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Research Article

Clinicopathologic Concordance Rate in the Dublin Brain Bank, 2008-2016

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Francesca Brett*, Alan Beausang, Albi Chalissery, Daphne SY Chen, Jane Cryan, Robert O Connell, Teresa Loftus and Michael Farrell

Department of Clinical Neurological Sciences, Royal College of Surgeons, Ireland

Abstract

Background: Ireland's first national brain bank was launched in October 2008 at Beaumont Hospital, Dublin to facilitate access to well-characterised human brain tissue for scientific research.

Objective: As neuropathology is the 'gold standard' for the diagnosis of diseases of the central nervous system, we aimed to correlate the ante-mortem clinical diagnosis with the final post–mortem neuropathologic diagnosis.

Methods: We reviewed all cases (N=275) submitted to the brain bank during the period October 2008-December 2015. The cases referred are neurodegenerative (N=141), traumatic (N=27), neoplastic (N=25), epilepsy (N=24), cerebrovascular (N=26) and miscellaneous (N=32). Frozen tissue is available in 119 of these cases.

Results: The majority of neurodegenerative cases included Alzheimer's disease (N=41) followed by motor neuron disease (N=32). Dual pathology was identified in 24% of the neurodegenerative cases.

Conclusion: Concordance between clinical and pathological diagnosis was good, occurring in 86.5% (122/141) of neurodegenerative cases. Discrepancies occurred in 13.5% of these cases, most of which involve the sub-classification of clinical dementia or parkinsonism.

Keywords: Brain Bank, Alzheimer's disease, Fronto temporal dementia, Lewy body, Parkinson's disease.

Introduction

Brain banks are a vital source of human brain tissue to support research in neurosciences [1]. Well characterised diseased and healthy control brain donations have facilitated the discovery of new diseases such as Dementia with Lewy bodies, variant Cruetzfeldt-Jakob disease (CJD) and TDP-43 related frontotemporal lobar degeneration (FTLD [2]. They have also facilitated research into the cellular and molecular mechanisms underlying common dementing illnesses such as Alzheimer's disease (AD). Limitations of the suitability of animal studies for research into human brain disorders where impaired cognition is an early feature have reinforced the urgency to harvest and carefully document age and disease-related changes in the human brain [1]. The demand from neuroscientists for access to well characterised human diseased and healthy brain tissue samples has been hampered both by decreasing autopsy rates and by various organ retention issues in Ireland, the UK and Australia [3]. Brain banking is now recognised as not merely the removal of tissue at post-mortem and its storage in a freezer, but as a facility to enable clinico-pathological correlation in patients with detailed clinical histories and, where available, genetic data [1].

Accuracy of clinical diagnosis is increasingly important for therapeutic and scientific investigations. It is not only a guide to prognosis and a prerequisite for organising clinical care and management, but is also essential for clinical trials. With respect to neurodegenerative disease, which constitutes the bulk of cases referred, it is suggested that a comprehensive analysis of the patient's clinical history, cognition and behaviour together with a full clinical examination should lead to a high degree of confidence in clinical diagnosis [2]. Nonetheless, the view persists that underlying pathology can be predicted on clinical grounds with only limited accuracy.

In this study, we set out to analyse the pattern of donations to Dublin brain bank and

***Corresponding Author:** Francesca Brett, Department of Clinical Neurological Sciences, Royal College of Surgeons, Ireland, Tel: 0035318093143, Email: francescabrett@beaumont.ie

the different types of neurological conditions that are available for researchers in neuroscience. We also decided to evaluate the clinico-pathological concordance in all brain donations made to the Brain Bank since its inception in 2008 and in doing so to gain an understanding of reasons for clinical and pathologic discordance.

Materials and Methods

All donated cases submitted to the brain bank during the period October 2008-December 2015 were reviewed. Following death and with appropriate signed consent forms the brain was either removed by the Neuropathologist within Beaumont Hospital or at post-mortem in another hospital and subsequently transported to the neuropathology department in Beaumont Hospital. Time from death to brain retrieval was determined. Frozen tissue was obtained in all donations harvested in Beaumont Hospital.

On receipt of the brain the brain bank co-ordinator and the Neuropathologist examined, photographed and weighed the brain. CSF was obtained where possible. The brain was dissected saggitally through the corpus callosum. One half of the brain was formalin-fixed for neuropathological evaluation. The other half was coronally sliced and representative sections were taken from different anatomical regions as per standardised protocol [4]. These were then snap-frozen for brain banking purposes.

