

Investigating Batten disease

Professor Jonathan Mink discusses a rare childhood neurological disorder – Batten disease – delving into its peculiarities, the difficulties associated with studying rare diseases, methods of clinical evaluation and potential future treatment options



You employ standardised measures to conduct your evaluations. How do you accommodate the unique phenotype of Batten disease?

Wherever possible we aim to use standardised measures that do not require adaptation; for example, assessment tools that do not necessitate examination of visual stimuli. However, when adaptations are necessary we carefully document and maintain them.

We developed the Unified Batten Disease Rating Scale (UBDRS) and used iterative methods to assure reliability. Even after a decade of evaluations, we continue to learn how to further refine our assessments to improve the sensitivity of the methods, especially during the latter stages of disease.

The Pediatric Quality of Life Family Impact Module assesses the health-related quality of life of parents and family in relation to the child's health. What conclusions were you able to draw from your research?

These results show the considerable impact of the disease upon the wellbeing of the family. Batten disease does not just affect a child, but an entire family system. The results also suggest that the care we provide must take into consideration the needs of the family as a whole.

Could you discuss some of the ongoing clinical trials evaluating disease-modifying therapies?

Disease-modifying therapies currently undergoing investigation in human trials include gene therapy, enzyme-replacement therapy and immunomodulation. For the forms of Batten disease that involve soluble enzymes (eg. CLN1 and CLN2 diseases), gene and enzyme-replacement therapy are promising strategies. In juvenile neuronal ceroid lipofuscinoses (JNCL, or CLN3 disease), the protein is membrane-bound and poorly understood, so therapy directed at replacing the mutant protein is less feasible.

However, work by David Pearce, PhD of the Sanford Children's Health Research Center has shown that children and mouse models with CLN3 disease have antibody-mediated autoimmunity. In mice, suppression of the immune response is protective. We are currently performing a phase II clinical trial of the immunosuppressant mycophenolate mofetil in children with CLN3 disease.

Due to the rarity of the condition, the Batten disease research community is relatively small. As such, do you find collaboration is an integral part of your work?

Collaboration is of critical importance in rare disease research generally and in Batten disease research specifically. Collaboration is necessary to develop consensus about how to prioritise treatment trials; develop agreement on meaningful endpoints for clinical trials; and enrol sufficient numbers of subjects in clinical trials.

Batten disease shares challenges with other lysosomal storage disorders. To what extent will your research advance knowledge on these rare diseases?

Our approach to studying the natural history of JNCL has significant potential to inform research on other rare childhood neurodegenerative diseases. We have developed a disease-specific rating scale that can be modified for other diseases. In fact, it has already been employed for Wolfram



Batten disease explained

Neuronal ceroid lipofuscinoses (NCLs) are a group of lysosomal storage diseases characterised by the accumulation of a lipopigment in neurons. There are at least 12 different forms of NCL, the most prevalent of which is the juvenile form (JNCL, or Batten disease), due to mutations in the CLN3 gene.

Batten disease is characterised by rapidly progressive blindness beginning between four and seven years, followed by progressive dementia, epilepsy and premature death (usually in the third decade). Incidence is estimated to be about two per 100,000 live births in the US.

disease, another rare childhood neurological disease. Our systematic approach to quantifying disease progression puts us in a strong position to test treatment efficacy.

It is becoming increasingly apparent that many neurodegenerative diseases have an inflammatory component. If immunomodulation can slow CLN3 disease progression, it could provide important insights into the treatment of other lysosomal storage disorders that affect the nervous system.

What are the main hurdles to developing effective treatments?

At this time, potential treatments are more likely to slow or halt disease progression than reverse it. In addition to the difficulty of identifying and testing such a treatment, this poses the challenge of identifying potential candidates as early in the disease course as possible, in order to have the best outcome – requiring early diagnosis.

Can you describe some of the greatest achievements your team has made to date?

Our greatest achievements have been conducting the largest longitudinal study of the natural history of any form of NCL, developing the methodology and infrastructure for clinical trials in Batten disease and initiating the first controlled clinical trial in JNCL.

