Childhood Dementia:

the case for urgent action

childhood dementia INITIATIVE

“Childhood dementia. The fact that these two words go together is appalling. We need to recognise this as a serious and urgent issue and fix it.”

Sean Murray, Director, Childhood Dementia Initiative

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www.childhooddementia.org/whitepaper

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Foreword

Today, there are an estimated 700,000 children and young people living with dementia worldwide.

Their short lives will be shaped by progressive brain damage, social isolation, pain and suffering. Many will not live into adulthood, some will die in their infant years.

With less than 5% of all identified conditions that lead to childhood dementia having a treatment, it is time to transform the way we approach therapy development and management of these disorders. Children are dying, we need to act; fast.

In 2013, following the shock diagnosis of both of my children with Sanfilippo Syndrome, a condition that causes childhood dementia, I started the Sanfilippo Children's Foundation. In the 7 years that followed, we raised over $9 million towards our cause and transformed funding and management of Sanfilippo research in Australia; the work of the Foundation continues. But during this time I was continuously and consistently dismayed watching small, often family-run foundations around the world all struggling to raise funds and drive research. Researchers, although well-intentioned, were also severely underfunded, and incentives or imperatives for research to be undertaken across multiple disorders with similar presentation were non-existent.

Childhood dementia is caused by a variety of genetic disorders and I suspected their collective impact was significant. Despite my best efforts, I couldn't find medical literature to confirm this, so I commissioned a burden of disease study to understand the breadth and depth of the problem. The subsequent paper *Childhood Dementia in Australia: quantifying the burden on patients, carers, the healthcare system and our society* (Burden Study) was generously developed by THEMA Consulting on a pro bono basis.

The Burden Study represents the first analysis of its kind in Australia, and to the best of our knowledge, anywhere in the world. The results are both horrifying and compelling.

The figures show that childhood dementia carries a significant burden and needs are overwhelmingly unmet. Behind these figures, are children and families living with childhood dementia. I encourage you to read Niki and Angelina's story on page 16, to give you insight into the devastating impact of this disease. Their experience of misdiagnoses, rapid decline and lack of treatment is too common. Children like Angelina are relying on us to build greater awareness of childhood dementia and critically, the research and collaborations that will lead to the development of effective treatments that will save them from harrowing physical and mental decline.

This white paper highlights the size, scale and wide-reaching impacts of childhood dementia and importantly outlines the overwhelming opportunity to act. The Childhood Dementia Initiative is launching to do just that.

The Childhood Dementia Initiative has a global vision to drive research and advocacy to urgently disrupt the impact of childhood dementia on children and families across the world.

Megan Donnell

CEO, Childhood Dementia Initiative

Contents

Executive Summary

Childhood dementia - a snapshot

Dementia is usually only associated with the elderly. Sadly, children can also suffer from dementia – loss of skills, change in behaviour and a severely shortened life. Dementia in childhood has long been recognised by the medical community but the collective group of disorders that cause childhood dementia have received little attention to date from the general public, governments, or research funders.

This white paper comes as a result of the *Childhood dementia in Australia: quantifying the burden on patients, carers, the healthcare system and our society* study by THEMA Consulting Pty Ltd (referred to as the 'Burden Study' in this report). Findings of this study include:

- Childhood dementia is more common than you might think. It is estimated that 1 in 2,800 children are born with a disorder that, if untreated, leads to childhood dementia: that is more common than well-known disorders like cystic fibrosis (Massie et al., 2000).
- Currently, 2,273 Australians live with childhood dementia. This prevalence is similar to that for motor neuron disease (Deloitte Access Economics Report, 2015).
- Disorders that cause childhood dementia are neurodegenerative, progressive, severe, and devastating in nature. They are complex disorders with high care needs and they cause a poor quality of life with flow on effects to the whole family.
- Childhood dementia is caused by more than 70 genetic conditions such as Batten disease, Sanfilippo syndrome, Niemann-Pick disease, Tay-Sachs disease, metachromatic leukodystrophy, Rett syndrome and some mitochondrial disorders (refer to 'Appendix A' for a full list of disorders).
- Alarmingly, less than 5% of these 70 disorders have treatments.
- Every year in Australia there are more than 90 premature deaths in people with childhood dementia. It is likely that most of these deaths occur in those under the age of 18. For comparison, there are 92 deaths per year in Australia from cancer in children aged 0–14 (Australian Institute of Health and Welfare, 2020).
- The annual cost of childhood dementia to the Australian economy is more than $389 million. The cost to the families who love these children is immeasurable.

By bringing together the many individual 'siloed' conditions and quantifying the associated collective economic burden, we aim to demonstrate the real and considerable health problem that childhood dementia poses to families and society, both now and in the future. In doing so, this analysis is intended to better inform decision-making, enhance collaborative efforts, and serve as a catalyst for meaningful action.

All patients living with childhood dementia deserve to receive an accurate and timely diagnosis, to have treatments that are available and accessible, and to realise improvements in their quality and quantity of life; in short, to be able to live the best life possible. The Childhood Dementia Initiative has been established to drive research and advocacy globally to urgently disrupt the impact of childhood dementia on children, families and society at large.

Key Facts

- Childhood dementia is caused by more than 70 individual genetic conditions.
- Fewer than 5% of the conditions causing childhood dementia have a treatment.
- 1 in 2,800 babies born will develop childhood dementia.
- Collectively, the life expectancy for childhood dementia is estimated to be 28 years. Many die in early childhood, even infancy.

