An exploration of the diagnostic journey of children with Neuronal Ceroid Lipofuscinosis (NCL).

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Statement of originality

I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision. The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

Alanna Gayko

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In memory of my fiancée Paul 'Swog' Schwager, and my sister Jacqueline Toohey.

Abbreviations

ad	autosomal dominant
AD	Alzheimer disease
ADHD	attention deficit hyperactivity disorder
AFI	amaurotic familial idiocies
AFSM	auto-fluorescent storage material
ALP	Autosomal-Lysosomal pathway
ALS	Amyotrophic Lateral Sclerosis
ANCL	adult neuronal ceroid lipofuscinosis
A&NZ	Australian and New Zealand
ASD	autism spectrum disorder
ATP	adenosine 5-triphosphate
AVV	adeno-associated virus
BARN	Batten Animal Research Network
BBB	blood brain barrier
BD	Batten disease
BDSRA	Batten Disease Support and Research Association
BDSRAA	Batten Disease Support and Research Association (Australia)
CF	Cystic Fibrosis
CI	chief investigator
CLN	*ceroid lipofuscinosis neuronal* (gene)
CLN	ceroid lipofuscinosis neuronal (disease)
CLN7	*large major facilitator superfamily (MFS) or MFSD8*
CLP	curvilinear profiles
CNS	central nervous system
CReDITSS	Clinical Research Design and Statistics
CTSF: (CLN13)	c*athepsin F (CTSF)*
DNAJC5: (CLN4)	Adult autosomal dominant Parry disease: *subfamily C member*
DNA	Deoxyribonucleic acid
Dx	diagnosis
DBS	dried blood spot
DMD	Duchenne Muscular Dystrophy
EEG	electroencephalogram
EM	electron microscopy
ERG	electroretinogram
ERT	Enzyme Replacement Therapy
EU	European Union
FDA	Food and Drug Administration
FPP	fingerprint profiles
FTLD	Fronto-temporal lobe degeneration
GAA	Genetics Alliance (Australia)
GD	Gaucher disease
GRN: *(CLN11)*	*granulins*
GP	general practitioner
GROD	granular osmiophilic deposits
GTIC	genetic testing in children
HGSA	Human Genetic Society of Australasia
HMRI	Hunter Medical Research Institute
HREC	Human Research Ethics Committee
ICV	Intracerebroventricular
ID	identification code
IEMs	inborn errors of metabolism
INCL	infantile neuronal ceroid lipofuscinosis
IQR	interquartile range
IVF	in-vitro fertilisation
JNCL	juvenile neuronal ceroid lipofuscinosis
LD Australia	Lysosomal Diseases Australia
LD NZ	Lysosomal Diseases New Zealand
LINCL	late infantile neuronal ceroid lipofuscinosis
LOTE	language other than English

LSD	lysosomal storage disorder
MD	macular degeneration
M-L scale	motor-language scale
MPS	Mucopolysaccharidosis
MRI	magnetic resonance imaging
MST	mass spectrum technology
MAE	myoclonic astatic epilepsy
NCATS	National Centre for Advancing Translational Health
NHMRC	National Health and Medical Research Council
NIP	National Immunisation Program
NIH	National Institutes of Health
NCL	Neuronal Ceroid Lipofuscinosis
NCLs	Neuronal Ceroid Lipofuscinoses
NSW	New South Wales
OIS	organisation information statement
OMIM	Online Mendelian Inheritance in Man
PD	Parkinson's disease
PBAC	Pharmaceutical Benefits Advisory Committee
PGD	pre-implantation genetic diagnosis
pH	potential for Hydrogen
PIND	progressive intellectual and neurological deterioration
PIS	participant information statement
PKU	Phenylketonuria
PME	progressive myoclonus epilepsies
PPT1	Palmitoyl-protein thioesterase 1
REA	research ethics advisor
REM	rapid eye movement
REDCap®	Research Electronic Data Capture
RIMS	Research Information Management System
RP	retinitis pigmentosa
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TPP1	Tripeptidyl peptidase 1
UK	United Kingdom
UoN	University of Newcastle, Australia
US	United States

