計畫編號：MOHW109-CDC-C- 114-133401

衛生福利部疾病管制署 109 年委託科技研究計畫

計畫名稱：我國庫賈氏病之發生、臨床病程及流行病學相關因子分析研究

年 度/全 程 研 究 報 告

執行機構：國立臺灣大學 醫學系 神經科
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研究人員：
執行期間：109 年 01 月 01 日至 109 年 12 月 31 日
研究經費：新臺幣 貳佰伍拾參萬元整

＊本研究報告僅供參考，不代表本署意見，如對媒體發布研究成果應事先徵求本署同意*

目錄

壹、摘要：

一、中文摘要

關鍵詞：普利昂蛋白、庫賈氏病、腦波、腦部磁振造影、生物標記、健保資料庫、診斷工作標準流程

普利昂蛋白為庫賈氏病致病原，經異常折疊變成具傳染性的變異普利昂蛋白。我國自 1996 年開始庫賈氏病之監測作業，因此擬藉本計畫針對我國人類庫賈氏病之發生、臨床病程及流行病學相關因子分析研究，並探討防疫制度之完整性。

第一年計畫已完成國際學者演講交流，組成跨領域團隊，從疾病管制署的通報資料庫與健保資料庫多面向的檢視我國庫賈氏病之發生率及臨床病程。從通報個案整理出分析包括平均發病年齡、高峰年齡、性別、症狀、平均診斷時間、診斷後平均存活時間、前驅症狀、發病病徵、臨床病程。腦波具週期性尖銳組合百分比、出現時間、腦波之敏感度、腦部磁振皮質緞帶徵象最常見部位，磁振的敏感度。由健保資料庫中依性別、年齡計算出年度發生率。

第二年計畫針對疾病管制署的通報資料庫進行庫賈氏病之流行病學相關因子分析，並進行相關因子與預後分析，利用人口學資料、臨床症狀、共病為獨立變項，預後（存活年數，或低或超過兩年）為因變項，進行回歸分析。與專科醫學會合辦繼續教育。**完成** 1 篇期刊論文並進行投稿至國際期刊。

第三年計畫

存活 2 年個案持續追蹤，依據地區疾病管制單位徵求到宅追蹤的意願，

進行臨床、核磁共振影像之追蹤。發現女性、發病年齡低者存活較長。腦波具週期性尖銳組合波以及癲癇的個案存活較短。

國際合作方面受到新冠肺炎的影響，會議改採視訊方式舉行台灣-澳洲的庫賈氏症國際會議由台灣與澳洲雙方各三名講者進行演講交流。

兩篇論文，一篇已刊登 Clinical Epidemiology,一篇審查中。

二、英文摘要

Keywords: Prion、Creutzfeldt-Jakob disease、EEG、MRI、Biomarkers, Taiwan CJD registry, 14-3-3

Misfolded prion protein （PrP^{sc}）is the pathogen of Creutzfeldt-Jakob disease (CJD) by. This is a 3-year project, we aimed to explore and analyze the epidemiological, clinical and biochemical characteristic feature of CJD and to improve our system of disease monitor on these relentless human prion diseases.

In the 2nd year of this project, we completed the analyses of epidemiological, clinical and biochemical related factors.

We alos held two continous education conferences on CJD on May 5th 2019 co-hosted by Taiwan Neurological Society in TICC, Taipei and on Nov 16th 2019 co-hosted by Taiwan Dementia Society in NCKU, Tainan.

We proposed suggestions on current registry and report system including open the 14-3-3-test service to reduce irrelevant notices and to simplify the report forms to improve the accuracy of reported information.

We prepared our report based on the epidemiological findings and submitted to an international scientific journal. In the thrid year of the project, we continued to follow those subjects lived longer than two years after the diagnosis by doing clinical and MRI follow-up according to the wish of the family. We found women lived longer than their male counters and the younger the onset age the longer they lived. Those with PSWCs and epileptic seizure lived shorter. Due to the COVID-19 the Taiwanese-Australia international conference on CJD will be held by remote videoconference. There will be three speakers on each side. We have already publsihed one paper in Clinical Epidemiology and the other is now in review process.

貳、本文

一、前言

（一）研究背景

為配合衛生福利部科技施政目標「確保衛生安全環境整合型計畫」及「全球衛生安全—追求防疫一體之傳染病整合防治研究計畫」等發展主軸，並依當前傳染病流行現況與防疫政策發展等需要，擬規劃進行普利昂病（prion disease）防治政策及創新普利昂蛋白檢驗技術之研究發展，並探討普利昂病防治機制等，透過本科技研究計畫，整理普利昂病的臨床盛行率以及發病的危險因子，研究成果做為制定健康促進為導向之政策，以提升防疫服務品質。

細胞普利昂蛋白（PrP^C）簡稱普利昂蛋白，是存在於各種器官與組織的一種細胞表面蛋白，尤其是在中樞以及周邊神經系統為最豐富(Bendheim et al., 1992)。 普利昂蛋白普遍存在於鳥類、哺乳類動物的細胞(Wopfner et al., 1999)，因此可能有它重要的生理功能。然而普利昂蛋白的錯誤折疊以及所導致的病原體普利昂蛋白（PrP^{Sc}）的聚集會引發致命的神經退化(Prusiner, 1982)。錯誤折疊的普利昂蛋白是一種病原體，可進行細胞對細胞，甚至是跨物種的傳染(Prusiner, 1998)。

在細胞膜上的普利昂蛋白所進行的蛋白分解有點類似於類澱粉前驅蛋白（amyloid precursor protein ），會進行 α-、β-、甚至 γ- 的分解 。分解的結果分別產生稱為 N1 + C1, N2 + C2 和 C3 的片段 (S. G. Chen et al.,

1995; Harris et al., 1993; Lewis et al., 2016; Walmsley, Watt, Taylor, Perera, & Hooper, 2009). α-分解的結果可以讓 C1 片段不易被轉變成病原體普利昂蛋白 （PrP^{Sc}）(Westergard, Turnbaugh, & Harris, 2011),且在疾病狀態下 β-分解的速度會增加(S. G. Chen et al., 1995)。

相對於主要是 α-helix 結構（40% α-helical，~ 3% β-sheet） 的非感染性的細胞普利昂蛋白（PrP^{C}）為可溶於清潔劑、可被蛋白酶分解，具傳染性的病原體普利昂蛋白（PrP^{Sc}）主要是 β-sheet 的結構（~30% α- helical and ~40% β-sheet），不容於清潔劑也無法被蛋白酶分解(Zahn et al., 2000)。這種不被蛋白酶分解的特性是我們在量測病原體蛋白（PrP^{Sc}）所利用的一種指標。而病原體蛋白（PrP^{Sc}）與細胞普利昂蛋白（PrP^{C}）接觸到之後會改變細胞普利昂蛋白的結構成為 β-sheet, 這種 β-sheet 結構的病原體蛋白除了具細胞到細胞之間的傳染性外，因為其結構較為規則，容易形成寡體（oligomers）進一步堆積成小纖維（fibrils），最後導致海綿樣腦病變 (Requena & Wille, 2017)。雖然病原體蛋白（PrP^{Sc}）因為其蛋白的難溶性（general insolubility）與易聚合性（propensity to aggregate）所以高解析度的構造分析有其相當的困難。從低溫電子顯微鏡與 X 光纖維繞射的研究了解. 病原體蛋白（PrPSc）是一種四階 β-螺旋筒狀結構。

人類普利昂病的診斷主要還是採取多重準則的綜合性判斷(Zerr et al., 2009)，其準則包括：臨床神經學檢查、腦波變化、磁振造影以及腦脊髓液檢測等。

臨床和神經學的檢查是診斷普利昂病的要件，包括初期出現記憶力

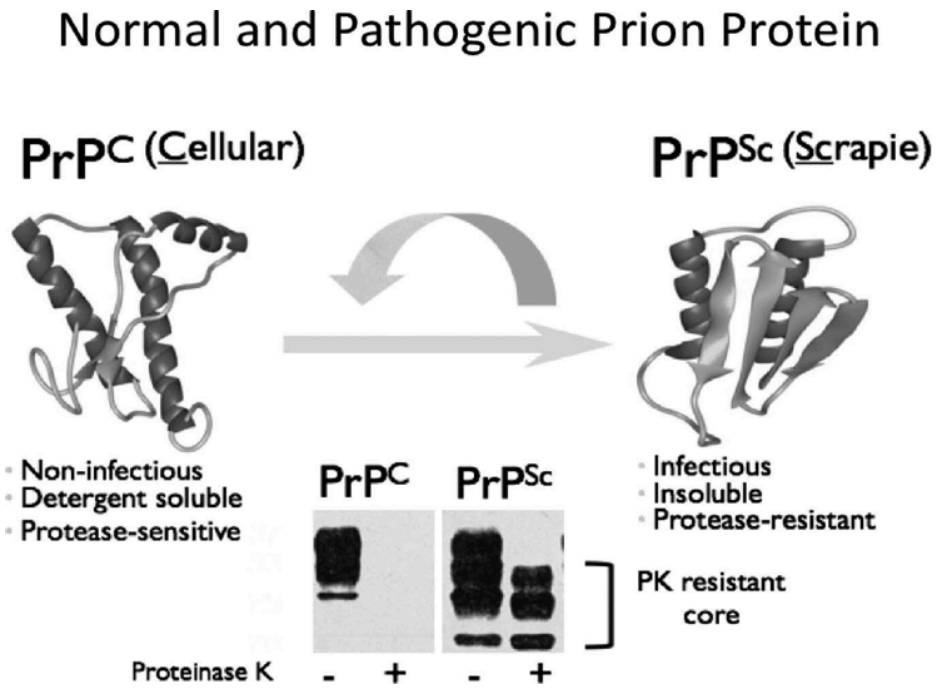
衰退的急性失智、行為異常及步態不穩或肢體共濟失調。隨著病程進展，除了上述症狀逐漸惡化，患者的四肢與軀幹會有劇烈肌躍性抽動（myoclonus）、發生視力模糊、肢體無力、麻木感、癲癇等。並在短期之內（數週～數月）導致臥床 (Kubler et al., 2003)。

患者的腦波變化則會出現週期性銳波-慢波（只在疾病的某些時期和階段）(Lanska, 2001)。磁振造影影像在特定部位出現訊號變化，如大腦皮質的皮質彩帶病徵（cortical ribbon sign），或基底核、視丘 T2 訊號增強，基本上磁振影像的敏感度相當高。然而需要注意的是還有其他疾病（例如：代謝性腦病變，癲癇發作後）也可能會有類似變化 (Meissner et al., 2009)。

還有腦脊髓液的蛋白質分析，國內大部分是分析 14-3-3 蛋白 (Gmitterova et al., 2009)，可惜 14-3-3 蛋白在國人罹患普利昂病的患者中只有 50%左右的敏感度。此外可由家族性病例分析 PrP 基因（familial *PRNP* mutations）(Llorens et al., 2017)，同理在在變異型庫賈氏病（vCJD）可以偵測 codon 129 (M/V) 的多形性 （polymorphisms）。

雖然我國自 1996 年開始庫賈氏病之監測作業，2007 年將其公告為第四類法定傳染病，國內迄今也已累計逾 400 名病例，惟因本國民情，病例死亡後接受解剖確診者極少，最後在防疫觀點的診斷，基本上是採取專家會議的共識決來確定診斷。因此 希望能夠藉由本計畫之施行，開發新的生物標記，比如用 RT-Quaking induced conversion 的方法來量測病原體的普利昂蛋白，做為診斷普利昂病的重要生物指標 (Schmitz et al., 2016)。

在追蹤我國 400 多例的病歷當中發現有些患者在發病後又存活了超過兩年的時間，這些患者需要進一步追蹤。因為最近的研究發現α-synuclein 的存在可能可以干擾病原體的普利昂蛋白轉化而延長病患者的存活。綜上所述，除發展新的生物標記外，我們團隊將探討我國人類庫賈氏病之發生、臨床病程及流行病學相關因子，與各國進行比較，另將藉由與國外知名學者專家進行相關交流，以提昇診斷及防治量能。



（二）研究目的

本計劃屬三年期之計畫

計畫全程目標：

探討我國庫賈氏病之發生、臨床病程及流行病學相關因子分析研究

【第1年】主要目標為經由國際專家學者以及研究人員的交流來提昇我國的診斷能力，其次是經由跨領域團隊的組成，多面向地檢視我國庫賈氏病之發生及臨床病程

- **跨領域團隊的組成**

- **邀請國外具普利昂病臨床診斷、檢驗、影像醫學、病理學專業之專家來台進行相關交流**。

- **進行我國庫賈氏病之發生及臨床病程相關研究**

比對傳染病通報系統健保申報庫賈氏病個案之差異性

歸納出我國庫賈氏病的臨床病程與特徵

【第2年】主要目標進行流行病學相關因子分析研究，定訂診斷工作標準流程並推廣標準流程，追蹤存活超過兩年個案

- **我國庫賈氏病之流行病學相關因子分析**

- **訂定我國通報庫賈氏病前之診斷工作標準流程**

訂定工作標準流程

辦理繼續教育課程

- **訂定長期存活（超過兩年）追蹤調查的方法**

- **完成 1 篇期刊投稿**。

【第3年】主要目標追蹤存活超過兩年庫賈氏並分析其原因

- **存活超過 2 年庫賈氏病個案之追蹤及調查，並進行相關分析**

- **辦理 1 場國際視訊研討會**

- **完成 2 篇期刊投稿**

- **修訂病例調查表**

（三）多年期計畫之執行成果概要

第一年計畫已經完成了邀請國際學者前來演講交流，組成跨領域團隊，從疾病管制署的通報資料庫與健保資料庫多面向的檢視我國庫賈氏病之發生率及臨床病程。本計劃自 1999 年起所通報的個案中整理出資料比較完整的 315 位庫賈氏病患的資料進行分析。已經分析歸納出包括平均發病年齡、發病高峰年齡、性別分布、症狀出現後平均診斷時間、診斷後平均存活時間、常見之前驅症狀、發病病徵、臨床病程。腦波具典型週期性尖銳組合波的百分比、典型腦波出現時間、腦波檢驗之敏感度、腦部磁振造影典型皮質緞帶徵象最常見部位、核磁共振的敏感度、腦部核磁共振出現特異病徵的平均時間。並由健保資料庫中依性別、年齡計算出年度發生率，與 10 年存活狀況。生物標記進行了前導研究。

第二年計畫之主要目標為進行流行病學相關因子分析研究，訂定診斷工作標準流程並推廣之，並追蹤存活超過兩年個案。

針對疾病管制署的通報資料庫進行庫賈氏病之流行病學相關因子分析，並與健保資料庫作對照，比對兩個資料庫庫賈氏病的個案年度發生及通報數的落差。庫賈氏病相關因子與預後分析，將利用人口學資料、臨床症狀、共病為獨立變項，診斷分類及預後（存活年數、如，低於或超過兩年之個案）為因變項，進行邏輯回歸分析。

訂定我國通報庫賈氏病之診斷標準工作流程的作業中，我們首先訂定一套暫定的標準工作流程，並與專科醫學學會（台灣臨床失智症學會、老年精神醫學會、神經學學會）合辦繼續教育課程。對象以診斷、照顧庫賈

氏病之醫師為授課主體。課程收集與會者的意見之後，訂定我國通報庫賈氏病前之診斷工作標準流程，確立必要的臨床資料、實驗室檢查的項目，以及治療照護的原則，並將最後資料提供各相關專科醫學會參考。

訂定長期存活個案追蹤方法上，以各種變數如性別、診斷以及 14-3-3 檢驗結果進行存活率分析，找出長期存活的可能原因。討論長期存活個案較多，可能與研究方法有關，我們採用發病-死亡，國外多採取診斷到失能性不語症（Akinetic Mutism） 的時間。我國資料庫顯示平均發病到診斷為 3 個月。故建議未來衛生局防疫系統的追蹤時設法取得失能性不語症的發生時間，以便與國外資料進行比較。

最後我們將兩年間研究分析所得資料撰寫成有關流行病學與發病率的論文「Incidence of and Mortality Due to Human Prion Diseases in Taiwan: A Prospective 20-Year Nationwide Surveillance Study from 1998 to 2017」, 並已**投稿**至國際期刊 *Clinical Epidemiology*。

新型生物標記研發項目，於第二年進度下已開發 IMR reagent 與臨床檢體腦脊髓液中的 total prion 蛋白，已取得初步成果並建立標準曲線。

二、實施方法及進行步驟：

第三年之主要目標為

（一）存活超過 2 年庫賈氏病個案之追蹤及調查

比較長期存活個案與非長期存活之個案之人口學變項、腦波、神經影像、共病、治療與照護模式等因子並分析其對臨床病程的影響和交互作用。

（二）辦理 1 場國際視訊研討會

內容包括我國庫賈氏症的臨床表現、流行病學、長期存活個案的保護因子、生物標記。

（三）國際期刊投稿

完成 1 篇期刊投稿內容台灣庫賈氏症患者長期存活個案之臨床、腦波與神經影像分析，將比較長期存活個案與非長期存活之個案之人口學變項、腦波、神經影像結果整理發表。

完成 1 篇期刊投稿內容就台灣庫賈氏症生物標記之研究，將所開發之新型庫賈氏症生物標記的結果整理發表。

（四）修訂病例調查表

就第 1 及第 2 年之研究成果，與各相關領域專家集思廣益，修訂病例調查表。

（五）庫賈氏症新型生物標記開發與驗證

應用庫賈氏病 p-Tau，PrPSc 等新型生物標記，針對台灣各地所通報新發個案經專家會議確診後的個案的 CSF 及血液樣本，進行長期追蹤研究，

探討病程與生物標記的關聯性。其中因 CSF 樣本重複取樣不易，血液樣本具追蹤之可行性較高。

三、結果

（一）存活超過 2 年庫賈氏病個案之追蹤及調查

1. 新增病例分析

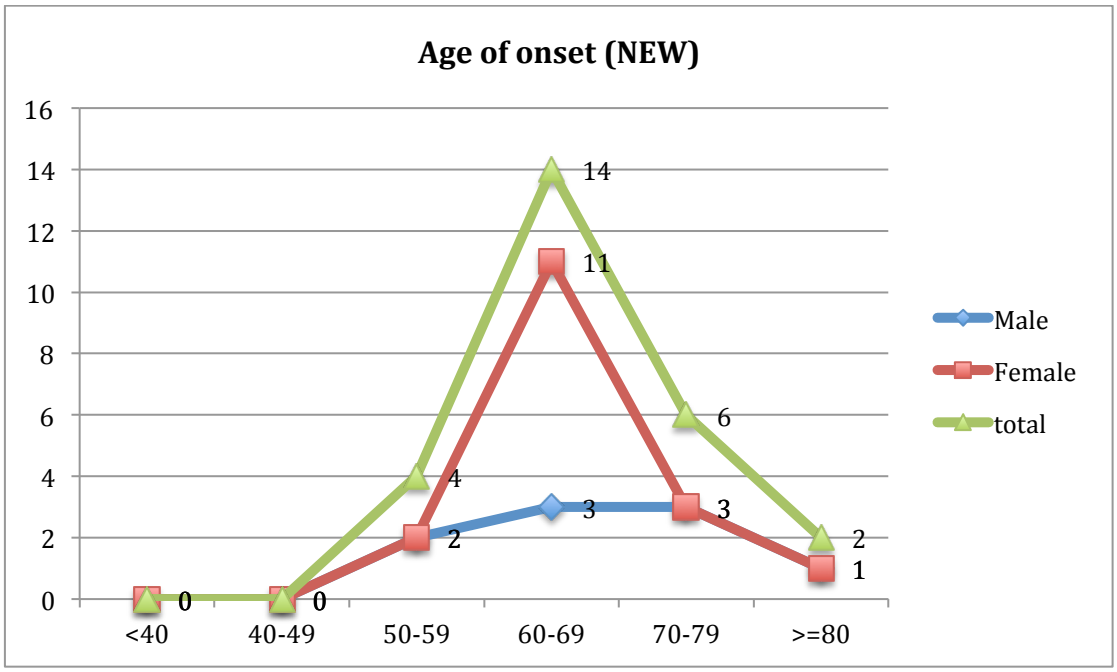
為了持續辦理新登錄庫賈氏病個案之分析調查，需持續對新增個案進行監測和登錄。在 109 年前半年扣除排除個案後，有 31 位登錄的庫賈氏病個案，其中 5 位是屬於繼續追蹤、等待審查或尚未能決定。其餘 26 位進行分析，並合併至資料庫。分析結果如表一：今年新增個案女性較多（65%），雖然與更新後整體資料庫的女性略高的有所不同，但因為只有半年應不至於影響整體趨勢，待進一步觀察。發生年齡的分佈如表二，其中的發病年齡高峰在 60-69 歲（圖一、二），一樣與更新後整體資料庫的趨勢並無顯著差異（p=0.084）。雖平均存活天數分別為 508.6 天以及 208 天，經統計分析後發現未達顯著差異（p=0.110），考量觀察期間不長，新增個案亦只有 26 例，較不易看到明顯變化。症狀發生至診斷平均天數同樣未達顯著（p=0.638）。

表一、半年新增個案與更新後整體資料庫之性別分布

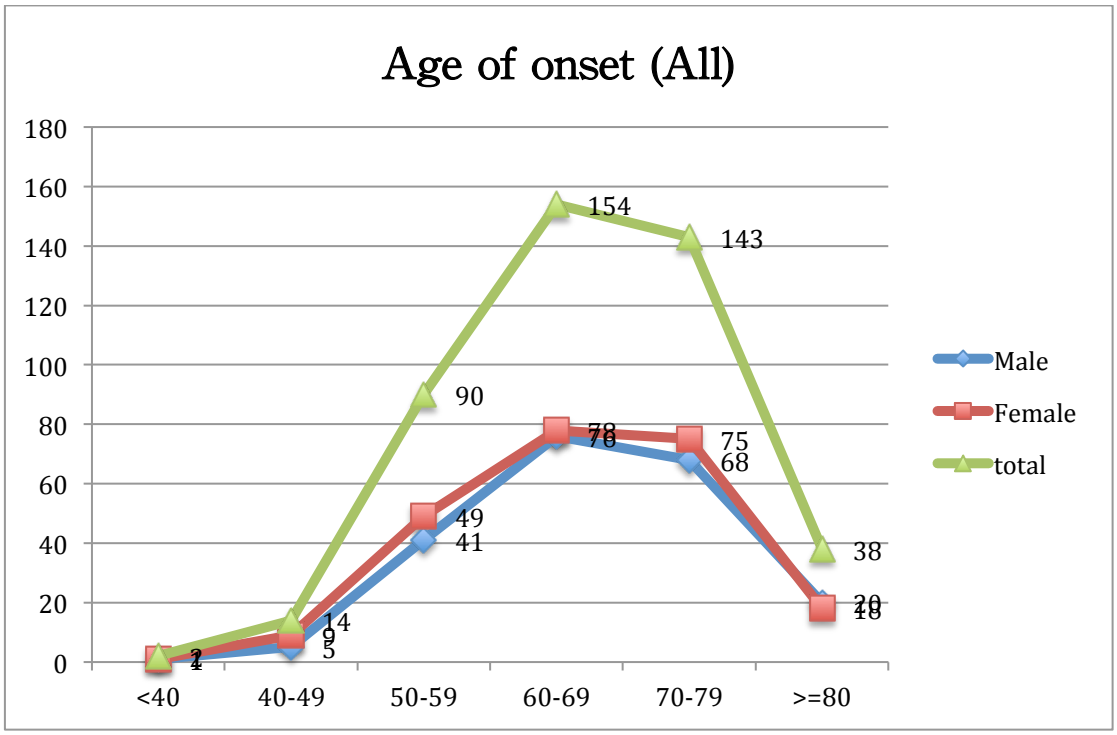
	性別	人數	百分比
All（n=441）	Male	211	48%
	Female	230	52%
New (n=26)	Male	9	35%
	Female	17	65%

表二、發病年齡、症狀發生至診斷平均天數、平均存活天數

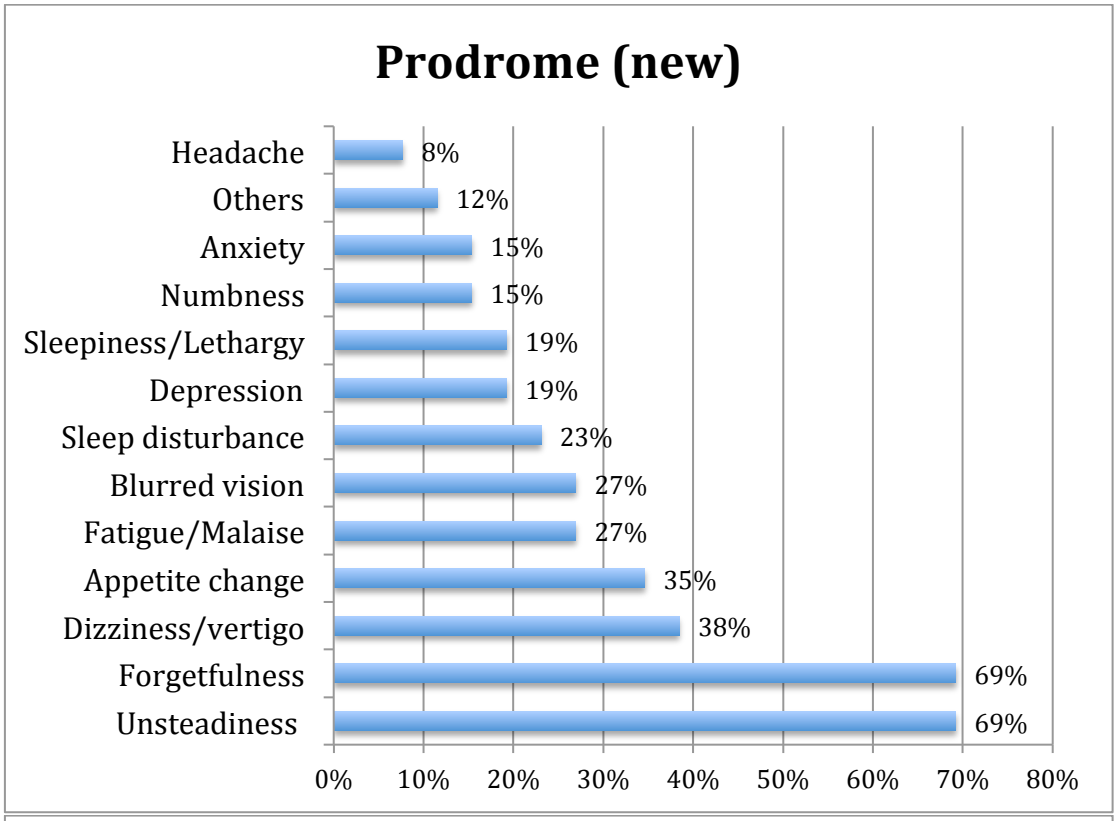
		Mean	SD	Median	Max	Min
All（n=441）	Age of Onset	66.8	9.9	68	91	22
	Onset_Diagnosis (D)	99.2	282.6	42	33.5	0
	Onset_Death (D)	508.6	507.1	383.5	3965	9
New (n=26)	Age of Onset	66.7	7.5	64.5	86	57
	Onset_Diagnosis (D)	95.8	110.0	53.5	422	5
	Onset_Death (D)	208.0	205.9	125	691	53

