

Batten Disease

Neuronal Ceroid Lipofuscinosis

An Easy to Understand Guide

A Publication of the Batten Disease Support and Research Association

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Introduction

Batten Disease is the common name for a group of illnesses whose medical term/name is Neuronal Ceroid Lipofuscinosis (NCL). When the NCLs are discussed they are often referred to as forms of Batten Disease. In fact, they all have the same basic cause, same progression and same outcome. However, they are differentiated by age of onset, rapidity of progression and are the result of defects of different genes.

Throughout this document whenever a word is shown in **BOLD**, it can be found in the glossary and the terms Batten Disease and NCL will be used interchangeably.

This document is meant to be a source of information in layman's language and is not intended to be a definitive treatise on Batten Disease.

Precise scientific and medical information is available through the Batten Disease Support and Research Association and its Medical/Scientific Advisory Group and other sources.

Table of Contents

What is Batten Disease ?.....	1
History of Batten Disease	2
Forms of Batten Disease	3
What causes Batten Disease ?.....	5
Batten Disease research	7
Additional chart of forms of Batten Disease.....	9
Infantile Batten Disease	10
“Classic” Late Infantile.....	12
Juvenile Batten Disease.....	13
“Variant” Late Infantile	15
Finnish and Turkish Late Infantile.....	16
Northern Epilepsy	17
Adult Onset – Kufs Disease.....	18
Adult Onset – Parry Disease	19
Inclusion body/deposit pictures	20
Autosomal recessive inheritance.....	21
Batten Disease and Ophthalmology.....	27
Batten Disease and Seizures	30
DNA testing	35
Batten Disease Support and Research Association.....	36
National Batten Disease Registry	39
Glossary	40

What is Batten Disease?

Batten Disease is the common, catch-all name for Neuronal Ceroid Lipofuscinosis (NCL). The NCLs are in actuality a group of disorders but because the name is so difficult to pronounce the name Batten Disease has been adopted to indicate all of them together. They all have a common denominator and that is that they are also known as lysosomal storage disorders and have the same basic cause, progression and outcome.

Being lysosomal storage means that the lysosome, a small membrane bound structure or compartment found in most cells stores material that it would normally recycle. The lysosome contains **enzymes** whose job it is to break down other **proteins** for recycling or elimination. A missing lysosomal protein can cause a build of proteins.

Who is affected by Batten Disease ?

Children are affected with this disease, although there is a rare form of NCL that affects adults. Depending upon the type or form of Batten Disease the age of onset will vary. Generally speaking children are born well and reach many developmental goals in the first few years of life. Onset is defined as the time when the illness manifests itself. Onset may be very subtle in the beginning. Initial symptoms may be any of three, i.e. seizures, diminishing vision, or “clumsiness”. All of these are common in many diseases/disorders and because Batten Disease is so rare initial diagnosis may be incorrect. Those initial diagnoses often include epilepsy, retinitis pigmentosa, macular degeneration and developmentally delayed or mentally retarded. However, as the disease progresses it soon becomes obvious that these simplistic diagnoses are incorrect and the hunt for the real disease begins. Batten Disease is, at best, extremely difficult to diagnose.

Over time, affected children suffer mental impairment, worsening seizures, and progressive loss of sight and motor skills. Eventually, children with Batten Disease become blind, bedridden, and unable to communicate. Batten Disease is always fatal. The illness does not affect any two children exactly the same. In general, it can be said that the children will have seizures, lose their vision, etc. However, the disease knows no timetable and it can not be predicted when these things will occur, nor can the severity of certain aspects of the disease. The same is true concerning the age at death.

Batten Disease is not contagious or, at this time, preventable.

History of Neuronal Ceroid Lipofuscinosis

The first probable instances of this condition were reported in 1826 by Dr. Christian Stengel in a Norwegian medical journal, who described 4 affected siblings in a small mining community in Norway. Although no pathological studies were performed on these children the clinical descriptions are so succinct that the diagnosis of the Spielmeyer - Sjogren (juvenile) type is fully justified.

More fundamental observations were reported by F. E. Batten in 1903, and by Vogt in 1905, who performed extensive clinicopathological studies on several families. Retrospectively, these papers disclose that the authors grouped together different types of the syndrome. Furthermore Batten, at least for some time, insisted that the condition that he described was distinctly different from Tay-Sachs Disease, the prototype of a neuronal lysosomal disorder now identified as GM2-Gangliosidosis type A. Around the same time, Spielmeyer reported detailed studies on three siblings, suffering from the Spielmeyer-Sjogren (juvenile) type, which led him to the very firm statement that this malady is not related to Tay-Sachs Disease. Subsequently, however, the pathomorphological studies of Schaffer made these authors change their minds to the extent that they reclassified their respective observations as variants of Tay-Sachs Disease, which caused confusion, lasting about 50 years.

In 1913-14 M. Bielschowsky delineated the Late Infantile form of NCL. However, all forms were still thought to belong in the group of "familial amaurotic idiocies", of which, Tay-Sachs was the prototype.

In 1931, the Swedish psychiatrist and geneticist, Torben Sjogren, presented 115 cases with extensive clinical and genetic documentation and came to the conclusion that the disease which we now call the Spielmeyer-Sjogren (juvenile) type is genetically separate from Tay Sachs.

Departing from the careful morphological observations of Spielmeyer, Hurst, and Sjovall and Ericsson, Zeman and Alpert made a determined effort to document the previously suggested pigmentary nature of the neuronal deposits in certain types of storage disorders. Simultaneously, Terry and Korey and Svennerholm demonstrated a specific ultrastructure and biochemistry for Tay Sachs Disease, and these developments led to the distinct identification and also separation of the NCLs from Tay Sachs Disease by Zeman and Donahue. At that time, it was proposed that the Late Infantile (Jansky-Bielschowsky), the Juvenile (Spielmeyer-Vogt), and the adult form (Kufs) were quite different from Tay-Sachs Disease with respect to chemical pathology and ultrastructure and also different from other forms of sphingolipidoses.

Subsequently, it was shown by Santavuori and Haltia that an infantile form of NCL exists, which Zeman and Dyken had included with the Jansky-Bielschowsky type.

What are the forms of NCL/Batten Disease?

When we discuss the different NCLs we often refer to them as “forms” of Batten Disease in order to simplify understanding. The chart below will act as a reference that can be used in the later descriptions of the different “forms” of Batten Disease.

Form	Name	Age of Onset	Gene Known ?	Gene designation
Infantile	Haltia-Santavuori	6 mos. - 2 yrs.	Yes	CLN1
“Classic” Late Infantile	Jansky-Bielschowsky	2 - 4 years	Yes	CLN2
“Variant” Late Infantile		2 - 5 years	Yes	CLN6
Juvenile	Batten-Spielmeier-Vogt	5 - 10 yrs.	Yes	CLN3
Adult	Kufs Parry	Usually before age 40	No	CLN4
“Finnish” Late Infantile	?????	4.5 - 6 years	Yes	CLN5
“Turkish” Late Infantile	?????	1 - 6 years	Yes	CLN7
Northern Epilepsy	EPMR	5 - 10 years	Yes	CLN8
“Variant” Juvenile	vJNCL	5 – 10 years	No	CLN9
Congenital	CTSD	Birth	Yes	CTSD

Infantile NCL (Santavuori-Haltia disease): begins between about 6 months and 2 years of age and progresses rapidly. Affected children fail to thrive and have abnormally small heads (microcephaly). Also typical are short, sharp muscle contractions called myoclonic jerks. Initial signs of this disorder include delayed psychomotor development with progressive deterioration, other motor disorders, or seizures. The infantile form has the most rapid progression and children live into their mid childhood years.

Late Infantile NCL (Jansky-Bielschowsky disease) begins between ages 2 and 4. The typical early signs are loss of muscle coordination (ataxia) and seizures along with progressive mental deterioration.. This form progresses rapidly and ends in death between ages 8 and 12.

Juvenile NCL (Batten Disease) begins between the ages of 5 and 8 years of age. The typical early signs are progressive vision loss, seizures, ataxia or clumsiness. This form progresses less rapidly and ends in death in the late teens or early 20s, although some may live into their 30s.

Adult NCL (Kufs Disease or Parry Disease) generally begins before the age of 40, causes milder symptoms that progress slowly, and does not cause blindness. Although age of death is variable among affected individuals, this form does shorten life expectancy.

How many people have these disorders?

Batten Disease and other forms of NCL are relatively rare, occurring in an estimated 2 to 4 of every 100,000 births in the United States. These disorders appear to be more common in Finland, Sweden, other parts of northern Europe; and Newfoundland, Canada. The disease has been identified worldwide. Although NCLs are classified as rare diseases, they often strike more than one person in families that carry the defective gene.

How are NCLs inherited?

Childhood NCLs are autosomal recessive disorders; that is, they occur only when a child inherits two copies of the defective gene, one from each parent. When both parents carry one defective gene, each of their children faces a one in four chance of developing NCL. At the same time, each child also faces a one in two chance of inheriting just one copy of the defective gene. Individuals who have only one defective gene are known as carriers, meaning they do not develop the disease, but they can pass the gene on to their own children.

Adult NCL may be inherited as an autosomal recessive (Kufs) or, less often, as an autosomal dominant (Parry) disorder. In autosomal dominant inheritance, all people who inherit a single copy of the disease gene develop the disease. As a result, there are no unaffected carriers of the gene.

What causes these diseases?

Symptoms of Batten Disease and other NCLs are linked to a buildup of substances called **lipopigments** in the body's tissues. These lipopigments are made up of fats and proteins. Their name comes from the technical word lipo, which is short for "lipid" or fat, and from the term pigment, used because they take on a greenish-yellow color when viewed under an ultraviolet light microscope. The lipopigments build up in cells of the brain and the eye as well as in skin, muscle, and many other tissues. Inside the cells, these pigments form deposits with distinctive shapes that can be seen under an electron microscope. Some look like half-moons (or comas) and are called curvilinear bodies; others look like fingerprints and are called fingerprint inclusion bodies and still others resemble gravel (or sand) and are called granule osmophilic deposits (grods). These deposits are what doctors look for when they examine a tissue sample to diagnose Batten Disease.

The biochemical defects causing NCLs have not been identified. Some scientists suspect these abnormal deposits result from a shortage of enzymes normally responsible for the breakdown of lipopigments. According to this theory, diseased cells produce inadequate amounts of enzymes or manufacture defective enzymes that function poorly. As a result, the cells cannot process enough of the lipopigments that occur within them, and the lipopigments accumulate. Scientists have pinpointed what specific enzymes are at fault for Infantile and "Classic" Late Infantile (PPT1 and TPP1 respectively) only. However it has not been determined how the stored lipopigments damage nerve cells.

