Principles and Practice of Clinical Electrophysiology of Vision

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Neuronal Ceroid Lipofuscinosis

Irene Gottlob

The term *neuronal ceroid lipofuscinosis* (NCL) is applied to a group of hereditary progressive diseases characterized by widespread accumulation in the body of autofluorescent lipopigments. This material is stored in the lysosomes of the cells and has, corresponding to the type of NCL, a characteristic ultrastructural appearance. According to the onset and course of the disease, an infantile type (Santavuori-Haltia), a late infantile type (Jansky-Bielschowsky), an early juvenile type (Lake-Cavanagh), a juvenile type (Stengel-Spielmeyer-Vogt), and an adult type (Kufs) are distinguished. (see Table 110–1).[29, 53] The diagnosis and clinical classification are confirmed by ultrastructural tissue analysis. The primary biochemical defect is still unclear. Such symptoms as visual failure, mental retardation, myoclonic seizures, and ataxia are determined by the site of involvement of the central nervous system.

Degeneration of rods and cones and optic atrophy are the origin of blindness. In addition, lipopigments are stored in most of the retinal cells.

Except for the autosomal dominant form of Kufs' disease, NCLs are inherited autosomal recessively, and consanguinity may be found in afflicted families.

CLINICAL AND ELECTROPHYSIOLOGICAL FINDINGS

Infantile Neuronal Ceroid Lipofuscinosis (Santavuori-Haltia)

Santavuori[44], Haltia,[21] and colleagues distinguished infantile NCL as a new type of NCL with early onset before the age of 2 years and a rapid progressive course. In Finland the incidence is 1 in 13,000, with the total number of patients over 80, in contrast to the reports of a total of 40 to 50 patients in other countries.[42]

The patients show a normal prenatal and perinatal history and a normal development until the age of 8 months. Mental retardation and microcephaly are observed after the age of 12 months. Generalized muscular hypotonia with truncal and limb ataxia, hyperexcitability, myoclonic jerks, and seizures are observed between 2 and 3 years; after the age of 5 years, flexion contractures are common. The mean age of death is 8 years.[5, 24, 40, 42, 44] The electroencephalogram (EEG) shows the first electrical changes in the occipital region and becomes isoelectric after 3 years of age.[24, 42, 43] Most patients show signs of severe visual deterioration by the age of 1 year. Pupillary reaction is slow or absent; dystrophy and brownish discoloration of the macula, optic atrophy, and involution of retinal vessels are observed. Due to a progressive hypopigmentation of the fundus, choroidal vessels are clearly visible.[5, 42, 45] The pigment aggregation, typical for retinitis pigmentosa and usually observed in other types of NCL, has only been seen in two patients in a late stage of infantile NCL and was associated with posterior polar cataracts.[1] The ERG is subnormal in all patients and abolished between the ages of 12 months to 4 years.[24, 42] The scotopic ERG seems to be affected earlier than the photopic ERG.[42] In the earlier phase of disease the VEP shows a reduced amplitude with poorly defined earlier components and becomes unobtainable after age of 2 to 5 years.[24, 42]

Late Infantile Neuronal Ceroid Lipofuscinosis (Jansky-Bielschowsky)

Patients with late infantile NCL were first described by Jansky[26] and Bielschowsky[4] at the begin-

TABLE 110–1.
Types of Neuronal Ceroid Lipofuscinosis

Feature	Infantile (Santavuori-Haltia)	Late Infantile (Jansky-Bielschowsky)	Early Juvenile (Lake-Cavanagh)	Juvenile (Stengel-Spielmeyer-Vogt)	Adult (Kufs)
Age of onset (yr)	<2	1–3	4–6	3–9	11–50
Early symptoms	Dementia, ataxia,	Disturbance of speech and gait, dementia, ataxia, seizures	Ataxia, drop attacks	Visual loss, seizures	Seizures/dementia
Late symptoms	Seizures, myoclonic jerks, visual loss	Visual loss, spastic tetraplegia	Dementia, visual loss, seizures	Seizures, slurred speech, anxiety, tetraplegia	Ataxia
ERG*	Subnormal/absent	Subnormal/absent	Subnormal/absent	Subnormal/absent	Normal/subnormal
VEP*	Reduced amplitude	Threshold elevation	Latency delay, reduced amplitude	Reduced amplitudes/absent	Normal/reduced amplitudes
Morphology	Granular bodies	Curvilinear bodies	Fingerprint bodies	Fingerprint bodies, vacuolated lymphocytes	Granular bodies/fingerprint bodies
Age of death (yr)	3–11	4–10	?	14–28	17–60

