Biochimica et Biophysica Acta 1852 (2015) 2256–2261

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Towards a new understanding of NCL pathogenesis☆

Jonathan D. Cooper *, Marta A. Tarczyluk, Hemanth R. Nelvagal

Pediatric Storage Disorders Laboratory (PSDL), Department of Basic and Clinical Neuroscience, King's College London, Institute of Psychiatry, Psychology & Neuroscience, James Black Centre, 125 Coldharbour Lane, London SE5 9NU, UK

ARTICLE INFO

Article history:
Received 20 April 2015
Received in revised form 20 May 2015
Accepted 21 May 2015
Available online 28 May 2015

Keywords:
Neuronal ceroid lipofuscinosis
Storage material accumulation
Selective neuron loss
Glial dysfunction
Pathogenesis

ABSTRACT

The Neuronal Ceroid Lipofuscinoses (NCLs, Batten disease) are a group of inherited neurodegenerative disorders that have been traditionally grouped together on the basis of certain shared clinical and pathological features. However, as the number of genes that appear to cause new forms of NCL continues to grow, it is timely to reassess our understanding of the pathogenesis of these disorders and what groups them together. The various NCL subtypes do indeed share features of a build-up of autofluorescent storage material, progressive neuron loss and activation of the innate immune system. The characterisation of animal models has highlighted the selective nature of neuron loss and its intimate relationship with glial activation, rather than the generalised build-up of storage material. More recent data provide evidence for the pathway-dependent nature of pathology, the contribution of glial dysfunction, and the involvement of new brain regions previously thought to be unaffected, and it is becoming apparent that pathology extends beyond the brain. These data have important implications, not just for therapy, but also for our understanding of these disorders. However, looking beneath these broadly similar pathological themes evidence emerges for marked differences in the nature and extent of these events in different forms of NCL. Indeed, given the widely different nature of the mutated gene products it is perhaps more surprising that these disorders resemble each other as much as they do. Such data raise the question whether we should rethink the collective grouping of these gene deficiencies together, or whether it would be better to consider them as separate entities. This article is part of a Special Issue entitled: Current Research on the Neuronal Ceroid Lipofuscinoses (Batten Disease).

1. Introduction

As detailed elsewhere in this special issue [62], considerable progress has been made in identifying the genes that are mutated in the series of inherited neurodegenerative disorders collectively called the Neuronal Ceroid Lipofuscinoses (NCLs, or Batten Disease). This grouping together is largely on the apparent similarities in their clinical presentation [81] and brain pathology [1,77,98], despite their widely disparate ages of onset and rates of disease progression. Perhaps the characteristic defining pathological feature of these disorders is the intralysosomal accumulation of a complex mixture of proteins, lipids and metals, which have characteristic autofluorescent properties [70,71]. Previously, the ultrastuctural appearance of this stored material was used diagnostically, in combination with the clinical presentation. However, more recently the availability of enzymatic assays and the identification of many new disease-causing mutations have enabled more rapid and reliable diagnoses of the different disease subtypes [106]. Indeed, in recent years, the availability and affordability of modern genomic methodology have seen the identification of a plethora of new disease forms [2,8,66,85,87,88,92], which display a similar clinical presentation and autofluorescent storage material accumulation. The hypothesised number of disease subtypes has expanded rapidly and currently stands at fourteen different forms of NCL [62,85].

Recently, a new classification of these disorders has emerged, which combines the mutated gene and age of onset [105]. Nevertheless, despite knowing the genetic basis of these disorders [62,102], progress towards understanding how these mutations exert their devastating effects has been frustratingly slow. With relatively little known about the normal function of most of the gene products [12,45], it has been difficult to determine how this may be disrupted in each disease subtype, and many fundamental questions remain unanswered. For example, which of the many phenotypes that have been reported represent primary consequences of mutation, and which are more secondary or further downstream parts of a disease cascade that progressively becomes ever more wide reaching? These are key issues that have direct relevance for devising therapeutic strategies.

The existence of an uptake mechanism for soluble enzyme deficient forms of NCL [53,89,99], means that a detailed knowledge of the normal function of these gene products and the consequences of their disruption may be less crucial for moving towards an effective therapy [107]. While this information would still be valuable to have, as reviewed elsewhere in this special issue [65], therapeutic efforts can instead concentrate on the considerable technical challenges of how to deliver these

☆ This article is part of a Special Issue entitled: Current Research on the Neuronal Ceroid Lipofuscinoses (Batten Disease).

* Corresponding author.
E-mail address: jon.cooper@kcl.ac.uk (J.D. Cooper).

http://dx.doi.org/10.1016/j.bbadis.2015.05.014
0925-4439/

missing proteins, whether by direct enzyme replacement [e.g. [13,37,54,58,59,101], gene therapy [31,32,56,74,90,91], or via neural stem cell transplantation [93]].

In contrast, distinguishing which are the key events that happen following gene mutation is of critical importance in the transmembrane protein deficient forms of NCL. With a lack of mechanism-based therapies, we run the risk of cataloguing a series of different events, and then try to block them and determine if this affords any benefit [e.g. 47,48,83]. Instead a more basic understanding of which of the different cell types within the NCL brain are affected, and how their interactions are compromised is needed. This should not, however, be limited to the interactions between neurons, or how the timing of disease pathology may track along different pathways. Rather, it should also encompass those functionally crucial interactions between neurons and different classes of glia, between these glial cell types, and the potential influence of the adaptive immune system.

Much information has emerged from, and continues to be uncovered in, a series of different disease models [6,23], which range from simple cellular organisms, to small vertebrate, mouse and large animal models of NCL. Perhaps more overlooked is the invaluable resource of human autopsy specimens and what they can reveal [1,77,98], bearing in mind their scarcity and that they can only inform about disease end-stage.

This review article will look at some of the main pathological features that have been reported across the different forms of NCL, and consider how these have informed our understanding of these disorders.

2. Obtaining a new perspective of NCL pathogenesis via animal models

In addition to aiding diagnosis, one of the major benefits of identifying disease causing genes has been the subsequent ability to generate animal models in which these genes have been mutated or to identify spontaneous mutants that carry similar gene defects [e.g. 20,21,29,35,44,46,60,79,86]. Each of these species has its benefits and drawbacks as disease models, but the most widely utilised models are genetically engineered mutant mice [84], with models now existing for the vast majority of disease sub-forms [23]. Particularly relevant for addressing the issues of how to deliver therapies, several different larger animal models of disease have also been identified [22], the most commonly used being dogs and sheep [e.g. 3,4,10,27,38,57,72,94]. As technology advances, it is now possible to generate models in species such as pigs [24,25], which are likely to prove especially valuable because of the perceived closeness of porcine and human physiology.

A significant advance was crossing the different mouse models of NCL onto a common strain background, which made it possible to make comparisons between these models and address key issues about the relative staging of disease progression [15,17,71,84]. Ultimately the disease end point is a brain that is atrophied, and contains many fewer neurons, all of which contain large amounts of storage material [77,98]. This is invariably accompanied by profound astrocytosis and microglial activation, and there may also be a relatively low level infiltration of lymphocytes into the NCL brain [33,52]. While these general pathological themes hold true across most, if not all forms of NCL, their relative severity and timing (or even whether they occur at all) can differ markedly between mouse models.