Definitions

adult	a person older than 18 years of age
Adult NCL	an adult-onset phenotype or genotype of NCL with an onset in early adulthood
child	reference to infants and children until the age of 18 years
classic	historical reference to original four NCL subtype groups: infantile, late-infantile, juvenile, adult
clinicopathological	a historical NCL diagnosis based on clinical presentation supported by pathology
Congenital NCL	usually CLN10 disease that is evident at birth or shortly afterwards but may have a later phenotype
diagnosis	estimated identification of a disease or condition based on clinical signs and symptoms, pathological, background, history, ultrastructural, and radiological findings
differential diagnosis	the process of differentiating between two or more conditions or diseases that may share a similar presentation of signs and symptoms
dysmorphia	subtle or distinct facial abnormalities that may be evident at birth or evolve
genotype	the mutations that make up the genetic makeup of an individual
heterogeneity	when the genetic mutation contains two different alleles of a gene
homogeneity	when the genetic mutation contains the two same alleles of a gene
hyposmia	a reduction in the sense of smell
incomplete diagnosis	a correct diagnosis such as epilepsy, which is not incorrect per se, but it is not the entire problem or disease that is emerging
infant:	from the post-natal period until the first twelve months of life
Infantile NCL	historical designation of this subtype commencing during infancy (referred to CLN1 if a genetic diagnosis is confirmed)
Juvenile NCL	historical designation of this subtype that began in middle childhood through the teens (referred to CLN3 if a genetic diagnosis is confirmed)
Late-infantile NCL	historical designation of this subtype that commenced during early childhood (now referred to CLN2 if a genetic diagnosis is confirmed)
nyctalopia	difficulty adapting or seeing in a dimly lit environment or at night
macrographia	progressively larger handwriting
micrographia	progressively smaller handwriting
neonate	newborn child, usually less than four weeks old
organomegaly	an enlarged organ such as engorged liver associated with a distended abdomen
pathognomonic	refers to signs, symptoms or investigation results which are characteristic or indicative of a particular disease or condition
phenoconversion	the interval during that the signs and symptoms present and become evident
phenotype	the disease presentation
polysomnography	sleep study
prenatal	prior to birth
sign	a tangible and overt indicator of a disease or condition
symptom	a subjective physical or psychological experience that is a precursor or concurrently occurring with the onset of a disease or condition
misdiagnosis	an incorrect diagnosis
missed diagnosis	a condition or disease that was overlooked at the time of presentation
teen	a child aged from ten years until 18 years of age
variant	reference to additional disease types such as the late-infantile variant: CLN5

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Abstract

Neuronal Ceroid Lipofuscinosis (NCL) or Batten disease, is a group of predominantly recessively-inherited neurodegenerative diseases that mostly affect children. It is the most common genetic cause of dementia in children, yet a rare cause of dementia in adults. Although NCL remains life-limiting, clinical trials are in development for specific disease types. NCL has a low Australian and New Zealand incidence, but a devastating impact on affected children and their families. Currently, neither country participates in an international NCL patient registry that leaves these families isolated from potential research and therapeutic agents. As recently as 2017, a historical milestone was passed with the approval of the first disease-modifying enzyme replacement therapy - Brineura® for ceroid lipofuscinosis, neuronal 2 or CLN2.

Research has consistently identified a protracted diagnostic period of NCL. Retrospectively identifying the earliest onset of the disease could feasibly impact future diagnostic delays. Subtle early signs and symptoms merge with other rare or common diseases and can be missed. This study describes the early phase of NCL in this cohort of A&NZ children. It uses parent-report to retrospectively identify the earliest sign or symptom that led to the diagnosis or that should have led to the diagnosis with hindsight. To achieve this aim, the parents' experiences, and any facilitators of a timely diagnosis of NCL were also explored.

Databases including PubMed and manual searches of reference lists provided a comprehensive historical and contemporary literature review, focused on the onset of NCL. Specific research of the initial presentation of NCL during childhood was limited; however, themes of early signs and symptoms were identified. Corresponding with the literature, the mnemonic 'NEURONS' was devised by the student researcher to incorporate the early signs and symptoms of childhood-onset NCL diseases. These include **N**eurological stalling and/or **E**pilepsy. **U**ltrastructural features are distinctive but not unique to each disease. **R**egression of milestones and abilities become evident. **O**phthalmic signs with visual loss behaviour and vacuolated lymphocytes are associated with CLN3. **N**ew-onset ataxia and early **S**peech delays are aligned with specific diseases such as CLN2.

After gaining University of Newcastle Human Research Ethics Committee approval [No. H-2018-0059], a purposive sample was obtained. Participation was offered to all A&NZ parents/legal guardians of children, alive or deceased, diagnosed with any NCL disease in the past five decades. Recruitment was initiated through the Australian chapter of the Batten Disease Research Association (BDSRA) family support group, two alternate organisations, and snowball recruitment. There were two phases of the study: The consultative phase comprised of key informant consultation in the design of the quantitative survey regarding children with an NCL diagnosis. The survey phase incorporated a structured cross-sectional survey devised by the research team. Potential participants were invited to complete the REDCap® on-line survey, using links on the Australian BDSRA Facebook® page or website. The anonymous survey asked parents to retrospectively explore the diagnosis of their child's disease in a chronological format, with an option to provide additional text.

Facilitators and hindrances of childhood-onset NCL diagnosis were identified. Pre-genetic clinical, enzymatic, and/or genetic diagnoses were categorised. There were 29 A&NZ parent participants of children with either CLN1, CLN2, CLN3, or CLN5 disease. Predominantly, the parents identified the earliest changes and prompted investigation of their child. Initial misdiagnoses included up to four alternate diagnoses. The primary outcome of the study identified a two-year median diagnostic delay, including a one-year delay before investigations were initiated. A cohort of 26 children of index cases with a confirmed age of onset, did not include two facilitated pre-symptomatic diagnoses.

The diagnostic 'odyssey' discussed in the rare disease literature, was similarly identified in this A&NZ study. The longest delay determined in this study was a recent protracted diagnosis of nine years and nine months for a child with CLN3. Early signs and symptoms were aligned with the NEURONS model based on the literature. Speech pathologists or ophthalmologists reviewed these children with either speech delays and/or loss or a new onset visual loss, associated with the early sign of clumsiness. Education programmes may increase specific health professionals’ awareness of NCL, reduce future diagnostic delays for NCL, and improve family access to emerging clinical trials and available treatments.