

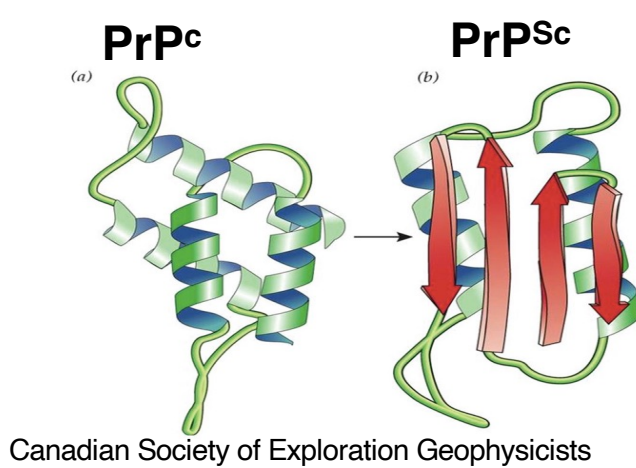
Cerebrospinal Fluid Findings in Rapidly Progressive Dementia

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INTRODUCTION

Prion diseases are a group of neurodegenerative disorders caused by the aggregation of abnormal prion protein.⁴ Most commonly the process of protein misfolding occurs sporadically, when this occurs the pathogenic prion induces conversion of normal prion protein and spreads exponentially through cortical or subcortical structures. The result is a spontaneous rapidly progressive dementia (RPD) named sporadic Creutzfeldt-Jakob Disease (sCJD). Another subset of prion disease is genetic and arises from mutations in the prion-related protein gene (*PRNP*).³ Familial CJD has a clinical presentation that mirrors sCJD and progresses rapidly with typical disease duration of 6 months to a year. Gerstmann-Sträussler-Scheinker syndrome (GSS) progresses more slowly and is typically characterized by parkinsonism with late onset dementia.³ Fatal familial insomnia (FFI) is characterized by progressive insomnia with dysautonomia and has a typical disease duration of 18 months.³ Given that pathogenic prions can form spontaneously throughout the cortex and subcortical structures, there are a wide variety of presentations from psychiatric manifestations to motor deficits. As a result, most sCJD patients are two thirds of the way through their course before the appropriate diagnosis is made. Since the incidence of sCJD is approximately 1 per million a year in the United States, there are not many large studies in this population. The current goal of diagnosis is an MRI with findings indicative of prion disease. However, this test is highly dependent on the familiarity of the MRI analyst with prion disease and is often missed.² The goal of this project is to document common cerebrospinal fluid findings in prion disease in order to better understand the expected range of general chemistries, inflammatory studies, and common biomarkers (total TTAU (TTAU), Neuron Specific Enolase (NSE), and phosphorylated TAU (PTAU) in this population.



METHODS

Inclusion/Exclusion Criteria:

- All patient data was derived from the RPD cohort of the Memory and Aging Center at UCSF must have had CSF data to be included in this study.
- sCJD: The patient must have been pathology proven with biopsy or autopsy, had an MRI indicative of sCJD per UCSF criteria, or an EEG with multiple periodic sharp waves.
- Genetic prion disease: all included patients were symptomatic during the time of assessment.
- Non-prion rapidly progressive dementia (npRPD): must have had RPD AND had a disease duration greater than 3 years, had symptomatic improvement, or have been pathology proven for another disease process.

Lumbar puncture selection and inclusion:

- The LP with the most comprehensive data was selected for secondary analysis.
- Samples were excluded based on high red blood cell (RBC) count for TTAU, IgG index, OCB, RT-QuIC, and 14-3-3 which have been shown to be sensitive to RBC level.
- NSE data is from Mayo clinic, 14-3-3 and RT-QuIC were measured by the National Prion Disease Pathology Surveillance Center (NPDPSC), TTAU is from Athena Diagnostics or NPDPSC, and PTAU is from Athena Diagnostics.

