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CASE REPORT

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An atypical case of Creutzfeldt-Jakob disease mimicking frontotemporal dementia: genotypic influence and clinical implications

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Abstract

We report an atypical case of Creutzfeldt-Jakob Disease (CJD) mimicking Frontotemporal Dementia (FTD) in a 68-year-old male. The patient initially presented with an anxious-depressive syndrome, progressing over 29 months to include dysexecutive syndrome, stereotyped speech, inertia, social withdrawal, verbal fluency impairments, and marked dyspraxia. Diagnostic imaging revealed signal alterations on MRI, while CSF analysis showed elevated T-TAU, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) levels. A second-generation RT-QuIC (SG-RT-QuIC) confirmed prion disease, with genetic testing identifying a codon 129 MV polymorphism and a deletion in the third octapeptide repeat. This case highlights the importance of integrating advanced diagnostic tools, such as SG-RT-QuIC and comprehensive genotyping, in evaluating atypical presentations of CJD. Early elevated GFAP levels highlight the usefulness of considering neuroinflammatory markers in slowly progressive forms of CJD.

Background

The Creutzfeldt Jacob Disease (CJD) is a rapid progressive dementia related to the conversion of the prion protein (PrPC) into a misfolded form (PrPSc) which accumulates in neuronal cells leading to intracellular spongiform changes and neuronal loss. Clinical presentation in CJD is extremely heterogeneous mimicking other diseases, MRI and RT-QuiC approved in the current criteria have improved the diagnostic efficiency. We present a case worth reporting for its atypical presentation, mimicking frontotemporal dementia instead of classic Creutzfeldt-Jakob Disease.

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Case presentation

A 68-year-old male presented in February 2022 with anxious-depressive syndrome. His neurological examination was unremarkable, and he had no family history of neurodegenerative diseases. His parents passed away, the mother due to heart disease and the father due to a cancer. His siblings and daughters were in good health. In May 2022, brain MRI showed bilateral signal alterations in the temporo-parietal and para-calcarine regions, consisting of restricted diffusivity on diffusion-weighted imaging (DWI) and hyperintense signals on FLAIR sequences (Fig. 1), with normal EEG results. By January 2023, his relatives reported the onset of stereotyped behaviors, such as an excessive need to ensure all doors were closed before going to bed, frequently rechecking and reopening/closing them multiple times due to persistent doubts. These episodes occurred numerous times daily, often in the middle of the night. There was a marked loss of interest and initiative in daily activities;

