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Neuronal Ceroid-Lipofuscinoses

[*Includes: PPT1-Related Neuronal Ceroid-Lipofuscinosis, TPP1-Related Neuronal Ceroid-Lipofuscinosis, CLN3-Related Neuronal Ceroid-Lipofuscinosis, CLN5-Related Neuronal Ceroid-Lipofuscinosis, CLN6-Related Neuronal Ceroid-Lipofuscinosis, CLN8-Related Neuronal Ceroid-Lipofuscinosis*]

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Summary

Disease characteristics. The neuronal ceroid-lipofuscinoses (NCLs) are a group of inherited, neurodegenerative, lysosomal-storage disorders characterized by progressive mental and motor deterioration, seizures, and early death. Visual loss is a feature of most forms. Phenotypes have been characterized clinically by age of onset and order of appearance of the clinical features: infantile neuronal ceroid-lipofuscinosis (INCL, Santavuori-Haltia), late-infantile (LINCL, Jansky-Bielschowsky), juvenile (JNCL, Batten disease, Spielmeyer-Vogt), adult (ANCL, Kuf's disease), and Northern epilepsy (NE, progressive epilepsy with mental retardation). Children with **INCL** are normal at birth; symptoms usually present acutely between six and 24 months of age. Initial signs include delayed development, myoclonic jerks and/or seizures, deceleration of head growth, and specific electroencephalographic (EEG) changes. Affected infants develop retinal blindness and seizures by two years of age, followed by progressive mental deterioration. The first symptoms of **LINCL** typically appear between two and four years of age, usually starting with epilepsy, followed by regression of developmental milestones, dementia, ataxia, and extrapyramidal and pyramidal signs. Visual impairment typically appears at age four to six years and rapidly progresses to blindness. Life expectancy ranges from age six to greater than 40 years of age. The onset of **JNCL** is usually between ages four and ten years. Rapidly progressing visual loss resulting in total blindness within two to four years is often the first clinical sign. Epilepsy with generalized tonic-clonic seizures, complex-partial seizures, or myoclonic seizures typically appears between ages five and 18 years. Life expectancy ranges from the late teens to the 30's. Initial signs and symptoms of **ANCL** usually appear around 30 years of age with death occurring about ten years later. Affected individuals have either progressive myoclonic epilepsy or behavior abnormalities, and all have dementia, ataxia, and late-occurring pyramidal and extrapyramidal signs. **Northern epilepsy** is characterized by tonic-clonic or complex-partial seizures, mental retardation, and motor dysfunction. Onset occurs between ages two and ten years.

Diagnosis/testing. The diagnosis of an NCL is often based on assay of enzyme activity and/or molecular genetic testing, and in some instances, on clinical findings and electron microscopy (EM) of biopsied tissues. The diagnostic testing strategy in a proband depends on the age of onset. Six genes — *PPT1*, *TPP1*, *CLN3*, *CLN5*, *CLN6*, and *CLN8* — are known to be associated with NCL. Assays of the enzymatic activity of palmitoyl-protein thioesterase 1

(PPT1), the protein product of the gene *PPT1*, and tripeptidyl-peptidase 1 (TPP-1), the protein product of the gene *TPP1* are clinically available. Molecular genetic testing of the *PPT1*, *CLN3*, *CLN5*, *CLN6*, and *CLN8* genes is available on a clinical basis.

Management. Treatment is symptomatic. Seizures, insomnia, malnutrition, gastroesophageal reflux, pneumonia, sialorrhea, hyperactivity and behavior problems, depression, spasticity, Parkinson-like symptoms, and dystonia can be palliated. Antiepileptic drugs (AEDs) should be selected with caution. Benzodiazepines (especially clorazepate clorazepate) also improve weight and help control seizures and spasticity. Trihexyphenydil improves dystonia and sialorrhea. Doxepin improves sleep, mood, and gastric emptying. Individuals with swallowing problems or gastroesophageal reflux may benefit from placement of a gastric (G) tube. Avoidance of carbamazepine (CZP) and phenytoin is recommended as they may actually increase seizure activity and result in clinical deterioration.

Genetic counseling. The NCLs are inherited in an autosomal recessive manner with the exception of ANCL, which can be inherited in either an autosomal recessive or an autosomal dominant manner. The parents of a child with an autosomal recessive form of NCL are obligate heterozygotes, and, therefore, carry one mutant allele. Obligate heterozygotes have no symptoms. At conception, each sib of such a proband has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Carrier testing is available on a clinical basis if the parental mutations are known. Prenatal testing is possible in pregnancies at 25% risk if biochemical studies in the proband have revealed deficient activity of the enzyme PPT1 or TPP-1, or if disease-causing mutations in *PPT1*, *TPP1*, *CLN3*, *CLN5*, *CLN6*, or *CLN8* have been identified in the proband and parents.

Diagnosis

Clinical Diagnosis

Clinically, the NCLs are characterized by the following (Table 1):

- Seizures
- Progressive deterioration of cognition (dementia, speech abnormalities)
- Motor function impairment (involuntary movement, ataxia, spasticity) and vision loss that contribute to the developmental disabilities

NCL phenotypes often associated with progressive vision loss:

- Infantile neuronal ceroid-lipofuscinosis (INCL)
- Late-infantile neuronal ceroid-lipofuscinosis (LINCL) of the cLINCL, fLINCL, vLINCL, and tLINCL types
- Juvenile neuronal ceroid-lipofuscinosis (JNCL)

NCL phenotypes most commonly without vision loss:

- Adult neuronal ceroid-lipofuscinosis (ANCL)
- Northern epilepsy (NE)

The first presenting symptom may vary among NCL phenotypes, which are typically distinguished on the basis of age of onset and clinical manifestations.

