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Batten the mistery disease: A brief on batten disease

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Abstract
The word Batten which it seems very rare and recessivene urder active disease which mainy found in children. Generally it grws with childhood which is the most common form of a group of diseasorder called as neuronal ceroid lipofuscinoses. In the field of medicine it is also called as Neuronal Ceroid Lipofuscinosis (NCL).The major difference between Batten and NCL are: Progressivness, age of onset, side effect, pathogenic response, mode of action to receptor etc.It is a genetic diseasorder which generay deveped during childhood The maximum risk factor is in between the age 5 to10.At eary stage the major symptoms are seizure and eye prbelms The earliest symptoms range from being fairly obvious, with a child experiencing seizures or vision problems, through to subtle signs such as mild personality changes or clumsiness. Now a day by through the development of many animal model and by the help of new technology gradually we controll over the disease.

Keywords: Batten, animal model, NCL, genetic, childhood, technology, treatment, therapy, nervous system, seizures

Introduction
Neuroal ceroid Lipofuscinoses which is also called as batten disease is an inerited disorder. Generally it starts from the childhood by through nervus system disorder. Batten disease (Neuronal Ceroid Lipofuscinoses) is an inherited disorder of the nervous system that usually manifests itself in childhood. Batten disease is named after the British paediatrician who first described it in 1903. It is one of a group of disorders called neuronal ceroid lipofuscinoses (or NCLs). The neuronal ceroid lipofuscinoses (NCLs) are a significant cause of childhood progressive intellectual and neurological deterioration (Hofmann *et al*, 2002) [21]. Collectively, this group of at least eight genetically distinct disorders is considered the most common pediatric neurodegenerative disease. Originally described as a form of 'amaurotic familial idiocy', these fatal disorders were subsequently renamed because of the characteristic intracellular accumulation of ceroid and lipofuscin. The precise relationship between the appearance of these lip pigments and cellular dysfunction remains unclear, but these disorders exert a profound effect upon the central nervous system (CNS) of affected individuals (Wisniewski *et al*, 2001; Mitchison *et al*, 2001) [57, 38]. The substantial impact of the NCLs upon carers has only recently begun to be evaluated (Labbe *et al*, 2002; Gardiner 2002) [30, 15]
Although Batten disease is the *juvenile* form of NCL, most doctors use the same term to describe all forms of NCL. Early symptoms of Batten disease (or NCL) usually appear in childhood when parents or doctors may notice a child begin to develop vision problems or seizures. (Hobert *et al*, 2006) [20] In some cases the early signs are subtle, taking the form of personality and behaviour changes, slow learning, clumsiness or stumbling. Overtime, affected children suffer mental impairment, worsening seizures, and progressive loss of sight and motor skills. (Rakheja *et al*, 2007) [47] Children become totally disabled and eventually die. Batten disease is not contagious nor, at this time, preventable. To date it has always been fatal. (Australian Chapter of Batten Disease Support and Research Association)
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. (Cooper JD, 2008) [11] 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. (Wisniewski *et al*, 2001) [57]. Batten disease is rare and occurs in an estimated 2 to 4 out of every 100,000 births in the United States.

It is inherited in an autosomal recessive pattern (Cooper JD, 2008) [11]. The mutation causes the buildup of pigments called lipofuscins in the brain, leading to neuronal death. Eventually, children with Batten disease become blind, bedridden, and demented. Batten Disease is a life limiting disease; life expectancy varies depending on the type or variation. Death usually occurs in middle childhood between the ages of 5 and 14 years, depending on the speed of disease progression (Rakheja *et al*, 2007) [47].

