that manifested by difficult-to-shift attention, transiently obstinate behavior, restlessness, and violent behavior, in a patient with frontotemporal dementia. Pneumonia and urine tract infection occurred during the course, and we discussed that this was not an isolated case of delirium or dementia. Infection as an etiology of delirium was excluded in this patient. Based on Tau positivity in CSF, we identified a significant association between Tau and delirium superimposed on dementia. Further investigation into the relationship between Tau and delirium superimposed on dementia is still needed. Our findings may guide clinicians caring for patients with delirium superimposed on dementia.

Acknowledgements

We thank Miss Jing-Wen Huang and Mr. Ming-Yu Tsai for assisting in the process of Western blotting. We thank Mr. Nicholas Doenges and Wallace Academy Editing for assisting in manuscript preparation and proofreading.

Author contributions

P.-C.Y. and C.-M.K. contributed to the critical revision of the manuscript for important intellectual content. I.-C.C. contributed to the acquisition of data and drafting of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Science and Technology Council [grant numbers: MOST 111-2635-B-075A-001].

Ethics approval

Ethical approval to report this case was obtained from the Ethics Review Committee in Taichung Veterans General Hospital (SF22141B).

Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

ORCID iD

I-Chun Chen https://orcid.org/0000-0002-1774-7210

References

1. Nitchingham A and Caplan GA. Current challenges in the recognition and management of delirium superimposed on dementia. *Neuropsychiatr Dis Treat* 2021; 17: 1341–1352.

2. Shrestha P and Fick DM. Family caregiver's experience of caring for an older adult with delirium: a systematic review. *Int J Older People Nurs* 2020; 15(4): e12321.
3. Ormseth CH, LaHue SC, Oldham MA, et al. Predisposing and precipitating factors associated with delirium: a systematic review. *JAMA Netw Open* 2023; 6(1): e2249950.
4. Mankhong S, Kim S, Lee S, et al. Development of Alzheimer's disease biomarkers: from CSF- to blood-based biomarkers. *Biomedicines* 2022; 10(4): 850.
5. Ossenkoppele R, Schonhaut DR, Schöll M, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain* 2016; 139(5): 1551–1567.
6. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010; 9(1): 119–128.
7. Idland AV, Wyller TB, Støen R, et al. Preclinical amyloid-β and axonal degeneration pathology in delirium. *J Alzheimers Dis* 2017; 55(1): 371–379.
8. Lin K-N, Wang P-N, Liu C-Y, et al. Cutoff scores of the cognitive abilities screening instrument, Chinese version in screening of dementia. *Dement Geriatr Cogn Disord* 2002; 14(4): 176–182.
9. Chan CK, Sieber FE, Blennow K, et al. Association of depressive symptoms with postoperative delirium and CSF biomarkers for Alzheimer's disease among hip fracture patients. *Am J Geriatr Psychiatry* 2021; 29(12): 1212–1221.
10. Liang F, Baldyga K, Quan Q, et al. Preoperative plasma Tau-PT217 and Tau-PT181 are associated with postoperative delirium. *Ann Surg* 2023; 277(6): e1232–e1238.
11. Fong TG and Inouye SK. The inter-relationship between delirium and dementia: the importance of delirium prevention. *Nat Rev Neurol* 2022; 18(10): 579–596.
12. McKay TB, Qu J, Liang F, et al. Tau as a serum biomarker of delirium after major cardiac surgery: a single centre case-control study. *Br J Anaesth* 2022; 129(1): e13–e16.
13. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol* 2010; 9(8): 776–785.
14. Kuswardhani RAT and Sugi YS. Factors related to the severity of delirium in the elderly patients with infection. *Gerontol Geriatr Med* 2017; 3: 2333721417739188.
15. Aliberti S, Bellelli G, Belotti M, et al. Delirium symptoms during hospitalization predict long-term mortality in patients with severe pneumonia. *Aging Clin Exp Res* 2015; 27(4): 523–531.
16. Choi CS, Gwin M, Voth S, et al. Cytotoxic tau released from lung microvascular endothelial cells upon infection with Pseudomonas aeruginosa promotes neuronal tauopathy. *J Biol Chem* 2022; 298(1): 101482.
17. Abboud H, Probasco JC, Irani S, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry* 2021; 92(7): 757–768.
18. Bang J, Spina S and Miller BL. Frontotemporal dementia. *Lancet* 2015; 386(10004): 1672–1682.
19. Gendron TF and Petrucelli L. The role of tau in neurodegeneration. *Mol Neurodegener* 2009; 4(1): 13.
20. Moore KM, Nicholas J, Grossman M, et al. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. *Lancet Neurol* 2020; 19(2): 145–156.
21. Kac PR, Gonzalez-Ortiz F, Simrén J, et al. Diagnostic value of serum versus plasma phospho-tau for Alzheimer's disease. *Alzheimers Res Ther* 2022; 14(1): 65.
22. Schirinzi T, Zenuni H, Grillo P, et al. Tau and amyloid-β peptides in serum of patients with Parkinson's disease: correlations with CSF levels and clinical parameters. *Front Neurol* 2022; 13: 748599.
23. Pereira C, Dani M, Taylor-Robinson SD, et al. Putative involvement of cytokine modulation in the development of perioperative neurocognitive disorders. *Int J Gen Med* 2022; 15: 5349–5360.