*ERG = electroretinogram; VEP = visual evoked potential.

ning of the 20th century. The incidence is unknown but estimated at a minimum of 1 in 44, 700 in British Columbia.[33]

The first clinical sign in Jansky-Bielschowsky disease is a disturbance of speech, intellectual functions, and gait at the age of 15 to 33 months. At the age of 2 to 4 years, ataxia and grand mal and myoclonic epilepsy appear. After the age of 3 years the children are unable to walk, and between 5 and 6 years spastic tetraplegia is present. Death typically occurs between 4 and 10 years.[5, 35, 48, 52] The EEGs of these patients show large-amplitude irregular slow activity with polyphasic spikes.[24]

Fundus changes have been described after the age of 3.5 years. The macula appears brown or reddish brown, sometimes light red surrounded by a gray zone, in other cases mottled. Diffuse retinal atrophy is common. Attenuation of retinal arterioles, mild optic atrophy, as well as classic pigmentary retinopathy have been observed.[5, 35, 48, 52] At an early stage of the disease the ERG may be present but is abolished as the disease progresses.[24, 35] The VEP threshold is elevated, and abnormal large early VEP components are observed.[24, 35]

Early Juvenile Neuronal Ceroid Lipofuscinosis (Lake-Cavanagh)

This subgroup, isolated by Lake and Cavanagh in 1978,[30] clinically resembles the late infantile form but has a more protracted course. Other cases have been reported with a similar history.[7, 19, 32, 55] Fewer than 20 patients have been described to date.

The first symptoms of ataxia and drop attacks appear between 5 and 6 years of age. Later symptoms are dementia, myoclonus, convulsions, and visual loss. The EEG shows gross poverty of the rhythmic activity appropriate to age, and during photic stimulation large polyphasic spikes are observed.[30, 32]

The patients have visual deterioration after the age of 6 years. Moderate arterial attenuation and optic atrophy[19, 30, 32] are observed by funduscopy. The ERG is absent except in a few patients where it is still present with a low amplitude. Figure 110–1 shows the scotopic and photopic ERGs of two children afflicted by early juvenile NCL, the ERGs of their parents, and those of their healthy siblings. The visual acuity of our first patient K.Y., a 7-year-old affected boy, was finger counting in both eyes. He had normal fundus pigmentation but optic atrophy and narrow vessels. Minimal responses were obtained in his scotopic ERG, while the photopic ERG was abolished. The second case (Ü.Y.), his 10-month-old sister, had histologically verified early juvenile NCL but no apparent fundus pathology. She had an almost extinguished scotopic ERG, but only mildly reduced a- and b-wave amplitudes in the photopic ERG. In both siblings the flash VEPs were within normal range, while the pattern VEPs, still normal in Ü.Y, showed reduced amplitudes and a latency delay in K.Y. The normal flash VEPs of both siblings and the normal pattern VEP and photopic ERG of Ü.Y. suggest that the pathology begins in the retinal periphery, while the function of the central retina is affected in a later stage of the disease.