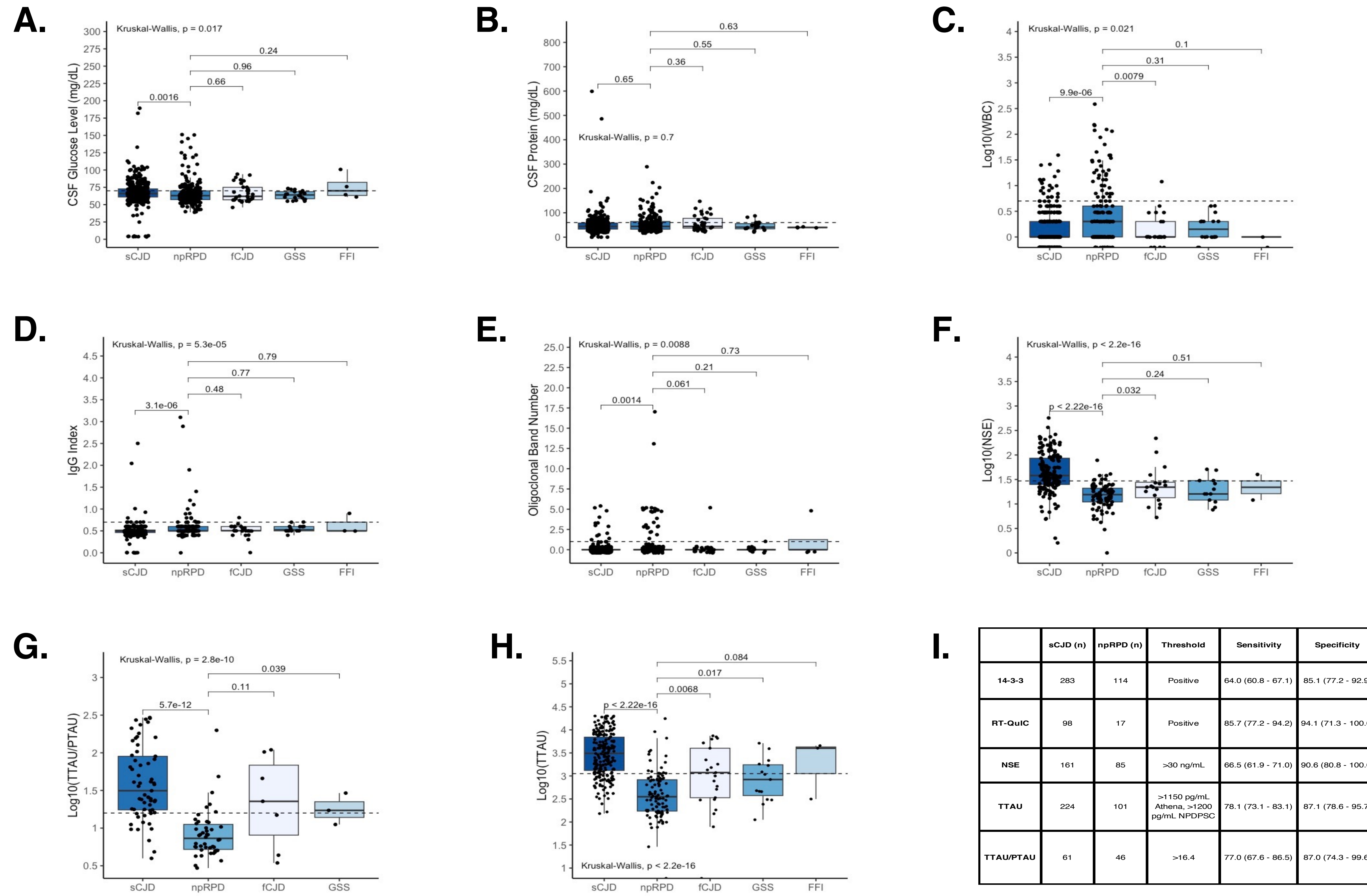
Data Analysis:

- Nonparametric data were analyzed using the Kruskal-Wallis test to determine if there were any statistically significant intergroup differences.
- Wilcoxon-Rank Sum testing was done for post-hoc analysis.
- All graphing and data analysis was done using R studio.

