

INTRODUCTION

AD is the most common cause of dementia, accounting for approximately 60–80% of typically progressive cases. Although uncommon, rapidly progressive presentations of AD do occur.¹ These cases present a diagnostic challenge, requiring clinicians to determine whether rapidly progressive dementia (RPD) reflects an atypical presentation of a common disorder—such as AD—or a typical presentation of a rare disorder, namely Creutzfeldt–Jakob disease (CJD).² This distinction is further complicated by overlapping clinical features and limitations in diagnostic testing, contributing to delays in diagnosis with potential consequences for management, counseling, and outcomes.

OBJECTIVE

Determine the clinical features and diagnostic tests that identify patients with prion disease who were initially misdiagnosed with rapidly progressive AD.

METHODS

- Inclusion criteria:**
 - Reported cases of RPD
 - Underwent prion-specific testing (MRI DWI, RT-QuIC, CSF t-tau, or 14-3-3) or had neuropathologic confirmation
 - Initially diagnosed as AD (amnesic or atypical AD variant) without early hallmark prion features (e.g., myoclonus, ataxia, akinetic mutism)
- Cases with classic early CJD features at first presentation were excluded
- Two reviewers independently screened and extracted data
- Additional cohort:** In addition to the systematic review, two AD mimic cases were identified from prospectively evaluated patients with RPD at Mayo Clinic in Florida

