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Review

The neuronal ceroid-lipofuscinoses: From past to present

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Abstract

The neuronal ceroid-lipofuscinoses (NCLs) are inherited lysosomal storage diseases and constitute the most common group of children's progressive encephalopathies. Most childhood forms of NCL are clinically characterized by progressive loss of vision as well as mental and motor deterioration, epileptic seizures, and premature death, while the rare adult forms are dominated by dementia. All forms of NCL share common pathomorphological features. Autofluorescent, periodic acid-Schiff- and Sudan black B-positive granules, resistant to lipid solvents, accumulate in the cytoplasm of most nerve cells, and there is progressive and remarkably selective neuronal degeneration and loss. For a long time, the NCLs were grouped under the heading of the "amaurotic family idiocies" and conceived as lipidoses. However, in the late 1980ies and 1990ies the NCL storage cytosomes were shown to consist largely of two hydrophobic proteins: either subunit c of mitochondrial ATP synthase or sphingolipid activator proteins A and D. Since 1995 numerous mutations in at least seven different genes have been shown to underlie the multiple human and animal forms of NCL. This review discusses the historical evolution of the NCL concept and the impact of the recent biochemical and molecular genetic findings on our views on the classification and pathogenesis of these devastating brain disorders.

Keywords: Neuronal ceroid lipofuscinoses; Batten disease; Lysosomal storage; Molecular pathology; Classification

1. Introduction

The neuronal ceroid-lipofuscinoses (NCLs, also referred to as Batten's disease) [90] are inherited lysosomal storage diseases and collectively constitute the most common group of children's progressive encephalopathies. Their overall incidence in the US has been estimated at 1:12 500 [49], and certain forms of NCL are relatively frequent in Northern European populations [74]. In addition to the human NCLs, a number of spontaneous animal forms of NCL have been described, discussed in detail elsewhere in this issue.

The clinical and pathological features of the human NCLs have been thoroughly reviewed in recent years [18,20,82]. With one exception, the NCLs show an autosomal recessive mode of inheritance, and may have a congenital, infantile, late infantile, juvenile or adult onset. Most childhood forms are clinically characterized by progressive loss of vision as well as mental and motor deterioration, epileptic seizures and premature death, while the rare adult-onset forms are dominated by dementia. Despite the varying clinical features, all forms of NCL share unifying pathomorphological characteristics. Autofluorescent, periodic acid-Schiff (PAS)- and Sudan black B-positive granules, resistant to lipid solvents, accumulate in the cytoplasm of most nerve cells (Fig. 1) and, to a lesser extent, of many other cell types. There is progressive and remarkably selective neuronal loss, coupled with astrocytic proliferation and hypertrophy as well as macrophage infiltration. In the most severe congenital and infantile NCLs the cortical and retinal neurons may be almost completely destroyed, resulting in extreme brain and retinal atrophy. The ultrastructure of the accumulating storage cytosomes varies between the different forms of NCL [13] (Fig. 2) and has long served as the basis of their classification, along with the age of clinical onset [18,20,82].

The biochemical nature of the materials accumulating within the pathological autofluorescent cytosomes first began to be understood in the late 1980ies [43,45,70], and the first genomic defects causing NCL were identified in 1995 [1,79]. Since then,

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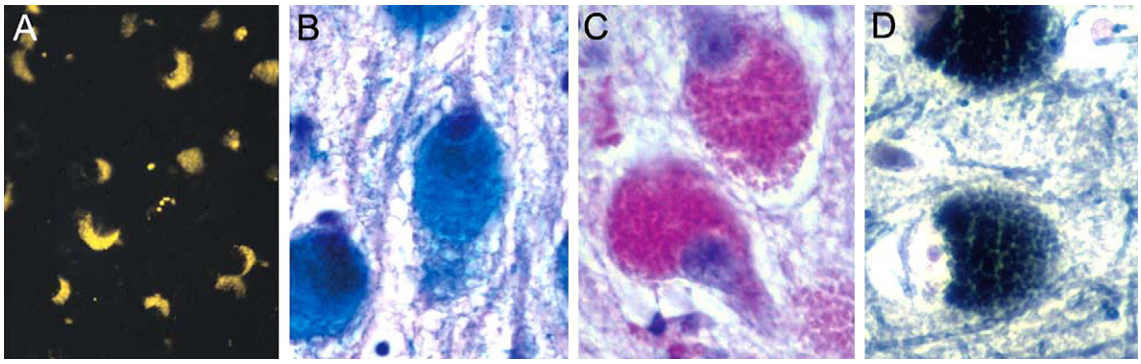

