The Winston Churchill Memorial Trust of Australia

Nicholas Smith

2007 Churchill Fellow

The Bob and June Prickett Churchill Fellowship to study the diagnosis and management of neurotransmitter function disorders in infants and children

Index

Introduction

The inherited disorders of neurotransmitter function encompass a group of individually rare, though increasingly recognised, genetic disorders resulting from an inborn error in neurotransmitter synthesis, metabolism or transport.

The majority of these disorders present in infancy and childhood with a somewhat broad range of features including seizures (often in the neonatal period), disorders of movement, abnormalities of muscle tone and intellectual impairment. In addition, late presentation of disease (usually milder in severity) is recognised in adult patients.

Diagnosis of these disorders is complex, relying upon the initial clinical suspicion of the treating physician, appropriately timed and collected diagnostic samples and highly specialised equipment for their analysis. Most importantly, personnel with the expertise to interpret these investigations are crucial. At present effective treatment options are limited to a few specific neurotransmitter disorders with supportive management the only available option in the majority. The implications of a missed diagnosis can be profound and accurate diagnosis is important for the families of children with these disorders. Not only for peace of mind in what are clearly difficult circumstances but also to ensure the provision of appropriate genetic counselling.

As a physician specialising in the care of children with neurological disorders I have developed a specific interest in the management of neurometabolic disease and the disorders of neurotransmitter function. I am greatly appreciative of the opportunity to expand my knowledge in the diagnosis and management of these rare diseases. It is through the vision of the Churchill Memorial Trust of Australia and the individual generosity of Mr. Dusty Bob Prickett and his Late wife June that I have been able to do so. I feel truly honoured to be included amongst the growing legacy of health professionals to have received the Bob and June Prickett Churchill Fellowship and through this award contribute to improving the quality of health care in Australia.

I wish to extend my sincerest gratitude to the dedicated and tireless group of professionals who welcomed me to their institutions and took time out of their overbooked schedules to

accommodate a visiting Australian traveller, thank you. Finally I wish to thank the many children and families who were only too happy to share their experiences with me.

Executive Summary

Nicholas J. Smith

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Project Description:

The Bob and June Prickett Churchill Fellowship provided me with the opportunity to visit and train with internationally recognised clinical and scientific experts in the field of neurometabolic disease and the inherited disorders of neurotransmitter function. These are rare genetic disorders, the majority of which present with severe neurological symptoms in infancy and childhood.

Fellowship Highlights:

- The opportunity to develop expertise in the clinical assessment, laboratory diagnosis and management of inherited disorders of neurotransmitter function.
- The establishment of a network of contacts with senior, internationally recognised, clinicians and scientists practising in the field of neurometabolic disease.
- The opportunity to observe the operational management of clinical neurometabolic and diagnostic services in the United States of America and the United Kingdom.
- The opportunity to discuss current and future research initiatives for the investigation of new diagnostic approaches (biochemical, molecular and neuroimaging) and potential treatment options for the inherited disorders of neurotransmitter function.
- The privilege of meeting the many children and families living with these severe neurological disorders who generously shared their experiences with me.

Recommendations:

- Encourage a greater awareness of the inherited disorders of neurotransmission (beyond specialist paediatric neurologists, clinical biochemists and geneticists).
- Refine diagnostic protocols and develop a nationally standardised approach to the diagnosis of inherited disorders of neurotransmitter function (in conjunction with established biochemical diagnostic services).
- Advocate for the establishment of a national centre of excellence / national advisory group for the management of neurotransmitter disorders.
- Advocate for federal, state and private (philanthropic) funding dedicated to the establishment of infrastructure, the support of specialist clinical training and research into paediatric neurometabolic and neurodegenerative disease.

Implementation / Dissemination:

I intend to share the insights I have gained through the completion of my Churchill Fellowship at several levels.

- At a personal level I will incorporate my experience into my own clinical practice when managing children with suspected disorders of neurotransmitter function.
- I aim to present the information I have gained, where appropriate, in presentations to patient / family support groups, health professional forums and clinical and scientific meetings.
- I aim to contribute to clinical and basic scientific research in the field of neurometabolic disease and will present this in the relevant professional literature.

Fellowship Programme

March 3rd – March 30th 2008:

The Mass Spectrometry Laboratory
The Kennedy Krieger Institute
Baltimore, Maryland, USA

The Clinic for Special Children
535 Bunker Hill Road
Strasburg, Pennsylvania, USA

March 31st – April 10th 2008:

Department of Neurology
The Children's National Medical Center
Washington D.C., USA

April 14th – April 27th 2008:

Department of Paediatric Neurology
Addenbrooke's Hospital
Cambridge, Cambridgeshire, UK

Inherited Disorders of Neurotransmitter Function: An overview

Neurotransmitters are chemical mediators of neural function which relay, amplify and modulate signals between neurones within the central (brain and spinal cord) and peripheral nervous system. The inherited disorders of neurotransmitter function encompass a group of genetically acquired abnormalities in the synthesis, metabolism or transport of these chemicals.