Table 1. Distinguishing Clinical Features of the NCL Phenotypes and Their Associated Genes

Clinical Forms		Affected Individuals by Gene		Age of Onset	Presenting Symptoms
		% of Affected Individuals	Gene Symbol		
Infantile (INCL) (Santavuori-Haltia)		50%	*PPT1*	6-24 months	Cognitive/motor decline, visual loss, seizures [1, 2]
		50%		3-38 years	Chronic course: all of above and behavior abnormalities [1, 2, 3]
Late infantile (LINCL)	Classic (cLINCL) (Jansky-Bielschowsky) and others	8%	*PPT1*	2-8 years	Motor/cognitive decline, visual loss, seizures [3, 4, 5]
		80% [4]	*TPP1*		
		12% [5]	*CLN5, CLN6, CLN8*		
	Finnish variant (fLINCL)	94%	*CLN5*	4-7 years	Cognitive/motor decline, visual loss, seizures [3, 6]
	Gypsy/Indian, early-juvenile variant (vLINCL)	8-15%	*CLN6*	18 months - 8 years [7, 8]	Motor/cognitive decline, visual loss, seizures [3, 9, 10]
	Turkish variant (tLINCL)	Unknown	*CLN8*	3-7.5 years	Motor decline, visual loss, seizures [3, 8 9]
Juvenile (JNCL) (Batten disease, Spielmeyer-Vogt disease)		21%	PPT1	4-10 years	Visual loss, cognitive/motor decline, seizures [2, 3, 10]
		7%	TPP1		
72%	CLN3				
Northern epilepsy (NE) (progressive epilepsy with mental retardation [PEMR])		100%	*CLN8*	5-10 years	Cognitive decline, seizures, sometimes vision problems [9]
Adult (ANCL) (Kuf's disease)		Unknown	*PPT1* [11] *CLN3* [12] *CLN4* [9, 13]	15-50 years	Type A: Motor/ cognitive decline, seizures Type B: Behavior abnormalities, motor/cognitive decline

Wisniewski & Zhong 2001
1. Rapid progression
2. Das et al 1998
3. Subacute or chronic course [Ranta et al 2004]
4. Zhong et al 1998
5. Zhong, Moroziewicz et al 2000
6. Pineda-Trujillo et al 2005
7. Gao et al 2002
8. Teixeira et al 2003
9. Ranta et al 2004
10. Mole et al 1999, Mole et al 2004
11. van Diggelen et al 2001
12. Wisniewski & Zhong 2001
13. Berkovic et al 1988

Testing

Pathologic diagnosis. EM studies can be performed with 5-10 mL of heparinized whole blood (lymphocytes) or biopsies of skin, conjunctiva, or other tissues. The tissues are immediately immersed in 2.5% glutaraldehyde prepared in 0.1 mol/L phosphate buffer and changed to 0.1 mol/L phosphate buffer after two hours of fixation. EM studies (Table 2) show the presence of the following:

- Granular **osmophilic** deposits (GROD) in INCL

- Predominantly curvilinear profiles (CV) in LINCL
- Fingerprint (FP) in JNCL
- Mixed-type inclusions (CV, FP, and GROD), found in ANCL, CLN5, CLN6, CLN8, and in the late-infantile variant forms (fLINCL, vLINCL, tLINCL) [Wisniewski et al 1999, Goebel & Wisniewski 2004]

Note: The appearance of the pathologic inclusions also depends on the tissue examined.

Biochemical analyses of the deposits, available on a research basis only, have shown that subunit c of the mitochondrial ATP synthase complex is the major storage component of CV and FP. The GROD characteristic of INCL mostly consists of saposins A and D, also called sphingolipid activator proteins, or SAPs.

Enzyme activity. Two lysosomal enzymes (Table 2) have been identified as being deficient in the neuronal ceroid-lipofuscinoses in white blood cells, fibroblasts, and chorionic villi.

- **Palmitoyl-protein thioesterase 1 (PPT1)** encoded by the gene *PPT1*. A fluorimetric assay for PPT1 based on the fluorochrome 4-methylumbelliferone detects no PPT1 activity in leukocytes, fibroblasts, lymphoblasts, amniotic fluid cells, or chorionic villi in forms of NCL caused by mutations in the *PPT1* gene [Vesa et al 1995, Voznyi et al 1999].
- **Tripeptidyl-peptidase 1 (TPP-1)** encoded by the gene *TPP1*. Individuals with mutations of the *TPP1* gene usually have no enzymatic activity in leukocytes, fibroblasts, amniotic fluid cells, or chorionic villi [Junaid et al 1999].
- A carrier of a mutation in *PPT1* or *TPP1* typically has 50% of normal enzymatic activity in PPT1 or TPP-1, respectively [Das et al 1998; Zhong et al 1998; Sleat et al 1999; Zhong, Moroziewicz et al 2000].

Table 2. Electron Microscopic (EM) Findings and Enzyme Activity by NCL Genotype

Locus Name	Gene Symbol	Pathologic Diagnosis on EM	Lymphocytes	Enzyme Activity
CLN1	*PPT1*	GROD		PPT1 deficient
CLN2	*TPP1*	CV		TPP-1 deficient
CLN3	*CLN3*	FP	Vacuolated	Unknown
CLN4	NA	Mixed		
CLN5	*CLN5*	FP	Not vacuolated	
CLN6	*CLN6*	CV, FP, RL		
CLN8	*CLN8*	CV- or GROD-like structures		

EM = electron microscopy
GROD = granular osmophilic deposits
CV = curvilinear profiles
FP = fingerprint profiles
RL = rectilinear complex
Mixed = CV, FP, RL, GROD
PPT1 = palmitoyl-protein thioesterase 1
TPP-1 = tripeptidyl peptidase 1
NA = Not applicable

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US*

clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.

Molecular Genetic Testing—Genes. The genes *PPT1* (at locus CLN1), *TPP1* (at locus CLN2), *CLN3*, *CLN5*, *CLN6*, and *CLN8* are known to be associated with neuronal ceroid-lipofuscinosis [Mole et al 1999, Peltonen et al 2000, Mole et al 2001, NCL Mutation Database].

Other loci

- **CLN4.** The gene at the CLN4 locus has not been identified.
- **CLN7.** The phenotype previously thought to be associated with the CLN7 locus (the vLINC Turkish variant) now appears to be caused by mutations in both the *CLN8* gene [Mitchell et al 2001, Ranta et al 2004] and the *CLN6* gene [Siintola et al 2005].

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Predictive testing
- Carrier testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods (Table 3)

Targeted mutation analysis

- ***PPT1.*** The common mutations are c.364A>T (R122W) and c.451C>T (R151X) [Das et al 1998].
- ***TPP1.*** The common mutations are c.622C>T (R208X) and IVS5-1G>C (g. 3556G>C) [Zhong et al 1998, Sleat et al 1999].
- ***CLN3.*** The common mutation is a 1-kb deletion that removes exons 7-8 [Zhong et al 1998, Bodzioch et al 2000, Mole et al 2001].
- ***CLN5.*** The mutation c.1175_1176delA(p.Y392X) is observed in 94% of individuals with CLN5 who are of Finnish descent. The other mutation, c.225G>A(p.W75X), is rare [Savukoski et al 1998, Pineda-Trujillo et al 2005].
- ***CLN8.*** Individuals of Finnish origin are homozygous for the missense mutation c. 70C>G (R24G) [Ranta et al 2001].