Abbreviations

ANCL adult neuronal ceroid lipofuscinosis
CNS central nervous system
GABA a-amino butyric acid
GAD glutamic acid decarboxylase
INCL infantile neuronal ceroid lipofuscinosis
JNCL juvenile neuronal ceroid lipofuscinosis
LINCL late infantile neuronal ceroid lipofuscinosis
NCL neuronal ceroid lipofuscinosis
PPT palmitoyl-protein thioesterase
TPP-1 tripeptidyl peptidase-1

Batten's Syndrome

Pathogenesis

It is caused by a mutation in the CLN3 gene at gene locus 16p12.1. This group of diseases represents a new class of lysosomal storage disorders. (Bennett *et al*, 1999) [5] Of the nine clinical variants (CLN1-CLN9), six have been genetically identified. (Persaud *et al*, 2007) [46]

As well as the CLN3 gene, these include CLN1, CLN2, CLN5, CLN6 and CLN8. The pathological features are severe, widespread neuronal degeneration resulting in simple retinal atrophy and in massive loss of brain substance and accumulation of lipofuscin in neuronal perikaryon. (Ceroid Lipofuscinosis) There are a number of useful tests: There is a deficiency of leukocyte peroxidase. This might also be useful in detecting heterozygotes. There are vacuolated peripheral blood lymphocytes and characteristic ultra-structural fingerprint profiles. (Brod *et al*, 1987) [6] Both homozygotes and heterozygotes can be identified on the basis of metachromasia in skin fibroblasts in cell culture. (Danes *et al*, 1968) [12] Polyacrylamide gel electrophoresis (PAGE) shows low molecular weight peptides in the urine and this may be a specific marker. (LaBadie *et al*, 1990) [29] PAGE can also be used on chorionic villous samples for pre-natal diagnosis. MRI shows general brain atrophy, more in the cerebrum than the cerebellum. Density is reduced in the thalami. If MRI spectroscopy is available it will show almost complete loss of N-acetylaspartate, reduction increatine- and choline-containing compounds, raised levels of my inositol and raised lactate in both grey and white areas. Direct gene analysis has been used for antenatal diagnosis. (Munroe *et al*, 1996) [23]

Epidemiology

It is a rare condition with a variable incidence across different countries. In Western Germany it has been estimated as occurring in 0.71 per 100,000 live births. (Claussen *et al*, 1992) [10] It occurs in about 1 to 5 cases per 100,000 generally, but in Finland the figure is around 8 per 100,000. There appear to be slightly different mutations across Europe.

Risk factors

As with other rare autosomal recessives, the main risk is consanguineous marriage. If a child is affected, both parents will be carriers. The risk for further children is that

1 in 4 will have the disease
2 in 4 will be normal but carriers of the gene 1 in 4 will be normal and not a carrier

Presentation

Onset is between 5 and 10 years old:
There is often rapid deterioration of vision and a slower, but progressive deterioration of intellect.
Seizures and psychosis develop later. There may be features of Parkinson's disease. In some cases, the early signs are subtle, taking the form of personality and behavioural changes, slow learning, clumsiness.

Management

There is little that can be done for the child, but genetic counselling for the parents is essential. Anticonvulsants will help the management of epilepsy in children and adolescents. If there are features of Parkinsonism, L-DOPA seems to be of benefit, but not selegeline. (Aberg *et al*, 2001) [1] Other treatments are of no proven value. Vitamin E, other antioxidants and selenium are all without benefit and, inthe few cases where bone marrow transplantation has been tried, there has been no benefit (Persaud *et al*, 2007) [46]. However, there isthe prospect of new therapies following use of allogeneic hematopoietic stem cell transplantation. (Krivit *et al*, 2004) [28] Normalenzymatic activity has been reported, without the need for any medication. Reconstruction of the central nervous system has also been reported. However numbers of treated patients are small and further research is neededon safety.