Other scientists believe that abnormal lipopigment buildup may result from a glitch in the cell's production or processing. For example, diseased cells could be producing too much of a normally needed lipoprotein.

How are these disorders diagnosed?

Because vision loss is often an early sign, Batten Disease may be first suspected during an eye exam. An eye doctor can detect a loss of cells within the eye that occurs in the three childhood forms of NCL. However, because such cell loss occurs in other eye diseases, the disorder cannot be diagnosed by this sign alone. Often an eye specialist or other physician who suspects NCL may refer the child to a neurologist, a doctor who specializes in diseases of the brain and nervous system. In order to diagnose NCL, the neurologist needs the patient's medical history and information from various laboratory tests.

Diagnostic tests used for NCLs include:

- blood or urine tests: These tests can detect abnormalities that may indicate Batten Disease. For example, elevated levels of a chemical called dolichol are found in the urine of many NCL patients. Electronmicroscopy of blood may reveal inclusion bodies or deposits.
- skin or tissue sampling: The doctor can examine a small piece of tissue under an electron microscope. The powerful magnification of the microscope helps the doctor spot typical NCL deposits. These deposits are common in skin cells, especially those from sweat glands.
- electroencephalogram or EEG: An EEG uses special patches placed on the scalp to record electrical currents inside the brain. This helps doctors see telltale patterns in the brain's electrical activity that suggest a patient has seizures.
- electrical studies of the eyes: These tests, which include visual-evoked responses and electroretinograms, can detect various eye problems common in childhood NCLs.
- brain scans: Imaging can help doctors look for changes in the brain's appearance. The most commonly used imaging technique is computed tomography (CT), which uses x-rays and a computer to create a sophisticated picture of the brain's tissues and structures. A CT scan may reveal brain areas that are atrophying in NCL patients. A second imaging technique that is increasingly common is magnetic resonance imaging, or MRI. MRI uses a combination of magnetic fields and radio waves, instead of radiation, to create a picture of the brain.
- DNA: Extracted from a blood sample, specific genes are examined for defects.
- Enzyme Assay: Infantile & Late Infantile are missing a lysosomal enzyme (PPT1 & TPP1 respectively). A blood test will measure enzyme levels.

Is there any treatment?

As yet, no specific treatment is known that can halt or reverse the symptoms of Batten Disease or other NCLs. However, seizures can be reduced or controlled with anticonvulsant drugs, and other medical problems can be treated appropriately as they arise. At the same time, physical and occupational therapy may help patients retain function as long as possible.

Some reports have described a slowing of the disease in children with Batten Disease who were treated with vitamins C and E and with diets low in vitamin A. However, these treatments did not prevent the fatal outcome of the disease.

Support and encouragement can help children and families cope with the profound disability and losses caused by NCLs. The Batten Disease Support and Research Association enables affected children, adults, and families to share common concerns and experiences.

Meanwhile, scientists pursue medical research that could someday yield an effective treatment.

What research is being done?

Within the Federal Government, the focal point for research on Batten Disease and other neurogenetic disorders is the National Institute of Neurological Disorders and Stroke (NINDS). The NINDS, a part of the National Institutes of Health (NIH), is responsible for supporting and conducting research on the brain and central nervous system. The Batten Disease Support and Research Association and the Children's Brain Diseases Foundation also provide financial assistance for research.

Through the work of several scientific teams, the search for the genetic cause of NCLs is gathering speed.

In September 1995, The International Batten Disease Consortium announced the identification of the gene for the juvenile form of Batten Disease. The specific gene, CLN3, located on Chromosome 16, has a deletion or piece missing. This gene defect accounts for 73% of all cases of Juvenile Batten Disease. The rest are the result of other defects of the same gene.

Also, in 1995, scientists in Finland announced the identification of the gene responsible for the infantile form of Batten Disease. The gene, CLN1, is located on Chromosome 1. It was then found that an enzyme is missing from the lysosome as a result of the defective CLN1 gene. This enzyme is known as Palmitoyl Protein Thioesterase 1 or PPT1.

In 1998, the gene for “Classic” Late Infantile, CLN2, was identified and is located on Chromosome 11. In addition, it was found that there was a missing lysosomal enzyme associated with Late Infantile. This missing enzyme is known as TPP1.

Identification of the specific genes for Infantile, “Classic” Late Infantile and Juvenile Batten Disease has led to the development of DNA diagnostics, carrier and prenatal tests.

Scientists are continuing to work toward identifying the remaining genes for the other forms of NCL, additional enzymes and proteins associated with the specific genes. Additionally, some are working to identify a possible gene that is common to all forms of NCL.

At the same time, other investigators are working to identify what substances the lipopigments contain. Although scientists know lipopigment deposits contain fats and proteins, the exact identity of the many molecules inside the deposits has been elusive for many years. Recently, however, scientists have unearthed potentially important clues. Researchers have found in the late infantile and juvenile forms that a large portion of this built-up material is a protein called Subunit C. This protein is normally found inside the cell's **mitochondria**, small structures that produce the energy cells need to do their jobs. Storage material for the infantile form has been identified as a protein called Saposins A & D, also known as sphingolipid activator proteins. Scientists are now working to understand what role these proteins may play in NCL, including how this protein winds up in the wrong location and accumulates inside diseased cells. Other investigators are also examining deposits to identify the other molecules they contain.

In addition, research scientists are working with NCL animal models to improve understanding and eventually develop treatment of these disorders. At this time there are sheep dog, fly, nematode, cow and zebrafish models for some forms of NCL. Mouse models have also been developed. Mouse models make it easier for scientists to study the genetics of these diseases, since mice breed quickly and frequently.

At this time there are research initiatives underway to develop means for doing enzyme replacements, gene therapy, stem cell transplantation and possibly drug/chemical treatment.

Chart of Forms of Batten Disease

Throughout this guide you will see references to the different forms of Batten Disease (NCL) and the proteins associated with the forms. Below is a chart that will perhaps aid you in deciphering the references.

Form	Initials	Gene Name	Protein Name
Infantile	INCL	CLN1	PPT1
Classic Late Infantile	LINCL	CLN2	TPP1
Juvenile	JNCL	CLN3	CLN3
Adult	ANCL	CLN4	Unknown
Finnish Late Infantile	fLINCL	CLN5	Unknown
Variant Late Infantile	vLINCL	CLN6	Unknown
Turkish Late Infantile	vLINCL	CLN7	Unknown
Northern Epilepsy	vLINCL	CLN8	CLN8
Variant Juvenile	vJNCL	CLN9	Unknown
Congenital	CTSD	CTSD	CTSD

An explanation of late infantile and variant late infantile is also in order. “Classic” late infantile is the most commonly seen form of late infantile. It has an age of onset typically between 2 - 4 years of age. The “Variant” late infantile has an age of onset between 2 - 5 years of age and is the next most common form of late infantile. The “variant” late infantile falls between the classic late infantile and juvenile forms of Batten Disease and the children have all the symptoms of the classic form, however, the variant does have the later onset and the disease is protracted. Additionally, the storage bodies found in classic late infantile are almost always curvilinear and those found in the variant are mixed curvilinear and fingerprint. The gene for the classic late infantile CLN2 is located on chromosome 11 and the gene for variant late infantile CLN6 is located on chromosome 15.

Infantile Batten Disease

Haltia - Santavuori Disease

The Infantile form of Batten Disease (INCL) is found primarily in Finland with the birth rate being approximately 1:20,000. In the United States there are a few cases of Infantile but not near the numbers as found in Finland.

Initially, children with Infantile Batten Disease have a normal development. Most learn to sit up, many learn to stand and some to walk a little. Some children learn to speak a few words.

Following this normal period of development after birth the initial onset most often observed is psychomotor delay beginning between 8 and 18 months of age, soon accompanied by **ataxia, myoclonic jerks, progressive microcephally**, onset of seizures, physical clumsiness and blindness. The children lose their ability to speak and eat and become **hypotonic** and ataxic and by age two, **microcephalic**.

The myoclonic jerks start between 16 and 24 months. A characteristic "knitting" or "washing" movement of the hands (**hyperkinesia**) is observed between 18 and 24 months and will last a few months.

As with other forms of Batten Disease, seizures are always present. Simple and/or Complex Partial seizures are usually the first to develop followed by Petit Mal (Absence) and Grand Mal (Tonic-clonic). The **EEG** shows loss of rhythmic components with increased slow waves, disappearance of sleep spindles and a gradual attenuation in amplitude. This diminution in amplitude is first noticeable in the occipital leads. Irregular, sharp discharges seen early on disappear and by age three the EEG is **isoelectric**.

Additionally, short partial seizures may occur with staring and swallowing, laughing, turning of eyes, and protrusion of the tongue.

Blindness usually occurs after age two although light perception remains longer.

As the illness progresses **spasticity (pyramidal)** and tremors and shaking (**extrapyramidal**) develop. The children stiffen and develop **contractures** but at the same time have little or no head control. Sleep disturbance is common as well as restlessness and crying. Girls may show signs of puberty at age seven.

There is no way to determine the life expectancy of a child with Infantile NCL. Normally children with this disorder live to between 8 and 14 years of age.

Diagnosis of Infantile Batten Disease (INCL) has been historically done by a combination of clinical history and electronmicroscopy (EM) of skin or rectal biopsy. The EM study looks for granular osmiophilic deposits, also known as GRODS, in several different cells. These GRODS are usually found in the Infantile form of NCL. Today, DNA testing and an enzyme activity assay are available to assist in diagnosis as well as carrier and prenatal testing.

In 1995 the gene for Infantile NCL was identified and designated as CLN1. This gene is located on Chromosome 1 at location 1p32. In addition the gene codes for palmitoyl-protein thioesterase (PPT1), an enzyme that resides in the lysosome. The PPT1 enzyme is missing in children with Infantile Batten Disease. The PPT1 enzyme's apparent job is to remove strongly bound lipids that are attached to proteins within the lysosome. An accumulation of Saposin (Sphingolipid Activator Protein) is also found within the lysosome but is apparently not the result of the PPT1 enzyme being absent.

A few children have been identified who have the same symptoms, progression and outward appearances as children with Juvenile Batten Disease (CLN3).

These children have an onset of progressive vision loss between ages seven and ten, motor problems between ages six and eight, cognitive decline between ages seven and 13 and the onset of seizures between eight and 16.