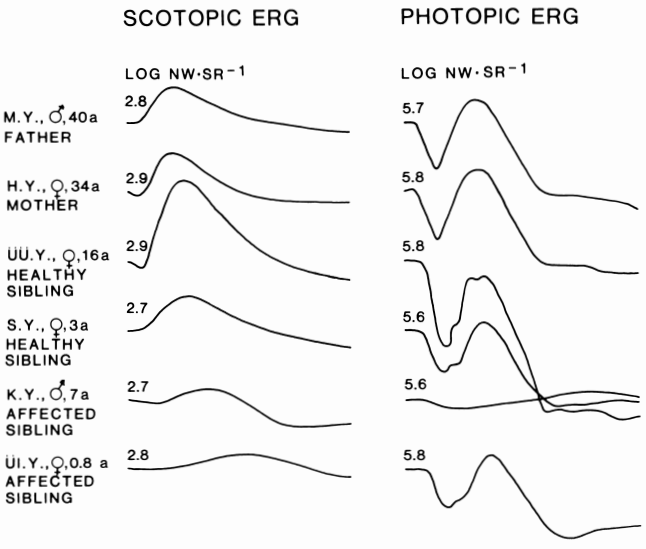

FIG 110–1.
Original recordings of scotopic *(left column)* and photopic *(right column)* ERGs of a family afflicted with early juvenile NCL. Case 1 (K.Y.) and case 2 (Ül.Y.) are the patients and show clearly reduced ERG amplitudes. The father and the mother are obligate carriers for NCL. Their scotopic ERG is reduced as compared with the 16-year-old healthy sibling (ÜÜ. Y.). The 3-year-old healthy sibling S.Y. also has small ERG amplitudes and is suspected to be a heterozygote. (From Gottlob I, Leipert KP, Kehlschütter A, Goebel HH: *Graefes Arch Clin Exp Ophthalmol* 1988; 226:518–522. Used by permission.)

Juvenile Neuronal Ceroid Lipofuscinosis (Stengel-Spielmeyer-Vogt)

This disease was first observed by Stengel in 1826.[47] The incidence presumably varies and was found to be 1 in 50,000 in Sweden,[39] where 1% of the population are heterozygotes.

The first clinical sign is deterioration of vision, which appears between 3 and 9 years of age. Seizures, slurred speech, and mental retardation appear between the age of 6 and 13 years. Emotional upset, anxiety, nightmares, and aggressiveness are common symptoms. Between the age of 8 and 15 years disturbance of gait begins. In the late stage of the disease spastic tetraplegia is present, and the patients are unable to communicate. Death occurs at ages 14 to 28 years.[10, 46, 50, 52, 53, 55] The EEG shows various unspecific abnormalities in the cases examined.[24]

Since the first symptom is visual impairment, the ophthalmologist will be frequently involved in the early diagnosis. A fine mottling of the macula often precedes visual deterioration and may indicate juvenile NCL in younger siblings of affected children. Subsequently, attenuation of retinal arterioles and optic atrophy occur. A granular pigmentary dystrophy of the macula with irregular granules or a bull's-eye appearance, with or without a "dull red" spot in the center, is observed next in the course of the disease. Between 7 and 13 years of age a peripheral pigmentary retinopathy with bone spicule–like pigments or of the "salt-and-pepper" type is frequently seen.[5, 10, 18, 19, 35, 38, 46, 50–52, 55] Fundus hypopigmentation and clearly visible choroidal vessels were observed in some patients.[19]

A clear red-green deficiency could be detected with the Farnsworth D-15 test in patients who still had a well-functioning blue mechanism.[23] Relatively good night vision was found in a series of patients.[22] At the beginning, only central vision is affected. By static perimetry a flat profile is shown in young patients. Then the scotomas rapidly progress and show increasing density and extension with a breakthrough to the upper nasal periphery, which may cause a hemianopic type of defect with loss of the nasal field.[23]

In general, the scotopic and photopic ERG is markedly decreased even when there are few signs of retinal abnormality. When the b-wave and the oscillatory potentials were already severely affected, a normal a-wave remained (Fig 110–2). This suggests that the photoreceptors are still functioning in the early course of juvenile NCL and that the primary damage is located in the inner part of the retina.[10, 19, 24, 37, 48, 51, 52] EOGs were found to be normal in the earliest stages of the disease.[37] This argues against a primary affection of the pigment epi-

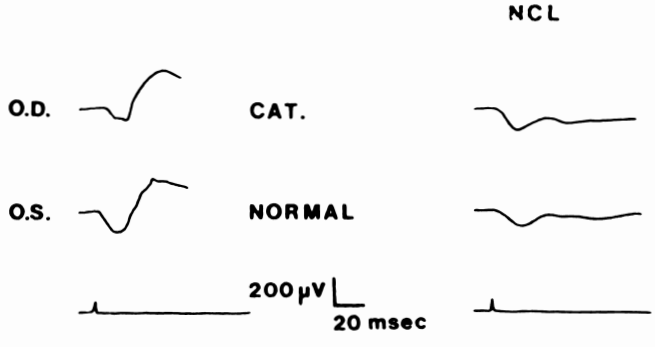

FIG 110–2.
Dark-adapted ERG of a patient with a cataract on the right eye and a normal left eye *(left column)* and of both eyes of a 5-year-old patient with juvenile NCL *(right column).* While the b-waves were reduced significantly, the a-waves revealed only a slight decrease. (From Wachtmeister L: *Doc Ophthalmol Proc Ser* 1982; 31:209–215. Used by permission.)