Sequence analysis

- ***CLN5.*** Affected individuals to date have been mainly identified in Finland except for two in Sweden, two in the Netherlands, and three in Colombia [Pineda-Trujillo et al 2005].
- ***CLN6.*** Affected individuals have been identified in many countries, (e.g., Costa Rica, Pakistan, Portugal, Roma, USA) [Sharp et al 2003, Teixeira et al 2003].
- ***CLN8.*** About 2-4% of individuals are of non-Finnish heritage (e.g., Turkish, Italian, and US).

Table 3. Molecular Genetic Testing Used in NCL

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Rate [1]	Test Availability
PPT1	Targeted mutation analysis	c.364A>T (R122W)	Finnish:98% [2] Non-Finnish: 10% [3]	Clinical Testing
		R151X	60% [3]	
	Sequence analysis	*PPT1* sequence alterations	>98% [3]	
TPP1	Targeted mutation analysis	IVS5-IG>C, R208X	60-90% [4]	Clinical Testing
	Sequence analysis	*TPP1* sequence alterations	97% [4]	
CLN3	Deletion/duplication testing	1.02-kb deletion	96% [5]	Clinical Testing
	Sequence analysis	*CLN3* sequence alterations	>98% [5]	
CLN5	Targeted mutation analysis	p.Y392X	Finnish: 94% [6]	Clinical Testing
		p.W75X	Rare	
	Sequence analysis	*CLN5* sequence alterations	90-95%	
CLN6	Sequence analysis	*CLN6* sequence alterations	92% [7]	Clinical Testing
CLN8	Targeted mutation analysis	c.70C G (R24G)	Finnish: ~100% [8]	Clinical Testing
	Sequence analysis	*CLN8* sequence alterations	90-95%	

1. Percent of individuals with at least one identifiable mutation
2. PPT-deficient individuals with INCL [Vesa et al 1995, Bellizzi et al 2000]
3. PPT-deficient individuals [Das et al 1998, Hofmann et al 1999]
4. TPP-1 deficient individuals with LINCL [Zhong et al 1998; Hartikainen et al 1999; Lauronen et al 1999; Sleat et al 1999; Zhong, Wisniewski et al 2000]
5. Individuals with JNCL [Munroe et al 1997, Mao et al 2003, Mole et al 2004, Leman et al 2005]
6. Individuals with Finnish variant LINCL and the *CLN5* mutation (c.1175delAT) [Savukoski et al 1998]
7. Families with vLINCL with linkage to CLN6 locus [Gao et al 2002, Sharp et al 2003, Teixeira et al 2003]
8. Ranta et al 2001, Ranta et al 2004

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

The diagnostic testing strategy in a proband depends on the age of onset. See Figure 1.

1) If onset is before age two years:

- Assay the enzyme activity of PPT1.
- If PPT1 enzyme activity is deficient, perform molecular genetic testing of *PPT1* to identify the family-specific mutations for carrier detection among at-risk family members and for prenatal diagnosis.
- If PPT1 enzyme activity is normal, assay of the enzyme activity of TPP-1.
- If TPP-1 enzyme activity is deficient, perform molecular genetic testing of *TPP1* to identify the family-specific mutations for carrier detection among at-risk family members and for prenatal diagnosis.

2) If onset is between ages two and four years:

- Assay of the enzyme activity of TPP-1.

- If TPP-1 enzyme activity is deficient, perform molecular genetic testing of *TPP1* to identify the family-specific mutations for carrier detection among at-risk family members and for prenatal diagnosis.
- If TPP-1 enzyme activity is normal, assay of the enzyme activity of PPT1.
- If PPT1 enzyme activity is deficient, perform molecular genetic testing of *PPT1* to identify the family-specific mutations for carrier detection among at-risk family members and for prenatal diagnosis.
- If PPT1 enzyme activity is normal and a skin biopsy shows suggestive storage material by EM, consider molecular genetic testing of *CLN5*, *CLN6*, and *CLN8* [Mitchell et al 2001, Wisniewski & Zhong 2001].

3) If onset is between ages five and 12 years:

- Evaluate CBC for vacuolated lymphocytes.
- If vacuolated lymphocytes are present, perform molecular genetic testing of *CLN3*.
- If the common *CLN3* mutation is not present, assay the enzyme activity of PPT1.
- If PPT1 enzyme activity is deficient, perform molecular genetic testing of *PPT1* to identify the family-specific mutations for carrier detection among at-risk family members and for prenatal diagnosis.
- If the enzyme activity of PPT1 is normal, assay of the enzyme activity of TPP-1.
- If TPP-1 enzyme activity is deficient, perform molecular genetic testing of *TPP1* to identify the family-specific mutations for carrier detection among at-risk family members and for prenatal diagnosis.

4) If onset is after age 12 years (adulthood):

- A skin biopsy for EM in all adult individuals who are not of Finnish or Turkish ethnic background provides initial screening.
- If characteristic inclusions are present, PPT1 enzyme testing may be helpful, as adults have been identified with mutations in the *PPT1* gene.
- If the PPT1 is normal, *CLN8* gene testing may be pursued.
- Molecular genetic testing of *CLN8* is indicated in individuals who are of Finnish or Turkish heritage or in individuals who are not of Finnish or Turkish heritage but have CV- or GROD-like inclusions on EM.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in the *PPT1*, *TPP1*, *CLN3*, *CLN5*, *CLN6*, or *CLN8* genes.

Clinical Description

Natural History

All affected individuals have neurodegeneration, cognitive/motor dysfunction (dementia, involuntary movement, ataxia, spasticity), progressive vision loss, and seizures, resulting in developmental disabilities. With the exception of ANCL and NE, NCL phenotypes are rarely associated with progressive visual loss. A direct correlation between genotype and phenotype does not always exist (see Table 1 and Genotype-Phenotype Correlations); for example, individuals with mutations in *PPT1* can present with four different phenotypes (INCL, LINCL, JNCL, and ANCL). Nonetheless, describing the NCLs by phenotype is clinically useful for

diagnosis and prognosis (Table 1). Classic INCL presents acutely between six months and 24 months of age, late infantile between two and four years, juvenile between four and five years, and adult onset after 15 years of age [Das et al 1998;Wisniewski, Zhong, Kaczmarski, Kaczmarski, Kida et al 1998;Wisniewski et al 1999;van Diggelen et al 2001;Wisniewski et al 2001].