While the mouse models of earlier onset forms of NCL generally display more pronounced phenotypes, there are certain anomalies such as the relative severity of Tpp1/Cln2 deficient mice compared to Ppt1/Cln1 deficient mice [35,86]. These may be due to technical issues encountered in generating this mouse model of Cln2 disease, but may also reflect an as yet unidentified species-specific consequence of Tpp1 deficiency in mice. It is also apparent that the extent of brain pathology is much less pronounced in mouse models, than in a larger animal model of the same form of NCL, or in the human condition itself [e.g. 63,68,69,98]. This may be due to the fact that mice do not live long enough to develop the full range of human pathology. However, in general, it seems to be that the larger and more complicated a brain is, the more severely affected it will be by this disease.

3. New lessons from mouse models of NCL

Despite such apparent limitations, much valuable information has been gained from mouse models of NCL [reviewed in 6,23,84], not just about pathogenesis [17,61,71], but also in testing experimental therapies [reviewed in 65]. Indeed, analysing these mice has given us a series of novel perspectives about the relationship between the events that occur during disease progression. These include the extent to which specific brain regions, pathways and cell types are affected, and how this may vary between forms of NCL. This is not necessarily surprising given the widely different nature, and probable intracellular location, of the gene products that are deficient in these disorders [12,45]. Indeed, perhaps more surprising is that these disorders resemble each other as much as they do. Another key concept to emerge from studying these mouse models is that several long-standing theories about the pathogenesis of the NCLs may not hold true upon closer examination [15].

4. Selective neuron loss in the NCL brain

Perhaps the first of these novel insights was the discovery that although the brain is indeed severely impacted by the time of death, albeit to different extents in disease subtypes, as reviewed in this article, the nature of neuron loss is actually rather selective in the earlier stages of disease. The initial observations of such selective vulnerability focused upon populations of hippocampal and cortical interneurons [e.g. 5,16,63,69,75,76], but were subsequently extended to the cerebellum [55,104], and thalamocortical system (see below), and it is likely that other examples will be found. However, just taking the first example, comparing interneuron loss across mouse models reveals a bewildering array of specific effects upon interneurons that express different calcium binding proteins or neuropeptides, or those that are located in different hippocampal subfields or cortical regions [5,49,63,69,75,76,103]. Despite any mechanistic evidence for why these subpopulations of neurons are specifically affected, such marked differences highlight that while a pathological feature may be broadly shared across NCL subtypes, it is too simplistic to assume that these events occur in the same fashion.

Another surprising observation made in mouse models was the pathological targeting of the thalamus relatively early in disease progression. This phenotype so far holds true across nearly all forms of NCL [e.g. 39,49,63,73,76], with the loss of thalamic relay neurons preceding neurodegeneration in the corresponding region of the cortex to which it projects. Certainly, within any given mouse model the death of neurons that relay different modalities of information to the cortex does not occur at the same time, but is staged at different points of disease progression [e.g. 39]. Nevertheless, the relative timing of these events within the thalamocortical system also varies between forms of NCL [reviewed in 71], and while these may at first glance appear to be relatively minor variations, they reveal further evidence for different consequences of mutations in these genes at a cellular level. A starker example of the contrasting effects of gene mutations comes from *Cln5* deficient mice in which the sequence of neuron loss is reversed [100], and apparently occurs in the cortex before the thalamus, a feature that is so far unique amongst mouse models.

5. Pathway dependent pathology and synaptopathy

The progressive staging of pathological events in the thalamocortical system highlighted the possible importance of connectivity in determining the order in which neuron populations are lost in the NCL brain. The concept of neurodegeneration spreading along pathways in either an anterograde or retrograde direction is not a new one, but has

gained certain tractability in other disorders [7,26,78,109]. Various theories can be proposed about how such pathway-specific events may occur, and these may range from the involvement of target-derived trophic support to the transport of prion like particles. While there is currently no substantive evidence for any of these possibilities in the NCLs, an emerging theme is the vulnerability of synaptic terminals in many different neurodegenerative disorders [30]. The NCLs are no exception, with synapse rearrangement appearing to predate synaptic loss, which in turn occurs before neuron loss. The evidence for these events is best established in Cathepsin D deficient mice, representing the earliest onset congenital form of NCL, in which ultrastructural evidence for altered vesicle density and docking, plus accompanying electrophysiological effects have been reported [43,73]. Although such phenotypes have not been systematically characterised across all forms of NCL, it is apparent that synaptic pathology occurs in multiple forms of NCL [e.g. 40,42], but that its precise nature may (like many other phenotypes) differ between disease subtypes.

6. New sites of brain pathology

The discovery of staged pathology along the interconnected pathways of the thalamocortical system raised the obvious question of whether the brainstem nuclei that project to the thalamus would be affected at an earlier stage of disease progression, or indeed at an even earlier stage within the spinal cord. Preliminary data does not seem to support this hypothesis, but it is now becoming evident that relatively severe pathology may exist in brain regions not expected to be affected in the NCLs [64]. It seems likely that the extent and timing of this pathology may differ between forms of NCL, and it will be important to systematically characterise these events in those brain regions that are newly revealed as being pathologically targeted in these disorders. Although the functional consequences of such pathology are unclear, or whether these effects extend into the peripheral nervous system, there are obvious implications for the delivery of therapies. Indeed, failing to target this pathology may be a serious oversight.

7. What is the influence of storage material accumulation?

The earliest attempts to explain the cause of neuron loss in the NCLs focussed upon storage material accumulation as the most obvious pathological hallmark of these disorders. Indeed, perhaps because it is so simple to detect by shining UV or fluorescent light upon unstained tissue sections, much importance was placed upon storage material accumulation, with the suggestion that this material may itself be toxic. However, more recent evidence reveals no direct relationship between where and when storage material accumulation occurs and the distribution of neuron loss [reviewed in 15,17,71]. Indeed, with the few surviving neurons at disease end stage being hugely distended with autofluorescent storage material [98], a counterargument could be provocatively made that the presence of storage material is actually neuroprotective. Such a conclusion is almost certainly wrong, but rhetorically highlights the dangers of making inferences from a set of phenotypes in the absence of a mechanistic explanation.

Nevertheless, the level of storage burden continues to be used as a valuable readout of therapeutic efficacy [19], and approaches that directly aim to deplete the levels of storage material continue to be assessed, especially in CLN1 disease. Building upon previous reports of phosphocysteamine reducing storage burden in fibroblasts from CLN1 disease patients [110], a pilot study has reported beneficial effects of combined oral cysteamine bitartrate and N-acetylcysteine in this disease including the delay of isoelectric EEG, depletion of storage in lymphocytes, but did not prevent the progression of brain atrophy [51]. The same group have more recently proposed the use of a hydroxylamine derivative, N-(tert-Butyl) hydroxylamine (NtBuHA) to mediate lysosomal ceroid depletion [80]. This compound not only reduces the levels of lysosomal storage in patient derived fibroblasts, but also has similar effects in Ppt1 deficient mice apparently slowing neurological deterioration and moderately extending life span [80]. It remains to be seen whether such compounds will by themselves be able to afford therapeutic benefit, but they may act together with other approaches such as gene therapy [111] to provide synergistic effects.