Although these disorders constitute a rare group of neurological syndromes, they are gaining greater recognition with increasing knowledge of their existence and improved methods of diagnosis. The majority are severe and present during infancy and childhood with an often broad phenotype including intellectual impairment, disorders of movement (both voluntary and involuntary), abnormalities of muscle tone and in many cases intractable seizures. Sadly many lead to premature death. At present the diagnosis of neurotransmitter disorders relies upon the biochemical analysis of cerebrospinal fluid. However, these assays are highly sensitive to variations in sampling technique and transportation methods and clinicians must be aware of specific collection protocols to ensure results are standardised. Furthermore, the analysis of these samples and interpretation of results requires specialised expertise which is limited in Australia to a select number of clinical scientists only.

The impact of these disorders on Australian children and their families can be devastating. Not only from the often debilitating manifestations of the disease but from the significant emotional trauma inherent in caring for a child, or in some families multiple children, with severe neurological illness. The need for accurate diagnosis is therefore important in ensuring appropriate care and therapeutic intervention is provided (where available) and is also of value when counselling families regarding the genetic risk to future pregnancies.

Beyond the personal cost to individual patients and their families these disorders, like many rare diseases, impact upon the wider community. It is a tenant of the Australian social healthcare system that all individuals have an equal right to high quality healthcare. However, it is a reality that the public purse is finite and health economics must also be considered. Although rare the inherited disorders of neurotransmitter function are increasingly recognised as a potential diagnosis in children presenting with a variety of neurological symptoms, often as part of a long list of similarly rare diseases. An improved awareness of these disorders amongst clinicians, in addition to the development of more

accurate, expedient and cost effective diagnostic methods will help reduce the overall costs of work up in such cases.

Our national experience in this field continues to expand as clinicians and scientists become more familiar with these disorders. As with many rare diseases our federal health approach may be best served by the establishment of a national centre of reference or advisory group where professionals with appropriate expertise can collaborate in their efforts to manage these disorders and serve as a resource for local treating physicians.

Fellowship Report

The Winston Churchill Memorial Trust through the Bob and June Prickett Churchill Fellowship afforded me the valuable opportunity of visiting internationally recognised medical centres specialising in the treatment of rare neurometabolic disorders within the United States of America and the United Kingdom.

I commenced my fellowship programme in the United States of America with an extended visit to the Kennedy Krieger Institute in Baltimore, Maryland. The Kennedy Krieger Institute has evolved from its inception in 1937 as the Children's Rehabilitation Institute, to become an international resource for the diagnosis and management of children with neurological disorders. It is closely affiliated with the Johns Hopkins University Hospital, another esteemed institution with a strong history in the management of neurogenetic disorders. Here I had the privilege of spending time with Professor Richard Kelley and his clinical and scientific team. Professor Kelley is a renowned authority in the biochemical diagnosis and management of inborn errors of metabolism. I had the opportunity to join Professor Kelley during his outpatient clinics and spend time with him and his colleagues reviewing their approach to the biochemical analysis of patient specimens for the diagnosis and longitudinal monitoring of patients with a wide variety of metabolic disorders. I greatly enjoyed the opportunity to meet with a number of clinical and research specialists working in the fields of neurology, medical genetics, clinical biochemistry and metabolism at both the Kennedy Krieger Institute and Johns Hopkins Hospital. All were very welcoming and only too happy to share their expertise and strengthen ties within the global community of physicians managing rare neurogenetic diseases.

Through my contact with Professor Kelley and his colleagues Dr. Holmes Morton, Dr. Kevin Strauss and Dr. Eric Puffenberger, I was provided with another highlight of my Fellowship programme; The opportunity to visit, observe and participate in clinical sessions at The Clinic for Special Children (CSC) in Strasburg, Pennsylvania. The CSC is a remarkable medical service established in 1989 due to the vision, commitment and determination of Dr. Morton, his wife Caroline and the support and backing of the local community. The CSC operates as an independent, non-profit medical service for Amish and Mennonite children with genetic disorders, a significant proportion of which involve the central nervous system. As a result of their unique population genetics the Amish and Mennonite community experience an increased frequency of genetic disorders which in the wider community are exceedingly rare. The clinic utilises an in depth knowledge of local genetics and modern molecular analysis techniques to provide rapid diagnoses in their patients. These techniques include the use of microarray technology to produce whole genome single nucleotide polymorphism (SNP) profiles for individual patients and can be utilised for assays such as autozygosity mapping and copy number detection as well as facilities for gene sequencing. The application of molecular diagnostic techniques in the primary care environment translates to the initiation of early treatment (where available) and demonstrably improved outcomes to the children under the clinic's care. In addition screening protocols allow detection of familial disease before symptoms arise.