Fig. 1. The intraneuronal storage material in all forms of neuronal ceroid-lipofuscinosis shows autofluorescence in ultraviolet light, seen here as moon-like crescents around the nuclei of cortical neurons (A). The storage granules stain positively with Luxol fast blue (B), periodic acid-Schiff (C) and Sudan black B (D) methods. Paraffin sections from the cerebral cortex of a patient with CLN5 ×300 (A) and CLN8 ×1000 (B–D). Reproduced with permission from the Journal of Neuropathology and Experimental Neurology.

altogether 7 different NCL genes have been isolated. The purpose of this paper is to review the historical development of the NCL concept and to discuss the impact of the recent molecular findings on our views on the classification and pathogenesis of these devastating brain disorders.

2. The first clinical description

The credit for the first clinical description of any form of NCL is usually given to Dr. Otto Christian Stengel, physician at the Copper Mining Company of Røros, a small Norwegian town. His "Account of a singular illness among four siblings in the vicinity of Røraas" (Fig. 3) was published in the first volume of the first Norwegian medical Journal in 1826 [66] and coupled systematic clinical observation with scientific thinking. The four consecutive children, two boys and two girls, of apparently healthy parents did well until the age of 6 years when their sight began to deteriorate. Within years, the disease led to blindness, progressive mental deterioration and loss of speech, epileptic fits, and premature death (by the time of publication the two oldest siblings had died at the ages of 21 and 20 years). No autopsies were performed. Stengel's report, written in Norwegian, remained unnoticed until attention was brought to its significance by his countrymen more than a century later.

3. "The amaurotic family idiocies"

The concept of "amaurotic family idiocy" [51] was created by the American neurologist Sachs, based on his observations in a set of siblings of rapidly progressive loss of vision, combined with severe mental retardation of infantile onset. The disease was morphologically characterized by accumulation of material of lipid nature within markedly ballooned nerve cells of the central nervous system. Between the years 1903 and 1914 a number of further patients with progressive loss of vision and psychomotor retardation but with a later onset were described in a familial setting. Patients with both late infantile and juvenile onset were reported by Batten [3,4] and Vogt [83–85], patients with a juvenile onset by Spielmeyer [63–65], and patients with late infantile onset by Janský [29] and Bielschowsky [6]. At neuropathological autopsy, all these further patients showed accumulation within nerve cells of granular material with lipid-like staining qualities. Inspired by the clinical similarities (familial occurrence, progressive loss of

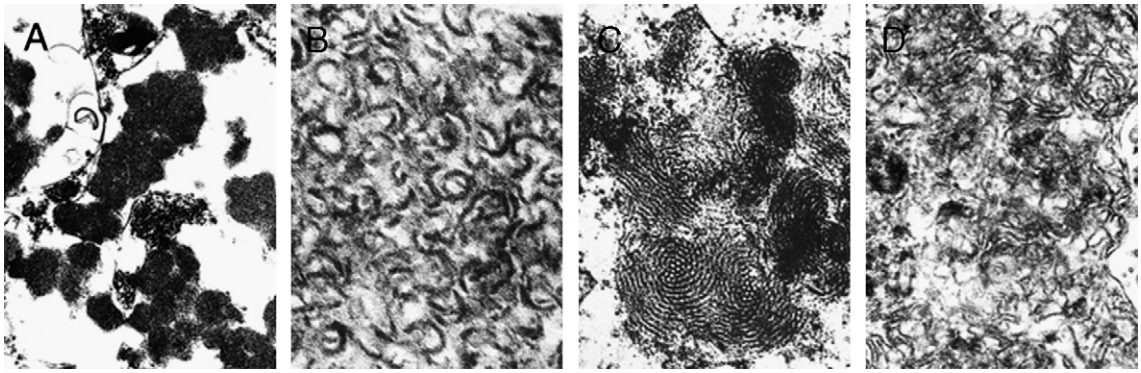

Fig. 2. The ultrastructural appearances of the intraneuronal storage deposits vary between the different forms of the neuronal ceroid-lipofuscinoses. Four basic types can be delineated: (A) granular osmiophilic deposits are characteristic of the infantile and other forms of CLN1, ×10,000; (B) curvilinear profiles are typical of classic late infantile neuronal ceroid-lipofuscinosis CLN2, ×20,000; (C) fingerprint patterns are the predominant type of intraneuronal inclusions in the juvenile form CLN3, ×30,000; (D) many inclusions in the variant forms of late infantile neuronal ceroid-lipofuscinosis correspond to the rectilinear complex, ×15,000. Reproduced with permission from the Journal of Neuropathology and Experimental Neurology.