		Genetic CJD				
		sCJD	npRPD	fCJD	GSS	FFI
Country	Total (n)	591	271	42	22	4
	% USA (n)	90.0 (532)	98.2 (266)	95.2 (40)	95.4 (21)	100.0 (4)
Sex	sex % F (n)	49.9 (295)	47.6 (129)	50.0 (21)	31.8 (7)	0.0 (0)
	% (n)	59.2 (350)	52.0 (141)	66.7 (28)	68.1 (15)	50.0 (2)
Age of Onset (years)	mean ± sd	60.8 ± 30.8	56.5 ± 29.6	52.8 ± 26.6	42.9 ± 22.9	52.0 ± 30.3
	median (IQR)	62.0 (12)	58.0 (14)	50.5 (14)	46.0 (13)	52.0 (5)
	range	22-83	6-80	27-72	10-59	47-57
	% (n)	51.4 (304)	18.1 (49)	66.7 (28)	60.0 (13)	50.0 (2)
Disease Duration (months)	mean ± sd	12.8 ± 13.2	53.9 ± 46.2	16.0 ± 19.2	89.2 ± 83.7	8.0 ± 0.0
	median (IQR)	8.5 (15)	41.0 (59)	9.5 (19)	63.0 (34)	8.0 (0.0)
	range	1-101	2-186	1-78	27-346	8-8
Pathology Proven	% (n)	53.4 (316)	17.7 (48)	66.7 (28)	40.9 (9)	0.0 (0)

Table 1: Percentages are relative to total number of patients in each disease category. Disease duration is defined as time from first symptom to date of death. Pathology proven cases were either autopsy or biopsy proven for PrD cases. Genetic CJD cases were symptomatic at time of inclusion assessment.

RESULTS



Figures (A-H): Each dot represents a patient, bold lines indicate the median, the top and bottom lines of the box are the third and first quartile respectively, the dashed line is the threshold for elevated values, and the whiskers extend to the cohort maximum and minimum or to 1.5*interquartile range (IQR)+Q3 or 1.5*IQR-Q1, values that are outside of the range of the whiskers are outliers, p-values are derived from Wilcoxon ranked sum test and are significant if p<0.05

Figures (A-I): A) threshold glucose is 70 mg/dL, B) threshold protein is 60 mg/dL, C) threshold WBC is above 5 cells/microL, D) threshold IgG Index is 0.7, E) threshold for OCB is 1, F) threshold for NSE is 30 pg/mL, G) threshold for TTAU/PTAU is 16.4¹, H) threshold for TTAU is 1175, I) n represents the number of patients that met inclusion criteria for the indicated test, sensitivities and specificities are listed with 95% CI

	sCJD (n)	npRPD (n)	Threshold	Sensitivity	Specificity
14-3-3	283	114	Positive	64.0 (60.8 - 67.1)	85.1 (77.2 - 92.9)
RT-QuIC	98	17	Positive	85.7 (77.2 - 94.2)	94.1 (71.3 - 100.0)
NSE	161	85	>30 ng/mL	66.5 (61.9 - 71.0)	90.6 (80.6 - 100.0)
TTAU	224	101	>1150 pg/mL, Athena, >1200 pg/mL NPDPSC	78.1 (73.1 - 83.1)	87.1 (78.6 - 95.7)
TTAU/PTAU	61	46	>16.4	77.0 (67.6 - 86.5)	87.0 (74.3 - 99.6)

