

# Infantile Batten Disease

of help and supervision needed over and above that which a healthy child of the same age would need. Just because a child has a particular disease does not mean that the application will automatically be successful, each case is judged on its merits. There is an appeals process if the claim is unsuccessful.

If a parent has to care for the child for more than 16 hours per day and the child receives DLA then the parent may be entitled to **Invalid Carers Allowance**.

Further advice can be obtained from a social worker, the citizens' advice bureau or the benefits agency.

### Equipment

As the illness progresses, various kinds of equipment and aids become needed:-

- Car seats
- Pushchairs / wheelchairs
- Seating for in the home
- Protective headwear for when the child is still mobile but falling frequently
- Postural splints for the torso or limbs
- Feeding related - feed pumps and consumables (feed, containers and syringes)
- Suction for pharyngeal secretions
- Incontinence pads ["nappies"]
- Hoisting equipment or even lifts
- Bath aids
- Bed with safe sides
- Specialist mattress

The ease or difficulty of obtaining these items and resources varies greatly around the country, but all should be available without any cost to the family. Very expensive equipment provision may be means tested.

### Education

In the early stages of the illness, often before the correct diagnosis has been made, it is recognised that there is going to be some help needed with nursery and schooling. Most families find this very difficult and upsetting. At a time when the realisation is sinking in that their son or daughter isn't going to be "OK" and will need a lot of extra help to make progress at school, they often find many bureaucratic obstacles to overcome to get the help they feel their child needs. In trying to get through the process of "statementing", parents need a lot of guidance, understanding and support.

"Statementing" is the process where the child becomes the subject of a **Statement of Educational Needs**. This is a formal document drawn up by the local education authority, based on advice from the health professional and other professionals involved – usually at least a community paediatrician and an educational psychologist. It describes the child's educational needs and makes recommendations for the appropriate educational provision and allocation of resources. Unfortunately the resources provided often fall short of the resources needed. Adequate schooling is a field where considerable experience exists with BDFA.

**Introduction and Terminology** THE IDEA BEHIND PRODUCING THIS LEAFLET IS TO PROVIDE FAMILIES AND THE PEOPLE AROUND THEM WITH AN OVERVIEW OF THE ILLNESS. OUR UNDERSTANDING OF WHAT CAUSES THE ILLNESS IS GROWING RAPIDLY AND THIS LEAFLET TRIES TO EXPLAIN THE SCIENCE IN AN EASY TO COMPREHEND WAY.

The terminology is confusing; this is mainly because what we call Batten Disease is in fact several different genetic illnesses each with a different gene defect. They do however, have a lot of similar features. Traditionally, the different types of "Batten Disease" were classified according to the age of the child when the illness began, so we have Infantile, Late Infantile and Juvenile Batten disease for example - with the illness seeming to start at around 1, 3 and 7 years of age respectively.

As our understanding at the level of molecular genetics has increased, things have become more complex. The Batten Disease group of illnesses now tend to be referred to as the **Neuronal Ceroid Lipofuscinoses (NCL's)**. This term describes the abnormal appearance of affected cells as seen down a microscope. We also now recognise that there are more types of the illness than the Infantile, Late Infantile and Juvenile types etc, there are some less common "variant" types. Some of these are quite rare and only occur in significant numbers in certain parts of the world.

### Molecular Genetics

Our chromosomes contain thousands of genes, all of which code for proteins. Nine different genes causing different varieties of NCL have been identified so far. They are called CLN1 to CLN10. (CLN4 is the gene name given to a theoretical gene causing adult onset Batten disease. It has not yet been identified.) The nine genes are different and so are the abnormal proteins, but all result in similar disturbances of cell function and lead

to similar clinical symptoms. All the Batten disease proteins seem to be involved with the function of the lysosome – this is a tiny part of a cell that is involved in breaking down and recycling certain chemicals in the cell. When this process doesn't work properly, there is a build up of substances that aren't being broken down properly.

