Title:

UNDERSTANDING NEURODEGENERATION: A NEUROPATHOLOGIST'S PERSPECTIVE

RESEARCH ACHIEVEMENTS

This document together with an accompanying Curriculum Vitae, has been prepared to support an application for consideration for the degree of *Doctor of Science* at the University of Warwick.

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Declaration

I declare that five of the 105 publications discussed in this document (Refs: **56, 57, 59, 61, 62**) were part of my PhD by Published Work at the University of Warwick.

Publication metrics

Peer-reviewed publications	N = 332
Book chapters	N = 21
Hirsch Index (Web of Science; ResearcherID: A-8732-2010)	78
Hirsch Index (Scopus)	83
Hirsch Index (Google Scholar)	93
Citations (Web of Science)	22,842
Citations (Scopus)	24,576
Citations (Google Scholar)	32,264

Grant income

Total income: £3,407,900

Total income as primary investigator**:** £1,860,000

INTRODUCTION

I was introduced to research when, as member of the 'Scientific Student Association' of the Semmelweis Medical University, Budapest, Hungary, I joined a neurotoxicology laboratory where I was involved in a project which aimed to establish the effect of an insecticide on the brain function of experimental animals (**Ref**: 332 in the reference list given in the Curriculum Vitae document). After I had received my MD with distinction (*Summa cum Laude*) from the Semmelweis Medical University, I continued to maintain an interest in research during my specialist training with the aim of understanding better neurological diseases.

My dedication to combining academic work with clinical work, determined that I applied for a clinical academic position after successfully completing my training in Neuropathology in the UK and becoming a member of the Royal College of Pathologists.

Since my appointment as Senior Lecturer, Honorary Consultant Neuropathologist at the UCL Queen Square Institute of Neurology and The National Hospital for Neurology and Neurosurgery, London in 1991, I have led a research group and successfully completed several major research programs.

Initially, I established a close collaboration with other clinical scientists of our institution with expertise in research in different aspects of multiple sclerosis (MS). However, at around the mid-1990s my main research interest shifted to neurodegenerative diseases, in particular, to dementias and Parkinsonian movement disorders. I established new successful and longstanding collaborations with both clinical and basic scientists working in our institution, other UK or overseas institutions, active in these research areas. My research in neurodegenerative diseases was further strengthened with my appointment as the Neuropathologist Director of the Queen Square Brain Bank for Neurological Disorders (QSBB) in 2001, which houses a unique, large collection of movement disorder and dementia cases.

As a recognition of my academic achievements, I became Reader in Neuropathology in 2001 and Professor of Neuropathology in 2004.

Despite my retirement in 2013, I have continued to hold a part-time research position at the UCL Queen Square Institute of Neurology and have continued to lead a research group supported by a grant.

My publication list currently consists of 332 peer-reviewed publications and 21 book chapters. Since my retirement I have published 59 peer-reviewed papers and 2 book chapters.

As outlined in my Curriculum Vitae I have a significant teaching portfolio; I regularly contributed with lectures to the postgraduate courses organised by the UCL Queen Square Institute of Neurology, and I supervised 10 PhD students, several MSc and BSc students and have had significant grant income to support my research. I regularly give lectures at teaching courses organised by EuroCNS and other organisations. I have also supervised several post-doctoral scientists.

The publications that I have assembled and discuss in this document, demonstrate my long-standing interest and achievements in research in neurodegenerative diseases overarching over thirty years. In this area of research, I have published a total of 240 peer-reviewed papers and 17 book chapters. In addition, as defined by PubMed, I am a 'collaborator' of a further 22 peer-reviewed research papers with a neurodegenerative topic.

Of the 240 peer-reviewed papers and 17 book chapters with a neurodegenerative topic, I have selected 93 papers and 12 book chapters to support my application. These also include my latest publication from January 2020, which demonstrates that despite my retirement in 2013, I have remained active in research. In view of my initial research interest in multiple sclerosis, I have also included two frequently cited original publications in this topic and an editorial article to show my achievements in this area of research.

The references of the 105 publications (93 peer-reviewed papers and 12 book chapters), which support this application, are listed at the end of this document. In the reference list, I provide the DOI-s of the 93 peer-reviewed papers, which allow viewing full-length papers on the publishers' websites. Separately, the pdf-s of the relevant pages of the 12 book chapters are also given (see book chapters folder). My complete reference list is available in my Curriculum Vitae.

