Review article

Towards understanding the neuronal ceroid lipofuscinoses

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Received 4 November 2008; accepted 10 December 2008

Abstract

The neuronal ceroid lipofuscinoses (NCLs) are a group of genetic progressive brain diseases of children and young adults, characterized by a decline of mental and other capacities, epilepsy, and visual loss through retinal degeneration. The common pathology of NCLs is that of a storage disorder with accumulation of an autofluorescent material, ceroid lipofuscin, in combination with the degeneration of neuronal cells. At least 10 genetically distinct NCLs, designated CLN1 to CLN10, are presently known. Several NCLs exhibit a widely variable clinical picture, depending on the severity of the individual mutation. Some NCLs are not particularly rare. With increasing awareness of these disorders and better diagnostic techniques available, the number of recognized patients is rising. This overview briefly summarizes recent developments (or quotes corresponding literature) that are important to understand, diagnose, and manage patients suffering from one of these incurable disorders.

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Keywords: Dementia; Retinopathy; Lysosomal storage disorder; Neurodegeneration

1. Introduction

The neuronal ceroid lipofuscinoses (NCLs) are a heterogeneous group of genetic degenerative brain diseases characterized by a progressive decline of mental and motor capacities, epilepsy, and visual loss through retinal degeneration. NCLs can affect humans from birth to young adulthood. Some representatives of this group are not extremely rare. With increasing awareness of these disorders and better diagnostic techniques, the number of recognized patients is rising. The number of established NCL disease entities has also risen to a number of presently at least 10 different disorders (Table 1). While the NCLs are now classified according to the designation of the mutated gene, Table 1 lists the single disorders in order of the age at which they typically become manifest. It must be noted, however, that genetic variants with “mild” mutations can have a significantly later onset than their “classical” forms.

For physicians as for basic scientists, it is practical to look upon the different types of NCL as a group of disorders as they have many things in common. Clinically, they are progressive neurological diseases characterized almost always by a combination of retinopathy, dementia, and epilepsy. Their pathology is that of a storage disorder with accumulation of a material termed ceroid lipofuscin in combination with the degeneration of neuronal cells. The purpose of this short overview is not to review the NCLs, for which comprehensive accounts exist [1,2], but to give a report on progress in the NCLs that is of importance when confronted with patients suspected or proven to suffer from such a disease. Readers more interested in basic mechanisms are referred to recent reviews [3].

In the following, the single NCLs are dealt with in the order of their genetic designation CLN1 to CLN10.
Table 1
Classification of neuronal ceroid lipofuscinoses.

<table>
<thead>
<tr>
<th>Age at manifestation</th>
<th>Designation</th>
<th>Chromosomal location</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital or later</td>
<td>CLN10</td>
<td>11p15</td>
<td>CD*</td>
</tr>
<tr>
<td>Infantile or later</td>
<td>CLN1</td>
<td>1p32</td>
<td>PPT1*</td>
</tr>
<tr>
<td>Late infantile or later</td>
<td>CLN2</td>
<td>11p15</td>
<td>TPP1*</td>
</tr>
<tr>
<td></td>
<td>CLN3</td>
<td>13q22</td>
<td>Partially soluble protein</td>
</tr>
<tr>
<td></td>
<td>CLN5</td>
<td>15q21</td>
<td>Membrane protein</td>
</tr>
<tr>
<td></td>
<td>CLN6</td>
<td>4q28</td>
<td>Membrane protein</td>
</tr>
<tr>
<td></td>
<td>CLN7</td>
<td>8p23</td>
<td>Membrane protein</td>
</tr>
<tr>
<td>Juvenile</td>
<td>CLN3</td>
<td>16p12</td>
<td>Membrane protein</td>
</tr>
<tr>
<td></td>
<td>CLN9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>CLN4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Lysosomal enzymes, CD, cathepsin D; PPT1, palmitoylprotein thioesterase 1; TPP1, tripeptidylpeptidase 1.

2. The single NCL disorders

**CLN1.** The classical infantile NCL (INCL) manifests itself in the second half of the first year of life and progresses dramatically with seizures, mental decay, loss of vision, and brain atrophy. Some mutations cause manifestation at any age, including adulthood [4]. The underlying defect is the lack of activity of the lysosomal palmitoylthioesterase 1 (PPT1) which can be used for diagnosis. As the enzyme cleaves fatty acid thioesters in plasma membranes, it was suggested that the drug cysteamine, a simple aminothiol used in the treatment of cystinosis, may have utility in the treatment of CLN1. In vitro studies, however, have cast doubt on this concept [5]. Experimental treatment with injection of human fetal neuronal stem cells [6] has been performed but cannot yet be evaluated.

**CLN2.** Classical late infantile NCL starts around the third year of life with seizures and a standstill of mental development while the retinopathy frequently is not prominent early in the course and may be missed after progression to more generalized deficits. The basic defect is the lack of activity of the lysosomal tripeptidylpeptidase 1 (PPT1), which can be used for diagnosis. An experimental treatment approach uses intracerebral injection of viral vectors containing normal coding segments of the CLN2 gene. In a mouse model of CLN2, this procedure resulted in cerebral enzyme expression, reduced brain pathology and increased survival. A small number of human patients have recently been treated in the same way [7]. Intraventricular enzyme replacement in a mouse model improved the disease phenotype [8]. Experimental treatment with human fetal neuronal stem cells [6] is also being performed.