RESULTS

Figure 1. Prisma flow diagram of Included Cases

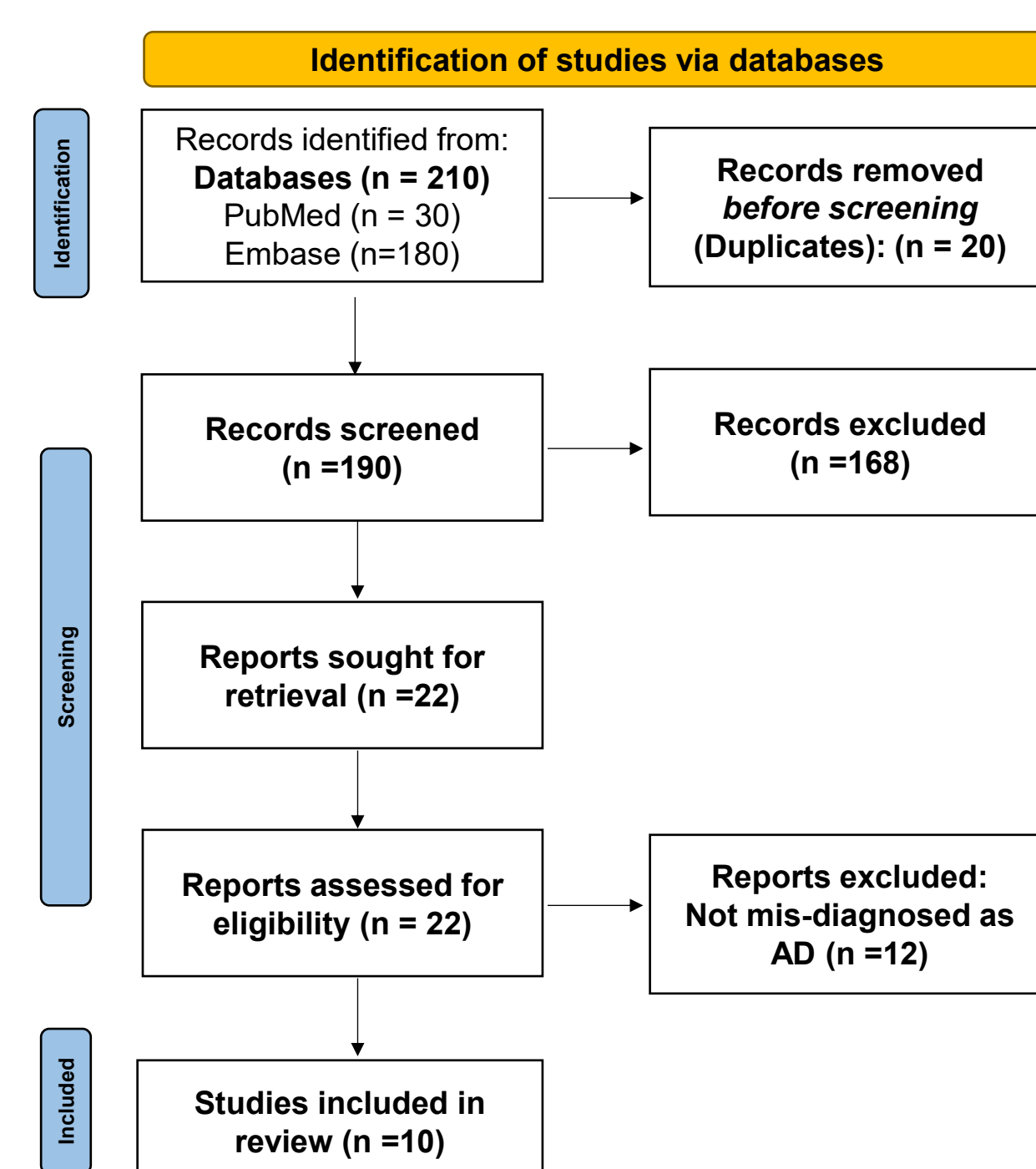


Table 1. Clinical and Biomarker Features of Additional CJD Cases Identified from a Prospective Cohort

Feature	Case 1	Case 2
Age, years	67	80
phenotype	Amnesic–aphasic	logopenic variant primary progressive aphasia
Symptom duration, months	13	5.8
Early prion red flags	No	No
MRI finding	AD-like atrophy; DWI negative	Age-appropriate; DWI negative
CSF AD profile		
Aβ42 (pg/mL)	>1700	1138
p-tau181 (pg/mL)	30.4	76.3
t-tau (pg/mL)	822	>1300
p-Tau/Abeta42	low	High
CJD biomarkers		
RT-QuIC	Negative	Positive
CSF t-tau (pg/mL)	4408	5983
CSF 14-3-3 (AU/mL)	16,385	31,073
Time to CJD suspicion, months	1.3	4.6
Final diagnosis	Definite CJD	Probable CJD

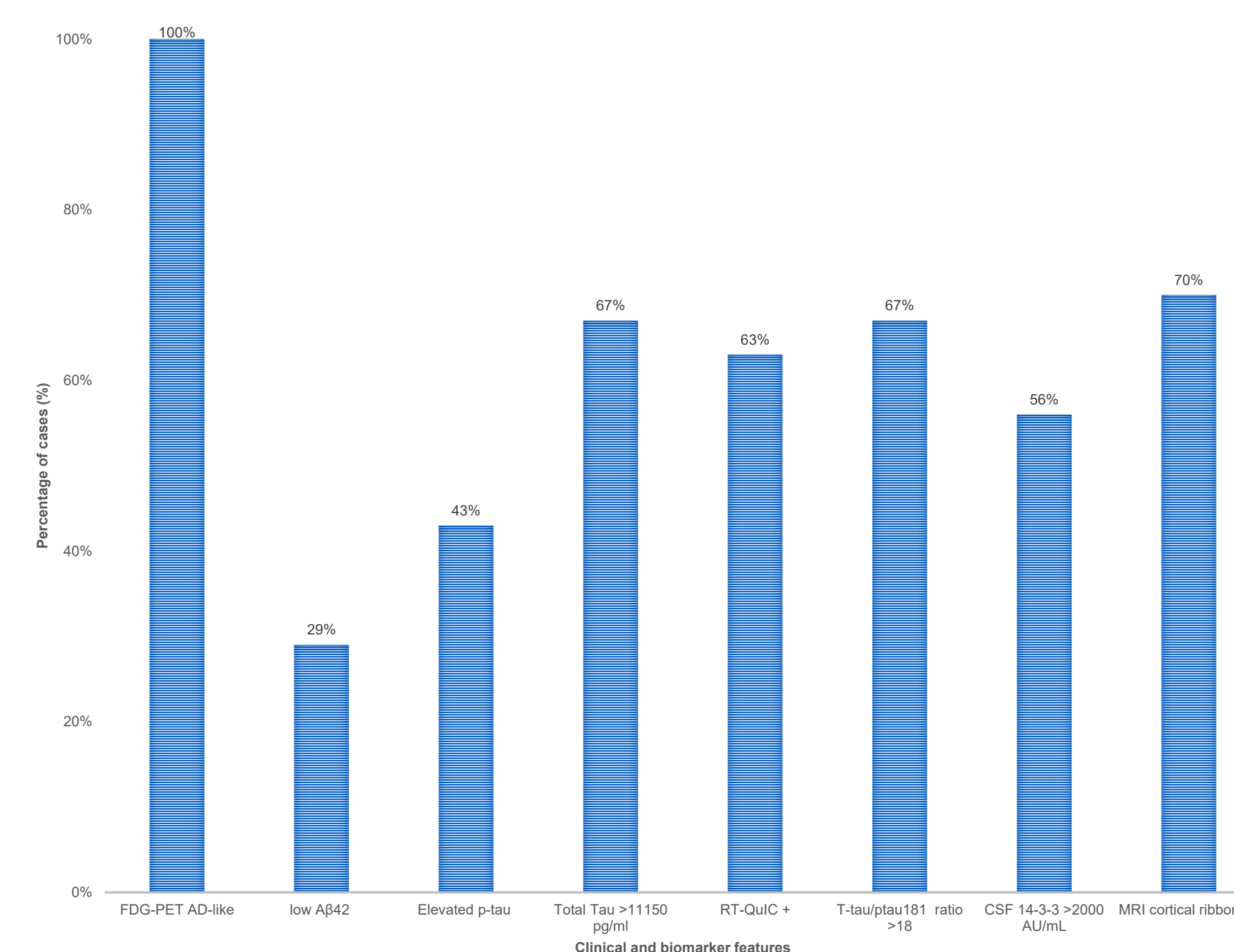
Both cases: MRI not suggestive of CJD, CSF not AD-consistent; RT-QuIC initially negative in Case 1 and positive in Case 2; autopsy-confirmed CJD in Case 1