MAIN RESEARCH INTERESTS AND ACHIEVEMENTS

A) NEURODEGENERATIVE DISEASES

Since the mid-1990s, I have concentrated on research in neurodegenerative diseases, in particular, neurodegenerative dementias, such as novel cerebral amyloid diseases as well as frontotemporal dementias and movement disorders, including Parkinson's disease and atypical parkinsonian conditions.

A.1 CEREBRAL AMYLOID DISEASES: FAMILIAL BRITISH DEMENTIA AND FAMILIAL DANISH DEMENTIA

I was the neuropathologist lead of a research team which aimed to decipher the cause of and understand disease mechanisms underlying two closely related hereditary cerebral amyloid diseases observed in a large English family and a smaller Danish pedigree. This research was carried out in collaboration between my team and a research group of basic scientists at the New York University (NYU), School of Medicine with expertise in cerebral amyloid diseases, and also clinical researchers of the National Hospital for Neurology and Neurosurgery, Queen Square, London.

A.1.1 Our initial studies, published in ***Brain*** and ***Acta Neuropathologica*** aimed to extend our knowledge about the British pedigree and to understand the neuropathology of this condition (Ref: **1** current citations: 119; Ref: **2** current citations: 52; Ref: **3** current citations: 73).

A.1.2 In 1999 and 2000 our joint research led to the discovery of the causes of the two diseases, which we re-named familial British dementia (FBD) and familial Danish dementia (FDD). In these studies, we showed that both FBD and FDD are associated with unique mutations in the novel *BRI2* gene. Our paper which dealt with the British condition was published in ***Nature*** (Ref: **4** current citations: 322) while the study about the Danish pedigree was published in the ***Proceedings of the National Academy of Science, USA*** (Ref: **5** current citations: 224**).** In these two seminal studies, we showed that by abolishing the normal stop codon, both mutations (a Stop-to-Arg point mutation in the British pedigree, and a 10-nucleotide insertion mutation in the Danish kindred) result in elongation of the BRI precursor protein. Furin-like processing of the mutated precursor proteins releases the novel, 34 amino acid-long amyloid peptides, ABri in FBD and ADan in FDD, which are different from one another in their 12 C-terminal amino acids.

A.1.3 The discovery of the causes of the two diseases triggered several further, biochemical and neuropathological studies (Refs: **6-14**). Among others, we were the first, who were able to study with our newly generated antibodies specific to either ABri or ADan, the cerebral distribution of the ABri and ADan deposits in FBD and FDD cases, respectively. Among the many novel findings, our studies demonstrated that, as in Alzheimer' disease, in both FBD and FDD there are amyloid plaques, cerebral amyloid angiopathy and neurofibrillary tangles, despite the fact that there is no similarity between the Alzheimer disease's amyloid-β peptide and the two closely related amyloid peptides, ABri and ADan, indicating a general link between cerebral amyloid formation and neurofibrillary degeneration. We also showed that, as in Alzheimer's disease, the neurofibrillary tangles are composed of both major classes of the tau isoforms and that ultrastructurally the tau filaments forming neurofibrillary tangles are classical paired helical filaments in both FBD and FDD (Ref: **6** current citations: 94; Ref: **7** current citations**:** 86).

A.1.4 In one of our collaborative studies we investigated the morphological patterns and biochemical characteristics of ABri deposited in systemic organs. Our findings showed that a soluble form of ABri is circulating in the plasma of individuals carrying the Stop-to-Arg mutation and that post-translationally modified ABri species, biochemically similar to those deposited in

brain parenchyma and walls of cerebral blood vessels, widely deposit in blood vessels and parenchyma of peripheral organs such as pancreas and myocardium (Ref: **8**).

A.1.5 In another study we found a significant chronic inflammatory response to the ABri and ADan parenchymal and vascular amyloid deposits in FBD and FDD brains. In particular, we demonstrated by immunohistochemistry the presence of complement activation components of both the classical and alternative pathways as well as the neo-epitope of the membrane attack complex indicating that these pathways are fully activated. Using experimental approaches specific for the complement activation products, we showed that ABri and ADan are able to fully activate the complement cascade at levels comparable to those generated by $A\beta_{1-42}$ (Ref: **9**).