Although these signs and symptoms are typical of classic Juvenile Batten Disease, none have **vacuolated lymphocytes** and no defects or mutations can be found in the CLN3 gene. The biochemistry is similar to Infantile Batten Disease in that there is no accumulation of the Subunit C protein in the lysosome and there is an accumulation of Saposin protein as is normally found in the infantile form. There is a deficiency of the PPT1 enzyme. The gene defect is different than those found with other forms of INCL.

Another smaller group of children have been found whose onset and progression is very similar to the Classic, Variant, and Finnish forms of Late Infantile. In these children Granular Osmiophilic Deposits (GRODs) have been identified rather than the curvilinear inclusion bodies that are normally found. Here again, the biochemistry is similar to Infantile Batten Disease in that there is no accumulation of the Subunit C protein in the lysosome and there is an accumulation of Saposin protein as is normally found in the Infantile form. There is a deficiency of the PPT1 enzyme. The gene defect is different than those found with other forms of INCL.

"Classic" Late Infantile Jansky - Bielschowsky Disease

The "Classic" Late Infantile (LINCL) form of Batten Disease is the type of Late Infantile most often seen in the United States, Canada, Australia, New Zealand and United Kingdom. Early development proceeds in a normal fashion with attainment of walking, talking and other motor skills at appropriate age. There have been reported cases of delayed speech or clumsiness before age three. The initial onset is approximately age three and first symptoms are **ataxia** or either grand mal or myoclonic seizures. These symptoms are followed by visual decline leading to blindness and both motor failure and cognitive decline. **Hypotonia** presents early but gives way to **myoclonus**, **spasticity** with jerking, and eventually **contractures**.

Decline both in motor skills and cognition is rapid between ages three and five. Seizures become more frequent and are often very difficult to control. Children lose their speech as time goes by and eventually end up immobile. Poor circulation is noticeable by coldness of hands and feet.

ERG is abnormal within a year of the onset. Pale optic discs and a brown discoloration develops to the macula. Ophthalmic examination later on will show either the salt and pepper appearance associated with retinitis pigmentosa or the "Bull's Eye" lesion. Pupils become large and inactive.

Historically diagnosis was done by clinical history and usually skin, muscle or rectal tissue biopsy. Electronmicroscopy of tissue samples will reveal curvilinear inclusion bodies (deposits) within several different types of cells. Occasionally fingerprint inclusion bodies may also be observed with the curvilinear. These tests remain valid today. The gene for this form of Batten Disease was identified in 1997 and DNA is now used for additional diagnosis as well as carrier and prenatal testing. Identification of the associated missing enzyme has also given rise to an enzyme activity test for diagnosis, carrier and prenatal testing.

The gene for the "Classic" Late Infantile has been designated CLN2 and is located on Chromosome 11 at location 11p15. The gene CLN2 encodes for an **enzyme** designated as TPP1. This enzyme resides in the **lysosome** and its apparent job is to degrade or breakdown proteins in the lysosome. In "Classic" Late Infantile the TPP1 enzyme is absent. Both Late Infantile and Juvenile Batten Disease are also characterized by an accumulation of Subunit C protein within the lysosome. It remains unclear if the TPP1 enzyme's purpose is to also degrade or breakdown the accumulated Subunit C protein. The absence of the TPP1 enzyme in affected children and an approximate 50% absence in carriers is what provides for the enzyme activity test as persons who are neither affected or carriers show a 100% activity.

Juvenile Spielmeyer - Vogt - Batten Disease

The Juvenile form of Batten Disease (JNCL) has an age of onset between ages five and ten. Initial symptoms may be slow decline of vision, clumsiness, or seizures. The juvenile form is often misdiagnosed as retinitis pigmentosa, macular degeneration, mental retardation, epilepsy, ADHD, autism and, even, schizophrenia.

Diagnosis of Juvenile Batten Disease is similar to that done for the Infantile and Late Infantile forms. Skin, muscle, rectal and conjunctiva tissue samples seen under an electronmicroscope will reveal inclusion bodies within several different types of cells. These inclusion bodies are normally seen in the form of "fingerprints" and look just exactly as the name implies. Additionally, "**buffy coat**" tests have been used but are not definitive for diagnosing juvenile but are an indicator for additional testing. Electronmicroscopy of blood will often reveal inclusion bodies. A rarely used test is bone marrow. Today with the known identification of the gene, DNA testing is also available.

In the beginning these children have normal birth and reach usual developmental milestones on schedule. The initial symptoms do not all occur simultaneously but may manifest themselves over a period of time. The most common initial symptom is the slow gradual decline of vision. Initial ophthalmic examination usually fails to find any particular indication of Batten Disease. As the illness progress the normal course of the vision decline is loss of central vision and colorblindness followed by loss of night vision. When central vision is lost the children continue to function with their peripheral vision until it, too, leaves. In the early stages the diagnosis for the decline in vision is retinitis pigmentosa or macular degeneration and, indeed, the symptomolgy is similar. A pale optic disc along with the granulation and occasionally the salt and pepper appearance or "Bulls eye" lesion is seen.

The trait of clumsiness is often attributed to the decline in vision or natural uncoordination associated with growth.

The first seizures may be either petit mal (absence) or grand mal (tonic-clonic) and initially the diagnosis is epilepsy. Like the other forms of Batten Disease the children will suffer multiple forms of seizures which over time may become difficult to control. In addition to petit mal and grand mal the children may also suffer from drop seizures (atonic), psychomotor (complex partial or temporal lobe), myoclonic, and Jacksonian (simple partial). It not uncommon for these children and young adults to be on more than one anticonvulsant in order to maintain control of the seizures.

As the disease progresses motor skills become more affected. Loss of fine motor skills become noticeable followed by the decline of gross motor skills as is evidenced by the growing difficulty they have handling simple objects such as a fork. **Ataxia** progresses and walking becomes a "shuffling" walk and eventually leads to the loss of mobility and the necessity of a wheelchair. **Spasticity** and **rigidity** begins in the teens as does **contractures** in the later years. Tremors are noticeable early in the progression.

Dementia is defined as the loss of cognizance. Some children with Juvenile Batten Disease will develop a severe dementia that is often similar to psychotic behavior. This can include long periods of sleeplessness or extended sleep. Hysterical sobbing, uncontrolled laughter, screaming, biting, belligerence, apathy, swearing, and hallucinations may also appear. There is no way to predict what will trigger these episodes or how long they may last. The severe dementia may continue for several years. In extreme cases neuroleptics or other drugs may be tried to control the dementia but one needs to be aware of possible side affects.

Children with Juvenile Batten Disease will also undergo a period of repetitive speech, saying the same thing over and over. This is known as **echolalia**, which will pass with time. However they will eventually lose their speech totally.

The children's growth is the same as a normal child and they will achieve their normal physical stature. However, both boys and girls will reach puberty before their more normal peers. An increase in both seizure activity and the dementia problems may be observed in girls as their menstrual period arrives.

The gene for Juvenile Batten Disease was identified in 1995 and was designated as CLN3 and is located on chromosome 16 in position 16p12.1. The CLN3 gene encodes for an as yet unidentified protein. Research has shown that unlike the enzymes for Infantile and Late Infantile, the CLN3 protein does not reside in the lysosome but may be located in the membrane.

Identification of the gene has now provided for DNA diagnostic, carrier and prenatal testing.

"Variant" Late Infantile

The "Variant" Late Infantile (vLINCL) was identified as a separate form of Batten Disease in 1996. It was originally thought to be the same as the "Classic" Late Infantile but was eventually shown to be a distinctly different illness apart from the classic form. Once this was discovered, advances in the identification of the gene and enzyme for the "Classic" Late Infantile was rapid.

The "Variant" form has also been alluded to as the "Costa Rican" Late Infantile as all the children in Costa Rica have the same form of the illness. This form of NCL has also been identified in the Czech Republic, Portugal and a few other European countries. The age of onset is slightly later than the classic late infantile and the progression is slightly slower. The initial symptom is decline in vision.

The primary difference between the two forms of Late Infantile is that the "Variant" has predominant fingerprint storage bodies as opposed to the usual curvilinear storage bodies found in the "Classic" form. Though this makes it similar to Juvenile Batten Disease, there are no **vacuolated lymphocytes** as found in Juvenile. This form of NCL has also randomly been called "early juvenile".

The actual progression of the "Variant" form is the same as the "Classic" form. Longevity is also the same. Diagnosis can be made through DNA testing. An electronmicroscopy will reveal fingerprint and curvilinear inclusion bodies.

The gene has been designated as CLN6 and resides on chromosome 15 at position 15q21-23. The gene codes for the production of a transmembrane protein, TPP1.

Oddly enough, there are two naturally occurring animals with this form of NCL; a mouse designated as *nclf mouse* and the South Hampshire sheep. Studies are being done on these animals in hopes of better understanding CLN6 in humans.

"Finnish" Late Infantile

The "Finnish" Late Infantile (vLINCL), as its name indicates, is found almost exclusively in Finland. This form of NCL has a later age of onset and is slower in progression than the "Classic" Late Infantile (CLN2). Initial symptoms begin between ages four and seven and include clumsiness and poor muscle tone. Seizures begin between ages seven and eight, **ataxia** between seven and ten and myoclonic jerks between eight and nine. Children with this form also develop sleep disturbance, contractures and may develop **scoliosis**. As with other forms of Late Infantile, this form also causes blindness, loss of mobility, etc. Longevity can be 14 + years.

Announcement of the identification of the gene was made in June 1998. It is a much smaller group of children and the gene has been designated CLN5 and is located on chromosome 13 at location 13q21. The gene product is a lysosomal enzyme whose function has not been determined. The storage material is Subunit C, the same as is found in "Classic" Late Infantile, Variant Late Infantile and Juvenile NCL.

"Turkish" Late Infantile

The "Turkish" Late Infantile (vLINCL) was newly identified in 1998. This form of NCL is found primarily in children in Turkey and families of Turkish descent now living outside of Turkey. Some children have been found to have only curvilinear storage bodies as is found in "Classic" Late Infantile, some with only fingerprint inclusion bodies as found in "Variant" Late Infantile and others to have a mix of both. As of mid 1999 only 14 cases had been identified.

Onset is between one and six years of age and initial symptoms are usually poor mobility and seizures. Because of the small number of children with this form of NCL progression and longevity are not well defined.

The gene for this form of NCL has been designated CLN7 and has been mapped to Chromosome 4 at location 4q28.2.