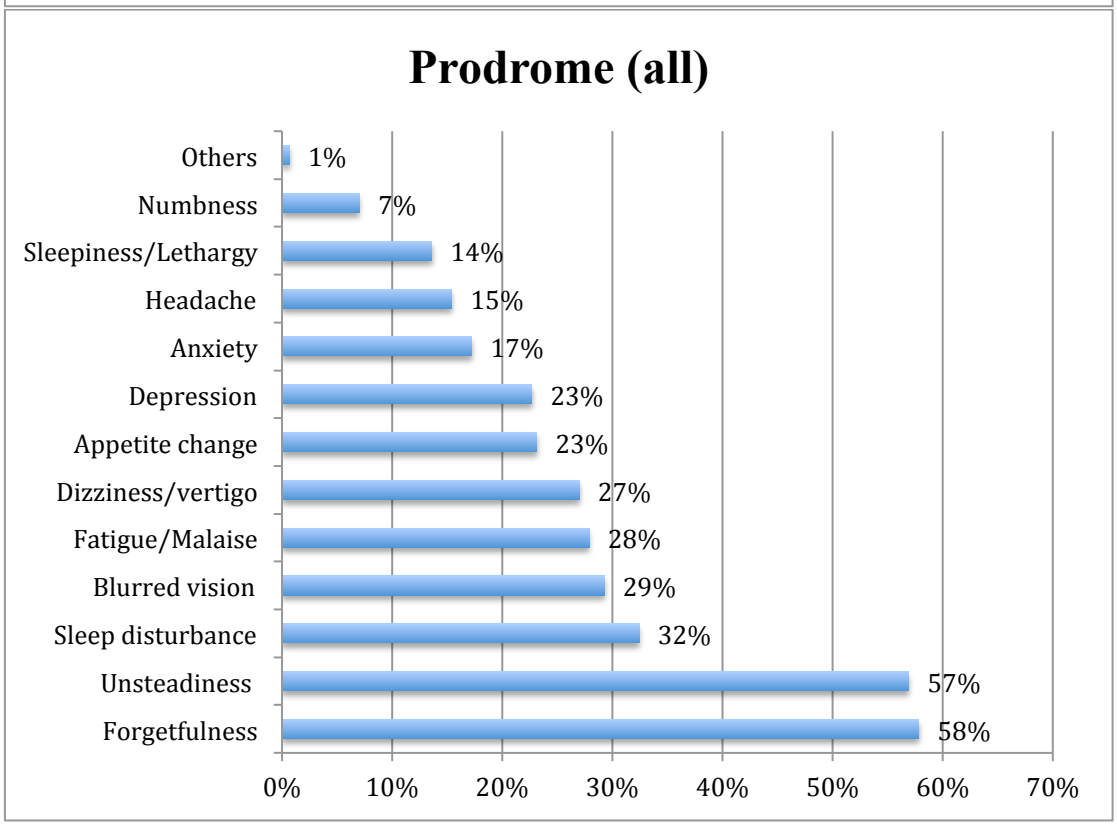


圖一、上半年新增個案發病年齡分佈



圖二、更新後整體資料庫個案發病年齡分佈

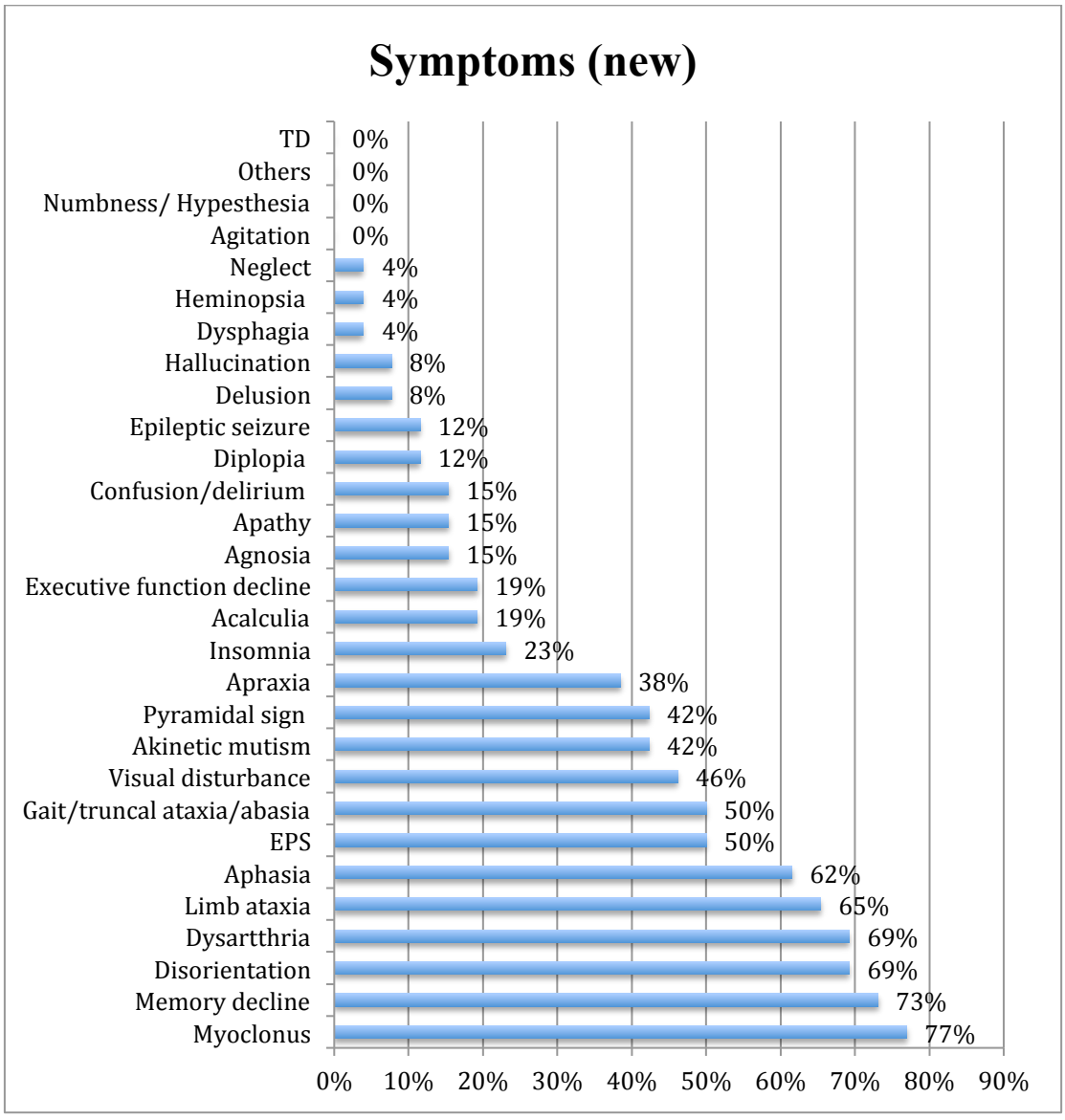




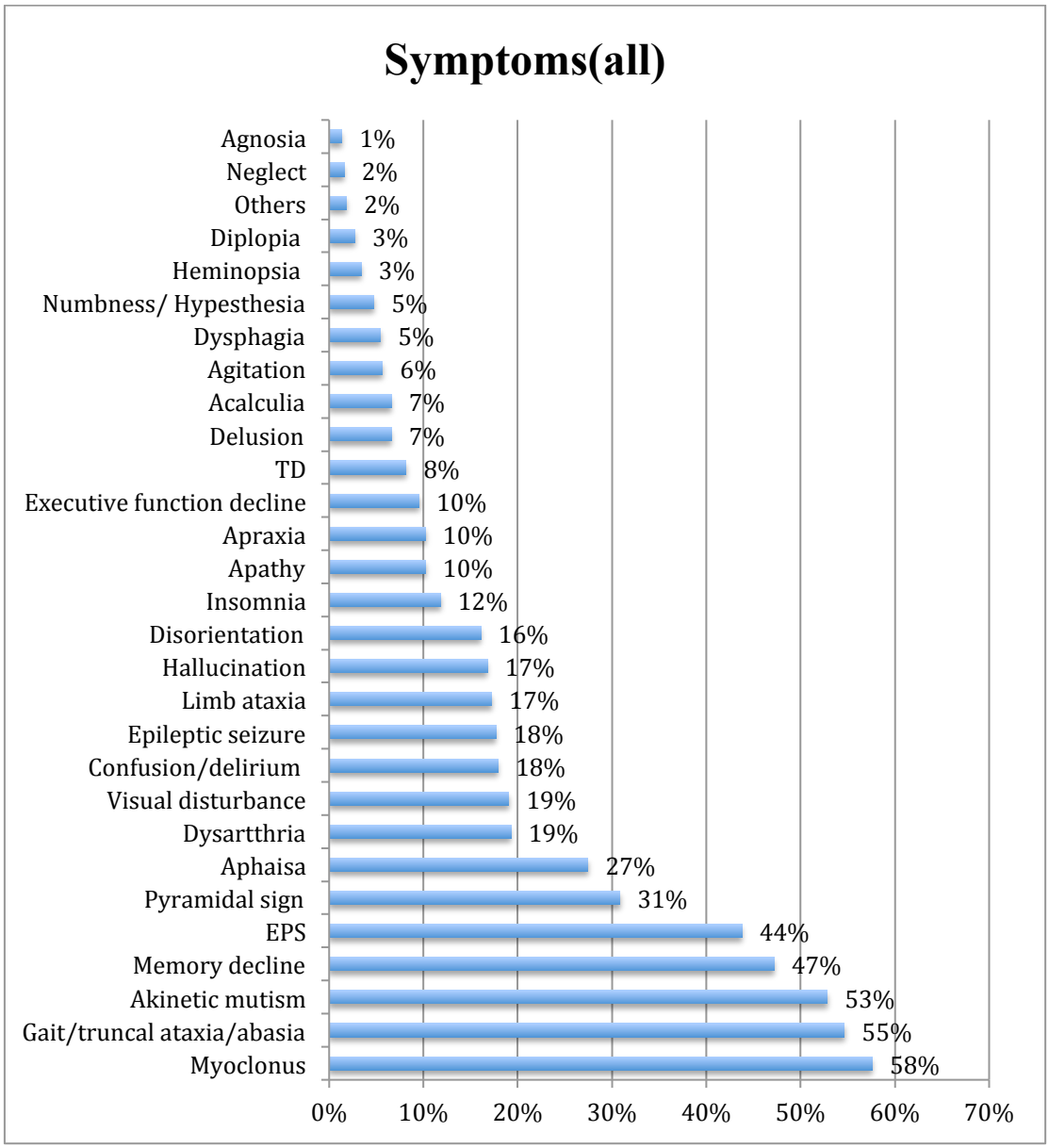
圖三、庫賈氏病發病的前驅症狀上圖新增個案、下圖整體資料庫個案

臨床症狀上的表現，在前驅症狀方面，上半年新增個案與整體資料庫都是以健忘與步履蹣跚為第一、第二位（圖三、上跟下）。

至於發病後的症狀新增個案與整體個案之間的差異比較明顯（圖四、圖五）。新增個案以記憶障礙、定向困難、構音障礙、肢體共濟失調、語言障礙為多（圖四）。跟整體資料庫的肌躍性抽搐、軀幹共濟失調、不動不語、椎體外運動系統症狀有所不同（圖五）。但是記憶障礙為共通的前五名症狀。

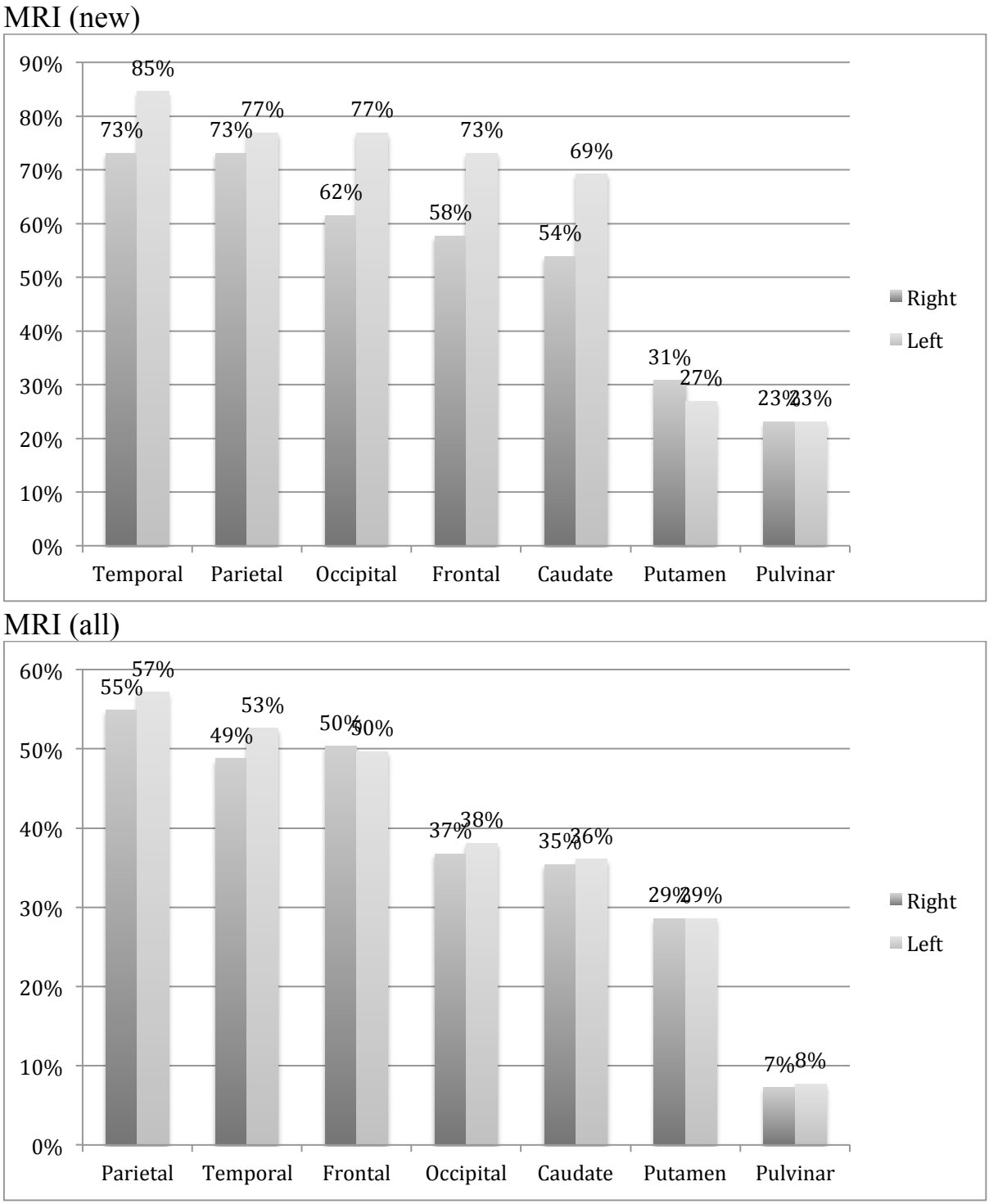


圖四、庫賈氏病新增個案的發病的症狀



圖五、庫賈氏病整體資料庫個案的發病的症狀

在 MRI 的腦區分佈上，雖然在腦皮質區有所消長，但在臨床意義上不大，通常跟臨床症狀的出現會有相關性。但是在尾核或丘腦病徵上有上昇，這一部分則需要進一步留意後續發展（圖六）。



圖六、庫賈氏病大腦 MRI 皮質緞帶病徵分佈

（上圖新增個案、下圖整體資料庫個案）

在腦波的診斷方面，不管是在與大腦 MRI 皮質緞帶病徵的間隔時間或特殊波形的表現上新增個案與整體個案都呈現類似的型態（patterns）。PSWC（週期性銳-慢複合波形）的間隔長度也在 0.8-1.1 之間非常穩定（表三）。

表三、庫賈氏病腦波型態（上表新增個案、下表圖整體資料庫個案）

EEG (new)

Onset - PSWC (D)=84.7±84

Cortical ribbon – PSWC (D)= 26.3±16

EEG tested	26	
PSWC	13	50%
Left PSWC	2	8%
Right PSWC	2	8%
Bi/General PSWC	9	35%
Slow waves	12	46%
Atyical sharp waves	12	46%
PSWC lower rage	0.85	min=0.7
PSWC higher rage	1.06	max=2

EEG (all)

Onset - PSWC (D)=97.4±289

Cortical ribbon – PSWC (D)= 35.8±62.8

EEG tested	413	
PSWC	215	52%
Left PSWC	17	4%
Right PSWC	25	6%
Bi/General PSWC	173	42%
Slow waves	134	32%
Atyical sharp waves	70	17%
PSWC lower rage	0.82	min=0.5
PSWC higher rage	1.09	max=2

2. 存活超過 2 年庫賈氏病個案資料分析

為持續辦理存活超過 2 年庫賈氏病個案之追蹤及調查，除了上述的持續對新增個案進行監測和登錄外，我們也針對更新後資料庫的所有超長存活的個案（兩年以上）進行整理和特徵分析。

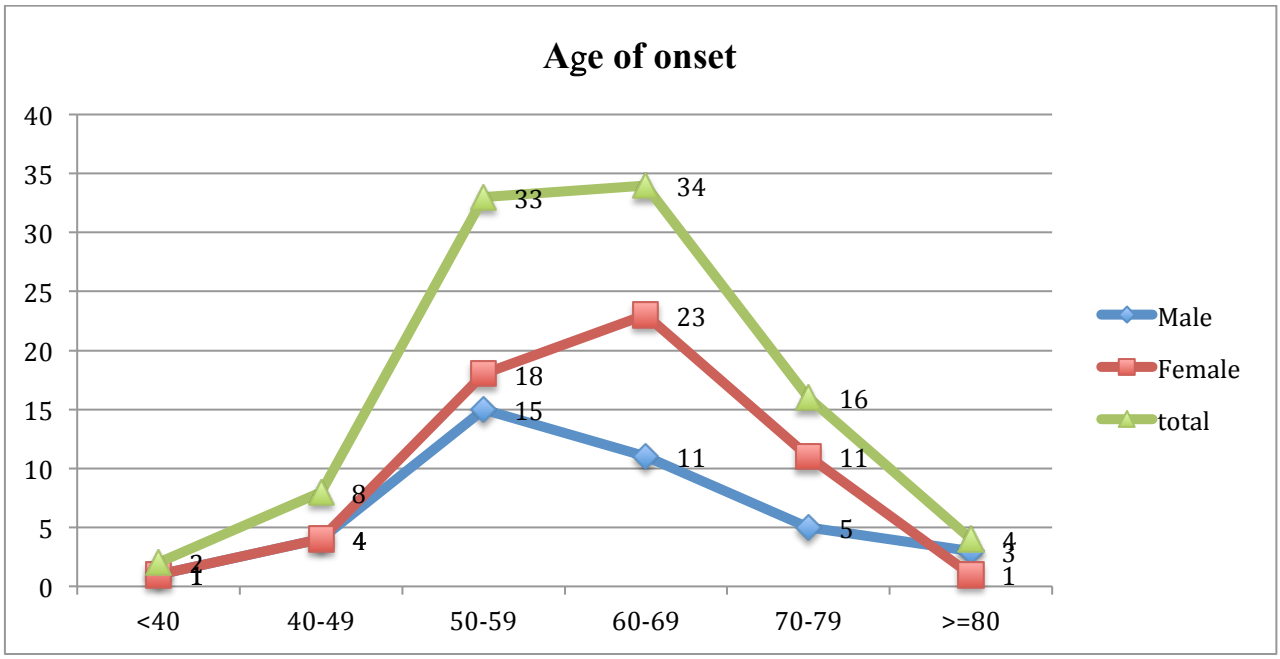
表四、超長存活個案**之性別分布**

	性別	人數	百分比
n=97	Male	39	40.2%
	Female	58	59.8%

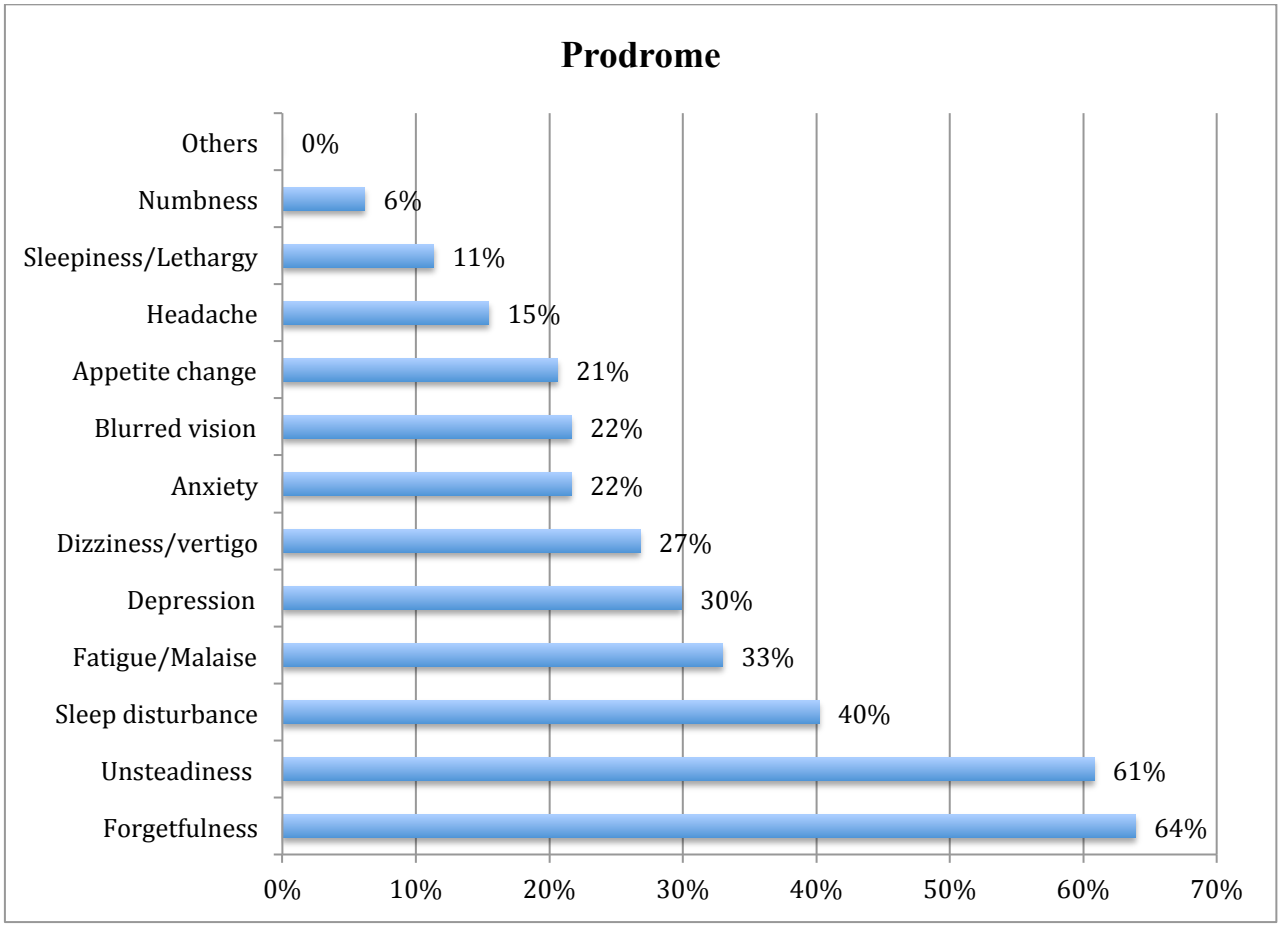
表五、發病年齡、症狀發生至診斷平均天數、平均存活天數

	Mean	SD	Max	Min
Age of Onset	60.9	10.9	84	22
Onset_Diagnosis (D)	187.1	450.1	3305	5
Onset_Death (D)	1272.5	669.6	4459	729
Onset_Death (Y)	3.5	1.8	12.2	2

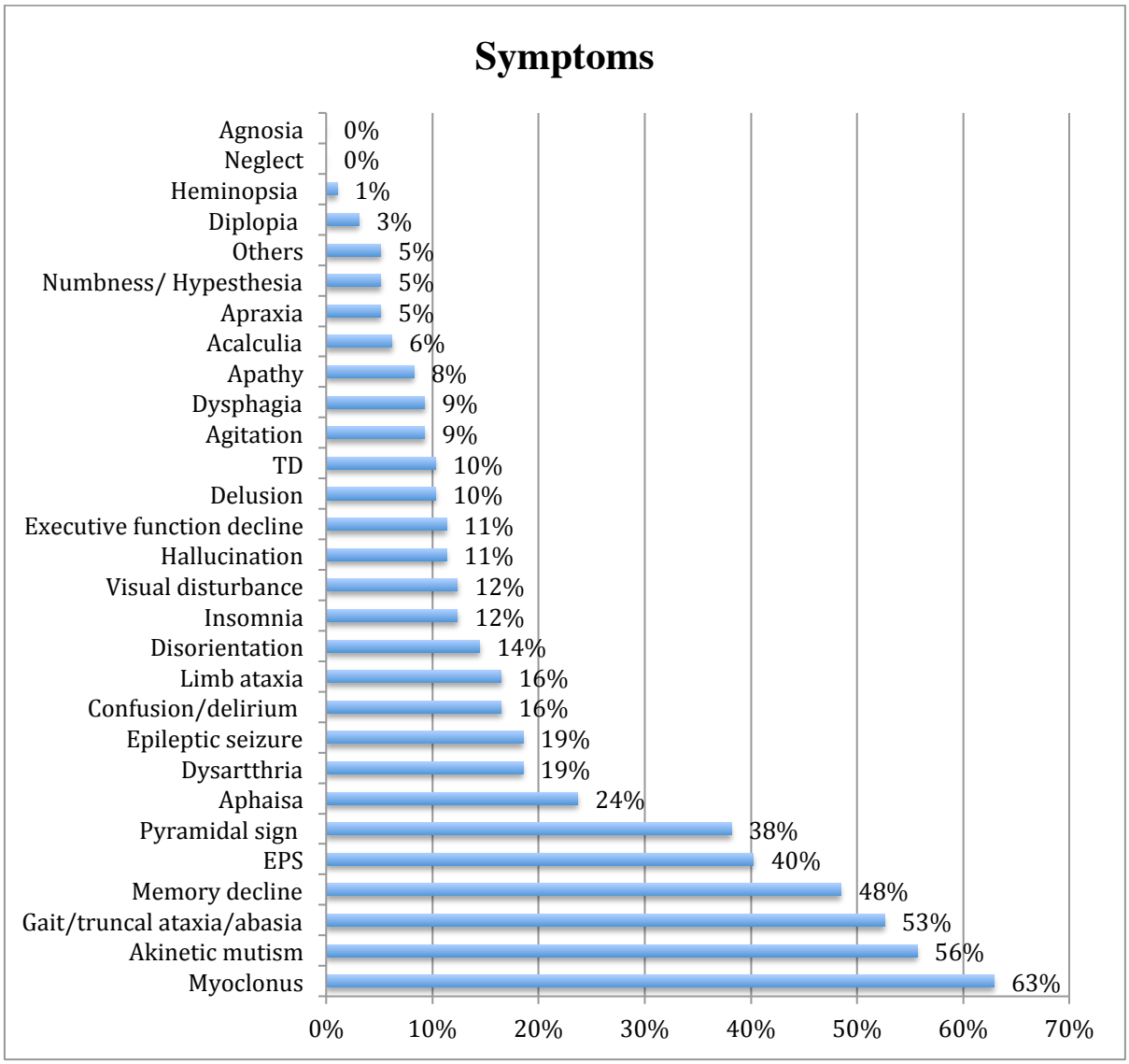
超長存活（兩年以上）女性占 59.8%比整體資料庫的 52%高，如果與存活一年以下之 38.8%相比達顯著差異（Pearson *chi* 10.776, $p = 0.001$）。也就是說女性是長期存活的保護因子。超長存活的發病年齡平均為 60.9（SD 10.9）比整體資料庫平均 66.8 歲高，與存活一年以下的 69.3（SD 8.9）達統計上顯著差異（t=6.978, $p < 0.001$）。發病的高峰從在 50-69 歲的區間（圖七），比整體資料庫的 60-79 歲的區間（圖二）約提前了 10 年。從初發徵狀開始到確診的時間超長存活的平均天數為 185.7 天比與存活一年以下的平均 75.4 天相比達統計上顯著差異（t=-2.725, $p = 0.007$）。也就是說發病年齡較低、病程比較和緩的容易存活比較長。在前驅症狀、臨床表現等質性表象上差異不大。在磁振造影的皮質緞帶病徵的分佈上並未有太大的差異。整體而言，超長存活的診斷確定性極可能為 81.6%低於存活一年以下的 90%但未達統計上顯著差異（p= 0.094）。



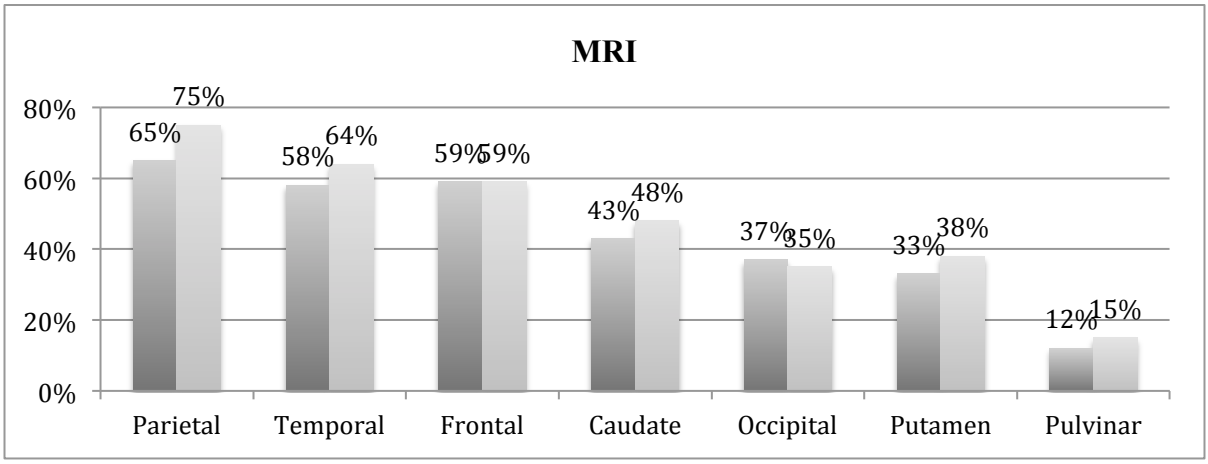
圖七、超長存活個案發病年齡分佈



圖八、超長存活個案之發病前趨症狀



圖九、超長存活個案之發病症狀



圖十、超長存活個案 MRI 皮質緞帶病徵分佈

表六、超長存活個案之腦波型態

Onset - PSWC (D)=119.3±157.1
Cortical ribbon – PSWC (D)= 36.9±52

EEG tested	78	
PSWC	40	51.3%
Left PSWC	5	4%
Right PSWC	4	5.1%
Bi/General PSWC	31	39.7%
Slow waves	37	47.4%
Atyical sharp waves	17	21.8%
PSWC lower rage	0.8	min=0.5
PSWC higher rage	1.1	max=2