Infantile NCL (INCL, Santavuori-Haltia)—Classic INCL usually presents acutely between six and 24 months of age. Onset before six months and after two years of age also occurs [Das et al 1998; Wisniewski, Zhong, Kaczmarski, Kaczmarski, Kida et al 1998; Wisniewski et al 1999; van Diggelen et al 2001; Wisniewski et al 2001]. Initial signs include delayed development, myoclonic jerks, and/or seizures. In one series of 21 affected children, the early signs of INCL were deceleration of head growth and specific electroencephalographic (EEG) changes (from 13 months of age) [Vanhanen et al 1995]. In a study of eight newly diagnosed children with INCL (ages 15-27 months), mild to moderate deterioration of mental ability was observed in all [Riikonen et al 2000]. The children had speech problems and lost interest in playing and in toys; however, they remained interested in their surroundings. They had moderate motor dysfunction.

Retinal blindness and seizures are evident by two years of age. The ERG (electroretinogram) is unrecordable by age four years.

Psychomotor abilities deteriorate rapidly. Children fail to thrive and develop microcephaly [Santavuori 1988]. Life expectancy varies from two to 53 or more years.

MRI findings are variable cerebral atrophy, strong thalamic hypointensity in the white matter and basal ganglia, and thin, hyperintense, periventricular high-signal rims of white matter [Vanhanen et al 1995, Riikonen et al 2000]. The progressive diffuse brain atrophy seen on MRI in individuals with INCL during the first four years of life then stabilizes [Vanhanen et al 1995]. If the onset occurs after two years of age, the changes in the brain are similar to those seen in other forms of NCL [Wisniewski, personal observation].

Late-Infantile NCL (LINCL)—Classic late-infantile NCL (Jansky-Bielschowsky). The first symptoms of LINCL usually appear between two to four years of age, usually starting with epilepsy. Myoclonus is most characteristic, but generalized tonic-clonic seizures or absence (partial or secondary generalized) seizures may be observed.

Regression of developmental milestones becomes evident soon thereafter, followed by dementia, ataxia, and extrapyramidal and pyramidal signs.

Visual impairment appears at four to six years of age and rapidly progresses to blindness.

Affected children are usually bedridden before age six years. Children with LINCL usually develop severe disabilities and have considerable nursing care needs by mid-childhood. Life expectancy varies from six to greater than 40 years of age [Wisniewski, Zhong, Kaczmarski, Kaczmarski, Kida et al 1998; Wisniewski et al 1999].

Electroencephalogram (EEG) shows spikes in the occipital region in response to photic stimulation at 1-2 Hz.

Electroretinogram (ERG) is usually abnormal at presentation and becomes undetectable soon thereafter. On occasion, the ERG may be normal at presentation [Weleber 1998].

Visual evoked potentials (VEPs) are enhanced for a long period and diminish in the final stage of the disease.

MRI shows progressive cerebral and cerebellar atrophy with normal basal ganglia and thalami.

Variants of late-infantile NCL

- Finnish variant late-infantile NCL (fLINCL). The onset of disease is later (usually age 4.5-7 years). Life expectancy is between 13 and 35 years.
- Gypsy/Indian variant late-infantile NCL (vLINCL). Visual loss and seizures may be the initial signs and symptoms. In children with onset after age four years, epilepsy, ataxia, and myoclonus may be the initial features.
- Turkish variant late-infantile NCL (tLINCL). Onset is usually age two to six years [Sharp et al 2003].

Juvenile NCL (JNCL)—Classic juvenile NCL (Batten Disease, Spielmeyer-Vogt). Onset is usually between four and ten years of age (mean age ~5f years).

Rapidly progressing visual loss is often the first clinical sign of the disease. Children become totally blind within two to four years of the onset of visual loss [Spalton et al 1980]. Visual loss is often the only sign for two to five years. Ophthalmologic examination early in the course of the disorder may reveal macular changes only; gradually, typical signs of pan retinal degeneration develop: pigmentary changes in the retinal periphery, vascular attenuation, and optic nerve pallor. The electroretinogram (ERG) shows loss of photoreceptor function early in the course of the disorder [Weleber 1998].

Epilepsy with generalized tonic-clonic seizures, complex-partial seizures, or myoclonic seizures typically appears between ages five and 18 years. The EEG shows disorganization and spike-and-slow-wave complexes.

Little variation is observed in the visual symptoms and seizures, but variation is observed in the progression of motor and mental deterioration [Munroe et al 1996]. Speech disturbances (festinating stuttering, often mislabeled as echolalia) and slow decline in cognition occur after age eight to 14 years.

Behavioral problems, extrapyramidal signs, and sleep disturbance occur in the second decade. Backman et al (2005) found that some individuals with JNCl experience multiple psychiatric problems, such as disturbed thoughts, attention problems, somatic complaints, and aggressive behavior. Depression was uncommon.

Most individuals with classic JNCL live until the late teens or early 20's; some may live into their 30's.

CT and MRI reveal cerebral, and to a lesser degree, cerebellar atrophy in the later stages (after age 15 years).

Atypical JNCL. Individuals with atypical JNCL are compound heterozygotes for *CLN3* mutations with the 1-kb deletion and a point mutation, G295K [Wisniewski, Zhong, Kaczmarski, Kaczmarski, Sklower-Brooks et al 1998]. All have visual failure, but vary in the severity of seizures and other neurologic complications.

In one family with two affected children, progressive visual loss began around age five years with blindness after age 12 years. One sib developed cognitive/motor dysfunction and epilepsy after age 40 years. In another instance, an individual who had visual loss from age six years developed epilepsy at age 19 and polyneuropathy at age 20 years [Lauronen et al 1999]. The

cause of these phenotypic differences is unknown. Other individuals with atypical JNCL with a protracted course and with pigmentary retinopathy have not been studied molecularly.

Adult NCL (ANCL, Kuf's Disease)—Initial signs and symptoms usually appear around age 30 years, with death occurring about ten years later. Symptoms may appear as early as age 11 years. Ophthalmologic studies are normal.

Two major clinical phenotypes exist [Berkovic et al 1988]:

- **Type A,** characterized by progressive myoclonic epilepsy with dementia, ataxia, and late-occurring pyramidal and extrapyramidal signs. Seizures are often uncontrollable.
- **Type B,** characterized by behavior abnormalities and dementia, which may be associated with motor dysfunction, ataxia, extrapyramidal signs, and suprabulbar signs. Ivan et al (2005) described an African-American with type B adult NCL.

In the presenile form, with onset after 50 years of age, dementia, cognitive decline, motor dysfunction, seizures, and suprabulbar (brain stem) signs with mixed inclusion at EM level are present [Constantinidis et al 1992].