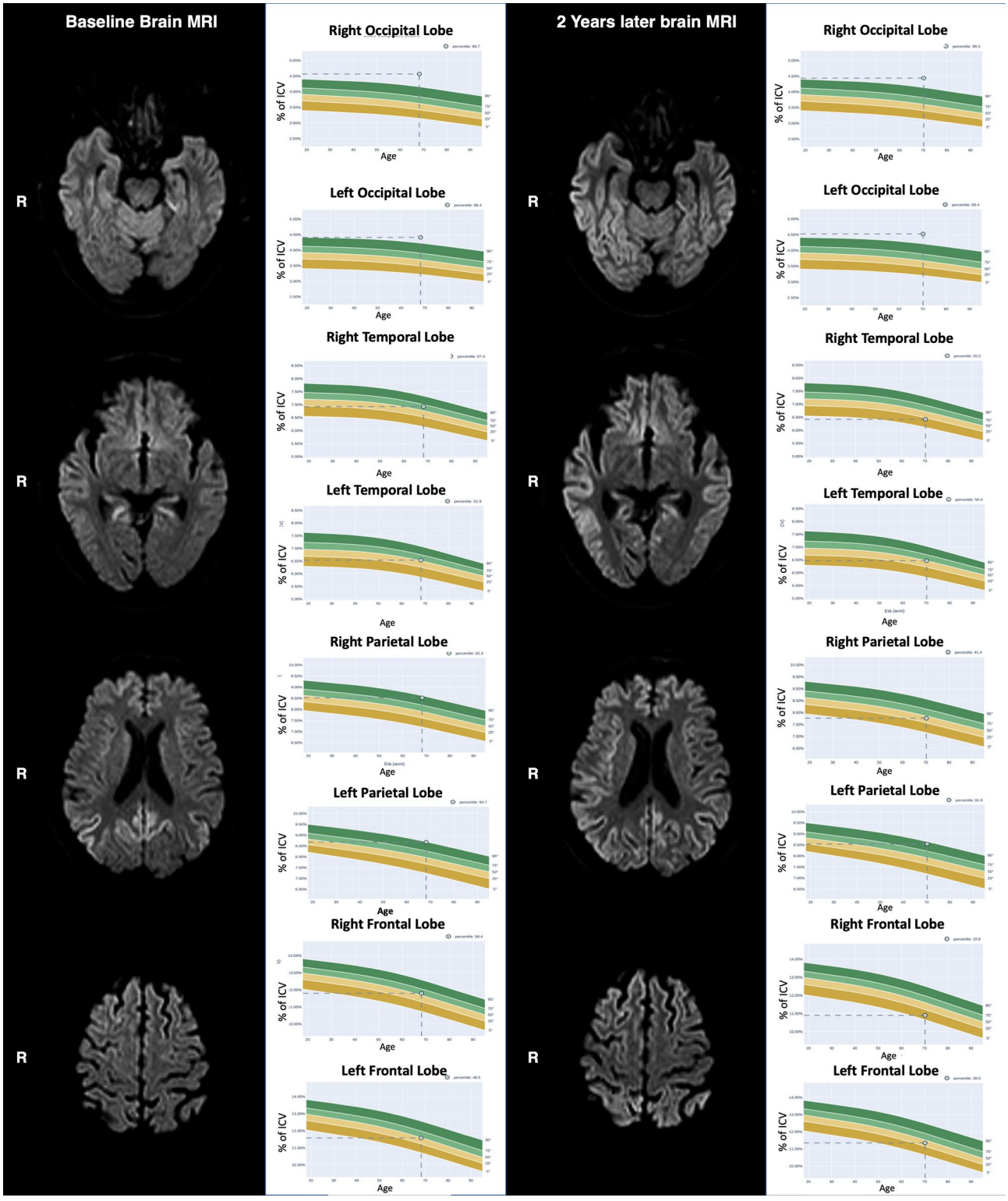

Fig. 1 The figure shows the DWI sequence of the brain MRI at baseline and after 2 years. Additionally, the values of the cerebral lobe volumes of our patient, as a percentage of total intracranial volume (ICV) corrected for age, are reported in relation to normative values

for example, he no longer wished to accompany his wife grocery shopping and refused to participate in household chores. These features were accompanied by socially inappropriate behaviors, such as neglecting personal hygiene for weeks. Relatives also described unusual behaviors stemming from an increased perception of danger, including the decision to cut down all the trees on his property in the middle of winter due to an irrational fear of spontaneous fires. He also repeatedly refused to sit on chairs due to an unfounded fear of falling. Additionally, there was a clear reduction in social engagement, with marked apathy, inertia, and withdrawal from conversations. He refused to leave the house and preferred to remain seated watching television alone. Stereotyped speech and sporadic episodes of confusion—such as mixing up petrol and diesel—were also reported. An episode of spatial disorientation while driving was also reported, along with an incident in which he was unable to find the keys to his home. Four months later, a comprehensive neuropsychological evaluation revealed impairments in functions associated with the fronto-temporal brain areas, with deficits of attention, verbal phonemic and semantic fluency, and long-term memory. The Montreal Cognitive Assessment (MoCA) score adjusted for education was 5 and all domains were impaired, with minimal preservation of the ability to draw the clock face (1 point), visual recognition and naming (2 points), and orientation (1 point). The Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score was 6, while neurological examination remained unchanged. Both the MoCA and CDR assessments were administered by an experienced neuropsychologist. CSF analysis revealed elevated levels of total-TAU (T-TAU, 386 pg/ml; n.v. <275), neurofilament light chain (NfL, 816.39 pg/ml), and glial fibrillary acidic protein (GFAP, 12,884.80 pg/ml). T-TAU was measured using the validated LUMIPULSE automated immunoassay with a chemiluminescence-based methodology, following the manufacturer's instructions, on the LUMIPULSE® G600II system (Fujirebio, Ghent, Belgium). CSF NfL and GFAP concentrations were assessed using the Simoa™ Neurology 2-Plex B Assay Kit (Catalog #103520; Quanterix, Billerica, MA, USA) by the semi-automated, ultrasensitive SR-X Biomarker Detection System (Quanterix), and their levels were deemed elevated by comparison with our in-house reference cohort of healthy individuals which has already been published [1].

