

Editorial

Neuronal Ceroid Lipofuscinoses: Why Early Diagnosis Matters?

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EDITORIAL

Neuronal Ceroid Lipofuscinoses (NCL) are a group of progressive neurodegenerative disorders leading to early death. NCL as a group is considered to be the most common neurodegenerative disorder with childhood onset [1,2]. 14 distinct NCL types have been identified and are indicated as CLN 1 through CLN 14. For 13 of them the genetic defect has been identified. To-date no genetic defect has been identified for CLN 9 disease. NCL types differ by their age of onset and disease course (Figure 1). A unifying feature of all types is the presence of characteristic autofluorescent lysosomal storage material referred to as lipofuscin. The lipofuscinosis is most prominent in neuronal cells, but is also observed in other cellular types. Clinically most NCL types start with progressive vision loss, which is followed by cognitive decline, seizures and early death. In types CLN 4, 12 and 13 no vision impairment is observed. All NCL are with autosomal recessive inheritance with the exception of the autosomal-dominant, adult-onset CLN 4 disease. The reported incidence of NCL varies quite significantly in different countries and ranges from 1.3 to 7 in 100,000 live births. The most common types, CLN 1, 2 and 3 represent the vast majority of the cases. All the remaining types are uncommon. Specific storage inclusions are observed in various peripheral cells in all NCL types using Electron Microscopy (EM) [3]. Study of patient's peripheral cells for such EM inclusions may be done as an initial laboratory screening test when NCL is suspected. In types CLN1,2 and 10 the protein products are soluble lysosomal enzymes. Clinical enzyme activity assays were developed for diagnostic confirmation of CLN 1 and 2 [4,5]. General diagnostic algorithms for determining the particular NCL type have been suggested [1,2]. More recently, Next Generation Sequencing based diagnostic panels including most NCL genes have been developed. Such panels are becoming more popular in the diagnostic evaluation of suspected NCL patients because of the high degree of clinical overlap between different NCL types. In addition, the EM study may be with lower diagnostic efficacy in the adult-onset forms [6,7]. Currently three US-based and two Europe-based laboratories listed on "Genetests.org" website offer such NCL gene panel testing [8].

Strategies for specific therapy have been in development for the common types – CLN 1, 2 and 3. NCL exclusively affect the Central Nervous System (CNS), and every potentially effective treatment should be able to reach the brain cells. The blood brain barrier prevents the passage of most large molecules when applied peripherally. It is thus difficult to deliver the deficient

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gene or protein via the peripheral circulation. Accordingly, the clinical trials that aim to introduce such large molecules have relied on direct CNS delivery. In addition, many of the deficient protein products, most notably the product of the gene CLN3 are membrane bound and insoluble. This makes the correction of such protein deficits impossible by delivering a normal copy of the mutant gene or of its protein product because the protein molecule is insoluble and would not reach the deficient cells. Despite these difficulties several clinical trials for NCL are currently in progress. Several different strategies for specific treatment are currently being evaluated:

- Gene Therapy: Direct CNS delivery of an AAV vector that incorporates the CLN2 gene has been promising in animal models of CLN2 disease [9]. A human clinical trial using this approach is conducted at Cornell University and is currently recruiting participants [10].
- Enzyme Replacement Therapy: A clinical trial for the direct delivery of the CLN2 product - the lysosomal enzyme TTP1 is carried by the company Biomarin and is currently recruiting patients [11].
- Substrate Reduction Therapy: The deficiency of the CLN1 protein product (the lysosomal enzyme PPT1) leads to lysosomal accumulation of cysteine

thioesters. The agent Cystagon was found to inhibit the formation of this storage material. A pilot treatment trial with PO Cystagon in four patients with atypical, later onset CLN1 disease was carried by our group during seven years. The participants' disease progression was compared to five untreated controls with the same mutations. While no significant differences in the disease course was noted with the treatment, some symptomatic improvement was observed in one of the participants for whom a higher Cystagon dose was achieved [12]. In addition, no serious side effects were observed. Another trial using N-Acetylcysteine along with Cystagon in younger typical CLN 1 patients was recently completed, but no results of this trial have been published to-date [13].

- Immune Modulation: Neuroimmune alterations were shown to be part of the disease pathway in CLN 3 disease using an animal model [14]. Currently a clinical trial for patients with CLN 3 disease using the immune

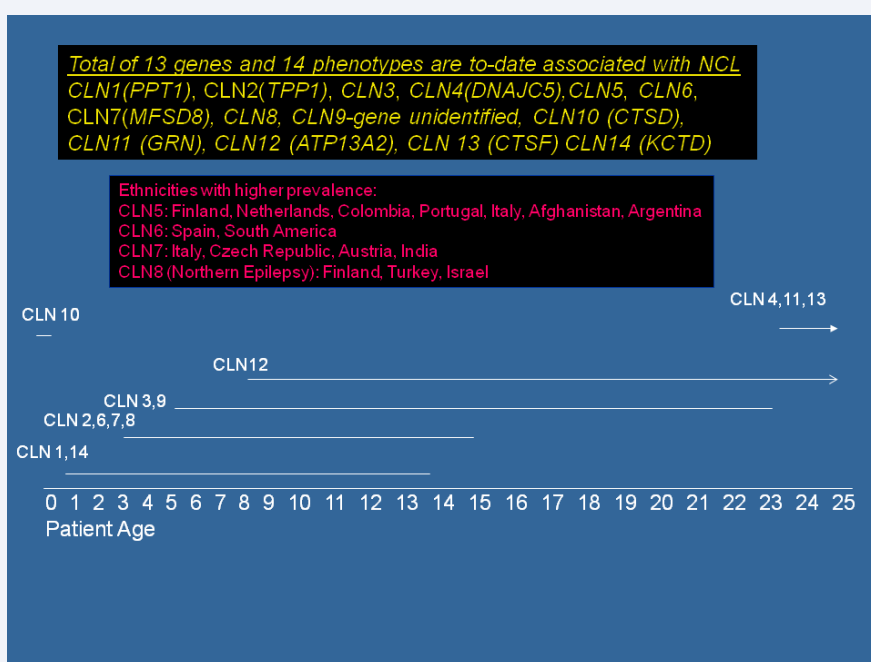


Figure 1 Genes involved in NCL (top), population with increased prevalence of some of the types (middle), and typical ages of onset and progression (bottom).

modulator Mycophenolate Mofetil is conducted at the University of Rochester. This trial is recruiting patients [15]. Development of a secondary site for this trial in our Institute is underway.

For the inclusion in such clinical trials, a confirmed molecular defect is a necessary pre-condition. Patients with advanced stages of NCL may not be eligible for inclusion. This emphasizes the importance of early diagnosis of NCL. The paradigm of supportive only treatment for NCL is changing and early molecular diagnosis has become imperative for these patients. Such early diagnosis may make it possible to refer the patient for inclusion in a clinical trial. In addition an early molecular diagnosis would make prenatal diagnosis available for future pregnancies in these families.

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