



appropriate information, should be allowed to follow their intuitions, and to decide themselves what they want and how much they need for their child or children. Following diagnosis it is important that parents 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, from the surrounding professional team.

Respite care should be introduced at an appropriate stage. Usually parents need some time to come to terms with needing this, especially if this involves a children's hospice. Hospices - both those for adults and children, still carry a stigma and an association with advanced terminal illness and death. It takes time and sensitive care to bring families to a stage where they can feel safe handing over the care of their child in such an environment.

The family should be informed about the existence of parent **organizations** and contact groups (such as the BDFA or the BDSRA in USA). The rarity and lack of knowledge of the disease among physicians (most GPs will have never heard about Batten Disease and most general paediatricians will have very limited experience of it - if any) and friends poses a significant problem in itself. A close and continuing cooperation between the family doctor and a physician experienced in the management of NCL patients is required.

Benefits

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 caring for themselves at home. It comprises two benefits; **care allowance** and **mobility allowance**, which is applicable from the age of 3 years. In the early stages of the illness, parents have often been frustrated by applications being turned down or awarded at a low level. When applying (or

appealing against a decision) it is important to stress how much more care, attention and supervision your child needs over and above that which a healthy child of the same age would need.

To get a blue disability vehicle badge a young person would normally have to qualify for high level **Disability Living allowance**. The High Rate Mobility Component of your DLA can sometimes be used to lease or hire a vehicle through the **Motability Vehicle Scheme**, see www.motability.co.uk 0845 456 4566.

Mobility allowance can sometimes be used for the **Motability scheme** to fund a vehicle. Just because a young person has a particular disease does not mean that the application will automatically be successful, it is the level of disability that is important - not the diagnosis. Each case is judged on its merits. As the disease progresses, the level of disability increases, it is important not to "give up" if unsuccessful - keep trying. 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**.

Young people aged 16 who are unable to work are entitled to claim **Incapacity Benefit**, but there are qualifications.

Further advice can be obtained from the Citizens' Advice Bureau, The Benefits Agency or a social worker.

Equipment

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

- Car seats
- Pushchairs / wheelchairs
- Specialist mattress
- Seating for use at home and at school
- Protective headwear, if 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

The ease or difficulty of obtaining these items and resources varies greatly around the country, but all should be available at no 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 already clear that help will be needed with schooling. Most families find this very difficult and upsetting. At a time when the realisation is beginning to sink 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, parents often find many bureaucratic obstacles to be overcome in order to get the help they feel their child needs. In trying to get through the process of "statementing", parents need guidance, understanding and support. "Statementing" is the process where the child becomes the subject of a **Statement of Special 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 within BDFA.

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 Juvenile NCL by Dr I Hofman et al in *The Neuronal Ceroid Lipofuscinoses*, Goebel, Mole & Lake (Eds), IOS Press 1999 and is used with permission.

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Juvenile Batten Disease

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 (named after the British neurologist who described the condition in 1903) is in fact several different genetic illnesses each caused by a different gene defect. They do however have many similar features. The different types of "Batten Disease" are often classified according to the age of the child when the illness begins, so there are infantile, late infantile and juvenile types of 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 tends to be referred to as the **Neuronal Ceroid Lipofuscinoses** (NCL) this term describes the abnormal appearance of affected cells as seen down a microscope. It is now clear that 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

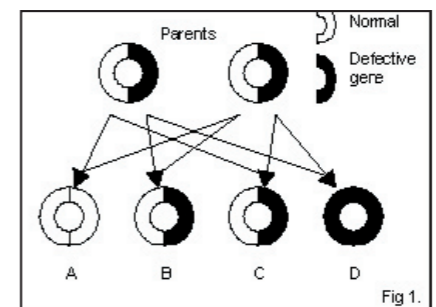
Our chromosomes contain tens of thousands of genes, most of which control the production of proteins. These proteins have various functions and include enzymes which act to speed up molecular chemical reactions. We know that the NCLs are caused by abnormal genes, and that the required proteins are not made properly. Eight gene defects are known so far, and they cause the different varieties of NCL - these are known as CLN 1 to 8. The 8 gene defects are all different and so are the abnormal proteins.

