Received: 5 May 2026 | Revised: 26 May 2026 | Accepted: 31 May 2026

DOI: 10.1002/dad2.70405

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

SHORT REPORT

Transient plasma p-tau217 elevations after electroconvulsive therapy: A two-case report

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Abstract

INTRODUCTION: Plasma phosphorylated tau (p-tau217) is increasingly used in the evaluation of Alzheimer's disease (AD). However, factors influencing its interpretation in real-world settings remain incompletely defined.

METHODS: We describe a patient with repeated measurements of p-tau217 after an acute course of electroconvulsive therapy (ECT), complemented by a second patient with repeated measurements obtained during maintenance ECT.

RESULTS: In the primary case, p-tau217 was markedly elevated 3 weeks after completion of an acute ECT course (5.360 pg/mL; normal < 0.185 pg/mL), followed by a decline toward normal levels within weeks and normalization at follow-up. Cerebrospinal fluid biomarkers and neuropsychological assessment were normal. A second patient undergoing maintenance ECT demonstrated fluctuating levels of p-tau217.

DISCUSSION: ECT may induce transient elevations of p-tau217 that could be misinterpreted as suggestive of AD pathology. The temporal profile suggests a reversible process distinct from amyloid-driven tau pathology. Deferring p-tau217 testing after ECT may reduce false-positive results.

KEYWORDS
biomarker interpretation, blood biomarkers, diagnostic specificity, electroconvulsive therapy, false-positive biomarker results, neurodegeneration, tau phosphorylation

Highlights

- Electroconvulsive therapy (ECT) may be associated with marked, transient elevations of plasma phosphorylated tau 217.
- Elevations may reach ranges typically interpreted as suggestive of Alzheimer's disease.
- Deferring testing after ECT may reduce false-positive interpretations.

1 | INTRODUCTION

Blood-based biomarkers have emerged as promising alternatives to cerebrospinal fluid (CSF) and imaging biomarkers of Alzheimer's disease (AD) pathology.[1] Among these, plasma phosphorylated tau (p-tau) 217 has demonstrated particularly high diagnostic accuracy and is increasingly being adopted in clinical practice.[2] However, interpretation of p-tau217 requires consideration of comorbid conditions, including chronic kidney disease and a history of myocardial infarction or stroke.[3] Identifying such confounders is critical as blood-based biomarkers transition from research settings into routine clinical practice.

Electroconvulsive therapy (ECT) is an effective and well-established treatment for medication-resistant major depressive disorder, particularly in middle-aged and elderly patients.[4] Transient disorientation after individual ECT sessions is common, whereas persistent cognitive impairment beyond the treatment course is rare.[5] Nevertheless, concern about ECT's cognitive safety continues to influence both patient perceptions and clinical decision making, prompting ongoing investigation into the neurobiological effects of ECT.

In this context, several studies have examined the impact of ECT on blood-based biomarkers of neuronal injury. In general, these studies have suggested that ECT may induce measurable, but reversible, biological changes without evidence of neuronal injury.[6,7]

Here, we report a case in which plasma p-tau217 concentration was transiently elevated after an acute course of ECT, and another case showing elevation during maintenance treatment, highlighting ECT as a potential and previously unrecognized confounder in the clinical interpretation of blood-based AD biomarkers.

RESEARCH IN CONTEXT

1. **Systematic review**: Plasma phosphorylated tau-217 (p-tau217) has demonstrated high diagnostic accuracy for Alzheimer's disease (AD) and is increasingly used in clinical practice. Prior studies have identified several clinical factors influencing p-tau217 levels. Research on electroconvulsive therapy (ECT) indicates transient, reversible changes in some fluid biomarkers without evidence of neurodegeneration. However, the effect of ECT on plasma p-tau217 has not previously been evaluated.
2. **Interpretation**: These two cases provide initial clinical evidence that ECT may be associated with transient elevations of plasma p-tau217 that can reach ranges typically interpreted as suggestive of AD, creating a risk of false-positive results. In Case 1, marked elevation followed by normalization in the absence of other evidence of neurodegeneration supports a reversible mechanism not related to amyloid pathology. These findings identify ECT as a potential confounder in the interpretation of blood-based AD biomarkers.
3. **Future directions**: Prospective studies are needed to characterize the magnitude, duration, and mechanisms of p-tau217 changes associated with ECT. Key questions include the time course of elevation and normalization, the relative contributions of central versus peripheral sources, the impact of ECT parameters, reproducibility in larger cohorts, and the optimal interval between ECT and biomarker testing to ensure accurate clinical interpretation.