FOR AUSTRALIANS THE IMPACT IS:

- Each year 129 babies are born with a condition that will lead to childhood dementia. That is one born every 3 days.
- It is estimated that there are 2,273 Australians currently living with childhood dementia, 1,396 of whom are under the age of 18.
- Every year more than 90 young Australians die, having lived their short lives suffering from childhood dementia.
- The total economic cost of childhood dementia in Australia is $389 million annually. The cost to the families who love these children is immeasurable.

GLOBALLY THE IMPACT OF CHILDHOOD DEMENTIA IS:

- 50,000 births every year.
- 700,000 individuals currently living with childhood dementia.
- 48,300 premature deaths annually.

"Childhood dementia is devastating, not only for the child suffering from dementia but for the family around them having to watch them fade away."

~ Kelly, mother of Penny (right) who has childhood dementia.

Recommendations

In response to the findings outlined in the Burden Study, the Childhood Dementia Initiative has identified 7 key recommendations to be implemented in order to address this heartbreaking problem.

RECOMMENDATION 1: Increase general awareness of childhood dementia, its breadth, impact and level of unmet need. Current levels of awareness are very low, however, the Burden Study gives a strong case to raise awareness and advocate for systemic change.

RECOMMENDATION 2: Promote and enable research that concurrently investigates multiple childhood dementia disorders thereby achieving economies of scale and scope. This requires systemic change in how research into childhood dementia is undertaken, from funding of scientific research to clinical trial design and everything in between.

RECOMMENDATION 3: Foster and harness collaborative and diverse networks. The development and delivery of innovative, fast-tracked research programs for childhood dementia requires collaborative networks of leading minds: researchers, funders, clinicians, industry experts and patients. Importantly, increased collaboration between adult-onset and childhood dementia researchers must be encouraged, as this is very likely to be mutually beneficial.

RECOMMENDATION 4: Enable delivery of advanced therapeutics such as gene therapy to children with dementia through the development of streamlined platform technologies. To effectively and efficiently develop, produce and deliver these high-cost therapies, processes and infrastructure must be shared and streamlined across this group of conditions.

RECOMMENDATION 5: Provide and promote collaborative utilisation of technology, data and infrastructure. This includes patient data collection and sharing, biobanking platforms, clinical trial resources, outcome measures and scientific infrastructure. This will reduce the current high level of duplication and promote innovation, efficiency and capacity across the board.

RECOMMENDATION 6: Significantly improve early diagnosis and increased access to carrier screening. Earlier diagnosis through newborn and other early screening programs will allow early intervention and improved outcomes for patients. Increased education, awareness and access to carrier screening will assist with the prevention of many cases of childhood dementia.

RECOMMENDATION 7: Enable equitable access to new and emerging therapies. Patients have the right to hope, to be allowed swift access to new effective therapies, and opportunities to participate in clinical trials of experimental treatments.

What is Childhood Dementia?

Characteristics

Childhood dementia is defined as global neurocognitive decline with multiple developmental skill loss after a period of normal development (Nunn, 2002). One of the hallmark characteristics of childhood dementia is enduring and progressive loss of previously acquired developmental skills, in contrast to static or transient loss, for example in the case of head injury, encephalitis[1] or hypoxia[2] (Nunn, 2002; Verity, 2010). Furthermore, childhood dementia may be distinguished from conditions such as intellectual disability or developmental delay, which are characterised by slower development compared with normal development (Nunn et al., 2002; Haugen et al., 2019), as illustrated in figure 1.

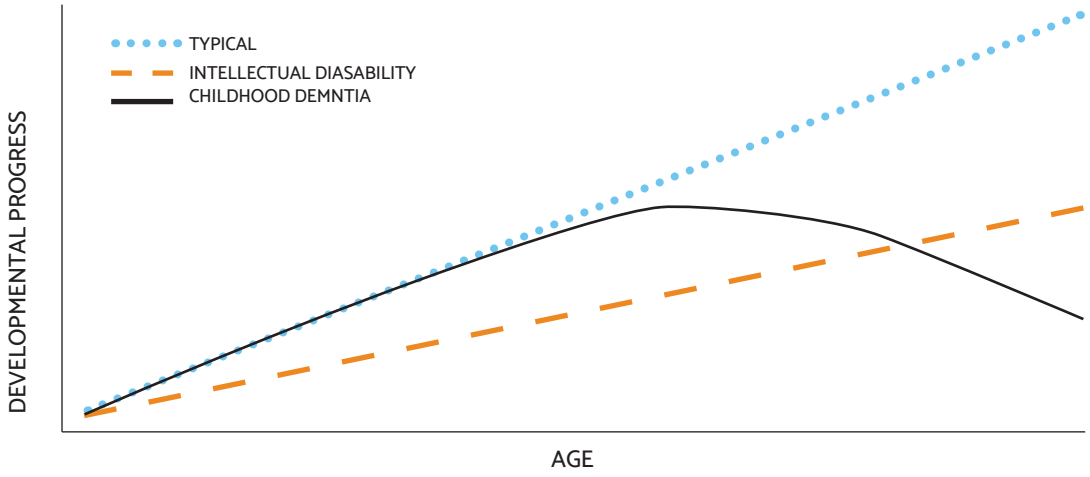


Figure 1: Developmental trajectories of individuals with typical development, intellectual disability and childhood dementia. The trajectory of childhood dementia classically proceeds in line with normal development for a long or short interval then decelerates and ultimately regresses (adapted from Haugen et al., 2019).

The pathway to diagnosis varies between diseases, and typically involves a combination of early clinical symptom assessment, brain imaging, detection of biochemical markers in urine and blood, and genetic testing. Given the non-specificity of initial presenting symptoms, the rarity of the individual diseases and general lack of awareness in the medical community, the diagnosis of childhood dementia disorders are often delayed, sometimes for years after the first symptoms are noticed (Nunn et al., 2002). Commonly, children are misdiagnosed with autism, developmental or intellectual delay, attention deficit hyperactivity disorder (ADHD) and others, before reaching a definitive diagnosis. This long, uncertain and stressful journey to diagnosis is often referred to as the 'diagnostic odyssey'.

