childhood dementia INITIATIVE

NHMRC Targeted Call for Research Proposal Submission

Childhood dementia: transforming research to deliver therapeutics for this neglected group of patients.

5 February 2021

Question 1: What is the research gap you consider to warrant a TCR?

Consider:

- What is the health issue that is not being sufficiently considered by current research efforts or funding
- Does it relate to diagnosis, treatment or management options?

Dementia is usually only associated with the elderly. Tragically, children also suffer from dementia. Today, there are an estimated 700,000 children and young people living with dementia worldwide. Their short lives are shaped by progressive brain damage, social isolation, pain and suffering. Most will not live to adulthood, some will die in their infant years.

Childhood dementia is a recognised, albeit little known group of disorders. It is estimated that 1 in 2,800 babies are born with a childhood dementia disorder. That is more common than well-known disorders like cystic fibrosis (1 in 2,874 births).

As with other disease groups such as the aging dementias and cerebral palsy, childhood dementia has multiple causes. More than 70 genetic childhood dementia disorders have been identified including Batten disease, Sanfilippo syndrome, Niemann-Pick disease, Tay-Sachs disease, metachromatic leukodystrophy, Rett syndrome and some mitochondrial disorders. Alarmingly, fewer than 5% of the childhood dementia disorders have treatments.

Childhood dementia has received little research investment from major funding bodies. To illustrate this point, in the past 3 years the NHMRC has granted 38 times more research dollars to motor neurone disease ($17.9 million versus $475,000) and 29 times more research dollars to cystic fibrosis ($13.8 million). This is despite the similar prevalence and incidence of childhood dementia to motor neurone disease and cystic fibrosis respectively. A Childhood Dementia TCR would significantly address this gap.

There is a high level of unmet need in all three areas of diagnosis, treatment and management options but the most pressing need is the development of treatments. Advanced therapeutics now offer the real possibility of effective treatments, even cures, for childhood dementia and drug repurposing and targeting mechanisms in common across the childhood dementias could deliver much needed improvements in quality of life.

Question 2: How significant an issue is this proposed topic?

Consider:

- Who does this health issue affect (e.g. population group, individuals)?
- What percentage of the population is affected by this issue (e.g. burden of disease, mortality and morbidity)
- How does the issue impact on the quality of life of the individual,their family, carers and/or community?
- What is the impact of this issue on the health system?

A childhood dementia burden of illness study was published in 2020 (Tilden et al., 2020). It was commissioned by the Childhood Dementia Initiative and completed in partnership with health economists at THEMA Consulting Pty Ltd and expert Australian clinicians. Key points from the report are:

- It is estimated that the collective incidence of disorders that cause childhood dementia is 36 per 100,000 live births. This equates to 129 births in Australia each year.
- In 2021, it is estimated there will be 2,273 Australians living with childhood dementia, 1,396 of whom will be under the age of 18. This prevalence is on a par with motor neurone disease which was estimated to affect 2,094 Australians in 2015 (Deloitte Access Economics Report, 2015).
- The average life expectancy for childhood dementia in Australia is estimated to be 28 years. The outlook is bleaker for some of the disorders with death in infancy or early childhood.
- The Years of Life Lost (YLL) and Years of Life lost due to Disability (YLD) from 2021 to 2030 in Australia is estimated to be 10,962 and 4,513, respectively.

Using Australian Bureau of Statistics population data from 2016, approximately 0.02% of Australians under the age of 18 have childhood dementia (0.01% of the Australian population overall). The impact on the immediate and extended family of the child is also significant (Wu et al., 2020).