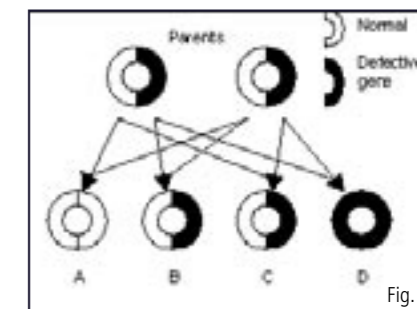
CLN1, CLN2 and CLN10 are genes coding for lysosomal enzymes, responsible for breaking down and recycling proteins in the lysosomes. Enzymes are often able to move inside and between cells. Some of the other genes code for proteins which are stuck in cell membranes and cannot move between cells, for example CLN3 and CLN5.

### How are NCLs inherited?

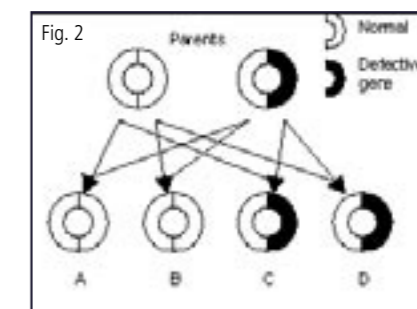
Apart from some very rare types, the NCLs are inherited in an "Autosomal Recessive" fashion. *Autosomal* means that the abnormal gene is carried on the normal chromosomes as opposed to the "sex" chromosomes – this means that the illness has nothing to do with gender. (Some illnesses are carried on the sex chromosomes and are said to be sex-linked and principally affect either males or females - such as colour blindness or haemophilia).

*Recessive* means that the abnormal gene does not lead to an affected individual if he or she has a normal gene as well, we each have a pair of genes – one from each parent. If both genes are normal the individual would clearly not have the disease, if a person has one normal gene and one abnormal gene, that individual would not have the disease (but would be a carrier and could pass the gene on to his or her child) but if a person has two abnormal genes he or she will have symptoms of the disease eventually.

The diagram above (Fig 1) tries to illustrate the various ways parental genes come together at conception when both parents



are carriers of the disease. Child A has 2 normal genes so does not have the disease, child D has 2 abnormal genes so does have the disease, children B and C have one normal and one abnormal gene – they do not have the illness but will be carriers. On average one in four (25%) of these parents' children will be normal, one in four (25%) will have the disease and two in four (50%) will not have the disease but will be carriers.



If only one of the parents is a carrier as in the diagram above (Fig 2), there are no diseased children but 50% will be carriers (on average), this explains how the gene can be passed down family trees from our ancestors for many generations without it being expressed as an affected individual until **bad luck** brings two carriers together. When this happens as shown above, **each child** this couple has will have a **one in four** chance of being affected by Batten Disease.

This leaflet is for basic information only; any decisions regarding an individual child should be done through the appropriate medical services. Some of the information in this leaflet is based on the chapter on Classic Late Infantile NCL by Dr RE Williams et al in The Neuronal Ceroid Lipofuscinoses, Goebel, Mole & Lake (Eds), IOS Press 1999 and 2008 and is used with permission.

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**Classical Infantile onset NCL**

Classical infantile NCL is due to a mutation in the CLN1 gene on chromosome 1 which leads to a deficiency of an enzyme that the gene is meant to make. This enzyme (a kind of protein) is called palmitoyl protein thioesterase 1 (PPT1). The lack of adequate amounts of PPT1 leads to the build up of waste products in the cell which somehow leads to cell death. These accumulations of materials can be seen with an electron microscope and are known as granular osmiophilic deposits (GROD). There are hundreds of cases diagnosed world wide, many of them in Finland. The highest incidence of a mutated CLN1 gene is in Finland, where the carrier frequency is 1 in 70 and the incidence in the population is 1 in 20,000. The incidence outside Finland is unknown, but INCL comprises 11% of all neuronal ceroid lipofuscinosis cases in the USA.