Newborn screening for these conditions is limited, in part justified by a lack of therapeutic intervention for many of these disorders. However, early diagnosis would have other benefits including avoiding the diagnostic odyssey, allowing early participation in clinical trials and giving parents of affected children knowledge to inform future family planning decisions.

[1] Encephalitis is inflammation of the brain, usually caused by a viral infection

[2] Brain hypoxia is when there is insufficient supply of oxygen to the brain, for example during near drowning, choking or suffocating.

The set of symptoms characteristic of childhood dementia varies between individual conditions. Childhood dementia does however, share 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 including anxiety, fear and panic attacks
- Personality and behavioural changes which can include aggression, irritability, and hyperactivity
- Sleep disturbance which is often severe
- Deterioration of social skills
- Psychosis including hallucinations
- Loss of speech
- Incontinence

In addition to these cognitive, neuropsychological and behavioural manifestations, childhood dementia disorders are commonly associated with seizures, loss of vision and hearing, movement disorders such as muscle spasms and tremors and loss of movement (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.

Some types of childhood dementia present 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 relatively 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.

Causes

The causes and biological mechanisms of childhood dementia are wide ranging and in some individual cases remain undefined. A large proportion of the disorders are attributable to inherited metabolic disorders. Most inherited metabolic disorders result from an enzyme defect in biochemical and metabolic pathways that affect the essential metabolism of cellular proteins, fats or carbohydrates, or impaired organelle function.

The Burden Study identified more than 70 genetic disorders that fit the defined set of disease criteria for childhood dementia (Appendix 1). The true number of conditions is considerably higher than the 70 listed because, for the purposes of the study, some conditions were grouped together rather than defining every subtype, for example the 11 types of childhood onset neuronal ceroid lipofuscinoses (Batten disease) and the many types of mitochondrial disease. The current list is not exhaustive since there are likely children without a definitive diagnosis ('syndromes without a name') and other ultra-rare[3] conditions that fit the definition. These disorders will be added to the list over time.

The Burden Study grouped the identified disorders based on their cause and characteristics, resulting in 11 broad categories. The largest proportion of childhood dementia births belong to the lysosomal disease category (21%) followed by mitochondrial disorders (20%). Third most frequent is the group of "other rare[4] neurodegenerative conditions" which includes disparate conditions such as Rett syndrome and Juvenile Huntington's disease (19%).

The range of causes and biological mechanisms demonstrates the vulnerability of the brain and neuropsychological processes, and highlights the remarkable complexity in cause, diagnosis and treatment of childhood dementia. Importantly however, and central to the purpose of this white paper, this analysis identifies numerous overlapping disease processes between the subgroups of childhood dementia disorders, highlighting potential common drug targets and opportunities for research and development.

[3] Ultra-rare diseases are defined as having a prevalence of <1 per 50000 persons
Source: National Institute for Clinical Excellence. NICE Citizens Council Report Ultra Orphan Drugs. London, NICE, 2004. https://europepmc.org/article/NBK/NBK401721
[4] The most widely accepted definition of a rare disease is one that affects less than 5 in 10,000 people. Source: National Strategic Action Plan for Rare Diseases, February 2020. https://rva.blob.core.windows.net/assets/uploads/files/NationalStrategicAPRD.pdf

Incidence and prevalence

Although each individual childhood dementia condition is considered rare or ultra-rare, the Burden Study estimated that the collective incidence is 36 per 100,000 live births (1 in 2,800 births). This equates to 129 births in Australia per year.

This can be extrapolated to 50,000[5] childhood dementia births worldwide annually.

This incidence is similar to that for cystic fibrosis which occurs in 1 in 2,874 live births (Massie et al., 2000).

The Burden Study estimated the prevalence of childhood dementia in Australia from the incidence and life expectancy data. 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 similar to that for motor neuron disease, which was reported to be 2,094 Australians living with MND in 2015. (Deloitte Access Economics Report, 2015).

There is an estimated 700,000[6] people currently living with childhood dementia worldwide.

Of the 70 identified childhood dementia disorders, accurate data was not available for 32, all of which are classified as 'ultra-rare'. As such, data from the remaining 38 conditions was used to calculate the incidence and prevalence, therefore the results are likely to be an underestimate.

"Childhood dementia is every parent's worst nightmare. We've had to watch our beautiful 7-year-old daughter lose the ability to run, to walk, to dance. She's lost cognitive skills so she can no longer count or sing her favourite nursery rhymes. She's lost the ability to speak. She's going blind, she's finding it harder and harder to recognise family and friends. We also have the challenges of her behaviour and personality changes that all come along with childhood dementia."

~ Bobbie, mum to Tayla (right) who has childhood dementia.

[5] Calculated from the world number of births (140.11 million) in 2019 and an incidence of 1 in 2800 births. Source: United Nations, Department of Economic and Social Affairs, Population Division (2019). World Population Prospects 2019, Online Edition. Rev. 1. https://population.un.org/wpp2019

[6] Calculated from the Australian prevalence and the current world and Australian populations (Source: United Nations as above). The average life expectancy is likely to be lower in less developed countries where access to medical care is limited and consequently the prevalence will be lower in those countries.