Table 2. Summary of Clinical and Diagnostic Findings in Included Cases

Cas e	14-3-3 >2000	RTQ	t-tau >1150	t-tau/p-tau >18	CSF biomarkers of AD	MRI DWI	AD-like PET Pattern
77 M	+	–	+	–	Aβ42/Aβ40 = 0.20; ApoE ε4 present	–	+
57 M		++	–		Aβ42 low; p-tau normal	+	
78 M	+		+			+	+
66 M	–	+	–			–	–
56 M	–		+	+	Aβ42 low-normal; p-tau mildly ↑	+	
82 F	–	+			NR; AD pathology at autopsy	+	
52 F	+	++	+	+	Aβ42 normal; p-tau normal	+	+
68 M	+	+	+	+	Aβ42 normal; p-tau ↑	+	+
58 F	+	+	+	+	Aβ42 normal; p-tau ↑	+	+
59 F	–	+	–	–	Aβ42 slightly low; p-tau normal	+	+

M= Male; F= Female, † = Initially negative → repeat positive; + = Positive, – = negative; RTQ = RT-QuIC

Figure 2. Frequency of Clinical, Imaging, and Biomarker



CJD frequently mimicked AD, including AD-consistent CSF biomarkers and AD-like PET patterns (6/6). Most cases (7/10) presented as atypical AD variants. MRI abnormalities were present in 7/10 cases, while RT-QuIC was positive in 5/8 (including 2 on repeat testing). Elevated CSF total tau (>1200 pg/mL) was seen in 6/9, and t-tau/p-tau181 >14 in 4/6 cases.

SUMMARY

- Eight studies (10 cases) met inclusion criteria through systematic review (median survival 18.5 months), supplemented by two additional Mayo Clinic cases
- CJD may mimics AD across clinical, imaging, and biomarker domains, including AD-consistent CSF profiles and AD-like PET patterns
- Early recognition of mimics (elevated t-tau, ratio↑, MRI changes); RT-QuIC as confirmatory test
- Absence of early prion features and non-diagnostic imaging can delay recognition
- Mayo Clinic cases; both showed non-diagnostic MRI, variable AD biomarkers, and discordant RT-QuIC results
- Accurate diagnosis relies on clinical progression and multimodal testing

CONCLUSION

CJD may be misdiagnosed as AD, particularly in the presence of AD-consistent CSF biomarkers, AD-like FDG-PET patterns, and absence of MRI findings typical of CJD. These findings support routine use of prion-specific biomarkers (e.g., RT-QuIC) in patients with RPD.

REFERENCES

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