Northern Epilepsy

This form of NCL (vLINCL) was identified in 1998 and is found primarily in Finland. It is also known as Progressive Epilepsy with Mental Retardation (EPMR). The age of onset is between two and ten years of age and the initial symptoms are generalized tonic-clonic seizures. Other forms of seizures, i.e. complex partial, have been observed. Seizure frequency increases through puberty but with adulthood the frequency drops to approximately four to six per year. After age 35 the frequency further drops to zero to four per year. Mental deterioration to the point of mild mental retardation occurs in the early school years. The teen years and early adult years sees the beginning of clumsiness. By age 40 these individuals have moderate mental retardation along with increased motor skill deficits and vision losses. Of the 23 originally diagnosed with this form of NCL, 19 are well beyond 40 years of age.

Curvilinear inclusion bodies are found in many cells.

The gene for this form of NCL has been designated CLN8 and has been mapped to Chromosome 8 at location 8p23.

CLN10 – CTSD

CLN10 was originally designated Congenital NCL because the onset was at birth and was very rapid. Children born with CLN10/CTSD would only live a few days to a few weeks. However, it has now been found that children with CLN10/CTSD can live to be different ages, similar to other forms of NCL (Batten disease). CLN10/CTSD is similar to Infantile and Late Infantile Batten disease because there is a missing lysosomal enzyme. That enzyme is Cathepsin D. The progression of CTSD is similar to other forms of Batten disease with loss of vision, onset of seizures and deterioration of motor skills. The gene for CLN10/CTSD has been identified as 11.p15.5. CLN10/CTSD has also been identified as a naturally occurring disease in Landrace Sheep and American Bulldogs.

Adult Onset Batten Disease Kufs and Parry Diseases

Kufs Disease

The Adult Onset NCLs (ANCL) are the rarest of the NCLs and have been divided into two groups based on the mode of their genetic inheritance. The type of Adult NCL showing autosomal recessive inheritance was first described by Kufs and is classified as the recessive or Kufs type of Adult NCL.

At onset the initial symptoms may be either seizures, motor difficulties or mental deterioration, visual loss is very rare. Age of onset may be between 11 and 35 years of age.

The progression of Kufs is very slow as compared to Infantile, Late Infantile and Juvenile. Kufs exhibits a wide range of symptoms which makes a firm clinical diagnosis very difficult. The disease usually presents as a cerebellar syndrome. Other consistencies include **ataxia**, **myoclonus**, rigidity, and seizures. **EEGs** of persons with Kufs show high voltage spikes and **atypical** spike-slow wave complexes. Although no **ERG** changes have been reported, some patients have been described with visual difficulties, although this is usually not thought to be a problem associated with Kufs.

At autopsy, moderate to little **atrophy** of the brain is observed. The nerve cells may be grossly distended with **autofluorescent lipopigment**, as is seen in the other forms of NCL. *The inclusion bodies found within the cells have a granular matrix, often with lipid vacuoles.*

The wide variation of clinical symptoms, particularly at an early age causes additional difficulty in making a firm diagnosis, in view of the proposed late onset and/or protracted forms of Juvenile NCL. Muscle, brain and rectal tissue can be used for the diagnosis of Kufs when examined at the ultrastructural level (electronmicroscopy). However, the ultrastructural morphology of lipofuscin makes the disorder difficult to distinguish from the accumulation of age pigment in the tissues of aging persons.

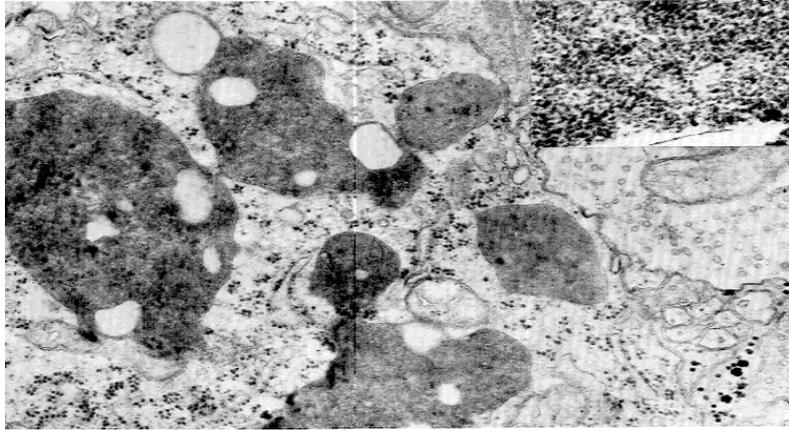
To date the gene for Kufs has not been identified. However, when identified, DNA will become a useful tool in the diagnosis of Kufs as well as for carrier testing. As opposed to persons with the other forms of Batten Disease, persons with Kufs, having the later onset, often marry and have children. These children are carriers.

Parry Disease

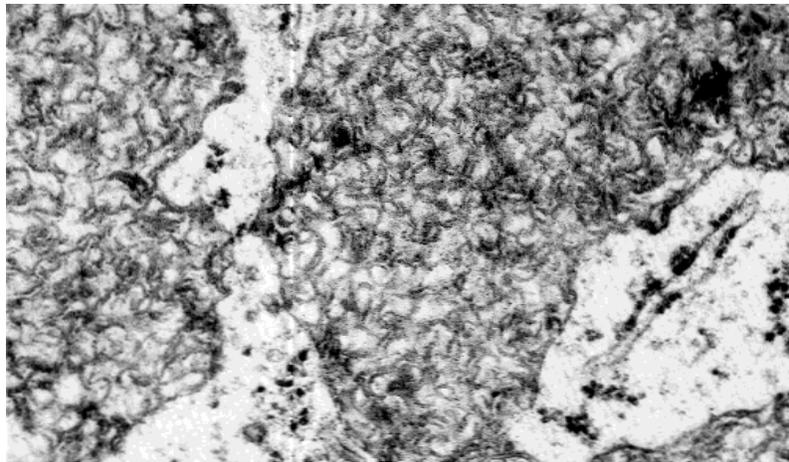
Parry Disease is an Adult Onset NCL that is even rarer than Kufs Disease. It is a dominant gene inheritance as opposed to recessive as in Kufs. This form of NCL begins late in life with an average age of onset at 32 years of age.

The first symptom of Parry is seizures and the presentation is very similar to Kufs, i.e. dementia, **ataxia**, **myoclonus**, rigidity, and seizures. EEG examinations show the same patterns as Kufs. The ultrastructural morphology is also the same as Kufs. Visual impairment is also rare.

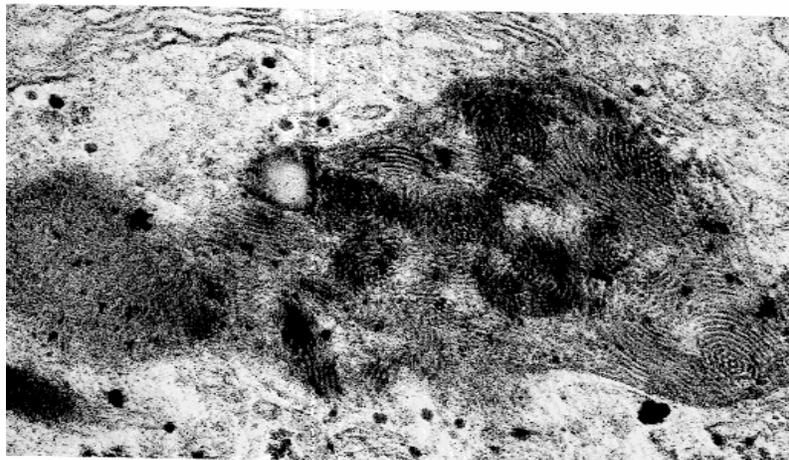
This disorder is rarer than Kufs and is transmitted in an autosomal dominant fashion. With the exception of a few sporadic cases, this disorder appears to be confined to 11 persons, all in one family spanning four generations. The gene remains unidentified.



Granular Osmiophilic Deposits – (GRODS)



Curvilinear Inclusion Bodies



Fingerprint Inclusion Bodies

Autosomal Recessive Inheritance

All forms of Batten Disease are autosomal recessive. Autosomal meaning it is not sex linked, affecting just males or just females. In fact, the numbers of children with Batten Disease shows that it is almost equally distributed between males and females. Recessive means that both parents must be carriers in order to have the possibility of passing an abnormal gene to their child.

Each person has two copies of each gene. When a person has one good copy of a gene and one abnormal copy they are a carrier. Persons who are carriers do not have symptoms of the disease or warning signs telling them they are carriers.

Refer to Figure 1 ("Autosomal Recessive Inheritance"). Every time a child is conceived, the child receives one copy of each gene from each parent. The following combinations are possible when each parent is a carrier:

The child gets both normal copies (25% chance). This child is neither a carrier nor affected.

The child gets a normal copy from one parent and an abnormal copy from the other parent (50% chance). This child is a carrier.

The child gets both abnormal copies of the gene (25% chance). This child will have Batten Disease.

When two carriers have children, at each pregnancy there is a one in four chance (25%) that the child will be born with Batten Disease. Which combination occurs is based on chance alone and the percent risk is a statistical estimate.

What makes an abnormal gene ?

Genes are packets of DNA containing the instructions for making proteins. A gene is made up of amino acids and are constructed like beads on a string. Each amino acid (or bead) must be present and in a specific order for the gene to be normal. Mutations are errors in the instructions. There are different types of mutations that can disrupt a gene. These include **deletions**, in which pieces of the gene are missing; **insertions**, in which pieces are added; **point mutations**, which are small coding errors; **nonsense**, which means the information is jumbled; **missense**, which means an amino acid has been replaced by another amino acid.

Each form of Batten Disease is the result of an error in a different gene. In each case the genes have a common error. If a gene does not have a common error, and is abnormal it will have a different mutation.

Infantile (INCL) - 40 % of affected children have a common nonsense mutation. To date 21 additional mutations have been identified in the CLN1 gene.

Late Infantile (LINCL) - There are two common mutations of the CLN2 gene. One is a nonsense mutation and the other a splice junction mutation (see page 19). To date 25 other mutations have been identified in the CLN2 gene.

Juvenile (JNCL) - 73 % of affected children have a common (same) deletion. The remaining 27 % have other mutations of the CLN3 gene. To date 24 other mutations have been identified.