All somehow end up with a similar disturbance in cell function which results in similar clinical symptoms. All the proteins involved seem to be involved with the function of the lysosome. This is a tiny part of a cell, and its function is to break down and recycle certain chemicals in the cell. When this doesn't work properly, there is a build up of substances that can't be broken down properly. This 'build up' becomes toxic to the cell and eventually the cell dies.

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 passed down from each parent. If both genes are normal the individual does not have the disease. If a person has one normal gene and one abnormal gene, he or she does not have the disease (but is a carrier and could pass the gene on to his or her child). If a person has two abnormal genes, he or she has or will get the disease.

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

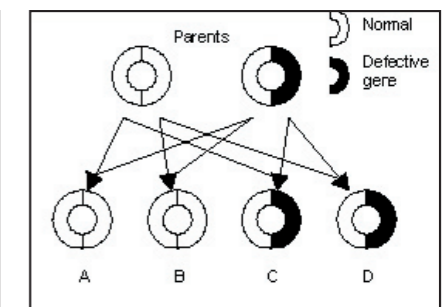


of the disease. Child A has two normal genes and does not have the disease. Child D has two abnormal genes and so does have the disease. Children B and C have one normal and one abnormal gene - they do not have the illness but will be carriers. For each pregnancy, there is a one in four (25%) chance that the baby will be affected; a one in four chance that the baby will have two normal genes and be healthy, and a two in four (50%) chance that the baby will be healthy but a carrier. Two out of three healthy children will be carriers.

If only one of the parents is a carrier as in Fig 2, no children have the disease 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 showing until **bad luck** brings two carriers together. When this happens (as shown above, in Fig.1) each child of this couple will have a one in four chance of being affected by Batten Disease.

Juvenile NCL

Juvenile NCL (JNCL) usually begins at early school age. It often begins with vision problems. Later short-term memory loss, epilepsy, motor problems and declining school progress become apparent. Death often occurs in early adulthood. Juvenile onset NCL is usually caused by mutations in a gene called CLN3 which is located on chromosome 16. Most young people carry a common deletion (called 1kb del) on both affected chromosomes. The exact function of this gene in health and disease is still unknown.





Symptoms

- **Eyes.** The leading symptom is isolated onset of visual failure due to retinal degeneration, usually detected between 4 to 7 years of age. Progression is mostly rapid and leads to blindness within 2 to 4 years. Initially, there are no other medical problems. During this early phase of the disease, fundoscopy (examination of the back of the eye) shows a characteristic appearance. Patients seem to preferably use their peripheral sight, giving rise to the "overlooking" phenomenon: the patients look up to a point above the person they are talking to. For the same reason, patients may walk with their head turned sideways. By the age of 20 years, they suffer from an almost complete loss of light perception.
- **Loss of memory, awareness and altered ability to think and understand** becomes evident several years after the onset of visual problems. Teachers may suspect a problem in a child who unexpectedly starts to have difficulties in short-term memory and word finding as well as in arithmetic at about 8 to 9 years of age. Finding the most appropriate



educational placement can be problematic around the age of 10 to 11, when coping in mainstream education may become difficult. Often schools for visually impaired children or those with special needs are appropriate.

- **Speech.** Speech gradually becomes strange and understandable only to the family. The speech pattern is peculiar with rapid, monotonous, staccato-like repetitive words and phrases. Echolalia (repeating words) is frequent. Around puberty, some children seem upset about their inability to express their thoughts correctly. Speech is mostly lost after the age of 20.
- **Epilepsy.** The severity of the epilepsy is quite variable. Most Young People suffer a first seizure between the ages of 5 and 18 years, at an average of 11 years of age. The predominant seizure types are generalized tonic-clonic ("grand mal" type convulsion of whole body with loss of consciousness) and myoclonic jerks while complex partial seizures and tonic (loss of tone) seizures have been seen in some Young People. Individuals with a late onset and easily controlled seizures remain active and well for a longer period of time.