8. Glial involvement in NCL pathogenesis

One of the biggest shifts in thinking regarding the NCLs is that they are very likely not simply diseases of neurons. Certainly the health of neurons is severely compromised in these disorders, but it is becoming apparent that the biology of other cell types within the brain and in the rest of the body is also disrupted. The first hints at a non-neuronal involvement in NCL pathogenesis arose when considering the spatial and temporal relationship between glial activation and neuron loss. Characteristically described in sheep [68], but substantiated in multiple mouse models of NCL [39,49,63,73,75,76,82,96,100], it became apparent that the distribution of glial activation accurately predicted the subsequent distribution of neuron loss in these disorders. While variable in nature and extent, the concept that glial activation of one form or another always precedes neuron loss is now widely accepted. Indeed, presented with a new mouse model, it is now routine practice to survey glial activation as a tool to reveal where neurodegenerative changes will occur.

Nevertheless, this broad similarity masks some markedly different types of glial response. Although astrocytosis and microglial activation both occur long before significant neuron loss can be detected in Cln3 deficient mice [75,76], the activation of these cell types is apparently attenuated with a failure to fully transform morphologically. Such observations have lead to the suggestion that glia may themselves be dysfunctional in Cln3 disease [18]. Compelling in vitro evidence exists and continues to emerge for Cln3 deficient microglia and astrocytes displaying a range of altered properties and responses to stimulation [11,18,108]. These phenotypes have obvious implications for neuronal health, and it will be important to determine how such negative effects may be mediated. Despite such evidence, it seems improbable that Cln3 disease is solely down to glial dysfunction, with the consequences of Cln3 mutation also likely to impact neurons in a variety of ways. The most likely scenario is that dysfunction of both glial and neurons contributing to an on-going pathological cascade that worsens with disease progression. The advent of cell-type specific *Cln3* mice would be especially informative in addressing these issues.

It will also be important to investigate whether such effects extend to other forms of NCL. Certainly, the NCL genes are largely expressed in both neurons and glia, and the potential exists for glia to be important players in the events following their mutation and subsequent deficiency. Emerging preliminary data from astrocyte and microglial monocultures suggests that this may be the case in both Cln1 and Cln2 diseases [18,50], but that the nature of these glial defects varies between forms of NCL. Indeed, it appears that the timing of glial activation may be atypical in some forms of NCL [9], despite cumulating in pronounced glial activation towards disease end stage. Such novel information about NCL pathogenesis is also informing therapeutic efforts [41,95], something that is especially important in Cln3 disease. If glia contribute negatively to disease progression, then different strategies to block specific pathways, or even generalised anti-inflammatory approaches may prove to be beneficial, and the results of such studies are eagerly anticipated.

It is not just cells of the innate immune system that can be detected in NCL brains. The neuroimmune response in Cln3 disease does not appear to be confined to cells of the innate immune system [14,52], and the beneficial effects of immunosuppression with mycophenolate mofetil prove this to be the case [83]. Lymphocyte infiltration into the CNS may be relatively late in Cln3 disease [52], but appears to happen much earlier in Cln1 disease progression [33]. Although this remains at a relatively low-level, genetic blockade of these events leads to a

slowing of disease progression and promising beneficial effects upon lifespan and visual function [33,34]. Although blocking either innate or adaptive immune responses either genetically or pharmaceutically does not directly address the underlying gene defect, such approaches may be of value in combination with other therapeutic strategies and offer some hope in the transmembrane protein deficient forms of NCL where a mechanistic-based therapy remains a distant prospect.

9. Moving outside the CNS

Recent evidence suggests that the accepted name of these disorders as 'neuronal' may be a misnomer, since it is emerging that the effects of disease are certainly not confined to neurons, or even within the brain. As therapeutic strategies prove able to prolong lifespan, it is probable that other disease related phenotypes might appear elsewhere within the body. Such phenotypes are likely to be masked by the profound impact of disease upon the brain, but may be revealed if these events can be slowed down. In this respect targeting the body as well as the brain is likely to afford further beneficial effects. Certainly it is apparent that the heart is also affected in some forms of NCL, with the most robust data available for Cln3 disease [36,67,97], and emerging evidence for other forms of NCL [28]. Whether these phenotypes are intrinsic to the heart or are related to events within the brain must be addressed, as well as defining the contribution of the peripheral and autonomic nervous system.

10. Concluding comments

The main goal of researchers studying the NCLs is to devise effective therapies that can alleviate the burden of these fatal disorders. As reviewed elsewhere in this special issue, advances have recently been made towards achieving this goal for some NCL subtypes [65]. Nevertheless, the final form these therapies may take, and how they will be delivered, remains unclear. However, gaining a better understanding of which brain regions are affected, the sequence in which this occurs and how each of the different cell types contributes to these events will be crucial. This information about disease pathogenesis can certainly guide the delivery of therapies to where they can be maximally effective, but it can perhaps have a more central role to play in those forms of NCL where the precise therapeutic target, or what form the therapeutic agent will take, is still uncertain. It is very likely that combination therapies that target different parts of the disease cascade, different regions of the brain, or organs of the body, will be required.

From a pathological perspective, the net result of the many studies in animal models is a range of broadly similar phenotypes across the different forms of NCL. These involve the progressive loss of different neuron populations, and its spatial and temporal relationship to glial activation and storage material accumulation. At a relatively superficial level this series of similar events may be taken as evidence to reinforce the notion of the NCLs as a defined family of disorders. However, a more systematic and in depth consideration of these data reveals more fundamental differences in the nature, extent and timing of these events [reviewed in this article and [15]]. As such, while broadly similar pathological themes have emerged, a case can also be made that markedly different features have also been highlighted. Indeed, it cannot be assumed that the existence of apparently common pathological endpoints is the result of anything like a similar disease mechanism in each subtype.

This already muddled situation has been further complicated by the recent addition of multiple disorders that are now labelled as novel forms of NCL [85]. However, it is not always apparent that the pathological evidence is sufficiently strong to warrant the assignment of a new CLN gene name. The end result is large grouping of disorders that may not share as many similarities as was first apparent. The criteria for defining these 'new forms of NCL' need careful deliberation, as the presence of autofluorescent storage material, with an ultrastructural appearance resembling that seen in NCLs, plus a clinical presentation that involves seizures and/or visual impairment cannot necessarily be taken as conclusive proof of a new disease subtype.

Indeed, it may be time to reconsider the traditional grouping of the NCLs altogether, and whether this has hampered our progress towards understanding these mechanisms properly. Perhaps we have been fooled into thinking of the NCLs as a group of disorders, when it may be more productive to focus more upon characterising what is the mechanistic basis of each individual gene defect.

Acknowledgements

The many studies from the PSDL cited in this review were funded from a wide variety of sources including: The US National Institutes of Health, Wellcome Trust, UK Medical Research Council, European Union FP6 and FP7, Sparks, Batten Disease Support and Research Association, Batten Disease Family Association, Beyond Batten Disease Foundation, NCL Stiftung, The Saoirse Foundation and Health Research Board of Ireland, The Natalie Fund, and The Bletsoe Family. The support of these organisations and individuals is greatly appreciated, as is the outstanding efforts of all members of the laboratory over the years.