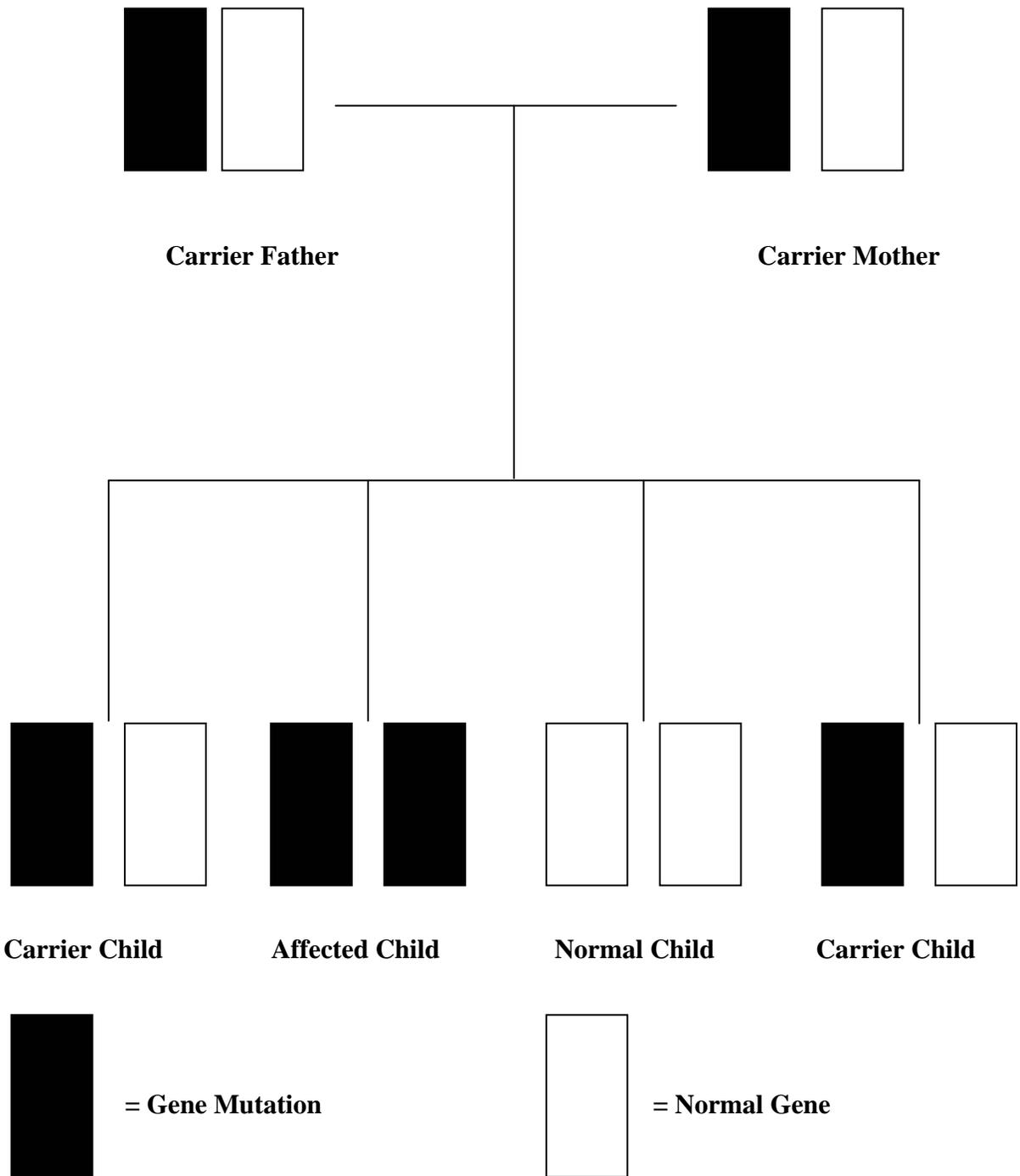
What does this mean for your family? (Fig. 1)

In some families, both parents carry the common mutation. In others, one parent carries a common mutation and the other a different mutation which disrupts the gene. In some, neither parent carries a common mutation, both carry other mutations of the same gene. The following figures will demonstrate how the different combinations work. A deletion is used as the example for a common mutation.

Both parents are carriers of a common mutation. (Fig. 2). In this figure the common mutation (deletion) is represented by the shaded box. When both carry the common (deleted) gene the affected child (Child 2) inherits two common (deleted) copies. The carrier child (Child 1 and Child 4) each inherit one copy of the common (deleted) gene and one copy of the normal gene.

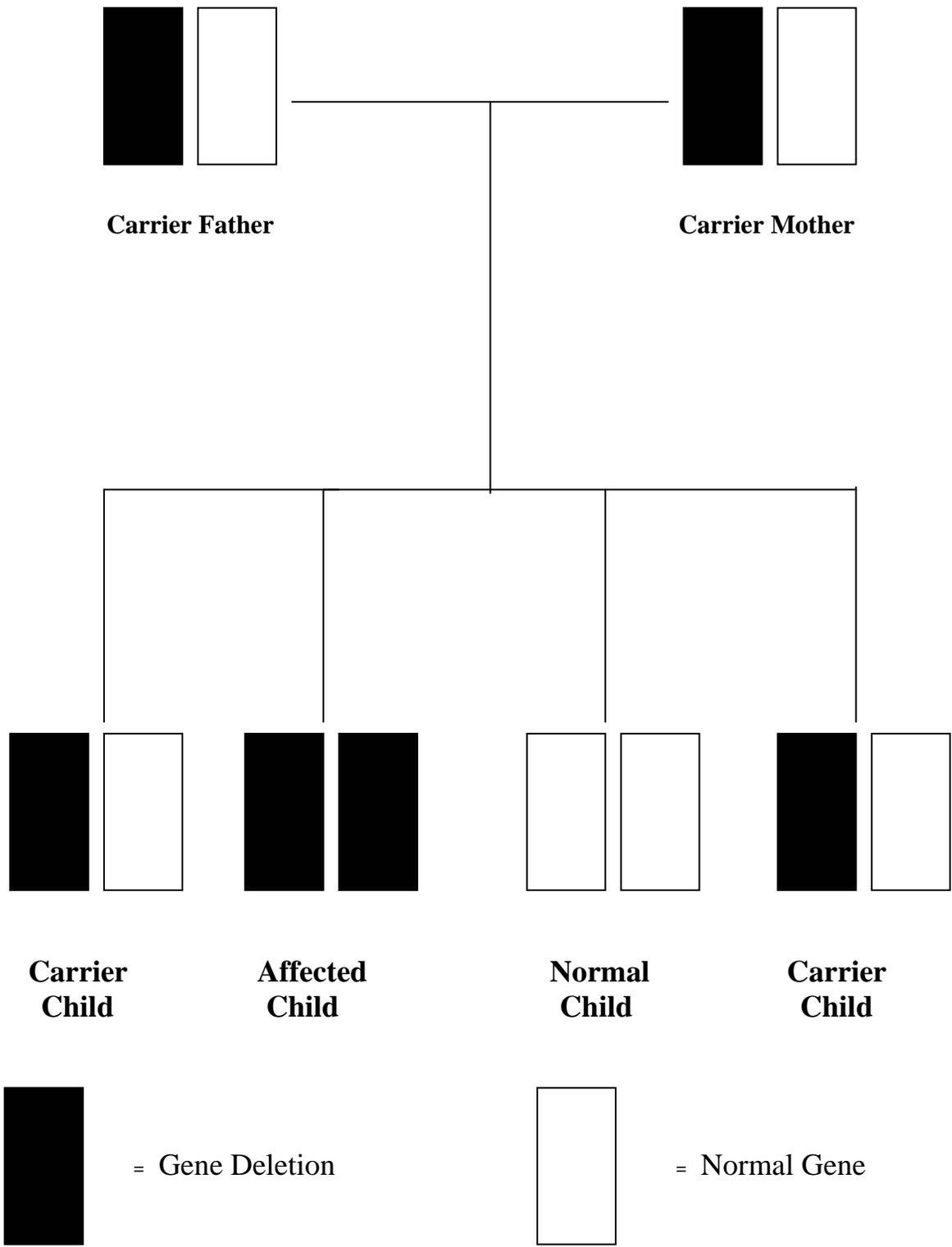
One parent is a carrier of a common (deleted) gene and one parent is a carrier of a different mutation of the same gene (Fig. 3). In this example, the common mutation (deletion) is represented by the dark box and a point mutation is represented by the shaded box. The affected child (Child 2) will inherit one common (deleted) copy of the gene and one copy of the gene with the point mutation. The carrier children will inherit the normal gene and either a copy of the common (deleted) (Child 1) or point mutation (Child 4).

Neither parent carries a common mutation (Fig. 4). In this example, both parents are carriers of mutations other than a common mutation. These mutations are represented by the dotted and striped boxes, respectively. The affected child (Child 2) inherits one copy of each mutation. The carrier children (Child 1 and Child 4) each will inherit one normal gene and one mutated gene.