The quality of life for children with dementia is poor. Childhood dementia shares many similarities with the hallmark features of adult-onset dementias, including:

- Decline in cognitive ability
- Problems with attention and concentration
- Memory loss and learning difficulties
- Problems with thinking and reasoning
- Confusion and disorientation
- Uncooperative and disruptive behaviour
- Wandering and restlessness
- Emotional disturbance (anxiety, fear, panic attacks, etc)
- Personality and behavioural changes (aggression, irritability, hyperactivity, etc)
- Sleep disturbance (often severe)
- Deterioration of social skills, and socially appropriate behaviour
- Psychotic symptoms and hallucinations
- Loss of speech
- Incontinence

In contrast to most adult-onset dementias however, and in addition to these cognitive, neuropsychological and behavioural manifestations, childhood dementia disorders are commonly associated with seizures, sensory decline (vision and hearing), movement disorders including ataxia, spasticity, dyskinesia, dystonia, gait disturbances, muscle weakness and abnormal muscle tone, and progressive neuromotor decline.

Some childhood dementia disorders also involve other organs and physiological systems in addition to the central nervous system, including, peripheral nerve disease, visceromegaly (enlargement of abdominal organs), liver disease, growth retardation, gastrointestinal disease, bone and joint anomalies, and cardiac involvement.

The timeline of disease onset and progression varies among the childhood dementia disorders, with some presenting in infancy, progressing rapidly and leading to death in the first year of life. For other disorders, initial symptoms may not present until later in childhood and progress slowly, with survival typically into the teens or early adulthood. The cause of death in childhood dementia

disorders is usually attributed to respiratory complications of end-stage disease (such as pneumonia), neurological complications (for example, intractable epilepsy), or cardiac events.

The complexity and severity of paediatric rare genetic conditions pose substantial challenges to families. Delayed diagnosis, lifelong caring, limited capacity for independent living, lack of treatment options and large health service needs have severe impacts, termed as 'spillover effects', on parent's physical and psychosocial wellbeing. Studies have shown that parents with a child with a rare genetic condition have a significantly reduced quality of life in comparison to their non-impacted counterparts (Wu et al., 2020).

The burden study estimated the impact of childhood dementia on the healthcare system (Tilden et al., 2020). In an average year, the estimated economic cost is substantial: $40.4 million to the Australian healthcare system, $39.7 million in indirect costs, $233.5 million in costs of life years lost and $75.0 million costs to the NDIS.

The total economic cost of childhood dementia in Australia from 2021 to 2030 is estimated to be $3.9 billion, with an annual average of $389 million. While this may be considered low in comparison to other childhood conditions, there are two attributing factors that must be considered; childhood dementias confer only a short life expectancy of around 28 years and given the lack of treatment options across the 70 identified conditions, the burden of care is disproportionately met by the affected families themselves, support services and carers. There is also limited robust data on the costs attributed to each childhood dementia condition identified in the burden study and almost half of the conditions were excluded from analysis due to a lack of incidence and life expectancy data. Therefore, the costs attributed to childhood dementia as a whole are expected to be higher

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Question 3: How would research on this topic benefit the health of Australians?

Consider how research would:

- Change health outcomes for the community generally, affected groups within the community, and people with a specific health condition
- Influence health policy development or health service delivery including diagnosis, treatment or management

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Increased investment into childhood dementia research will accelerate the development of treatments for the childhood dementia population, giving many of these patients their first and only opportunity for relief from their relentlessly progressing disease. The health outcomes that could be realised by research on this topic include:

- increased opportunities for childhood dementia patients to participate in clinical trials and gain early access to potentially disease modifying therapeutics

- the development of tools such as biomarkers that will make clinical trials more efficient and less invasive for participants
- new therapeutic options for the significant and ever-growing aging dementia population through the targeting of common disease mechanisms between childhood and adult onset dementia
- improved clinical care and management of childhood dementia through increased awareness of childhood dementia.

For most patients with childhood dementia the only opportunity to access potentially disease modifying treatments is through clinical trials and for many of the disorders there are no clinical trials yet underway. Drug repurposing is an attractive approach to rapidly address this area of unmet need because existing drugs with safety and efficacy data available can quickly be accessed by patients. Drug repurposing is an Australian Medical Research and Innovation priority for 2020-2022.