Other forms of adult-onset NCL with GORD observed on EM are an autosomal dominant form without deficient PTT1 enzyme activity [Nijssen et al 2003, Burneo et al 2003] and an autosomal recessive form with deficient PPT1 enzyme activity [van Diggelen et al 2001].

Northern Epilepsy [NE, Progressive Epilepsy with Mental Retardation (PEMR)]—Northern epilepsy is characterized by epilepsy with tonic-clonic or complex-partial seizures, mental deterioration, and motor dysfunction. NE has been described in individuals with late-infantile, juvenile, and adult onset.

Visual problems similar to those seen in variant late infantile NCL can occur.

The frequency of the epileptic manifestations decreases after puberty, but slow cognitive decline continues throughout life. Some individuals have lived beyond 60 years of age.

Genotype-Phenotype Correlations

Mutations in *PPT1* can be associated with infantile, late-infantile, juvenile, and adult onset of NCL [Wisniewski et al 1992; Das et al 1998; Mitchison et al 1998; Wisniewski, Connell et al 1998; Hofmann et al 1999; Voznyi et al 1999; Wisniewski et al 1999; Zhong, Moroziewicz et al 2000; van Diggelen et al 2001]. The later onset of clinical symptoms most likely results from the presence of residual PPT-1 enzyme activity.

A genotype/phenotype correlation exists in those INCL forms in which the mutations in the following genes are known: *PPT1*, *TPP1*, *CLN3*, *CLN5*, *CLN6*, and *CLN8*. The common mutations usually have typical presentation, while the uncommon mutations have atypical presentations [Das et al 1998; Munroe et al 1998; Zhong et al 1998; Hartikainen et al 1999; Mole et al 1999; Sleat et al 1999; Wisniewski et al 2000; Zhong, Wisniewski et al 2000; Gao et al 2002; Teixeira et al 2003].

Prevalence

Neuronal ceroid-lipofuscinoses (NCLs) represent the most common hereditary progressive neurodegenerative disease with a prevalence of 1:25,000.

The incidence of NCL ranges in different countries from 0.1 to 7 per 100,000 live births [Santavuori 1988, Uvebrant & Hagberg 1997].

- About half of the reported cases of **INCL** have been diagnosed in Finland, where the disease incidence is 1:20,000.
- The incidence of **cLINCL** is about 0.36 - 0.46 per 100,000 live births [Claussen et al 1992, Cardona & Rosati 1995].
- *CLN6*-related NCL has been observed in Finland, Pakistan, Romanian Gypsy families, the Czech Republic, and Portugal [Teixeira et al 2003].
- The incidence of the **juvenile NCL** varies in different countries, e.g., from 7.0 per 100,000 live births in Iceland [Uvebrant & Hagberg 1997] to 0.71 per 100,000 live births in West Germany [Claussen et al 1992].

For several genes, carrier frequency in the Finnish population has been estimated (Table 4).

Table 4. Carrier Frequency of NCL Genes in the Finnish Population

Gene Symbol	Carrier Frequency	Reference
PPT1	1:71	
CLN5	1:24	Savukoski et al 1998
CLN8	1:135	Ranta et al 2001

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Infantile NCL. Other progressive neurologic diseases with onset from birth to two years of age need to be considered. These include: Tay-Sachs disease, Krabbe disease, Canavan disease, Rett syndrome, metachromatic, infantile form of adrenoleukodystrophy (see Peroxisomal biogenesis disorders, Zellweger syndrome spectrum), Neimann-Pick types A and B, and Leigh syndrome (see also Mitochondrial Disorders Overview). While some of these disorders are associated with cortical blindness, none includes retinal dystrophy.

Late-infantile NCL. Other progressive neurologic diseases with onset from two to four years of age need to be considered. These include: other lysosomal storage disorders, mitochondrial disease, and leukodystrophies.

Juvenile NCL. In the initial stage when individuals present with visual loss, retinitis pigmentosa (RP) or cone-rod dystrophy may be considered. The ophthalmologic involvement of JNCL differs from classic RP in that the vision loss in JNCL is typically central at first (rather than peripheral) and rapidly progressive, with total blindness occurring in one to two years [Spalton et al 1980, Weleber 1998]. In contrast, RP is indolent and progresses slowly over decades. Other disorders in which a cone-rod retinal dystrophy occurs are Bardet-Biedl syndrome, Joubert syndrome, juvenile nephronophthisis, and Alstrom syndrome, all of which can be distinguished from JNCL by clinical findings.

Behavioral changes may be seen in late-onset lysosomal storage diseases such as hexosaminidase A deficiency, X-linked adrenoleukodystrophy, and some of the organic acidemias.

Northern epilepsy (NE). NE needs to be distinguished from other neurological conditions with seizures [Zupanc & Legros 2004]. Myclonus is not feature of NE, and thus a large number of disorders with myoclonic seizures and mental retardation can be excluded. The clinical course of NE differs from Landau-Kleffner syndrome, Rasmussen syndrome, and epilepsy with electric status epilepticus during slow sleep. Tuberous sclerosis complex and the Sturge-

Weber syndrome can be distinguished from NE on the basis of clinical and neuroradiologic features. Lack of pyramidal or extrapyramidal signs and lack of cerebellar ataxia distinguishes NE from degenerative disorders such as juvenile Huntington disease, PKAN (previously called Hallervorden-Spatz syndrome), juvenile GM2 gangliosidosis (see Hexosimindase A deficiency), Niemann-Pick disease type C, giant axonal neuropathy, or neuronal intranuclear inclusion disease [Hirvasniemi 1996].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with neuronal ceroid-lipofuscinosis (NCL), the following are recommended:

- Neurologic examination
- Ophthalmologic examination
- Developmental assessment

Treatment of Manifestations

Symptomatic treatment can sometimes be successful in mitigating the manifestations of NCL. Seizures, insomnia, malnutrition, gastroesophageal reflux, pneumonia, sialorrhea, hyperactivity and behavior problems, depression, spasticity, Parkinson-like symptoms, and dystonia can be palliated.

Seizures. Antiepileptic drugs (AEDs) should be selected with caution. The stage of the disease, age of the affected individual, and quality of life are important to consider in the evaluation of the effectiveness of AEDs.

Lamotrigine (LTG) had a favorable effect on 23/28 individuals, 13/19 being continued on monotherapy with 100% control, compared to 70% control for those receiving VPA, 60% control for VPA-CZP, and 60% control for LTG-CZP [Aberg et al 1997, Aberg et al 1999, Aberg et al 2000].