References

[1] G.W. Anderson, H.H. Goebel, A. Simonati, Human pathology in NCL, Biochim. Biophys. Acta 1832 (2013) 1807–1826.
[2] T. Arsov, K.R. Smith, J. Damiano, S. Franceschetti, L. Canafoglia, C.J. Bromhead, E. Andermann, D.F. Vears, P. Cossette, S. Rajagopalan, A. McDougall, V. Sofia, M. Farrell, U. Aguglia, A. Zini, S. Meletti, M. Morbin, S. Mullen, F. Andermann, S.E. Mole, M. Bahlo, S.F. Berkovic, Kufs disease, the major adult form of neuronal ceroid lipofuscinosis, caused by mutations in CLN6, Am. J. Hum. Genet. 88 (2011) 566–573.
[3] T. Awano, M.L. Katz, D.P. O'Brien, J.F. Taylor, J. Evans, S. Khan, I. Sohar, P. Lobel, G.S. Johnson, A mutation in the cathepsin D gene (CTSD) in American Bulldogs with neuronal ceroid lipofuscinosis, Mol. Genet. Metab. 87 (2006) 341–348.
[4] T. Awano, M.L. Katz, D.P. O'Brien, I. Sohar, P. Lobel, J.R. Coates, S. Khan, G.C. Johnson, U. Giger, G.S. Johnson, A frame shift mutation in canine TPP1 (the ortholog of human CLN2) in a juvenile Dachshund with neuronal ceroid lipofuscinosis, Mol. Genet. Metab. 89 (2006) 254–260.
[5] E. Bible, P. Gupta, S.L. Hofmann, J.D. Cooper, Regional and cellular neuropathology in the palmitoyl protein thioesterase-1 (PPT1) null mutant mouse model of infantile neuronal ceroid lipofuscinosis, Neurobiol. Dis. 16 (2004) 346–359.
[6] M. Bond, S.M. Holthaus, I. Tammen, G. Tear, C. Russell, Use of model organisms for the study of neuronal ceroid lipofuscinosis, Biochim. Biophys. Acta 1832 (2013) 1842–1865.
[7] H. Braak, K. Del Tredici, Alzheimer's pathogenesis: is there neuron-to-neuron propagation? Acta Neuropathol. 121 (2011) 589–595.
[8] J. Bras, A. Verloes, S.A. Schneider, S.E. Mole, R.J. Guerreiro, Mutation of the parkinsonism gene ATP13A2 causes neuronal ceroid-lipofuscinosis, Hum. Mol. Genet. 21 (2012) 2646–2650.
[9] H. Brooks, L. Van Trigt, H.R. Nelvagal, M. Micsenyi, S.U. Walkley, J.D. Cooper, Defining the onset and progression of neuropathological changes in mouse models of LINCL. NCL2014 poster presentation P10, Medicina 74 (Suppl. II) (2014) 26.
[10] M.F. Broom, C. Zhou, J.E. Broom, K.J. Barwell, R.D. Jolly, D.F. Hill, Ovine neuronal ceroid lipofuscinosis: a large animal model syntenic with the human neuronal ceroid lipofuscinosis variant CLN6, J. Med. Genet. 35 (1998) 717–721.
[11] M. Burkovetskaya, N. Karpuk, J. Xiong, M. Bosch, M.D. Boska, H. Takeuchi, A. Suzumura, T. Kielian, Evidence for aberrant astrocyte hemichannel activity in Juvenile Neuronal Ceroid Lipofuscinosis (JNCL), PLoS One 9 (2014) e95023, http://dx.doi.org/10.1371/journal.pone.0095023. eCollection 2014.
[12] J. Cárcel-Trullols, A.D. Kovács, D.A. Pearce, Cell biology of the NCL proteins: what they do and don't do, Biochim. Biophys. Acta 1852 (2015) 2242–2255.
[13] M. Chang, J.D. Cooper, D.E. Sleat, S.H. Cheng, J.C. Dodge, M.A. Passini, P. Lobel, B.L. Davidson, Intraventricular enzyme replacement improves disease phenotypes in a mouse model of late Infantile Neuronal Ceroid Lipofuscinosis, Mol. Ther. 16 (2008) 649–656.
[14] S. Chattopadhyay, M. Ito, J.D. Cooper, A.I. Brooks, T.M. Curran, J.M. Powers, D.A. Pearce, An autoantibody inhibitory to glutamic acid decarboxylase in the neurodegenerative disorder Batten Disease, Hum. Mol. Genet. 11 (2002) 1421–1431.
[15] J.D. Cooper, The neuronal ceroid lipofuscinoses: the same, but different? Biochem. Soc. Trans. 38 (2010) 1448–1452.
[16] J.D. Cooper, A. Messer, A.K. Feng, J. Chua-Couzens, W.C. Mobley, Apparent loss and hypertrophy of interneurons in a mouse model of neuronal ceroid lipofuscinosis: evidence for partial response to insulin-like growth factor-1 treatment, J. Neurosci. 19 (1999) 2556–2567.
[17] J.D. Cooper, C.R. Russell, H.M. Mitchison, Progress towards understanding disease mechanisms in small vertebrate models of neuronal ceroid lipofuscinosis, Biochim. Biophys. Acta 1762 (2006) 873–889.

[18] J.D. Cooper, L. Parviainen, S. Dihanich, J. Lange, G. Anderson, L. Van Trigt, B.P. Williams, Assessing the contribution of glial dysfunction to NCL pathogenesis. NCL2014 oral presentation P12, Medicina 74 (Suppl. II) (2014) 15.

[19] J.D. Cooper, H.R. Brooks, H.R. Nelvagal, Quantifying storage material accumulation in tissue sections, Methods Cell Biol. 126 (2015) 349–356, http://dx.doi.org/10.1016/bs.mcb.2014.11.010 (Epub 2015 Jan 19).

[20] S.L. Cotman, V. Vrbanac, L.A. Lebel, R.L. Lee, K.A. Johnson, L.R. Donahue, A.M. Teed, K. Antonellis, R.T. Bronson, T.J. Lerner, M.E. MacDonald, Cln3(Deltaex7/8) knock-in mice with the common JNCL mutation exhibit progressive neurologic disease that begins before birth, Hum. Mol. Genet. 11 (2002) 2709–2721.

[21] M. Damme, L. Brandenstein, S. Fehr, W. Jankowiak, U. Bartsch, M. Schweizer, I. Hermans-Borgmeyer, S. Storch, Gene disruption of Mfsd8 in mice provides the first animal model for CLN7 disease, Neurobiol. Dis. 65 (2014) 12–24.

[22] C. Drögemüller, G.S. Johnson, M.L. Katz, F. Lingaas, D.N. Palmer, I. Tammen, Large Animal Models. Chapter 18 in the Neuronal Ceroid Lipofuscinoses (Batten Disease), in: S.E. Mole, R.E. Williams, H.H. Goebel (Eds.), Oxford University Press, 2011.

[23] K.M. Faller, R. Gutierrez-Quintana, A. Mohammed, A.A. Rahim, R.I. Tuxworth, K. Wager, M. Bond, The neuronal ceroid lipofuscinoses: Opportunities from model systems, Biochim Biophys. Acta (2015 Apr 29) pii: S0925-4439(15)00128-3. http://dx.doi.org/10.1016/j.bbadis.2015.04.022. [Epub ahead of print] Review. PMID: 25937302.

[24] N. Fan, L. Lai, Genetically modified pig models for human diseases, J. Genet. Genomics 40 (2013) 67–73.

[25] T. Flisikowska, A. Kind, A. Schnieke, Genetically modified pigs to model human diseases, J. Appl. Genet. 55 (2014) 53–64.