Basic research that studies the underlying pathological mechanisms will also identify pathways that could rapidly be addressed by available therapeutics or lead to the development of novel therapeutics. Research to date suggests there are a number of overlapping disease mechanisms occurring among the various childhood dementia disorders. In addition, similar techniques, disease models and equipment can be used to study the cells of the brain to understand these disorders and develop treatments. Yet globally, research into childhood dementia disorders remains disparate and siloed in nature, with focus on a single disorder and replication of infrastructure. By studying mechanisms common to multiple types of childhood dementia this type of research could achieve economies of scale and wider patient benefit (Childhood Dementia Initiative Report, 2020).

In this time of unprecedented technological advancement there exists on the horizon encouraging emergent therapies including gene transfer and editing technologies. In contrast to therapies that target common cellular mechanisms across multiple disorders, gene-based therapies would be specifically designed to target and correct genetic defects in small groups of patients. Such advanced gene-based therapies have enormous potential to significantly improve patient outcomes and dramatically reduce - or prevent altogether – the burden of these debilitating conditions. Given the significant costs associated with gene therapy research and development, funding targeted to this group of disorders will enable a collaborative research model utilising shared resources, platform technologies, and clinical trial infrastructure. This is not only logical but essential if we are to deliver benefit to childhood dementia patients in a timely, cost-effective manner.

To complement the development of therapeutics, biomarkers and imaging technology to accurately measure and predict disease progression could be developed through a TCR. Such tools are essential for successful and efficient clinical trials and to decrease the burden of clinical trials for participants. Current clinical trial outcome measures in the few ongoing studies globally rely on cognitive testing, which is notoriously unreliable and difficult for children with intellectual and behavioural disabilities. Measurement of substances in the cerebral spinal fluid via lumbar puncture is also often used. The development of less invasive measures would not only be better for patients but allow more regular monitoring and more accurate determination of treatment efficacy. Such biomarkers or imaging technology could also provide information to families on prognosis to allow planning for the future and inform decisions around clinical trial participation.

There is the potential for research into childhood dementia to also benefit the significant and ever-growing aging dementia population. A growing body of literature suggests that common disease mechanisms exist between childhood dementia disorders and more prevalent adult-onset neurodegenerative disorders such as Alzheimer's and Parkinson's disease (Qureshi et al., 2020; Torres et al., 2019; Platt et al., 2018). To provide an example of how research into common underlying mechanisms in dementia subtypes can prove beneficial, in recent years study of younger-onset adult dementia ('younger-onset' defined as dementia first presenting in persons under 65

years of age) has led to new knowledge which has also been applicable to the more common later-onset dementias. This has subsequently improved our understanding of both dementia subtypes and revealed new opportunities for the development of therapies (Rossor et al, 2010).

In addition to increasing capability and capacity in the childhood dementia research field, greater awareness of these disorders in the scientific and medical community through a TCR will have a flow on effect to the clinical care and management of childhood dementia. Families with children suffering from childhood dementia report that care and support is inadequate, poorly coordinated and inconsistently delivered and this needs to change.

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Question 4: Would a TCR on this topic build on existing research or government initiatives?

Consider providing details on:

- Current or previous research, initiatives, action plans or strategies
- International or overseas research or initiatives that a TCR would build on to address this issue

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There is considerable research expertise in Australia in the individual silos of childhood dementia, for example Sanfilippo syndrome and other lysosomal storage disorders at the Childhood Dementia Research Group (Flinders University), Niemann Pick disease at The Florey and Rett Syndrome at Kids Research, NSW. However, these individually rare disorders struggle to attract significant funding. A Childhood Dementia TCR has the opportunity to bring together this expertise and realise great academic, commercial and translational potential through a truly multidisciplinary, cross disorder approach to childhood dementia. This approach is an opportunity for world leadership in this field, taking advantage of Australian Government and NCRIS funded infrastructure.