Tissue blocks were cut from the formalin-fixed hemisphere to include all major cortical, subcortical, midbrain, brainstem, cerebellar and spinal cord regions (where available). Sections were cut at 6 μm and stained with haematoxylin and eosin (H&E). Following examination of the H&E sections, immunocytochemical stains were requested and evaluated. These included TAU (Innogen 1:2000), Amyloid-β protein (Dako 1:100), α-Synuclein (Zymed 1:500), GFAP (Dako 1:7000), Ubiquitin (Leica 1:750), and where appropriate transactive response DNA binding protein 43 (TDP-43) (Proteinase 1:1500), Fused in sarcoma (FUS) (Sigma 1:600), and P62 (Santa Cruz 1:1000).

Cases were examined for the presence of neuritic plaques and neurofibrillary tangles (in frontal, temporal, cingulate, entorhinal, inferior parietal and occipital cortices, hippocampus, amygdala, locus coeruleus, substantia nigra and cerebellum), Lewy bodies (in cerebral cortex, limbic regions and brain stem), and TDP-43 intra-cytoplasmic and intranuclear inclusions in temporal cortex including hippocampus and amygdala. FUS positive intranuclear and intra-cytoplasmic inclusions were also sought. Although Beaumont Neuropathology is the national centre for CJD surveillance, clinically suspect CJD cases were not included in the brain bank population. In all cases the presence of cerebrovascular disease (small vessel, amyloid angiopathy and vasculopathy) was ascertained both macroscopically and microscopically.

Diagnosis was made using standardised neuropathological consensus criteria for AD [5], dementia with Lewy Bodies (DLB [6], FTL [7], Corticobasal degeneration (CBD) [8], and progressive supranuclear palsy (PSP) [9]. Co-morbidities were noted. The clinical information was collected from electronic patient records and notes from neurologists and compared with neuropathological diagnosis made.

Results

Of the 275 donations frozen and formalin fixed tissue was available on 119 and formalin tissue only on 156 cases. There were 169 males and 106 females. The age ranged from premature stillbirth infants to 92 years of age with the bulk of referred brains (N=77) ranging from 60-69 years. Neurodegenerative disorders constituted the majority of the referrals (N=141; 51.3%). The remainder of the donations were categorized as traumatic (N=27), cerebrovascular (N=26), neoplastic (N=25), epilepsy (N=24), and 'miscellaneous' group (N=15). No abnormality was detected in 17 brains donated (Figure 1).

Of the neurodegenerative donations (N=141) (Table 1), the majority were AD (N=41) (Figure 2), followed by MND (N=32). In an additional three cases with clinical diagnosis of MND, two could not be confirmed as the spinal cords were unavailable and remainder showed generalised accumulation of Tau; appearances consistent with Frontotemporal dementia (FTD) with MND. Six donations had fronto-temporal dementia with co-existent MND present in two. Movement disorders were represented by idiopathic parkinson's disease (N=14) and a range of parkinson's 'plus' disorders such as PSP (N=18), Lewy body disease (N=10) (Figure 2), multiple system atrophy (MSA) (N=5) (Figures 3 and 4) and CBD (N=4). Chronic traumatic encephalopathy (CTE) accounted for one case [10]. Friedreich's ataxia accounted for two cases and Huntington's disease for one case. The remaining four cases included leukodystrophy, hereditary spastic Para paresis, idiopathic neuropathy, and subacute combined degeneration of the cord.

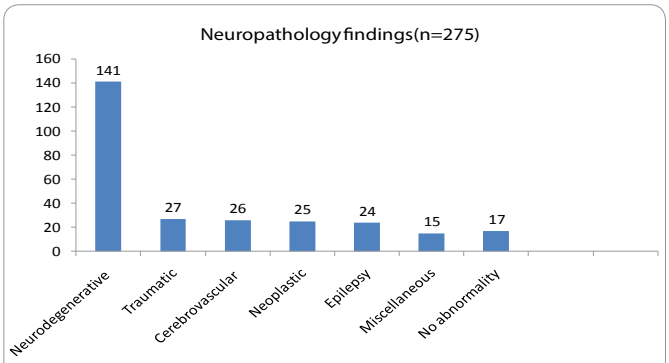

Figure 1: Showing the breakdown of neuropathological diagnoses in all donated brains in Dublin brain bank.

