Progress Report

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Title of Project: Defining the clinical phenotype of neuronal autoantibody associated epilepsy

Summary:
We are pleased to report that the project has cleared HREC review and the committee concerns were adequately addressed, and the project was allowed to continue as planned. The governance and agreements between the involved institutions has also been approved and we were able to start recruitment 2 weeks ago.
Since our receipt of the Brain Foundation Gift the project has received further funding from local and international sources, such that it is now almost fully funded. The capacity of our epilepsy department has also increased, therefore the recruitment feasibly has also significantly improved since our receipt of the grant. This will enable us to make up for the unexpected delays encountered during the HREC and governance process and complete the project within the proposed timeline. We would however given the delays outlined wish to request and extension of the funding for a further 12 months.
In addition, Dr Gillinder has received two fellowships which support research FTE so she is able to dedicate more time to the project, focussing on recruitment and data collection at this stage.
Importantly since our receipt of the Gift we have made significant international connections and several sites in the US have joined the study. Recruitment will now also be conducted at several centres in the US including New York University Langone and Jefferson University. The project has received IRB approval in those sites and recruitment has begun. Additionally, testing of serum and CSF will also be performed in conjunction with clinician researchers at the Neuroimmunology laboratories of the Mayo Clinic and Barcelona University. This will not only allow us to confirm our local results at the highest international standards but also begin research to discover novel antibodies in these cases.
We will also be creating a CSF repository which will be utilized to test and implement mechanisms of a focal epilepsy biorepository, which will serve as a platform for future studies of immune dysregulation in epilepsy (directly related to this study), for which CSF provides additional value to serum in measurement of various immune markers, and potentially other epilepsy mechanism research.
These collaborations are a testament to the urgent need for further research in this area and that the study is expected to produce such results and is designed to the

highest standard. This will significantly increase the impact of the work supported by the Brain Foundation.

Hypothesis vs Findings

Our hypotheses remain unchanged:

1. *There is a defined clinical phenotype associated with neuronal autoantibodies in chronic epilepsy and that this will be identifiable by a clinical syndrome of perisylvian seizure semiology and low amplitude mid temporal electrographic changes.*
2. *The prevalence of autoantibody-associated epilepsy is higher than currently reported.*
3. *Autoantibody positive epileptics will have detectable inflammation using advanced imaging techniques.*
4. *Mental health disorders are more common than in other epilepsy subtypes.*

Unanswered Questions

What these research outcomes mean

This will be the first study to extensively analyse clinical features and define a clinical phenotype in neuronal autoantibody associated epilepsy which is an important, yet under-recognised condition. Our results will vastly change clinical approach of epileptologists and neurologists both in Australia and internationally, and lead to this condition being included in the differential diagnosis of chronic epilepsy. It will change the lives of many people with refractory debilitating seizures and could offer a cure (ie: seizure freedom) for this epilepsy subgroup.

The data gathered from this study will enable us to create diagnostic criteria, similar to what exists for autoimmune encephalitis. Therefore, in the future these patients will be more readily identifiable, so the condition is less likely to be missed. As a result, many patients will be correctly diagnosed and receive more effective treatments. This means many patients who were previously told they had exhausted all therapeutic options will have a new possibility for seizure freedom. It will also ensure that patients are managed in a holistic manner and their mental health issues are adequately addressed. When these patients are easier to identify, it will be possible to recruit enough participants for future research.

The results of this study will also inform our understanding of the underlying pathophysiology of this condition and strongly guide the direction of further studies. Storage of serum and CSF will enable evaluation of immune activation in these patients by way of cytokine analysis, immunophenotyping and cytogenetics. This will inform treatment choices and assist in the design of, and choice of agents for an RCT to adequately analyse therapeutic options. It will also set the foundation for the creation of an animal model and eventually allow us to understand the aetiology of this condition and determine if this association represents true CNS autoimmunity.