

Preface

Special issue: Molecular basis of NCL

The neuronal ceroid lipofuscinoses (NCL), also known as Batten disease, are a group of rare and devastating neurodegenerative disorders. They are genetic diseases, usually inherited in an autosomal recessive manner, and at present are incurable. Disease can present at any age, from before birth up to late in life, although those most affected are children.

An international meeting on the NCLs—the 14th international conference, NCL2014 (<http://www.nclcordoba.com>) together with the 2nd international patients organization meeting — was held in October 2014 in Córdoba, Argentina, the first such international meeting on the NCLs in Latin America. It was organized by Prof Dr Inés Noher de Halac and colleagues. It was attended by a total of 116 clinical, scientific and professional experts from around the world. There were 60 talks and 41 posters. Following the meeting there was an additional day spent at the National University Cordoba with further academic presentations on the NCLs and a special workshop.



In addition to these scientific and clinical activities, the parallel Family Conference was hosted by the UK Batten Disease Family Association and the USA Batten Disease and Support Research Association. This was attended by 14 families and representatives from 4 organisations, and gave families from Argentina in particular their first chance to meet together. Some sessions were separate, but others were held jointly with the scientific conference. These included an interactive 'Market Place' event that shared the wide expertise of all of those present and a 'Round Table' to discuss research gaps and how these could be filled. This integration of science, clinical, professional and lay perspectives extended this progressive format initiated at the last international meeting, and will continue in future scientific congresses in this field.

This special issue allowed us to request a series of reviews from attending experts. The aim of these

reviews is to provide a broad range of articles that summarise the current status of some aspects of the NCL field. They are not meant to be comprehensive, but it is hoped that they will be useful to those new to this disease as well as those long familiar with the NCLs. Shared co-authorship across different institutions for some of these reflects the excellent cooperative international expertise that exists in research into this rare disease.

We can read about the translational research experience in Argentina over more than a decade, covering hundreds of patients (Kohan et al). Cismondi leads an international authorship and presents guidelines for incorporating scientific knowledge and practice on rare diseases such as the NCLs into higher education and continuous learning programmes that were suggested at the post-Congress workshop, with a special perspective within Latin America.

Rare diseases are those with a particularly low prevalence; in Europe, diseases are considered to be rare when they affect not more than 5 in 10 000 persons in the European Union, and fewer than 200 000 persons in the USA. Rodwell and Aymé present a perspective on policies for rare diseases to improve patient care in Europe, taking into account the significant public health challenges such as the limited number of patients and scarcity of knowledge and expertise. Over the last 16 years, a political framework at the European level has provided legislation that is progressively improving care for families with rare diseases. Kohlschütter et al. draws on discussion in a workshop at NCL2014 to provide an ethical perspective on providing artificial nutrition in children with degenerative diseases, including a checklist that summarizes important considerations.

The current genetic basis of the NCLs is summarized by Mole and Cotman, with at least 10 clear NCL genetic forms and a few further atypical and rarer subtypes that span some very diverse disease phenotypes. Links to the web-based NCL Mutation Databases are provided. Cárcel-Trullols presents a complementary perspective on the current understanding of the cell biology of the NCLs. There remain significant gaps in knowledge that hamper therapeutic development. The pathomorphology of the NCLs is summarised by Radke et al. All share loss of nerve cells, particularly in the cerebral and cerebellar cortices, and the formation of lipopigments that have distinct ultrastructural patterns. Little is known about extracerebral pathology, and a full description of neuropathology is awaited for the more recently recognised forms of NCL, dependent on autopsy. Pathology can still be important in establishing a diagnosis of NCL.

A review of model systems used to understand the NCLs and to reach new therapies is provided by Faller et al. The focus is on the advantages of each individual model, describing some of the contributions that different models have made to our understanding of the broader disease biology and highlighting new techniques and approaches relevant to the study and potential treatment of the NCLs. The models used may be generated by genetic engineering or arise naturally, and include simple unicellular organisms, small vertebrates such as zebrafish and mice, and large animals such as sheep and dogs. Technological advances now allow new models that provide additional benefits in the future, such as pigs that share some common physiology.

Studies using such models extend understanding of NCL pathogenesis (Cooper et al), for example, evidence for the pathway-dependent pathology and involvement of more brain regions, glial dysfunction, and pathology beyond the brain. Palmer et al provide a specific summary of studies using the sheep model, and a separate perspective on subunit c of mitochondrial ATP synthase, the main protein storage material in many of the NCLs

An up to date summary of experimental therapies and approaches used in the development of effective treatments for the different NCLs, including small molecule, enzyme replacement and gene therapies, stem cells, and current clinical trials is provided by Neverman et al. This area is expanding

each year, and the families have a keen interest in any progress.

Finally, Stehr and van der Putten, who work for one of the several non-profit organisations initiated by parents around the world that fill essential gaps in support and funding, provide a perspective on bridging research gaps, summarizing discussion by diverse stakeholders around eight themes at the round table on this topic.

This special issue closes with a short future perspectives. There remain many unanswered questions around the NCLs. Not least is whether these are a true grouping of diseases. Progress in the NCL field will continue to be reported at biennial international meetings, with the next being the 15th International Conference on NCL and Patient Organisation Meeting planned for Boston, USA, in October 2016.

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