Features to facilitate early diagnosis

The neuronal ceroid lipofuscinoses has recently been demonstrated that this material is two thirds protein. (Ekazi *et al*, 2004) [13] Clinical features, including age of onset and the presence/ ultra-structural appearance of this lysosomal storage material, have traditionally classified NCLs as infantile, late infantile, juvenile, and adult. The term Batten disease should refer only to the juvenile onset form of NCL, but this eponym has been applied to all NCLs. (Spalton *et al*, 1980) [50] Current genetic classification of NCLs distinguishes eight different disorders, which often encompassclinical heterogeneity. (Goebel *et al* 2004) [17] Two genes, CLN1 and CLN2, encode for lysosomal proteases palmitoyl protein thioesterase and tripeptidyl peptidase, respectively. Lysosomal membrane proteins of currently unknown function are encoded for by CLN3, CLN5, CLN6, and CLN8.(Goebel *et al* 2004) [16] The majority of cases of juvenile onset NCL are caused by mutations in CLN3 which maps to chromosome 16p21. (Cell 1995) [53] To date 31 mutations in this gene have been reported, the commonest of which is a 1.02 kb deletion that is present on approximately 85% of disease chromosomes. (Moles *et al*, 2004) [39] Juvenile phenol types have also been observed following mutations in the CLN1 and CLN2 genes.4 The primary biochemical defect in these disorders is yet to be ascertained and to date there is no available treatment. It is juvenile NCL (jNCL) that is of particular interest to the ophthalmologist as these children usually present with rapidly progressive visual failure between the ages of 4– 10 years, generally leading to legal blindness within 3 years. (Taylor *et al*, 2004) [52] The incidence of jNCL is estimated at up to one in 25000 with an increased prevalence in north European populations.6It is an important cause of childhood blindness in the United Kingdom as up to 25% of the children registered as blind each year presenting with retinal or macular disease

may have JNCL (Taylor *et al*, 2004) [52]. Early diagnosis of JNCL by the ophthalmologist has several Implications. In particular, it allows families to receive the appropriate counselling and also enables appropriate provision of educational and family support. The diagnosis is based on clinic pathological findings and can be confirmed by molecular genetic testing. Retinal signs include bull's eye maculopathy, peripheral pigmentary or atrophic changes, disc atrophy, and attenuation of retinal arterioles (Mantel *et al* 2004) [35]. However, fundus examination at presentation may be normal causing great diagnostic difficulty. Features including behavioural changes, cognitive impairment, motor disturbance, and seizures follow the ophthalmic signs. The disease follows an inexorable path to death in the second or third decade. Analysis of the peripheral blood film demonstrates vacuolated lymphocytes with the characteristic fingerprint profile pattern on ultra-structural appearance. The diagnosis is confirmed by molecular analysis of the CLN3 gene, with the majority of disease alleles having the common 1.02 kbdeletion (Taylor *et al*, 2004) [52]. Electrophysiological testing may facilitate the early diagnosis of jNCL and electro retino grams (ERGs) typically demonstrate an electronegative waveform under both scotopic and photopic conditions. A series of patients with jNCL is reported and their clinical, electro diagnostic, blood, and molecular genetic findings as certained to identify features for early investigation and diagnosis of this condition (Persaud *et al*, 2007) [46]. We also highlight the need for support measures to be available once the diagnosis has been made. Some data on three of these patients have previously appeared (Mantel *et al* 2004; Marshman *et al* 1998) [35, 36].

Process of diagnoses

As vision loss is often an early sign, Batten disease/NCL may be first suspected during an eye exam. An eye physician can detect a loss of cells within the eye that occurs in the three childhood forms of Batten disease/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 Batten disease/NCL may refer the child to a neurologist, a doctor who specializes in disease of the brain and nervous system (Palmer *et al*, 1992) [44]. In order to diagnose Batten disease/NCL, the neurologist needs the patient's medical history and information from various laboratory tests. (Verkruyse *et al*, 1996) [34]