- **Motor disorders.** By their mid-teens, children may develop signs of Parkinsonism. They show a characteristic standing posture with bent knees and some degree of stiffness. They sometimes have a stooped gait (with shuffling later on) and difficulty in initiating movement. Physiotherapy can be helpful. Spasticity is rarely observed and then only at a later stage of the disease. Loss of mobility may occur as early as the age of 10 years or well beyond the age of 20 years. The drug Co-beneldopa can be useful in reducing some of the symptoms and side effects of Parkinsonism.
- **Psychological, psychiatric and behavioural problems.** Some time after the onset of visual loss, psychiatric disturbances of various types may occur. Many children become emotionally unstable, either quiet and secluded or moody and easily upset. Signs of anxiety and fear may be overwhelming. Angry outbursts and violent behaviour may sometimes terrorize the family. The children may appear depressed because they sense their loss of abilities and become frustrated. Depression and frustration may worsen and result in a vicious circle. Hallucinations (seeing or hearing things that aren't there) are frequent and easy to recognise when the child is still able to communicate. It can be difficult, however, to diagnose hallucinations when verbal communication is no longer possible. As psychotic symptoms may still exist, they must be considered. Part of the unrest and outbursts of youngsters may be a consequence of hallucinations. Hallucinations occasionally are of long duration. Their subjective content is not always upsetting, and the family may adapt to a life with "non-existing" things and animals. Hallucinations can be controlled by 'Anti-Psychotic' drugs such as 'Risperidone'. Altogether, the intellectual, emotional, behavioural and psychotic symptoms form a complex psycho-organic syndrome that is rather unique in pubertal and adolescent patients with Juvenile NCL. Understanding this syndrome is a prerequisite for optimum management.
- **Sleep disturbance and unrest.** Often the young child experiences what are described as "night terrors" these can be very frightening and can cause frequent waking during the night. In their mid-teens many patients lose their normal sleep rhythm. The patients will not fall asleep even late in the evening and keep going and talking. This insomnia has been regarded as a symptom of depression but may also be due to epileptic activity. It becomes less frequent during the later course of the disease. Again this can be controlled by drugs such as 'Risperidone'.
- **Other features.** Most young adults have poor circulation leading to cold hands and feet and the lower legs may become puffy, these symptoms are more common in young people who are wheel chair dependant. Sexual

maturation in both sexes proceeds normally, although many females may experience absent or prolonged menstruation, and be more prone to seizures and hallucinations around the time of menstruation. Skin abnormalities such as acne seem to occur more frequently than in healthy teenagers.

Investigations

Diagnostic investigations usually include neurophysiological tests, a brain scan (MRI) and blood tests. A skin biopsy (or in some places rectal biopsy) may also be needed.

1. **Neurophysiology**
These tests look at "brain waves" with electrodes on the scalp. This is not painful and doesn't usually cause any distress. The tests would generally include an electro-encephalogram (EEG), electro-retinogram (ERG) and visual evoked potentials (VEP). The results of these will usually be abnormal.
2. **Neuroradiology**
Brain imaging (CT or MRI scan) is often performed as part of the investigation of children with seizures and visual impairment. The changes found in classic JNCL are relatively non-specific, and the value of imaging lies mainly in excluding other causes. Early in the course of the disease, scans are usually normal. Later there is progressive cerebral and cerebellar atrophy (generalised shrinkage or loss of brain tissue).
3. **Blood tests**
Blood tests will reveal the presence of vacuolated lymphocytes. Lymphocytes are a kind of white blood cell, and in JNCL they seem to have big holes known as vacuoles.
Blood cells can also be examined using an electron microscope and will show the typical fingerprint profile appearances of abnormal storage material in JNCL.
DNA tests looking for the common mutation (change) in the CLN3 gene should also be done.

Treatment

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

Medical management involves a number of aspects:

- Vision aids in the early stages
- Seizure control

- Psychological, psychiatric and behavioural problems
- Motor problems - Physiotherapy, wheelchairs, hoists and other equipment
- Swallowing and Nutrition.
- Management of continence

Seizure Control

Epilepsy is treated following general rules. There is some dispute whether treatment should be instituted immediately after the first convulsion, as some Young people may experience a mild form of epilepsy. Therapy with a single drug is usually possible for many years. Sodium Valproate, which has a broad spectrum of efficiency in generalized tonic-clonic and myoclonic seizures, is well tolerated and safe in the early stages. Lamotrigine and Topiramate are useful in Juvenile Battens also. Carbamazepine, which is effective against a variety of seizures and usually has a low incidence of side effects, is not effective against the typical myoclonic seizures of juvenile NCL and is sometimes felt to even increase seizure activity.