thelium. In older patients, depending on age, EOG subnormal light peaks as well as no changes between dark and light have been observed.[19, 52] In the early stage of the disease the VEP shows clearly reduced amplitudes and becomes unobtainable later in the course.[19, 24, 48]

Adult Neuronal Ceroid Lipofuscinosis (Kufs)

Kufs' disease[28] is the late-onset form of NCL and differs from the other forms by its absence of fundus changes and blindness. To date 50 cases fulfill the criteria for this diagnosis.[2] In contrast to the other forms of NCL, which are all autosomal recessive, forms of adult NCL (Kufs' disease) have been reported as autosomal recessive or dominant.[2, 6, 9, 31]

The mean age of onset is 30 years. Two clinical phenotypes are seen in the disease: (1) progressive myoclonic epilepsy and (2) dementia with motor disturbance. The mean length of the illness is 13 years. The EEG shows nonspecific changes.

The photopic ERG has been found to be normal[2, 49] or shows a decreased b-wave amplitude.[8] Both normal and reduced pattern ERG amplitudes have been described.[2, 49] Normal VEPs have been recorded in some patients,[49] while pattern VEPs revealed reduced amplitudes[8] in other patients.

Atypical Forms of Neuronal Ceroid Lipofuscinosis

Several atypical forms of NCL show a combination of temporal, clinical, and pathological features that do not fit the above forms of NCL. Some of them represent isolated observations; others share common characteristics and are grouped together in subgroups as the congenital form, observed in six patients so far,[11] and as the protracted form of juvenile NCL described by Goebel et al.[14]

ULTRASTRUCTURAL CHANGES

Since the primary biochemical defect is still unclear, the diagnosis and clinical classification of the different forms of NCL must rely on ultrastructural findings. Biopsy samples of skin, skeletal muscle, peripheral nerve, rectum, conjunctiva, and lymphocytes have been used for electron microscopy. In general, granular lysosomal residual bodies appear in the infantile form, curvilinear bodies in the late infantile form, and fingerprint bodies in the early juvenile and juvenile form (Fig 110–3).[7, 12] In Kufs' disease fingerprint bodies or granular osmiophilic deposits are found.[2] Lymphocytes may be easily and repeatedly obtained, and besides the characteristic inclusions of the different types of NCL, they reveal pathological vacuolization in patients with juvenile NCL.[25]

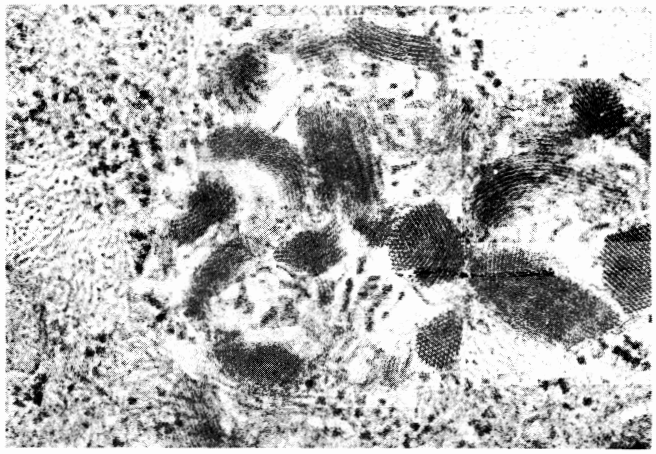

FIG 110–3.
Electron microscopy of a skin biopsy specimen of an 8-year-old patient afflicted by juvenile NCL. Lipopigments with fingerprint bodies are present (12,500×). (From Gottlob I, Goebel HH, Kohlschütter A, Leipert KP, Eckl G: *Spektr Augenheilk* 1988; 2:64–70. Used by permission.)

