

BRAIN MATTERS 2019

The newsletter from Queen Square Brain Bank
for Neurological Disorders



Professor Tom Warner,
Clinical Director of Queen Square
Brain Bank welcomes you to the
latest edition of Brain Matters.

The continuing strategy of **Queen Square Brain Bank** has been to curate a world-class collection of brain tissue to further our own and global research into the causes and treatments of neurodegenerative illness. 2017 was a record year for brain donations with a total of 112 received. It is a testament to the dedication and hard work of the administrative, laboratory and neuropathology staff that we were able to process and diagnose these donations, making tissue available for vital investigations into disorders such as Parkinson's disease, dystonia and dementia. It has been a productive year and a number of important projects are highlighted in this edition of Brain Matters. As you can see the articles reflect a common theme, the crucial influence that pathological findings have on clinical practice.



Professor Tom Warner

Previously we reported the risk of repeated blows to the head in professional football players in developing chronic traumatic encephalopathy, which is a potential cause of dementia. We have now begun a collaborative study with The International Concussion & Head Injury Research Foundation and Dr Michael Turner, former medical officer to the British Horse Racing Authority, to collect brain tissue from ex jockeys and examine the effect of head injuries to the brain. This joint venture featured in the *Daily Telegraph* and *Horse and Hound*.

Other highlights include a publication by one of our clinical research fellows, Dr Eduardo De Pablo-Fernandez, suggesting that type 2 diabetes increases the risk of developing Parkinson's disease, which aroused interest in the national press and world media.

As always we are grateful to those who have given money to help us, in particular Luke Courtney, John Toomey and Charlie Sawyer who all ran the 2018 London Marathon raising £2,300.

The QSBB team appreciate the fact that none of our achievements would be possible without the selfless generosity and support of our brain donors and their families, to whom we send our sincere thanks.



Research

Dr Daniela Hansen, Clinical Research Fellow working with QSBB Directors, Professors Tom Warner and Janice Holton, gives an update on her studies into the pathology of memory problems in Lewy body dementias:

Cerebral amyloid angiopathy (CAA) refers to a group of disorders affecting brain vessels. The protein amyloid forms dense clumps if allowed to build-up inside blood vessel walls of the brain and brain surface. This can result in haemorrhage (bleeding), stroke and some dementias, and contributes to nerve cell loss. These problems are likely to be due to restricted blood supply or micro-bleeds, both of which can be seen on an MRI scan.

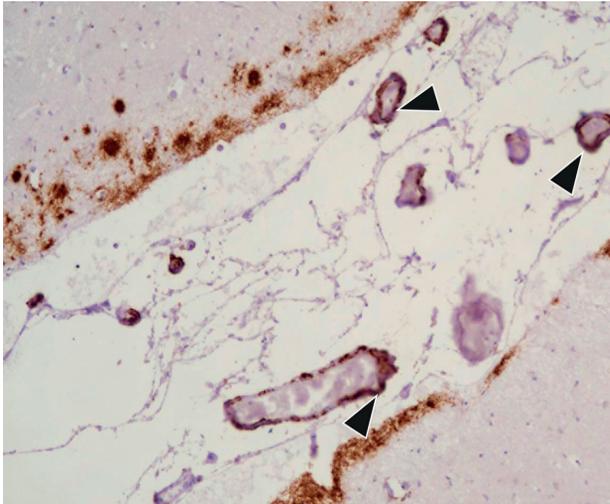


Image above: Microscopic view of cerebral amyloid angiopathy seen (with arrows) in vessel walls.

Previous studies have shown a link between CAA and memory decline in 'Lewy body dementias', which include Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). The question whether PDD and DLB are facets of the same disease or different entities has yet to be resolved. As neurologists we diagnose them by using the 'one year rule', where memory problems precede motor symptoms of PD by one year. However, it is hard to distinguish between them under the microscope due to overlapping abnormalities including Lewy bodies, Alzheimer-type pathology and other co-existing conditions.

Our research aimed to identify robust neuropathological differences between Parkinson's disease dementia and

dementia with Lewy bodies to improve diagnostic criteria. By looking at donors' medical records and matching data with examination of post-mortem tissue, we were able to show CAA in vessels of different regions and in the brain's surface vessels in both conditions. This confirmed that CAA in these areas can be associated with symptoms such as visual hallucinations and memory decline.

Early indications suggest that individuals with amyloid accumulation in brain vessels may have a worse prognosis than those without. Hopefully, our research can influence clinical practice and the development of targeted treatments for these illnesses.

Dr Zane Jaunmuktane, Clinical Lecturer and Honorary Consultant Neuropathologist, Mr Glen Hoti, Medical Student, and Dr Sebastian Schreglmann, Clinical Research Associate discuss their investigations into dystonia. This work is funded by the National Institute of Health Research UCLH/UCL Biomedical Research Centre:

Dystonia is a debilitating disorder of involuntary muscle spasms, causing twisting movements and postures. It affects over 70,000 people in the UK and manifests in various parts of the body such as the neck or hand, or even the whole body. Although dystonia is thought to be caused by abnormal function in certain brain regions, including the 'substantia nigra' one of the areas involved in controlling movement, it has proven difficult to identify consistent pathological changes in the brain.