Six months later, the MoCA score declined to 4, and the CDR-SB score increased to 17. Given the clinical suspicion of a possible behavioral fronto-temporal dementia (FTD), in accordance with the diagnostic criteria of Rascovsky et al. (2011) [2], an FDG-PET was requested. The scan revealed hypometabolism in the pre-frontal areas, parieto-temporal cortex, posterior cingulum, and precuneus bilaterally, as well as in the left fronto-mesial area and anterior cingulum, supporting the diagnosis of FTD (Fig. 2). Subsequent CSF analysis revealed further increases in T-TAU (692 pg/ml, n.v. <275), NfL (893,03 pg/ml) and GFAP (18778,2 pg/ml) with elevated CSF protein levels (65.9 mg/dl, n.v. 20–40). Antibody assessments (Amphiphysin, CV2, GAD65, Hu, PNMA2, Recoverin, Ri, SOX1, Titin, Tr, Yo, Zic4, CASPR2, LGI1, N-methyl-D-aspartate receptor) were negative and performed using Blot methodology (Euroimmun Italy, Cod: DL 1111-1601-7 G). Microbiological assessments for Adenovirus, CMV, EBV, HHV6, HSV 1–2, HTLV-1, Mycoplasma pneumoniae, and Picornavirus were also negative and conducted using PCR-DNA testing. Full-length RT-QuIC (FL-RT-QuIC) from CSF was inconclusive, while a 2-year follow up brain MRI showed diffuse hyperintensity in the whole cortex with sparing of the left precentral gyrus and an increase in brain atrophy in the right fronto-temporo-parietal region (Fig. 1). A prion disease was hypothesized and a CSF second-generation RT-QuiC (SG-RT-QuiC) using a truncated form of prion protein turned positive. Genetic testing identified a MV codon 129 polymorphism and a non-pathogenic deletion (based on current knowledge) of the third octapeptide repeat (R3) in the prion protein. No further information regarding prion protein misfolded subtype 1 or 2 was obtained due to the absence of electrophoretic analysis. By twenty-nine months, the patient exhibited marked dyspraxia syndrome (Video) (ideomotor, gait, and dressing apraxia) and visual hallucinations. After thirty-five months, the patient is still alive, although bedridden and requiring full assistance.

Discussion and conclusion

We present an atypical case of Creutzfeldt-Jakob disease (CJD) that mimics FTD, characterized by a prolonged disease duration, dysexecutive syndrome, behavioral changes and alterations in verbal fluency. The clinical phenotype observed in our case is likely influenced by the genotype, which exhibits a polymorphism at codon 129 (MV) and a deletion of the third octapeptide repeat. The combination of unusual clinical features along with a unique genetic profile (MV codon 129 polymorphism and octapeptide repeat deletion) provides new insights into the phenotypic variability of the disease. Notably, the MV polymorphism may present with slower disease progression, and literature indicates a negative correlation between the length of the octapeptide repeat and both the age of onset and disease duration [3]. Furthermore, the deletion of the octapeptide repeat has previously been linked to CJD cases mimicking FTD [4] and has been reported in a case of FTD [5].

A noteworthy aspect of our case is the CSF biomarkers profile. CSF T-TAU e CSF NfL were relatively lower than expected; other authors have proposed different cut-offs