Neurodegenerative disease: Pathology Findings	Number of Cases
Alzheimer's disease (AD)	41
Motor neuron disease	30
Motor neuron disease-Frontotemporal degeneration	2
Progressive supranuclear palsy	18
Parkinson's disease	14
Diffuse Lewy body disease	10
Multiple system atrophy	5
Corticobasal degeneration	4
Frontotemporal lobar degeneration	6
Combined AD and cardiovascular disease	1
Chronic traumatic encephalopathy	1
Friedereich's ataxia	2
Huntington's disease	1
Hereditary spastic paraparesis	1
Idiopathic Neuropathy	1
Leukodystrophy	1
Spinal cord degeneration	3
Total	141

Table 1. Showing subtypes of neurodegenerative disease in brain bank.

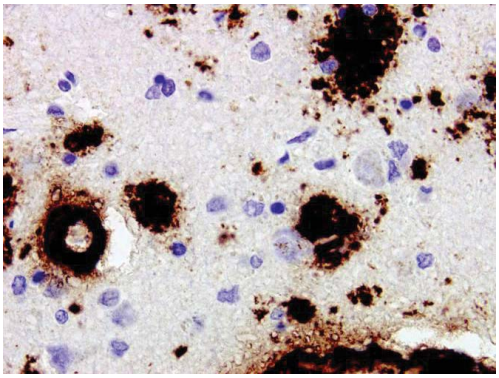

Figure 2. Saggital section of a case of Alzheimer's Disease showing marked fronto-temporal atrophy (2A). Superficial spongiosis noted on haematoxylin and eosin X 20 (2B). Tau showing senile plaques and neurofibrillary tangles x 40 (2C) and BA4 showing amyloid plaques and amyloid angiopathy (2D) X 40.

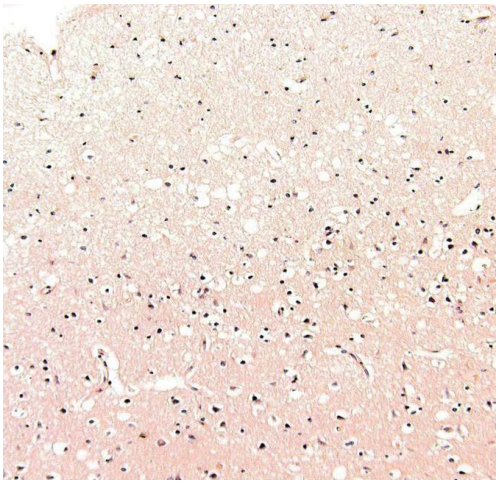

Figure 3. Lewy body dementia with superficial microvesicular spongiform change on haematoxylin and eosin X 20 (3A). Pigmentary incontinence in the substantia nigra x haematoxylin and eosin X 20 (3B). Lewy bodies in pigmented cells of the substantia nigra x 60 (3C). Alpha Syneuclin positivity x 60 (3D).

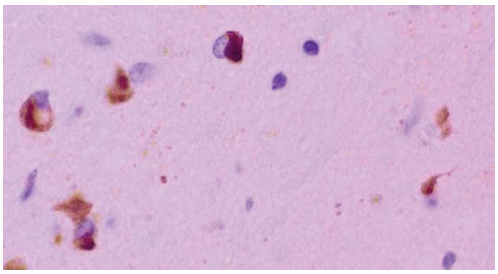

Figure 4. Pallor of the substantia nigra (4A) and slate-grey discolouration of the Putamen (4B) in a case of Multiple Systems Atrophy. Neuronal cytoplasmic inclusions haematoxylin and eosin x 60 (4C) and glial cytoplasmic inclusions Alpha Syneuclin x 40 (4D).

With respect to the cerebrovascular cases (Table 2), the majority were due to infarction (N=13). Haemorrhage accounted for five cases and there were two cases of cerebral amyloid angiopathy [11]. Neoplastic disease accounted for 25 cases and the most common

Cerebrovascular disease: pathological findings	Number of Cases
Infarct	13
Haemorrhage	5
Arteriosclerosis	2
Amyloid angiopathy	2
Aneurysm	2
CADASIL	1
Hypoxic-ischaemic encephalopathy	1
Total	26

Table 2. Showing pathological findings in cerebrovascular disease

Neoplastic disease: *Pathology Findings*	Number of Cases
Glioblastoma	7
Astrocytoma	4
Meningioma	3
Paraneoplastic syndrome	3
Non-Hodgkin's lymphoma	2
Metastatic disease	1
Adenocarcinoma	1
Subependymoma	1
Pituitary Adenoma	1
Leukaemia	1
Myeloma	1
Total	25

Table 3. Showing pathological findings in neoplastic category.

group was glioblastoma (N=7) (Table 3). The "miscellaneous" category included meningitis (N=1), muscular dystrophy (N=1), preterm infants (N=2), multiple sclerosis (N=6), neuropathy (N=1), demyelination (N=1), hypoxic-ischaemic encephalopathy (n=1), Niemann-Pick Type C (n=1), and West syndrome (N=1). Seventeen brains with no detected neuropathological abnormality were cognitively normal adults who donated their brains for research.