Life expectancy and mortality

The average life expectancy of all childhood dementia disorders was estimated to be 28 years in the Burden Study. Most of the disorders (71%) included in the Burden Study had average life expectancies of 18 or below, with the lowest being an average life expectancy of just 1 year of age for Gaucher disease type 2 and Zellweger spectrum disorder. At the other end of the spectrum, 3 conditions are assumed to have close to normal life expectancies, due to the availability of a treatment (see section 2.5).

The average life expectancy was used to estimate the mortality rate. Every year in Australia there is an estimated 94[7] premature deaths in people with childhood dementia. Based on the life expectancy ranges reported in the Burden Study, it is likely that most of these deaths occur in those under the age of 18.

From these figures it is estimated that there are 48,300[8] premature deaths each year globally in people with childhood dementia.

It is of interest to note that in Australia, the childhood dementia mortality rate is comparable to that of childhood cancer, with 92 cancer-related deaths per year in children aged 0–14 years[9]. Moreover, cancer was the second leading cause of death in this age group, after injury-related deaths.

Despite the considerable number of childhood dementia conditions and a mortality rate comparable to the well-recognised and championed cause of childhood cancer, childhood dementia remains unrecognized as a class of disease in the World Health Organisation's International Classification of Diseases (ICD), the Diagnostic and Statistical Manual of Mental Disorders (DSM) or any other diagnostic system worldwide. Not only does this highlight the vast lack of recognition and awareness of this devastating group of diseases, it means that the statistics on childhood dementia incidence, prevalence and death are not accurately collected or reported.

"An end to childhood dementia would mean these children are able to live the lives they deserve to live."

~ Anna, mother of Sebby (right) who died at just 22 months from childhood dementia.

[7] The estimate of 94 was calculated from the incidence and number of births in Australia in 1992: 264,151 (1992 was used because this is 28 years - the average life expectancy - prior to 2020) (Source: https://aifs.gov.au/facts-and-figures/births-australia/births-australia-source-data).

[8] Calculated from the incidence and world number of births in 1992: 135.16 million (Source: United Nations as above). The average life expectancy is likely to be lower in less developed countries where access to medical care is limited but given that worldwide birth rates have been relatively steady for the past 30 years this figure is a reasonable estimate.

[9] Source: Australian Institute of Health and Welfare 2020. Australia's children. Cat. no. CWS 69. Canberra: AIHW https://www.aihw.gov.au/reports/children-youth/australias-children/contents/health/cancer-incidence-and-survival

Treatments

Less than 5% of the conditions causing childhood dementia could be considered to have widely available treatments with a close-to-normal life expectancy (assuming timely diagnosis). Those that do include Wilson disease, biotinidase deficiency and holocarboxylase synthetase deficiency.

For most patients with childhood dementia, however, there are no therapies available to slow the inevitable decline and therefore symptom management and palliative care are the only options. This includes medications to manage seizures and behaviour, physiotherapy, occupational therapy, speech therapy and gastrostomy for feeding difficulties.

Several of the 70 disorders have non-pharmacological treatments such as dietary restrictions, simple supplementation with certain vitamins, minerals or amino acids. In the majority, however, success of these treatments is variable and at best, may only slow disease progression.

More sophisticated treatments have been developed for a handful of disorders including enzyme replacement therapies (ERT) which aim to replace the missing or dysfunctional protein. While 5 ERT products are currently approved for clinical use, 4 are delivered via intravenous route and are not effective for the neurological aspects of these diseases. The fifth product for the treatment of a subtype of Batten Disease (CLN2 disease), Brineura® (TGA approved in 2018), is delivered directly into the brain via intraventricular infusion[10] and has been shown to slow progression of motor and language deficits (Schulz et al., 2018). Its long-term effectiveness however, remains unknown.

In addition, bone marrow transplant is conducted at a limited number of paediatric centres for some disorders including metachromatic leukodystrophy, Krabbe disease, Hurler and Hunter syndromes and X-linked adrenoleukodystrophy. The treatment effect is variable however, and needs to be weighed against the significant risks that can lead to death (Boelens, 2014). There are a number of gene therapies for childhood dementia disorders currently being investigated in ongoing clinical trials. Preliminary data from some of these studies is promising, however, regulatory approval has not yet been granted for any of these therapies.

As a general comment, it is acknowledged that due to the highly complex and variable nature of childhood dementia disorders, the response of individual patients to treatments is often inconsistent, making it therefore difficult to capture accurately the true number of current 'effective treatments'.

[10] Intraventricular infusion directly delivers the drug into the fluid surrounding the brain, known as the cerebrospinal fluid

Cost

The Burden Study estimated the impact that childhood dementia has on affected children and their families. All costs reported in the analysis are in terms of Australian dollars at 2020 values (A$2020). Please refer to the Burden Study for a full description of methods.

Economic modelling was used to estimate the financial cost of childhood dementia. In an average year, it is estimated that the economic and societal costs to Australia are:

- $40.4 million to the Australian healthcare system (hospital and community health services)
- $75.0 million to the NDIS[11]
- $39.7 million in indirect costs (costs incurred due to lost productivity arising from reduced participation in the workforce by the affected individual and the carer)
- $233.5 million in costs of life years lost (the total opportunity cost of premature mortality associated with childhood dementia)

The average total economic cost of childhood dementia per year is $389 million.

The projected total economic cost of childhood dementia in Australia for the next decade is currently estimated to be $3.9 billion.

The economic cost of childhood dementia to the healthcare system may be considered low in comparison to other conditions affecting children. This can be explained by the short life expectancy and lack of available treatment options. The burden of childhood dementia is therefore disproportionately met by the patients themselves, support services and carers. Furthermore, the indirect costs incurred by carers of individuals with childhood dementia are underestimated since research has shown that paediatric rare genetic conditions are associated with significant negative health impacts on parents, thus resulting in a substantial 'flow on' effect to the healthcare system (Wu et al., 2020). These costs were not accounted for in the Burden Study.