[26] A. Fornito, A. Zalesky, M. Breakspear, The connectomics of brain disorders, Nat. Rev. Neurosci. 16 (2015) 159–172.

[27] T. Frugier, N.L. Mitchell, I. Tammen, P.J. Houweling, D.G. Arthur, G.W. Kay, O.P. van Diggelen, R.D. Jolly, D.N. Palmer, A new large animal model of CLN5 neuronal ceroid lipofuscinosis in Borderdale sheep is caused by a nucleotide substitution at a consensus splice site (c.571+1G>A) leading to excision of exon 3, Neurobiol. Dis. 29 (2008) 306–315.

[28] S. Fukumura, Y. Saito, T. Saito, H. Komaki, E. Nakagawa, K. Sugai, M. Sasaki, A. Oka, I. Takamisawa, Progressive conduction defects and cardiac death in late infantile neuronal ceroid lipofuscinosis, Dev. Med. Child Neurol. 54 (2012) 663–666.

[29] H. Gao, R.M. Boustany, J.A. Espinola, S.L. Cotman, L. Srinidhi, K.A. Antonellis, T. Gillis, X. Qin, S. Liu, L.R. Donahue, R.T. Bronson, J.R. Faust, D. Stout, J.L. Haines, T.J. Lerner, M.E. MacDonald, Mutations in a novel CLN6-encoded transmembrane protein cause variant neuronal ceroid lipofuscinosis in man and mouse, Am. J. Hum. Genet. 70 (2006) 324–335.

[30] T.H. Gillingwater, T.M. Wishart, Mechanisms underlying synaptic vulnerability and degeneration in neurodegenerative disease, Neuropathol. Appl. Neurobiol. 39 (2013) 320–334.

[31] M. Griffey, E. Bible, C. Vogler, B. Levy, P. Gupta, J.D. Cooper, M.S. Sands, Adeno-associated virus 2-mediated gene therapy decreases autofluorescent storage material and increases brain mass in a murine model of Infantile Neuronal Ceroid Lipofuscinosis (INCL), Neurobiol. Dis. 16 (2004) 360–369.

[32] M.A. Griffey, D. Wozniak, M. Wong, E. Bible, K. Johnson, M.R. Rothman, A.E. Wentz, J.D. Cooper, M.S. Sands, CNS-directed AAV2-mediated gene therapy ameliorates functional deficits in a murine model of infantile neuronal ceroid lipofuscinosis, Mol. Ther. 13 (2006) 538–547.

[33] J. Groh, T.G. Kühl, S. Duckett, C.W. Ip, M. Mirza, T. Langmann, H.R. Nelvagal, S. Sri, J.D. Cooper, R. Martini, Immune cells mediate neuronal damage in a mouse model of Infantile Neuronal Ceroid Lipofuscinosis, Brain 136 (2013) 1083–1101.

[34] J. Groh, D. Stadler, P. Crocker, R. Martini, Sialoadhesin-positive microglia/macrophages promote neuroinflammation and axonal perturbation in the retinotectal system of two mouse models of neuronal ceroid lipofuscinosis. NCL2014 oral presentation P15, Medicina 74 (Suppl. II) (2014) 15.

[35] P. Gupta, A.A. Soyombo, A. Atashband, K.E. Wisniewski, J.M. Shelton, J.A. Richardson, R.E. Hammer, S.L. Hofmann, Disruption of PPT1 or PPT2 causes neuronal ceroid lipofuscinosis in knockout mice, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 13566–13571.

[36] I.L. Hofman, A.C. van der Wal, K.P. Dingemans, A.E. Becker, Cardiac pathology in neuronal ceroid lipofuscinoses—a clinicopathologic correlation in three patients, Eur. J. Paediatr. Neurol. 5 (Suppl. A) (2001) 213–217.

[37] J. Hu, J.-Y. Lu, A.M.S. Wong, L.S. Hynan, S.G. Birnbaum, D.S. Yilmaz, B.M. Streit, E.M. Lenartowicz, T.C.M. Thompson, J.D. Cooper, S.L. Hofmann, Intravenous high-dose enzyme replacement therapy with recombinant palmitoyl-protein thioesterase reduces visceral lysosomal storage and modestly prolongs survival in a preclinical mouse model of infantile neuronal ceroid lipofuscinosis, Mol. Genet. Metab. 107 (2012) 213–221.

[38] M.L. Katz, S. Khan, T. Awano, S.A. Shahid, A.N. Siakotos, G.S. Johnson, A mutation in the CLN8 gene in English Setter dogs with neuronal ceroid-lipofuscinosis, Biochem. Biophys. Res. Commun. 327 (2005) 541–547.

[39] C. Kielar, L. Maddox, E. Bible, C.C. Pontikis, S.L. Macauley, M.A. Griffey, M. Wong, M.S. Sands, J.D. Cooper, Successive neuron loss in the thalamus and cortex in a mouse model of infantile neuronal ceroid lipofuscinosis, Neurobiol. Dis. 25 (2007) 150–162.

[40] C. Kielar, T.M. Wishart, A. Palmer, S. Dihanich, A.M. Wong, S.L. Macauley, C.H. Chan, M.S. Sands, D.A. Pearce, J.D. Cooper, T.H. Gillingwater, Molecular correlates of axonal and synaptic pathology in mouse models of Batten disease, Hum. Mol. Genet. 18 (2009) 4066–4080.

[41] T. Kielian, Therapeutic targeting of neuroinflammatory pathways in juvenile Batten disease. NCL2014 oral presentation P14, Medicina 74 (Suppl. II) (2014) 15.

[42] S.J. Kim, Z. Zhang, C. Sarkar, P.C. Tsai, Y.C. Lee, L. Dye, A.B. Mukherjee, Palmitoyl protein thioesterase-1 deficiency impairs synaptic vesicle recycling at nerve terminals, contributing to neuropathology in humans and mice, J. Clin. Invest. 118 (2008) 3075–3086.

[43] S. Koch, S.M. Molchanova, A.K. Wright, A. Edwards, J.D. Cooper, T. Taira, T.H. Gillingwater, J. Tyynelä, Morphological and functional correlates of synaptic pathology in the cathepsin D knock-out mouse model of congenital neuronal ceroid-lipofuscinosis, J. Neuropathol. Exp. Neurol. 70 (2011) 1089–1096.

[44] M. Koike, H. Nakanishi, P. Saftig, J. Ezaki, K. Isahara, Y. Ohsawa, W. Schulz-Schaeffer, T. Watanabe, S. Waguri, S. Kametaka, M. Shibata, K. Yamamoto, E. Kominami, C. Peters, K. von Figura, Y. Uchiyama, Cathepsin D deficiency induces lysosomal storage with ceroid lipofuscin in mouse CNS neurons, J. Neurosci. 20 (2000) 6898–6906.

[45] K. Kollmann, K. Uusi-Rauva, E. Scifo, J. Tyynelä, A. Jalanko, T. Braulke, Cell biology and function of neuronal ceroid lipofuscinosis-related proteins, Biochim. Biophys. Acta 1832 (2013) 1866–1881.

[46] O. Kopra, J. Vesa, C. von Schantz, T. Manninen, H. Minye, A.L. Fabritius, J. Rapola, O.P. van Diggelen, J. Saarela, A. Jalanko, L. Peltonen, A mouse model for Finnish variant late infantile neuronal ceroid lipofuscinosis, CLN5, reveals neuropathology associated with early aging, Hum. Mol. Genet. 13 (2004) 2893–2906.