About half the cases of NCL caused by mutations in the CLN1 gene are of later onset, sometimes as late as mid teens/early adulthood.

**Age at Onset and First Symptoms**

The child seems to progress normally initially. Parents do not become worried about the motor and/or mental development of their children until the age of 10 to 18 months. However, the rate of head growth begins to decrease in several children as early as 5 months, indicating that the symptoms become apparent several months after the onset of the disease. Hyper excitability [being unsettled, including sleep problems], muscular hypotonia [floppiness] and lack of normal development in the fine motor skills are additional early signs. In the majority of children with INCL, the normal development begins to slow down during the second year of life. Until that time the children seem to be quite normal and happy, usually very "easy" children still learning new skills. But a careful examination often reveals muscular hypotonia, clumsiness in fine motor control and retarded growth of the head.

There is quite a lot of variation in how different stages of the illness progress but there is a gradual slowing of normal milestones and eventually a loss of skills that have been acquired. Loss of vision tends to start at around 18 months and usually progresses fairly rapidly. Alongside this is deterioration in mental functions, there is

developmental regression [loss of skills e.g. speech, coordination, continence]. These become apparent around this time or within a few months. Ataxia [clumsiness] increases as motor skills decline. Abnormal limb and body movements can occur and lead to spasticity (continued muscle contraction and exaggerated reflexes). Epileptic seizures of various kinds can occur but tend to be mainly myoclonic [jerks]. Feeding becomes more difficult with resulting poor weight gain and frequent symptoms of aspiration [difficulty coordinating swallowing with subsequent coughing / choking, food & drink "going down the wrong way"]. Most children now receive nutritional support using a nasogastric or gastrostomy tube.

In spite of this inexorable deterioration in all faculties, children with INCL are not in a vegetative stage but are able to smile, laugh and enjoy the presence of familiar people and music. If the medication is adequate these abilities are preserved until death, which usually takes place at the age of 8-13 years.

**Investigations**

Diagnostic investigations may include neurophysiology tests, samples for microscopy (biopsy - usually skin [taken from perhaps the arm under local anaesthetic]) and genetic analysis. Blood samples may now also be collected for enzyme assay; this can now give the diagnosis without the need for a biopsy. Whilst the list of biopsy samples does not include a rectal biopsy, this may be preferred by some pathologists in place of the skin biopsy.

**1. Neurophysiology**

These tests involve measuring "brain waves" with electrodes on the scalp; this is not painful and doesn't usually cause any distress. There are various tests in this area and include an electro-encephalogram (EEG), electro-retinogram (ERG) and visual evoked potentials (VEP).

**2. Neuroradiology**

Brain imaging (CT or MRI scanning) is performed as part of the investigation of children with multiple seizures and developmental regression. The changes found in classic infantile NCL are relatively non-specific, and the value of imaging lies mainly in excluding other causes. Early in the course of the disease there is mild cerebral atrophy [generalised shrinkage or loss of

brain tissue], but a normal scan does not exclude the diagnosis.

**3. Biochemical tests**

We now have a blood test enzyme assay, which measures the amount of the deficient enzyme PPT1. This is low in children with INCL.

**Treatment**

Therapy for children with classic INCL is essentially supportive. Psychological support around the time of diagnosis, and as the disease progresses for both parents and healthy siblings is important. Families should be given contact addresses for local parent support groups.

Most INCL patients need medication from the first stage onwards throughout life. The first used drug is usually Baclofen which is used for muscle spasms. The antiepileptic drugs of choice are Valproate, Clonazepam and Topiramate. Sometimes it may be necessary to use high doses of Baclofen in later years and it is sometimes necessary to administer the medication 3-5 times (daily) with regular intervals night and day. In some patients during the advanced phase of the disease, a fentanyl patch and orally administered morphine derivatives have been of great help in addition to the other medications.

