Establishing an Australian paediatric peripheral neuropathy biobank

RESEARCH TEAM:

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Research

Spinal muscular atrophy (SMA) is a rare genetic disease characterized by progressive loss of motor neurons in the brain stem and the spinal cord. This condition affects a child's ability to crawl, walk, sit up, and control head movements. Severe SMA can damage the muscles used for breathing and swallowing. With an occurrence of 1:10,000 newborns, SMA is the number one genetic cause of death for infants. The therapeutic landscape for SMA transformed since the therapy, nusinersen in 2018. Nusinersen resulted in improvements in survival, reduction in morbidity and achievement of functional motor skills across the spectrum in treated patients. There is sufficient data to highlight the importance of early diagnosis and initiation of treatment with the most beneficial response to treatment to date, in these disorders, seen in patients treated prior to the commencement of symptoms.

The nusinersen clinical trials in SMA have established that not all patients have the same response to therapy. The current dose of nusinersen is standard across all patients at 12mg/5 mls. It is not understood how long therapy is required for and lifelong therapy may be essential for some children. Parents of children with SMA are interested in understanding how well the children will respond to treatment, and if having higher dosing improves the response to treatment. Furthermore, we are interested in understanding how the disease develops over time. Our study hopes to answer these questions by using laboratory-based experiments to test for specific proteins and genetic signatures in biological specimens obtained from the children with SMA.

For us to achieve the above, it is imperative to establish specific research infrastructures to ensure collection and management of high-quality specimens and data. We therefore performed a study to address these issues by establishing an Australian biobank for children with SMA. The main aim is to use these biological specimens to gain information about the disease pathway and answer the questions regarding response to treatment and dosage. This information will enable us to improve our understanding and knowledge of SMA and guide clinicians to eventually improve the outcomes for children with SMA.

Outcome

The Brain Foundation Research Grant has greatly enabled us to establish a biobank of 300 biological samples from patients affected with SMA at Sydney Children's Hospital, Randwick in a period of 12 months. These specimens (cerebrospinal fluids and serum) were analysed to complete proof of concept studies utilising high throughput protein and gene sequencing technologies.

Preliminary findings identified a panel of biomarkers involved in various molecular and biological processes of SMA. These are involved in protease binding, lyase activity, cysteine-type endopeptidase inhibitor activity, neutrophil degranulation and amyloid fiber formation. Some of these protein species have been previously identified in other research as possible biomarkers for neuropathies, including amyotrophic lateral sclerosis.

Using gene technologies, we identified genetic signatures as a response to nusinersen treatment and the potential of these miRNAs to monitor disease progression and response to therapeutic intervention. With new SMA therapeutics on the horizon, our findings indicate the potential clinical application of these genetic signatures as promising non-invasive biomarkers for this disease.

We will promote ongoing collection of biological data and utilise banked samples to carry out molecular work to expand scientific knowledge regarding pathophysiology and treatment responses. Taken together, this will provide a rich resource for future studies and enhance collaboration for SMA research nationally. The present project represents a key step essential to translate research into clinical practice and to drive improved clinical outcomes and achieve best care for children with SMA.

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