腦波的表現上雖 PSWC（週期性銳慢複合波）出現平均天數較長但未達統計上顯著差異。但是 PSWC 的出現比例 43.6%（表六）遠低於存活一年以下的 60% (Pearson *chi* 5.869, *p* =0.015)。另外 14-3-3 出現的比例在長期存活組為 57.4%遠低於遠低於存活一年以下的 72.5% (Pearson *chi* 4.891, *p* =0.027)。所以 PSWC 與 14-3-3 可視為不利於長期存活的生物標記(表七)。

表七、CSF 14-3-3 之陽性比率

	Tested	positive	negative	sensitivity
All	346	229	117	66.2%
New	26	19	7	73.1%
長期存活個案	78	45	33	57.7%

3. 存活超過 2 年尚存個案追蹤調查

從通報資料庫當中尋得目未有死亡通報的個案有 9 位。其中三位極可能病例無法追蹤，但因發病的時間都在很早以前（25 年以上），以目前台灣存活最久都在 10 年左右，且目前如尚存活年紀都已超過百歲，所以可以視為都已經往生。另 6 位在衛生局協助下取得回覆的追蹤調查表，其中 3 名個案同意家訪或電訪。此 6 名病例依照追蹤狀況可以視為已達到疾病終點（國際上以不動不語即 Akinetic Mutism 或植物人狀態為臨床終點）。庫賈氏症的 prion 蛋白對於人類的腦幹（呼吸心跳的生命中樞）及下運動神經元包括橫膈等呼吸肌肉的控制，相對比較輕。在照護良好的情況下，即使以以不動不語或植物人狀態都可以存活多年。

表八、2 年以上尚存活個案追蹤表

No.	性別	發病年齡	已存活（年）	最後追蹤	語言	行動	進食	失禁	完全無自發運動	完全緘默不語	
45	男	67	26.2								發病超過20年且年紀超過百歲視同去世
79	男	62	44.0								
84	女	63	37.6								
287	女	53	12.3	2020/8/14	4	4	3	1	2008/6	2008/4	已家訪
545	女	58	5.8	2020/6/23	3	4	3	1	1	0	不同意訪視
681	男	51	2.9	2020/8/15	4	4	3	1	2017/10		已家訪
703	男	59	2.9	2020/6/9	3	4	3	1	2017/10	2017/12	不同意訪視
657	女	57	4.3	2020/6/9	3	3	3	na	2017/9	2017/9	不同意訪視
720	女	64	2.8	2020/6/9	3	4	3	1	2018	2018/4	已電訪

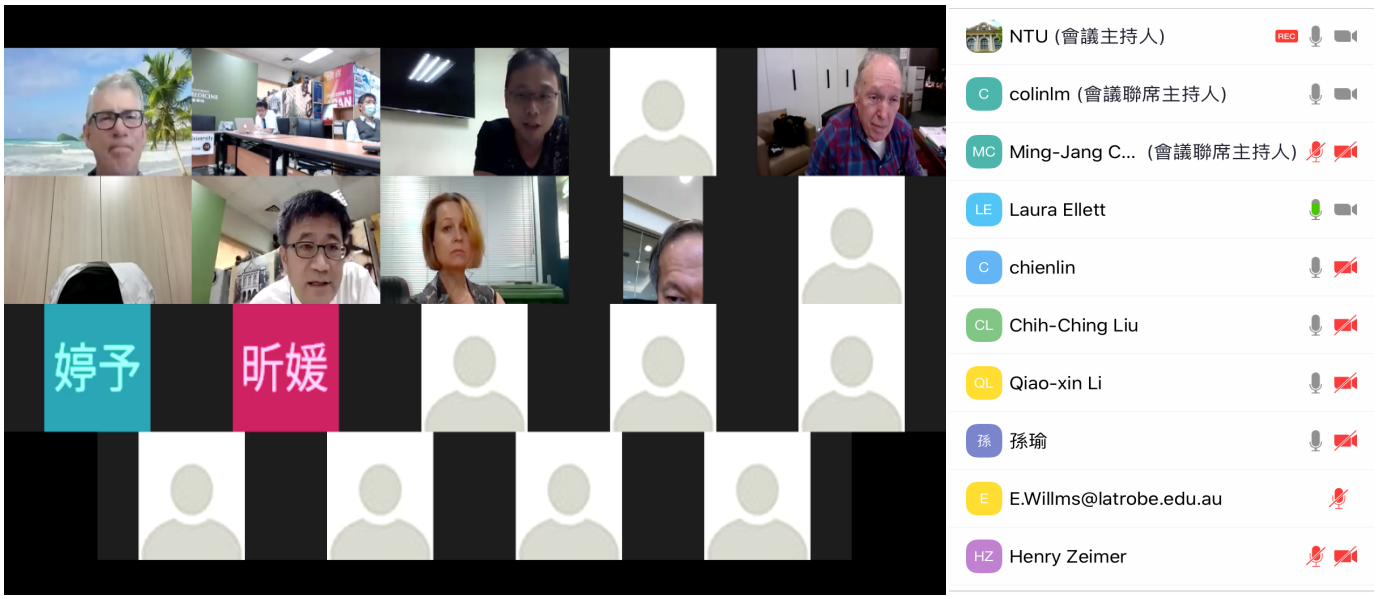
註：表中數字所代表之追蹤個案狀態，計分標準詳如附錄一

	語言能力	行動能力	進食能力	大小便失
1	尚可對話	能自行獨立行走/使用輔具行	可自行進食/偶有吞嚥困難	0=否
2	勉強對話	需他人協助行走/或使用輪椅	需他人餵食/偶有吞嚥困難	1=是
3	無法理解指令/只能發出聲	臥床但可仍可偶有自發性動	完全無法進食，需使用管	
4	完全緘默不語	完全無自發性運動	na	

（二）辦理 1 場國際視訊研討會

於 2020 年 11 月 16 日於台大醫學院辦理國際視訊研討會，內容包括我國庫賈氏症的臨床表現、流行病學、長期存活個案的保護因子、生物標記。共 30 人報名，與會者包括墨爾本大學學者、疾管署同仁以及病審會專家。由召集人張揚全教授主持，副招集人呂建榮醫師說明我國庫賈氏病通報系統之執行現況，並邀請到流行病學專家孫瑜醫師分享 20 年間全國性的調查資料，從流行病學角度探討我國庫賈氏病之概況。

國際學者則邀請澳洲墨爾本大學專精神經科學研究的 Professor Colin Masters，以及澳洲國家庫賈氏病登錄中心（ANCJDR）的負責醫師 Steven Collins 與負責整個登錄中心資料管理與行政的 Dr. Christiane Stehmann 舉辦視訊演講。藉由台澳之間的經驗交流，提升我國在通報與監測系統上的品質與效率。



視訊會議畫面

Australia-Taiwan Creutzfeldt-Jakob Diseases International Conference 議程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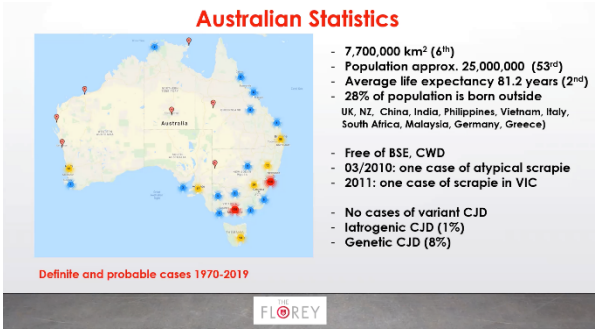
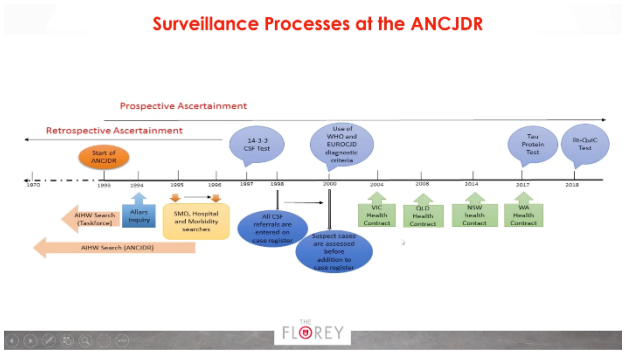
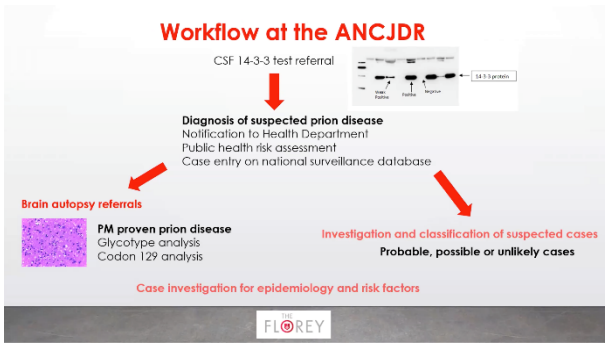
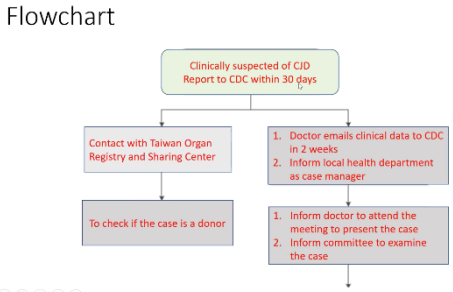


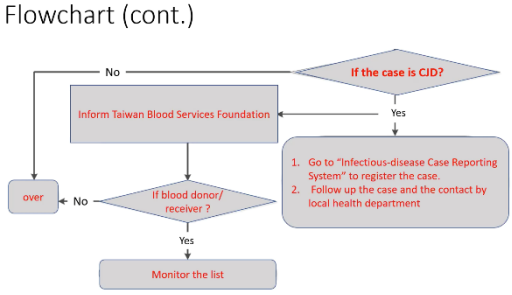


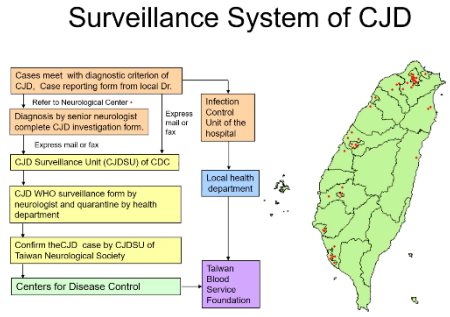


Dr. Christiane Stehmann- Australian National CJD Registry

介紹澳洲的通報流程與管理經驗，並針對病例調查表分享澳洲的作業模式，作為我們修訂時的重要參考。

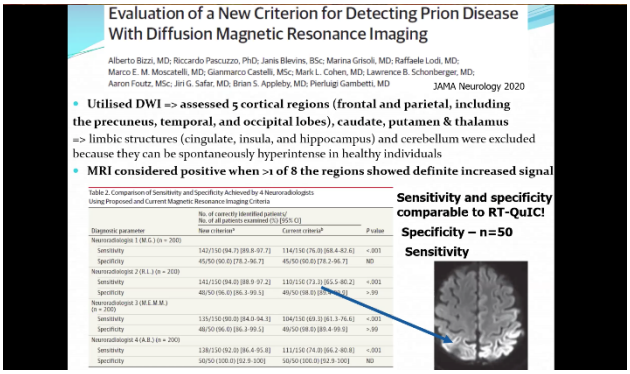


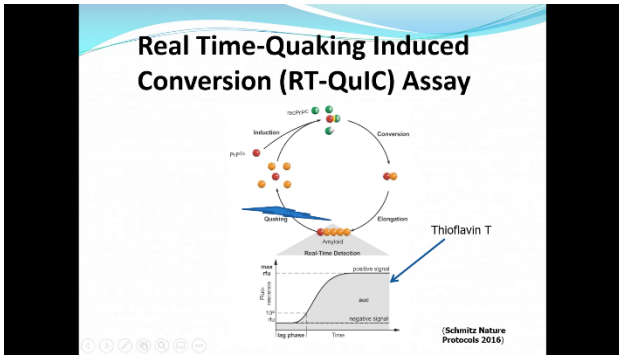


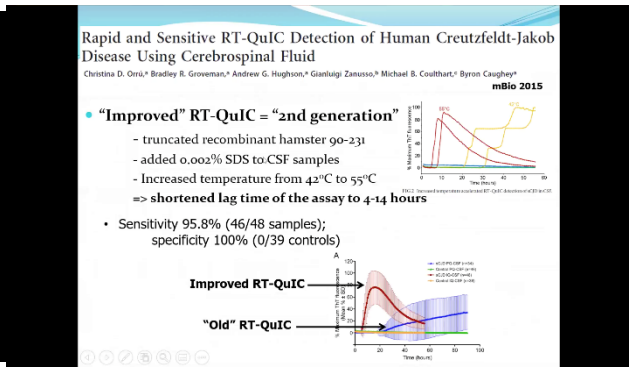


Dr. Chien-Jung Lu- Taiwan CJD Surveillance Unit

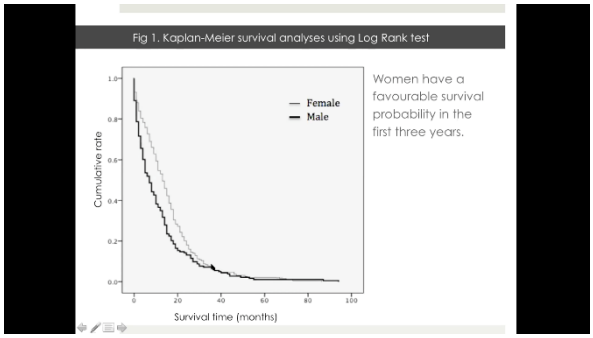
講述台灣監測系統的發展歷程與架構，與澳洲方進行交流比較。並同樣自監測與病例審查經驗中提供良好建議與討論，大力協助調查表的修訂。

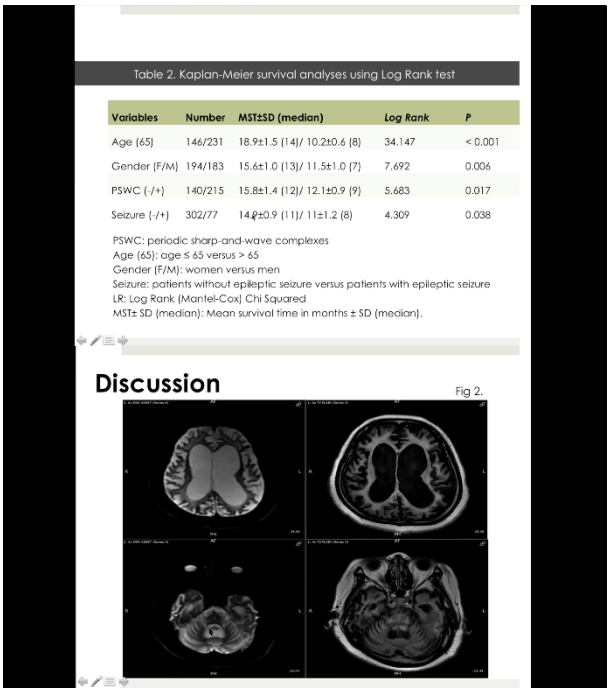




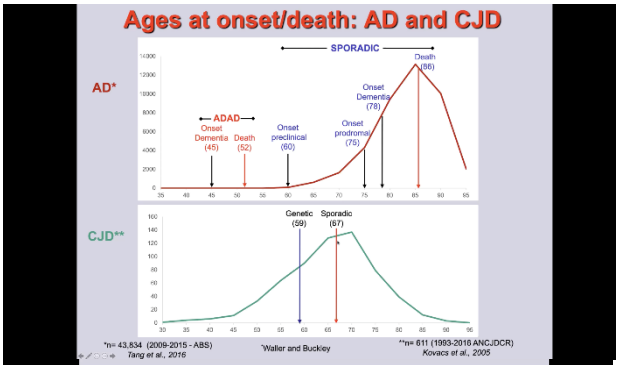


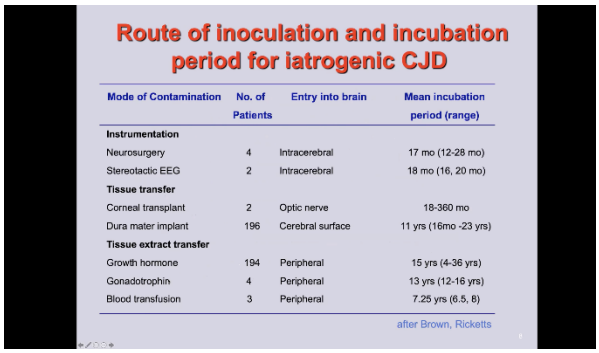
Prof. Steven Collins- Investigations for suspected sporadic Creutzfeldt-Jakob Disease
介紹各式新型診斷工具，包括新的 MRI criteria for CJD，在敏感度與特異度上可比擬 RT-QuIC，而新一代的 RT-QuIC 除了提升敏感度外更大幅縮減檢驗時間。澳洲在這方面的經驗相對成熟，可作為我國發展 RT-QuIC 的重要參考。

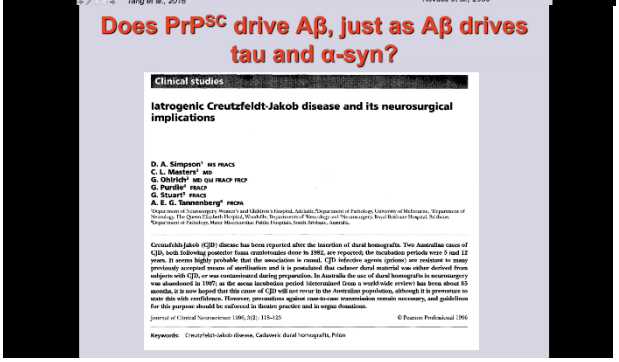




Prof. Ming-Jang Chiu- Clinical, laboratory & prognostic features of sporadic Creutzfeldt-Jakob disease – an analysis of nationwide surveillance in Taiwan
整理分析我國 400 例 sCJD 病例，得出存活率、臨床症狀與檢驗效能，作為未來防疫與診斷的依據。

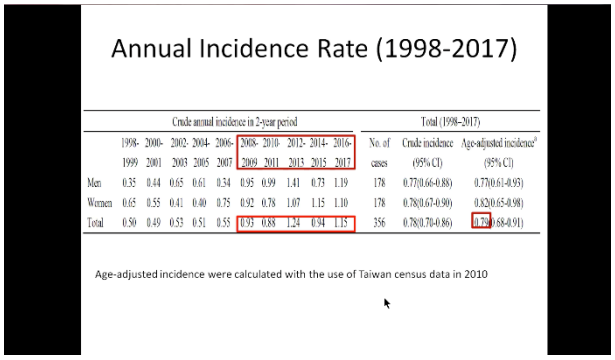


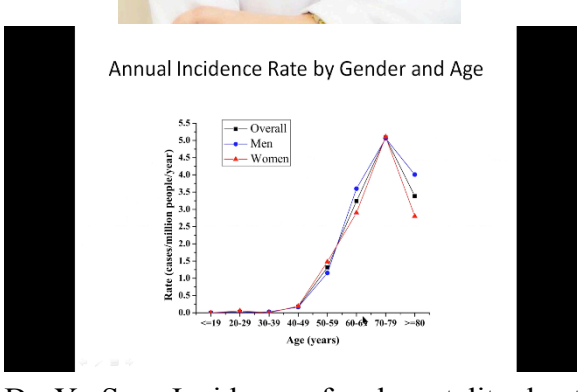


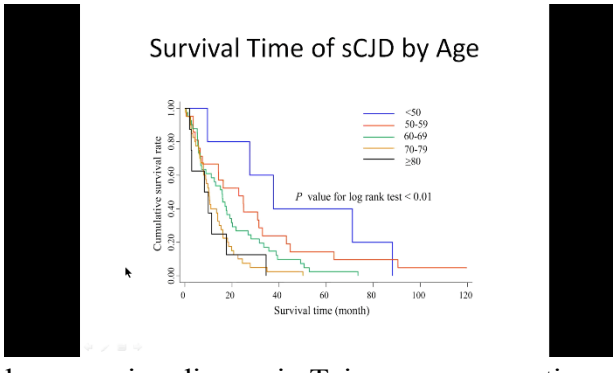


Prof. Colin L Masters-Preclinical CJD: genetic vs sporadic

探討 CJD 的臨床前階段，說明自感染到症狀出現的潛伏期其實很長，應把握這段時間。作為阿茲海默症致病因類澱粉蛋白的發現者，Colin 教授期望 CJD 也能同 AD 一般及早發現及早治療，因此開發便於檢驗的、可普及的新型生物標記是一個值得努力的目標。







Dr. Yu Sun- Incidence of and mortality due to human prion disease in Taiwan: a prospective 20-year nationwide surveillance study from 1998 to 2017

運用流行病學專業對資料庫做全面性的分析，並且將前後十年的資料進行比對，對監測系統建立以來所收集的資料做了詳盡的檢視與討論。

（三）國際期刊投稿

將 3 年來計畫中整理資料庫所得之臨床資料整合檢驗資料撰寫成論文「Clinical, laboratory and prognostic features of sporadic Creutzfeldt-Jakob disease – an analysis of nationwide surveillance in Taiwan」投稿國際期刊 *Journal of Neurology, Neurosurgery and Psychiatry*，針對本國散發型庫賈氏病之特性與檢驗效能進行全面性的分析，具未來診斷與通報上的參考價值，摘要如下：

Taiwan has started prospective nationwide surveillance of human prion diseases since 1996. We present clinical manifestations, laboratory features, and prognostic factors of 400 patients (women 52%) ascertained as definite or probable sporadic Creutzfeldt-Jakob disease (sCJD). The mean onset age was 67 ± 9.9 years old. The mean survival duration, defined from sCJD diagnosis to documented death, was 13.3 ± 14.2 (median 10) months. The most common prodromes were forgetfulness (59%) and unsteadiness (57%), and the most common onset symptoms (at the admission of diagnosis) were gait disturbance/truncal ataxia (53%) and memory decline (47%). In the end, the leading clinical symptoms were myoclonus (59%) and akinetic mutism (54%). *PRNP* polymorphism in 197 patients showed 195(99%) methionine homozygous genotype at codon 129 (M129M). The sensitivity of periodic sharp wave complexes (PSWCs) in EEG was 59.7%, with a mean delayed interval following MRIs' diffusion restriction of about 36 days. The sensitivity of CSF 14-3-3 protein was 69.7%, and the sensitivity of CSF total tau protein (a threshold of 1200 pg/mL) was 75.6%. Kaplan-Meier analyses identified four prognostic factors, including age, gender, PSWCs, and epileptic seizures. Age (dichotomized at 65 years old, HRs 0.516, $P< 0.001$) is the most crucial prognostic factor for sCJD survival time. The younger the onset ages are, the longer they live. Women (HRs 0.729, $P= 0.003$) lived longer than their men counterparts. Epileptic seizures though not commonly seen, are the only prognostic factor of clinical manifestations for sCJD survival time with HRs 0.759 ($P=0.043$, univariate).

Keywords: Cortical ribbon signs, Periodic sharp waves complexes, 14-3-3, tau, epileptic seizure.

將新型生物標記研發成果撰寫成論文投稿國際期刊，題為「Detection of prion protein in the CSF of subjects with probable Creutzefeldt-Jakob diseases – An immunomagnetic-reduction based measurement with small-molecule chemical-modification approach」，摘要如下：

Definite diagnosis of sporadic Creutzfeldt-Jakob disease (CJD) can only be made by brain pathology. However, real-time quaking-induced conversion (RT-QuIC) assays have made a considerable impact on its clinical diagnosis. This technique exploits the ability of the misfolded pathological form of prion protein (PrP^{Sc}) found in cerebrospinal fluid (CSF) of the subjects with CJD to induce conversion of normal PrP^{Sc} to the misfolded form, which subsequently aggregates. This provides indirect evidence the existence of PrP^{Sc} in the CSF of the subjects with sporadic CJD. The difficulty of the detection of PrP^{Sc} is twofold. The first is the low concentration of total prion protein and there is only conformational difference between the physiological cellular prion protein PrP^{c} and the pathological PrP^{Sc}. Therefore, the conventional detection method using monoclonal antibody is easily confounded by the existence of physiological PrP^{c}. The second difficulty is that the PrP^{Sc} aggregates very easily and the misfolded conformation may prevent it from detection by immunomagnetic reduction (IMR) assay. The task of measuring PrP^{Sc} specific prion protein is to distinguish it from PrP^{c} with identifical primary structure i.e., aminoacid sequence. In this report, we proposed an IMR-based assay with small-molecule chemical- modification approach. In brief, we used small molecule to modify the structure of the prion proteins, both PrP^{Sc} and PrP^{c}. Theoretically, acetylation of the lysine in the prion protein by acidic anhydride (Ac_2O) can reduce the amount of peptide detected by 3F4 (with MKHM epitope at 109-112) in the PrP^{c} and at the same time exposes the 109-112 epitope by acetylation of the near-by lysines (at 101, 104 and 106) to 3F4 monoclonal antibody detected by IMR. In addition, both PrP^{c} and PrP^{sc} aggregate easily which believed to be formed by disulfide bonds. Therefore we used dithioreitol (DTT) to reduce the disulfide bonds to sulfhydryl to open up the disulfide bonds and reduce the aggregation. Preliminary results from 25 CSF samples from subjects with CJD and 10 CSF from non-CJD neurological disease controls showed that by using two-way reactions, the CJD CSF samples have more hidden epitopes which mainly from PrP^{sc} than their non-CJD control CSF.