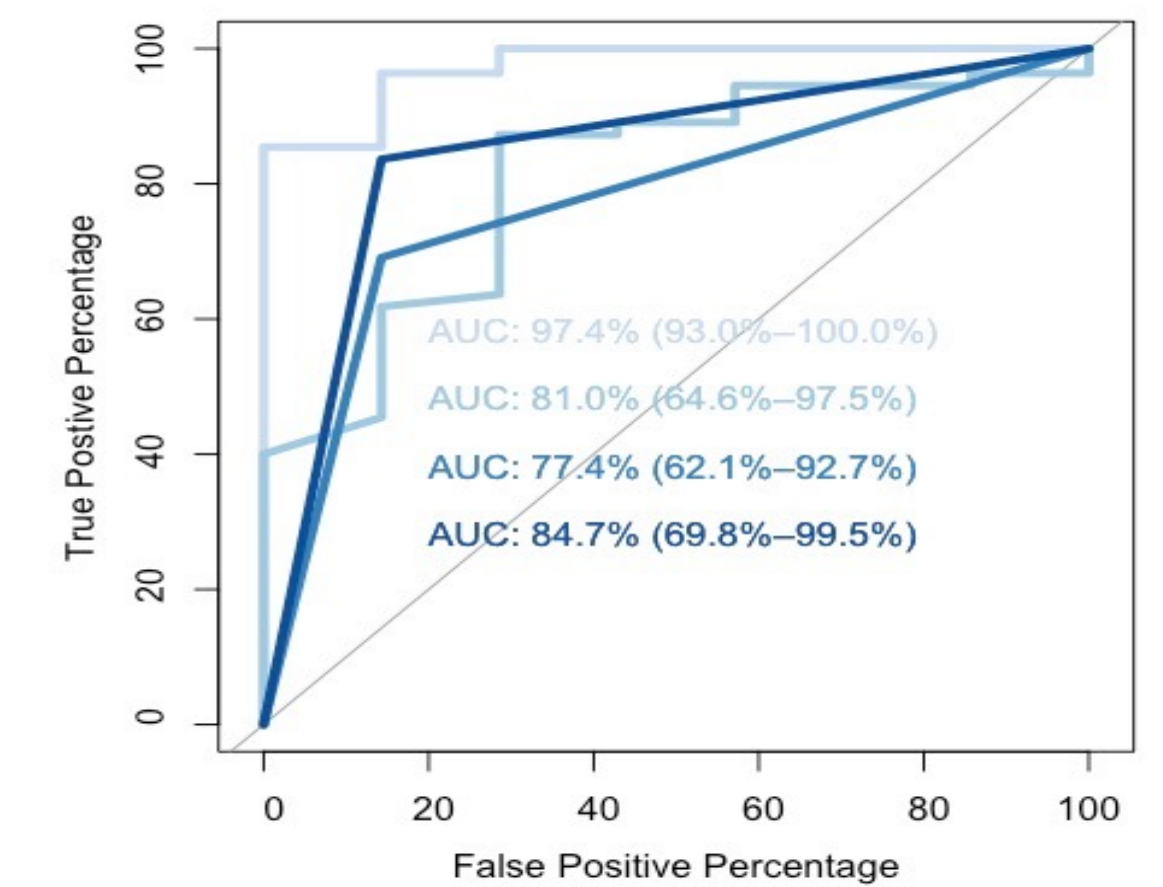
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Figure: G) AUC are listed in order of TTAU, NSE, 14-3-3, RT-QuIC. N=7 npRPD and N=55 sCJD.

CONCLUSIONS

- The sCJD cohort had significantly higher levels of glucose in CSF compared to npRPD.
- There are no differences in expected CSF protein levels between groups.
- Some sCJD patients have markers of inflammatory disease.
- Anti-VGKC and Anti-LGI1 encephalitis led to a false positive RT-QuIC. There were 16 false negatives, 5 of these sCJD cases were pathology proven.
- Direct comparison between the available biomarkers, implicates total TAU as the test with the highest accuracy for distinguishing sCJD and npRPD. However, this test is limited by small number of patients in the npRPD group.
- Familial CJD generally has similar markers relative to sCJD.
- TTAU/PTAU is superior to TTAU for distinguishing FFI from npRPD.
- Utilizing multiple methods for of prion diagnosis improves diagnostic certainty.

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