Management of psychological, psychiatric and behavioral problems

It is useful to recognise that these problems usually evolve in three stages. During puberty and adolescence (under the age of 20 years) the patients are usually active and cheerful but may suddenly need considerable attention and medical intervention. A second stage is seen in young adults (20 to 25 years) who clearly recognize their declining skills. They now use a wheelchair and have increasing difficulties with communication, feeding, and urinary continence. During a third stage (20 to 40 years) young people will become wheel chair dependant, have little communication, but may experience severe medical and psychiatric problems. Creating a more peaceful environment of warmth and security can frequently diminish anxiety as the cause of unrest. Enabling as ordinary life as possible with opportunities to reminisce, and offering activities that the person has enjoyed when more able with a structured and predictable routine can minimise these symptoms.

Motor unrest and insomnia are difficult to control with medication. Melatonin has been recommended in an attempt to re-introduce a circadian rhythm in children but has not appeared widely useful in Juvenile NCL. If needed, benzodiazepines (for example, oxazepam) may be used temporarily as anxiolytic agents. If depression seems to be the underlying mental problem an antidepressive drug may be tried. In a young person unable to communicate effectively, discomfort due to constipation or urinary infections should be considered.

When the nature of the hallucinations and delusions is alarming to the young person, they must be treated with anti-psychotic drugs, although Parkinsonian symptoms may worsen with such drugs. Risperidone can provide great relief. **Expert help by a clinician experienced in JNCL is advisable.**

Motor Problems

Motor activities of all kinds, supported by physiotherapy, should be encouraged, as they seem to slow the progression of the disease. Muscular rigidity can pose considerable problems. Myoclonic jerks are particularly disturbing and often resistant to treatment. The muscle relaxant Baclofen is often used for muscle spasms later on.

Swallowing and Nutrition

Young people should become used to a regular, fibre-enriched diet to avoid constipation. During the later course they invariably develop swallowing difficulties. Adequate hydration and nutrition can be maintained using gastrostomy and tube feeding.

Treatment

Many drugs have been tried. A combination of antioxidant drugs was advocated as treatment in the 1970s and 1980s. It seems to be used only rarely outside Finland. Supplementing patients with polyunsaturated fatty acids has been advocated on the basis of biochemical observations in blood components but has not led to wide application yet.

In trials of new or unconventional drugs or diets one should keep in mind that the regimen proposed may not be as harmless as sometimes suggested. One has to consider interactions with other prescribed medication such as anticonvulsive drugs. Special diets may result in poorer quality of life because many of the food items do not taste very good. Nevertheless the family should be encouraged to consider and discuss all treatment suggestions they receive from medical and non-medical sources.

Genetic Considerations

Because the diagnosis of classic Juvenile NCL is usually made when children are 7-14 years old, there are often younger siblings who may also be affected but pre-symptomatic (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 if families wish using blood samples from siblings. Prenatal diagnosis is based on the analysis of cells obtained by chorionic villus sampling (a test involving obtaining some cells from the edge of the

placenta done in early pregnancy). The idea of prenatal testing is that the test shows whether or not the baby will be affected by Batten Disease. If the test is positive, termination of the pregnancy (an abortion) can be considered.

Family support & social issues

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

Once the diagnosis is made, the family must be appropriately informed about the nature of the disease. The diagnosis frequently puts an end to a nerve-racking uncertainty, but now reveals the grim certainty of a long, downhill course and early death. It is not necessary to discuss all the details of future problems at the beginning, but the family must get a basically correct conception of the disease early. This is important for several reasons. Recognition of the brain disease will ease tensions by establishing more realistic educational goals at home and at school. Practical life plans of the family can be modified. The inevitable first convulsion will cause less turmoil than if it occurred unexpectedly.

The level of support and the professionals involved will vary from family to family and depend on many things 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 include: GP and members of the primary health care team - health visitor, district nurse; paediatrician (and/or paediatric neurologist), specialist paediatric community nurse, children's hospice staff, social worker, and agencies such as Crossroads. Specialist teachers for visually impaired children may also be involved.

It is important that parents be encouraged to take some control of their own situation. The services supporting them should include parents and carers in decisions and plans of action. Families' wishes should be recognised to be of paramount importance. Families do not often fit exactly into packages of care provided by the authorities. Parents, encouraged and supported by Professionals and armed with