（四）修訂病例調查表

我們以相對精簡的複檢表為基礎結合調查表做編修，將原表前半部的臨床表現、症狀以及檢查結果等條目製成表 A，由通報單位在第一時間就臨床醫師能取得的資訊填寫。

而原表中 A5-A10 的欄位，比較偏向疾管署內部接收到通報進行一系列檢測後才能獲知的資訊，如 CSF 14-3-3、基因分析以及最終診斷與分類。因此我們將此部分另規劃為表 B，由監測單位填寫。

原表後半部的飲食習慣、動物接觸史等欄位我們認為比較偏向過去針對新型庫賈氏病所做的調查，一些問題其實也已不符現時所需，各條目又極為瑣碎，佔原表頁數一半以上。縱觀這 3 年研究期間所覽資料庫病例檔案，我們發現此部分資料缺漏嚴重，推究可能的原因在於，填寫的臨床醫師往往沒有時間進行太細緻的調查，或因過於細節的題目就連家屬也不知如何回答，而有諸多資料缺漏不全或謬誤的情形，進而影響研究品質。

並且從分析結果來看，其實未見此類看似高風險的生活背景或習慣與發病之間有顯著關連，如我們在第二年成果報告中危險因子分析所揭露的，畜牧、屠宰、販售或餐飲相關的行業並無顯著增加。再從病例分類來看，441 例中僅一例被判定為新型庫賈氏病，是故這些項目的需要度其實值得商榷，因此在初步修訂時我們針對相關欄位進行刪減。

完成初步的修訂後，我們設計問卷邀請病審會專家填寫，評估各題目之需要度與合適度。回收問卷共 11 份，填答專家涵蓋神經學、流行病學、病理以及神經影像。

統整後發現專家們大致同意我們保留的條目皆有其必要性，平均需要度與合適度除了一項外其餘均在 4 分以上；於問卷中也未見專家表示現行版調查表中有其他需要保留的項目。初修版調查表以及專家意見如下表。

經視訊研討會與澳洲 ANCJDR 的專家交流，以及專家會議的深入討論，得到的一項重要結論是 TOCC 相關的評估仍有其必要性，但原表中過於繁雜的項目也確實需要精簡化。

因此會後我們採納各方意見對表 A、B 中合適度有疑慮的條目再行編修，並新增表 C，在個案確定研判後由衛生單位填寫。內容著重疫調相關條目，包括較詳盡的醫療史，尤其針對工作手冊所列中高風險組織調查手術史；以及旅遊史與飲食習慣，但刪去原表的冗長條目僅保留高風險動物組織，力求簡單扼要。最後修訂完成之調查表如附件。

表	填寫者	內容	目的
A	通報單位	個案基本資料 臨床表現、症狀 基本檢查結果	掌握個案臨床資訊，協助病例研判。
B	監測單位	檢驗結果（病理、基因、CSF） 病例研判、分類	執行各項檢驗，進一步確定診斷。
C	衛生單位	醫療史、旅遊史、飲食習慣	進行疫調作業。

表九、「庫賈氏病 Creutzfeldt-Jakob Disease, CJD」病例調查表 (A)-專家問卷回覆

R1. 基本資料		**需要度（0-5 分）**	**合適度（0-5 分）**	**合適度區間**	**修正意見**
R1.1	醫院名稱	5.0	4.9	4-5	
R1.2	填表醫師姓名	4.8	4.6	1-5	負責醫師(VS)也需要和填寫醫師應該分開
R1.3	填表日期	5.0	5.0	5	
R1.4	患者姓名	4.9	5.0	4-5	有關患者的數據應放在單獨的項目中, 有關醫師的信息應為 R0
R1.5	病歷號碼	5.0	4.9	4-5	
R1.6	身分證字號	5.0	5.0	5	
R1.7	性別	4.9	5.0	5	
R1.8	職業	4.8	4.7	3-5	
R1.9	電話	4.7	4.1	0-5	聯絡人電話或主要照顧者電話
R1.10	出生日期	5.0	5.0	5	
R1.11	發病日期	5.0	4.7	2-5	很難確定哪一天發病，建議只要年、月即可
R1.12	診斷日期	4.9	4.8	3-5	
R1.13	現在住址	4.2	4.2	0-5	1.發病時住址（至少提供縣市資料） 2.患者診斷時的地址
R2. 婚姻狀況及教育程度					
R 2.1	教育程度	4.6	4.1	0-5	新增小學肄業/初中肄業/技術學校/專科
R 2.2	婚姻狀況	4.9	4.3	0-5	發病時婚姻狀況：喪偶/離婚幾年___
A1. 以往病史及外科治療史					
A1.1	神經外科手術（含硬腦膜移植）	4.8	4.8	4-5	加 日期
A1.2	人體生長激素治療	4.9	4.8	4-5	加 日期
A1.3	角膜移植	4.9	4.8	4-5	加 日期
A1.4	輸用白蛋白或其它血液製劑	4.8	4.9	4-5	加 日期

A1.5	發病前十年內曾接受過侵入性檢查		4.9	4.9	4-5	加 日期
A1.6	多發性腦梗塞症		4.7	4.4	3-5	1.是要有症狀還是沒症狀也算？ 2.臨床或影像學診斷
A1.7	阿茲海默症		4.8	4.7	3-5	如何定義 發病/診斷日期
A1.8	惡性腫瘤		4.8	4.8	4-5	發病/診斷日期
A1.9	家族中有其它 CJD 病患		4.9	5.0	4-5	與病人關係：
A1.10	其它，請註明		4.9	4.7	4-5	
A2. 前驅症狀 Prodromal symptoms						
A2.1	焦慮 Anxiety		4.6	4.4	3-5	
A2.2	頭暈、暈眩 Dizziness, vertigo		4.4	4.6	3-5	
A2.3	沒有食慾 Appetite disturbance		4.6	4.4	3-5	
A2.4	嗜眠 Lethargy		4.7	4.7	4-5	
A2.5	頭痛 Headache		4.2	4.3	3-5	
A2.6	睡眠障礙 Sleep disturbance		4.7	4.6	4-5	可以改成 "Other Sleep Disturbance; 另外加一項 insomnia
A2.7	視力模糊 Blurred vision		4.6	4.6	4-5	
A2.8	步態不穩 Unsteadiness		4.8	4.8	4-5	
A2.9	憂鬱 Depression		4.7	4.7	4-5	
A2.10	異樣感覺 Paresthesiae		4.8	4.7	4-5	
A2.11	健忘 Forgetfulness		4.1	4.2	0-5	
A2.12	倦怠 Malaise		4.4	4.4	3-5	
A3. 發病情況						
A3.1	□急性或突發症狀	□逐漸發病	5.00	5.00	5	
A3.2.1	□單側發病	□左側□右側	4.33	4.11	0-5	1.若症狀為 dementia 或 ataxia 怎麼知道是 unilateral 或 bilateral？ 2.CJD 的發病通常病人及家屬都不易察覺，等到病人症狀
A3.2.2	□雙側發病		4.33	4.11	0-5	

					明顯時很難確定什麼是單側。比如 dementia+dystonia 怎麼算是單側或雙側?
A4. 發病時症狀 Symptoms and signs at onset（門診或第一次住院時所登載之症狀）					
A4.1	認知功能障礙 Cognitive impairment	5.00	4.89	4-5	Ex: forgiveness, aphaisa,…etc
A4.2	失語症 Aphasia	4.22	4.33	0-5	如上意見
A4.3	視野或視覺功能障礙 Visual field or cortical visual dysfunction	4.89	4.89	4-5	
A4.4	複視及動眼異常 Diplopia, EOM problem	4.67	4.67	4-5	
A4.5	步態或肢體運動失調 Gait or limb ataxia	4.89	4.67	3-5	gait ataxia 和 limb ataxia 分兩項
A4.6	說話不流利 Dysarthria	4.89	4.89	4-5	
A4.7	肌躍症 Myoclonus	4.89	4.89	4-5	
A4.8	其它不自主運動 Other dyskinesia	4.89	4.78	4-5	另外加一項 parkinsonism
A4.9	椎體束症狀 Pyramidal syndrome	4.89	4.89	4-5	
A4.10	感覺異常 Sensory dysfunction	4.78	4.67	4-5	
A4.11	精神症狀 Psychiatric symptoms	4.78	4.78	4-5	
A4.12	失眠 Insomnia	4.78	4.78	4-5	
A4.13	其它 （請註明）	4.75	4.75	4-5	可以另外加 confusion 一項
A5. 病程中出現的症狀 Symptoms and signs duration course（住院或追蹤過程期間） Absent/ Mild or equivocal/ Severe or definite					
A5.1	失智症 Dementia	4.44	4.44	0-5	
A5.2	肌躍症 Myoclonus	5.00	4.89	4-5	
A5.3	巴金森症候群 Parkinsonism	4.89	4.89	4-5	
A5.4	啞症運動不能狀態 Akinetic mutism	5.00	4.89	4-5	
A5.5	失語症 Aphasia	4.78	4.89	4-5	
A5.6	失用症 Apraxia	4.89	4.67	3-5	如何定義 mild 或 severe
A5.7	意識混亂 Confusion	4.67	4.89	4-5	

A5.8	視野或視覺功能障礙 Visual field or cortical visual dysfunction		4.78	4.44	2-5	如何定義 mild 或 severe
A5.9	複視及動眼異常 Diplopia, EOM problem		4.78	4.78	4-5	如何定義 mild 或 severe
A5.10	步態或肢體運動失調 Gait or limb ataxia		4.78	4.67	3-5	gait ataxia 和 limb ataxia 分兩項
A5.11	說話不流利 Dysarthria		4.78	4.78	4-5	
A5.12	癲癇發作 Seizure		4.89	4.78	4-5	
A5.13	其它不自主運動 Other dyskinesia		4.78	4.89	4-5	
A5.14	椎體束症狀 Pyramidal syndrome		4.67	4.78	4-5	
A5.15	感覺異常 Sensory dysfunction		4.78	4.89	4-5	
A5.16	精神症狀 Psychiatric symptoms		4.78	4.67	3-5	如何定義 mild 或 severe
A5.17	失眠 Insomnia		4.67	4.89	4-5	
A5.18	其它 （請註明）		4.75	5.00	5	失智症宜列入 A5.6 之後
A6. 檢查結果						
A6.1	EEG		5.00	5.00	5	加 left or right; Hz 數
	□僅檢查一次	□檢查兩次以上				
A6.1.1	EEG 結果		4.89	5.00	5	
	□ slow wave activity	□ unilateral PSWC				
	□ bilateral PSWC	□ normal				
	□ other (or atypical)					
A6.2	磁振造影(MRI)		3.89	3.78	0-5	1.建議把 only DWI 改為 Incomplete data 2.要求通報醫師提供完整的資料應該不必列這一項，或把 only DWI 改為 incomplete data
	□ only DWI					
	□ complete data					
A6.2.1	MRI 結果		5.00	5.00	5	
	□ normal					
	□ abnormal（請回答以下問題）					

A6.2.1.1	皮質緞帶病徵		5.00	4.89	4-5	1. 加 Left, right 2. 改為 Frontal only, Temporal only, Parietal only, Occipital Only; FT or FT junction; TO or TO junction, TP or TP junction, PTO junction
	□ Frontal	□ Parietal				
	□ Temporal	□ Occipital				
A6.2.1.2	皮質下高密度變化		4.89	5.00	5	加 Left, right
	□ Caudate	□ Pulvinar				
	□ Putamen					
A6.2.1.3	其他		5.00	5.00	5	一些患者有非對稱性 MR 發現
A6.3	其它檢查項目					
A6.3.1	CSF		4.89	4.78	4-5	承上，請列出所做的 CSF test, 並標註 negative or positive finding ; 改為 6.3.1.1
A6.3.2	其它自體免疫性腦炎(autoimmune encephalitis) 或腫瘤伴生腦炎 (paraneoplastic encephalitis)相關檢驗		4.78	4.67	4-5	我們需要具體說明已完成多少種類型??或肯定需要某些類型??
A6.3.3	Prion test		5.00	4.78	4-5	改為項目 A.6.3.1.2. 1433: protein ; 請加 A6.3.2 Serum test : A6.3.2.1: r/o autoimmune encephalitis or paraneoplastic encephalitis positive or negative finding. A.6.3.2.2: 1433 protein
A6.3.4	CT		4.56	4.67	4-5	建議 A6.3.4-7 改為 option 即可
A6.3.5	Gene study		4.89	5.00	4-5	
A6.3.6	Brain biopsy		4.89	4.67	3-5	可列但未必可行
A6.3.7	Autopsy		4.78	4.67	2-5	極度困難

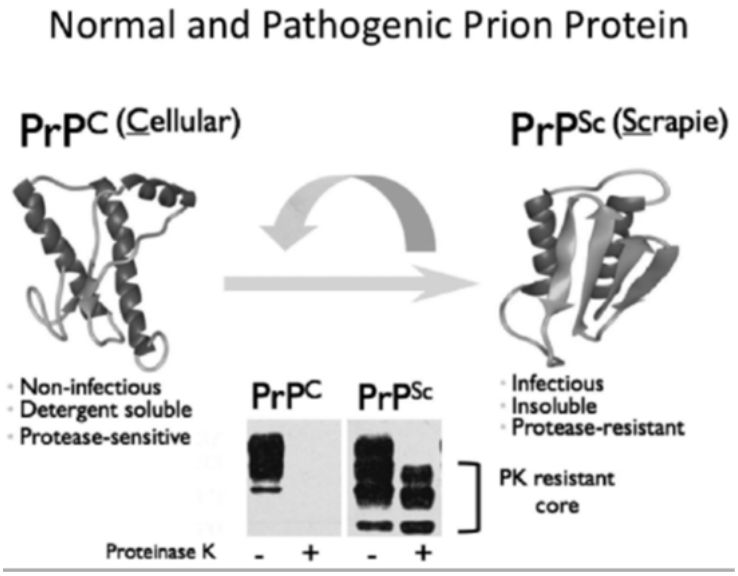
表十、「庫賈氏病 Creutzfeldt-Jakob Disease, CJD」病例調查表 (B)-專家問卷回覆

B1. 神經病理學		**需要度（0-5 分）**	**合適度（0-5 分）**	**合適度區間**	
B1.1	病理解剖（Post mortem autopsy）	4.60	4.20	2-5	In Taiwan it is not practicable
	如果有做，請回答以下問題：				
B1.2	確定 CJD 診斷	5.00	4.83	4-5	
B1.3	神經病理學的表現（post mortem）:	5.00	5.00	5	
B1.3.1	Neuron loss（神經元喪失）	4.83	4.83	4-5	
B1.3.2	Gliosis（神經膠質過多）	5.00	5.00	5	
B1.3.3	Spongiform change（海綿樣變化）	5.00	5.00	5	
B1.3.4	Immunohistochemically positive	4.83	4.83	4-5	Positive immunochemical stain
	如果有，請回答以下二題：				
B1.3.4.1	-immunostaining	5.00	5.00	5	immunocheminal stain
B1.3.4.2	-Westwrm blot test	4.83	4.83	4-5	Western blot
B1.3.5	Scrapie associated fibrils	4.67	4.67	4-5	
B1.3.6	Amyloid immunostaining	4.50	4.67	4-5	
B1.4	Biopsy	4.83	4.50	3-5	
	如果有做，請回答以下的問題：				
B1.5	確定 CJD 診斷	4.83	5.00	5	
B1.6	神經病理學的表現（biopsy）	4.83	4.80	4-5	
B1.6.1	Neuron loss（神經元喪失）	4.83	5.00	5	
B1.6.2	Gliosis（神經膠質過多）	4.83	5.00	5	
B1.6.3	Spongiform change（海綿樣變化）	4.83	5.00	5	
B1.6.4	Immunohistochemically positive	4.83	4.83	4-5	Positive immunochemical stain
	如果有，請回答以下二題：				
B1.6.4.1	-immunostsining	4.83	4.83	4-5	immunostaining / immunocheminal stain
B1.6.4.2	-Westerm blot test	4.83	4.83	4-5	Western blot

B1.6.5	Scrapie associated fibrils	4.83	4.83	4-5	
B1.6.6	Amyloid immunostaining	4.83	4.83	4-5	
B2. Prion protein gene analysis（Chrom 20）					
B2.1	Prion protein gene analysis（Chrom 20）	4.83	4.83	4-5	
	如果有做，請回答以下的問題：				
B2.1.1	Mutation present	4.83	4.83	4-5	
B2.1.1.1	如果有,specify PRNP mutation	4.83	4.83	4-5	
B2.1.2	Condon 129 polymorphism	4.83	4.83	4-5	
B2.1.2.1	Met/Met	4.83	4.83	4-5	
B2.1.2.2	Val/Val	4.83	4.83	4-5	
B2.1.2.3	Mel/Val	4.83	4.83	4-5	
B3. Creutzfeldt-Jakob disease 分類					
	（Definite）Probable Possible				
B3	CJD 分類（依據診斷標準）	4.83	4.83	4-5	
B4.**遺傳性庫賈氏病 Genetic Creutzfeldt-Jakob disease**					
B4	Genetic CJD	4.83	4.83	4-5	
B4.1	確定或極可能 CJD 患者且其一等親中亦有確定或極可能病例	4.83	4.83	4-5	
B4.2	神精精神方面的異常且有特異性的 PrP 基因（PRNP）突變	4.83	4.83	4-5	
B5. 散發性庫賈氏病 Sporadic Creutzfeldt-Jakob disease					
B5	Sporadic CJD	4.83	4.83	4-5	
B6. 醫源性庫賈氏病 Iatrogenic Creutzfeldt-Jakob disease					
B6	Iatrogenic CJD	4.83	4.83	4-5	B6 提供 Hx; B7. Vriant CJD , 提供 Hx

（五）庫賈氏病新型生物標記的開發與研究

為了開發普利昂蛋白蛋白的檢測技術我們進行了一系列實驗，由於普利昂蛋白的定量，傳統上是建立在對於 protienase K 的非特異性切除（溶解蛋白質）的抵抗性(resistance to proteinase K， 如圖十一)。



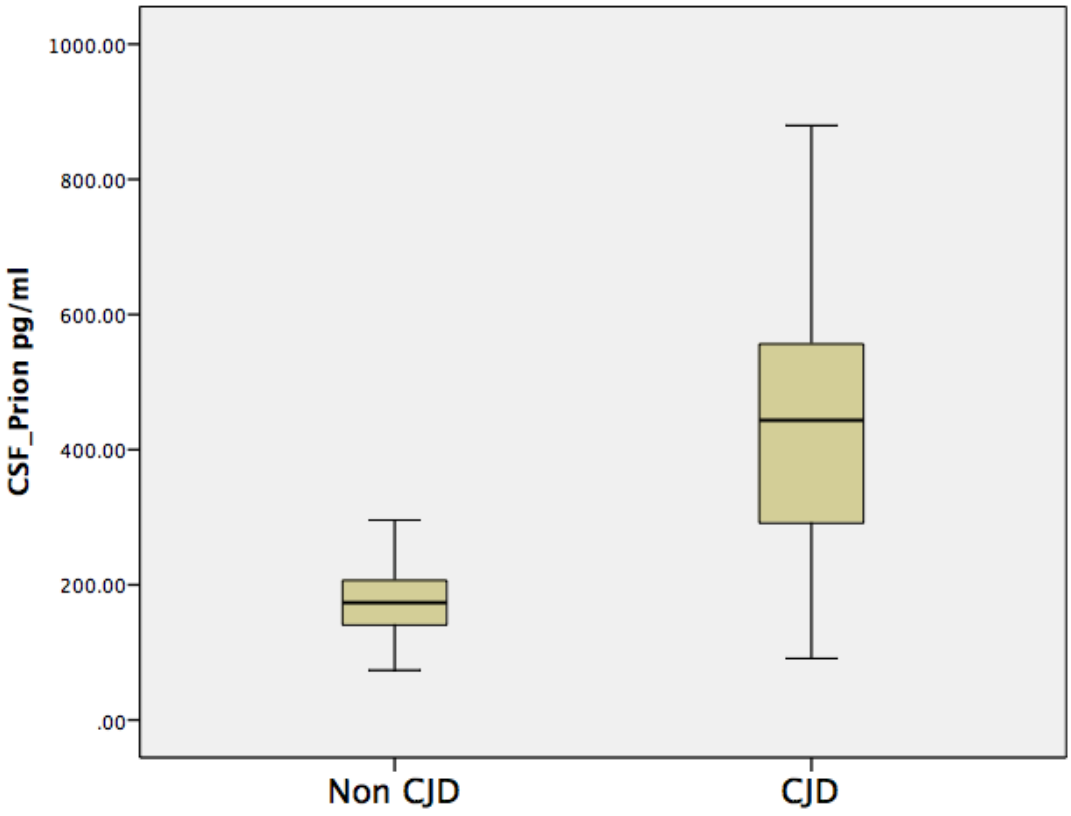
圖十一、正常細胞普利昂蛋白與病理性普利昂蛋白對於 Proteinase K 的抵抗性

在第二年的計畫裡我們已經完成了 IMR（磁減量），量測普利昂蛋白的準備，利用單株抗體(MAB1562，Anti-Prion Protein Antibody, a.a. 109-112, clone 3F4；Epitope: Human Prion protein) 製作磁珠建立了標準曲線，在去年年底，初步也應用了庫賈氏病的腦脊髓液與非庫賈氏病的神經退化性疾病的的腦脊髓液進行普利昂蛋白濃度的量測和比較。

我們曾針對庫賈氏病的腦脊髓液 35 組及非庫賈氏病的神經退化性疾病的的腦脊髓液 12 組量測普利昂蛋白濃度，結果在庫賈氏病的腦脊髓液的濃度為 473.7±176 pg/ml 而在對照組為 172.9±59.5 pg/ml 兩組濃度達到顯著差異（t=-5.08, $p < 0.001$）（圖十二）。

進一步以 14-3-3 蛋白質（西方墨點的檢驗）分陽性、陰性兩組則兩組之間的腦脊髓液普利昂蛋白濃度未達統計上顯著差異。由於本實驗未加入

Proteinase K 所以所測得的普利昂蛋白是總量（正常細胞普利昂蛋白加上病理性普利昂蛋白的總和）。



圖十二、腦脊髓液的普利昂蛋白質濃度在庫賈氏病與非庫賈氏病對照組

為了進一步量測Proteinase K resistant 的蛋白我們首先是利用重組普利昂蛋白尋找Proteinase K 作用的最佳條件。包括濃度(Proteinase K, 30、120、250μg/ml)、反應時間（0、30、60、90、120、150、210 min 之後加入 PMSF 去終止 Proteinase K 的作用），甚至反應溫度。

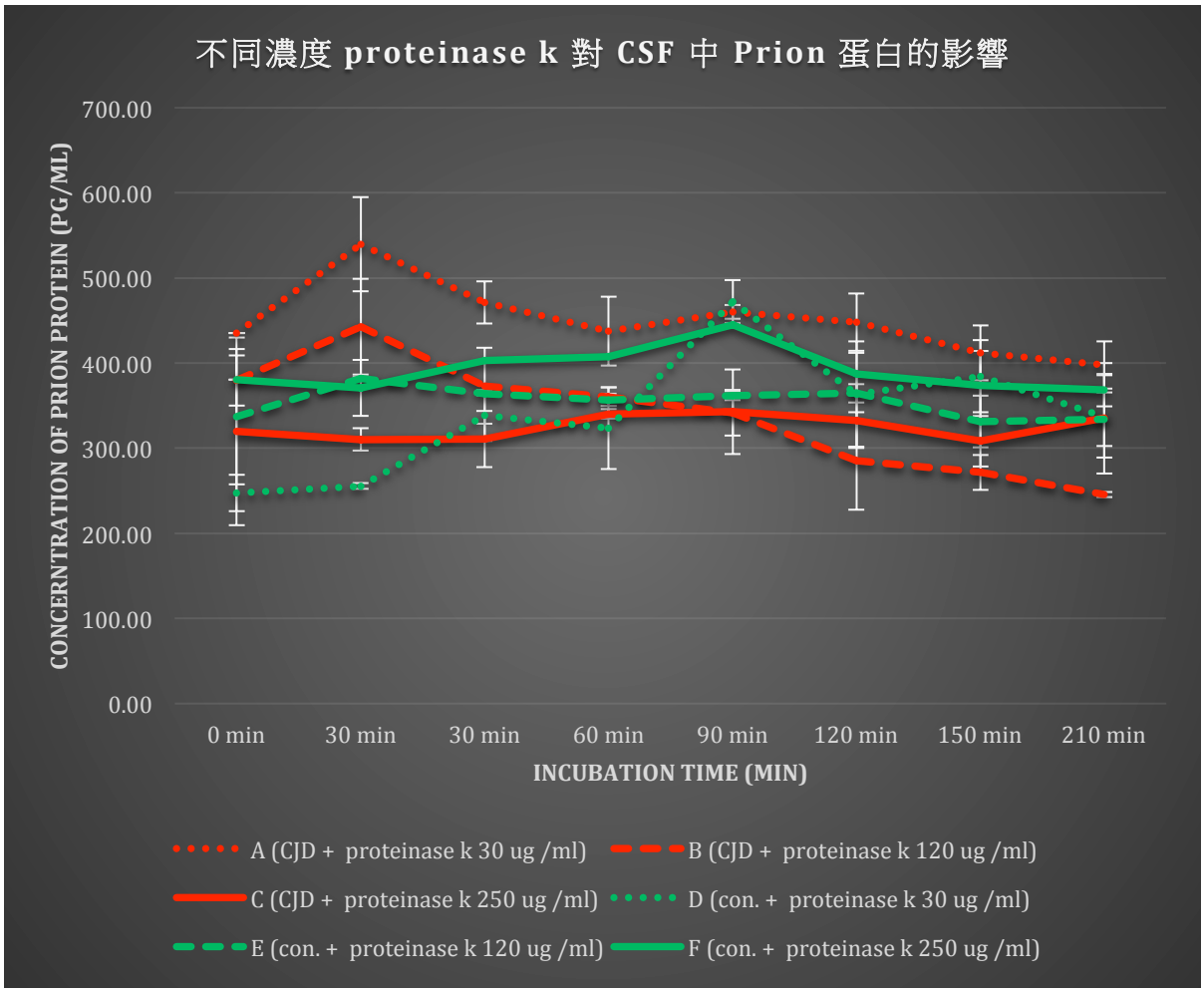
所得 Proteinase K 作用的時間-濃度的結果見見表九、十。觀察圖十三的 A 及 B 皆是數值皆是先上升後下降，推測可能是病理性普利昂蛋白會容易形成聚合體。.

表十一、測試 Proteinase K 水解庫賈氏病 CSF 中檢體 Prion 蛋白的能力

Proteinase K 濃度 (μg/ml)	30		120		250	
Reaction time	Mean	SD	Mean	SD	Mean	SD
0 min	435.10	######	379.68	29.58	319.57	110.16
30 min	539.57	55.19	442.79	56.44	310.40	13.41
30 min	471.30	24.83	373.31	44.76	310.48	33.01
60 min	437.64	40.46	360.40	10.95	340.40	5.95
90 min	460.35	8.21	341.63	26.74	342.69	49.52
120 min	448.00	33.55	285.14	57.38	332.52	32.51
150 min	412.03	32.23	271.51	20.45	308.29	29.80
210 min	397.88	27.93	245.62	3.24	335.30	65.06

表十二、測試 Proteinase K 水解對照組 CSF 中檢體 Prion 蛋白的能力

proteinase k 濃度 (ug/ml)	30		120		250	
Reaction time	Mean	SD	Mean	SD	Mean	SD
0 min	247.39	21.64	336.86	79.58	380.46	######
30 min	255.44	3.46	382.06	1.22	371.01	33.00
30 min	338.54	29.98	364.05	1.94	402.68	######
60 min	323.46	48.22	356.72	7.06	407.83	######
90 min	471.99	25.22	361.83	5.34	444.66	######
120 min	363.61	62.06	364.55	10.77	387.26	24.95
150 min	384.58	42.30	331.24	30.30	373.76	40.23
210 min	337.36	48.45	334.22	31.60	368.32	19.11

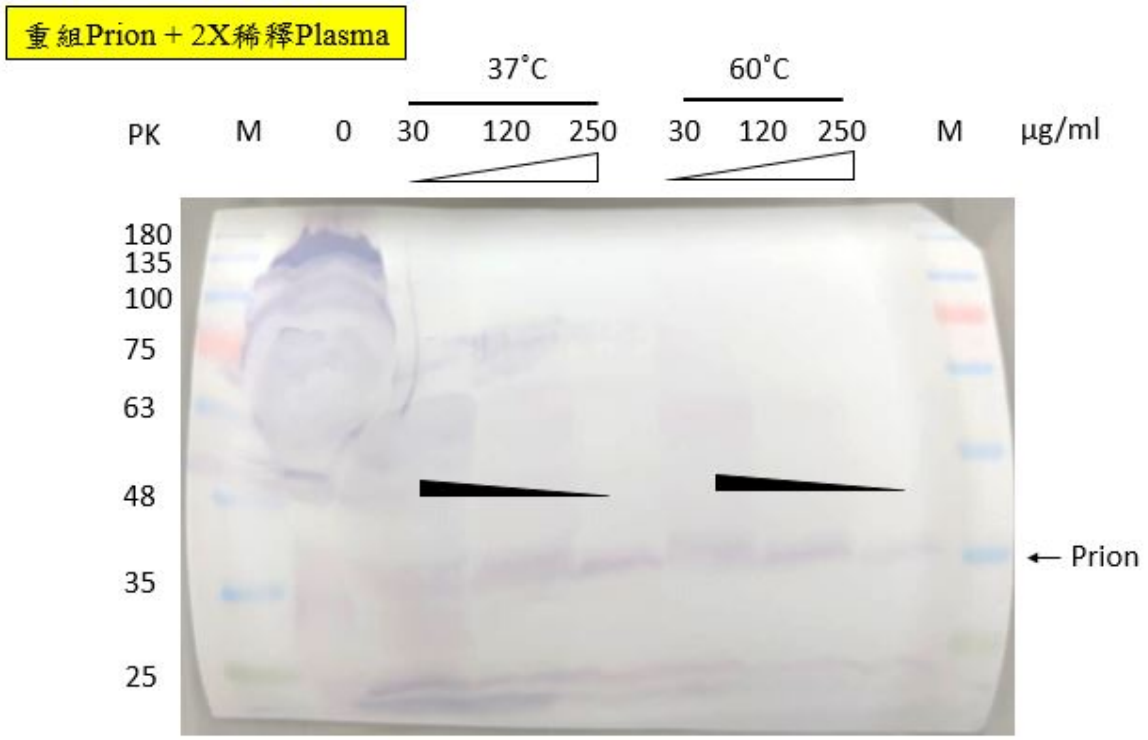


圖十三、不同濃度 proteinase k 對 CSF 中 Prion 蛋白的影響

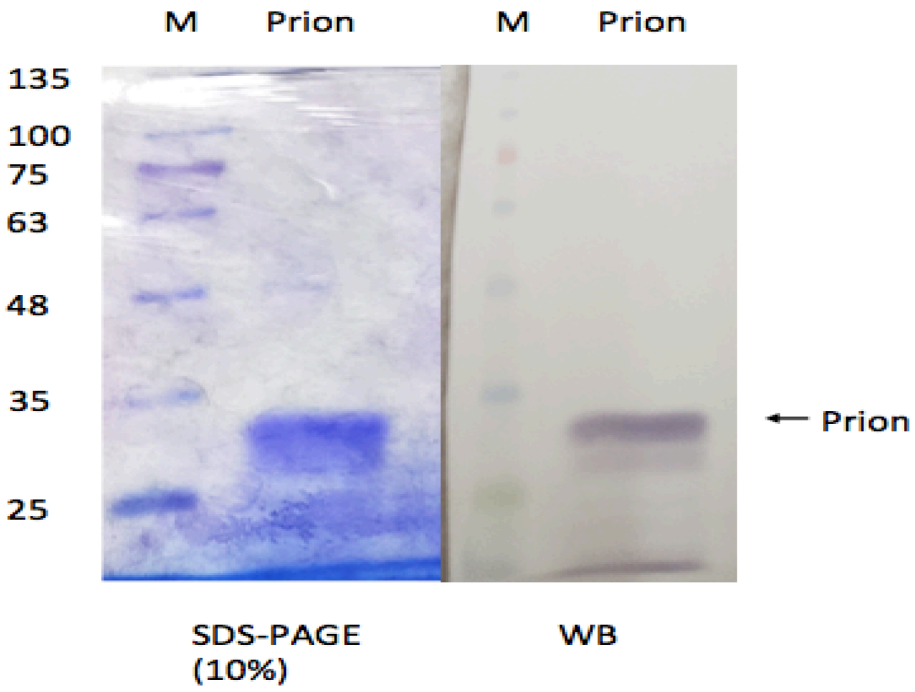
因為 Proteinase K 使大聚合體先變成小蛋白，這時 epitope 可能會有較多的暴露出來，之後再被 PK 繼續作用而分解。而在高濃度 Proteinase K 的 C 一開始的普利昂蛋白濃度就偏低了，表示其溶解力的確與 Proteinase K 的濃度相關。反之 D、E、F 對照組的濃度不是數值幾乎持平或在 90 分鐘才向上升，是否表示正常細胞普利昂蛋白經溶解之後，切割下來的 peptides 仍可能被 IMR 單株抗體磁珠所偵測(相同的單株抗體針對 aa 109-112) 。或者我們所用的 Proteinase K 是否效能有問題。