Attention to posture, seating, skin and mouth care is essential, with professional guidance from physiotherapists and occupational therapists. Chest physiotherapy may be needed intermittently to help clear infections. Most children will require nutritional support at some stage, and parents often find that the use of a nasogastric tube or gastrostomy tube makes life much easier. Gastro - oesophageal reflux can often be troublesome and may require medication or surgery (e.g. Nissen's fundoplication).

Research is continuing into ways to treat or slow down the disease, e.g. gene therapy where the normal gene is reintroduced back into the cells & tissues and enzyme therapy where the defective or missing enzyme [kind of protein] is reintroduced.

**Genetic Considerations**

Because the diagnosis of classic infantile NCL is usually made when children are 18 months to two years old, there is the

possibility of younger siblings who may also be affected but presymptomatic [before the onset of symptoms but destined to get the disease]. In addition, the question of future pregnancies and prenatal diagnosis may arise. Once the diagnosis is certain, presymptomatic testing can be performed for siblings using blood samples. Prenatal diagnosis is usually available and based on genetic testing of the baby very early in pregnancy. The idea of prenatal testing is that if the test shows that the baby would be affected by Batten Disease then a termination of pregnancy [abortion] can be considered. Early advice from Local Clinical Genetics Service should be sought.

**Family Aspects**

From the time parents detect that their son or daughter is not developing properly, the family will need support. Sadly - probably because of the vagueness of the early clinical features - parents are often reassured that there isn't a problem and their worries are minimised, they are left feeling that they are worrying too much. This seems to be quite common and can be quite damaging in terms of the relationship between the family and health professionals.

The level of support and the personnel involved will vary between cases and depend on many variables such as the needs of the child and family at any one time, the rate at which the illness is progressing, the level of existing care and support from family and friends. The professionals usually involved would include; GP and members of the primary health care team - health visitor, district nurse; paediatrician (and / or paediatric neurologist), specialist paediatric community nursing, children's hospice staff, social worker, agencies such as Crossroads etc. There will be important involvement with education personnel from special nursery schools and input from specialist teachers for the visually impaired.

Given the appropriate level of professional support around the family - it is important that parents should be encouraged to take some control of their situation; for the services around to include them in decisions and plans of action; and for the families' wishes to be of paramount importance. This is not about families fitting into packages of care provided by the authorities, and parents should be encouraged and supported thoroughly, by appropriate giving

of information - to follow their intuitions, and to decide themselves what they want and need for their child or children. Following diagnosis it is important that parents can feel empowered - and able to provide quality of life for the little time they have left with their child. This kind of situation needs the full support, implemented sensitively and carefully, by the surrounding professional team.

Respite needs introducing at an appropriate stage and plenty of time needs to be given for parents to come to terms with needing this. It takes time and sensitive care to bring families to a stage where they can feel safe handing over the care of their child even for a short period of time. Paediatric health facilities and or children's hospices may be available locally or in the home for the families. Hospices - both adult and children's can still carry a stigma associated with use only at the end stages of life, however, most children's hospices are able to offer specialised and earlier respite and emotional support to families than this.

**Financial Support**

Finances often become much tighter as one or both parents often have to sacrifice their career to care for their child. Some benefits are available, these include the following. Disability Living Allowance (DLA) is a benefit that is available to people if they need help with mobility and/or are being cared for at home. **Disability Living Allowance (DLA)** comprises two benefits; **care allowance** and **mobility allowance** which is applicable from the age of 3. To get a blue disability vehicle badge, which is valid throughout the E.U., the child would usually have to qualify for mobility allowance i.e. be 3 or older although it is sometimes possible to get one sooner. Mobility allowance can sometimes be used for the Motability scheme to fund a vehicle. The High Rate Motability component of your DLA can sometimes be used to lease or hire a vehicle through the Motability Vehicle Scheme see [www.motability.co.uk](http://www.motability.co.uk) & [www.direct.gov.uk](http://www.direct.gov.uk) or 0845 456 4566.

It is important to realise that DLA criteria apply to the level of disability and the level