2 | CASE 1

A woman in her late forties presented to the emergency department with a subacute onset of neuropsychiatric symptoms, including anxiety, insomnia, confusion, and psychomotor agitation. Her psychiatric history was notable for a depressive episode with comorbid anxiety requiring inpatient treatment 3 years earlier, after which she had remained in full remission and returned to full-time employment. At presentation, her regular medications included doxylamine and zopiclone for insomnia.

Three months prior, the patient had been diagnosed with metastatic breast cancer involving the liver. She had completed four cycles of chemotherapy consisting of docetaxel, trastuzumab, and pertuzumab.

After admission to a psychiatric ward, her condition initially deteriorated. Comprehensive somatic and neurological evaluations revealed no identifiable etiology for suspected delirium. Psychotic symptoms proved refractory to pharmacological treatment, and the patient underwent an acute course of ECT. Bitemporal ECT was administered three times weekly under general anesthesia with propofol and succinylcholine. A total of 15 treatments were completed (Figure 1), producing adequate generalized seizures (electroencephalogram [EEG] duration 25–53 seconds). After completion of ECT, psychotic symptoms resolved; however, marked psychomotor slowing and anterograde amnesia persisted.

Given the prolonged cognitive recovery, an underlying neurodegenerative disorder was considered. Three weeks after the final ECT session, plasma p-tau217 was markedly elevated at 5.360 pg/mL, ≈ 30-fold above the upper reference limit (normal < 0.185 pg/mL; Lumipulse G CLIA assay, Fujirebio). Serum neurofilament light chain (NfL) sampled at the same time was 13 pg/mL, well below the age-specific upper reference limit (normal < 17.5 pg/mL). Two weeks later, the concentration of p-tau217 had decreased to 0.375 pg/mL. Renal function was normal throughout admission. The patient demonstrated gradual clinical improvement and was discharged 1 week later, with outpatient neurological follow-up arranged.

Approximately 4 months after the final ECT session, CSF biomarkers for AD were all normal. One month later at follow-up, the patient had resumed part-time work and reported no residual cognitive complaints. Plasma p-tau217 had normalized to 0.108 pg/mL. Furthermore, formal neuropsychological testing revealed no evidence of a neurodegenerative disorder.

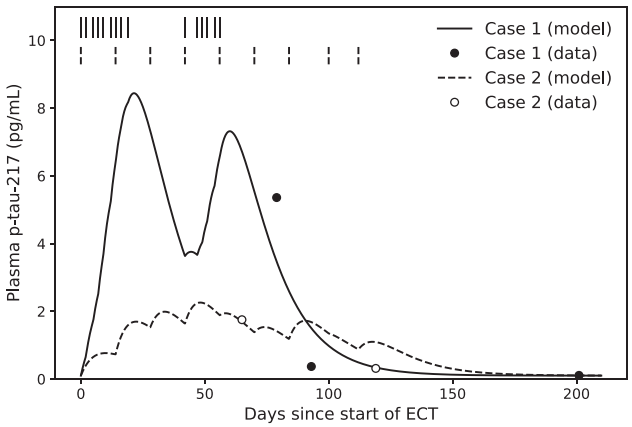

FIGURE 1 Plasma p-tau217 concentrations after ECT in two patients. Circles represent measured values and lines represent a shared two-compartment model with first-order kinetics linking a tissue source to a blood compartment. ECT sessions were modeled as transient increases in the source compartment proportional to seizure duration. Fixed parameter values included a blood elimination half-life of 5 days, based on literature, and a source-to-blood transfer half-life of 10 days, a representative value to illustrate plausible kinetics. Vertical bars denote ECT sessions. ECT, electroconvulsive therapy; p-tau, phosphorylated tau.