為了確認 Proteinase K 是否能水解 plasma 中 普利昂蛋白的實驗，並瞭解溫度對於反應效能的影響。我們先放下 IMR，應用重組普利昂蛋白，

以及西方墨點方法去偵測。設計了下列實驗（三種 Proteinase K 濃度與上一個實驗相同 30、120、250μg/ml，兩種反應溫度 37、60 度 C）。結果顯示 60 度 C 效果比 37 度 C 較好但是差異不大。相同的從普利昂蛋白+ plasma 的數據，可以得知 Proteinase K 的濃度的確與重組普利昂蛋白的水解情形成正比。另外從普利昂蛋白+ plasma 的數據，可以得知如果要把所有的蛋白都水解，可能還需要延長反應時間（圖十四）。最後為了確定單株抗體辨識重組普利昂蛋白的有效性又跑了一次西方墨點（圖十五）。



圖十四、重組普利昂蛋白以西方墨點檢測在不同溫度、Proteinase K 濃度的結果



圖十五、比較 SDS-PAGE 與西方墨點檢測單株抗體偵測重組普利昂蛋白

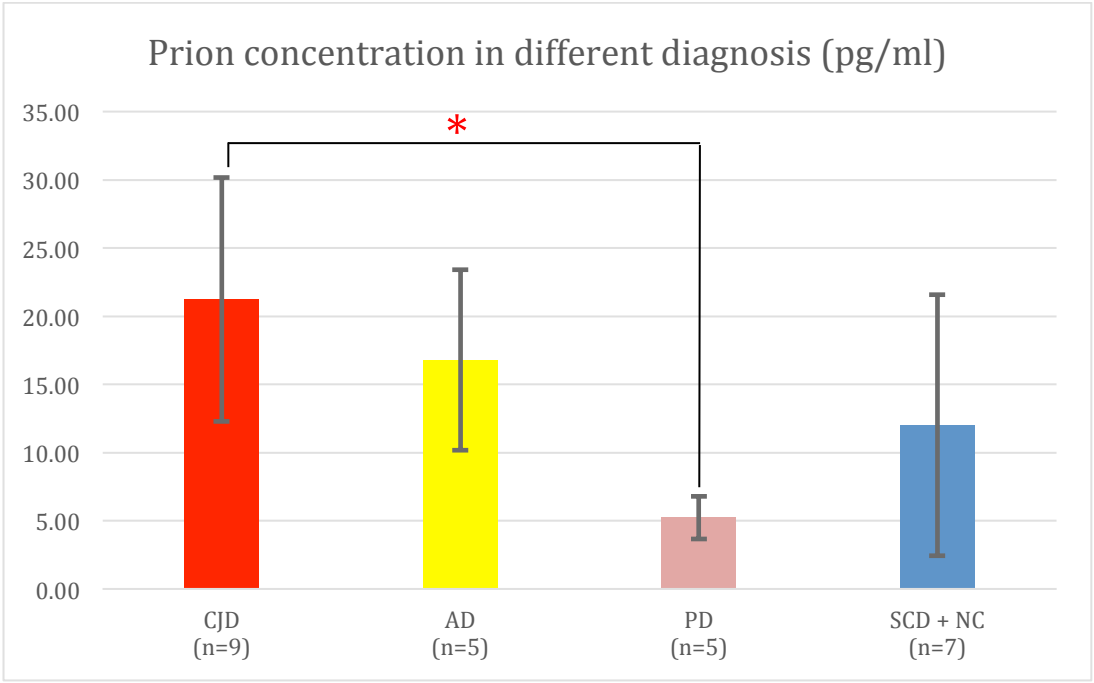
綜上所述，目前我們所用的 Proteinase K，單株抗體的效能以重組普利昂蛋白，以及西方墨點方法都證實有效。

目前比較能解釋的是細胞普利昂蛋白也有可能會跟血漿或腦脊髓液的其他蛋白結合（或者細胞普利昂蛋白也會有較弱的自我聚集的傾向），這些都可以被 Proteinase K 溶解。另外病理性普利昂蛋白的聚集力量雖然強大，但是有些片段也是會被 Proteinase K 所溶解。因此經過 Proteinase K 作用以後仍會有些 Proteinase K resistant 的部份遺留下來。Proteinase K。其主要的切割位點是脂肪族胺基酸和芳香族胺基酸的羧基端肽鍵。由於其廣泛地的切割能力，在實驗室中很常用屬於絲氨酸(serine)蛋白酶。然而目前所用的單株抗體針對的 Epitope 是普利昂蛋白 aa 109-112。從我們使用的應用重組普利昂蛋白的胺基酸序列（圖十六）來看，的確有可能 Proteinase K 會切下一段單株抗體仍可偵測的片段而影響到 IMR 的量測濃度。

```
                                KKRPKPGG WNTGGSRYPG QGSPGGNRYP
PQGGGGWGQP HGGGWGQPHG GGWGQPHGGG WGQPHGGGWG QGGGTHSQWN
KPSKPKTNMK HMAGAAAAGA VVGGLGGYML GSAMSRPIIH FGSDYEDRYY
RENMHRYPNQ VYYRPMDEYS NQNNFVHDCV NITIKQHTVT TTTKGENFTE
TDVKMMERVV EQMCITQYER ESQAYYQRGS
```

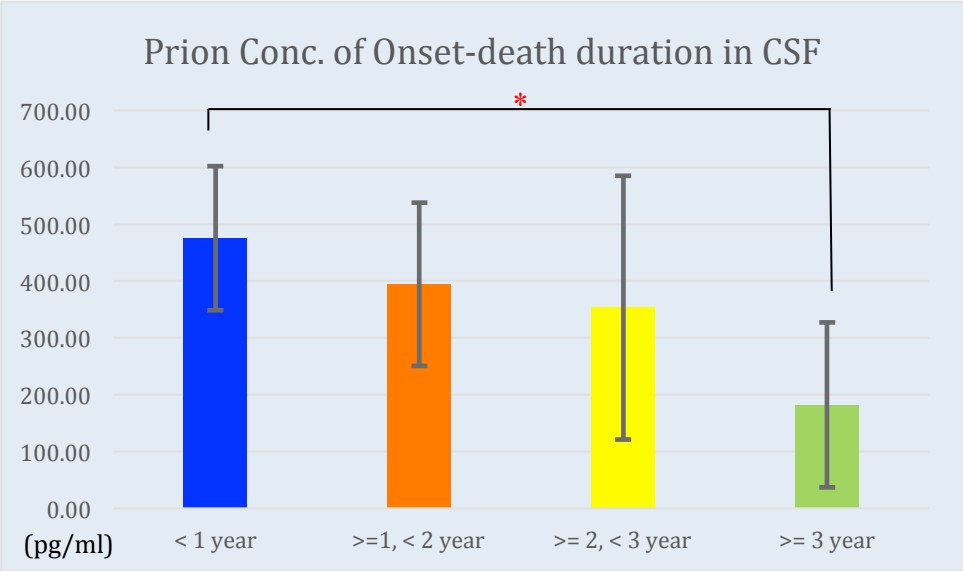
圖十六、應用重組普利昂蛋白的胺基酸序列

由於之前在未使用 Proteinase K 的時候，IMR 所偵測腦脊髓液的結果可以區分出庫賈氏病與非庫賈氏病對照組。所以我們就進行血液的檢測不同診斷組別的對照組的普利昂蛋白濃度（圖十七）。由於個案數很少目前只顯示與巴金森病患者組的血液利昂蛋白濃度有顯著差異。另一個值得注意的是阿茲海默症組的濃度比較高接近於庫賈氏病患者的濃度。這個跟目前在腦脊髓液的研究是一致的。



CJD 與 PD 達顯著差異 ($p = 0.014$)，與其他組均未達顯著差異

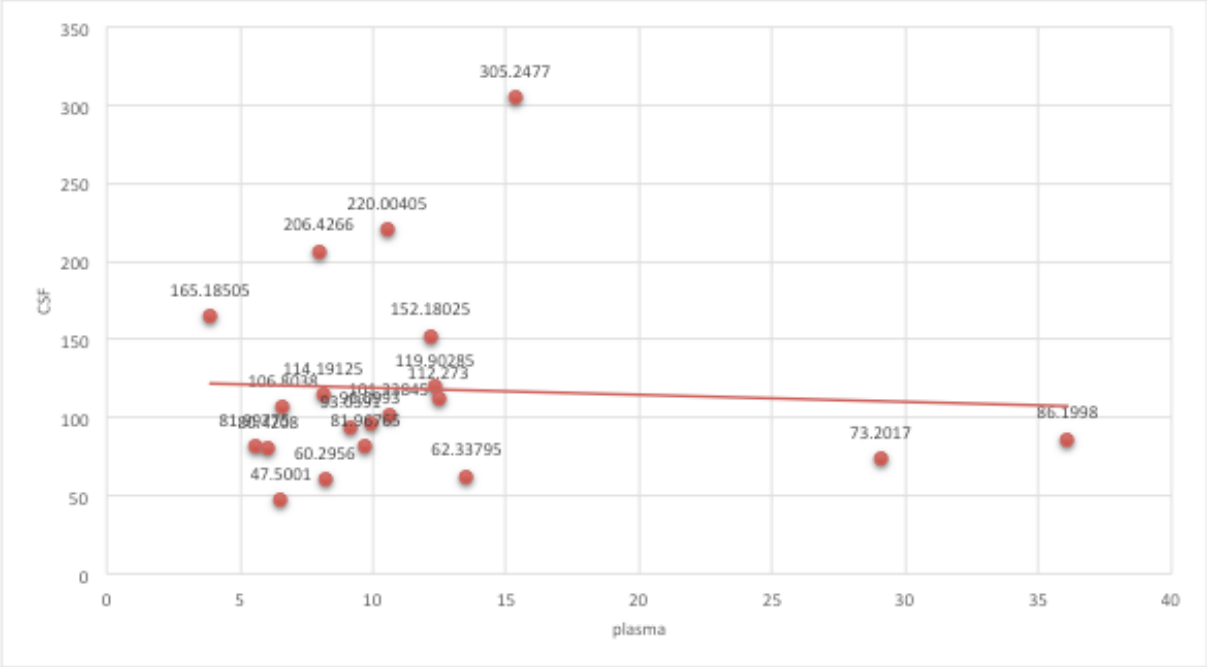
圖十七、血液中普利昂蛋白 IMR 量測濃度



存活時間越長的 CJD 患者血液中可測得的普利昂蛋白蛋白濃度越低。存活少於 1 年的 CJD 患者血液中普利昂蛋白蛋白濃度與存活 3 年以上 CJD 患者達顯著差異 (p =0.008)。

圖十八、腦脊髓液中的普利昂蛋白在不同存活期的庫賈氏病患者

這種存活越長腦脊髓液中的普利昂蛋白 IMR 量測濃度越低的情況與每一個病人病程進展速度有關。通常在大腦組織中普利昂蛋白的量越大，病人的臨床狀況惡化速度也會比較高。這個可以視為我們的脊髓液的普利昂蛋白量測的一種臨床驗證（clinical validation）。



圖十九、CJD 患者血液與 CSF 中 total prion 濃度之相關性

（Plasma mean=13.39, SD=8.41; CSF mean=125.42, SD=70.79 (pg/ml)）

生物標記發展的最終目標在於正確量測出檢體中（CSF 或 Plasma）的病理性普利昂蛋白的含量以做為輔助診斷人類普利昂疾病的目的。由於以 Proteinase K（屬於絲氨酸蛋白酶）切割來偵測 proteinase K resistant 的病理性普利昂蛋白的意圖，因為切割後的片段仍可被我們所發展的 IMR 所採用的 clone 3F4 的單株抗體所偵測，而不成功。

因此我們改採以小分子化合物進行病理性普利昂蛋白化學修飾，希望能解決細胞普利昂蛋白與病理性普利昂蛋白的胺基酸系列相同但次級結構（conformation）相異的問題。

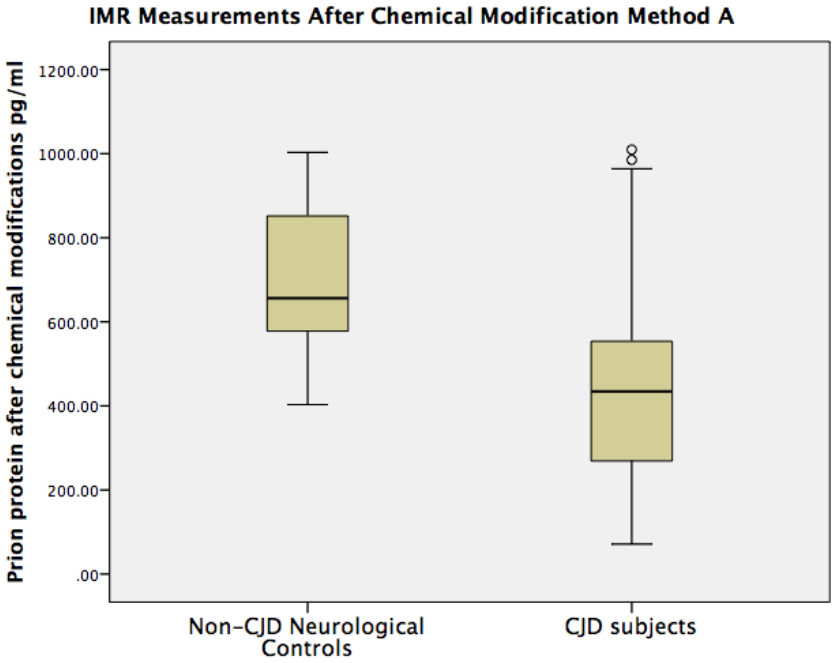
在病理性普利昂蛋白的次級結構下，3F4 的抗原表位（epitopes）在人類的普利昂蛋白分子為 109-112 的 MKHM，是屬於包埋在裡頭的，不易被 3F4 的單株抗體所作用偵測到。因此我們希望使用 Acidic anhydride

(Ac_2O)把主要是 lysine residues 的 aminogroup 進行 Acetylation (**ε**-aminogroup)， 讓 109-112 抗原表位 暴露出來可供 3F4 進行結合達到 IMR 訊號偵測的目的。Ac2O 使用 trifluoracetate (TFA) 來終結反應，另外細胞普利昂蛋白與病理性普利昂蛋白皆有雙硫鍵也可能影響到抗原表位的偵測。因此使用 dithiothreitol (DT) 用來還原（打開）雙硫鍵，即將其轉變成氫硫鍵，並用 Iodoacetamide (IAA) 來終結 DTT 作用並進行 Alkylation 預防雙硫鍵再形成。但 DTT 的使用要注意濃度，以免把 3F4 單株抗體上輕鍵-重鍵的雙硫鍵破壞了 IMR 磁珠的功能。

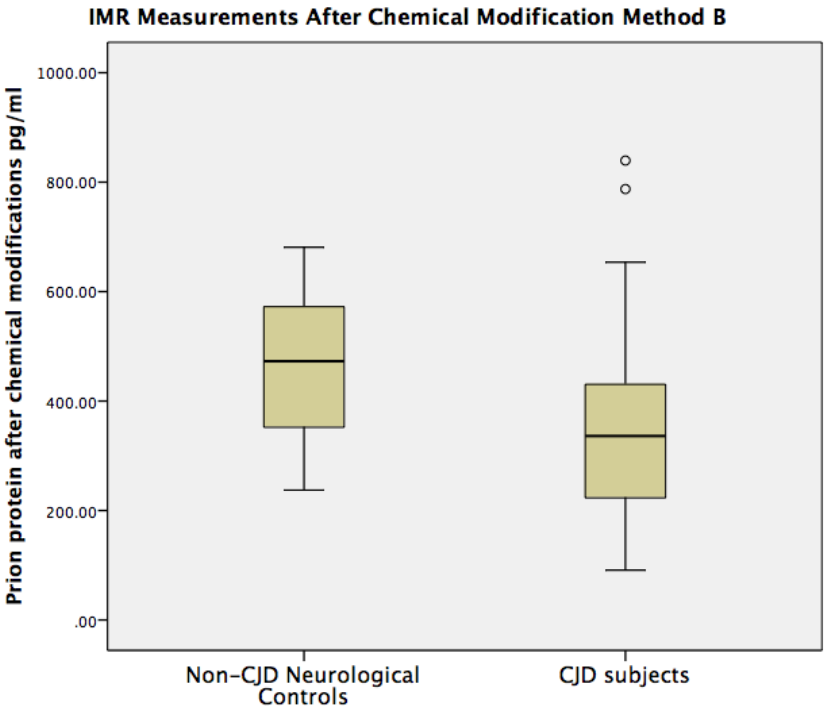
實驗方法描述如下：

1. Method A: Ac2O (5 x 10^{-9} g in 100 uL, RT 30 min) + TFA (0.4%; RT 5 min) => 高濃度 DTT (225 mM, 30 min) + IAA (450 mM, 5 min) => 3F4 IMR 量測 (DTT may reverse **ε**-acetylation) （maximal available total PrP combining PrP^{sc} and PrP^{c}）
2. Method B：低濃度 DTT (20 mM, 30 min) + IAA (40 mM, 5 min) => Ac2O (5 x 10^{-9} g in 100 uL, RT 30 min) + TFA (0.4%; RT 5 min) => 3F4 IMR 量測(conformation concealed 3F4 assumed mainly PrP^{sc})
3. 將在 Method A 測到的濃度減去 Method B 測到的濃度(conformation non-concealed 3F4 epitopes, assumed PrP^{c} level)
4. 將在 Method A 測到的濃度減去 Method B 測到的濃度除以 Method A 測到的標準化濃度比值 (conformation non-concealed 3F4 epitopes, assumed PrP^{c} ratio of total PrP)

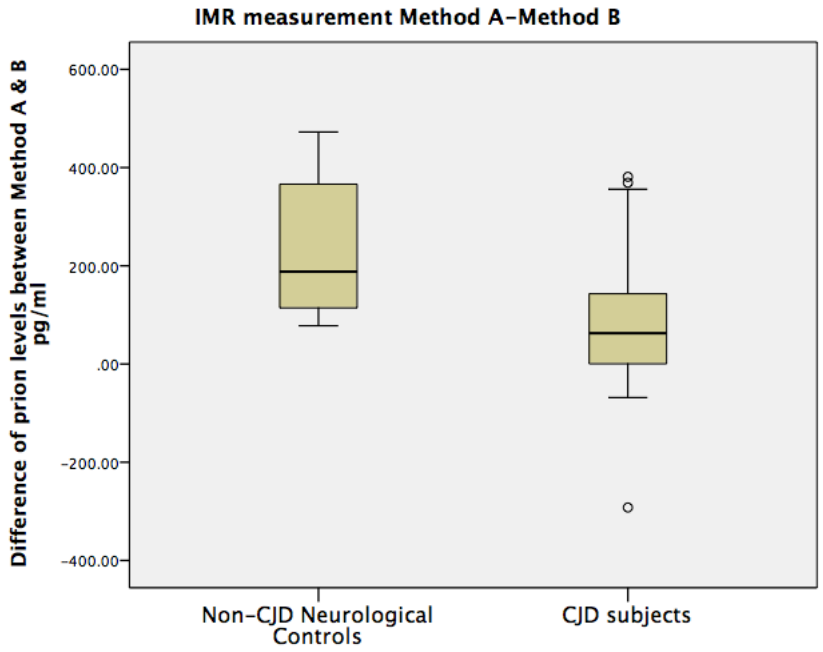
結果顯示 Method A 化學修飾之後，在 CJD 病人樣本（n=25）與非 CJD 的神經退化性疾病的對照組(n=10)達到統計上顯著差異(P =0.006)。Method B 化學修飾之後，在 CJD 病人樣本（n=25）與非 CJD 的神經退化性疾病的對照組(n=10)則未達到統計上顯著差異(P =0.129)（圖二十、二十一）。



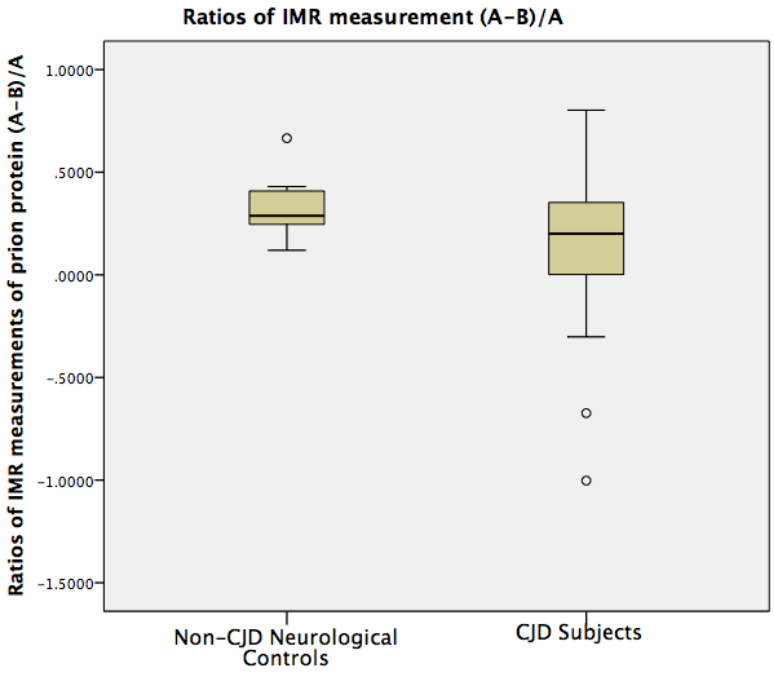
圖二十、Method A 化學修飾之後 prion protein 組間濃度達顯著差異(P =0.006)。



圖二十一、Method B 化學修飾之後 prion protein 組間濃度未達顯著差異(P =0.129)。



圖二十二、將 MethodA、Method B 化學修飾之後 prion protein 相對濃度（A-B），組間濃度達顯著差異 (P=0.013)。



圖二十三、將 MethodA、Method B 化學修飾之後 prion protein 相對濃度比值（A-B）/A，組間濃度達顯著差異 (P=0.036)。

進一步計算經 Method A、B 兩種化學修飾之後的差值結果顯示，在 CJD 病人樣本（n=25）與非 CJD 的神經退化性疾病的對照組(n=10)達到統計上顯著差異(P =0.013)，經標準化後相對差值仍達組間差異(P =0.036)（圖二十二、圖二十三）。

總而言之，經化學修飾之後可以分辨出兩組間之差異。不過 PrP^{sc} 的結果仍待與澳洲及疾管署南區實驗室的 RTQuIC 的結果來交互印證。

四、討論

經由兩場與國際學者的交流會議認識了台灣庫賈氏症與其他國家的異同。日本的文化民情與台灣較為接近，診斷後平均存活年數超過一年與最長存活年數可長達十年，其醫療照護系統及對於神經退化性疾病終末期的照護態度，包括使用管灌飲食、氣切甚至靜脈營養都與台灣相似。

澳洲方面雖然人數與台灣接近，約 2400~2500 萬，但是診斷之後大多採安寧照護，故平均存活年數少於一年，而在相關檢查方面，民眾接受脊椎穿刺及病理解剖的意願高對於確診有相當大的幫助。

在生物標記的部分，我們已經完成針對庫賈氏症 p-tau/total tau 比值，於 p-tau 與 total tau 的開發檢驗中發現除了 total tau 以外並不如文獻上所言的那麼有效。Total prion protein 部分的檢驗也已開發完成，目前看來對於 CJD 的診斷輔助仍然有限。至於特異性比較高的 $PRUP^{SC}$ 與 $PRUP^{C}$ 的鑑別，已經完成小分子對於 PRUP 的轉譯後修飾的實驗但尚待 RT-Quic 及質譜儀的驗證。

經由健保資料庫與疾病管制資料庫的分析比對方面，在發生率的差異以性別、年齡及年份而言並未達顯著差異。這說明目前的通報系統在效能上有其有效性。

比較 1998-2007、2008-2017 前後十年的發生率，發現有上升的現象，從第一個十年的每年每百萬人 0.63 上升至第二個十年的每年每百萬人 0.95，增加率為 1.5 倍。其可能原因為診斷醫師對於庫賈氏病認知增加且

診斷方法進步的結果，與世界醫療趨勢相同。但是整體發生率台灣還是和日本比較接近，在每年每百萬人一人以下，在世界各國中是屬於比較低的。

五、結論與建議

（一）簡化病例調查表

我們將調查表分為三部份，第一部分為臨床醫師在通報時填寫，就個案的基本資料、過去病史與臨床表現做簡要的調查。第二部分由疾管署收到通報完成相關檢驗後填寫，如 14-3-3 與基因的結果。第三部分為衛生單位在個案確定研判為可能/極可能病例後，展開疫調時填寫，可於此階段進行詳盡的 TOCC 調查（旅遊史、職業、接觸史、群聚）。

如此分工的好處有以下三點：

(1) 提升資料品質：原本多達 30 頁的瑣碎的題目皆由通報醫師填寫，對醫師跟家屬都是一項負擔。對醫師來說，部分內容如基因檢測的結果並非他們可以確實回答的；於家屬而言，一些有關個人習慣的題目在病房之類的公共空間被調查，其實也涉及隱私問題，徒增困擾之外更有可能取得不正確的答案。我們認為調查表在精簡分工後，各單位就自己可掌握的資訊據實填寫，獲得的資料品質會相對提升。

(2) 提升作業效率：若最終判決結果為排除病例，那麼原先進行的冗長調查其實也就白做了。因此建議 TOCC 相關問題在通報時只要取得簡要資訊即可，詳盡調查可放到確定研判之後再進行，避免耗費不必要的人力與時間，以提升整體效率。

(3) 善用資訊系統：現在電腦資訊系統發達，衛生單位獲得權限後可利用出入境系統、健保資訊系統查旅遊史與手術史，取得的資料會是完整

而精確的。相較原調查表耗費大量人力與時間在瑣碎項目的填寫上，家屬提供的資訊也往往充滿不確定性，若能利用便利的資訊系統進行全面性的調查，減輕調查者與被調查者負擔之外亦能大幅提升效率與資料品質。

（二）落實基因檢測並建立 RT-QuiC 系統

第一篇流行病學的論文中提到，本國基因型病例僅 2%，遠低於全世界的 10-14%，探討可能的原因在於早期監測系統基因檢測的執行率較低。考量接近六成的基因型病例其實並無家族史，我們很有可能遺漏了一些未做基因檢測的基因型病例，因此若家屬同意做基因檢測則應盡量執行。並建議盡速建立第二代 RT-QuiC 系統，可以利用腦脊髓液的檢體達成輔助診斷的目的。

（三）提升民眾對疾病的認知

目前我國由病審會研判為新型庫賈氏病的病例僅一例，醫源型病例為零。我們在防疫上必須謹慎小心，但也可以知道目前病例的致病因幾乎不是由外在途徑導致，過去的大規模盛行有其特殊的時空背景，現在無須有過度的恐慌心理。在照護上也需讓家屬以及照護機構了解，只要遵循正確的照顧方法，在感染上的風險是非常低的。希望能加強民眾與護理人員對庫賈氏病的正確認知，減少不必要的歧視，讓個案在病程終末時一樣能獲得良好的照護品質。

六、重要研究成果及具體建議

1. 計畫之新發現或新發明

一、 存活超過兩年個案資料分析

針對自症狀發生至死亡時間達兩年以上之長期存活個案進行資料整理與分析，並且與僅存活一年以下個案做比較，得出長期存活的性別年齡分佈、症狀與臨床表現等特徵。進一步比較檢驗結果，發現兩組在 MRI 表現上未觀察到明顯差異，但腦波的 PSWC 出現比例以及 CSF 14-3-3 陽性比例皆達顯著差異，可視為不利於長期存活的生物標記。

二、 國際期刊投稿

將 3 年來計畫中整理資料庫所得之臨床資料整合檢驗資料撰寫成論文「Prognostic features of sporadic Creutzfeldt-Jakob disease – and analysis of nationwide surveillance in Taiwan」投稿國際期刊 *Alzheimer's Research & Therapy*，針對本國散發型庫賈氏病之特性與檢驗效能進行全面性的分析，具未來診斷與通報上的參考價值。

第三篇論文預計將新型生物標記研發成果發表國際期刊，題目暫定為「Detection of prion protein in the CSF of subjects with probable Creutzefeldt-Jakob diseases – An immunomagnetic-reduction based measurement with small-molecule chemical-modification approach」