Other new AEDs such as Keppra®, Trileptal®, and Topamax® could also be beneficial [Author, personal experience].

Carboxyl anticonvulsant medication has been successful in treating individuals with NCL [Zupanc & Legros 2004].

Cystagon™ has been used in the treatment of individuals with CLN1 [Zhang et al 2001; Wisniewski et al, personal observation].

Other. Benzodiazepines (especially clorazepate) also improve weight and control seizures and spasticity.

Trihexyphenydil improves dystonia and sialorrhea.

Doxepin improves sleep, mood, and gastric emptying.

Individual with swallowing problems or gastroesophageal reflux may benefit from placement of a gastric (G) tube.

Agents/Circumstances to Avoid

Carbamazepine (CZP) and phenytoin may actually increase seizure activity in NCL and may be associated with clinical deterioration [Philippart 1988, Philippart et al 1994]. In a series of 60 individuals with JNCL, valproic acid (VPA) was withdrawn in 20% and clonazepam (CZP) in 16% because of side effects [Aberg et al 2000]. Half of the 28 individuals receiving VPA had sleep disturbances or excessive sedation. CZP stimulates salivation and respiratory secretions, increasing the risk of pneumonia in bedridden individuals, many of whom have gastroesophageal reflux. CZP is a sedative and can cause behavior disturbances.

Therapies Under Investigation

With identification of the genes for most forms of NCL, the molecular mechanisms of the mutations are being studied as a first step in devising rational therapies [Zhang et al 2001].

Crystal et al (2004) initiated gene therapy for children with LINCL caused by mutations in *CLN2*. They administered a replication-deficient adeno-associated virus (AAV) vector expressing human *CLN2* cDNA directly into the brains of children with either severe or moderate LINCL in an attempt to produce sufficient amounts of TPP-1 to prevent further loss of neurons and hence limit disease progression. The research is ongoing.

Stem cell therapy for CLN1 and CLN2 is in progress [Author, personal communication].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Psychotropic medications are not helpful in the treatment of the psychiatric manifestations of JNCl.

The excessive peroxidation known to be a secondary manifestation of NCL can be palliated to some extent by administration alpha-tocopherol (vitamin E) and selenium [Santavuori & Moren 1977, Maertens et al 1995]. Selenium supplementation is appropriate if selenium deficiency is a concern (as it is in the Finnish diet), but it has not been demonstrated to be of value in individuals with NCL in the United States.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

The NCLs are inherited in an autosomal recessive manner with the exception of adult NCL, which can be inherited in either an autosomal recessive or an autosomal dominant manner [Boehme et al 1971; Berkovic et al 1988; Philippart 1988; Zhong, Wisniewski et al 2000; Constantinidis et al 1992].

Risk To Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes are asymptomatic.

Sibs of a proband

- At conception, each sib of a proband has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes are asymptomatic.

Offspring of a proband

- Probands with INCL, LINCL, and classic JNCL do not reproduce.
- Very rarely, individuals with atypical JNCL reproduce [Wisniewski, Zhong, Kaczmarski, Kaczmarski, Sklower-Brooks et al 1998]. The offspring of an individual with NCL are obligate heterozygotes (carriers) for a mutant allele causing NCL.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

- Carrier testing is available on a clinical basis once the mutation(s) in *PPT1*, *TPP1*, *CLN3*, *CLN5*, *CLN6*, and *CLN8* has/have been identified in the proband.
- Carrier testing is available by assaying enzyme activity for palmitoyl-protein thioesterase 1 and tripeptidyl-peptidase I [Junaid et al 1999; Zhong, Wisniewski et al 2000; van Diggelen et al 2001].

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA particularly when the gene responsible has not yet been identified, not all disease-causing mutations have been elucidated, or testing is available on a research or linkage basis only. See 

for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal testing is possible in pregnancies at 25% risk if biochemical studies in the proband have revealed deficient activity of the enzyme PPT1 [de Vries et al 1999] or the enzyme TPP-1, or if disease-causing mutations in *PPT1*, *TPP1*, *CLN3*, *CLN5*, *CLN6*, or *CLN8* have been identified in the proband and parents [Chow et al 1993, Rapola et al 1999]. In these instances, testing is performed on fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation or amniocentesis usually performed at about 15-18 weeks' gestation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Prior to the availability of enzyme analysis and DNA-based testing, prenatal testing was based on demonstration of characteristic inclusion bodies by EM from fetal cells obtained by CVS or amniocentesis. Such testing is unreliable because inclusions are not detectable until the second trimester in LINCL and JNCL [MacLeod et al 1988, Munroe et al 1996, Lake et al 1998, Rapola et al 1999]. However, inclusions are reported to be detectable in INCL at as early as eight weeks' gestation [Rapola et al 1990, Rapola et al 1993].

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Neuronal Ceroid-Lipofuscinosis

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
CLN1	*PPT1*	1p32	Palmitoyl-protein thioesterase 1
CLN2	*TPP1*	11p15.5	Tripeptidyl-peptidase I
CLN3	*CLN3*	16p12.1	Protein CLN3
CLN4	Unknown	Unknown	Unknown
CLN5	*CLN5*	13q21.1-q32	Ceroid-lipofuscinosis neuronal protein 5
CLN6	*CLN6*	15q21-q23	Ceroid-lipofuscinosis neuronal protein 6
CLN8	*CLN8*	8pter-p22	Protein CLN8

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Neuronal Ceroid-Lipofuscinosis

204200	CEROID LIPOFUSCINOSIS, NEURONAL 3, JUVENILE; CLN3
204300	CEROID LIPOFUSCINOSIS, NEURONAL 4; CLN4
204500	CEROID LIPOFUSCINOSIS, NEURONAL 2, LATE INFANTILE; CLN2
256730	CEROID LIPOFUSCINOSIS, NEURONAL 1, INFANTILE; CLN1
256731	CEROID LIPOFUSCINOSIS, NEURONAL 5; CLN5
600143	CEROID LIPOFUSCINOSIS, NEURONAL 8; CLN8
600722	PALMITOYL-PROTEIN THIOESTERASE 1; PPT1
601780	CEROID LIPOFUSCINOSIS, NEURONAL, LATE-INFANTILE, VARIANT
606725	CLN6 GENE; CLN6
607042	CLN3 GENE; CLN3
607837	CLN8 GENE; CLN8
607998	CLN2 GENE; CLN2
608102	CLN5 GENE; CLN5