In the NCL the retina has two types of pathological alterations: (1) early loss of photoreceptors followed by atrophy of the remaining inner part of the retina with degeneration of the pigment epithelium and (2) cytoplasmic accumulation of autofluorescent lipopigments in various cell types.[13, 15, 17]

PRENATAL DIAGNOSIS AND FINDINGS IN HETEROZYGOTES

To date, biochemically the carrier state of NCL is undetectable. Nevertheless, a successful prenatal diagnosis of the Jansky-Bielschowsky type, where curvilinear profiles were found by electron microscopy in amniotic fluid cells, has been reported.[34] Morphological detection of heterozygotes has been unsuccessful so far. In contrast, we could find subtle electrophysiological changes in carriers. We found statistically significant differences between scotopic b-wave amplitudes, pattern ERGs, and electro-oculographic (EOG) light peaks between obligate carriers of NCL and an age-matched control group (see Figs 110–1 and 110–4). Although the decrease in the electrophysiological parameters of heterozygotes is variable, in individual families genetic counseling can be aided by electrophysiological findings.[20]

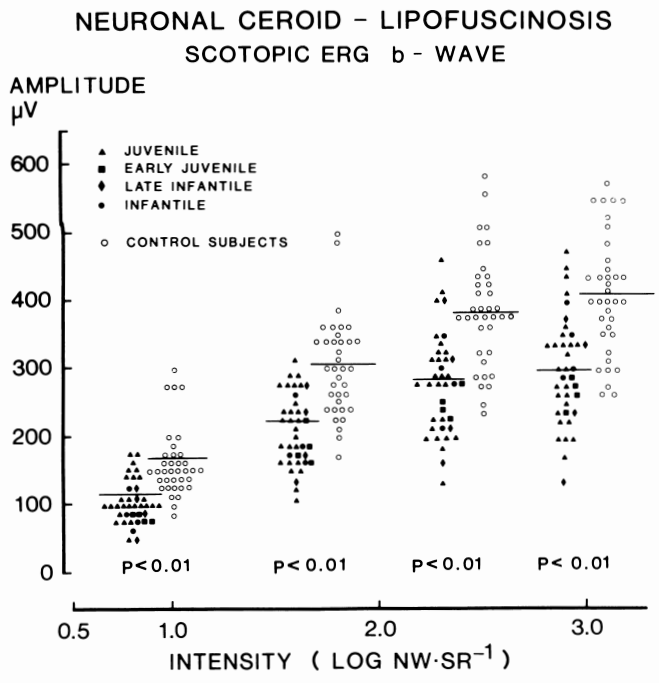

FIG 110–4.
Scotopic b-wave amplitudes of the right and left eyes of 19 heterozygotes for NCL *(filled symbols)* and 18 control subjects *(open symbols)* at four light intensities. (From Gottlob I, Leipert KP, Kohnschütter A, Goebel HH: *Graefes Arch Clin Exp Ophthalmol* 1988; in press. Used by permission.)

ANIMAL MODELS

Various animals such as the English setter, sheep, cattle, swine, the Siamese cat, the Australian chihuahuas, the dachshund, and goldfish have been shown to have intracellular inclusions similar to curvilinear or fingerprint bodies.[27] The canine, a model for juvenile NCL, reveals preservation of photoreceptors early and late in the disease[16] and only a 40% reduction in the ERG a- and b-waves,[3] although specific lipopigments are present in all cell types of the retina. Therefore one may assume that the retinal degeneration in human NCL is not caused by the intracellular accumulation of lipopigments and that two different pathological mechanisms are present. Nilsson et al.[36] found a markedly reduced c-wave amplitude and a reduced variation of the standing potential in afflicted canines and suggested early damage of the pigment epithelium. In the ovine model, in contrast, like in humans already in the initial stage of the disease, photoreceptor damage and pigment epithelial degeneration occur.[41]

EXPERIMENTAL TREATMENTS

Enzymatic defects are unknown in the various NCLs, but a disturbance in the peroxidation of polyunsaturated fatty acids has been proposed, and the possibility to counteract this reaction with antioxidants has been suggested. A combination of vitamin E, vitamin C, methionine, and butylated hydroxytoluene was recommended.[54] Recently in a study including the data of 125 patients with juvenile NCL, Santavuori at al.[45] showed that treatment with a combination of sodium selenite and vitamin *E could* retard the progress of the disease but not cure the patients.

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