三、 庫賈氏症新型生物標記開發與驗證

成功開發 IMR reagent 技術量測腦脊髓液中的普利昂蛋白，並可看到在非庫賈氏病的神經退化性疾病等病人的檢驗上與庫賈氏病的濃度有顯著差異。但我們希望進一步達到偵測病理性普利昂蛋白的目的，實驗仍在持續進行中，目前採以小分子化合物進行病理性普利昂蛋白化學修飾，希望能解決細胞普利昂蛋白與病理性普利昂蛋白的胺基酸系列相同但次級結構（conformation）相異的問題。

2. 計畫對民眾具教育宣導之成果

三年來對通報資料庫進行全面性的重新檢視，更透過健保資料庫的分析比對，切合研究要旨得出我國庫賈氏病之發生及流行病學相關因子分析結果，可以知道目前病例的致病因幾乎不是由外在途徑導致，過去的大規模盛行有其特殊的時空背景，現在無須有過度的恐慌心理。可以讓家屬以及照護機構了解，只要遵循正確的照顧方法，在感染上的風險是非常低的。分析結果可強化民眾與護理人員對庫賈氏病的正確認知，減少不必要的歧視，讓個案在終末時一樣能獲得良好的照護品質。

3. 計畫對醫藥衛生政策之具體建議

一、 病例調查表的簡化

建議將修訂版病例調查表投入運用，並依各表分階段執行，提升調查效率與資料品質。

二、 落實基因檢測

第一篇流行病學的論文中提到，本國基因型病例僅 2%，遠低於全世

界的 10-14%，探討可能的原因在於早期監測系統基因檢測的執行率較低。考量接近六成的基因型病例其實並無家族史，我們很有可能遺漏了一些未做基因檢測的基因型病例，因此若家屬同意做基因檢測則應盡量執行。

三、 盡速建立 RT-QuIC 系統並持續發展相關檢驗與生物標記

透過國際研討會可以得知澳洲在各項檢驗技術上相對成熟，對我國 RT-QuIC 系統的建立可提供諸多借鑑。目前已與澳洲 ANCJDR 建立良好合作關係，建議日後可持續進行交流，盡速建立第二代 RT-QuIC 系統，並繼續完善新型生物標記的技術開發，提升通報與診斷效能。

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十、附錄

附錄一、衛生福利部疾病管制署庫賈氏病病例追蹤報告單

通報單編號	
追蹤日期	
過去病史	
目前用藥	

目前患者狀況：

1. 語言能力

   甲、尚可對話（可理解指令及回應）

   乙、勉強對話（部份理解及自發性言語）

   丙、無法理解指令/只能發出聲音

   丁、完全緘默不語（大約開始時間民國_____年____月）

2. 行動能力

   甲、能自行獨立行走/使用輔具行走

   乙、需他人協助行走/或使用輪椅

   丙、臥床但可仍可偶有自發性動作

   丁、完全無自發性運動（大約開始時間民國_____年____月）*

3. 進食能力

   甲、可自行進食/偶有吞嚥困難

   乙、需他人餵食/偶有吞嚥困難

   丙、完全無法進食，需使用管餵（鼻胃管/胃造廔管）

4. 大小便失禁_____是 （使用尿布/導尿管/膀胱造廔/直腸栓劑）_____否

5. _____ 是_____否同意疾病管制署委託研究計畫案，台大醫院神經科專科醫師到宅（機構）探視，針對患者目前狀況由醫師進行專業評估，若有需要可協助安排追蹤檢查。如果同意請提供電話先行聯絡_____

*可偶有眼睛睜開跟隨聲音或照護者移動，或反射性動作（如疼痛刺激之肢體收縮或觸碰或聲音引發之驚嚇肌躍性抽搐）。

附錄二、庫賈氏病病例調查表（修訂版）

「庫賈氏病 Creutzfeldt-Jakob Disease, CJD」病例調查表 (A)

醫院名稱：　　填表日期：西元　　年　　月　　日

填表醫師姓名：　　主治醫師姓名：

R1. 基本資料			
姓　　名		病歷號碼	
性　　別		出生日期	西元　　年　　月　　日
職　　業			
發病日期	西元　　年　　月　　日	診斷日期	西元　　年　　月　　日
聯絡人		聯絡電話	
現在住址			

R2 婚姻狀況及教育程度		
教育程度	☐ 無	☐ 高中（畢/肄業）
	☐ 小學（畢/肄業）	☐ 大專以上（畢/肄業）
	☐ 國中（畢/肄業）	_____年
婚姻狀況	☐ 單身	☐ 已婚或同居
	☐ 喪偶 _____年	☐ 離婚 _____年

R3. 出生及居住地區	
出生地：	_____
病人是否曾到國外旅遊？	☐ 是　☐ 否
病人是否曾長期居住國外?	☐ 是　☐ 否
如果是，請填寫曾居住過的國家：	_____
居住時間為	_____年

A1. 以往病史及外科治療史（請打✔）			
	外科手術（尤其神經外科手術）　　手術日期：西元　　年　　月　　日 手術名稱：_____		
	人體生長激素治療 Human growth hormone treatment		多發性腦梗塞症 Multiple cerebral infarcts
	角膜移植 Corneal transplantation		阿茲海默症 Alzheimer's disease
	輸血 Receive blood transfusion		惡性腫瘤 Cancer
	輸用白蛋白或其它血液製劑 Albumin or other blood products transfusion		家族中有其它 CJD 病患(關係:_____) Family history
	其它，請註明：_____		
	發病前十年內曾接受過侵入性檢查 請註明：_____		

A2. 前驅症狀 Prodromal symptoms（請打✔）					
	焦慮 Anxiety		頭痛 Headache		憂鬱 Depression
	頭暈、暈眩 Dizziness, vertigo		睡眠障礙 Sleep disturbance		異樣感覺 Paresthesia
	沒有食慾 Appetite change		視力模糊 Blurred version		健忘 Forgetfulness
	失眠 Insomnia		步態不穩 Unsteadiness		倦怠 Malaise

A3. 發病情況		
☐ 急性或突發症狀 acute onset	☐ 逐漸發病 gradual onset	
☐ 單側發病 Unilateral/asymmetric （運動肢體或感覺神經）	☐ 左側	☐ 右側
☐ 雙側發病 Bilateral/symmetric		

A4. 發病時症狀 Symptoms and signs at onset（門診或第一次住院時所登載之症狀）					
	記憶/認知功能障礙 Forgetfulness/ Cognitive impairment		失語症 Aphasia		視野或視覺功能障礙 Visual field or cortical visual dysfunction
	複視或動眼異常 Diplopia or EOM problem		步態或肢體運動失調 Gait or limb ataxia		構音障礙 Dysarthria
	肌躍症 Myoclonus		其它不自主運動 Other dyskinesia		椎體束症狀 Pyramidal syndrome
	感覺異常 Sensory dysfunction		精神症狀 Psychiatric symptoms		失眠 Insomnia
	其它，請註明：_____				

A5. 病程中出現的症狀 Symptoms and signs duration course（住院或追蹤過程期間）					
	失智症 Dementia		肌躍症 Myoclonus		巴金森症候群 Parkinsonism
	啞症運動不能狀態 Akinetic mutism		失語症 Aphasia		失用症 Apraxia
	意識混亂 Confusion		視野或視覺功能障礙 Visual field or cortical visual dysfunction		複視或動眼異常 Diplopia or EOM problem
	步態或肢體運動失調 Gait or limb ataxia		構音障礙 Dysarthria		癲癇發作 Seizure
	其它不自主運動 Other dyskinesia		椎體束症狀 Pyramidal syndrome		感覺異常 Sensory dysfunction
	精神症狀 Psychiatric symptoms		失眠 Insomnia		
	其它，請註明：_____				

A6. 檢查結果		
EEG	☐ 僅檢查一次	☐ 檢查兩次以上
EEG 結果	☐ Slow wave activity ☐ Unilateral PSWC ☐ Bilateral PSWC	☐ Other (or atypical) ☐ Normal
MRI	☐ Complete data	☐ Incomplete data (only DWI)
MRI 結果	☐ Normal	☐ Abnormal （請回答以下問題）
皮質緞帶病徵	☐ 無	☐ 有（請回答以下問題） Frontal ☐ 左 ☐ 右 Temporal ☐ 左 ☐ 右 Parietal ☐ 左 ☐ 右 Occipital ☐ 左 ☐ 右
皮質下高密度變化	☐ 無	☐ 有（請回答以下問題） Caudate ☐ 左 ☐ 右 Putamen ☐ 左 ☐ 右 Pulvinar ☐ 左 ☐ 右
其它，請註明：_____		

其它檢查項目，是否進行該項檢查（**請打✔**）	是	否
腦脊髓液(CSF)		
其它自體免疫性腦炎(autoimmune encephalitis)或腫瘤伴生腦炎 (paraneoplastic encephalitis)相關檢驗		
Prion test		
CT		
Gene study		
Brain biopsy		
Autopsy		

「庫賈氏病 Creutzfeldt-Jakob Disease, CJD」病例調查表 (B)

通報編號： _____ **填寫日期：**_____年_____月_____日

B1. 神經病理學		
B1.1	病理解剖（Post mortem autopsy） 如果有做，請回答以下問題：	☐ 無 ☐ 有
B1.2*	確定 CJD 診斷	☐ 否 ☐ 是
B1.3*	神經病理學的表現（post mortem）：	
B1.3.1	☐ Neuron loss（神經元喪失）	
B1.3.2	☐ Gliosis（神經膠質過多）	
B1.3.3	☐ Spongiform change（海綿樣變化）	
B1.3.4	Positive immunochemical stain 如果有，請回答以下二題：	☐ 無 ☐ 有
B1.3.4.1	☐ Immunostaining	
B1.3.4.2	☐ Western blot test	

B1.4	Biopsy 如果有做，請回答以下問題：	☐ 無 ☐ 有
B1.5*	確定 CJD 診斷	☐ 否 ☐ 是
B1.6*	神經病理學的表現（post mortem）：	
B1.6.1	☐ Neuron loss（神經元喪失）	
B1.6.2	☐ Gliosis（神經膠質過多）	
B1.6.3	☐ Spongiform change（海綿樣變化）	
B1.6.4	Positive immunochemical stain 如果有，請回答以下二題：	☐ 無 ☐ 有
B1.6.4.1	☐ Immunostaining	
B1.6.4.2	☐ Western blot test	

B2. Prion protein gene analysis（Chrom 20）			
B2.1	Prion protein gene analysis（Chrom 20） 如果有做，請回答以下的問題：	☐ 無	☐ 有
B2.1.1*	Mutation present	☐ 無	☐ 有
B2.1.1.1	如果有,specify PRNP mutation: _____		
B2.1.2*	Condon 129 polymorphism ☐ Met/Met ☐ Val/Val ☐ Mel/Val		

B3. Creutzfeldt-Jakob disease 分類				
B3	CJD 分類（依據診斷標準）			
	☐ 確定 Definite	☐ 極可能 Probable	☐ 可能 Possible	☐ 疑似 Suspected

B4.遺傳性庫賈氏病 Genetic Creutzfeldt-Jakob disease			
B4	Genetic CJD 是，請回答以下的問題：	☐ 否	☐ 是
B4.1*	☐ 確定或極可能 CJD 患者且其一等親中亦有確定或極可能病例		
B4.2*	☐ 神精精神方面的異常且有特異性的 PrP 基因（PRNP）突變		

B5.散發性庫賈氏病 Sporadic Creutzfeldt-Jakob disease			
B5	Sporadic CJD	☐ 否	☐ 是

B6.醫源性庫賈氏病 Iatrogenic Creutzfeldt-Jakob disease			
B6	Iatrogenic CJD	☐ 否	☐ 是

「庫賈氏病 Creutzfeldt-Jakob Disease, CJD」病例調查表 (C)

填表單位：　　填表人：

填表日期：西元　　年　　月　　日

R1. 基本資料			
姓　　名		身分證字號	
性　　別		出生日期	西元　　年　　月　　日
職　　業			
發病日期	西元　　年　　月　　日	診斷日期	西元　　年　　月　　日
聯絡人		聯絡電話	
現在住址			

R2. 醫療史

R 2.1　Surgery

病患是否曾接受外科手術?　☐ 無　☐ 有

如果有，有幾次?　＿＿＿＿次

這次住院前所接受手術是否涉及以下部位？若有請填入手術名稱及日期

R 2.1.1　**腦 (brain)**　☐ 無　☐ 有

第一次手術：＿＿＿＿＿＿　年　月　日

最近一次手術：＿＿＿＿＿＿　年　月　日

R 2.1.2　**脊髓 (spinal cord)**　☐ 無　☐ 有

第一次手術：＿＿＿＿＿＿　年　月　日

最近一次手術：＿＿＿＿＿＿　年　月　日

R 2.1.3　**顱神經 (cranial nerves)**　☐ 無　☐ 有

第一次手術：＿＿＿＿＿＿　年　月　日

最近一次手術：＿＿＿＿＿＿　年　月　日

R 2.1.4　**顱神經節 (cranial ganglia)**　☐ 無　☐ 有

第一次手術：＿＿＿＿＿＿　年　月　日

最近一次手術：＿＿＿＿＿＿　年　月　日

R 2.1.5	**後眼部 (posterior eye)**	☐	無	☐	有		
	第一次手術：_____					年	月 日
	最近一次手術：_____					年	月 日
R 2.1.6	**腦下垂體 (pituitary gland)**	☐	無	☐	有		
	第一次手術：_____					年	月 日
	最近一次手術：_____					年	月 日
R 2.1.7	**脊神經節 (spinal ganglia)**	☐	無	☐	有		
	第一次手術：_____					年	月 日
	最近一次手術：_____					年	月 日
R 2.1.8	**嗅覺上皮 (olfactory epithelium)**	☐	無	☐	有		
	第一次手術：_____					年	月 日
	最近一次手術：_____					年	月 日
R 2.1.9	**扁桃腺 (tonsil)**	☐	無	☐	有		
	第一次手術：_____					年	月 日
	最近一次手術：_____					年	月 日
R 2.1.10	**脾 (spleen)**	☐	無	☐	有		
	第一次手術：_____					年	月 日
	最近一次手術：_____					年	月 日
R 2.1.11	**闌尾 (appendix)**	☐	無	☐	有		
	第一次手術：_____					年	月 日
	最近一次手術：_____					年	月 日
R 2.1.12	**胸腺 (thymus)**	☐	無	☐	有		
	第一次手術：_____					年	月 日
	最近一次手術：_____					年	月 日
R 2.1.13	**腎上腺 (adrenal gland)**	☐	無	☐	有		
	第一次手術：_____					年	月 日
	最近一次手術：_____					年	月 日

R 2.1.14	**淋巴結 (lymph nodes) 和其它含有濾泡結構淋巴組織 (lymphoid tissues containing follicular structures)**	☐ 無	☐ 有				
	第一次手術：_____			年	月	日	
	最近一次手術：_____			年	月	日	
R 2.1.15	**腸相關淋巴組織 (gut-associated lymphoid tissue)，包含直腸 (rectum)**	☐ 無	☐ 有				
	第一次手術：_____			年	月	日	
	最近一次手術：_____			年	月	日	
R 2.1.16	其它手術	☐ 無	☐ 有				
	第一次手術：_____			年	月	日	
	最近一次手術：_____			年	月	日	

是否曾接受下列處置？

R2.2	**接受輸血或血液製劑**	☐ 無	☐ 有	_____次		
	第一次輸血時間		年	月	日	
	最近一次輸血時間		年	月	日	
R2.3	**捐血**	☐ 無	☐ 有	_____次		
	第一次捐血時間		年	月	日	
	最近一次捐血時間		年	月	日	
R2.4	**器官移植**	☐ 無	☐ 有	_____次		
	若有，移植了哪些器官？	_____				
R2.5	**人類腦下垂體萃取物治療**	☐ 無	☐ 有	_____次		
	第一次注射時間		年	月	日	
	最近一次注射時間		年	月	日	

R3 出生及居住地區			
R 3.1	出生地點：		
R 3.2	診斷地點：		
R 3.3	病人是否搬離其出生地?	☐ 否	☐ 是
R 3.4	病人是否曾居住鄉村地區?	☐ 否	☐ 是
R 3.5	病人是否經常在國內旅遊?	☐ 否	☐ 是
R 3.6	病人是否曾至國外旅遊?	☐ 否	☐ 是
	☐ 歐洲	☐ 亞洲	☐ 北美 ☐ 南美
	☐ 非洲	☐ 澳洲	☐ 紐西蘭

R 3.7	病人自 1985 年後是否到以下國家旅遊?	無	有	次數
R 3.7.1	英國			
R 3.7.2	美國			
R 3.7.3	法國			
R 3.7.4	德國			
R 3.7.5	義大利			
R 3.7.6	荷蘭			
R 3.7.7	比利時			
R 3.7.8	西班牙			
R 3.7.9	瑞士			

R4 飲食

是否曾食用以下動物製品？

R4.1 碎肉(於國外食用) ☐ 無 ☐有 （請勾選下表）

來源/頻率	每年不到一次	每年數次	每月至少一次	每週至少一次	每天一次
羊					
牛					
馬					
豬					
家禽					
其它					

R4. 脊髓或周邊神經組織 ☐ 無 ☐有 （請勾選下表）

來源/頻率	每年不到一次	每年數次	每月至少一次	每週至少一次	每天一次
羊					
牛					
馬					
豬					
家禽					
其它					

R4.3 腦 ☐ 無 ☐有 （請勾選下表）

來源/頻率	每年不到一次	每年數次	每月至少一次	每週至少一次	每天一次
羊					
牛					
馬					
豬					
家禽					
其它					

R4.3 扁桃腺 ☐ 無 ☐有 （請勾選下表）

來源/頻率	每年不到一次	每年數次	每月至少一次	每週至少一次	每天一次
羊					
牛					
馬					
豬					
家禽					
其它					

R4.3 迴腸 ☐ 無 ☐有 （請勾選下表）

來源/頻率	每年不到一次	每年數次	每月至少一次	每週至少一次	每天一次
羊					
牛					
馬					
豬					
家禽					
其它					

附錄三、論文手稿（流行病學）

Incidence and mortality of Creutzfeldt-Jakob disease in Taiwan: a prospective 20-year nationwide surveillance from 1998 to 2017

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Abstract

This nationwide prospective surveillance was initiated since 1996 aimed to identify the cases and types of Creutzfeldt-Jakob disease (CJD) as each reported case was ascertained by an expert committee at Taiwan Centers of Disease Control. In total, there were 645 suspected cases reported to the surveillance unit of CJD from 1998 to 2017. Among them, 356 CJD cases (women, n=178) were diagnosed, including 3 biopsy-confirmed sporadic CJD, 344 probable or possible sporadic CJD (sCJD), 8 cases of genetic CJD and 1 imported variant CJD. Total number of deaths was 325. The age-adjusted incidence (95%CI) for this 20-year cohort was 0.79 (0.68-0.91) per million person-year with the incidence in the second decade significantly higher than that in first decade (2^{nd} decade 0.95 vs 1^{st} decade 0.63, adjusted incidence rate ratio, 1.51, $p<0.001$). Age-specific incidence rate increased after 40 years old with the peak at 70–79 years. The age-adjusted annual mortality rate (95%CI) was 0.72 (0.61-0.83) per million persons. There was no difference between men and women regarding the incidence and mortality rates. The 10-year survival curve for sCJD patients with onset date before Dec. 31, 2007 showed that the 1-, 5-, and 10-year cumulative survival rate was 52 %, 5 % and 1%, respectively with mean (±SD) disease duration was 19.1 (± 20.2) months. Among patients with sCJD, women and those with younger age at onset had longer survival time (both $p<0.01$).

Introduction

Epidemiologic studies on the incidence of Creutzfeldt-Jakob disease (CJD) had been undergoing worldwide since the outbreak of transmissible spongiform encephalopathy when new variant CJD (vCJD) first described in 1996 in the United Kingdom [1]. A nationwide hospital-based case report system, Creutzfeldt-Jakob Disease Surveillance Unit (CJDSU), which was directed by the Centers for Disease Control of Taiwan was established since 1997 to identify the incident cases including sporadic CJD (sCJD), genetic forms, and acquired forms including iatrogenic CJD (iCJD), and variant (vCJD).

The incidence of sCJD is commonly reported to be approximately 1 case per million per year worldwide [2]. Our first long-term epidemiology study has been published 10 years ago reporting the incidence of CJD in Taiwan from 1998 to 2007 [3]. The main findings are summarized as follows: (1) all the ascertained cases were sCJD; (2) the overall annual incidence rate remained in the range between 0.5 and 0.6 per million per year, which is lower than other countries [4, 5]; (3) the incidence of onset age after 80 years was still high without sharply decline, which was also different from other reports [6, 7]; and (4) the study of prion protein gene (*PRNP*) polymorphism at codon 129 revealed that our patients were all homozygous for methionine.

Globally most countries reported the increasing trends of incidence as CJD surveillance mechanisms have been optimized and capabilities of diagnostic testing improved, in parallel with a greater awareness of this rare disease among physicians [8]. Since Taiwan CJDSU has been operating for more than 20 years, whether the incidence and mortality of our CJD cases have temporal trend should be assessed. Besides, very long disease duration was noted in some of our cases. Varied disease durations were reported between countries with average survival time ranging from 5 to 17.4 months [9-11]. Long-term survivors have been reported in either sCJD or vCJD cases [9, 12-14]. The aims of this prospective study is (1) to report all forms of CJD cases identified in Taiwan; (2) to calculate the temporal trend of incidence by gender and age; and (3) to assess the mortality rate and disease duration.

Method

Surveillance methods

The operation of Taiwan CJDSU has been reported in our previous article [3]. In brief, since1997, all neurologists throughout Taiwan were requested to notify the CJDSU of any

patients with clinically suspected CJD encountered in their medical practice. Once a case was reported to CJDSU, the expert committee which is composed of neurologists, neurosurgeons, neuroradiologists and neuropathologists would hold a case-identifying meeting to discuss the reported cases and determine the diagnosis of CJD. Cases ascertained by the CJDSU committee, would then be reported to the Taiwan Centers for Disease Control (CDC). CJDSU and Taiwan CDC are responsible to follow up all the diagnosed and suspected CJD cases. Clinical diagnosis for definite, probable or possible CJD was made according to the criteria recommended by the World Health Organization (WHO) [15, 16] and updated clinical diagnostic criteria for sCJD [17]. The reporting neurologist has to fill out a structured questionnaire sheet recording the medical history of symptoms and clinical course, demographic data, and history of potential iatrogenic exposure such as dura matter implants, corneal graft, or human cadaveric pituitary hormone, as well as physical examination and results of laboratory investigations including biochemistry tests of blood and cerebrospinal fluid (CSF), electroencephalography (EEG) and brain magnetic resonance imaging (MRI). Recently, more and more reports by neurologists in Taiwan included test results of autoimmune encephalitis or paraneoplastic encephalopathy. The specimens of whole blood and CSF of reported cases were sent to CJDSU for further tests including CSF 14-3-3 protein measured by western blot assay and CSF total-tau protein concentration by enzyme-linked immunosorbent assay (cutoff value, 1200 pg/ml). *PRNP* genetic study was performed in some cases by CJDSU. Patients with CJD symptom onset in the period 1998–2017 and diagnosed before the end of 2018 were enrolled in these analyses.

Statistical analysis

The crude annual incidence rates or mortality rates were calculated as per million person-years with the number of incident cases divided by the number of population at risk using the census data of each year in Taiwan. Incidence and mortality rates were provided respectively for the entire population and for every 10-year age groups by sex and age at disease onset. The confidence intervals of incidence and mortality rates were calculated according to the Poisson distribution. They were also estimated by adjustment for the sex and age distribution according to the census data of Taiwan in 2010. Poisson regressions were performed to analyze the change of incidence and mortality rate between genders, age groups, residence areas and calendar year of recording. Residence areas were classified into north,

middle, south and east (including surrounding islands) areas of Taiwan to check the geographical distribution of CJD cases. Trend tests were also performed to compare temporal change of incidence and mortality rate between first and second decade. The survival time from disease onset to death was analyzed in overall as well as in gender and age groups. Standardized mortality ratio (SMR) was calculated for the ratio of observed CJD deaths to expected deaths in the general population based on the age- and gender-specific mortality rates in the period from 1998 to 2017.

Results

Diagnostic classification, genetic and laboratory study

From 1998 to 2017, there were 645 cases referred to the CJDSU for further confirmation. Among them, 356 cases (women, n=178) were ascertained to be CJD, including 347 sCJD (3 pathology proved definite cases, 314 probable and 30 possible), 8 cases of genetic form and 1 probable vCJD. No direct cases of surgically acquired CJD have been noted till the end of 2017 in Taiwan. The 8 genetically confirmed cases included 1 with a 72-base pair insertion-129M, 8 cases with point mutation (2 cases of E196A-129M, 1 case of R148H-129M, and 4 cases of P102L-129M). These four P102L inherited cases belonged to one family with phenotype of Gerstmann–Sträussler–Scheinker syndrome (GSS). Their mean onset age was 51.5±17.6 years old (range: 29-67 years) with cerebellar ataxia as onset symptom and a relatively chronic clinical course (mean survival time, 4.6±1.2 years, range, 2.9-5.5 years) [18]. Analyses for *PRNP* polymorphism in 170 patients showed 168 cases of methionine homozygous genotype at codon 129 (M129M) (98.8%) while 2 cases with methionine/valine (M129V) heterozygous genotype. Glutamic acid homozygous at codon 219 (E219E) was found in 166 cases (97.6%) while 4 cases had glutamic acid/lysine heterozygous (E219K) polymorphism. The only case of vCJD was a 34-year-old man who had lived in the UK between 1989 and 1997 with disease onset in 2008. He had early psychiatric and sensory symptoms followed by gait ataxia and cognitive impairment, and had typical pulvinar sign on brain MRI. The patient developed akinetic mutism at 16 months and died at 28 months after onset [19]. The positive CSF 14-3-3 protein test was found in 66.7% (2/3) of definite cases, 67.0% (183/273) of probable cases, and 16.7% (4/24) of possible cases. The sensitivity of CSF 14-3-3 protein was 63.0%. And the specificity was 71.4% which was calculated from the data after 2011 because the laboratory records of the excluded cases before then were not

complete. With a threshold of 1200 pg/mL, CSF tau determination showed positive results in 66.7% (24/36) of probable cases and 66.7% (2/3) of possible cases.

Incidence, mortality and disease duration

The age-adjusted annual incidences (95% CI) of CJD from 1998 to 2017 in men, women and total were 0.77 (0.61-0.93), 0.82 (0.65-0.98), and 0.79 (0.68-0.91) per million persons, respectively, with the use of Taiwan census data in 2010 for adjustment. There has been a positive trend in the annual number of suspected cases of CJD since 2008. In the first decade from 1998 to 2007, the crude incidence was at a stable level remaining in the range between 0.5 and 0.6 per million person year. The crude incidence of second decade from 2008 to 2017 doubled to 1.03 as compared to 0.52 in previous decade. The highest incidence was 1.24 per million persons found in the period of 2012-2013 (Table). The age- and sex-specific average annual incidence was also significantly higher in second than in first decade (2^{nd} decade 0.95 vs. 1^{st} decade 0.63) with incidence rate ratio being 1.51 (95% CI 1.21-1.88, $p<0.01$). There was no significant difference in the incidences between men and women. The incidences increased with age reaching to the peak at the age 70-79 years in both men and women as low incidence rate observed below 50 years. Although a mild decline was observed, the incidence among patients aged above 80 years still remained high (Figure 1). The incidences of sCJD in middle and east region (including surround islands) were slightly higher than that in south regions (data not shown).

The temporal trend of mortality rate during the 20-year cohort was similar to the change of incidence. The number of deaths and the mortality rate were rising after 2008 with highest rate 1.26 per million persons noted in the period from 2012 to 2013. The age-adjusted mortality rate (95% CI) of CJD from 1998 to 2017 in men, women and all was 0.71 (0.56-0.87), 0.74 (0.58-0.89), and 0.72 (0.61-0.83) per million persons, respectively, adjusted by the use of census data of Taiwan in 2010 (Table). The higher incidence of CJD in the second decade resulted in a higher mortality rate than that in the first decade. The average age- and sex-adjusted annual mortality rates in the periods of 1998-2007 and 2008-2017 were 0.58 and 0.86, respectively. The adjusted mortality rate ratio of the second decade to first decade was 1.52 (p=0.01). There was no significant difference in mortality rate between men and women, and between geographical areas in Taiwan. Like the curve of incidence, the highest mortality rate was found in the age group of 70-79 years. The Kaplan–Meier survival

curve with 10-year follow-up after disease onset (onset date before Dec. 31, 2007) was plotted in Figure 2. The cumulative survival rate at the end of 1st, 5th and 10th year after onset was 52 %, 5 % and 1%, respectively. The median survival time was 13.5 months. The median survival time for patients less than 50 years and those aged 50-59 were 37.6 and 22.9 months, respectively. The mean (±SD) disease duration was 19.1 (±20.2) months for overall, 14.3 (±15.6) months for men and 22.3 (±22.8) months for women. Women and patients with younger age at onset had longer survival time (both $p<0.01$) (Figure 2).