Table C. Genomic Databases for Neuronal Ceroid-Lipofuscinosis

Locus Name	Gene Symbol	Locus Specific	Entrez Gene	HGMD
CLN1	*PPT1*	PPT1	5538 (MIM No. 600722)	PPT1
CLN2	*TPP1*		1200 (MIM No. 607998)	CLN2
CLN3	*CLN3*	CLN3	1201 (MIM No. 607042)	CLN3
CLN4	Unknown		1202 (MIM No. 204300)	
CLN5	*CLN5*	CLN5	1203 (MIM No. 608102)	CLN5
CLN6	*CLN6*	CLN6	54982 (MIM No. 606725)	CLN6
CLN8	*CLN8*	CLN8	2055 (MIM No. 607837)	CLN8

For a description of the genomic databases listed, click here.
Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Notwithstanding the well-documented clinicopathologic and genetic heterogeneity of NCLs, both human and animal forms of the disorders can be divided into two major groups based on the nature of the material accumulated in lysosomes: 1) those characterized by the prominent storage of saposins (SAPs) A and D; and 2) those showing the predominance of subunit c of mitochondrial ATP synthase accumulation [Palmer et al 1997]. In addition to proteins, storage material in NCLs contains other components such as lipids, metals, dolichyl pyrophosphoryl oligosaccharides, and lipid thioesters [Dawson et al 1997].

The relation between genetic defects associated with the major NCL forms, the accumulation of storage material, and tissue dysfunction and/or damage is still unknown. Furthermore, all individuals with NCLs manifest lysosomal storage in many tissues and organs, but severe degeneration and cell loss involve mostly neuronal cells. Thus, it appears that NCL proteins may be critical only for the metabolism of neurons. It is uncertain whether this phenomenon is caused by the specific metabolic requirements of a neuron as a postmitotic cell or results from the properties of NCL proteins per se.

The spectrum of mutations present in NCL have been reviewed [Mole et al 2001, Wisniewski et al 2001, Goebel & Wisniewski 2004].

PPT1

Normal allelic variants: The gene has nine exons spanning 25 kd.

Pathologic allelic variants: More than 40 mutations of *PPT1* are known. The common mutations are c.364A>T (R122W) and c.451C>T (R151X); the others are uncommon or private mutations.

Normal gene product: PPT1 is a globular enzyme consisting of six parallel βstrands alternating with αhelices organized in a structure known as the α/β hydrolast fold typical of lipases. A large insertion between β6 and β7 (residues 140-223) forms a second domain that forms most of the fatty acid-binding site. Catalytic active site residues are S115, D233, and H289. PPT1 is a housekeeping enzyme present in the lysosomes of many tissues. It removes long-chain fatty acids, usually palmitate, from cystine residues.

Based on the results of crystallographic and molecular modeling studies of recombinant bovine PPT-1 enzyme, a mechanism has been hypothesized to explain the milder INCL phenotype in individuals with *PPT1* mutations who retain low-level thioresterase activity [Bellizzi et al 2000].

TPP1

Normal allelic variants: *TPP1* has 13 exons.

Pathologic allelic variants: More than 50 mutations of *TPP1* are known. The common mutations are c.622C>T (R208X) and IVS5-1G>C (g.3556G>C); the others are uncommon or private mutations.

Normal gene product: TPP-1 consists of 365 amino acids. It is a lysosomal serine-carboxyl peptidase that sequentially removes N-terminal tripeptides from small peptides, including several peptide hormones.

Abnormal gene product: Wujek et al (2004) and Golabek et al (2003) found that TPP-1 has five potential N-glycosylation sites at Asn residues 210,222, 286,313, and 443. They demonstrated that TPP-1 in vivo utilizes all five N-glycosylation sites. Elimination of one of these sites, at N286, affected the folding of the enzyme. Steinfeld et al (2004) and Tsiakas et al (2004) made similar observations.

Kopan et al (2004) reported that the degradation of the neuropeptide, neuromedin B, by mouse brain cells is restricted to lysosomes and that the pattern of degradation products is consistent with a predominant role for TPP-1. Neuromedin B is degraded by a similar pathway in cultured human fibroblasts. The inability of cells from individuals with mutations in *CLN2*f to degrade neuromedin B and other neuropeptides may contribute to the pathogenesis of the disease.

CLN3

Normal allelic variants: The gene contains 15 exons.

Pathologic allelic variants: More than 30 mutations are presently known. The common mutation is a 1-kb deletion that removes exons 7-8; the others are uncommon or private mutations [Zhong et al 1998, Bodzioch et al 2000, Mole et al 2001, Leman et al 2005].

Normal gene product: The protein has 438 AA of unknown function. Phillips et al (2005) review the approaches used to examine the structure, trafficking, and localization of CLN3. It is concluded that CLN3 is most likely to be present in the lysosomal/endosomal membrane. In addition, CLN3 undergoes post-translational modification and is trafficked through the endoplasmic reticulum and Golgi apparatus.

Abnormal gene product: Although the function of CLN3 remains elusive, it is apparent that genetic alterations in CLN3 may have a direct effect on lysosomal function [Phillips et al 2005].

CLN5

Normal allelic variants: The gene contains four exons.

Pathologic allelic variants: Five mutations and one polymorphism are known. All affected individuals identified to date have been in Finland except for a few in Sweden, the Netherlands, and Colombia [Pineda-Trujillo et al 2005].

Normal gene product: The normal protein has 407 amino acids.

Abnormal gene product: CLN5 is a transmembrane protein of unknown function.

CLN6

Normal allelic variants: The gene has seven exons.

Pathologic allelic variants: To date, 18 mutations have been identified, including missense and nonsense mutations, small deletions or insertions, and two splice site mutations. Mutation E72X is significantly more common in persons from Costa Rica. The 1-bp insertion c.316insC is associated with families from Pakistan; 1154del may be common in Portugal. A group of Roma Gypsy families from the Czech Republic share two disease-associated haplotypes, one of which is also present in Pakistani family.

Normal gene product: This transmembrane protein of unknown function resides in the endoplasmic reticulum (ER) [Mole et al 2004].

Abnormal gene product: Heine et al (2004) discuss the defective endoplasmic reticulum resulting from *CLN6* mutations.

CLN7. The phenotype thought to be associated with the CLN7 locus appears to be caused by mutations in *CLN8* [Mitchell et al 2001] and *CLN6* [Siintola et al 2005]. The genetic background of the true Turkish vLINCL, CLN7, remains to be defined.

CLN8

Normal allelic variants: The gene has three exons. Two polymorphisms have been identified.