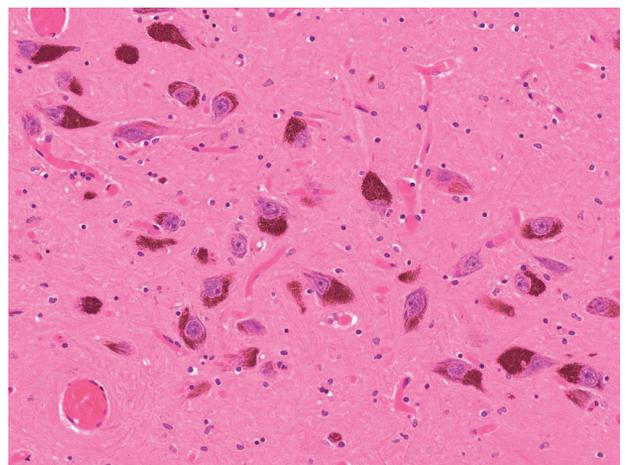


Image above: Microscopic image showing normal density and appearance of nerve cells with black pigment within the substantia nigra, one brain region thought to be affected in people with dystonia.

Recently, the discoveries of inherited kinds of dystonia have led to insights into the disease that also apply to the more frequent non-familial type. The group here at QSBB are currently examining unique brain samples from a person who had a rare genetic form not previously described. In order to confirm our initial results it is essential to compare these with both healthy tissue and tissue from people with other genetic and non-genetic dystonia. Building on observations from post mortem analysis, we would like to perform scans on patients to determine if these pathological findings can be seen during life.

We are optimistic that our investigations could bring to light a 'hallmark' identifiable on brain imaging which would improve diagnosis and potentially lead to more effective treatments for individuals with the condition.

Professor Janice Holton, Neuropathology Director, is collaborating with Neurologists Dr Helen Ling and Dr Yasuo Miki to improve the diagnostic criteria of multiple system atrophy:

Multiple system atrophy (MSA) is a neurodegenerative disorder causing balance abnormalities, slow movements, stiffness and tremor. A key symptom is autonomic dysfunction, which may lead to problems with bladder control and blood pressure. Certain medications can ease some of the difficulties for those affected, although at present there is no cure. Even experienced neurologists struggle to accurately classify multiple system atrophy. About a quarter of people can be wrongly diagnosed and at post mortem examination are shown to have had other neurodegenerative illnesses that share common features.

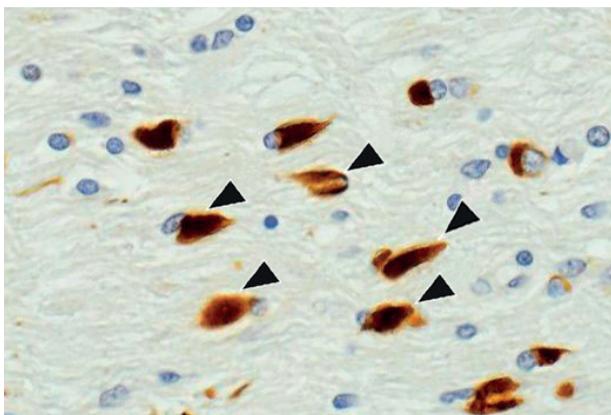


Image above: A microscopic view of 'glial cytoplasmic inclusions' (with arrows), the pathological hallmark seen in brain tissue affected by multiple system atrophy.

The Queen Square Brain Bank has one of the largest collections of tissue donated by individuals with the disease. We investigated 219 of those who were thought to have MSA between 1989 and 2017. Histology has revealed 79% were correctly diagnosed and the remaining 21% had other conditions such as Parkinson's, cerebrovascular, or Alzheimer's disease. These inaccuracies could relate to unusual presentation of signs and symptoms and the presence of co-existing pathologies in the patient, which may have influenced the clinicians' assessment. Identifying pitfalls to precision will help improve a person's diagnosis in life and enable the appropriate recruitment into future treatment trials.

Emeritus Professor Tamas Revesz, Post-doctoral Fellow Dr Teisha Bradshaw and Neurologist Dr Helen Ling continue their exploration into corticobasal degeneration with support from Karin & Sten Mortstedt CBD Solutions:

Our research group began a large-scale study of corticobasal degeneration (CBD) in 2014. CBD is a neurodegenerative illness usually affecting individuals in their sixties. It can manifest in several ways with some patients showing symptoms of a corticobasal syndrome, a form of atypical parkinsonism, while others present with frontotemporal dementia or a speech disorder. The reason for this is unknown. A definite diagnosis of CBD, which can only be made at post-mortem at present, relies on identifying under the microscope abnormal structures in nerve cells, composed of a brain protein called tau.