"Childhood dementia is when your daughter asks who you are."

~ Karen, mum to twins Amelia and Makenzie (right) who both have childhood dementia.

[11] NDIS: National Disability Insurance Scheme

Angelina's story

Angelina was like most other teenagers. She had no signs or symptoms or any abnormalities. She was extremely social, self-motivated, goal-driven, academic and had big dreams for her future. She was in school musicals and attending acting classes and wanted to become a makeup artist and business owner.

In September 2018, 14-year-old Angelina, was found unconscious in a corridor at her school. Her stepfather was at her side as she woke up. While he didn't know at the time she was waking from a seizure, he noticed an unusual expression on her face. "It almost looks like she's smiling when she comes out of a seizure", explains her mum, Niki.

Niki noticed Angelina seemed tired and was occasionally dropping things and falling over. On a night around 2 weeks after her seizure at school, Niki watched with horror as Angelina tried to set the table for dinner. "She was smashing the glasses. All of them. Just dropping them. I called our medical centre and they sent an ambulance. They were concerned it was a stroke." It was another week until Angelina had her first witnessed seizure. She was mid-conversation with a terrified Niki who managed to catch Angelina in her arms. "I thought she was dying", she remembers.

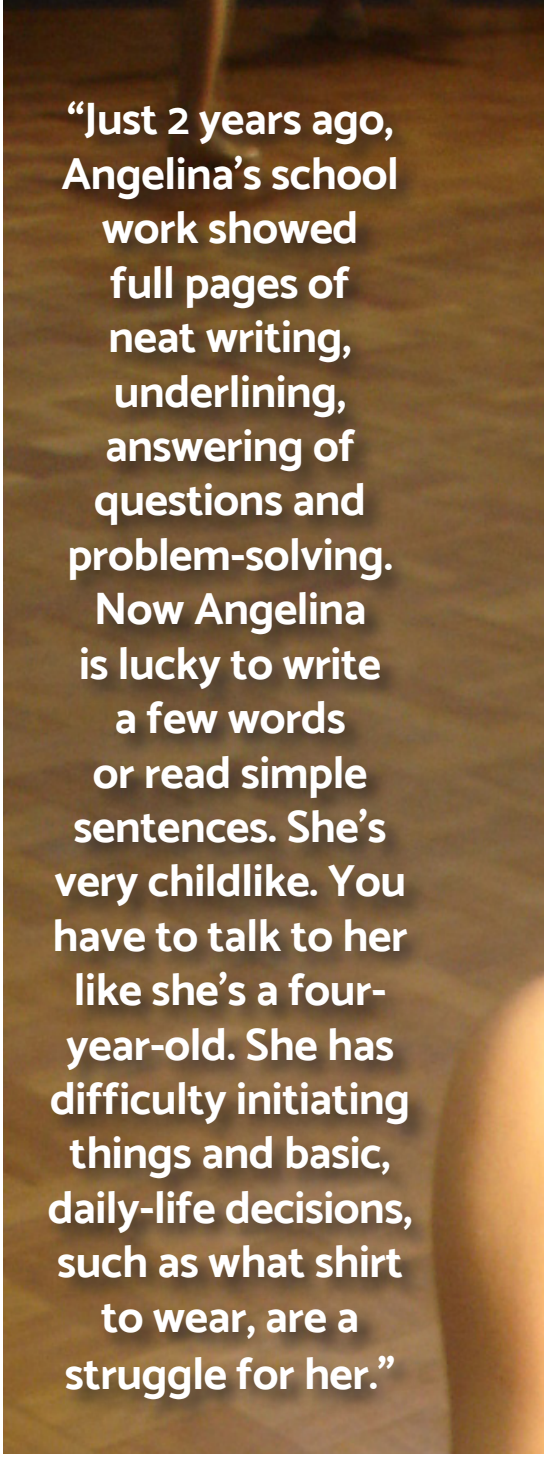
Angelina was initially diagnosed with a form of epilepsy, however, over the next 9 months her seizures worsened. Angelina also appeared to be suffering cognitive decline. "She came home very upset one day because her friends had lost patience with her during a game of UNO. She wasn't following the cards' directions and she wasn't aware when it was her turn."

After 3 months of testing, worried doctors gave Angelina and her family devastating news. Angelina was diagnosed with childhood dementia, caused by a rare genetic disorder called Lafora disease. Symptoms include seizures, muscle spasms, difficulty walking, behavioural changes, confusion and cognitive decline. Within just a few years from the onset of symptoms, children typically find it hard to complete daily activities. Most only live for around 10 years from those first symptoms.

Sadly, Angelina's condition declined in the year following her diagnosis. At times Angelina started to find it difficult to speak, swallow or walk unassisted. In May 2020 doctors inserted a gastrostomy tube so that she could be fed and given medications safely.

By June 2020, Angelina's behaviour started to change. This is a common result of progressive dementia. For Angelina, this made her irritable and impacted her mental health. She started to refuse to eat, co-operate with self-care, get out of bed, or take her medications. Angelina's short and long-term memory and cognitive abilities significantly declined too.

Angelina's body will eventually become tolerant to the medications that give her some respite from seizures and behavioural challenges. She is at high risk of Sudden Unexpected Death in Epilepsy (SUDEP).



"Every day is extremely challenging. The whole family is on high alert all day, every day. We must monitor her constantly", says Niki.

Niki wants to see more awareness of childhood dementia, more screening for it at birth and more research.

"How common is dementia in old people? It's upsetting to see a parent like that. To see that happening for a child who has lost all their future dreams is even more devastating", says Niki.