Different diagnostic tests

- **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 found in many different tissues, including skin, muscle, conjunctiva, rectal and others. Blood can also be used (Mantel *et al* 2004; Marshman *et al* 1998) [35, 36].
- **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 that a patient has seizures (Mitchison *et al*, 1997) [37].
- **Electrical studies of the eyes** these tests, which include visual-evoked responses (VER) and electro-retinagrams (ERG), can detect various eye problems common in childhood Batten disease/NCLs (Pearce *et al*, 1997) [45].
- **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 (Mitchison *et al*, 1997) [41]. A CT scan may reveal brain areas that are decaying 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 (Mantel *et al* 2004; Marshman *et al* 1998) [35, 36].
- **Enzyme assay** A recent development in the diagnosis of Batten disease/NCL is the use of enzyme assays that look for specific missing lysosomal enzymes for Infantile and Late Infantile forms only. This is a quick and easy diagnostic test. (Verkruyse *et al*, 1996) [55].

As 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 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 for additional testing. (Hellsten *et al*, 1996) [19]

In order to diagnose NCL, the neurologist needs the individual's medical and family 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 individuals with NCL (Mantel *et al* 2004; Marshman *et al* 1998) [35, 36]. The presence of vacuolated lymphocytes-white blood cells that contain holes or cavities (observed by microscopic analysis of blood smears)-when combined with other findings that indicate NCL, is suggestive for the juvenile form caused by CLN3 mutations. (Verkruyse *et al*, 1996) [34].
- Skin or tissue sampling. The physician 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 (Mitchison *et al*, 1997) [41].
- 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 an individual has seizures (Mitchison *et al*, 1997) [37].
- Electrical studies of the eyes. These tests, which include visual-evoked responses and electroretinograms, can detect various eye problems common in childhood NCLs. (Verkruyse *et al*, 1996) [55].
- Diagnostic imaging using computed tomography (CT) or magnetic resonance imaging (MRI). Diagnostic imaging can help doctors look for changes in the brain's appearance (Pearce *et al*, 1997) [45]. CT uses x-rays and a computer to create a sophisticated picture of the brain's tissues and structures, and may reveal brain areas that are decaying, or "atrophic," in persons with NCL. MRI uses a combination of magnetic fields and radio waves, instead of radiation, to create a picture of the brain (Mitchison *et al*, 1997) [37].
- Measurement of enzyme activity. Measurement of the activity of palmitoyl-protein thioesterase involved in CLN1, the acid protease involved in CLN2, and, though

more rare, cathepsin D activity involved in CLN10, in white blood cells or cultured skin fibroblasts (cells that strengthen skin and give it elasticity) can be used to confirm or rule out these diagnoses (Pearce *et al*,1997) [45].

- DNA analysis. If families where the mutation in the gene for CLN3 is known, DNA analysis can be used to confirm the diagnosis or for the prenatal diagnosis of this form of Batten disease (Mantel *et al* 2004; Marshman *et al* 1998) [35, 36]. When the mutation is known, DNA analysis can also be used to detect unaffected carriers of this condition for genetic counseling. If a family mutation has not previously been identified or if the common mutations are not present, recent molecular advanced have made it possible to sequence all of the known NCL genes, increasing the chances of finding the responsible mutation(s) (Mantel *et al* 2004; Marshman *et al* 1998) [35, 36].

Different forms of NCL

There are four other main types of NCL, including three forms that begin earlier in childhood and a very rare form that strikes adults. The symptoms of these childhood types are similar to those caused by Batten disease, but they become apparent at different ages and progress at different rates. (National Institute of Neurological Disorders and Stroke)