[47] A.D. Kovács, A. Saje, A. Wong, G. Szénási, P. Kiricsi, E. Szabó, J.D. Cooper, D.A. Pearce, Temporary inhibition of AMPA receptors induces a prolonged improvement of motor performance in a mouse model of juvenile Batten disease, Neuropharmacology 60 (2011) 405–409.

[48] A.D. Kovács, A. Saje, A.M.S. Wong, S. Ramji, J.D. Cooper, D.A. Pearce, Age-dependent therapeutic effect of memantine in a mouse model of juvenile Batten disease, Neuropharmacology 3 (2012) 769–775.

[49] M. Kuronen, A.-E. Lehesjoki, A. Jalanko, J.D. Cooper, O. Kopra, Selective spatiotemporal patterns of glial activation and neuron loss in the sensory thalamocortical pathways of neuronal ceroid lipofuscinosis 8 mice, Neurobiol. Dis. 47 (2012) 444–457.

[50] J. Lange, J.D. Cooper, B.P. Williams, G. Anderson, Evidence for impaired glial biology in infantile NCL. NCL2014 poster presentation P1, Medicina 74 (Suppl. II) (2014) 24.

[51] S.W. Levin, E.H. Baker, W.M. Zein, Z. Zhang, Z.M. Quezado, N. Miao, A. Gropman, K.J. Griffin, S. Bianconi, G. Chandra, O.I. Khan, R.C. Caruso, A. Liu, A.B. Mukherjee, Oral cysteamine bitartrate and N-acetylcysteine for patients with infantile neuronal ceroid lipofuscinosis: a pilot study, Lancet Neurol. 13 (2014) 777–787.

[52] M.J. Lim, N.A. Alexander, J.W. Benedict, S. Chattopadhyay, S.J.A. Shemilt, C.J. Guérin, J.D. Cooper, D.A. Pearce, IgG entry and deposition are components of the neuroimmune response Batten Disease, Neurobiol. Dis. 25 (2007) 239–251.

[53] J.Y. Lu, J. Hu, S.L. Hofmann, Human recombinant palmitoyl-protein thioesterase-1 (PPT1) for preclinical evaluation of enzyme replacement therapy for infantile neuronal ceroid lipofuscinosis, Mol. Genet. Metab. 99 (2010) 374–378.

[54] J.Y. Lu, H.R. Nelvagal, L. Wang, S.G. Birnbaum, J.D. Cooper, S.L. Hofmann, Intrathecal enzyme replacement therapy improves motor function and survival in a preclinical mouse model of infantile neuronal ceroid lipofuscinosis, Mol. Genet. Metab (2015 May 12) pii: S1096-7192(15)30012-3. http://dx.doi.org/10.1016/j.ymgme.2015.05.005. [Epub ahead of print] PMID: 25982063.

[55] S.L. Macauley, D.F. Wozniak, C. Kielar, Y. Tan, J.D. Cooper, M.S. Sands, Cerebellar pathology and motor deficits in the palmitoyl protein thioesterase 1-deficient mouse, Exp. Neurol. 217 (2009) 124–135.

[56] S.L. Macauley, M.S. Roberts, A.M.S. Wong, F. McSloy, A.S. Reddy, J.D. Cooper, M.S. Sands, Synergistic effects of CNS-directed gene therapy and bone marrow transplantation in the murine model of infantile neuronal ceroid lipofuscinosis, Ann. Neurol. 71 (2012) 797–804.

[57] S.A. Melville, C.L. Wilson, C.S. Chiang, V.P. Studdert, F. Lingaas, A.N. Wilton, A mutation in canine CLN5 causes neuronal ceroid lipofuscinosis in Border collie dogs, Genomics 86 (2005) 287–294.

[58] Y. Meng, I. Sohar, L. Wang, D.E. Sleat, P. Lobel, Systemic administration of tripeptidyl peptidase I in a mouse model of late infantile neuronal ceroid lipofuscinosis: effect of glycan modification, PLoS One 7 (2012) e40509.

[59] Y. Meng, I. Sohar, D.E. Sleat, J.R. Richardson, K.R. Reuhl, R.B. Jenkins, G. Sarkar, P. Lobel, Effective intravenous therapy for neurodegenerative disease with a therapeutic enzyme and a peptide that mediates delivery to the brain, Mol. Ther. 22 (2014) 547–553.

[60] H.M. Mitchison, D.J. Bernard, N.D.E. Greene, J.D. Cooper, M.A. Junaid, R.K. Pullarkat, N. Vos, M.H. Breuning, J.W. Owens, W.C. Mobley, R.M. Gardiner, B.D. Lake, P.E.M. Taschner, R.L. Nussbaum, Targeted disruption of the Cln3 gene provides a mouse model for Batten Disease. The Batten Mouse Model Consortium, Neurobiol. Dis. 6 (1999) 321–334.

[61] H.M. Mitchison, M.J. Lim, J.D. Cooper, Selectivity and types of cell death in the Neuronal Ceroid Lipofuscinoses (NCLs), Brain Pathol. 14 (2004) 86–96.

[62] S.E. Mole, S.L. Cotman, Genetics of the Neuronal Ceroid Lipofuscinoses (Batten disease), Biochim. Biophys. Acta 1852 (2015 May 27) 2237–2241.

[63] J.P. Morgan, H. Magee, A. Wong, T. Nelson, B. Koch, J.D. Cooper, J.M. Weimer, A murine model of variant late infantile ceroid lipofuscinosis recapitulates behavioral and pathological phenotypes of human disease, PLoS One 8 (11) (Nov 1 2013) e78694, http://dx.doi.org/10.1371/journal.pone.0078694.

[64] H.R. Nelvagal, J. Dmytrus, S. Sri, J. Dearborn, M.S. Sands, J.D. Cooper, Defining of the nature and progression of spinal cord and brainstem pathology in *Ppt1*$^{-/-}$ mice. NCL2014 oral presentation P17, Medicina 74 (Suppl. II) (2014) 16.

[65] N.J. Neverman, H.L. Best, S.L. Hofmann, S.M. Hughes, Experimental therapies in the neuronal ceroid lipofuscinoses, Biochim. Biophys. Acta 1852 (2015 May 6) 2292–2300.