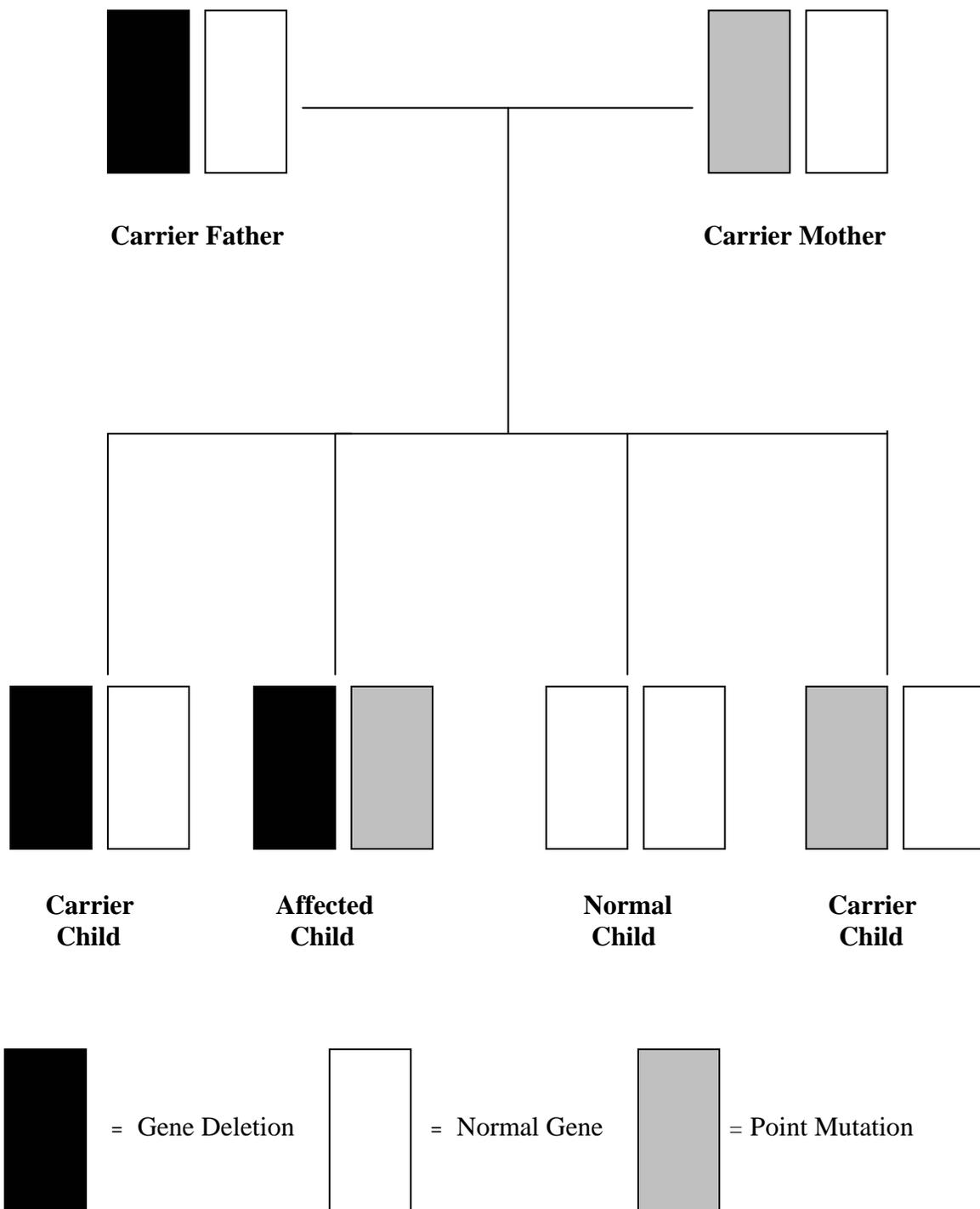
Autosomal Recessive Inheritance

Figure 1



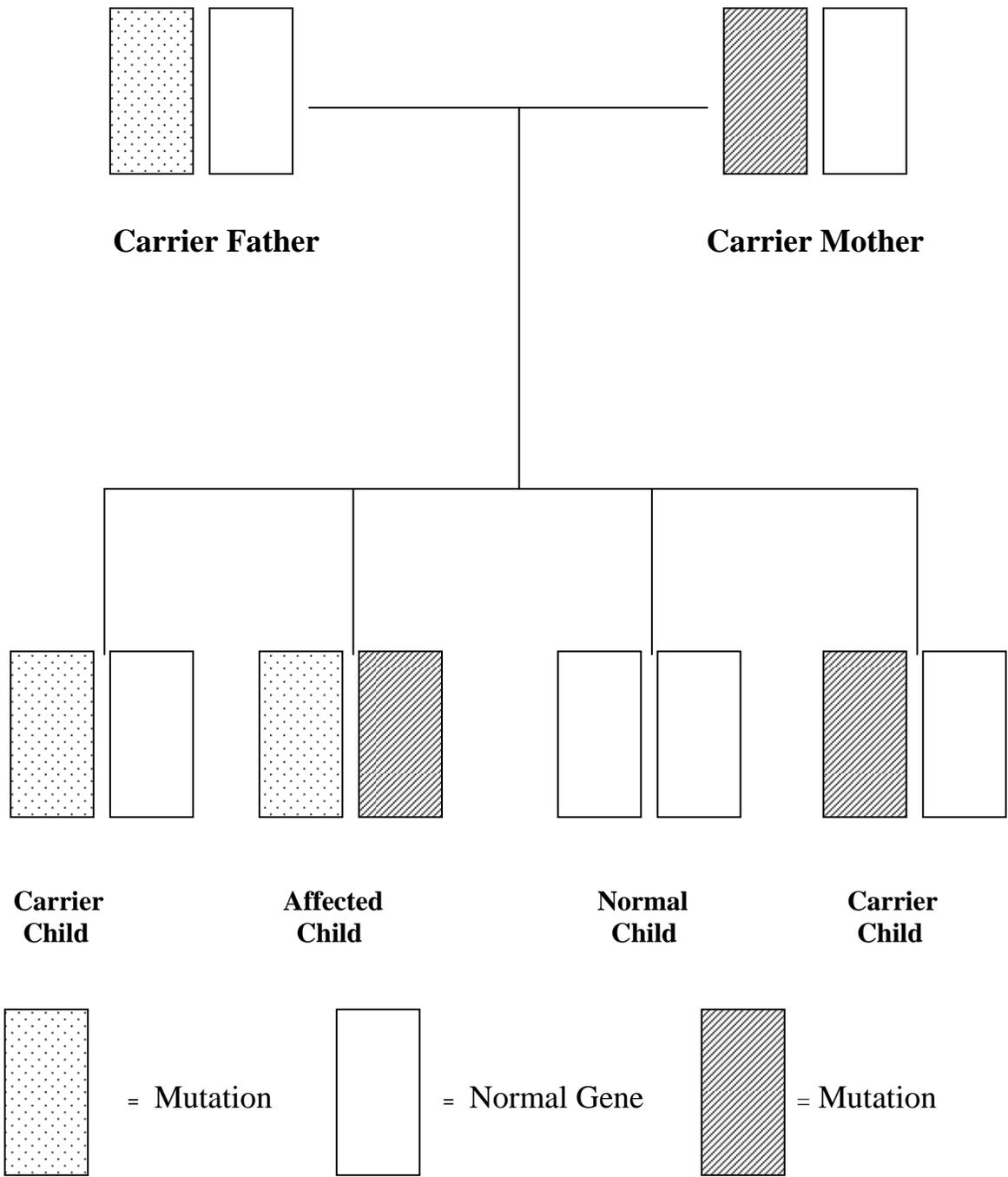
Both Parents Carry the Deleted Gene

Figure 2



One Parent Carries the Deletion, One A Point Mutation

Figure 3



Parents Carry Different Point Mutations

Figure 4

Batten Disease and Ophthalmology

Infantile

Optic atrophy, retinal degeneration and macular discoloration are common with Infantile and usually found after age two. Pigmentary aggregation normally found in retinitis pigmentosa and other NCLs are not found. Ophthalmoscopically, there is attenuation of the retinal vessels, early macular pigmentary changes, with late bone spicules and eventual optic atrophy. Cherry red spots are not seen. The ERG is extremely attenuated or absent at diagnosis. Progressive neuronal destruction with phagocytosis and fibrillary astrocytosis occurs. Most children with Infantile Batten Disease will lose their light perception sometime after 18 months of age.

The Late Infantiles

Initially the ERG becomes abnormal about a year after onset of symptoms, but like the Infantile form, ERG is extinguished early, but **VER** may initially show an extremely enlarged amplitude for reasons that are unclear. Discolored macula and pale optic discs are found. In some children the retina develops the salt and pepper appearance of retinitis pigmentosa. In others a Bull's Eye like lesion is occasionally found in the parafoveal area.

Juvenile

Most often the initial symptom of Juvenile Batten Disease is the beginning deterioration of vision. Ophthalmoscopically, there is an early bull's-eye maculopathy, but the entire retina is affected early, as evidence by full-field ERG changes. Early on there is characteristic attenuation of the b wave on ERG, with a normal EOG, but later there is a widespread photoreceptor degeneration with bone spicules, vascular attenuation, salt and pepper macula, Bull's Eye lesion, and optic atrophy. Loss of photoreceptor cells result in loss of central vision leaving the individual with peripheral vision for some time. Color blindness is normal. Eventually peripheral sight is lost leaving the individual with light/dark perception which also leaves and results in total blindness.

Adult

The general consensus among scientists and clinicians is that there is apparently no retinal involvement with the Adult form of NCL, as there is with the other forms. There have been, however, reports of the Adult form in which there is visual loss. Storage material has been reported in ganglion cells.

Since visual dysfunction may be an early and/or prominent feature of Batten Disease, an ophthalmologist may indeed be one of the first physicians to encounter many of these children, especially those with Juvenile Batten Disease. The ophthalmologist must be prepared to consider the diagnosis of Batten Disease in all children with maculopathy or tapetoretinal degeneration syndromes. Many of these children are initially misdiagnosed with Stargardt's disease, retinitis pigmentosa, or other entity. Early recognition and diagnosis offers the best chance to learn more about Batten Disease and the greatest hope for the child/ren once a successful treatment is developed.

The accompanying figures demonstrate the **fundus** findings in Batten Disease. Additional detailed information is available from BDSRA.

Figure 1: Pigmentary retinopathy with significant RPE granularity and "salt and pepper" fundus appearance.

Figure 2: Typical bull's-eye maculopathy of Juvenile Batten Disease.

Figure 3: Another bull's-eye maculopathy with notable optic disc pallor.

Figures 4-5: Progressive retinal vascular attenuation and optic atrophy.

Figure 6: End-stage disease appearance with marked arteriolar attenuation, optic atrophy, retinal ischemia, and pigmentary retinopathy with typical bone spicules.



Figure 1



Figure 2



Figure 3



Figure 4



Figure 5



Figure 6

Batten Disease and Seizures

What are seizures?

Seizures are often compared to electrical storms. In the spring and summer we see thunderstorms with lightening. Lightening is an electrical discharge from the storm clouds. Seizures are like lightening in that they are uncontrolled electrical discharges in the brain.

Neurons or brain cells communicate with each other through electrical impulses. The brain also communicates with the rest of the body and receives information through electrical impulses. The brain is like a switchboard sending and receiving electrical messages throughout the body. The body receives messages from the brain telling it to walk, talk, eat, sit, etc. The brain receives messages from the body giving information relative to position, temperature, pain, etc. Within the brain messages received from the body and senses are processed by the neurons and commands sent back out.

Sudden unexplained bursts of electrical activity cause other neurons to fire additional bursts and this spontaneous activity spreads through a portion of the brain, or can spread throughout the entire brain. This electrical “storm” results is what is known as a seizure. In some instances, a person experiencing a seizure may not be aware of what is happening to them, at other times, when they are having what are called simple partial or simple focal seizures, they may be fully aware but unable to stop the seizure. However, some persons experience what is called an “aura”, which is a forewarning of a coming seizure. Persons have related experiencing seeing color(s), smelling a specific odor, headache, stomachache or just feel “different”. Most often, though, seizures occur without warning. There are several different kinds of seizures and the key is to recognize, understand and know what to do with each one. When the neurons stop firing erratically and recover the seizure stops.

Seizures may last from a few seconds to several minutes. The type of seizure dictates what happens and may range from staring to full convulsion, in which a person may fall and experience full body shaking. Talk to a neurologist about how and where to learn more about seizure recognition and first aid.