3 | CASE 2

A man in his late sixties developed psychotic depression shortly after retirement. He was successfully treated with a course of ECT, achieving remission lasting several months. He subsequently experienced a relapse with prominent delusional symptoms and was readmitted to a psychiatric ward.

On admission, the patient exhibited pronounced rigidity and bradykinesia disproportionate to his low-dose antipsychotic regimen (quetiapine 25 mg daily). Neurological consultation resulted in a diagnosis of Parkinson's disease, and levodopa therapy was initiated with a favorable motor response. A new course of bitemporal ECT was commenced, followed by maintenance ECT administered biweekly under general anesthesia with propofol and succinylcholine (Figure 1), producing seizures of adequate duration (27–36 seconds).

Despite ongoing ECT treatment, the patient's overall condition deteriorated, and an underlying cognitive disorder was suspected. Approximately 10 days after a maintenance ECT session, plasma p-tau217 was elevated at 1.752 pg/mL (Figure 1). Serum NfL sampled at the same time was 16.2 pg/mL, well below the age-specific upper reference limit (normal < 30.9 pg/mL). One month later—again ≈ 10 days after maintenance ECT—the concentration had decreased to an indeterminate range value of 0.314 pg/mL (between 0.185 and 0.324 pg/mL). Mini-Mental State Examination (MMSE) score remained stable at 29/30, unchanged from 1 year earlier.

4 | DISCUSSION

Our two cases demonstrate that ECT may be associated with transient elevations in plasma p-tau217 concentration, leading to false-positive results suggestive of AD pathology. To our knowledge, this is the first report describing elevations of plasma p-tau217 after ECT.

TABLE 1 Summary of non-inflammatory fluid biomarker changes after electroconvulsive therapy.

Compartment	Biomarker	Direction of change	Reference
CSF	Aβ42	Increase	7
CSF	Total tau	No change	7
CSF	Phosphorylated tau	No change	7
Blood	Total tau	No change	6
Blood	NfL	No change	6
Blood	GFAP	Increase	6

Abbreviations: Aβ, amyloid beta; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain.

These findings have direct implications for the clinical use of blood-based AD biomarkers. Transient elevations of plasma p-tau217 after ECT may reach levels typically interpreted as indicative of AD pathology. Without awareness of recent ECT exposure, this could lead to false-positive diagnoses or unnecessary investigations. Clinicians should therefore consider recent ECT as a confounder and, when possible, defer testing for several weeks after treatment.

Our observations align with broader evidence indicating that plasma concentrations of total tau and p-tau isoforms may increase after major physiological stressors, including surgery with general anesthesia and traumatic brain injury.[8,9] Contrasting the primary source of p-tau217 in AD, the central nervous system (CNS), animal data suggest that surgery-related increases in plasma p-tau217 could also originate from peripheral sources.[10] Indeed, tau expression is not restricted to neurons,[11] and hyperphosphorylated tau isoforms have been identified in peripheral tissues.[12,13] Current p-tau217 assays do not differentiate between peripheral and central contributions. Accordingly, it remains uncertain whether the p-tau217 elevations observed in our cases reflect CNS release, peripheral generation, or a combination of both.

Besides peripheral contributions, ECT may affect the generation or release of CNS-derived hyperphosphorylated tau species. One possible mechanism is that seizure activity transiently enhances tau phosphorylation through activation of kinase pathways.[14] Tau isoforms are continuously secreted into the brain interstitial fluid,[15] which is cleared by the glymphatic system in a process which could potentially be enhanced by synchronous neuronal firing.[16] Furthermore, transient increase of blood–brain barrier permeability by ECT is a possibility, for which, however, human data are inconclusive.[17] Finally, it has been suggested that p-tau217 elevations seen in hypoxic states, such as birth and cardiac arrest, may reflect maintenance of synaptic homeostasis under stress.[18] Similarly, elevations seen in our cases could reflect transient synaptic remodeling events after ECT.

