Understanding Tuberous Sclerosis Complex (TSC): A Brief Overview

Tuberous sclerosis complex (TSC) is a genetic disease affecting multiple systems within the body. It is inherited in an autosomal dominant pattern, meaning a single copy of the mutated gene is enough to cause the disorder. The hallmark feature of TSC is the development of benign tumors, with the central nervous system, kidneys, and skin being the most commonly affected organs.

Impact on the Brain and Associated Symptoms

One of the most significant and debilitating aspects of TSC is the abnormal growths and changes in connectivity within the brain. These alterations often lead to a range of neurological issues including epilepsy, developmental delay, cognitive impairment, autism spectrum disorder, behavioral problems, and hydrocephalus.

Current Treatment Approaches

Presently, treatments for TSC primarily focus on managing symptoms. These may include antiepileptic medications to control seizures, surgical removal of tumors, and early intervention services such as occupational, physical, or speech therapy. While these interventions can be helpful, they do not address the underlying cause of the disease and may not fully modify long-term outcomes.

A Promising New Approach: mTOR Inhibitors

Recently, mTOR inhibitors such as everolimus have been introduced into the clinic. These drugs work by restoring metabolic balance in cells affected by mutation, potentially alleviating symptoms of TSC. However, their effectiveness in treating neuropsychiatric problems associated with TSC has proven to be limited. Importantly, clinical trials administering the drug were conducted on patients in the later stages of brain development.

The Importance of Early Intervention

Studies suggest that administering mTOR inhibitors during critical periods of brain development may yield more favorable outcomes. Understanding the developmental timeline of TSC is crucial for identifying these critical windows for effective treatment. Early detection is key here, and importantly feasible, as evidenced by cases where diagnosis was made even before birth.

Looking Ahead: Research Goals

Our goal is to pinpoint the optimal developmental period for administering mTOR inhibitors to address neuropsychiatric issues associated with TSC effectively. By conducting further research into the developmental changes occurring in TSC, we aim to improve clinical outcomes and enhance the quality of life for individuals affected by this complex disorder.

Identifying Critical Developmental Periods in Tuberous Sclerosis Complex (TSC): Our Research Approach

To pinpoint the best time for administering mTOR inhibitors in treating neuropsychiatric issues linked with TSC, we have devised a thorough research plan:

1. **Tracking changes in gene expression**: We will monitor developmental changes in gene expression associated with synaptic function, crucial for establishing proper connections in the brain during its development. We will utilize synaptoneurosomes in mouse models of TSC, determining when changes in synaptic gene expression occur.
2. **Assessing Early Treatment Efficacy**: Building on Task 1, we will explore if early treatment with mTOR inhibitor everolimus during the identified window can reverse gene expression changes seen in TSC.
3. **Studying synaptic plasticity**: We will assess whether early treatment with everolimus can restore synaptic plasticity at both structural and functional levels. We will also investigate the treatment's potential to restore functional connectivity between the thalamus and cortex, crucial for processing of somatosensory stimuli such as touch, which is disrupted in patients with TSC.

Through these approaches, we aim to understand critical developmental periods in TSC better, enhancing therapeutic strategies for affected individuals.