Table 1: Summary of the Burden Study results: incidence, prevalence and costs of all childhood dementia disorders in Australia

OUTCOME	ANNUALLY	2021 TO 2030
Australian birth cohort	363,074	3,630,736
Total childhood dementia births	129	1,295
Incidence per 100,000	35.67	35.67
PREVALENCE		
Children living with childhood dementia: 2021 to 2030		1,396 to 1,545
Persons living with childhood dementia: 2021 to 2030		2,273 to 2,516
	ANNUALLY	**2021 TO 2030**
Years of life lost	1,096	10,961
Life expectancy	27.81	27.81
Years of life lost due to disability	451	4,513
Costs to the healthcare system	$40,391,688	$403,916,877
Indirect costs	$39,715,290	$397,152,904
Costs of life year lost	$233,479,553	$2,334,795,527
Cost to National Disability Insurance Scheme	$75,022,926	$750,229,262
TOTAL COST OF CHILDHOOD DEMENTIA	**$388,609,457**	**$3,886,094,570**

Source: THEMA Consulting Report (2020). Childhood dementia in Australia: quantifying the burden on patients, carers, the healthcare system and our society.

Discussion

The Problem

Dementia is typically assumed to be a disease of adulthood and old age, however, tragically, children are affected too. The Burden Study demonstrated for the first time the burden associated with childhood dementia in Australia, the tremendous negative impact it has on affected children, families, and the community, and the resulting health and productivity costs.

Each year in Australia, around 129 babies are born with a condition that will lead to childhood dementia. This equates to more than 2 new cases each and every week. Currently an estimated 2,273 Australians are living with childhood dementia and every year more than 90 of them will die prematurely. The average life expectancy for the disorders identified in the Burden Study as causing childhood dementia was just 28 years of age. Some of these disorders have a much bleaker outlook with death typically occurring in infancy. The quality of those short lives is poor with progressive cognitive decline, multiple loss of already attained developmental skills and a multitude of debilitating neurological and other medical issues.

The estimated economic cost of childhood dementia in Australia is $389 million per annum. The intangible costs are felt by the entire family - grief, pain and suffering, an unspeakable emotional toll, stress, anxiety, depression, fear, guilt, exhaustion, social exclusion, and inevitably, impact on personal relationships.

Despite the devastating nature of childhood dementia and it's collective incidence, prevalence and mortality rate being largely comparable with well-known diseases such as cystic fibrosis, motor neurone disease and childhood cancer respectively, childhood dementia has received little recognition or coordinated action towards solutions.

The Opportunity

Current levels of awareness are very low, however, the harsh facts outlined in the Burden Study and this white paper give the Childhood Dementia Initiative a clear and strong mandate. We are unwavering in our mission to raise awareness of childhood dementia and to advocate for systemic change to the way in which childhood dementia is perceived by potential stakeholders, and to transform the research approach and processes in order to accelerate the development of greatly needed solutions for affected children.

RECOMMENDATION 1 : Increase general awareness of childhood dementia, its breadth, impact and level of unmet need.

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.

Widespread duplication of hypotheses, methodologies, technology and infrastructure deprives the childhood dementia research community of opportunities to innovate time-efficient, cost-effective collaborative approaches. Opportunities to bring together the brightest minds and hard-won resources are forgone. These challenges have long been recognised in rare disease research, whereby investigational therapeutics are laboriously tested on disorders one at a time, rather than in parallel, even where common disease mechanisms are involved. Rare disease experts agree that cross indication approaches will lead to enhanced efficiencies and greater patient benefit (Brooks et al, 2014).

This requires systemic change in how research into childhood dementia is undertaken, from funding of scientific research to clinical trial design, and everything in between.

RECOMMENDATION 2 : Promote and enable research that concurrently investigates multiple childhood dementia disorders thereby achieving economies of scale and scope.

In addition to the silos that exist in the study of individual disorders, there is limited collaboration across geographies and institutes which results in further replication of effort and resources and reduced opportunities for knowledge sharing and cross pollination of ideas.

To make strides forward in the development of effective treatments for childhood dementia, global collaborative research across multiple areas of expertise and disciplines must be encouraged and facilitated.

In addition to cross-disorder and cross-geographic collaborations, networks across related areas of research will also be critical. Indeed 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).

Cross pollination between childhood and adult-onset dementias could therefore lead to advancement in therapeutic development for both. 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).

The development and delivery of innovative, fast-tracked research programs for childhood dementia requires collaborative networks of leading minds: researchers, funders, clinicians, industry experts and patients. Importantly, increased collaboration between adult-onset and childhood dementia researchers must be encouraged, as this is very likely to be mutually beneficial.

RECOMMENDATION 3 : Foster and harness collaborative and diverse networks.

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, a collaborative research model utilising shared resources, platform technologies, and clinical trial infrastructure is not only logical but essential if we are to deliver benefit to childhood dementia patients in a timely, cost-effective manner.

To effectively and efficiently develop, produce and deliver these high-cost therapies, processes and infrastructure must be shared and streamlined across this group of conditions.

RECOMMENDATION 4 : Enable delivery of advanced therapeutics such as gene therapy to children with dementia through the development of streamlined platform technologies.