Pathologic allelic variants: All 22 cases published to date are individuals of Finnish origin who are homozygous for the missense mutation c.70C>G (R24G) [Ranta et al 2001].

Normal gene product: This protein of 286 amino acids is localized to the ER and ER Golgi intermediate compartment.

Abnormal gene product: Unknown

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Batten Disease Support and Research Association (BDSRA)
120 Humphries Drive Suite 2
Reynoldsburg OH 43068
Phone: 800-448-4570; 740-927-4298
Email: BDSRA1@bdsra.org
www.bdsra.org

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
Crewe CW2 6BG
United Kingdom
Phone: (+44) 0870 7700 326
Fax: (+44) 0870 7700 327
Email: steve@climb.org.uk
www.climb.org.uk

Children's Brain Diseases Foundation
350 Parnassus Avenue Suite 900
San Francisco CA 94117
Phone: 415-566-5402
Fax: 415-863-3452

National Tay-Sachs and Allied Diseases Association, Inc
2001 Beacon Street Suite 204
Brighton MA 02135
Phone: 800-906-8723; 617-277-4463
Fax: 617-277-0134
Email: info@ntsad.org
www.ntsad.org

Batten Disease Registry
Contact: K. Wisniewski M.D., Ph.D.
Department of Neurobiology
NYS Institute for Basic Research
1050 Forest Hill Road
Staten Island NY 10314
Phone: 718-494-0600/5202
Fax: 718-698-3803
Email: BattenKW@aol.com

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Author Notes

*Krystyna Wisniewski was a nationally and internationally known pediatric neurologist and neuropathologist/neurobiologist. She was the author or co-author of more than 300 scientific publications and numerous books and book chapters in the field of progressive neurogenetic diseases and mental retardation/developmental disabilities. She co-founded the International Registry for Batten Disease at the Institute for Basic Research (Staten Island, NY), where she worked for three decades. Dr. Wisniewski died May 31, 2008 following an illness.

Revision History

- 17 May 2006 (me) Comprehensive update posted to live Web site
- 15 August 2005 (bp) Revision: sequence analysis for CLN5 and CLN8 clinically available
- 19 November 2004 (bp) Revision: *CLN5* and *CLN8* sequence analysis
- 27 January 2004 (me) Comprehensive update posted to live Web site

- 12 June 2003 (kw) Revision: testing
- 10 October 2001 (me) Review posted to live Web site
- 20 February 2001 (kw) Original submission

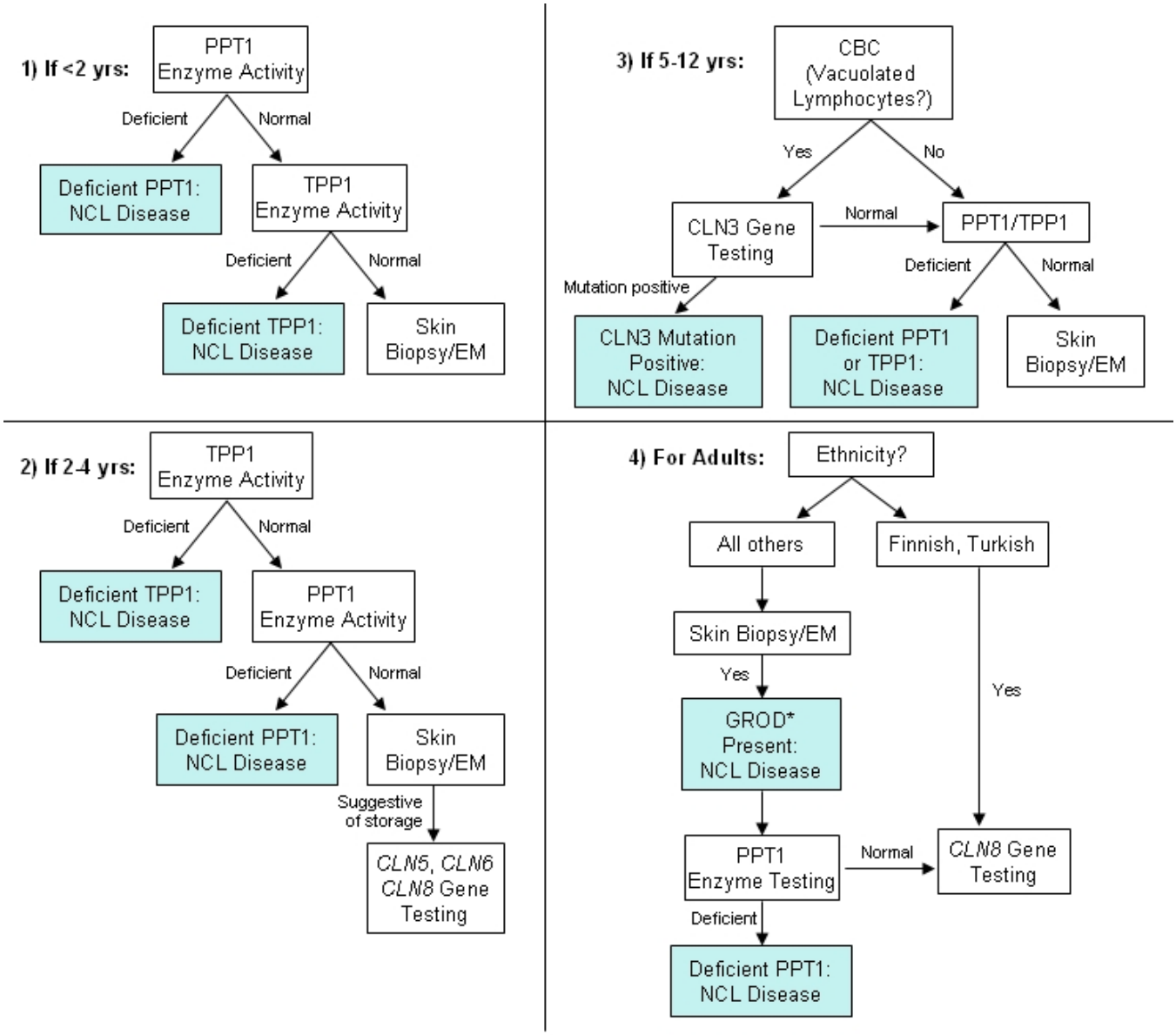

Figure 1. Diagnostic algorithm for NCL based on the presenting age of the individual: When attempting to diagnose NCL, the age of onset can help direct testing. (Adapted from Beaudoin et al 2004 with permission)
CBC = complete blood count
GROD = granular osmophilic deposits