Originally we aimed to recognise where in the brain CBD starts and how the condition may spread. In this research we studied over 120 brains, preparing histological slides from several brain regions and staining them with an antibody which only recognises tau protein if it is transformed into the disease-specific form. We then digitised the stained slides using a slide scanner and finally analysed the digital images with sophisticated software. Data indicated that tau initially deposits in the 'basal ganglia' located deep in the brain where movement is organised, and from there pathology gradually extends to the frontal lobe. The findings were published in the prestigious journal *Brain* in December 2016.

Encouraged by these results we decided to extend our investigations to understand the origin of the different disease variants of CBD. We think the explanation is that the behaviour of the abnormal, disease-associated tau may vary. If our theory is correct and we can show that each variant is associated with a unique form or strain of tau, this could significantly improve our understanding of disease mechanisms in CBD.

Mrs Linda Parsons, QSBB Manager gives an insight into a lifetime in brain banking:

I have been involved in the growth and evolution of the brain bank for over 30 years, from its humble beginnings in the mid 1980's at the Institute of Psychiatry when it consisted of a small laboratory, one freezer and three members of staff, through the move to the Institute of Neurology in 1988. Today I am the manager of the brain bank which occupies two floors of 1 Wakefield Street with fourteen freezers and twenty three members of staff including: neurologists, neuropathologists, researchers, brain bank nurse, technicians, administrator, data manager, and students.

Smooth operation of the department is my priority. Central to my role is overseeing the team, resources and finances and running the tissue request service where samples are selected, prepared and dispatched to researchers at institutions throughout the UK and worldwide. I liaise closely with requestors to ensure specimens are appropriately used for scientifically sound and ethically approved projects.

Although managing is often demanding, I continue to strive to develop my laboratory skills. You will regularly find me dissecting frozen tissue and training young, enthusiastic technicians in the art of brain anatomy. I am enjoying my long career here and it is a privilege to contribute to advances in medicine and science. Queen Square Brain Bank has an excellent reputation for being a valuable resource providing vital material for the highest calibre studies.

None of these achievements would be possible without the generous support of our donors and their families.



Mrs Linda Parsons



Contributors



Contributors from left to right: (top row) Dr Teisha Bradshaw, Dr Daniela Hansen, Professor Janice Holton, Mr Glen Hoti, Dr Zane Jaunmuktane, **(lower row)** Dr Helen Ling, Dr Yasuo Miki, Professor Tamas Revesz, Dr Sebastian Schreglmann, Ms Karen Shaw, Brain Bank Nurse and editor of Brain Matters.

Donations



Coordinators from left to right:

Lynn Haddon, Robert Courtney and Linda Parsons

Brain donation coordinators

QSBB Administrator, Lynn Haddon is often the first point of contact for potential donors. She coordinates the brain donor scheme and along with Linda Parsons, Brain Bank Manager and Robert Courtney, Senior Technician, arranges the safe receipt of donated tissue.

The team provide an on-call service during evenings and weekends, liaising with relatives, hospital staff, funeral directors and couriers, to ensure the careful donation of the brain with the minimum of distress to families.

The importance of controls

We encourage people without a neurological condition, 'controls', to register with our donor scheme. Control tissue is vital for comparison with disease and provides researchers with an understanding of the normal appearance and function of the brain.

If you would like further information please log on to the website:

www.ucl.ac.uk/ion/research/departments/clinical-and-movement-neurosciences/centres-and-projects/queen-square-brain
Or contact Lynn Haddon on 020 7837 8370
l.haddon@ucl.ac.uk

Brain banking

Brain banking is expensive and we continue to depend almost entirely on charitable benefactions for our survival. The QSBB is primarily funded by donations from the Reta Lila Weston Institute of Neurological Studies. We gratefully acknowledge the generosity of donor families, several other benefactors, in particular The Virginia Keiley Benefaction and also our support from the Medical Research Council.

If you would like to offer a financial donation to help our research, please visit our website:

www.ucl.ac.uk/ion/research/departments/clinical-and-movement-neurosciences/centres-and-projects/queen-square-brain or contact Lynn Haddon.

Thank you.

Sponsors

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Reta Lila Weston Institute of Neurological Studies

Multiple System Atrophy Trust

The Multiple System Atrophy Coalition

Fund Sophia managed by the King Baudouin Foundation

Alzheimer's Research UK

Karin & Sten Mortstedt CBD Solutions

Rosetrees Trust

Leonard Wolfson Experimental Neurology Centre

Medical Research Council

MRC Dementias Platform UK

European Research Council under the European Union's Horizon 2020 Research and Innovation Programme

The International Concussion & Head Injury Research Foundation

Cover image shows stained cerebellum sections by Ms Shauna Crampsie, Research Technician.