Both the volume and pace of research could be significantly increased by providing and utilising common resources. This will reduce the current high level of duplication and promote innovation, efficiency and capacity across the board. This might include, but not be limited to:

- The collection and sharing of patient data including the establishment and consolidation of patient registries and the sharing of data from completed clinical trials and natural history studies. A clear picture of the characteristics of the patient population will enable clinical trials and raise questions for further research that can be translated into patient benefit.
- Biobanking platforms to collect, store and share patient samples with researchers, such as blood, DNA, cerebral spinal fluid, skin samples and other tissues will accelerate research across the board.
- Outcome measures and biomarkers that accurately measure the progression of the disease are essential for the success of clinical trials and there is considerable work to be done in this area. Although some outcome measures and biomarkers may need to be specific to a particular type of childhood dementia, there is opportunity to develop tools that can be applied to a wide range of disorders.
- Clinical trial infrastructure such as networks of investigators experienced in conducting childhood dementia trials, innovative clinical trial designs (to accommodate small patient population and cross indication trials) and trial coordinators and administrative support that could be shared across multiple trials.
- World class research facilities and equipment should be shared amongst childhood dementia researchers and those in related fields. Previously mentioned collaborative networks will open up opportunities for such sharing

RECOMMENDATION 5 : Provide and promote collaborative utilisation of technology, data and infrastructure.

Early diagnosis and early intervention is critical to the success of any therapy developed for childhood dementia. The progressive, degenerative nature of childhood dementia means that earlier interventions have a greater chance of reducing the extent of irreversible brain damage. Implementation of screening programs such as newborn screening should be planned well in advance of the availability of treatments.

Earlier diagnosis will also avoid the diagnostic odyssey, the many years most families affected by childhood dementia spend searching for a diagnosis, allow early participation in clinical trials and give parents of affected children knowledge to inform future family planning decisions.

Expanded reproductive carrier screening, such as that being piloted by the Australian Reproductive Genetic Carrier Screening Project 'Mackenzie's Mission', aims to lower the incidence of life-limiting or disabling genetic conditions with childhood onset, including those that cause childhood dementia. More than 90% of the genes[12] known to cause childhood dementia are included in the Mackenzie's Mission carrier screening panel (Kirk et al., 2020). To maximise the impact and reach of this project, the Childhood Dementia Initiative will lend its support, endeavouring to make carrier screening available to every couple that wants it.

Earlier diagnosis through newborn and other early screening programs will allow early intervention and improved outcomes for patients. Increased education, awareness and access to carrier screening will assist with the prevention of many cases of childhood dementia.

RECOMMENDATION 6: Significantly improve early diagnosis and increased access to carrier screening.

Considerable advocacy to industry, government and regulatory bodies will be needed to ensure swift and equitable access to new and emerging therapies. Patient organisations can play an important role in ensuring that the patient voice is heard at every stage.

The rapidly progressive nature of childhood dementia disorders and the limited therapies currently available mean that for most children who suffer from childhood dementia today, participation in a clinical trial is likely to be the only opportunity they have to access any kind of therapy, albeit experimental. The opportunities for participation in trials should be maximised and equitable, regardless of a patient's geographical location or socio-economic status, and community input into the design and implementation of clinical trials should be facilitated.

Once a trial is completed and a new treatment shows patient benefit, swift and widespread access is vital. The current regulatory and reimbursement process, though necessary, takes too long and many children will miss out on the chance of treatment before it is too late. The urgency and unmet need must be made clear to regulators for each individual therapy as well as more broad advocacy for streamlined processes. In addition, a scheme to allow funded compassionate access to therapies, while the necessary regulatory and reimbursement processes are undertaken, urgently needs to be put in place.

Patients have the right to hope, to be allowed swift access to new effective therapies, and opportunities to participate in clinical trials of experimental treatments.

RECOMMENDATION 7: Enable equitable access to new and emerging therapies.

[12] The 70 conditions identified in the Burden Study are caused by mutations in at least 102 nuclear genes. Ninety five of these are included in Mackenzie's Mission. There are also a multitude of mitochondrial genetic causes which are not included in carrier screening.

The Childhood Dementia Initiative

In Australia and globally, the individual rare disorders which result in childhood dementia are largely underrepresented. The few patient groups that exist are typically family-led, largely volunteer-run, grossly under-resourced and are often limited to focusing reactively on the immediate support needs of their communities. This leaves little capacity for the identification, assessment, selection and management of effective research programs. Moreover, there remains virtually no capacity for these patient advocacy groups to build or advocate for collaborative research across multiple disorders, or to practically support global collaborations and research infrastructure. Yet without doubt, this is precisely what is required if the pathway to treatments is to be accelerated.

It is timely that the Childhood Dementia Initiative is launching in 2020. *The National Strategic Action Plan for Rare Diseases* (the Action Plan) was endorsed by the Australian Federal Government in February 2020. The Action Plan recognises the need to ensure that research into rare diseases is collaborative, person-centred and systematically addresses gaps.

Nicole Millis, CEO of Rare Voices Australia, the peak body for Australians living with a rare disease, said "the Action Plan identified the critical need for multi-stakeholder engagement; collaborative leadership; state, national and international partnerships; and the comprehensive collection and effective use of rare disease data to enable progress. These are all features of the Childhood Dementia Initiative and will lead to more innovative, collaborative and expert approaches."

The Childhood Dementia Initiative is a global organisation driving research and advocacy to urgently disrupt the impact of childhood dementia on children and families across the world.

By considering the 70 disorders that cause childhood dementia collectively, the Initiative will challenge the world to think differently. This will revolutionise childhood dementia research, enable economies of scale and gains in efficiency across all aspects of the medical research pipeline. Ultimately, accelerating the development of vital treatments and alleviating the devastating and wide-reaching impacts of childhood dementia.