Discussion

The overall incidence rate of CJD from 1998 to 2017 in Taiwan was 0.79 per million persons. The incidence showed a significant increase after 2008 to around 1 case per million persons per year, which was comparable with the worldwide incidence typically reported to be around 1-2 per million person-year on the basis of surveillance from 2005 onward [2, 20]. The incidence of patients with CJD onset after 80 years of age was still high without sharply decline, which was different from other reports [6, 21]. The increase of incidence for the second decade could be explained by the rising of clinical physicians' awareness, the improvements in diagnostic tests, and the increase of aging population in our country as the CJD cases showing old onset age with peak at 70-79 years. Since the start of CJDSU in 1997, several national or international symposiums focused on human transmissible spongiform encephalopathy have been held by Taiwan Neurological Society for educating neurologists and general physicians about the update of diagnostic criteria and management for CJD patients. Taiwan CDC has regularly revised the workbook [22]. In 2008, an imported vCJD was reported to CJDSU [19]. This first, acquired CJD case in Taiwan has created an important public health concern and might help raise the disease awareness among neurologists leading to the increase of reported cases afterward. In 2009, an updated criteria including findings from MRI was proposed and was soon adopted by CJDSU [17]. The pattern of high signal intensity with high sensitivity and specificity in the differential diagnosis of sCJD from other neurological diseases helped clinicians in the early detection of suspected cases, which was in part resulting to the increase of referrals in subsequent years.

The polymorphism at codon 129 (M129V) of *PRNP* is a recognized genetic marker for susceptibility to CJD in the Caucasians [23]. In Europe, 51% of general population has methionine/valine (MV) heterozygosity while 37% has methionine homozygosity (MM) [24,

25]. In east Asia, MM genotype was found in 94% of Korean [26] and 92% of Japanese [25]. The ethnic Han Chinese, which composes over 95% of Taiwanese population, has a remarkable high frequency (98%) of methionine homozygotes in general population [27]. The methionine homozygosity remains high percentage in both groups of the normal individuals and diseased patients with 98.8% of CJD cases in our surveillance being MM genotype and less than 2% carrying MV form. Prion susceptibility and protective alleles may exhibit marked geographic differences with the effects being different between Asian population and Caucasian [25].

Because of the short disease duration in most cases, the increase of mortality with time is parallel to temporal trend of incidence as the mortality rate significantly higher in the second decade than in first decade. There was no difference in the incidence and mortality between men and women in our surveillance. Some countries showed higher incidence in women than in men which is because of the higher number of women in the older age populations [28, 29]. The disease duration varied in types of CJD with relatively chronic course in some genetic form. The mean survival time was 56.4 (range, 35.1-67.4) months in four GSS cases (P102L), 15.4 (9.0, 21.7) months in two E196A cases and 11.9 months in a R148H case while quite short disease duration of 2.4 months was noted in a 72-base pair insertion case. Because of the small number of our gCJD, it is hard to compare to other countries in term of their survival time.

Among patients with sCJD, women and those with younger age at onset had longer disease duration. This finding is comparable with the results from a collaborative multi-national CJD surveillance program (EUROCJD) conducted by European Union and allied countries [30]. The mechanisms for age and gender effects to survival time are not clear. Age-related variations in care or resistance to terminal infection were proposed to be the possible explanations [30]. Whether there are sex-specific factors that influence the disease duration need to be studied. In this national cohort, we found some long-term survivors of sCJD with 3-, 5- and 10-year survival rate being 13%, 5% and 1%, respectively. The median survival time was 13.5 months (mean: 19.1 months) and 48% died within 1 year of onset. Our data was similar to the report from Japan whose mean survival time of sCJD was 15.7 (range: 1-126) months and 46.0% of all patients with prion disease died within 1 year [9]. But reports from other counties revealed much shorter survival time. The study of EUROCJD involving 2,451 sCJD patients showed that the median survival time was 5 months (range: 1-81) and

85.8 % died within one year of onset [31]. The median duration of a study involving 150 definite or probable sCJD cases in Argentina was 4.6 (range: 1-70) months [32], while a Swedish study involving 123 patients with prion disease found that 74.6% of patients died within one year [33]. A study from China also showed short survival time with median duration 7.1 months (range: 1.0–23.3) and 78.5 % of patients died within one year of onset [10].

Survival time among patients with sCJD in Japan and Taiwan was relatively longer than those reported from most of other countries in the world. This finding in Japan was explained by their well-organized health care system with robust public medical insurance system as well as the ethical and social environment allowing patients at end-stage neurological disease to receive intensive life-sustaining treatments such as tube feeding and intravenous high-calorie infusion [9, 34]. The Taiwanese government adopted a single-payment National Health Insurance (NHI) system since 1995 that provides comprehensive health insurance to Taiwan's 23.4 million citizens. Furthermore, patients who were diagnosed to have prion disease, which is classified as a catastrophic illness, would not even need to pay a co-payment for outpatient or inpatient care. Since the death among patients with CJD is usually caused by pneumonia related to the inability to swallow or recurrent complications of immobility and being bed bound such as bed sore or urinary tract infection, easy access to medical care with very low medical fees would be the important factors to prolong their survival time. All the procedures of medical treatments, including feeding tube insertion for patients, whether they are admitted into acute hospitals or live in long-term care facilities, are reimbursed by the NHI in Taiwan [35]. Tube feeding is one of the most crucial factors contributing to the survival time [34]. Like the situation in Japan, our social environment influence the decision making of family and allow patients with end-stage dementia to receive tube feeding and other intensive life-sustaining treatments [35].

There are several limitations in current study. First, the percentage of definite case of human spongiform encephalopathies is very low. Because of the traditional ethical values among general population in Taiwanese society, this meager rate of autopsy has long been known as an unfavorable and unavoidable reality. In recent years, the technique of real-time quaking-induced conversion assay to detect the pathological prion protein in the CSF or in other tissues has been developed with high diagnostic accuracy [36]. However, this technique was not used by CJDSU in Taiwan during our study period. Without obtaining the tissue

specimen or pathological prion protein, we are not only unable to make definite diagnosis but also unable to assess the various molecular sub-types of sCJD which is useful for phenotypic classification. Second, underreporting and underestimation of CJD are inevitable to exist. Because of the older age at onset, patients with CJD may be misdiagnosed as other diseases with rapid progression of neurological symptoms such as stroke [37], encephalitis [38], degenerative dementia [39], and epilepsy [40]. A retrospective archival survey published in 1995 showed only about 60% of prion disease cases with pathologically spongiform encephalopathy were identified clinically during life. In recent decades, the diagnostic accuracy can be improving by use of CSF biomarkers and brain MRI [17]. To minimize erroneous inclusion of encephalopathy mimicking CJD, a follow-up of clinical course and MRI/EEG for cases with uncertainty would be suggested by the committee to the primary care physicians, and they were obliged to report in the next concerned meeting. Furthermore, due to the comprehensive coverage of our NHI system, patients with spongiform encephalopathy received fully financial support covering all necessary MRI or EEG follow-up. It is almost a consensus of clinical practice among neurologists of Taiwan that for those patients with rapid cognitive decline, in addition to CSF study, MRI and EEG examination, tests to exclude autoimmune encephalitis or paraneoplastic encephalopathy would usually be performed. Third, the number 2% (8/356) of gCJD over all forms of CJD was far fewer than the corresponding figures elsewhere in the world which is around 10-14% [24, 41]. Though the incidence of gCJD varied considerably among countries, we speculated that the lower number of gCJD in our study is probably because the *PRNP* gene sequencing test was not routinely performed in all of the ascertained cases, with 165 among these 356 CJD cases were tested. Around 60% of genetic CJD cases were reported to have no family history [41], suggesting that they would have been misclassified without the *PRNP* genetic analysis.

In conclusion, this study provides the 20-year epidemiologic features of CJD in Taiwan. The incidence rate in the second decade was comparable with the corresponding figures among most of other countries in the world. The significant increase of incidence after 2008 suggests the rise of clinical physicians' awareness of this rare disease. The longer disease duration of patients with sCJD in Taiwan than in Western countries indicates the health care system in Taiwan may prolong survival time in patients with such rapid progressive and fatal disease.

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Table. Biennial age- and gender-adjusted incidence and mortality rate per 1,000,000 persons of CJD in Taiwan from 1998 to 2017

	Crude annual incidence in 2-year period										Total (1998–2017)		
	1998-1999	2000-2001	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013	2014-2015	2016-2017	No. of CJD cases	Crude incidence (95% CI)	Age-adjusted incidence[a] (95% CI)
Men	0.35	0.44	0.65	0.61	0.34	0.95	0.99	1.41	0.73	1.19	178	0.77(0.66-0.88)	0.77(0.61-0.93)
Women	0.65	0.55	0.41	0.40	0.75	0.92	0.78	1.07	1.15	1.10	178	0.78(0.67-0.90)	0.82(0.65-0.98)
Total	0.50	0.49	0.53	0.51	0.55	0.93	0.88	1.24	0.94	1.15	356	0.78(0.70-0.86)	0.79(0.68-0.91)
	Crude annual mortality in 2-year period										Total (1998–2017)		
	1998-1999	2000-2001	2002-2003	2004-2005	2006-2007	2008-2009	2010-2011	2012-2013	2014-2015	2016-2017	No. of deceased cases	Crude mortality (95% CI)	Age-adjusted mortality[a] (95% CI)
Men	0.49	0.44	0.35	0.56	0.52	0.69	0.82	1.24	0.85	1.15	165	0.71(0.60-0.82)	0.71(0.56-0.87)
Women	0.61	0.46	0.45	0.40	0.44	0.52	0.65	1.29	1.11	1.06	160	0.71(0.60-0.81)	0.74(0.58-0.89)
Total	0.55	0.45	0.40	0.48	0.48	0.61	0.73	1.26	0.98	1.10	325	0.71(0.63-0.79)	0.72(0.61-0.83)

[a]Age-adjusted incidence and mortality were calculated with the use of Taiwan census data in 2010

Figure Legends

Figure 1. Annual Incidence Rate of all CJD Patients by Gender and Age.

The incidences increased with age reaching to the peak at the age 70-79 years in both men and women as low incidence rate observed below 50 years.

Figure 2. Kaplan-Meier Survival Curves for Patients with Sporadic CJD by Gender (A) and Age (B).

Kaplan-Meier curves displaying time from disease onset to death or to the end of 120 months. All the patients who were diagnosed with sporadic CJD and onset date before Dec. 31, 2007 were followed. The 10-year cumulative survival rate for men and women were 0% and 2%, respectively. Longer survival time was noted in women than in men (A), and patients with younger age at onset (B).

Fig. 1. Annual Incidence Rate of all CJD Patients by Gender and Age.

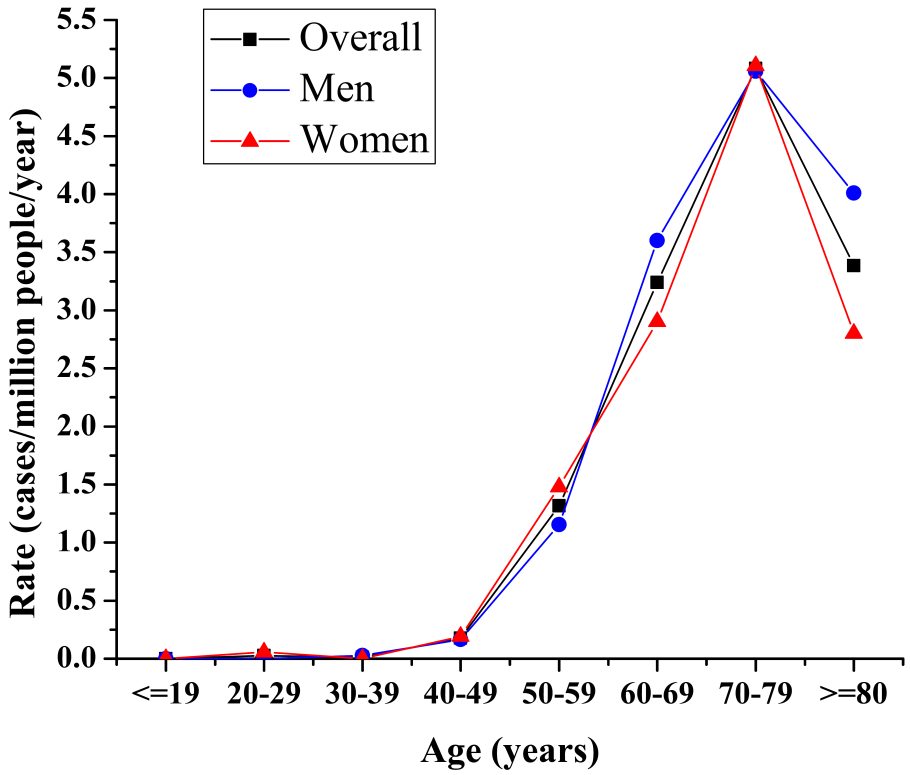
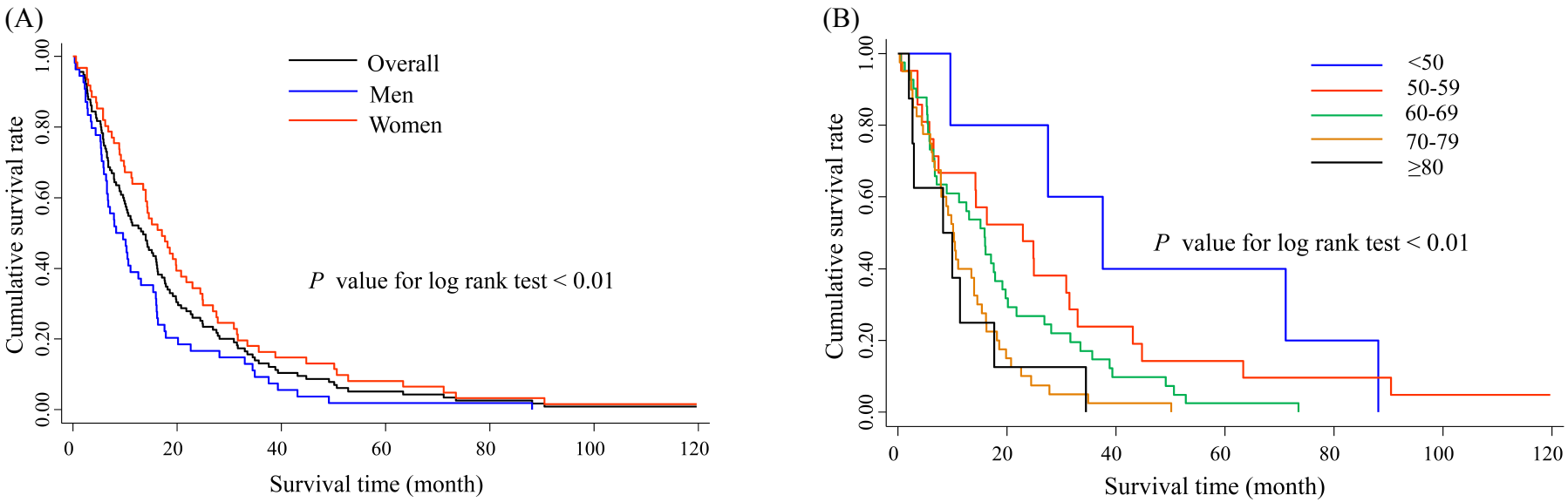


Fig 2. Kaplan-Meier Survival Curves for Patients with Sporadic CJD by Gender (A) and Age (B).



Supplement

Table S1. Secular trends of overall and sex-stratified incidence rates (per 1,000,000 persons) of CJD in Taiwan from first decade (1998-2007) to second decade (2008-2017)

Variable	1998-2007	2008-2017	Change[c] (%)	Trend test β	*p*[d]
Men					
Crude	0.48	1.05	118.75	0.79*	0.00
Adjusted[a]	0.56	0.98	75.00	0.56*	0.01
Women					
Crude	0.55	1.00	81.82	0.59*	0.00
Adjusted[a]	0.72	0.92	27.78	0.25	0.24
Total					
Crude	0.52	1.03	98.08	0.69*	0.00
Adjusted[b]	0.63	0.95	50.79	0.41*	0.01

[a] Adjusted for age (using Taiwan census data in 2010 as standardized population).

[b]Adjusted for age and sex (using Taiwan census data in 2010 as standardized population).

[c]Change (%): Percentage of changes in the incidence rates of CJD between 1998-2007 and 2008-2017.

[d]*P* for linear trend test <0.05

Table S2. Multivariate Poisson regression model on the incidence rates of CJD in Taiwan from 1998 to 2017

Variable	Crude IRR	95% CI	Adjusted IRR	95% CI
Year (Ref.=1998-2007)				
2008-2017	1.99*	1.60-2.48	1.51*	1.21-1.88
Age (Ref.=<50)				
50-59	27.38*	15.97 -46.94	26.13*	15.23 -44.82
60-69	67.92*	40.30 -114.50	65.25*	38.68 -110.05
70-79	109.37*	64.85-184.45	107.51*	63.73-181.38
≧80	64.30*	35.28-117.17	60.38*	33.10-110.15
trend test	b□=0.90, p<0. 01		b□=0.89, p<0. 01	
Sex (Ref.=Women)				
Men	0.97	0.79-1.19	1.04	0.84-1.28
Residence area (Ref.= South)				
North	1.19	0.88-1.60	1.25	0.93-1.68
Middle	1.28	0.99-1.67	1.40*	1.08-1.82
East and surrounding islands	1.92*	1.11-3.32	1.82*	1.05-3.15

IRR, incidence rate ratio; CI, confidence interval.

*p<0.05

Table S3. Secular trends of overall and sex-stratified mortality rates (per 1,000,000 persons) of CJD in Taiwan from 1998-2007 to 2008-2017

Variable	1998-2007	2008-2017	Change [c] (%)	Trend test β	*P*[d]
Men					
Crude	0.47	0.95	102.13	0.71*	0.00
Adjusted[a]	0.55	0.88	60.00	0.47*	0.04
Women					
Crude	0.47	0.93	97.87	0.68*	0.00
Adjusted[a]	0.63	0.85	34.92	0.30	0.17
Total					
Crude	0.47	0.94	100.00	0.69*	0.00
Adjusted[b]	0.58	0.86	48.28	0.39*	0.01

[a] Adjusted for age (using Taiwan census data in 2010 as standardized population).

[b] Adjusted for age and sex (using Taiwan census data in 2010 as standardized population).

[c] Change (%): Percentage of changes in the mortality rates of CJD between 1998-2007 and 2008-2017.

[d] *P* for linear trend test <0.05

Table S4. Multivariate Poisson regression model on the mortality rates of CJD in Taiwan from 1998-2017.

Variable	Crude MRR	95% CI	Adjusted MRR	95% CI
Year (Ref.=1998-2007)				
2008-2017	1.94*	1.58-2.51	1.52*	1.20-1.91
Age (Ref.=<50)				
50-59	24.28*	14.20 -42.19	23.35*	13.53 -40.27
60-69	59.82*	35.34 -101.26	57.40*	33.89 -97.22
70-79	98.94*	58.47-167.42	97.07*	57.35-164.30
≧80	64.23*	35.24-117.04	60.35*	33.08-110.09
trend test	bβ=0.91, p<0.01		bβ=0.89, p<0.01	
Sex (Ref.=Women)				
Men	1.01	0.81-1.26	1.18	0.87-1.34
Residence area (Ref.= South)				
North	1.09	0.81-1.49	1.15	0.84-1.56
Central	1.13	0.86-1.48	1.23	0.94-1.62
East and remote islands	1.49	0.83-2.67	1.40	0.78-2.51

MRR, mortality rate ratio; CI, confidence interval.

*p<0.05

Table S5 – Survival rate during ten years after CJD onset.

Years after CJD onset	Total		Men		Women	
	Survival rate	Cumulative survival rate	Survival rate	Cumulative survival rate	Survival rate	Cumulative survival rate
1	0.52	0.52	0.39	0.39	0.64	0.64
3	0.50	0.13	0.56	0.09	0.48	0.16
5	0.60	0.05	0.50	0.02	0.63	0.08
10	1.00	0.01	0.00	0.00	1.00	0.02

Table S6. Disease duration (months) of sporadic CJD with onset year from 1998 to 2007 by sex and age at onset*

Variable	Mean ± SD*	Median	Min*	Max*	Range
All patients (n=115)	19.07 ± 20.20	13.48	0.33	119.67	119.34
Sex					
Men (n=54)	14.33 ±15.63	8.90	0.33	88.10	87.77
Women (n=61)	23.27 ±22.84	17.05	0.56	119.67	119.11
Age at onset					
<50 (n=5)	46.77 ±32.18	37.57	9.57	88.10	78.52
50-59 (n=21)	28.84 ±30.45	22.89	0.56	119.67	119.11
60-69 (n=41)	18.83 ±16.63	15.90	0.49	73.51	73.02
70-79 (n=40)	12.32 ±9.86	10.20	0.33	50.10	49.77
≧80 (n=8)	11.13 ±10.81	9.07	1.93	34.43	32.49

Abbreviation: SD=Standard deviation; Max= Maximum; Min= Minimum
*All cases were followed until death or completion of 10-year period

Table S7. Standardized mortality ratio of CJD in Taiwan by sex and age at onset, 1998–2017

Variable	no. of deaths		SMR*	95% CI*
	Observed	Expected		
All patients	314	9.36	33.55	29.94-37.48
Men	160	5.22	30.67	26.10-35.81
Women	154	4.14	37.18	31.54-43.54
Age at onset, Men				
<50	4	0.09	46.30	12.46-118.53
50-59	22	0.33	67.57	41.71-100.80
60-69	57	1.14	50.21	38.03-65.06
70-79	56	2.17	25.86	19.53-33.58
≧80	21	1.50	14.01	8.67-21.41
Age at onset, Women				
<50	5	0.03	188.62	60.79-440.17
50-59	28	0.24	116.57	77.44-168.48
60-69	44	0.81	54.30	39.45-72.90
70-79	60	1.84	32.54	24.83-41.88
≧80	17	1.22	13.93	8.11-43.54

*SMR= standardized mortality ratio; CI=confidence interval.

Figures

Fig. S1 Biennial crude incidence and 95% CI of sporadic CJD in (A) overall, (B) women, and (C) men.

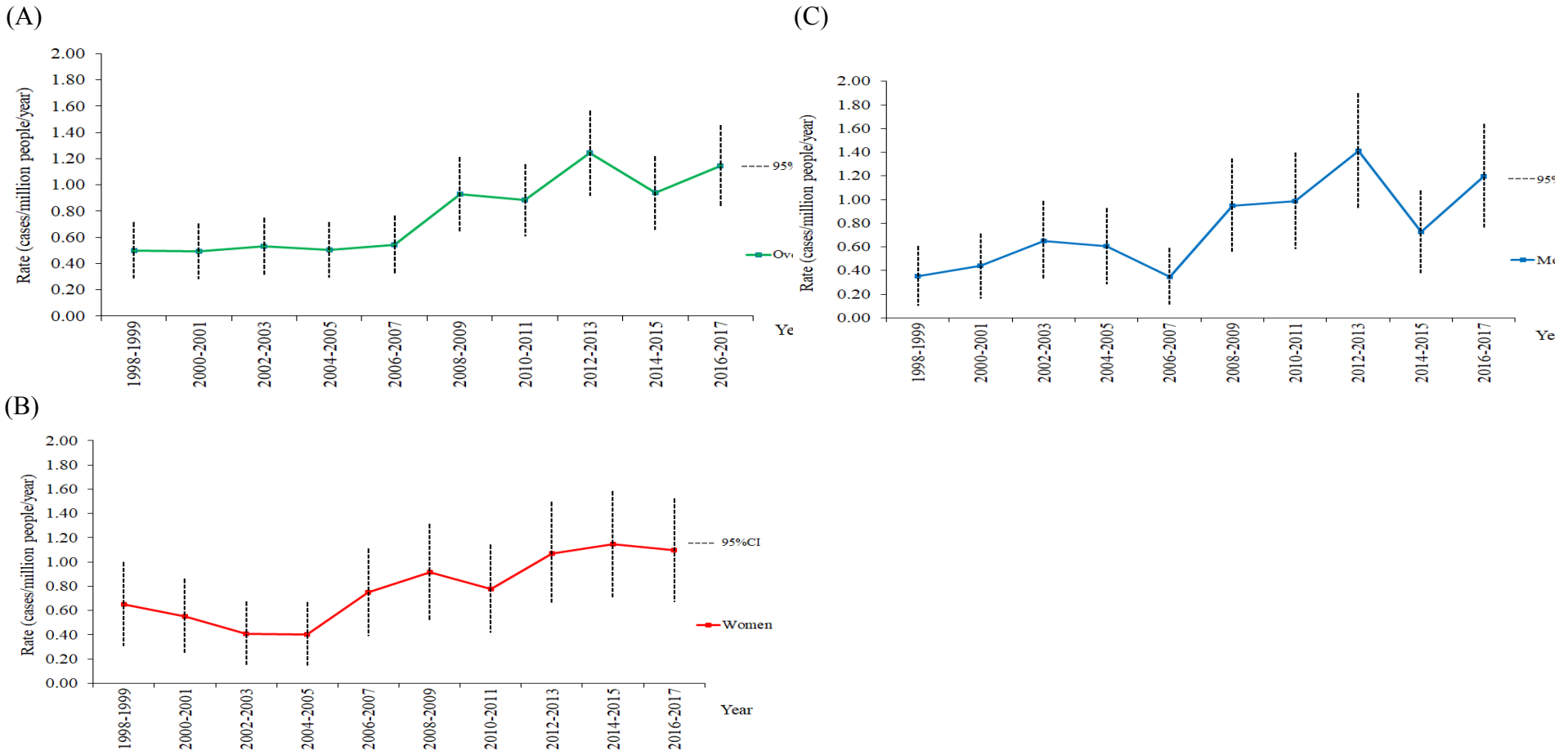


Fig. S2 Age- and gender-standardized incidence rates of sporadic CJD in Taiwan, 1998–2017, by residence area (using Taiwan census data in 2010 as standardized population).