There are many causes for seizures, including head injury/trauma, substance abuse, brain tumor, stroke and neurologic disorders. Batten Disease is one of the neurologic disorders that cause seizures. Many different kinds of seizures are associated with Batten Disease and may or may not be easily controlled. In Batten Disease an attempt to control seizures is through the use of drugs called anticonvulsants. Unfortunately, there is no specific drug that can be singled out as the one to be used with Batten Disease as anticonvulsants are chosen to effect the type of seizure and not for a specific disorder. With Batten Disease there is usually more than one type of seizure thus requiring more than one anticonvulsant.

As time goes on and research continues, more anticonvulsants are being developed that are broader in their treatment of several types of seizures. It is not uncommon to have to try several before finding the one(s) that will improve control of seizures.

Anticonvulsant dosages are prescribed based on age, weight, type of seizure, rate of absorption and other drugs being taken. Anticonvulsants have what is known as a “therapeutic range”. It is within this therapeutic range that seizures are controlled. However, there is no one dose that is therapeutic for everyone and until an individual is treated with the anticonvulsant you will not know the exact dose that will work for them. This is why some people get good control with no side effects on low doses and others may need higher doses which may be in what is reported to be a toxic range. The books are just guidelines, with the individual as the one who decides how their body will respond. This is why sometimes it may look like the doctors are experimenting with a child, but they are trying to find the dose that works best. Most people do respond within the therapeutic range if they are to get results from a medication. The neurologist will have to work with parents and patients to determine the correct dose for the child based on response and absence or presence of side effects.

Drop below the therapeutic range and seizure may start up, go above the range and the drug can become toxic resulting in more seizures or additional side effects. The amount of drug in the bloodstream at any given time is known as the drug’s “level”. The “level” determines whether or not it is within the therapeutic range. Be aware that many things can affect the drug’s “level”. Weight gain will cause a drug’s level to drop and, conversely, weight loss will cause it to increase. In recent years, some of the newer anticonvulsants are not monitored by drug levels, as the levels have not been determined for the majority of people. Only in some research centers is it even speculated what a level may or may not mean. The neurologist is the one to discuss the need for blood levels and other blood work to monitor for other side effects. Other factors will also affect a drug’s level, such as over the counter medicines, dehydration, antihistamines, sodium level, certain antibiotics, stomach medications, etc. Discuss this with the neurologist and pharmacist.

Every drug has side effects for some people and finding one that controls seizures with no or minimal side effects may require some trial and error. Some side effects to the medication can be life threatening and mean an immediate need to discontinue the medication. Other side effects are milder and may change as the dosage changes. Be sure to ask the neurologist and pharmacist about side effects of each drug, how to recognize them and what to do if it should occur.

As Batten Disease progresses it may become necessary to add additional anticonvulsants to maintain seizure control. It is not unusual for children with Batten Disease to eventually be on two or three different anticonvulsants at the same time.

Listed on the next page are several types of seizures and their characteristics. This list is by no means complete. A neurologist can provide additional information.

Seizures - Types

I. Generalized

There are six types of generalized seizures:

Absence or Petit Mal

Myoclonic

Atonic or Drop

Tonic-Clonic or Grand Mal

Tonic

Clonic

- Absence or Petit Mal seizures come on quickly and usually only last 30 seconds or less. The individual may exhibit eye blinking and appear “spaced out” and is non responsive neither hearing nor speaking. When the seizure ends the individual has no idea that it occurred and will continue on with whatever activity he/she was engaged in at the time the seizure occurred.
- Myoclonic seizures are sudden brief jerks of the body and may be limited to the face, extremities, head or involve the entire body. There may also be twitching of the face, eyebrows, nostrils and rapid eye movements back and forth. This type seizure may only last for one jerk or may continue on with multiple jerks.
- Atonic or Drop seizures cause sudden loss of muscle tone and the individual will fall without warning. There may be some convulsions and some confusion with this type seizure but after the seizure ends the individual is able to stand and walk.
- Tonic-Clonic or Grand Mal Seizures actually happen in two phases. The Tonic phase is the first stage of the seizure. The body becomes stiff, the pupils become enlarged, the eyes roll up or to the side, breathing becomes shallow and very slow and the heart rate may slow. The Clonic phase is the convulsive part which includes trembling or jerking of the entire body. The individual may lose control of the bladder or bowels or vomit and may stop breathing temporarily and attain a bluish color to lips, fingers or skin. This is called the *post-ictal* phase. After the seizure is over the body relaxes and goes limp. Breathing recommences and the individual usually sleeps for a period of time. This type of seizure is never remembered. People have always wanted to insert a spoon or other object in the mouth to prevent swallowing of the tongue. **DO NOT** put anything in the mouth, especially fingers. It is physically impossible to swallow the tongue.
- Tonic Seizures start the same way the Tonic-Clonic Seizures do but never go beyond this phase. The individual stiffens and may appear to “shiver”. When the seizure ends the body goes limp and the individual may experience the *post-ictal* phase the same as the Tonic-Clonic.

- Clonic Seizures cause the body to stiffen and relax repetitively in a rhythmic manner. It may appear like jerking of the entire body. As with the Tonic-Clonic and Tonic Seizures the body goes limp when the seizure ends and the individual may experience the *post-ictal* phase.

II. Partial Seizures

There are three types of Partial Seizures: Simple Partial, Complex Partial and Partial Seizures that become Generalized. These type seizures are caused by only part of the brain undergoing electrical discharging.

- Simple Partial Seizures are also called Focal Seizures. This type seizure is localized to one side of the body and may include any of the following; jerking of the arms or legs, “tingling” feeling on one side, turning the eyes or head to one side or a pained or fearful look on the face. An individual is aware that this is happening.
- Complex Partial Seizures are also called Psychomotor or Temporal Lobe Seizures. Begins with blank stare, and may be followed by random activity, chewing, picking at clothes, pick up objects, remove clothing, appear afraid and may run. Individual is awake but unaware of surroundings and may appear dazed, confused and mumble. May also exhibit anger, yelling, screaming, sobbing or laughter. Will fight if restrained. Has been mistaken for a person under the influence of drugs or alcohol. Can last several minutes and afterwards has no memory of experience. This type seizure may be preceded by an “aura” which was described earlier in this section.
- Partial Seizures that become Generalized are also called Jacksonian Seizures. This type seizure begins as a partial seizure then spreads to involve the entire body. The initial Partial Seizure may be short and soon lead to a Tonic-Clonic or other Generalized Seizure.

III. Status Epilepticus

Status Epilepticus is when seizures become repetitive, often with the interval shortening between each seizure and/or continuous seizure activity. This is not confined to convulsive type seizures only and is a situation requiring immediate medical attention.

What to do during a seizure.

Remain calm. Seizures can be terrifying but remaining calm is essential. Stay with the individual until the seizure stops. Protect from falling and/or striking against hard objects. In the case of Tonic-Clonic, Tonic, Clonic or Atonic Seizures, if standing or sitting, ease to floor and place individual on side in case of vomiting. Try to time the length of the seizure, as difficult as it seems.

What not to do.

Do not place anything in the mouth. This can damage gums or teeth. Never put fingers in mouth. The jaw muscles tighten during a seizure and fingers can be severely bitten. Remember.....it is impossible to swallow the tongue.

Do not try to stop or restrain movements during a seizure.

When to call for help.

This is often determined by a person's experience with seizures. Otherwise, call for help if the individual has trouble breathing/changes color, lasts more than five minutes, chokes on secretions (vomit, etc.), or is injured by fall. Check on the individual every five minutes after a seizure. It is usual for them to sleep but if unable to awake after a period of time, seek help. You will learn much about what to do, not to do and when to get help with experience.

DNA Diagnosis - Carrier Testing - Prenatal Testing

The identification of the genes for the Infantile, "Classic" Late Infantile, "Finnish" Late Infantile and Juvenile forms of Batten Disease now provides for diagnosis, carrier and prenatal testing. These tests are done with blood. When arrangements have been made with either of the two laboratories doing these tests, blood can be drawn locally and shipped overnight to the laboratory. It is important to have it done so that the blood arrives on Monday through Thursday so that it can be handled immediately upon arrival. Neither laboratory works on the weekends. When sending blood for diagnostic purposes all previous test results should be included.

For carrier and prenatal testing both parents need to submit blood. In the previous section on the inheritance of Batten Disease it was shown how each parent could have a different gene mutation.

DNA testing:

Massachusetts General Hospital
Neurogenetics DNA Diagnostic Lab
CPR Building North, 5th Floor, Suite 5300
185 Cambridge Street
Boston, MA 02114
Katherine B. Sims, M. D., Director
Telephone: (617) 726-5721
Website: <http://www.dnalab.org>

Dept of Pathology & Laboratory Medicine
University of Rochester Medical Center
601 Elmwood Ave., Box 626
Rochester, New York 14642
Paul G. Rothberg, PhD, Director
Telephone: (585) 273-2229

The Hospital for Sick Children
Molecular Genetics Laboratory
555 University Ave
Toronto, Canada, M5G1X8
Peter N. Ray, PhD, Director
Telephone: (416) 813-6590
Website: www.sickkids.ca/molecular

Laboratory of Molecular Genetics
Helsinki University Hospital, Finland
PL 140, Haartmaninkatu 2
Helsinki, Finland 00290
Irma Järvelä, Laboratory Supervisor
Website: www.EDDNAL.com

**Centro de Estudio de las
Metaboloopatias Congenitas (CEMECO)**
Director: Prof. Dra. Raquel Dodelson de Kremer
Pediatriat, Medical Genetician.
Address: Hospital de Niños de la
Provincia de Córdoba
Bajada Pucará y Ferroviarios
5000 Córdoba , Argentina
Telephone: +54 351 4586 473

Women's and Children's Hospital
72 King William Rd.
North Adelaide 5006
Australia
Michael Fietz, Ph.D. - Head
Telephone: 00-61-8-8204-8062
Email: michael.fietz@adelaide.edu.au

Electron microscopy:
NY State Institute for Basic Research
Neurogenetic Molecular Diagnostic Lab
1050 Forest Hill Rd.
Staten Island, NY 10314
Krystyna Wisniewski, M.D., Ph.D., Director
Telephone: (718) 494-5202

Enzyme Assay:
Children's Hospital & Regional Medical Center
Department of Laboratories
4800 Sand Point Way NE
Seattle, WA 98105
Rhona Jack, M.D. – Director
Telephone: (206) 987-2102

Please see the BDSRA website for a complete list of testing centers: www.bdsra.org

BDSRA recommends the services of a genetic counselor with carrier and prenatal testing.

Batten Disease Support and Research Association

The BDSRA Mission Statement...

. . . to be an international support and research networking organization for families of children and young adults with an inherited neurological degenerative disorder known as Batten Disease.