**CLN3.** Classical juvenile NCL on the basis of a CLN3 mutation starts at the age of four to six years with a progressive loss of vision due to retinal degeneration. After several years, dementia, epilepsy, and motor disturbances ensue. The diagnostic hallmark of this frequent NCL type are conspicuous vacuoles in the cytoplasm of lymphocytes which are detectable on a regular blood smear (Fig. 1). The basic defect is in a membrane protein of unknown function. Hypotheses offered for the function of the CLN3 protein are focussing on its role in lysosomal metabolism, on its properties as an anti-apoptotic agent, or fatty acid desaturase, and on other mechanisms [3]. An intriguing hypothesis is based on the very high evolutionary conservation of this protein, which would qualify it as a protein absolutely necessary for survival. In contrast to this consideration is the observation that the typical patients with CLN3 defects (usually with a large deletion in the CLN3 gene) suffer from one of the mildest clinical forms of NCL that manifests itself only many years of perfect health. It was therefore suggested that the CLN3 protein in the typical patients has some residual function and that a complete lack of the protein might cause much more severe phenotypes, possibly intrauterine death [9]. Humoral autoimmunity against glutamic acid decarboxylase is believed to play a role in the pathophysiology of CLN3 and has led to immunosuppressive intervention [10]. For the evaluation of any effects of new treatments, the natural variability of the clinical course must be studied more precisely [11].
CLN4. This is a term reserved for an adult form of NCL (Kufs disease) that is still defined by clinical and neuropathological findings alone [12].

CLN5. This variant of late infantile NCL develops symptoms somewhat later than classical CLN2. Regarded as a purely Finnish disease in the past, this type of NCL has recently been observed in the Netherlands, Colombia, Portugal, Italy [13], Afghanistan, and Pakistan. It should be considered in any exhaustive diagnostic approach to a patient with suspected NCL. The basic defect concerns a partially soluble protein, apparently localized in lysosomes, whose function seems to be related to the CLN2 and CLN1 proteins. These observations suggest that there may exist common molecular pathways underlying neuronal degeneration in various types of NCLs.

CLN6. This is also a later manifesting clinical variant of classical late infantile NCL, mostly observed in India, the Iberic peninsula, in middle and South America. The CLN6 protein is a polytopic membrane protein of unknown function resident in the endoplasmic reticulum.

CLN7. This Turkish variant of late infantile NCL is caused by mutations in a gene (also termed MFSD8) coding for a putative lysosomal transporter protein. The protein is expressed ubiquitously and localizes mainly to the lysosomal compartment [14].

CLN8. A disease known in Finland as “Juvenile Northern Epilepsy” has recently been shown to be caused by mutations in the CLN8 gene which are allelic to those causing CLN7 disease. It is characterized by a progressive epilepsy associated with dementia and differs from other juvenile NCLs in so far as the visual problems may be mild and go unnoticed. The disease was also observed in Italy, Turkey, and Israel [15].

CLN9. A juvenile NCL clinically not distinguishable from CLN3 was termed CLN9 but has resisted genetic clarification until now. Cells from CLN9 patients have shown multiple abnormalities when studied in vitro [16].

CLN10. A congenital form of CLN10 is characterized by primary microcephaly, neonatal (possibly already intrauterine) epilepsy, and death in early infancy [17]. Late-onset forms of this NCL may be seen in juveniles and adults [18]. The affected CTSD gene in CLN10 codes for cathepsin D, a lysosomal enzyme thought to be important for neuronal stability. Alterations in a macroautophagy-lysosomal degradation pathway seem to mediate neuron death in this NCL and possibly other diseases.

Unclassified NCLs. Patients with clinical findings suggestive of an NCL and electron microscopic evidence of intracellular storage material, but unable to be classified after thorough investigation, are being encountered in diagnostic institutions. Genes coding for ion channels have been suggested as candidates in such disorders [19].

3. Diagnostic strategy in suspected NCL disorders

An economical approach to diagnosis of a suspected NCL starts from the type of clinical manifestation (see Fig. 2). In a neonate with microcephaly and convulsions, CLN10 with cathepsin D deficiency is a possibility. The enzyme deficiency is detected best in cultivated skin fibroblasts. In young children with otherwise unexplained epilepsy and developmental standstill, CLN2 and CLN3 are the most frequent diagnoses which are detected by the respective enzyme deficiencies leukocytes, fibroblasts, or dry blood samples. In a school child with retinopathy, CLN3 is possible, and typical vacuoles in lymphocytes (Fig. 1) will proof the diagnosis. If all tests give normal results, the more rare NCL variants CLN5, CLN6, CLN7, or CLN8 must be considered. As molecular genetic studies in the rare NCLs can be laborious, it is advisable to prove the presence of a storage disorder by electron microscopic examination of skin biopsy material or isolated blood lymphocytes before proceeding to a mutation analysis. Mutated genes to consider in dependence of the age at manifestation are listed in Table 2.

4. Treatment of NCLs

NCLs are incurable. Long-term palliative treatment that takes into consideration specific aspects of the particular type of NCL in question, is of great importance to obtain the best attainable quality of life [2]. Some
experimental therapeutic trials aiming at the prevention of neurological progression have been mentioned above. The theoretical chances of enzyme replacement, gene therapy, cell-mediated therapy and pharmacological treatments in NCLs have been reviewed [20]. As the effects of treatment in slowly progressing neurological disorders are difficult to evaluate, precise knowledge of the natural variability of the clinical course in each genetically distinct type of NCL is needed. For this purpose, an international consortium is presently working on a clinical NCL database.

References