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Review

# The neuronal ceroid-lipofuscinoses: A historical introduction ☆

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ABSTRACT

The neuronal ceroid-lipofuscinoses (Batten disease) collectively constitute one of the most common groups of inherited childhood onset neurodegenerative disorders, and have also been identified in many domestic and laboratory animals. The group of human neuronal ceroid-lipofuscinoses currently comprises 14 genetically distinct disorders, mostly characterised by progressive mental, motor and visual deterioration with onset in childhood or adolescence. Abnormal autofluorescent, electron-dense granules accumulate in the cytoplasm of nerve cells, and this storage process is associated with selective destruction and loss of neurons in the brain and retina. The present paper outlines nearly 200 years of clinical, neuropathological, biochemical and molecular genetic research, gradually leading, since 1995, to the identification of 13 different genes and over 360 mutations that underlie these devastating brain disorders and form the basis of a new classification system. These genes are evidently of vital importance for the normal development and maintenance of cerebral neurons. Elucidation of their functions and interactions in health and disease is a prerequisite for the identification of possible therapeutic targets, but may also further our understanding of the basic mechanisms of neurodegeneration and ageing. An account is also given of the development of international cooperation and free access electronic resources facilitating NCL research. This article is part of a Special Issue entitled: The Neuronal Ceroid Lipofuscinoses or Batten Disease.



## 1. Introduction

The neuronal ceroid-lipofuscinoses (NCLs) [1,2] form a special group within the inherited lysosomal storage disorders. They are also collectively called Batten disease, according to the British neurologist and neuropathologist Frederick Batten (1865–1918), an early pioneer of the field, who contributed to the identification of two forms of NCL (see Section 2). The NCLs have a worldwide distribution, but their incidence rates may vary from 1:67 000 in Italy and Germany to 1:14 000 in Iceland, and their prevalence rates from 1:1,000 000 in some regions to 1:100 000 in the Scandinavian countries [3]. A genetic founder effect is well documented in some populations [3]. In addition to 14 genetically distinct human NCLs so-far identified (Table 1), numerous spontaneous forms of NCL have been discovered in domestic and laboratory animals.

Most human NCLs show an autosomal recessive mode of inheritance, and may have variable ages of onset such as congenital, infantile, late infantile, juvenile, adult or even late adult onset according to the severity of mutation. The clinical characteristics of most childhood forms include progressive loss of vision as well as mental and motor deterioration, epileptic seizures and premature death, while the rarer adult-onset forms are dominated by dementia.

Despite the molecular genetic and clinical differences, all forms of NCL share unifying pathomorphological features. Autofluorescent, electron-dense, periodic acid-Schiff (PAS)- and Sudan black B-positive granules, resistant to lipid solvents, accumulate in the cytoplasm of most nerve cells and, to a lesser extent, in many other cell types. In the brain, this storage process is associated with progressive and selective loss of nerve cells. In their distribution and physicochemical properties the NCL storage granules bear close resemblance to lipofuscin, the “wear-and-tear pigment”, accumulating in postmitotic cells during ageing.

Although the first clinical description of possible cases of NCL appeared as early as in 1826 [4], almost a century elapsed before subsequent papers were published, mostly under the generalised heading of “amaurotic family idiocy”. The field remained utterly confused until the introduction of the NCL concept by Zeman and Dyken in 1969 [1]. The present paper outlines nearly 200 years of NCL research, reviewing the early clinical, neuropathological, and biochemical studies that gradually led to the formulation of the NCL concept and definition of the “classic” clinico-pathological entities. This early work was the prerequisite for the identification, since 1995, of the responsible genomic defects, now forming the basis of a new classification system [2].

The NCL genes, many of them previously unknown, are evidently of vital importance for the normal development and maintenance of cerebral neurons. Elucidation of their specific functions and interactions in health and disease is important for the identification of

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**Table 1**
Classification and characteristics of human neuronal ceroid-lipofuscinoses (NCLs).

| Disease | Eponym | OMIM no. | Clinical phenotype | Ultrastructure | Gene | Gene product | Stored protein |
|---|---|---|---|---|---|---|---|
| CLN1 | Haltia–Santavuori | 256730 | Infantile classic, late infantile, juvenile, adult | GRODs | *CLN1*/ *PPT1* | PPT1 | SAPs |
| CLN2 | Janský–Bielschowsky | 204500 | Late infantile classic, juvenile | CL | *CLN2*/ *TPP1* | TPP1 | SCMAS |
| CLN3 | Spielmeyer-Sjögren | 204200 | Juvenile classic | FP (CL, RL) | *CLN3* | CLN3 | SCMAS |
| CLN4 | Parry | 162350 | Adult autosomal dominant | GRODs | *CLN4*/ *DNAJC5* | DNAJC5 | SAPs |
| CLN5 | Finnish variant late infantile | 256731 | Late infantile variant, juvenile, adult | RL, CL, FP | *CLN5* | CLN5 | SCMAS |
| CLN6 | Lake-Cavanagh early juvenile /Indian variant late infantile, adult Kufs type A | 601780 | Late infantile variant, adult (Kufs type A) | RL, CL, FP | *CLN6* | CLN6 | SCMAS |
| CLN7 | Turkish variant late infantile | 610951 | Late infantile variant, juvenile, adult | RL, FP | *CLN7*/ *MFSD8* | MFSD8 | SCMAS |
| CLN8 | Northern epilepsy/progressive epilepsy with mental retardation | 610003 | Late infantile variant, progressive epilepsy with mental retardation | CL-like, FP granular | *CLN8* | CLN8 | SCMAS |
| CLN9 | Juvenile variant | 609055 | Juvenile variant | | | | |
| CLN10 | congenital | 610127 | Congenital classic, late infantile, adult | GRODs | *CLN10*/ *CTSD* | Cathepsin D | SAPs |
| CLN11 | Adult variant | | Adult | FP | *CLN11*/ *GRN* | Progranulin | |
| CLN12 | Juvenile variant | | Juvenile, Kufor-Raheb syndrome | FP | *CLN12*/ *ATP13A2* | P type ATPase | |
| CLN13 | Adult Kufs type B | | Adult Kufs type | | *CLN13*/ *CTSF* | Cathepsin F | |
| CLN14 | Infantile | | Infantile, progressive myoclonus epilepsy 3 | | *CLN14*/ *KCTD7* | Potassium channel tetramerisation domain-containing protein 7 | |