- Congenital NCL is a very rare and severe form of NCL. Babies have abnormally small heads (microcephaly) and seizures, and die soon after birth (Taylor *et al*, 2004) [52].
- Infantile NCL (INCL or Santavuori-Haltia disease) begins between about ages 6 months and 2 years and progresses rapidly. Affected children fail to thrive and have microcephaly. Also typical are short, sharp muscle contractions called myoclonic jerks. These children usually die before age 5, although some have survived in a vegetative state a few years longer (Mantel *et al* 2004) [35].
- Late infantile NCL (LINCL, or Jansky-Bielschowsky disease) begins between ages 2 and 4. The typical early signs are loss of muscle coordination (ataxia) and seizures that do not respond to drugs. This form progresses rapidly and ends in death between ages 8 and 12 (Mantel *et al* 2004) [35].
- Adult NCL (also known as Kufs disease, Parry's disease, and ANCL) generally begins before age 40, causes milder symptoms that progress slowly, and does not cause blindness. Although age of death varies among affected individuals, this form does shorten life expectancy (Mantel *et al* 2004; Marshman *et al* 1998) [35, 36].

There are also "variant" forms of late-infantile NCL (v LINCL) that do not precisely conform to classical late-infantile NCL.

Batten disease and other forms of NCL are relatively rare, occurring in an estimated 2 to 4 of every 100,000 live births in the United States. These disorders appear to be more common in Finland, Sweden, other parts of northern Europe, and Newfoundland, Canada. Although NCLs are classified as rare diseases, they often strike more than one person in families that carry the defective genes (Mantel *et al* 2004) [35].

Process of 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 (Mantel *et al* 2004) [35]. 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. Because the mutated genes that are involved in certain forms of Batten disease are known, carrier detection is possible in some instances. (Palmer *et al*, 1992) [44].

Adult NCL may be inherited as an autosomal recessive or, less often, as an autosomal dominant 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. (Camp *et al*, 1993) [7]

Background

A brief on Neuronal Ceroid Lipofuscinoses and juvenile-onset neuronal ceroid lipofuscinosis

Historically, many different therapies have been assessed for their ability to alter disease progression of the NCLs. While some treatments have lead to minor improvements, none have been able to arrest disease progression or improve the quality or duration of life. (Autti *et al*, 1996) [3]. Presently, many new therapeutic strategies, such as chaperone therapy, enzyme replacement therapy, gene therapy, and stem cell therapy, are being investigated for their ability to alter the disease course of the NCLs (Hobert *et al*, 2006*;* Cialone *et al*, 2012) [20, 9].

Juvenile neuronal ceroid-lipofuscinosis (JNCL, Batten disease, Spielmeyer-Vogt-Sjogren disease, CLN3) is the most common inherited, autosomal recessive, neurodegenerative disorder in man (Autti *et al*, 1996) [3]. Like the other neuronal ceroid-lipofuscinoses, it is characterized by progressive loss of vision, seizures, and loss of cognitive and motor functions, leading to premature demise. JNCL is caused by mutations of CLN3, a gene that encodes a hydrophobic transmembrane protein, which localizes to membrane lipid rafts in lysosomes, endosomes, synaptosomes, and cell membrane. (Mitchison *et al*, 1997) [37] While the primary function of the CLN3 protein (CLN3P) may be debated, its absence affects numerous cellular functions including pH regulation, arginine transport, membrane trafficking, and apoptosis. We have recently suggested that the unifying primary function of CLN3P may be in a novel palmitoyl-protein Δ-9 desaturase (PPD) activity that in our opinion could explain all of the various functional abnormalities seen in the JNCL cells. Another group of researchers has recently shown a correlation between the CLN3P expression and the synthesis of bis (monoacylglycerol) phosphate (BMP) and suggested that CLN3P may play a role in the biosynthesis of BMP (*Rakheja D, Narayan SB, Bennett MJ).*

Causes and Symptoms

Basic causes of Batten disease

Symptoms of Batten disease/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 (Mantel *et al* 2004) [35]. The lipopigments build up in cells of the brain and the eye as well as in skin, muscle, and many other tissues. (Vesa *et al*, 1995) [54] Inside the cells, these pigments form deposits with distinctive shapes that can be seen under an electron microscope (Harter *et al*, 1992) [18].

These deposits are what physicians look for when they examine a skin sample to diagnose Batten disease.