A.1.6 We performed a detailed morphological and biochemical study of the parenchymal and vascular amyloid deposits in FDD. As Aβ co-deposits with ADan in FDD, biochemical characteristics of the Aβ species were also determined (Ref: **10**).

A.1.7 We investigated the presence of so-called amyloid-associated proteins (AAPs) in FBD and FDD as we wished to understand better the role of such proteins in the process of amyloidogenesis. Accordingly, we performed immunohistochemistry for a number of AAPs and found that the deposition patterns of AAPs in both FBD and FDD are similar to those seen in Alzheimer's disease indicating a generalised role for AAPs in amyloid formation. Their presence in so-called preamyloid lesions supports the notion that AAPs may also play a role in the early steps of amyloid fibril formation (Ref: **11**).

A.1.8 By using molecular techniques, we demonstrated that the source of the BRI precursor protein is primarily neuronal in the central nervous system. This finding has mechanistic significance, as it lands indirect support for the now widely accepted hypothesis that the amyloid peptides responsible for cerebral amyloid angiopathy are of neuronal origin in a number of cerebral amyloid diseases (Ref: **12**).

A.1.9 As a result of our work in this area, our team was invited to write several review articles (Ref: **15** current citations: 127; Ref: **16** current citations: 196; Ref: **17** current citations: 32; Ref: **18** current citations: 153; Refs: **19, 20**) and book chapters (Refs: **21-24**). The importance of our work is also highlighted by the fact that this research was supported by a grant from the National Institute of Health, USA.

Total number of publications in this area (see Curriculum Vitae): 29 peer-reviewed papers, 4 book chapters

A.2 FRONTOTEMPORAL DEMENTIAS

Since the 1990s my research group has carried out several major studies in the field of frontotemporal dementias/frontotemporal lobar degenerations (FTLDs). These studies were carried out in close collaboration with a group of clinical neurologists, geneticists and other scientists with an interest in dementias, who work at the UCL Queen Square Institute of Neurology. Some of the studies were carried out in collaboration with scientist of other UK or overseas institutions.

A.2.1 In a study, published in ***Brain***, we described that FTLD with ubiquitin-positive inclusions (FTLD-U), which at the time of our study was still a novel entity, is the underlying pathology in semantic dementia (Ref: **25** current citations: 111).

A.2.2 We were among the first to demonstrate that, in contrast to previous suggestions, 'dementia lacking distinctive histological features' is a rare condition, as we found that ubiquitin-positive positive inclusions are present in the vast majority non-tau FTLDs. This finding also implied that still unknown disease protein(s) were responsible for the majority of the non-tau FTLDs (Ref: **26** current citations: 127).

A.2.3 I led the research, in which we were the first to characterise a novel, sporadic frontotemporal dementia, which we described under the term of 'neurofilament inclusion body disease' (NIBD) (the condition subsequently became known as neuronal intermediate filament inclusion disease or NIFID) (***Brain*****,** Ref: **27** current citations: 142). Several years later, after the discovery that mutations of the *FUS* (fused in sarcoma) gene cause familial ALS type 6 and that the inclusions in NIBD/NIFID are FUS-positive, this condition has been re-classified as FTLD with FUS-positive inclusions (FTLD-FUS).

Studies described under B.2.2 and B.2.3 were carried out by a visiting research fellow under my supervision, who is now professor of Neurology at the Mayo Clinic, Rochester, Minnesota.

A.2.4 Through my long-standing international collaboration and collaboration with the Dementia Research Centre at our institution, we were able to study a large cohort of cases of the novel FTLD-FUS. The findings of this study, using neuropathological and biochemical approaches were published in ***Brain*** (Ref: **28** current citations: 44).

A.2.5 Using the same FTLD-FUS cohort, we showed for the first time by neuropathological and biochemical methods that transportin plays an important role in the disease mechanism of FTLD-FUS. Our study was published in ***Acta Neuropathologica*** (Ref: **29** current citations: 35).