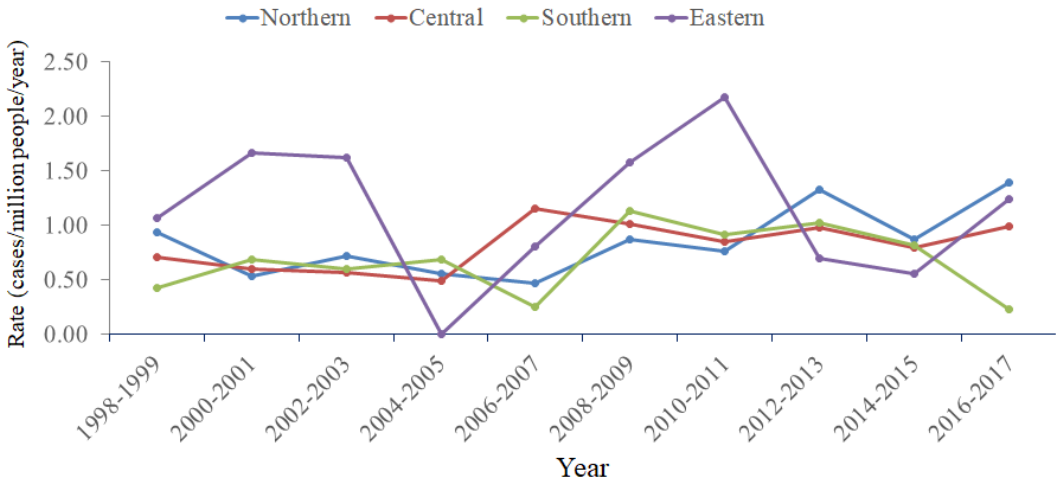
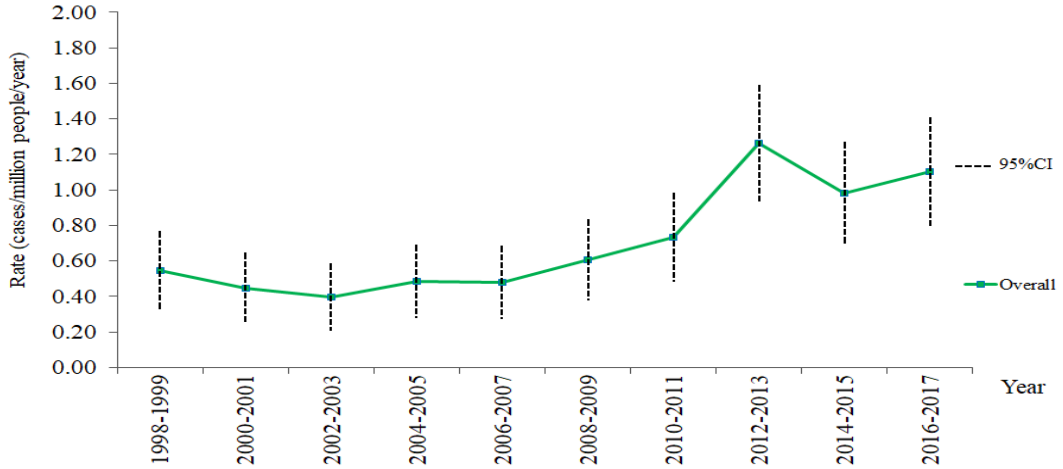
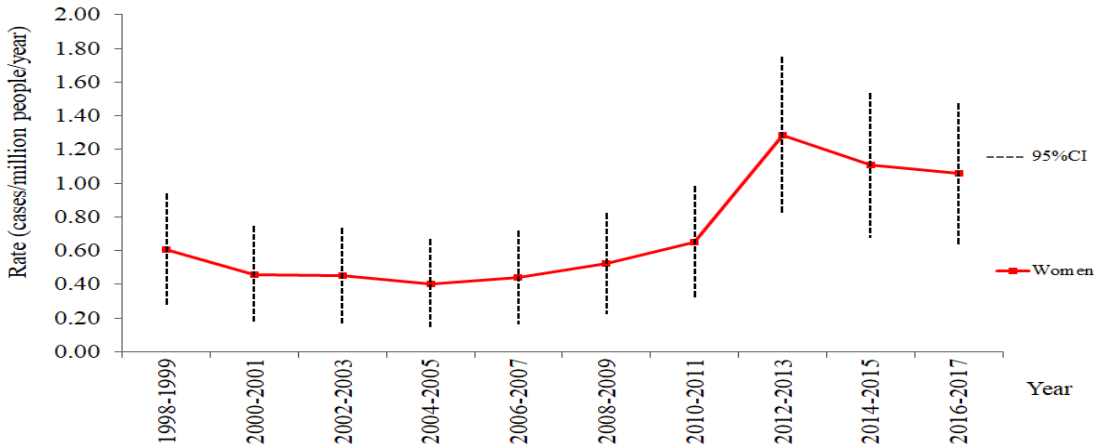


Fig S3. Biennial crude mortality and 95% CI of sporadic CJD in (A) overall, (B) women, and (C) men

(A)



(B)



(C)

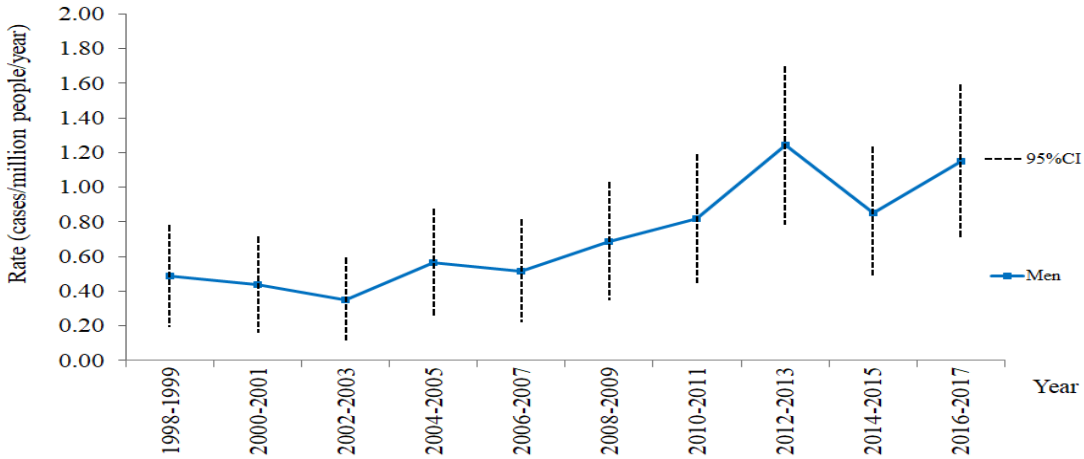


Fig S4. Age- gender -standardized mortality rates of sporadic CJD in Taiwan, 1998–2017, by residence area. (using Taiwan census data in 2010 as standardized population)

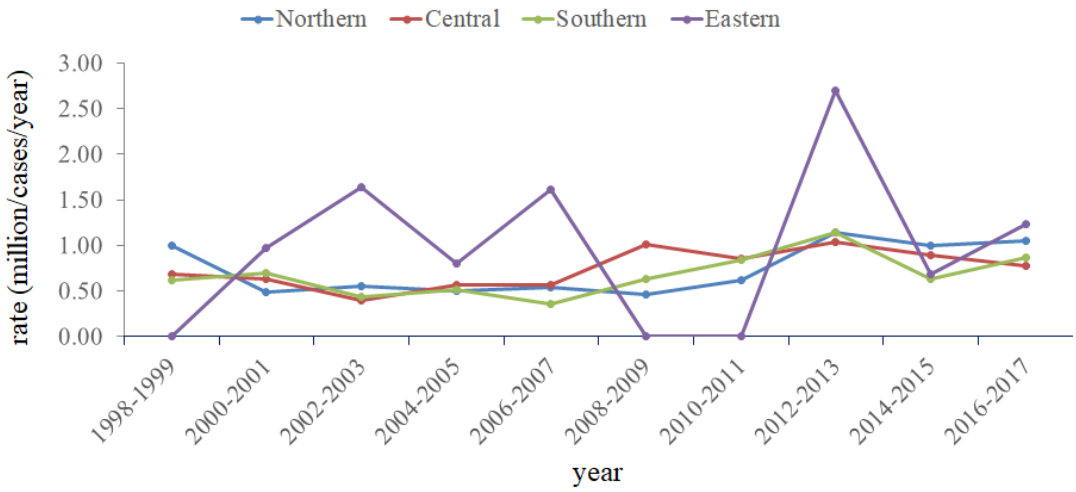
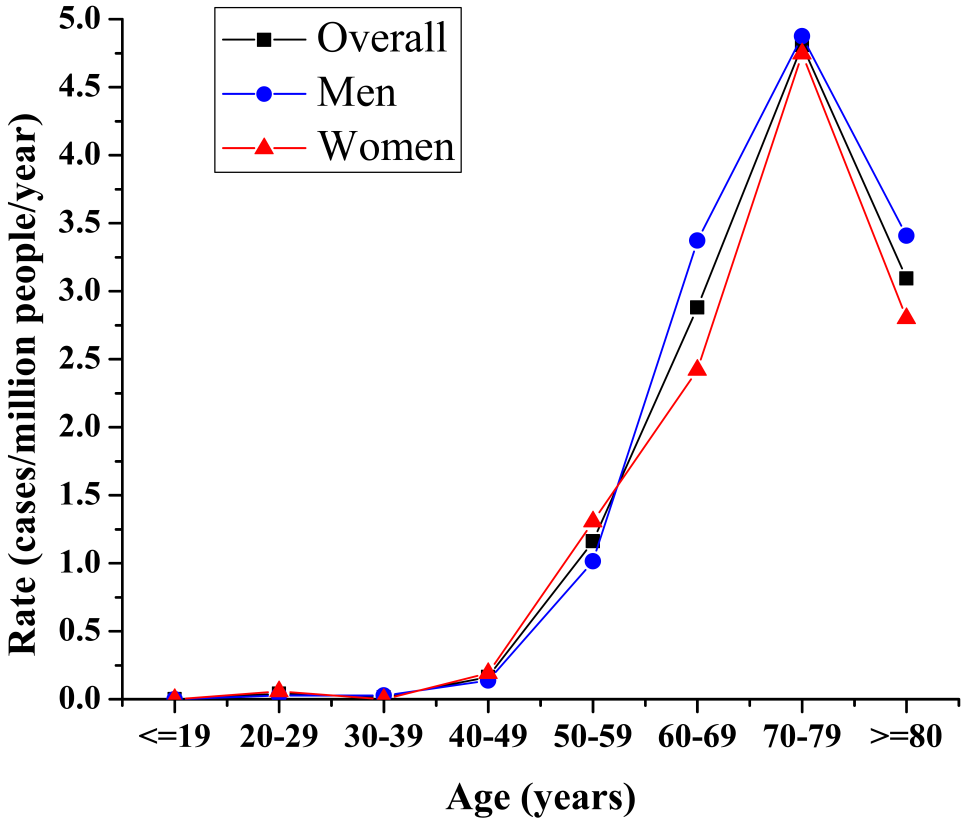


Fig S5. Annual mortality rate of sporadic CJD by gender and age



附錄四、論文手稿（臨床）

Prognostic features of sporadic Creutzfeldt-Jakob disease – an analysis of nationwide surveillance in Taiwan

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Ling-Yun Fan and Yu Sun contribute equally to this paper.

Abstract:

Background: Taiwan initiated prospective surveillance of human prion diseases in 1996. Detailed observation of the clinical, laboratory, and epidemiological features of Creutzfeltd-Jakob disease (CJD) might shed light on the increase in incidence and help predict prognosis.

Methods: We present the clinical manifestations and laboratory findings for 400 patients with a definite or probable diagnosis of sporadic CJD. We used Kaplan-Meier analyses and Cox proportional hazards model to identify prognostic factors.

Results: The mean onset age was 67 ± 9.9 years old. The mean survival duration, defined from sCJD diagnosis to documented death, was 13.3 ± 14.2 (median 10) months. Overall, the leading clinical symptoms were myoclonus (73%) and akinetic mutism (54%). Of 197 patients, *PRNP* polymorphism in 195 (99%) showed a methionine homozygous genotype at codon 129 (M129M). The sensitivity of periodic sharp wave complexes (PSWCs) on EEG was 59.7%, with a mean delayed interval following an MRI diffusion restriction of approximately 36 days. The sensitivity of CSF 14-3-3 protein and total tau protein (> 1200 pg/mL) was 69.7% and 75.6%, respectively. Age, gender, PSWCs, and epileptic seizures were identified as significant prognostic factors with hazard ratios of 0.466 ($P < 0.001$), 0.712 ($P = 0.005$), 0.788 ($P < 0.05$) and 0.768 ($P < 0.05$), respectively.

Conclusions: Age was the most crucial prognostic factor for survival time. Subjects with younger onset ages live significantly longer than those with onset ages over 65 years. Women have a favourable survival probability in the first three years than their male counterparts. PSWCs have a persistent negative effect on survival probability. Epileptic seizures, though not commonly seen, are the only risk factor of clinical manifestations for short survival time.

Keywords: Cortical ribbon signs, Periodic sharp wave complexes, 14-3-3, tau, epileptic seizure

Introduction

Human prion diseases are rapidly progressive and invariably fatal neurodegenerative disorders. These diseases are pathologically defined as spongiform encephalopathy and are pathogenically caused by an infectious prion protein (PrP^{sc}) that self-replicates by templating and misfolding of a normal cellular prion protein (PrP^{c}) [1]. Human prion diseases comprise both hereditary and non-hereditary forms. The hereditary forms include Gerstmann-Straussler-Scheinker (GSS) disease, fatal insomnia (FI), and genetic Creutzfeldt-Jakob disease (gCJD) [2]. Sporadic CJD (sCJD) accounts for more than 85% of all cases of human prion diseases; others involve exogenous sources such as iatrogenic (iCJD) and new variant CJD (vCJD) [3]. The clinical manifestations of CJD are highly heterogeneous.

A recent review showed that the incidence or mortality per million people in the world ranged from 0.32 (Estonia) to 1.73 (Switzerland) [4]. During the past decade, there has been an increasing trend of human prion diseases in many countries of the world [4-6]. This trend may be attributed to two factors: improvement of awareness among physicians and advances in diagnostic testing globally and ageing of the population in those who with older ages of onset, such as in Japan and Taiwan [6, 7].

Detailed observation of the clinical, laboratory, and epidemiologic features of CJD might shed light on this apparent increase in incidence and help predict prognosis [8]. This report explores the clinical manifestation, laboratory findings, and prognostic factors based on Taiwan's nationwide surveillance over the past 25 years.

Methods

Surveillance

The operation of the Taiwan CJDSU was detailed in our previous report [9]. Briefly, all physicians in Taiwan were requested to report suspected CJD patients to the CJDSU. The expert committee of the CJDSU, including neuropathologists, neurologists, neuroradiologists, and neurosurgeons, discussed the reported cases and designated a

consensus-based diagnosis. CJD cases ascertained by the committee were reported to the Taiwan Centers for Disease Control (CDC). CJDSU and the Taiwan CDC followed up on all CJD cases until the documented death of the patient. The clinical diagnosis of definite, probable, or possible CJD was made according to the updated clinical diagnostic criteria for sCJD recommended by the World Health Organization (WHO) [10-12]. The reporting physician completed a structured questionnaire detailing demographic data, medical history, clinical manifestations, natural course, potential iatrogenic exposure, physical examination results, and laboratory test findings, including blood and cerebrospinal fluid (CSF), electroencephalography (EEG), and brain magnetic resonance imaging (MRI). Test results concerning autoimmune encephalitis or paraneoplastic encephalopathy were more frequently included in these reports in recent years. We enrolled patients with CJD symptom onset from 1996 to 2020. Symptomatological information included prodromal symptoms, onset symptoms defined by those symptoms recorded at diagnosis, and cumulative symptoms throughout the clinical course. The survival duration was considered from the diagnosis of sCJD until documented death. Every EEG of the reported cases was reviewed and discussed by clinical EEG specialists of the CJDSU. The following defined periodic sharp wave complexes (PSWCs): from a morphological point of view, typical PSWCs consist of either simple sharp waves (biphasic or triphasic waves) or mixed spikes, polyspikes, and slow waves with a duration ranging from 100 to 600 ms, recurring every 0.5 to 2.0 seconds [13]. The intervening background activities usually consist of generalized low-voltage slowing. Topographically, PSWCs commonly show a bilateral hemispheric distribution, with a maximum at midline fronto-precentral regions [14]. We used MRI to detect diffusion restriction by hyperintensities in diffusion-weighted images (DWIs), with corresponding hyperintensities in the ADC map in the cortical gyri, so-called the cortical ribbon signs, and in the basal ganglia [15]. As for EEG, every MRI was reviewed and discussed by neuroimaging experts of the CJDSU.

Laboratory methods

Specimens of whole blood and CSF from reported cases were examined for CSF 14-3-3 protein by Western blot assay and CSF total-tau protein concentration by enzyme-linked immunosorbent assay. Whole blood was used for the *PRNP* genetic study.

14-3-3 Western blotting

Eighteen microlitres of CSF was mixed with an equal volume of Tris-Glycine SDS Sample Buffer (2X) (Invitrogen) at 95°C for 10 min and loaded onto a NuPAGER Novex 4-12% Bis-Tris Gel. The gels were electroblotted and transferred to PVDF membranes using a Western blot tank (Invitrogen). The membranes were immunoblotted using a polyclonal anti-14-3-3 pan (AB9748-I) antibody as the primary antibody; goat anti-rabbit IgG antibody conjugated with HRP (AP307P) was used as the secondary antibody. Western Lightning ECL Pro (PerkinElmer) was used to develop the membranes, and the results were visualized with VL FX7 (VILBER).

Tau ELISA

Total tau was determined and quantified by a Human Tau (total) ELISA Kit (KBH0042, Invitrogen), as directed by the manufacturer. A positive result for Creutzfeldt–Jakob disease was considered at a 1200 pg/ml cut-off level.

PRNP *gene sequence analysis*

Genomic DNA was extracted from whole blood using a Roche MagNa Pure LC DNA Isolation Kit. The *PRNP* gene was amplified by polymerase chain reaction (PCR) using the following primers: forward PR01-5'-TGATACCATTGCTATGCACTCATTC-3' and reverse PR02-5'-GACACCACCACTAAAAGGGCTGCAG-3'. The size of the amplicon was confirmed by agarose gel electrophoresis and sequencing. Sequence data were analysed using BioEdit software [16].

Statistical analysis

Definite and probable sCJD cases were included in the analysis. Categorical and continuous variables are presented as the mean ± standard deviation. The interaction between demographic factors was further examined by two-way ANOVA. Correlation coefficients

were calculated between biomarkers and clinical manifestations by using Spearman correlation analyses. We applied the Kaplan-Meier method to estimate cumulative survival dichotomized by biomarkers and symptomatology and to identify candidates of prognostic factors using a Log Rank (Mantel-Cox) test. We used the Cox proportional hazards model to calculate hazard ratios (HRs) with a 95% confidence interval by a Wald test forward selection method first in univariate analysis and then in multivariate analysis. Spearman correlation analyses were performed to examine associations between clinical manifestations and laboratory findings. The significance level was set at $P < 0.05$. The statistical analyses were performed with SPSS version 20.

Results

From 1996 to 2020, 809 cases were referred to the CJDSU for confirmation; of these, 441 cases (women, n=230) were determined to be sporadic CJD, including three pathologically proven definite cases, 397 probable cases, and 41 possible cases. We included definite and probable cases (n=400, 90.7%) in further analysis. By the time of analysis (June 30th, 2020), there were 379 subjects with documented death.

In this report, we present the clinical manifestations, laboratory findings, and prognostic factors of the 400 cases designated as definitive and probable CJD, 208 (52%) of whom were women, with a mean age at diagnosis of 67 ± 9.9 years old (median 68, range 22-91). The mean interval between the onset of prodrome and diagnosis was 1.8 ± 1.9 (median 1.3) months, and the mean survival duration, defined from sCJD diagnosis to documented death, was 13.3 ± 14.2 months (median 10 months). The longest survival time was 94 months (almost 8 years).

Clinical Manifestations

The most common prodromal symptoms were forgetfulness (59%), unsteadiness (57%), sleep (33%), and visual disturbance (29%). The most common onset symptoms (at the time of diagnosis) were gait disturbance/truncal ataxia (53%), memory decline (47%), myoclonus (34%), and extrapyramidal signs (32%). Cumulatively, 63.5% (254/400) of the

subjects had motor-related onset, including pyramidal, extrapyramidal, or cerebellar dysfunction; 32% (82/254) showed unilateral onset. The leading overall clinical symptoms were myoclonus (76%), akinetic mutism (54%), and extrapyramidal symptoms (44%). Epileptic seizures were not common (20%, 80/400; Table 1).

Laboratory features

Analyses for *PRNP* polymorphism in 197 patients revealed 195 cases of a methionine homozygous genotype at codon 129 (M129M) (99%), with only 2 cases of a methionine/valine (M129V) heterozygous genotype. Glutamic acid homozygosity at codon 219 (E219E) was found in 197 cases (98%), while there were 4 cases of glutamic acid/lysine (E219K) polymorphism heterozygosity.

MRI sensitivity in terms of cortical ribbon signs and basal ganglia hyperintensities was 95.7% (313/327). The most common cortical regions involved were the parietal lobes (67-71%), followed by the temporal lobes (60-64%) and frontal lobes (61-62%). The most common subcortical structure involved was the caudate nucleus (45-46%), followed by the putamen (36-37%). Pulvinar signs were seen in only 9% of the cases.

The sensitivity of EEG in terms of periodic sharp and wave complexes (PSWC) was 59.7% (225/377). There was a mean delayed interval of approximately 36 days between the appearance of PSWCs following cortical ribbon signs/basal ganglia hyperintensities. The sensitivity of CSF 14-3-3 protein was 69.7% (223/320), and the specificity was 79.6% (199/250). With a 1200 pg/mL threshold, the sensitivity of CSF total tau protein was 75.6% (229/303), and the specificity was 74.1% (157/212).

Prognosis

After sCJD diagnosis, women lived significantly longer than men did by a difference of almost 4 months (15.4 ± 1.0 versus 11.4 ± 1.0 months, *LogRank chi-squared test 7.514*, $P = 0.006$). In addition, those who were aged 65 and younger (n=160) lived longer than those older than 65 years (n = 234) after sCJD diagnosis (10.0 ± 0.6 versus 18.9 ± 1.6 months, *LogRank chi-squared test 34.699*, $P < 0.001$).

The Kaplan-Meier method was employed to estimate cumulative survival and to identify candidate prognostic factors. Only age (dichotomized 65 years old), gender, the appearance of PSWCs on EEG, and having epileptic seizures during the disease course reached significant levels (Table 2; Fig. 1 a-d). No other symptomatology or laboratory variables were significant. A Cox proportional hazards model was used to calculate the HRs of the selected prognostic factors first in univariate analysis and then in multivariate analysis (Table 3).

The interaction between age (dichotomized at 65) and gender was further examined by two-way ANOVA but was not significant ($F = 0.003$, $P = 0.956$).

Correlation coefficients were calculated between biomarkers (CSF 14-3-3, tau and PSWCs) and clinical manifestations by using Spearman correlation analyses. CSF 14-3-3 showed a positive correlation with PSWCs on EEG (Spearman $\rho = 0.137$, $P = 0.014$) and CSF tau (Spearman $\rho = 0.211$, $P < 0.001$). Moreover, PSWCs correlated positively with myoclonus (Spearman $\rho = 0.141$, $P < 0.001$), seizures (Spearman $\rho = 0.211$, $P < 0.001$) and akinetic mutism (Spearman $\rho = 0.186$, $P < 0.001$).

Discussion

Age is the most critical prognostic factor for sCJD survival time. The younger the patient is at disease onset, the longer they live, which is compatible with an Italian cohort for which a cut-off point of 65 years old was also used [17]. Another study including CJD subjects from several European countries, Canada, and Australia also showed that those aged 70 and over had a much higher mortality rate, especially males [18]. Gender is another favourable prognostic factor, whereby women live longer than their male counterparts after sCJD diagnosis [17]. Similar to other neurodegenerative diseases or terminal dementia patients, sCJD subjects had a high probability of dying from aspiration pneumonia, urosepsis, and pressure sore infection. The brainstem is relatively resistant to neuronal damage (Fig. 2) due to pathological prion protein [5]. Overall, younger sCJD patients have a greater chance of surviving these infection episodes, which may be due to better cardiovascular function, as

observed in subjects with a permanent vegetative state [19].

In recent reports, women have a longer life expectancy than men almost worldwide, which may involve biological, behavioural, and/or environmental factors, though but the exact mechanism is still unknown. Men have a higher smoking rate and begin smoking earlier than their women counterparts, which is an important cardiovascular risk factor. Other biological effects have been mentioned, such as a female preponderance of telomere length during mitotic cell division [20] or optimal cardiovascular compliance comparable to the effects of exercise created during the second half of the menstrual cycle or pregnancy [21].

The sensitivity of EEG in terms of typical PSWCs was 59.7% in this study. Depending on the stage when EEG is performed, the sensitivity of PSWCs ranges from 57-80% [22] and may vary among countries, such as 63.5% in a Chinese series [23] and 83.9% in a Japanese report [24]. EEG may show only non-specific alterations, such as slowing or frontal intermittent rhythmic delta activity (FIRDA), when EEG is carried out at the early stage. Indeed, PSWCs may be overlooked if EEG is performed at a too-early or too-late stage during the disease [14]. Notably, PSWCs are most prominent during wakefulness and tend to disappear during sleep [25]. During sleep, the disappearance of PSWCs may be related to the overriding of physiological sleep potentials, including vertex-sharp waves, sleep spindles, and K complexes, which bear scalp voltage topographies very similar to PSWCs. Both PSWCs and physiologic sleep patterns rely on thalamocortical loops [14]. The exact mechanism of PSWCs has not yet been elucidated. However, an EEG study using dipole sources responsible for the PSWCs in CJD showed that both cortical and subcortical areas account for the generalized periodic discharges. The dorsolateral and medial frontal cortices are the cortical sources of PSWCs, whereas the basal ganglia, especially the caudate nucleus and thalamus, are the subcortical locations [26]. PSWCs have been correlated with immunoreactivity for the calcium-binding protein parvalbumin in the thalamic nuclei of patients with sCJD [27]. Inhibitory neurons (GABAergic interneurons)

expressing parvalbumin are also reduced in the cerebral cortex and hippocampus in sCJD patients [28]. Patients with PSWCs show a predominant loss of parvalbumin-positive cells in the reticular thalamic nucleus. The reticular nucleus, serving as a pacemaker, plays an essential role in the generation of thalamic, cortical, or thalamocortical spindle rhythms or synchrony [29]. However, the subcortical-cortical or thalamocortical network's functional integrity is essential for the generation of PSWCs. Therefore, in the late stage, PSWCs should no longer be generated in the brain of sCJD patients, probably due to the destruction of this supportive network.

PSWCs exhibited a positive association with myoclonus and seizures in patients with sCJD in this study. A previous study using polygraphic recording showed that PSWCs were usually present in patients with myoclonic jerks but were not necessarily time-locked. PSWCs connect temporally with EMG bursts only in periodic myoclonus, suggesting a cortical origin of myoclonus [30].

Seizures are an uncommon finding, occurring in no more than 15% of patients, in sCJD and are even rarer (3%) as early manifestations [14]. In this study, the seizure prevalence was 5% for an early symptom and 20% cumulatively. Seizure-like EEG activity in patients with sCJD may suggest nonconvulsive status epilepticus (NCSE) [31]. Overall, it is not always easy to distinguish NCSE from PSWCs. PSWCs in sCJD are well known to be attenuated or even abolished by antiepileptic drugs, especially benzodiazepines [32]. Epileptic discharges are usually time-locked with clinical motor signs, such as epilepsia partialis continua; in NSCE, the drug effect should always correlate with significant mental status improvement [33].

In summary, the appearance of PSWCs suggests acute lesions in the thalamic reticular nucleus and hippocampal and cortical neurons, with relative sparing of the subcortical-cortical or thalamocortical projection structures. Epileptic seizures are not a common phenomenon of sCJD, and the recognition of seizure activity in sCJD is a difficult task that requires clinical acumen. Prolonged seizures frequently cause significant mortality

and morbidity in critically ill neurological patients [34], even in those with NCSE [35]. Furthermore, seizure or seizure activity by EEG does not necessarily warrant anticonvulsant treatment, and attending physicians must make decisions judiciously. In fact, treating electrographic seizures is unlikely to alter the relentless course of sCJD.

One previous study found that psychiatric symptoms or cerebellar disturbance increased the risk of akinetic mutism in sCJD subjects [8]. We used documented death as an endpoint in this study; however, we found that except for uncommonly seen epileptic seizures, no other clinical manifestations of sCJD, including prodrome, symptoms at diagnosis, and symptoms throughout the course, were prognostic factors for survival time. This was not an unexpected observation, as sCJD, similar to all other neurodegenerative diseases, is caused by pathological proteins, so-called proteinopathy, suggesting a seeding mechanism and cell-to-cell propagation [36]. Initial and subsequent clinical presentations correlate tightly with the anatomical regions vulnerably and sequentially affected by pathological prion protein.

This report is not without limitations. Our cohort included few cases of definite sCJD. We also have a very low autopsy rate, which is an unfortunate and unavoidable reality in Taiwanese society due to traditional ethical values. However, the Taiwan CDC followed the clinical course of all cases ascertained by the CJDSU committee until a documented death and recommended follow-up MRI/EEG in case of uncertainty.

In conclusion, we present the clinical manifestations, laboratory findings, and prognostic factors of cases designated as definite and probable sCJD. We found that age is the most crucial prognostic factor for sCJD survival time: the younger is the onset age, the longer the patient lives. Women live longer than their male counterparts. PSWCs suggest acute lesions in some specific subcortical and cortical structures. Epileptic seizures, though not common, are the only prognostic factor of clinical manifestations for short survival time.

Declarations

Ethics approval: The Research Ethics Committee approved the study of the National Taiwan University Hospital (201801019RINB). The written informed consent form was waived because the study was done retrospectively on the National Surveillance Data Bank of Taiwan Centers for Disease Control.

Consent to participate: All participants received PRNP gene sequencing had provided written informed consent by their proxy on reporting to CDC.

Consent for publication: Not applicable.

Availability of data and material: The data and raw material could be available after an application to and approval from the Taiwan CDC.

Competing interests: All authors declare no conflicts of interest.

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Author contribution

YS: assisting manuscript drafting, data analysis, and statistical analysis

LYF: clinical and laboratory data encoding and preprocessing, assisting manuscript drafting

CTH: PRNP gene sequence, prion protein Western Blot, tau ELISA measurement, and analysis

CCL: statistical analysis

TFC: assisting project coordination

CJL: assisting clinical cases ascertaining

WYG: neuroimages ascertain and interpretation

YCC: EEG and clinical data ascertain and interpretation

MJC: manuscript drafting finalization, coordination, and integration of all sorts of data acquisition, analysis, and interpretation

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參、經費支用情形

項　　目		本年度核定金額	支用狀況
人事費	研究助理	552,866	碩士級第五年專任助理薪資+勞健保+一個半月年終獎金。40,953 x 13.5 協助所有聯絡與資料處理，及初步資料分析。已全數支用完畢。
	主持人費	120,000	每個月 10000 元。已全數支用完畢。
業務費	國內旅費	10,000	需至各地醫院收集存活超過兩年庫賈氏病患資料並進行追蹤調查或訪視。高鐵、計程車車資。已全數支用完畢。
	國外旅費	100,000	至澳洲進行國外學術活動，參加研討會。已全數支用完畢。
	檢體運送費	150,000	國外檢體托運費及相關報關費用。已全數支用完畢。
	材料費	893,000	腦脊髓液或血液生物標記檢驗費（p-Tau， PrPSc）。已全數支用完畢。
	儀器使用費	100,000	腦脊髓液或血液生物標記檢驗儀器使用費（p-Tau，PrPSc）。已全數支用完畢。
	其他	92,634	文具、電腦耗材、郵電（追蹤存活超過兩年庫賈氏病患會增加郵電支出）。已全數支用完畢。
	出版費	70,000	Open Acess 雜誌出版費、英文編修費。已全數支用完畢。
	專家會議	30,000	協助修訂病例調查表專家諮詢會議，專家出席費每人 2000 元。交通費依國內差旅費標準核實報支。場地費、茶水費。已全數支用完畢。
	視訊研討會	50,000	辦理視訊研討會及講師費、教材費、場地費。已全數支用完畢。
管理費		361,500	(人事費+業務費- 主持人費- 所有協同主持人費/兼任研究員費) x15%
合　　計		2,530,000	