[66] L. Nosková, V. Stránecký, H. Hartmannová, A. Přistoupilová, V. Barešová, R. Ivánek, H. Hůlková, H. Jahnová, J. van der Zee, J.F. Staropoli, K.B. Sims, J. Tyynelä, C. Van

Broeckhoven, P.C. Nijssen, S.E. Mole, M. Elleder, M.S. Kmoch, Mutations in DNAJC5, encoding cysteine-string protein alpha, cause autosomal-dominant adult-onset neuronal ceroid lipofuscinosis, Am. J. Hum. Genet. 89 (2011) 241–252.
[67] J.R. Ostergaard, T.B. Rasmussen, H. Mølgaard, Cardiac involvement in juvenile neuronal ceroid lipofuscinosis (Batten disease), Neurology 76 (2011) 1245–1251.
[68] M.J. Oswald, D.N. Palmer, G.W. Kay, S.J.A. Shemilt, P. Rezaie, J.D. Cooper, Glial activation spreads from specific cerebral foci and precedes neurodegeneration in presymptomatic ovine neuronal ceroid lipofuscinosis (CLN6), Neurobiol. Dis. 20 (2005) 49–63.
[69] M.J. Oswald, D.N. Palmer, G.W. Kay, K.J. Barwell, J.D. Cooper, Location and connectivity determine GABAergic interneuron survival in the brains of South Hampshire sheep with CLN6 neuronal ceroid lipofuscinosis, Neurobiol. Dis. 32 (2008) 50–65.
[70] D.N. Palmer, M.J. Oswald, V.J. Westlake, G.W. Kay, The origin of fluorescence in the neuronal ceroid lipofuscinoses (Batten disease) and neuron cultures from affected sheep for studies of neurodegeneration, Arch. Gerontol. Geriatr. 34 (2002) 343–357.
[71] D.N. Palmer, L.A. Barry, J. Tyynelä, J.D. Cooper, NCL disease mechanisms, Biochim. Biophys. Acta 1832 (2013) 1882–1893.
[72] D.N. Palmer, N.J. Neverman, J.Z. Chen, C.-T. Chang, P.J. Houweling, L.A. Barry, I. Tammen, S.M. Hughes, N.L. Mitchell, Recent studies of ovine neuronal ceroid lipofuscinoses from BARN, the Batten Animal Research Network, Biochim. Biophys. Acta 1852 (2015) 2279–2286.
[73] S. Partanen, A. Haapanen, C. Kielar, C. Pontikis, N. Alexander, T. Inkinen, P. Saftig, T.H. Gillingwater, J.D. Cooper, J. Tyynelä, Synaptic changes in the thalamocortical system of cathepsin D-deficient mice: a model of human congenital neuronal ceroid-lipofuscinosis, J. Neuropathol. Exp. Neurol. 67 (2008) 16–29.
[74] M.A. Passini, J.C. Dodge, J. Bu, W. Yang, Q. Zhao, D. Sondhi, N.R. Hackett, S.M. Kaminsky, Q. Mao, L.S. Shihabuddin, S.H. Cheng, D.E. Sleat, G.R. Stewart, B.L. Davidson, P. Lobel, R.G. Crystal, Intracranial delivery of CLN2 reduces brain pathology in a mouse model of classical late infantile neuronal ceroid lipofuscinosis, J. Neurosci. 26 (2006) 1334–1342.
[75] C.C. Pontikis, C.V. Cella, N. Parihar, M.J. Lim, S. Chakrabarti, H.M. Mitchison, W.C. Mobley, P. Rezaie, D.A. Pearce, J.D. Cooper, Late onset neurodegeneration in the *Cln3*$^{-/-}$ mouse model of juvenile neuronal ceroid lipofuscinosis is preceded by low level glial activation, Brain Res. 1023 (2004) 231–242.
[76] C.C. Pontikis, S.L. Cotman, M.E. MacDonald, J.D. Cooper, Thalamocortical neuron loss and localized astrocytosis in the *Cln3*$^{\Delta ex7/8}$ knock-in mouse model of Batten disease, Neurobiol. Dis. 20 (2005) 823–836.
[77] J. Radke, W. Stenzel, H.H. Goebel, Human NCL Neuropathology, Biochim. Biophys. Acta 1852 (2015 May 16) 2262–2266.
[78] A. Raj, A. Kuceyeski, M. Weiner, A network diffusion model of disease progression in dementia, Neuron 73 (2012) 1204–1215.
[79] S. Ranta, Y. Zhang, B. Ross, L. Lonka, E. Takkunen, A. Messer, J. Sharp, R. Wheeler, K. Kusumi, S. Mole, W. Liu, M.B. Soares, M.F. Bonaldo, A. Hirvasniemi, A. de la Chapelle, T.C. Gilliam, A.E. Lehesjoki, The neuronal ceroid lipofuscinoses in human EPMR and mnd mutant mice are associated with mutations in CLN8, Nat. Genet. 23 (1999) 233–236.
[80] C. Sarkar, G. Chandra, S. Peng, Z. Zhang, A. Liu, A.B. Mukherjee, Neuroprotection and lifespan extension in Ppt1(−/−) mice by NtBuHA: therapeutic implications for INCL, Nat. Neurosci. 16 (2013) 1608–1617.
[81] A. Schulz, A. Kohlschütter, J. Mink, A. Simonati, R. Williams, NCL diseases — clinical perspectives, Biochim. Biophys. Acta 1832 (2013) 1801–1806.
[82] M.-L. Schmiedt, T. Blom, T. Blom, O. Kopra, A.M.S. Wong, C. von Schantz-Fant, E. Ikonen, M. Kuronen, M. Jauhiainen, J.D. Cooper, A. Jalanko, *Cln5*-deficiency in mice leads to microglial activation, defective myelination and changes in lipid metabolism, Neurobiol. Dis. 46 (2012) 19–29.
[83] S.S. Seehafer, D. Ramirez-Montealegre, A.M. Wong, C.H. Chan, J. Castaneda, M. Horak, S.M. Ahmadi, M.J. Lim, J.D. Cooper, D.A. Pearce, Immunosuppression alters disease severity in juvenile Batten disease mice, J. Neuroimmunol. 230 (2011) 169–172.
[84] J.J. Shacka, Mouse models of neuronal ceroid lipofuscinoses: useful pre-clinical tools to delineate disease pathophysiology and validate therapeutics, Brain Res. Bull. 88 (2012) 43–57.
[85] A. Simonati, F. Pezzini, F. Moro, F.M. Santorelli, Neuronal Ceroid Lipofuscinosis: The Increasing Spectrum of an Old Disease, Curr. Mol. Med (2014 Oct 10) [Epub ahead of print] PMID: 25323868.
[86] D.E. Sleat, J.A. Wiseman, M. El-Banna, K.H. Kim, Q. Mao, S. Price, S.L. Macauley, R.L. Sidman, M.M. Shen, Q. Zhao, M.A. Passini, B.L. Davidson, G.R. Stewart, P. Lobel, A mouse model of classical late-infantile neuronal ceroid lipofuscinosis based on targeted disruption of the CLN2 gene results in a loss of tripeptidyl-peptidase I activity and progressive neurodegeneration, J. Neurosci. 24 (2004) 9117–9126.
[87] K.R. Smith, J. Damiano, S. Franceschetti, S. Carpenter, L. Canafoglia, M. Morbin, G. Rossi, D. Pareyson, S.E. Mole, J.F. Staropoli, K.B. Sims, J. Lewis, W.L. Lin, D.W. Dickson, H.H. Dahl, M. Bahlo, S.F. Berkovic, Strikingly different clinicopathological phenotypes determined by progranulin-mutation dosage, Am. J. Hum. Genet. 90 (2012) 1102–1107.
