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Future perspectives: Moving towards NCL treatments

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Abstract

Clinicians, basic researchers, representatives from pharma and families from around the world met in Cordoba, Argentina in October, 2014 to discuss recent research progress at the 14th International Congress on Neuronal Ceroid Lipofuscinoses (NCLs; Batten disease), a group of clinically overlapping fatal, inherited lysosomal disorders with primarily neurodegenerative symptoms. This brief review article will provide perspectives on the anticipated future directions of NCL basic and clinical research as we move towards improved diagnosis, care and treatment of NCL patients.

Basic and drug discovery research

An impressive collection of lower organism and mammalian disease models has been developed since the discovery of the first NCL genes in 1995 (1, 2). These disease models, most recently summarized in this Special Issue, are increasingly well characterized and are being employed in both basic research and pre-clinical drug development for NCL. A major focus of research efforts is the search for the primary protein functions, which remain unsolved for most of the NCL proteins. Work in lower organism models should contribute further knowledge on the function of the evolutionarily conserved NCL proteins, complementing ongoing and new research efforts that utilize higher organism and human cell-based models. Expanded efforts into delineating the protein interaction networks for each of the NCL proteins should also shed important light on their molecular properties and the extent to which NCL protein interactomes overlap. With advancing technologies in the field of systems biology, such as transcriptomics, metabolomics, lipidomics and proteomics, it is anticipated that more systems level approaches will be applied to the study of NCL disorders. For example, in other neurodegenerative disease areas and in autoimmune

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disease, metabolomics research is leading to the development of important diagnostic and disease tracking biomarkers, as well as important insights into disease mechanisms (3–5). With the current array of NCL animal models, which now exist for CLN1-CLN8, and CLN10-CLN12, these methods could already be applied to the NCLs.

Patient-derived samples are increasingly being used for NCL-focused research. Expansion of biobanks that include clinical phenotype data linked to DNA, tissue samples, cell lines (e.g. EBV-transformed lymphoblastoid cells, fibroblasts), serum and plasma will be needed for biomarker development and for genetic modifier studies. The development of cellular reprogramming technology now makes it possible to establish collections of NCL patient induced pluripotent stem cell lines (iPSCs) that can be differentiated into any cell type of interest (6). The successful development of iPSCs from CLN1, CLN2, and CLN3 patients has recently been reported (Uusi-Rauva, 14th International Congress on the NCLs Abstract Book, Medicina v74, Suppl. II, O-5 and (7)). Efforts to expand the development of a more comprehensive set of NCL patient iPSCs are anticipated, and the use of these iPSCs for both basic disease mechanism and drug discovery research will undoubtedly continue to grow. Moreover, given increasing evidence that there are cell-type specific defects in many of the NCLs and that the interaction of different cell-types and even organ systems may play an important role, these reagents will help facilitate more complex disease modeling (e.g. iPSC-derived cerebral organoids (8)) to complement whole organism studies using genetic animal models (e.g. mouse, dog, sheep, pig models, see up to date review in this Special Issue), for an improved understanding of the full impact of the NCL disease process and how to treat it.

Several key questions that may be answered in the coming years include:

1. what are the primary functions of each of the NCL proteins?
2. what imparts the selective vulnerability of certain cells over others (e.g. neurons versus hepatocytes, or one neuronal subtype over another)?
3. what, if any, overlap is there in the function of each of the NCL proteins?

In addition to these important questions, it is anticipated that the fully developed cellular disease models, particularly those involving the human patient-derived cell lines (e.g. iPSCs and their differentiated derivatives), will greatly facilitate the application of phenotype-based genetic and pharmacologic modifier screens to identify lead drugs or target pathways for further development and testing as NCL treatments.