A,2,6 We had the opportunity to study one of the largest cohorts of frontotemporal dementia cases in the UK, which had been clinically characterised using neuropsychological tests, neuroimaging, genetics and laboratory tests at the Dementia Research Centre, The National Hospital for Neurology and Neurosurgery, Queen Square. These cases provided an excellent opportunity for us to establish important clinicopathological correlations. This study was published in ***Brain*** (Ref: **30** current citations: 161).

A.2.7 We carried out or contributed to studies aiming to understand better the effect of mutations of the *C9orf72* gene in frontotemporal dementias (Refs: **31-33;** Ref **33** is listed by Web of Science as 'highly cited') .

A.2.8 I was the lead author of a review article commissioned by the Editor of ***Neuropathology and Applied Neurobiology*** (Ref: **34** current citations: 64) and was also a co-author of a review, published in ***Lancet Neurology***, which was prepared with contributions by several research groups of the UCL Queen Square Institute of Neurology (Ref: **35** current citations: 120, listed by Web of Science as 'highly cited').

A.2.9 I was invited to be the **Guest Editor** of the 2019 **Annual Review issue of *Neuropathology and Applied Neurobiology***, which was entirely dedicated to frontotemporal dementias and published in 2019. This special issue includes six articles, including our own introductory article (Ref: **36**), prepared by research groups which are leaders of their chosen field.

A.2.10 Following our publication on a rare, novel form of FTLD (Ref: **37**), for which we coined the now widely accepted term globular glial tauopathy (GGT), the Editor of ***Acta Neuropathologica*** invited me to organise and lead a consensus project aiming to establish diagnostic criteria of GGT. GGT is a sporadic frontotemporal dementia with tau-positive pathology (FTLD-tau). The results of this large, international multi-centre project were published in 2013 (Ref: **38** current citations: 78).

A.2.11 I was also the lead author of a book chapter dedicated to the description of the neuropathology of neurodegenerative dementias, in which a significant section was dedicated to frontotemporal dementias (Ref: **39**).

A.2.12 I was part of the international panel which established the first modern neuropathological classification of FTLDs taking into account disease proteins forming characteristic inclusions and genetic abnormalities associated with the different forms (Ref: **40** current citations: 264) and contributed to its revision (Ref: **41** current citations: 490).

My work in the frontotemporal dementia field was supported by a grant from Alzheimer's Research UK, which enabled me to consolidate our research in this field. My colleague, Dr Tammaryn Lashley, who was my PhD student and subsequently became postdoctoral scientist working in my group, developed a strong research interest in frontotemporal dementias ensuring the continuity of research in this field in the QSBB. Her independent work is now acknowledged both nationally and internationally. She is currently Reader and is supported by several major grants, enabling her to lead her own, still expanding research group.

Total number of publications in this area (see Curriculum Vitae): 54 peer-reviewed papers; 1 book chapter; Guest Editor of the special Annual Review issue of *Neuropathology and Applied Neurobiology*.

A.3 MOVEMENT DISORDERS

Understanding the neuropathological basis of different forms of atypical parkinsonian disorders such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA), and deciphering the basis of pathological and clinical progression in these disorders as well as in Parkinson's disease (PD), have been a major research interest for me and other researchers of our brain bank.

A.3.1 Parkinson's disease

A.3.1.1 As data emerged from *in vitro* and, also *in vivo* animal studies indicating a 'crosstalk' between α-synuclein and the Alzheimer's amyloid-β peptide, we wished to investigate whether there is evidence for such an interaction in human disease. Using clinically well-documented PD cases, available in our brain bank, we performed two studies, which provided evidence for an association between the presence and severity of Alzheimer's pathological changes and the severity of the α-synuclein pathology in humans. Consequently, our data supported the notion that the Alzheimer's amyloid-β peptide contributes to disease progression and dementia in PD. Our first study was published in ***Acta Neuropathologica*** **(**Ref: **42** current citations: 89) while the second study was published in ***Brain*** (Ref: **43** current citations: 263). The second paper (Ref: **43**) is listed by Web of Science as 'highly cited'.