Concordance between the dominant clinical and dominant pathologic findings was present in 86.5% of neurodegenerative cases (Table 4). Discordance occurred mainly in donations with dementia (N=9), parkinsonian disorders (n=7), spinal cords were unavailable in two cases of motor neuron disease and in one case of clinically suspected to have motor neurone disease was found to have pathologic FTD-MND. Of the 141 neurodegenerative cases dual pathology was identified in 35 (35/141; 24%). Combined neurodegenerative and cerebrovascular disease occurred in 21 cases (60%). Combined neurodegenerative diseases occurred in 14 of the 35 cases (40%): mainly Alzheimer's together with a Parkinson's plus disorder.

Discussion

Since its inception in 2008, there are 275 donations to the Dublin bank and half of those have neurodegenerative pathology. The most significant observation in this study was the strong concordance between the clinical diagnosis and final pathological diagnosis (86.5%), supporting the observation that pathology can be predicted on clinical grounds with a high degree of accuracy [2]. Despite the fact that cases were derived from several sources the single most important factor in the discordant cases was the long interval between clinical diagnosis and death. This ranged from 3-10 years.

Most discordant cases were in the dementia group (N=9) (Table 4). Discordance between the clinical and pathologic findings in patients with dementia emphasises that patients sharing a common

Discordance in neuropathology and clinical diagnosis:	
Clinical Diagnosis	*Pathology Diagnosis*
Dementia (n=9)	
Alzheimer's disease	FTLD-FUS
Diffuse Lewy body disease	Parkinson's disease
FTLD	Diffuse Lewy body disease
FTLD	Alzheimer & Lewy body disease
FTLD	Alzheimers Disease
FTLD	Chronic traumatic encephalopathy
FTLD PPA	Alzheimer's disease
FTLD PPA	Alzheimer's disease
Normal cognition	Alzheimer's disease
Parkinsonism (n=7)	
Idiopathic Parkinson's disease	Progressive supranuclear palsy
Idiopathic Parkinson's disease	Tauopathy
Multiple system atrophy	Progressive supranuclear palsy
Progressive supranuclear palsy	Alzheimer's disease
Progressive supranuclear palsy	Alzheimer's disease
Corticobasal degeneration	Multiple system atrophy
Corticobasal syndrome	Alzheimer's disease
Motor neuron disease (n 3)	
Motor neurone disease	Minimal neuronal loss – spinal cord not available
Motor neurone disease	spinal cord not available
Motor neurone disease	Primary tauopathy: PSP or CBD
Total	***19***

Table 4. Showing cases with discordance in neuropathological and clinical diagnosis.
FTLD: Frontotemporal lobar degeneration, FTLD PPA: Frontotemporal lobar degeneration primary progressive aphasia: FTLD-FUS: Frontotemporal lobar degeneration with fused in sarcoma (FUS) inclusions

pathology are not clinically homogenous [2]. In AD, in particular there are marked phenotypic variations. In many AD patients, memory impairment is the initial and dominant feature making the clinical diagnosis relatively easy. Patients may however present with disorders of language, perception or spatial skills and are then often clinically labelled as primary progressive aphasia. FTLD is genetically and pathologically a heterogenous group of disorders that cause dementia especially in a young population. The behavioural variant FTD which is one of the most common clinical forms was found to be heterogeneous in a previous neuropathological study [12]. The involvement of multi-component cognitive function might contribute to the clinical and anatomical heterogeneity. In patients with primary progressive aphasia there is no clinical pattern pathognomonic of a specific neuropathology type, highlighting the critical role of biomarkers for diagnosing the underlying neuropathological disease. Patients with FTLD may be clinically diagnosed with AD and vice versa as observed in our cases. Similarly, corticobasal degeneration may be confused with AD.