[88] K.R. Smith, H.H. Dahl, L. Canafoglia, E. Andermann, J. Damiano, M. Morbin, A.C. Bruni, G. Giaccone, P. Cossette, P. Saftig, J. Grötzinger, M. Schwake, F. Andermann, J.F. Staropoli, K.B. Sims, S.E. Mole, S. Franceschetti, N.A. Alexander, J.D. Cooper, H.A. Chapman, S. Carpenter, S.F. Berkovic, M. Bahlo, Cathepsin F mutations cause type B Kufs disease, an adult-onset neuronal ceroid lipofuscinosis, Hum. Mol. Genet. 22 (2013) 1417–1423.
[89] I. Sohar, D.E. Sleat, M. Jadot, P. Lobel, Biochemical characterization of a lysosomal protease deficient in classical late infantile neuronal ceroid lipofuscinosis (LINCL) and development of an enzyme-based assay for diagnosis and exclusion of LINCL in human specimens and animal models, J. Neurochem. 73 (1999) 700–711.
[90] D. Sondhi, N.R. Hackett, D.A. Peterson, J. Stratton, M. Baad, K.M. Travis, J.M. Wilson, R.G. Crystal, Enhanced survival of the LINCL mouse following CLN2 gene transfer using the rh.10 rhesus macaque-derived adeno-associated virus vector, Mol. Ther. 15 (2007) 481–491.
[91] D. Sondhi, D.A. Peterson, A.M. Edelstein, K. del Fierro, N.R. Hackett, R.G. Crystal, Survival advantage of neonatal CNS gene transfer for late infantile neuronal ceroid lipofuscinosis, Exp. Neurol. 213 (2008) 18–27.
[92] J.F. Staropoli, A. Karaa, E.T. Lim, A. Kirby, N. Elbalalesy, S.G. Romansky, K.B. Leydiker, S.H. Coppel, R. Barone, W. Xin, M.E. MacDonald, J.E. Abdenur, M.J. Daly, K.B. Sims, S.L. Cotman, A homozygous mutation in KCTD7 links neuronal ceroid lipofuscinosis to the ubiquitin–proteasome system, Am. J. Hum. Genet. 91 (2012) 202–208.
[93] S.J. Tamaki, Y. Jacobs, M. Dohse, A. Capela, J.D. Cooper, M. Reitsma, D. He, R. Tushinski, P.V. Belichenko, A. Salehi, W.C. Mobley, F.H. Gage, S. Huhn, A.S. Tsukamoto, I.L. Weissman, N. Uchida, Neuroprotection of host cells by human central nervous system-stem cells in a mouse model of infantile neuronal ceroid lipofuscinosis, Cell Stem Cell 5 (2009) 310–319.
[94] I. Tammen, R.W. Cook, F.W. Nicholas, H.W. Raadsma, Neuronal ceroid lipofuscinosis in Australian Merino sheep: a new animal model, Eur. J. Paediatr. Neurol. 5 (Suppl. A) (2001) 37–41.
[95] M.A. Tarczyluk, C. Salzlechner, D. Smith, M.J. Lim, D.A. Pearce, F.M. Platt, B.P. Williams, J.D. Cooper, Combination therapies for juvenile Batten disease. NCL2014 poster presentation P26, Medicina 74 (Suppl. II) (2014) 30.
[96] M. Thelen, M. Damme, M. Schweizer, C. Hagel, A.M.S. Wong, J.D. Cooper, T. Braulke, G. Galliciotti, Autophagy, proteasomal degradation of mutant Cln6 and reactive gliosis are involved in the neuropathology of *nclf* mice, PLoS One 7 (2012) e35493 (Epub 2012 Apr 20).
[97] H. Tomiyasu, W. Takahashi, T. Ohta, F. Yoshii, M. Shibuya, Y. Shinohara, An autopsy case of juvenile neuronal ceroid-lipofuscinosis with dilated cardiomyopathy, Rinsho Shinkeigaku 40 (2000) 350–357.
[98] J. Tyynelä, J.D. Cooper, M.N. Khan, S.J.A. Shemilt, M. Haltia, Specific patterns of storage deposition, neurodegeneration, and glial activation in the hippocampus of patients with neuronal ceroid-lipofuscinoses, Brain Pathol. 14 (2004) 349–357.
[99] L.A. Verkruyse, S.L. Hofmann, Lysosomal targeting of palmitoyl-protein thioesterase, J. Biol. Chem. 271 (1996) 15831–15836.
[100] C. von Schantz, C. Kielar, S.N. Hansen, C.C. Pontikis, N.A. Alexander, O. Kopra, A. Jalanko, J.D. Cooper, Progressive thalamocortical neuron loss in Cln5 deficient mice: distinct effects in Finnish variant late infantile NCL, Neurobiol. Dis. 34 (2009) 308–319.
[101] B.R. Vuillemenot, D. Kennedy, J.D. Cooper, A.M.S. Wong, S. Sri, T. Doeleman, M.L. Katz, J.R. Coates, G.C. Johnson, R.P. Reed, E.L. Adams, M.T. Butt, D.G. Musson, J. Henshaw, S. Keve, R. Cahayag, L.S. Tsuruda, C.A. O'Neill, Nonclinical evaluation of CNS-administered TPP1 enzyme replacement in canine CLN2 neuronal ceroid lipofuscinosis, Mol. Genet. Metab. 114 (2015) 281–293.
[102] V. Warrier, M. Vieira, S.E. Mole, Genetic basis and phenotypic correlations of the neuronal ceroid lipofusinoses, Biochim. Biophys. Acta 1832 (2013) 1827–1830.
[103] J.M. Weimer, A.W. Custer, J.W. Benedict, N.A. Alexander, E. Kingsley, H.J. Federoff, J.D. Cooper, D.A. Pearce, Visual deficits in a mouse model of Batten disease are the result of optic nerve degeneration and loss of dorsal lateral geniculate thalamic neurons, Neurobiol. Dis. 22 (2006) 284–293.
[104] J.M. Weimer, J.W. Benedict, A.L. Getty, C.C. Pontikis, M.J. Lim, J.D. Cooper, D.A. Pearce, Cerebellar defects in a mouse model of juvenile neuronal ceroid lipofuscinosis, Brain Res. 1266 (2009) 93–107.
[105] R.E. Williams, S.E. Mole, New nomenclature and classification scheme for the neuronal ceroid lipofuscinoses, Neurology 79 (2012) 183–191.
[106] R.E. Williams, L. Aberg, T. Autti, H.H. Goebel, A. Kohlschütter, T. Lönnqvist, Diagnosis of the neuronal ceroid lipofuscinoses: an update, Biochim. Biophys. Acta 1762 (2006) 865–872.
[107] A.M. Wong, A.A. Rahim, S.N. Waddington, J.D. Cooper, Current therapies for the soluble lysosomal forms of neuronal ceroid lipofuscinosis, Biochem. Soc. Trans. 38 (2010) 1484–1488.
[108] J. Xiong, T. Kielian, Microglia in juvenile neuronal ceroid lipofuscinosis are primed toward a pro-inflammatory phenotype, J. Neurochem. 127 (2013) 245–258.
[109] D. Yates, Neurodegenerative disease: neurodegenerative networking, Nat. Rev. Neurosci. 13 (2012) 288–289.
[110] Z. Zhang, J.D. Butler, S.W. Levin, K.E. Wisniewski, S.S. Brooks, A.B. Mukherjee, Lysosomal ceroid depletion by drugs: therapeutic implications for a hereditary neurodegenerative disease of childhood, Nat. Med. 7 (2001) 478–484.
[111] M.S. Roberts, S.L. Macauley, A.M. Wong, D. Yilmas, S. Hohm, J.D. Cooper, M.S. Sands, Combination small molecule PPT1 mimetic and CNS-directed gene therapy as a treatment for infantile neuronal ceroid lipofuscinosis, J. Inherit. Metab. Dis. 35 (5) (2012) 847–857, http://dx.doi.org/10.1007/s10545-011-9446-x.