A.3.1.2 Our research, carried out jointly with a group of scientists at the University of Lund, Sweden, for the first time provided indirect evidence for the hypothesis that cerebral α-synuclein pathology may spread via prion-like mechanism in humans. We observed that embryonal mesencephalic dopaminergic neurons, transplanted into the striatum of PD patients, develop Lewy bodies when patients survive at least ten years post-transplantation. This work resulted in a frequently cited paper, published in ***Nature Medicine*** (Ref: **44** current citations: 893) and a review/concept article in ***Nature Reviews Neuroscience*** (Refs: **45** current citations: 208). The work was equally shared between the Lund group and our research group and I led the study at UCL. It was our group at UCL, which recognised that our findings support the hypothesis of a prion-like disease spread and suggested that this hypothesis should be included in the ***Nature Medicine*** paper. My contribution to this project is shown by the fact that I am 'shared senior author' of the ***Nature Medicine*** (Ref: **44**) paper and last author of the paper, published in ***Nature Reviews Neuroscience*** (Refs: **45**).

A.3.1.3 In a series of clinicopathological studies, all published in ***Brain***, we established pathological features underlying clinical progression in PD (**Refs: 46-48** current total citations of the three papers is 516).

A.3.1.4 We also had the opportunity to study a number of genetically determined parkinsonian variants.

A.3.1.4.1 After the discovery by geneticist colleagues of our institution, which indicated that mutations of the *PINK1* gene are associated with a recessive form of parkinsonism, we were

the first to characterise the distribution of the PINK1 protein in the human brain. The data of this study were published in ***Brain*** (Ref: **49** current citations: 233).

A.3.1.4.2 We also studied an autosomal recessive disease due to mutations in the *PLA2G6* gene (Ref: **50** current citations: 101).

A.3.1.4.3 Our studies have conclusively established that, contrary to previous reports, the condition due to mutations in the *PANK2* gene (Ref: **51**) and the neurodegeneration associated with *PARK2* gene mutations (Ref: **52**) are not α-synucleinopathies.

A.3.1.4.4 In our brain bank a large cohort of PD cases were identified with heterozygous glucocerebrosidase mutations, which are important genetic risk factors of sporadic PD and we performed a clinicopathological study (Ref: **53** current citations: 322; listed by Web of Science as 'highly cited').

A.3.1.4.5 Our research group also characterised the neuropathology in cases with the novel G51D *SNCA* mutation. In this study we demonstrated that this mutation is associated with a neuropathological phenotype, in which features of both PD and MSA are present. Our study contributed to a better understanding of the link between α-synuclein biology and disease phenotype. This study was published in ***Acta Neuropathologica*** (Ref: **54** current citations: 194) and is listed by Web of Science as 'highly cited'.

A.3.1.4.6 We also studied the expression of the DJ1 protein in normal human brain and in PD (Ref: **55** current citations: 289).

A.3.2 Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD)

A.3.2.1 Our research group played a key role in identifying the neuropathological, biochemical and genetic basis of atypical forms of PSP (Refs: **56-61**) and understanding the patterns of disease progression in both PSP and CBD (**Refs: 59**, **62**, **63**). Five of the above publications were published in ***Brain*** (Refs: **56-59, 62)**. Five publications (**Refs: 56, 57, 59, 61, 62**) from this area of research formed the basis of my PhD (PhD by Published Work, University of Warwick).

These studies underpinned the concept of atypical PSP (Refs: **56-61**) and provided neuropathological, biochemical and genetic data supporting this hypothesis.

A.3.2.2 In 2014 we started a largescale study of CBD, which has been supported by a grant from CBD Solutions AB, Stockholm, Sweden. The long-term aim of this project is to understand disease progression in CBD and also decipher the biological basis of the different clinicopathological variants of this condition. In the first of two recent studies (Ref: **62**), published in ***Brain***, we identified for first time the cerebral networks that are first affected in CBD. This information is essential for understanding disease progression in this condition (Ref: **62**) and could be the foundation of future imaging studies using appropriate PET traces, which will wish to detect disease progression in humans *in vivo*. The significance of our findings is underpinned by the fact that the Editor of ***Brain*** commissioned a scientific commentary to accompany our paper (Kobylecki and Mann, *Brain 139:3059-3062, 2016*). In our second study (Ref: **63**), published in ***Acta Neuropathologica*** (latest impact factor: 18.174) we characterised a fulminant variant of CBD. Further studies aiming to characterise the tau species that may influence disease progression are in progress.