Emerging clinical trials: need for developing good natural history data

While some forms of NCL remain more challenging for researchers to solve because they involve loss of function of transmembrane proteins that are poorly understood (e.g. CLN3, CLN6, CLN7, CLN8, and CLN12), there are exciting developments in the treatment of the enzymatic forms of NCL (CLN1, CLN2, CLN5), which are most amenable to gene therapy and enzyme replacement approaches. The most advanced therapies to date target the CLN2 enzyme, TPP1 (tripeptidyl peptidase I). Strong pre-clinical data utilizing a Tpp1 knockout mouse model and a naturally occurring dog model (9–13) led to the development of clinical trials testing gene transfer (14)(ClinicalTrials.gov NCT01414985) and enzyme replacement

therapy (Biomarin, BMN 190, ClinicalTrials.gov NCT01907087). While these trials are still ongoing, they are groundbreaking in the NCL field because they have led to the establishment of strong international collaborative networks that are succeeding to develop much needed natural history data and rating scales with across-site consistency for this form of NCL (14) (Crystal, 14th International Congress on the NCLs Abstract Book, Medicina v74, Suppl. II, L-5, Schultz et al., 14th International Congress on the NCLs Abstract Book, Medicina v74, Suppl. II, O-39). This is critical for the fair and accurate assessment of efficacy in current and future clinical trials. As candidate treatments for other forms of NCL make their way into clinical trials, the successful efforts for CLN2 will serve as an important model. The first CLN3 human clinical trial is also under way (Phase 2 trial of CellCept, ClinicalTrials.gov NCT01399047) and is aiding in the optimization of an across-site CLN3 rating scale for future analysis of efficacy (15–17).

Improved diagnosis and supportive care

One of the most significant advances in the past decade in genetic disease research is the development of next generation sequencing technology, which is expected to widely impact the speed and scope of clinical genetic testing for all inherited disorders. There are nevertheless significant challenges in the analysis of the vast genetic data generated and in its interpretation. Continued use of complementary classical genetics methods is typically needed. Major efforts around the world to improve this technology and data interpretation are expected to help facilitate the implementation of next generation sequence analysis into clinical genetics testing laboratories.

Through collaborative and NCL genetics consortia efforts, the application of whole exome sequencing has contributed to the expansion of the clinicopathologic and genetic spectrum of the NCLs. From eight genes in 2010, the list of genes implicated in NCL is now thirteen, and the phenotypic spectrum of disease arising from a single gene has considerably broadened. Of note, several of these newer implicated genes are also involved in rare forms of Parkinsonism (18), Progressive Myoclonic Epilepsy without lysosomal storage (19), and in the second most common form of adult onset dementia, frontotemporal dementia (FTD) (20), consistent with overlap in disease mechanisms across these neurodegenerative brain disorders. A more comprehensive summary of NCL genetics and these recent advances can be found elsewhere in this Special Issue (‘Genetics of the NCLs’).

It is expected that additional rare NCL genes will be identified as there continue to be patients with an unsolved genetic etiology for their disorder despite full sequence analysis of the known NCL genes. The collection of large datasets and mutation databases, such as the NCL mutation database (http://www.ucl.ac.uk/ncl/mutation.shtml), particularly if they include functional variant information, will continue to expand and should further inform our understanding of the molecular basis of the NCL disorders and should greatly facilitate genetic diagnosis of NCL patients. The broadening of the pathogenetic spectrum of the NCLs should also bring together experts from across disciplines, which will have a positive impact on the breadth of research into the role of the NCL proteins in maintaining healthy brain function.

Despite major advances in clinical genetics, the diagnosis of NCL remains a challenge, even in highly developed countries. Improved awareness and health professional training should be emphasized. Specific recommendations from a panel of experts to improve knowledge on rare diseases, and in particular on the NCLs, can be found in a separate chapter in this Special Issue. In addition to ultimately finding a treatment that will prevent or delay the degenerative symptoms of this devastating group of disorders, research that is aimed at better management of symptoms should also be emphasized. For example, associated psychiatric disturbances and seizures in some forms of NCL are challenging to manage. Clinicians often have little information to make rational choices for treatment of these symptoms because a mechanistic understanding of them is lacking. These gaps in the NCL clinical and research arenas are beginning to be addressed and should be further supported if we hope to have an impact on the lives of NCL patients and their caregivers.

15th International Congress on NCL

In two years, the international NCL research community will once again come together to discuss new research findings and to build upon old and new research networks. The meeting will be held in Boston in the fall of 2016.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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