GRODs, granular osmiophilic deposits; CL, curvilinear profiles; FP, fingerprint bodies; RL, rectilinear profiles; SCMAS, subunit c of mitochondrial ATP synthase; SAPs, sphingolipid activator proteins.

possible therapeutic targets, but may also further our understanding of the basic mechanisms of neurodegeneration and ageing.

## 2. Early clinical and neuropathological studies of the NCLs

The first clinical description of patients who may have suffered from NCL [4] was published in 1826 by Dr. Otto Christian Stengel, a general practitioner at the small copper-mining community of Røros in South-Eastern Norway. During his long career he had observed a "singular illness" affecting four children of a local family. The parents were apparently healthy. By the age of 6 years, after unremarkable early development, the sight of two sons and two daughters began to deteriorate. Within years, the disease led to blindness, progressive mental deterioration, loss of speech, and epileptic seizures. The two oldest siblings had died by the age of 20 and 21 years [4]. No autopsies were performed but, in retrospect, the clinical features are compatible with CLN3 disease, classic juvenile. Unfortunately, Stengel's report, written in Norwegian, remained unnoticed by the scientific community until Nissen focused attention to its significance in the 1950s [5].

By the end of the 19th century the American neurologist Sachs formulated the influential concept of "amaurotic family idiocy", based on his observations in a set of siblings of rapidly progressive loss of vision and severe mental retardation of infantile onset [6]. At autopsy, accumulation of material of lipid nature was observed within markedly ballooned nerve cells of the brain. This disease, subsequently known as Tay–Sachs disease, was later identified as GM2-gangliosidosis type A, a prototype lysosomal storage disorder.

In the first two decades of the 20th century a number of further clinico-pathological studies of familial cases with progressive loss of vision and psychomotor retardation were described, but many of these had a later onset. Batten [7,8] and Vogt [9,10] reported patients with both a late infantile and juvenile onset, while Spielmeyer [11–13] described only individuals with a juvenile onset and Janský [14] and Bielschowsky [15] patients with a late infantile onset. At neuropathological investigation, all these patients with either late infantile or juvenile onset of their disease showed intraneuronal accumulation of granular material with lipid-like staining qualities. In their early papers both Batten and Spielmeyer had distinguished their cases from those reported by Sachs. However, inspired by the superficial clinical similarities (familial occurrence, progressive loss of vision, and psychomotor retardation) and the newly introduced unifying pathological concept of intraneuronal "thesaurismosis" [16,17] or "storage", all these cases were gradually grouped together. They were simply considered to represent variants of "amaurotic family idiocy" of either infantile (Tay-Sachs), late infantile (Janský-Bielschowsky) or juvenile (Spielmeyer-Sjögren) onset. In 1925 Kufs published his first report [18] on adult onset mental deterioration with similar intraneuronal storage but without evident loss of vision.

## 3. The NCL concept and clinico-pathological classification of the NCLs

In the 1930s two studies were published which began to undermine the validity of the prevailing unitarian view of the "amaurotic family idiocies". Sjögren [19] carried out extensive clinical and genealogical studies of patients with "juvenile amaurotic idiocy" and their families in Southern Sweden. Based on statistical analyses of about 4500 members of affected families he concluded that "juvenile amaurotic idiocy" showed, with high probability, a "monohybrid recessive inheritance", and was genetically distinct from "infantile amaurotic idiocy" (Tay–Sachs disease). A further argument against the unitarian view was provided by Klenk [20] who demonstrated an increased cerebral ganglioside concentration in the infantile form (Tay–Sachs) but not in the juvenile type (Spielmeyer–Sjögren). Klenk's findings were later confirmed by Svennerholm [21] in 1962 who finally identified the major storage material in the infantile form (Tay–Sachs) as GM2-ganglioside.

The final blow to the unitarian view came, however, through the histochemical and electron microscopic studies of Zeman and his collaborators in the 1960s. They showed [22] that the intraneuronal storage cytosomes in the late infantile (Janský–Bielschowsky) and juvenile (Spielmeyer–Sjögren) forms of "amaurotic idiocy" radically differed from the membraneous cytoplasmic bodies described in the infantile form (Tay–Sachs) by Terry and Korey [23]. While the storage material in the infantile Tay–Sachs form was easily extractable, the autofluorescent and electron-dense storage cytosomes in the late infantile (Janský–Bielschowsky) and juvenile (Spielmeyer–Sjögren) forms were largely resistant to lipid solvents, and showed characteristic