The paper that introduced the concept of PSP-Parkinsonism (PSP-P) (Ref: **58**) has been cited 386 times while the study in which we showed that the two major PSP variants, the classical PSP-Richardson's syndrome (PSP-RS) and PSP with parkinsonism (PSP-P), are associated with characteristic tau pathologies (Ref: **59**), has been cited 209 times. The pioneering contribution made by our research group at the QSBB to identifying PSP variants and their genetic, biochemical and neuropathological characteristics, is widely acknowledged by researchers of other prestigious centres which are active in the field of PSP research (*Dickson*

DW et al. Neuropathology of variants of progressive supranuclear palsy. Curr Opin Neurol 23:394–400, 2010).

A.3.2.3 The QSBB was the second largest contributor of pathologically confirmed cases to an international, multi-centre study which aimed to establish genetic risk factors of PSP. The results of this large-scale study using genome wide association (GWA) approach, were published in ***Nature Genetics*** (Ref: **64** current citations: 258).

A.3.2.4 In further studies we investigated the role of astrocytes in Parkinsonian disorders (Refs: **65**), including PSP and CBD, carried out clinicopathological studies (Refs: **66**) and, using 9.4 T MRI of post-mortem tissue with histological validation, defined the MRI neuroanatomy of the subthalamic nucleus, which is prominently affected in PSP (Refs: **67)**. The study on astrocytes (Refs: **65**) was carried out by a visiting PhD student from the University of New South Wales, Sydney, Australia, who spent six months in my laboratory and carried out a significant part of this project under my supervision.

A.3.3 Multiple system atrophy (MSA)

A.3.3.1 Our research group had the opportunity to study the largest cohort of post-mortem cases with MSA held by any brain bank and is available in the QSBB, which resulted in a significant number of original publications and reviews (Refs: **68-74**). The data of our studies underpinned the role of oligodendroglia in the MSA neurodegenerative process.

Three of the above studies (Refs: **68-70**) were carried out by a visiting research fellow who is currently Professor of Neurology at Niigata University, Niigata, Japan. One of the three studies was published in ***Brain*** (Ref: **68** current citations: 258).

A.3.3.2 By invitation, I was part of the panel which, under the aegis of the National Institute of Neurological Disorders and Stroke (NIH, USA), established clinical and neuropathological diagnostic criteria of MSA (Ref: **75** current citations: 1186 and Ref: **76** current citations: 136). I was one of the two neuropathologists who were invited to participate in the work of the panel.

A.3.4 Review articles and book chapters with a 'Movement Disorder' topic

A.3.4.1 We published frequently cited reviews and the high impact journals in which such review articles appeared include ***The Lancet*** (Ref: **77** current citations: 1132 - listed by Web of Science as 'highly cited'), ***Nature Reviews Neuroscience*** (Ref: **45** current citations: 207) and ***Acta Neuropathologica*** (Ref: **78** current citations: 191).

A.3.4.2 I was part of the team, which wrote the large, comprehensive chapter entitled 'Akinetic Movement Disorders' for the 8th edition of **Greenfield's Neuropathology** (Ref: **79**). Since its first edition in the 1950s, this textbook, which now consists of two large volumes, has been the leading reference book in Neuropathology. In the above chapter, among others, I was responsible for writing the sections on PD, PSP and CBD. In the most recent 9th edition of **Greenfield's Neuropathology**, I was the lead author of the chapter entitled 'Extrapyramidal Disorders' (Ref: **80**).

A.3.4.3 I was also co-author of five further book chapters related to movement disorders (Refs: **81-85**).

Projects related to Movement Disorders have been supported by Parkinson's UK, The Sarah Matheson Trust, MSA Trust, Progressive Supranuclear Palsy Association and CBD Solutions.

Total number of publications in Movement Disorders (see Curriculum Vitae): 102 peer-reviewed papers; 5 book chapters

A.4 CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE)

In the past fifteen years, considerable attention has been paid to CTE, which has emerged as an important consequence of repetitive, relatively mild head injury. CTE has been frequently documented post-mortem in individuals, who pursued contact sports and, also in military personnel with blast injuries. Consequently, CTE is now considered a condition of significant public health importance.