Of note one of our patients though clinically well had a pathological burden of amyloid and tau. This raises the question as to why some individuals retain cognitive function right up to the time of death and yet have a very high burden of amyloid and Tau pathology at brain examination - a burden that without knowledge of the patient's cognitive status might erroneously lead to an autopsy diagnosis of dementia. In a recent study it has been shown that ante mortem hippocampal and total brain volumes are significantly larger in patients with normal cognitive function after adjusting for gender, age at magnetic resonance imaging [MRI] of brain, time from MRI to death, Break stage, CERAD neuritic plaque score, and overall presence of vascular disease. It was concluded that larger brain and larger hippocampal volumes are associated with preserved cognitive function during life despite a high burden of AD pathologic lesions at death [13].

Other discordant cases were in the 'Parkinson plus' group. Making the diagnosis of Parkinson's disease, a common clinical situation faced by neurologists, geriatricians and general physicians is not always easy [14]. The clinical diagnosis is dependent on interpreting a combination of clinical features, their onset and response to treatment. This is subjective and so liable to error. The diagnostic accuracy of the commonest parkinsonism syndrome, idiopathic Parkinson's Disease (PD) is reported to be very high (98%) in tertiary hospitals by movement disorder specialists. For general neurologists the reported accuracy in the early 1990's was 76%, which improved to 90% a decade later [15]. Atypical parkinsonian syndromes are rare making the accuracy of clinical diagnosis even more challenging. For PSP and MSA it has been reported to be 78% and 86% respectively [16,17]. Although it is reported that the diagnosis of CBD is highly accurate, in our cohort there were two cases with neuropathological discordance. The sensitivity of CBD clinical diagnosis is low with only half of patients being diagnosed during life [18]. In the Parkinsonian syndromes defects in vertical gaze tend to be identified with progressive supranuclear palsy (PSP) [19]. PSP and AD can be clinically confused in some cases, with both have similar age of onset and progressive course with varying degrees of cognitive and extrapyramidal features. If supranuclear vertical gaze palsy is present, it should help to differentiate PSP from AD. Similarly Amnesia is a hallmark of AD. Early postural instability and falls with early onset akineto-rigid Parkinsonism is also seen with PSP. If present, aphasia is also usually associated with AD. Our results highlight the difficulties faced in making the clinical diagnosis of parkinsonian syndromes and the need to pay attention not only to the atypical features but also to secondary extra pyramidal symptoms in patients with primary cognitive problems [14].

The burden of vascular and AD type pathologies are leading and independent causes of dementia in the older age groups, suggesting an additive or synergistic effect of both lesion types on cognitive decline [20]. This is borne out in our study with most of our cases with dual pathology i.e, combined AD and cerebrovasular disease (24%) being older with three surviving into the tenth decade. The other type of dual pathology we identified was a combination of AD and diffuse Lewy body disease or Parkinson's disease. Here cognitive decline is due to the combined burden of α-synucelin pathology with senile plaques and phosphorylated tau adding to the overall deficits [21]. Imaging modalities such as amyloid-beta positron emission tomography (PET) imaging (Florbetapir Aβ imaging) of AD pathology may aid the clinical evaluation of parkinson's disease dementia patients to determine if the cognitive decline is due to the presence of Aβ accumulation [22] and this has been confirmed at autopsy. There is also evidence that Tau PET ligand can be used to accurately quantify the distribution of hyperphosphorylated tau protein as confirmed neuropathologically in MAPT mutation carriers [23]. Although these emerging imaging modalities are helpful, if available in a clinical scenario, it is still critical to gain more understanding of the validity, and neuropathological confirmation is necessary at present.

A limitation of our brain bank to date is the overrepresentation of neurodegenerative disease and the relative paucity of other cases and of controls. Recruiting neurologic disease free controls is difficult

because although people may be willing to donate their brains, very few programmes focus on recruiting healthy controls. Several barriers to obtaining "control brains" have been identified. Firstly, healthy donors may live for many years after giving consent and clinical follow-up is expensive, potentially involving inconvenient annual neurologic assessments. Similarly, there may also be a paucity of clinical information where brains are donated following medico-legal autopsies.

Nonetheless this has not limited our ability to collaborate with other researchers with approximately 88 samples being sent to various studies [24-30]. Going forward our aim is to attract more controls to our brain bank and also encourage donations from other disease categories. Dublin Brain bank provides an excellent opportunity for neuroscience researchers in Ireland to study complex processes underlying these conditions. Results of this research will improve quality of services provided to patients and ultimately quality of life in patients with different neurological conditions. Neuroscience researchers are encouraged to apply for tissue samples.

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