The diseases cause death of neurons (specific cells found in the brain, retina and central nervous system). The reason for neuron death is still not known.

To date, eight genes have been linked to the varying forms of NCL. Mutations of other genes in NCL are likely since some individuals do not have mutations in any of the known genes. More than one gene may be associated with a particular form of NCL. The known NCL genes are:

CLN1, also known as PPT1, encodes an enzyme called palmitoyl-protein thioesterase 1 that is insufficiently active in Infantile NCL (Mantel *et al*. 2004) [35].

CLN 2, or TPP1, produces an enzyme called tripeptidyl peptidase 1-an acid protease that degrades proteins. The enzyme is insufficiently active in Late Infantile NCL (also referred to as CLN2) (Vesa *et al*, 1995) [54].

CLN3 mutation is the major cause of Juvenile NCL. The gene codes for a protein called CLN3 or battenin, which is found in the membranes of the cell (most predominantly in lysosomes and in related structures called endosomes). The protein's function is currently unknown.

CLN5, which causes variant Late Infantile NCL (vLINCL, also referred to as CLN5), produces a lysosomal protein called CLN5, whose function has not been identified (Palmer *et al*, 1992) [44].

CLN6, which also causes Late Infantile NCL, encodes a protein called CLN6 or linclin. The protein is found in the membranes of the cell (most predominantly in a structure called the endoplasmic reticulum). Its function has not been identified. (Vesa *et al*, 1995) [54].

MFSD8, seen in variant Late Infantile NCL (also referred to as CLN7), encodes the MFSD8 protein that is a member of a protein family called the major facilitator superfamily. (Vesa *et al*, 1995) [54]. This superfamily is involved with transporting substances across the cell membranes. The precise function of MFSD8 has not been identified (Palmer *et al*, 1992) [44].

CLN8 causes progressive epilepsy with mental retardation. The gene encodes a protein also called CLN8, which is found in the membranes of the cell—most predominantly in the endoplasmic reticulum. The protein's function has not been identified.

CTSD, involved with Congenital NCL (also referred to as CLN10), encodes cathepsin D, a lysosomal enzyme that breaks apart other proteins. A deficiency of cathepsin D causes the NCL

Current research

The NINDS, a part of the National Institutes of Health, is the Federal government's leading supporter of biomedical research on the brain and central nervous system. As part of its mission, the NINDS conducts research and supports studies through grants to major medical institutions across the country. Through the work of several scientific teams, the search for the molecular basis of the NCLs is gathering speed. (Lu *et al*, 1996) [34]

Studying the lipopigment deposits that contain fats and proteins, one NINDS-supported scientist, using animal models of NCL, found that a large portion of this built-up material is a protein called subunit c. (Munroe *et al*, 1997) [37] This protein is normally found inside the cell's mitochondria, small structures that produce the energy cells need to do their jobs. Scientists are now working to understand what role this protein may play in NCL, including how this protein accumulates inside diseased cell and whether its accumulation-or the accumulation of other components in the storage material-is harmful to the cell. An important aspect of these studies is looking at how the different gene mutations lead to the lipoprotein deposits, which may involve the same processes. (Fearnley *et al*, 1990) [14]

In addition, research scientists are working with NCL animal models to improve understanding and treatment of these disorders (Pearce *et al*, 1997) [45]. These include naturally occurring sheep and dog models, and genetically engineered mouse models. Simpler models in lower organisms (such as yeast, zebrafish, and the fruit fly) are useful tools that are being implemented by scientists to study the function of the NCL proteins, most of which remain unknown. Research suggests that many of the NCL genes have conserved functions in the lower organisms; in other words, they work the same way in yeast, fly, or zebrafish cells as they do in humans. Because mice and lower organisms breed or propagate quickly and can be genetically manipulated, their use can speed NCL research. (Letourneur *et al*, 1992) [32]

More recently, advances in human cell research will assist the translation of findings in the model organisms to individuals with NCL dis orders (Fearnley *et al*, 1990) [14] Skin or other cell types taken from those with an NCL disorder can now be manipulated in the laboratory to become "pluripotent," meaning they can made into cells that have the potential to become any cell type—including brain cells. This process—known as cellular reprogramming—is used to establish patient-derived induced pluripotent stem cells (iPS cells). (Lu *et al*, 1996) [34].