Rare disease clinical trials

The **University of Rochester Medical Center**, a Batten disease Center of Excellence, is conducting the first controlled clinical trial for the juvenile form of the disease. It is hoped their work characterising the course of the condition will improve diagnosis and treatment, benefiting child patients and their families alike



From left to right: Heather Adams, Sara Defendorf, Lisa de Blicq, Jonathan Mink, Frederick Marshall, Amy Vierhile, Paul Rothberg, Alyssa Thatcher, Erika Augustine.

discovered an immune component to JNCL, a monumental finding for a disease about which so little is understood. URBC researchers take a quantitative approach to the study of JNCL progression, which will inform neurobiological investigations and clinical trials.

There are many challenges associated with studying Batten disease: like all rare diseases, the number of affected people willing to enter clinical trials is small; those who are willing need to be diagnosed early, which can be a difficult proposition; and by its rare nature, there are relatively few people working on the disease.

Overcoming these many and varied obstacles requires collaboration, training a new generation of rare disease researchers and leveraging existing resources. However, great advances in genetics alongside growing knowledge of JNCL's clinical features suggest meaningful therapeutics could be available in the not too distant future.

RESEARCH CATEGORIES

The overarching aims of studies at URBC are to advance knowledge of the clinical manifestations of Batten disease and to develop improved treatments. Under this umbrella, research is divided into four basic categories: natural history; neurobehavioural and neurocognitive features; determinants of JNCL severity; and experimental therapeutics.

Neurobehavioural assessment of patients with JNCL is particularly demanding. Dementia and vision loss in JNCL place limits on assessment, as many intelligence tests evaluate both verbal and visual reasoning skills. The URBC team has attempted to overcome this difficulty using standardised measures with modifications which accommodate the unique phenotype of Batten disease.

URBC investigations have shown that JNCL disease progression can vary between individuals, and this does not seem to be due simply to different mutations in CLN3. The researchers are now working to understand which factors determine disease severity. One may be gender, as Mink and collaborators recently revealed: "In females, the disease progresses more rapidly once symptoms begin". Further research into the basis for these gender differences may lead to a better understanding of the biological mechanisms underpinning the disease as a whole.

SCALE OF DISEASE

The Unified Batten Disease Rating Scale (UBDRS) was developed by the URBC to provide a consistent and disease-specific method of evaluating children with JNCL. It is a multi-component system, comprising a physical exam, medical history review and questioning about symptoms. The UBDRS is used both as part of clinical evaluation and as a research tool.

The Scale is modelled after scales in similar adult disorders and has four subscales: physical impairment, seizures, behaviour and functional capability. Since 2002, 120 children have been evaluated using the UBDRS, and many return each year. Repeat evaluations allow the team to consistently track disease progression over time. Ultimately, the system enables the identification of symptoms which lead to disability and factors which are associated with fewer symptoms.

The URBC investigators have recently shown that the physical impairment subscale can be used remotely by a trained non-physician. Telemedicine has real potential to be a valuable tool in NCL research and clinical assessment, a real benefit given the geographically scattered nature of patients.

CLINICAL TRIAL

The past 20 years of JNCL research has seen a shift from the bench to the bedside. Forming part of this transition, URBC has developed a clinical research infrastructure, research cohort and disease-specific clinical outcome measure.

Designing and carrying out meaningful clinical trials is a major emphasis of URBC research. In 2012, URBC began the JNCL Mycophenolate Phase II Clinical Trial (JUMP), led by Drs Erika Augustine and Frederick Marshall. It is a randomised control trial to determine whether mycophenolate mofetil – a drug approved by the US Food and Drug Administration (FDA) to suppress the immune system of children undergoing organ transplants – is safe to use in children with JNCL. The trial will enrol 30 individuals, each of whom will take study medication for eight weeks, and placebo for eight weeks.

The trial is the result of collaboration with Dr David Pearce, now at the Sanford Children's Health Research Center, and based on preclinical models. The UBDRS will be integral to the JNCL clinical trial as a tool to quantify the progression of impairment, preventing subjective results.

ALTHOUGH RELATIVELY RARE, neuronal ceroid lipofuscinoses (NCLs) represent the most common neurodegenerative disorders of childhood. The University of Rochester Medical Center (URMC) studies Batten disease, the most common form of NCL.