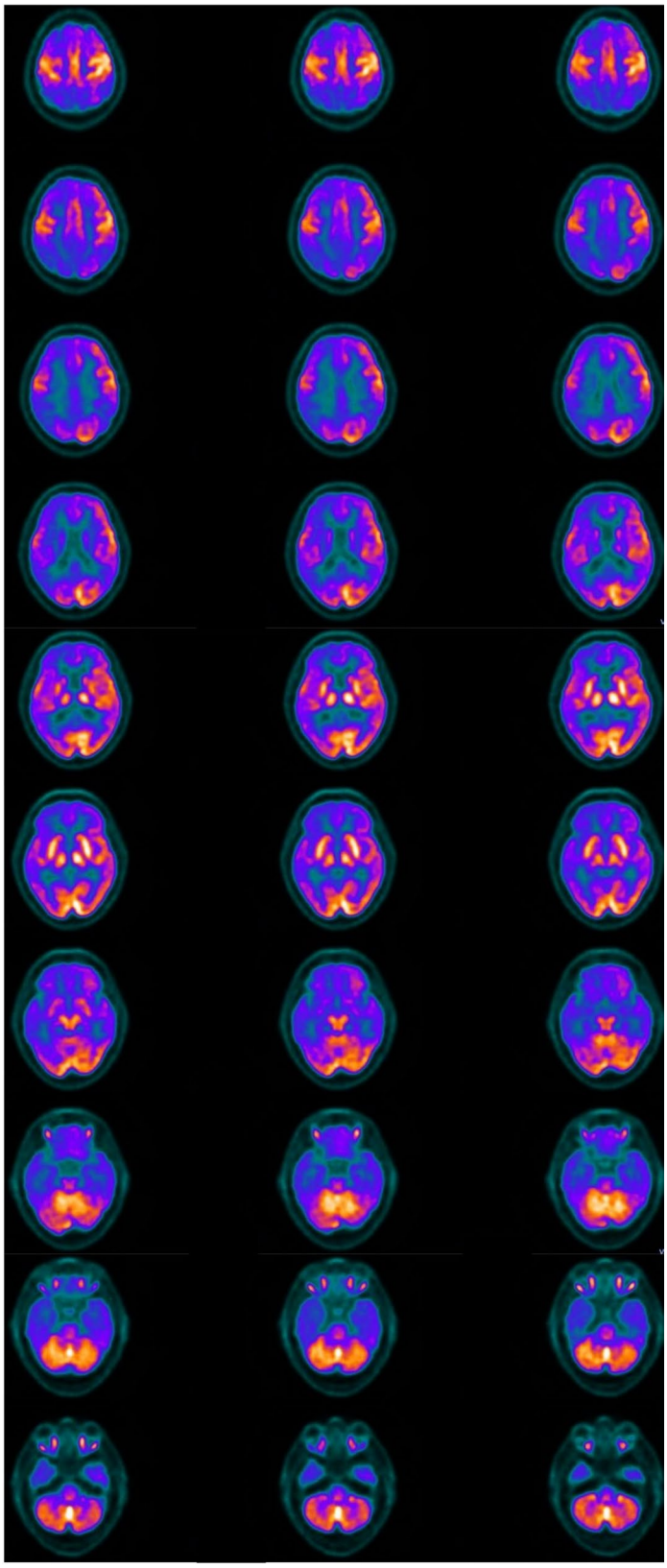

Fig. 2 FDG-PET scan showing hypometabolism in the prefrontal areas, parieto-temporal cortex, posterior cingulum, and precuneus bilaterally, as well as in the left fronto-mesial area and anterior cingulum

for CSF T-TAU (>1072 pg/ml etc., using ELISA) and for CSF NfL (>5016 pg/ml or >10 500 pg/ml using ELISA), highlighting reduced sensitivity in MV subtype [6]. Conversely, elevated CSF GFAP levels were observed, likely due to early astrocytosis, which precede neuronal loss [7] and are more pronounced at symptom onset in slow-progressing forms of CJD. From a neuroimaging perspective, our patient showed DWI sequence alterations in brain MRI already extensively documented [8] and integrated into the diagnostic criteria [9]. Furthermore, the quantitative brain volume analysis [10] at the 2-year follow-up showed increased atrophy localized in the initially affected regions, sparing the recently involved ones (Fig. 1), possibly due to a neurotoxic exposure from prion-related substances [7]. In fact, prion-related neurotoxicity may not stem directly from prions themselves but from prion isoforms or assemblies that disrupt membranes, interact with ion channels, or trigger toxic responses from microglia and astrocytes [7].

Finally, RT-QUIC is a widely employed method in the diagnosis of CJD [9], based on the ability of misfolded prion proteins to induce the conversion of normal prion protein into the misfolded form. Recently, a second generation of RT-QuIC (SG-RT-QuIC) has been developed. Unlike the first generation, which utilizes full-length human prion protein as a substrate; SG-RT-QuIC employs a truncated hamster recombinant PrP substrate (amino acids 90–231) alongside modifications to the original RT-QuIC protocol [11]. This method accelerates the seed conversion efficiency and reduces assay time, offers higher sensitivity (94% vs. 88%) and a faster application compared to FL-RT-QuIC [11]. Currently there is no common consensus on the use of SG-RT-QuiC, particularly useful for ambiguous results or atypical cases.

This case highlights the need for a better understanding of genotypic influence, particularly alterations involving the octapeptide repeat in relation to the highly heterogeneous clinical phenotype in CJD. Neuroinflammatory biomarkers, although potentially unspecific, could serve as an additional tool, particularly in distinguishing organic from functional neuropsychiatric presentations. Their consideration may be relevant in slowly progressive forms where neurodegeneration is less pronounced. Furthermore, while first-generation RT-QuIC is favored for its exceptional specificity, the higher sensitivity of second-generation RT-QuIC may aid in diagnosing more complex and atypical cases.

Abbreviations

CDR-SB	Clinical Dementia Rating Scale Sum of Boxes
CJD	Creutzfeldt-Jakob Disease
DWI	Diffusion-weighted imaging
FTD	Frontotemporal Dementia
GFAP	Glial fibrillary acidic protein
MoCA	Montreal Cognitive Assessment
NfL	Neurofilament light chain
PrPC	Prion protein
PrPSc	Misfolded form prion protein
SG-RT-QuIC	Second-generation RT-QuIC

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-06290-0.

Supplementary Material 1.

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Clinical trial number

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Authors' contributions

CM: main writer, data validation and review; DR: supervision and data collection; BP: data collection; BD: data collection; AM: data collection; ND: project coordinator; DP: project coordinator, data reviewer and validator.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The data collection and publication were approved with a favorable opinion by the Regional Ethics Committee for Clinical Trials of the Tuscany Region (Italy) under Protocol Number 24397.

Consent for publication

The patient signed the consent form approved by the ethics committee for the collection and publication of the clinical data presented in this scientific article.

Competing interests

The authors declare no competing interests.

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