The Childhood Dementia Initiative model involves 2 key elements:

RESEARCH	ADVOCACY
Bring great minds together traversing countries, diseases and specialities, combining advances in emerging fields, to enable economies of scale and scope in all aspects of the research pipeline. Drive a global, collective approach, with innovative, fast-tracked and collaborative research programs that lead to treatments and cures for suffering children.	Raise awareness and understanding of childhood dementia and the devastating impact it has on children, their families and our economy. Advocate for funding, research and systemic change across government, regulatory bodies, patient groups, medical and scientific communities and the general public to fast track solutions for children and families living with the devastating impacts of childhood dementia.

There is no time to lose. Children are suffering immeasurably, their families burdened with unthinkable challenges. The costs to our economy are great. And yet still each week, more children are being born who will suffer the same inevitable journey and premature death. We have an opportunity to change their future. Time is against us; we must act now.

“When we look at this constellation of diseases, identifying subsets with similar mechanisms empowers us to have learnings across individual diseases - achieving economies of scope and opportunities for impact across patient populations. By working under the umbrella of childhood dementia, there is tremendous potential to translate this research into therapeutics and diagnostics. It is such an innovation.”

Tiffany Boughtwood, Director, Childhood Dementia Initiative

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And we would particularly like to extend our heartfelt gratitude to the families of children with childhood dementia who have so generously shared their stories.

Appendix A: Childhood dementia disorders

Childhood dementia definition

The inclusion criteria for childhood dementia used for the Burden Study includes any child (under 18 years of age at onset of symptoms) with any illness that fulfils ALL of the following criteria:

- Multiple losses of already attained development skills
- Duration of illness greater than 3 months
- Skill loss most likely due to central nervous system (CNS) dysfunction
- Evidence of generalised (not merely focal) brain dysfunction
- Has a condition which will in the future, in all probability, lead to progressive deterioration as above
- Is monogenic in origin

List of disorders

LYSOSOMAL DISEASES

Lysosomal disorders of lipid metabolism and transport

- Combined saposin (prosaposin) deficiency
- Farber disease
- Gaucher disease (type 2)
- Gaucher disease (type 3)
- Globoid cell leukodystrophy (Krabbe disease)
- GM1 gangliosidosis
- GM2 gangliosidosis - AB variant
- GM2 gangliosidosis (Tay-Sachs disease)
- GM2 gangliosidosis (Sandhoff disease)
- Metachromatic leukodystrophy
- Multiple sulfatase deficiency
- Niemann-Pick disease type A
- Niemann-Pick disease type C
- Saposin A deficiency
- Saposin B deficiency
- Saposin C deficiency

Glycoproteinosis

- Alpha-mannosidosis
- α-N-acetylgalactosaminidase deficiency (Schindler disease type I)
- Aspartylglucosaminuria (AGU)
- Beta-mannosidosis
- Fucosidosis (type I and II)
- Galactosialidosis (cathepsin A mutation)
- Mucolipidosis type I (sialidosis)
- Mucolipidosis (type II) (i-cell disease)
- Mucolipidosis (type IV)

Mucopolysaccharidoses

- MPS I (Hurler syndrome)
- MPS II (Hunter syndrome)
- MPS III (Sanfilippo syndrome)
- MPS VII (Sly syndrome)

Other lysosomal diseases

- Neuronal ceroid lipofuscinoses (NCLs or Batten Disease); 14 subtypes (except those that are adult onset CLN 4, 11, 13)
- Sialic acid storage disease

OTHER DISORDERS OF LIPID METABOLISM AND TRANSPORT

- Abetalipoproteinaemia
- Cerebrotendinous xanthomatosis

DISORDERS OF AMINO ACID AND OTHER ORGANIC ACID METABOLISM

- Canavan disease
- Glutathione synthetase deficiency
- Glycine encephalopathy / nonketotic hyperglycinemia
- Holocarboxylase synthetase deficiency
- Sulfite oxidase deficiency

VITAMIN-RESPONSIVE INBORN ERRORS OF METABOLISM

- Biotinidase deficiency
- Biotin-thiamine-responsive basal ganglia disease
- Cerebral folate deficiency
- Cobalamin C disease / deficiency (Cbl-C)
- Molybdenum cofactor deficiency
- SLC5A6 deficiency

DISORDERS OF MINERAL ABSORPTION AND TRANSPORT

- Menkes disease
- Wilson disease

PEROXISOMAL DISEASE

- X-linked adrenoleukodystrophy
- Zellweger spectrum disorder

MITOCHONDRIAL DISORDERS

Including but not limited to: Leighs, KSS, MELAS and Alpers-Huttenlocher syndrome.

OTHER INBORN ERRORS OF METABOLISM

- Congenital disorders of glycosylation (subset of e.g. CDG1E, CDG1J, CDG2A)
- Lafora disease

LEUKODYSTROPHIES NOT OTHERWISE CATEGORISED

- Alexander disease (type I)
- Pelizaeus merzbacher disease
- POLR3-related leukodystrophies
- Vanishing white matter disease

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION

- Beta propeller protein associated neurodegeneration (BPAN)
- Coenzyme A synthase protein-associated neurodegeneration (COASY)
- Fatty acid hydroxylase-associated neurodegeneration (FAHN)
- Kufor-Rakeb syndrome
- Mitochondrial membrane protein-associated neurodegeneration (MPAN)
- Pantothenate kinase-associated neurodegeneration (PKAN)
- Woodhouse-Sakati syndrome (DCAF17)

NEURODEGENERATIVE DISEASES NOT OTHERWISE CATEGORISED

- Cockayne syndrome
- Giant axonal neuropathy
- Huntington's disease (Juvenile Form)
- Infantile neuroaxonal dystrophy
- Juvenile Parkinson's disease PARK19A (DNAJC6)
- MECP2 duplication syndrome
- Other HD-like variants (particularly HDL3)
- Rett syndrome

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