A.4.1 Our first major post-mortem study of young individuals pursuing contact sports such as boxing and rugby and who died of head injury, was one of the first studies, which provided indirect evidence for involvement of small cortical blood vessels in CTE. This observation supports the currently widely held view that damage to small cortical blood vessels during repetitive head injury is the likely primary event that initiates changes in neurons and glial cells, which finally result in tau hyperphosphorylation and filament formation in both neurons and glia (Ref: **86** current citations: 180).

A.4.2 We established the prevalence of CTE in a cohort of neurodegenerative cases and normal controls available in our brain bank (Ref: **87** current citations: 35), and our findings indicate that mild CTE pathology may not be uncommon in this patient population. This study was published in ***Acta Neuropathologica***.

A.4.3 We also studied brains of ex-footballers with dementia and showed that CTE may occur in individuals with a long career in football (soccer) and concluded that CTE may contribute to dementia in such individuals (Ref: **88** current citations: 38). This study, published in ***Acta Neuropathologica*** in 2017, has attracted significant attention in both the UK and international media with its Altmeric score being such that it is in the top 5% of all research outputs scored by Altmetric.

A.4.4 I was part of the team which recently re-examined a large, archival collection of cases of ex-boxers with suspected CTE (Ref: **89**). This cohort was originally studied by researchers of the Institute of Psychiatry, London (Corsellis et al) in the 1970s and has been considered the first systematic investigation of CTE. However, this frequently cited study had been carried out before modern techniques such as immunohistochemistry became available, hence its re-investigation was timely. Our study these archival cases demonstrated that, using up-to-date methods and current diagnostic criteria, CTE can be confirmed only in about 50% of the cases originally studied by Corsellis's group. These data indicate that a.) high impact sports do not inevitably lead to CTE and that b.) environmental and/or genetic factors may also be required for the development of this disorder.

A.4.5 In an invited review for ***Neuropathology and Applied Neurobiology*** we summarised the recent developments, including the new developed diagnostic criteria of CTE (Ref: **90**).

Total number of publications in this area of research (see Curriculum Vitae): 7 peer-reviewed papers (see Curriculum Vitae)

A.5 OTHER NEURODEGENERATIVE TOPICS

A.5.1 Other areas of research include studies on dystonias (Ref: **91**), vascular parkinsonism (Ref: **92** current citations: 202), Alzheimer's disease (Refs: **93-95**), the association of the p.A152T *MAPT* variant with tauopathies (Ref: **96**).

A.5.2 I was member of the team (and one of the lead authors of a consensus paper), which established the diagnostic criteria of the novel anti-IgLON5 tauopathy (Ref: **97** current citations: 47).

A.5.3 Further publications include a study on a novel form of human prion disease (***New England Journal of Medicine*** Ref: **98**), a Commentary entitled 'Clinical Implications of Basic Research (***New England Journal of Medicine*** Ref: **99**), studies on the tau isoform

composition of different tauopathies (Ref: **100, 101**), and a practical guidance for the neuropathological diagnosis of dementias, which summarises the experience obtained by both clinicians and neuropathologists at the National Hospital for Neurology and Neurosurgery (Ref: **102**).

Total number of publications in this area of research (see Curriculum Vitae): 47 peer-reviewed papers

B. DEMYELINATING CONDITIONS; MULTIPLE SCLEROSIS

My research in this area led to the first systematic description of the neuropathological basis of the primary progressive form of multiple sclerosis (PPMS), which was a rather poorly understood entity at the time when this study was carried out. This study was particularly timely as in the early 1990s emerging MR imaging data questioned the inflammatory nature of this form of MS. Our neuropathological investigations confirmed unequivocally that PPMS is an inflammatory condition with the caveat that the inflammatory changes are significantly less severe in PPMS than in the common, secondary progressive form of MS (Ref: **103** current citations: 245). In the second study we systematically investigated the involvement of the cerebral cortex in MS and demonstrated that, in contrast to previous suggestions, cortical lesions are common. This study also provided a detailed morphological classification of cortical lesions and mapped their relationship to cortical venous blood channels (Ref: **104** current citations: 537). I was the lead or senior author of both studies, which were published in ***Brain***. As a recognition of my contribution to the MS field, I was invited to write an editorial article for ***Brain*** (Ref: **105**).

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