Unfortunately such approaches are not easily transferrable to the diagnosis of neurotransmitter disorders. Although our understanding of the genetic mutations responsible for many of these disorders is expanding, a large number remain undefined and mutation analysis is not readily available. Furthermore, many of the techniques applied by the CSC are dependent upon a patient group with tightly defined population genetics which is not usually the case in ethnically diverse societies such as Australia. Consequently, initial diagnosis of the disorders of neurotransmitter dysfunction continues to rely heavily on biochemical analysis which has a number of limitations including the need for specifically timed, processed and collected samples and expert personnel trained to interpret them.

My Fellowship programme next took me to Washington D.C. and the Children's National Medical Center, Department of Neurology. Here I had the true pleasure of meeting and spending time with Professor Phillip Pearl and his clinical team. Professor Pearl is a Paediatric Neurologist and Epileptologist with a special interest in the diagnosis and management of neurogenetic disorders, particularly the disorders of neurotransmitter function. Professor Pearl maintains an active research focus in this area and his current research is addressing one of the more commonly identified disorders of neurotransmitter

function, succinic semialdehyde dehydrogenase (SSADH) deficiency (to date approximately 350 cases have been described).

The opportunity to meet with Professor Pearl and discuss his approach to the management of patients with both suspected and confirmed disorders of neurotransmitter function was another of the great highlights of my Churchill Fellowship. His experience and insights have provided a valuable resource for my own practice in the field of neurotransmitter disease and I look forward to sharing these with my colleagues and future Australian physicians electing to pursue a career in the field of neurometabolic disease.

I concluded my fellowship by travelling to the Department of Paediatric Neurology at Addenbrooke's Hospital, Cambridge, United Kingdom. During my visit (and for an independently funded period beyond the completion of my fellowship programme) I had the opportunity to meet with Dr. Alasdair Parker a Paediatric Neurologist with a specific interest in neurometabolic disorders and take part in the Paediatric Neurotransmitter clinic he has established at the hospital. This allowed me to undertake direct involvement in the clinical assessment and work up of children with suspected neurotransmitter disorders and helped me to consolidate many of my earlier fellowship experiences into an effective working approach to the investigation and care of these children.

Of particular interest over the course of my fellowship was the opportunity to discuss the difficulties faced in confirming a suspected diagnosis of neurotransmitter dysfunction with clinicians and scientists working in this rare field. At present diagnosis relies heavily on the biochemical analysis of cerebrospinal fluid. However, sampling is complex and requires a standardised approach to ensure reliable results are achieved. In Australia, we are fortunate to have a senior clinical scientist (based in Sydney) who is expert in the interpretation of these studies. However diagnosis also relies upon clinicians identifying potential cases of neurotransmitter disease and obtaining appropriate samples for analysis. It is therefore important to ensure awareness of sampling techniques, particularly amongst junior medical staff who are most likely to be performing collection procedures. Researchers, including Professor Pearl, are actively pursuing improved technologies for the diagnosis and monitoring of neurotransmitter disorders. Exciting progress has been made in the use of functional imaging modalities such as Positron Emission Tomography and molecular techniques are also being developed. Nevertheless biochemical analysis is likely to remain the mainstay of current diagnostic protocols.

Conclusion

The inherited disorders of neurotransmitter function constitute a rare subclass of neurometabolic diseases which can have a devastating impact on affected children and their families. Diagnosis of these disorders is often complex and requires specialist clinical and scientific expertise. The Bob and June Prickett Churchill Fellowship has allowed me to increase my own experience in the management of these diseases. I greatly look forward to working with my clinical and scientific colleagues, health service providers and most importantly patients and their families to improve Australian health services for these children.

Recommendations:

- Encourage a greater awareness of the inherited disorders of neurotransmission (beyond specialist paediatric neurologists, clinical biochemists and geneticists).
- Refine diagnostic protocols and develop a nationally standardised approach to the diagnosis of inherited disorders of neurotransmitter function (in conjunction with established biochemical diagnostic services).
- Advocate for the establishment of a national centre of excellence / national advisory group for the management of neurotransmitter disorders to provide;
    - A specialist clinical consultation service
    - Specialist diagnostic services
    - Collaborative research groups
    - Coordinated patient and family support services
- Advocate for federal, state and private (philanthropic) funding dedicated to the establishment of infrastructure, the support of specialist clinical training and research into paediatric neurometabolic and neurodegenerative disease.

Implementation / Dissemination:

I intend to share the insights I have gained through the completion of my Churchill Fellowship at several levels.

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- I aim to contribute to clinical and basic scientific research in the field of neurometabolic disease and will present this via the relevant professional literature.