In order to effectively combat the devastation of the disease and to fully support research efforts to unravel the mysteries of Batten Disease, the worlds of medical science and the victims and their families must meet and work closely together to reach understanding and common goals.

In an effort to bring those common goals to fruition, the Batten Disease Support and Research Association (BDSRA) was formed in July, 1986, by Gary and Judith Grant of Spanaway, Washington, who are parents of three children with Batten Disease. Seeing the tremendous need for a unified entity that would work toward important goals and recognizing, as well, the need for support among children and their families, the founders designed the association to:

- maximize the opportunities of victims of Batten to lead as normal lives as possible.
- provide a parent communication network, information and emotional support to families of persons with Batten Disease.
- educate lay persons and professionals about the special needs of the children and their families.
- act as a national registry for NCL researchers throughout the world.

All of the services of BDSRA are available internationally, for a minimal membership fee, and are available at all levels of participation. BDSRA is a not for profit 501(c)(3) organization. Some of the individuals who turn to the association have need of the full range of services - contact, newsletter, research, and registry information - and are willing to assist the Association in compiling information and providing professionals with facts and observations. Others want simply to receive the newsletter and remain anonymous to all other aspects of BDSRA. Whatever the needs, BDSRA can meet them.

Our Family Services Include:

Information and education about Batten Disease and related medical and educational issues.

Family support through networking with other families.

A 1-800 telephone number available to everyone.

Quarterly Newsletter

Medical referrals and a medical advisory board whose purpose is to assist families.

Family directory for those families who desire to have contact with other families.

An annual three day conference designed to bring families together for the purpose of education, support, and sharing.

17 Chapters in the United States, Canada, Australia, South Africa, South America and Spain.

Sibling Support Group

Parent Mentoring Program

Bereavement Outreach Program

Website with information, news, bulletin board, chat rooms and children's pictures
<http://www.bdsra.org>

Medical Equipment Exchange Program

Grandparent Support Program

Education Support Program

BDSRA and Research

BDSRA promotes, supports and funds research through:

Active participation in research projects.

Participation in and support of cell banks at Massachusetts General Hospital and the Institute for Basic Research.

Participation in the National Batten Disease Registry.

An annual research grant award program.

Tissue Donation Program.

State, Regional & International Chapters of BDSRA:

Alabama Chapter – beckylucas7@peoplepc.com

Australian Chapter – gvjcando@ozemail.com.au

Northern California Chapter – jallio@sbcglobal.net

Canadian Chapter – gmaxim@accesscomm.ca

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Southeast Chapter – lowther@windstream.net

Spanish Chapter – judy100201@yahoo.es

Tennessee Chapter – coach23baseball@bellsouth.net

National Batten Disease Registry

The National Batten Disease Registry is located at and maintained by the New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY. The information maintained in the registry includes a family tree (or pedigree), clinical information (that is, information on physical and mental status), educational background and occupational history and is used to help research into Batten Disease worldwide.

The Batten Disease Research Roster is used to help research in two ways:

1) Investigators may request information from the roster. Before the registry gives out this information, a signed consent form from the family is required. All information is coded and any information which could identify a family is removed. 2) Researchers may also contact the registry if they need volunteers to participate in research projects. If a family fits the specifications of the investigator, the registry contacts the family with complete details of the project, including what the investigator wishes and what biological samples (if any) may be needed, and asks for their participation. Families are not contacted by investigators unless they wish to be and have signed the appropriate consent form. Otherwise, families will be contacted by either the Registry or BDSRA. Families participating in research projects are required to sign consent forms for each individual project. All requests for research volunteers are screened by the Institute Review Committee of the registry to insure that the requests are appropriate and ethical. Families are under no obligation to participate in any research project.

New families joining BDSRA are referred to the National Batten Disease Registry. The Registry will mail questionnaires to the families. The registry is **TOTALLY VOLUNTARY!** Families may withdraw from the registry at any time.

For further information about the National Batten Disease Registry call: 1-800-952-9628

Glossary

Amino Acid - any of the alpha-amino acids that are the chief components of proteins and are synthesized by living cells or are obtained as essential components of the diet.

Ataxia - an inability to coordinate voluntary movements that is symptomatic of nervous system disorders. Often associated with problems walking.

Atrophy - decrease in size or wasting away of a body part or tissue.

Atypical - irregular, does not conform to type.

Autofluorescent - having a natural fluorescence when exposed to ultraviolet light.

Biochemical - characterized by, produced by, or involving chemical reactions in living organisms.

Buffy coat - thin yellow white layer of white blood cells between red blood cells and serum when spun down in a centrifuge.

Ceroid - a naturally occurring lipid pigment with characteristics similar to lipofuscin.

Clinical-Pathology - the practice of Pathology as it pertains to the care of patients. The sub-specialty in pathology concerned with the theoretical aspects of laboratory technology that pertains to the diagnosis and prevention of disease.

Clonus - involuntary, rapid contractions and relaxations of a muscle.

Cognition - meaning what a person or child knows and understands, or the process of knowing.

Cognitive - relating to or being conscious, thinking, reasoning, remembering, imagining or learning words.

Computerized Transaxial Tomography (CT Scan) - a sectional view of the body constructed by computed tomography.

Conjunctiva - the mucous membrane that lines the eye and eyelid.

Contractures - a permanent shortening (as of muscle or tendon).

Dysarthria - a condition where the swallowing muscles and muscles required for speech are not moving properly or not in a coordinated fashion giving the speech a loose and nasal quality.

Dystonia - a condition where the hand, foot or neck assume a stiff and involuntary posture which may involve unusual movements.

EEG-Electroencephalograph - an apparatus for detecting and recording brain waves.

Enzyme - a complex produced by living cells that catalyzes chemical reactions in organic matter.

ERG - Electroretinogram - A graphic record of electrical activity of the retina.

Extra pyramidal - involuntary movements of specific types originating in the basal ganglia area of the brain. Tremors or shaking.

Fundus - the part of the eye opposite the pupil.

Genotype - the genetic blue-print of an organism.

Grand Mal - epilepsy due to an inborn, usually inherited dysrhythmia of the electrical pulsations of the brain as demonstrated by an EEG and characterized by attacks of violent convulsions, coma, constitutional disturbances, and usually amnesia.

Heterozygous - meaning only one copy of a gene is defective.

Histo-chemical - a science that combines the techniques of biochemistry and histology in the study of chemical makeup of cells and tissues.

Homozygous - meaning both copies of a gene are defective.

Hyperkinesia - constant and excessive movement and motor activity.

Hyperexcitability - the state or condition of being unusually or excessively excitable.

Hypotonia - low or poor muscle tone.

Inclusion body - descriptive term used for deposits contained within sack-like structures usually found in the lysosome. When talking about Batten Disease refers to Granular Osmiophilic Deposits (GRODs), curvilinear, or fingerprint formations.

Isoelectric - pertaining to the electric baseline of an electroencephalogram (EEG).

Lipid - fat molecule.

Lipofuscin - a yellow-brown waste material deposited in many nerve and skin cells, where it interferes with cellular metabolism. Lipofuscin is made up of cross-linked, peroxidized lipids and cross-linked proteins. Lipofuscin deposits in skin are colloquially called "age spots" or "liver spots".

Lipopigment - aging pigments; lipofuscin or ceroid.

Lymphocyte - a type of white blood cell.

Lysosome - the recycling center of the cell where large molecules are broken down into small molecules to be reused.

MRI - Nuclear Magnetic Resonance Imaging- a noninvasive diagnostic technique that produces computerized images of internal body tissues and is based on nuclear magnetic resonance of atoms within the body induced by the application of radio waves.

Macula - a portion of the retina.

Microcephalic - see microencephaly.

Microencephaly - a condition in which the head and brain are significantly smaller than normal for age and sex (head circumference less than the 5th percentile for age).

Mitochondria - a specialized cellular part found outside the nucleus that produces energy for the cell.

Myoclonic - A sudden shock like twitching of muscles or parts of muscles without any rhythm or pattern, occurring in various brain disorders.

Myoclonus - jerking, twitching or spasm of a muscle or group of muscles. Difficult to distinguish from myoclonic seizures.

Neurophysiological - physiology of the nervous system. The science which treats the functioning of a living organism and its parts. And, of the physical and chemical factors and processes involved.

Neuroradiology - radiology of the nervous system. The use of x-rays in the diagnosis and treatment of nervous system disorders.

Neuron - an excitable cell specialized for the transmission of electrical signals over long distances. Neurons receive input from sensory cells or other neurons and output to muscles or other neurons. Neurons with sensory input are called sensory neurons, neurons with muscle outputs are called motoneurons, and neurons that connect only with each other are called interneurons. Neurons connect with each other via synapses.

Nystagmus - involuntary, erratic eye movements.

Oxidation - the process whereby fatty acids are degraded.

Pathology - 1) The study of the essential nature of disease and changes because of the disease; 2) The physical and chemical changes brought about by disease; 3) An overall view of abnormalities.

Peroxidation - oxidation of lipids.

Petit-Mal - Epilepsy caused by an usually inherited dysrhythmia of the electrical pulsations of the brain and characterized by attacks of mild convulsion, seizures with transient clouding of consciousness without amnesia, and with or without slight movements of the head, eyes, or extremities.

Phenotype - what is expressed in an organism or cell. Some genes are not important to some things or cells so a mutation in them has no affect on the appearance and function of those cells. The importance of some genes, such as the one responsible for phenylketonurina (PKU) can be overcome by environmental factors, in this case diet. In this example the disease phenotype is avoided without altering the genotype.

Proteolipid - molecularly bound fat to protein.

Protein - any of a large group of naturally occurring complex organic compounds, each composed of amino acids containing the elements carbon, hydrogen, oxygen and nitrogen.

Ptosis - droopy eyelids.

Pyramidal - voluntary movements originating in the brain.

Rigidity - the quality or state of being stiff or without flexibility; abnormal stiffness of muscle.

Scoliosis - curvature of the spine.

Seizures - brief changes in the normal functioning of the brain's electrical system causing unusual body movements, changes in behavior or consciousness.

Spasticity - a spastic state or condition: especially muscular hypertonicity with increased tendon reflexes. **Rigidity.**

Symptomatology - a branch of medical science concerned with symptoms of disorders.

Tonic-Clonic - Characterized by tonus (contraction of muscle) also marked by or being prolonged muscular contractions. Clonus - contraction (spasm).

Vacuoles – holes.

VER -Visual Evoked Potential - the measurement that results from the recordings of an EEG from the occipital area of the scalp as the result of retinal stimulation by a light flashing at quarter-second intervals, as given by a computer that averages the EEG response of 100 consecutive flashes.

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