Data on tau and other fluid biomarkers in the context of ECT remain limited and inconsistent across markers (Table 1). Prior studies have reported no significant changes in CSF total tau or p-tau after ECT,[7] while blood-based studies have demonstrated transient increases in

glial fibrillary acidic protein (GFAP) but not in NfL or total tau.[6] Notably, plasma p-tau217 was not assessed in these investigations.

Our study is not without limitations. First and foremost, it includes only two patients. Second, concurrent measurements of other CNS biomarkers were limited and included only NfL. Third, Case 1 had a history of metastatic breast cancer, which is known to express tau.[19] In addition, prior to admission to the psychiatric ward, the patient had received chemotherapy including the microtubule-binding agent docetaxel, which is well known to have neurotoxic side effects. Despite the > 4-month-long interval from the last dose of docetaxel to the first measurement of p-tau217, it cannot be definitively ruled out that chemotherapy-induced effects, including chemotherapy-induced neurotoxicity, or the human epidermal growth factor receptor 2–targeting antibodies, which the patient continued to receive, may have contributed to the initial high value of p-tau217. Finally, in Case 2, ECT-free measurements were not available, and amyloid pathology cannot be ruled out as a contributor to elevated p-tau217, despite the stable MMSE score.

Another possible explanation for the markedly elevated p-tau217 concentration in Case 1 is immunoassay interference caused by heterophilic antibodies.[20] Such interference can produce falsely elevated results, particularly when concentrations are unexpectedly high. Additional analyses to exclude this possibility were not performed. However, the progressive decline and eventual normalization of p-tau217 over serial measurements are more consistent with a transient biological process than with persistent assay interference.

Interestingly, in Case 1, the initial high value was measured 3 weeks after completion of ECT, considerably exceeding the reported ≈ 5-day half-life of p-tau217.[15] This suggests that the signal driving tau phosphorylation or release may accumulate during a treatment course and decline more slowly than the biomarker itself is cleared from circulation (see Figure 1 for an illustrative kinetic model).

5 | CONCLUSION

ECT may be associated with transient elevations of plasma p-tau217 that can lead to false-positive interpretations suggestive of AD. Clinicians should consider recent ECT when interpreting p-tau217 results and, pending further studies, may wish to defer testing for several weeks after treatment.

AUTHOR CONTRIBUTIONS

Henri Hokkanen wrote the first draft of the manuscript and wrote the code for the figure. Emilia Hintsala was a treating physician, acquired data for this report, and revised the manuscript. Jaakko Hotta substantively revised the manuscript. Terhi Rantamäki-Häkkinen was a treating physician, acquired data for this report, and substantively revised the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

The authors have nothing to report. Open access publishing facilitated by Helsingin yliopisto, as part of the Wiley - FinELib agreement.

CONFLICT OF INTEREST STATEMENT

Henri Hokkanen reports serving as a sub-investigator on clinical studies sponsored by Verge Genomics and Roche and receiving financial support from BioArctic for travel to a scientific congress. Emilia Hintsala reports having served on an advisory board for Takeda and receiving travel support from AbbVie to attend a scientific congress. Jaakko Hotta reports serving as a sub-investigator on clinical studies sponsored by the European Union (Horizon 2020 research and innovation programme grant agreement No. 964220 and Horizon Europe programme grant agreement No. 101155955) and receiving honoraria for an invited lecture from Eisai and BioArctic. Terhi Rantamäki-Häkkinen reports no competing interests. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. The code used to generate the figure is available from the corresponding author on reasonable request.

ETHICS STATEMENT

According to the policies of Helsinki University Hospital (HUS), ethical committee approval was not required for these case reports. These case reports were conducted in accordance with the principles of the Declaration of Helsinki.

CONSENT TO PARTICIPATE

Written informed consent was obtained from all individual patients included in this report. A copy of the written consent is available for review by the editor-in-chief of this journal.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patients for publication of these case reports and any accompanying images.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hokkanen H, Hintsala E, Hotta J, Rantamäki-Häkkinen T. Transient plasma p-tau217 elevations after electroconvulsive therapy: A two-case report. *Alzheimer's Dement*. 2026;18:e70405.
https://doi.org/10.1002/dad2.70405