Although no therapies at currently available for NCL disorders, a number of NINDS-funded science teams are working toward developing therapies and identifying therapy targets for NCL. The approaches undertaken by scientists include: gene therapy (for example, in CLN1 and CLN2). (Fearnley *et al*, 1990) [14] enzyme replacement therapy (CLN1 and CLN2). (Fearnley *et al*, 1990) [14]

- Stem cell therapy
- Identification of the normal protein functions that are lost as a result of the gene mutations.(Lu *et al*, 1996) [34]
- Testing candidate drugs that modify known disease abnormalities (for example, immune suppression to eliminate the observed autoimmunity in JNCL/CLN3); and screening to identify drugs or other factors that normalize cellular abnormalities in the NCL disease models. (Fearnley *et al*, 1990) [14]

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. (Hellsten *et al*, 1996) [19] 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. (Johnson *et al*, 1992) [26] 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

(Hellsten *et al*, 1996) [19]. 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 (Lu *et al*, 1996) [34].

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. (Lu *et al*, 1996) [34].

At the same time, other investigators are working to identify what substances the lipo- pigments 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. (Lu *et al*, 1996) [34] 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 under- standing 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 development. Mouse models make it easier for scientists to study the genetics of these diseases, since mice breed quickly and frequently. (Lu *et al*, 1996) [34]. 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 (Hellsten *et al*, 1996) [19].

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 (Hellsten *et al*, 1996) [19].

Support and encouragement can help patients and families cope with the profound disability and dementia caused by NCLs. Often, support groups enable affected children, adults, and families to share common concerns and experiences. There is currently no specific treatment that can cure or slow progression of this condition and therapy is instead focused on preventing and relieving symptoms. For example, anticonvulsant drugs may be used in cases where patients suffer form seizures and physiotherapy can help individuals retain function of their body for as long as possible. Meanwhile, scientists pursue medical research that could someday yield an effective treatment.

Future Research Directions

Scientists are now working to understand what role this protein may play in NCL, including how this protein accumulates inside diseased cell and whether its accumulation—or the accumulation of other components in the storage material—is harmful to the cell. More recently, advances in human cell research will assist the translation of findings in the model organisms to individuals with NCL disorders. (Goebel *et al* 2004) [16] Skin or other cell types taken from those with an NCL disorder can now be manipulated in the laboratory to become "pluripotent," The U.S. Food and Drug Administration approved cerliponasealfa as a treatment for slow loss of walking ability (ambulation) in children 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2). No specific treatment is known that can reverse the symptoms of Batten disease or other NCLs. However, seizures can sometimes 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 (Hobert *et al*, 2006) [20].

Conclusion

The neuronal ceroid lipofuscinoses, collectively referred to as Batten disease, make up a garoup of inherited childhood disorders that result in blindness, motor and cognitive regression, brain atrophy, and seizures, ultimately leading to premature death without a detailed understanding of the precise mechanisms that operate within each form of NCL, successful treatments for these fatal disorders will remain a distant prospect. The identification of gene products is now complete for the majority of different forms and has enabled the investigation of normal and pathological cell biology. Many issues remain to be resolved, but several lines of evidence point to the critical involvement of the lysosomal–endosomal system. Nevertheless, it will be vital to establish whether CLN gene products play other specific roles within the nervous system. The development of new animal models and the application of novel technologies is gradually creating a detailed picture of the progressive effects of disease. These efforts must be mirrored by the continued development of appropriate means to follow the clinical course in affected individuals.

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