NCLs are a broad class of diseases. Although they share some symptoms and pathology, there are great differences in terms of age of onset, biochemistry and genetics; there are at least 20 genes associated with Batten disease alone. The most prevalent form of Batten disease is juvenile NCL (JNCL), which is linked to mutations in CLN3. CLN3 encodes Battenin, a ubiquitously expressed membrane protein localised to the lysosomal membrane. Although its function is unknown, modelling studies suggest it may play a role in substrate trafficking along the lysosomal pathway in cells.

This pathway is hugely important to cellular transport and metabolism; lysosomes essentially form the digestive system of the cell. As intracellular vesicles containing enzymes which break down bacteria, biological polymers and obsolete or dysfunctional cellular components, defects in lysosomal function result in the accumulation of abnormal storage material in neurons and other cell types, giving rise to the devastating consequences of NCLs.

RARE DISEASE CHALLENGES

URMC's Batten Disease Diagnostic and Clinical Research Center (URBC) is directed by Dr Jonathan Mink, and represents the largest single-centre Batten disease clinical research group in the world. The Center offers clinical services, education about Batten disease, clinical consultation and genetic diagnosis. It is also at the vanguard of Batten disease research; for example, the Center

Having successfully overcome many of the challenges associated with the study of JNCL, Mink and his team at URBC will continue to work to improve outcomes for those living with the disease

Although URBC researchers have considered many medications for their potential use in the treatment of JNCL, mycophenolate is the first to progress to the stage of a controlled clinical trial. Preclinical studies using an animal model suggested that immune suppression can in fact slow disease progress, so it is hoped that neurodegeneration can also be slowed – and perhaps even arrested – in children with the disease.

APPLICABLE FINDINGS

Beyond JNCL, the findings of the research at URBC can be applied to other neurodegenerative and lysosomal storage disorders, both in terms of the knowledge gained and clinical trial methodologies. Mink's future priorities are to continue to improve understanding of disease pathophysiology and natural history. Future therapeutic development will be supported by his continued efforts to build expertise in clinical trial design and infrastructure.

The underlying mechanisms of JNCL are still to be fully elucidated, and research remains in its infancy, but the future is promising: "We plan to move from a phase II safety and tolerability study of mycophenolate to a phase III efficacy trial," Mink enthuses. "We will also continue to characterise the disease course and will begin to perform studies of disease mechanisms." Having successfully overcome many of the challenges associated with the study of JNCL, Mink and his team at URBC will continue to work to improve outcomes for those living with the disease.

INTELLIGENCE

CLINICAL AND NEUROPSYCHOLOGICAL INVESTIGATIONS IN BATTEN DISEASE

OBJECTIVES

- To develop a genetic diagnosis of Batten disease
- To clinically evaluate Batten disease
- To continue development of the Unified Batten Disease Rating Scale (UBDRS)
- To interact with current research into Batten disease
- To develop and design clinical trials for juvenile neuronal ceroid lipofuscinosis (JNCL)

KEY TEAM MEMBERS AND COLLABORATORS

Frederick J Marshall, MD • Jennifer M Kwon, MD • Erika F Augustine, MD • Heather Adams, PhD • David A Pearce, PhD • Paul G Rothberg, PhD • Elisabeth de Blic, MPA, CCRC • Amy Vierhile, RN, PNP • Nicole Newhouse • Sara Defendorf • Alyssa Thatcher

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PROFESSOR JONATHAN MINK leads the Batten Disease Diagnostic and Clinical Research Center and the Division of Child Neurology in the Department of Neurology, University of Rochester Medical Center. Mink has examined over 100 children with JNCL while developing the UBDRS, and is familiar with other forms of NCL through his practice and training as a child neurologist.

Juvenile neuronal ceroid lipofuscinose

JNCL successively deprives children of their abilities to see, reason and move. Symptoms typically emerge between five and eight years of age. Although age of onset and progression can vary, the disease is ultimately terminal. Average survival is 15 years from symptom onset and there are no available treatments to prevent, reverse or halt the disease's progression.



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