A salient example of research that at TCR could build on, is a program funded by the Sanfilippo Children's Foundation, with a grant from the MRFF, that is utilising patient derived neuronal cell models to identify drugs for repurposing for one type of childhood dementia (Sanfilippo syndrome). The project is a collaboration between the Foundation and four South Australian partners - Flinders University, Women's and Children's Hospital, SAHMRI and University of Adelaide. This high throughput screening platform could be expanded to other types of childhood dementia, taking advantage of the already purchased equipment, streamlined protocols and established team.

As mentioned in question 3, there is great potential for cross pollination between the aging dementia and childhood dementia fields with disease mechanisms in common as well as shared research methods, expertise and infrastructure used to study the brain. There has been considerable investment into aging dementia in recent years with the NHMRC's National Institute for Dementia Research and Boosting Dementia Research Initiative and the MRFF's Dementia, Ageing and Aged Care Mission. A TCR for childhood dementia could leverage this increased capacity and capability in dementia research for children as well as adults.

The "National Strategic Action Plan for Rare Diseases" was endorsed by the Australian Federal Government in February 2020 (Rare Voices Australia, 2020). The Action Plan recognises the need to ensure that research into rare diseases is collaborative, person-centred and systematically addresses gaps. A Childhood Dementia TCR would address a very significant gap and give opportunities for collaborative, cross disorder research to realise economies of scale not usually possible for rare diseases.

One of the most promising approaches for these rare genetic disorders is gene therapy, which uses genetic material, such as DNA, to treat or even cure genetic disorders. Spinal muscular atrophy is one example that is demonstrating great success with gene therapy proving to be transformative for children born with this lethal disease (Al-Zaidy, 2019). Capability and capacity has been growing in Australia in recent years to develop and deliver advanced therapeutics, including individualised gene therapeutics. The Sydney Children's Hospitals Network (SCHN) / the University of Sydney and associated research institutes have particular expertise in advanced therapeutics for rare diseases of the central nervous system, including bioengineering of viral vectors for specific clinical applications and complementary clinical grade viral vector manufacturing capability that is currently being established in Westmead. Other researchers around the country are demonstrating ingenuity and capability in this area too, for example with regards to nanoparticles for gene delivery. This growing expertise in gene therapy could be harnessed through a Childhood Dementia TCR and technologies and platforms developed to deliver advanced therapeutics in a cost-effective way.

A Childhood Dementia TCR could also build upon the work of the Australian Genomics TCR (GNT1113531) to expand the availability and utility of genomics to childhood dementia in both diagnosis and reproductive genetic carrier screening. This will leverage Australian Genomic's established genomic research capabilities and infrastructure to improve the efficiency, impact and translation of the Childhood Dementia TCR.

The Childhood Dementia Initiative was established in 2020. A key strategic activity planned for the Initiative in 2021/22 is to build and coordinate a National Childhood Dementia Research Network and convene the first Global Childhood Dementia Solution Summit. This could complement a childhood dementia TCR by bringing together leading researchers from around the country to work collaboratively on the development of therapeutic solutions for children suffering from dementia. Key outcomes from the network and summit will include:

- the establishment of new collaborative research networks to grow the capacity and capability for childhood dementia research
- support and promote the collaborative utilisation of technology, data and infrastructure such as biobanks.

This network will be managed by the Childhood Dementia Initiative and will include multidisciplinary representatives from leading research institutes, universities and hospitals nationally and will bring together the necessary skills for a holistic approach to solving childhood dementia. The network will also include researchers already working on individual childhood dementia disorders, clinician researchers and consumer and industry representatives. The network will ensure that any successful childhood dementia research, funded by a TCR or otherwise, is translated into patient benefit in a coordinated and sustainable fashion.

The initiative is also committed to involving consumers in all aspects of our work including health care policy, research, education and advocacy programs to improve the outcomes and experiences of people affected by childhood dementia. A National Childhood Dementia Consumer Network will be established, and research conducted on patient journeys and health system usage that will inform both therapeutic research priorities and programs to improve the management and quality of life for these families.

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