CLN8 Disease, Variant Late-Infantile and Epilepsy with Progressive Mental Retardation (EPMR)

BDFA
BATTEN DISEASE FAMILY ASSOCIATION
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Are there any alternative names?

There are two different clinical diagnoses linked to mutations of the CLN8 gene. It has previously been called Variant Late Infantile Neuronal Ceroid Lipofuscinosis (LINCL); though was more commonly known as Variant Late-Infantile Batten Disease. Epilepsy with Progressive Mental Retardation (EPMR) was often referred to as Northern Epilepsy (NE).

What are Neuronal Ceroid Lipofuscinoses (NCLs)?

These refer to several different genetic life-limiting neurodegenerative diseases that share similar features. Although the different forms of NCL are sometimes described according to the age of the child at the onset of the disease, they are actually classified according to the gene identified as the cause e.g. CLN8 (gene) disease, variant late-infantile (age of onset) and CLN3 (gene) disease, juvenile (age of onset).

What causes NCL?

Since the first genes causing NCL were identified in 1995, over 400 mutations in 14 different genes have been described that cause the various forms of NCL disease. Our cells contain thousands of genes that are lined up along chromosomes. Human cells contain 23 pairs of chromosomes (46 in total). Most genes control the manufacture of at least one protein. These proteins have different functions and include enzymes which act to speed up molecular chemical reactions. The NCLs are caused by abnormal genes, which are unable to produce the required proteins. As a result, the cells do not work properly and this leads to the development of symptoms associated with these diseases.

What specifically causes CLN8 disease?

The gene called CLN8 was discovered in 1999 and lies on chromosome 8. Mutations in the CLN8 gene are responsible for at least two quite different clinical diagnoses. CLN8 normally directs production of a protein that is embedded in internal cell membranes and its precise function has not yet been established. Cells are unable to function effectively and this leads to the development of the symptoms associated with CLN8 disease. CLN8 disease, variant late-infantile, may also be referred to as variant late-infantile CLN8 disease.

How are NCLs inherited?

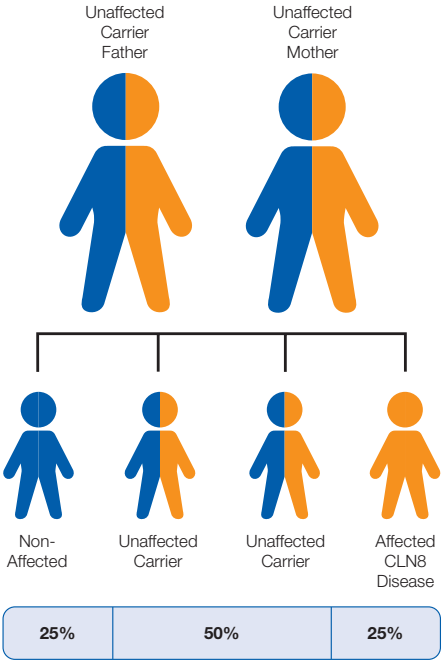
Most forms of NCL are inherited as “autosomal recessive” disorders. This is one of several ways that a trait, disorder, or disease can be passed down through families. An autosomal recessive disorder means that both copies of the gene are abnormal (one inherited from each parent) with neither working properly. The disease does not depend on the sex of an individual.

What are the chances of inheriting CLN8 disease?

CLN8 disease is inherited as an autosomal recessive disorder, which means that both chromosomes carry mutations in the CLN8

gene. Therefore both biological parents, of a child with this diagnosis, will be carriers of the disease but physically unaffected by it.

A child born to parents who both carry the autosomal recessive mutation in the CLN8 gene, has a 25% (1 in 4) chance of inheriting the abnormal malfunctioning genes from both parents and developing CLN8 disease.



They will have a 50% (1 in 2) chance of inheriting one abnormal gene, which would make them a carrier who is unaffected by the disease. There is a 25% (1 in 4) chance of the child being born with two normal genes and therefore being non-affected (not a carrier).

When it is known that both parents are carriers of the abnormal gene, we refer to there being a 2 in 3 chance of a child being a carrier, once it is established that they are unaffected by the disease.

With any pregnancy, the probability of a child inheriting one or both genes from their parents is the same each time, irrespective of any sibling's status.

How is it diagnosed?

Children will probably have been seen by a paediatrician and paediatric neurologist because of symptoms such as seizures. A number of investigations will have been done to look for the cause of the seizures.

The diagnosis of variant late-infantile CLN8 disease or EPMR requires an integrated approach using neurological investigations and tests on blood samples. A skin biopsy may be necessary and when viewed with an electron microscope, blood and skin samples will usually show abnormal storage bodies in the cells. The abnormal storage material takes on a mixed appearance with curvilinear bodies (CVB) and fingerprint profiles (FPP) usually apparent.

How common is it?

Approximately 1 - 2 children are diagnosed with variant late-infantile CLN8 disease or EPMR each year in the UK. We estimate only a few children and young people are currently affected in the UK. Children have been diagnosed with variant late-infantile CLN8 disease in many countries and from various ethnic backgrounds; however EPMR is rarely seen outside of Scandinavian countries.

What are the symptoms and how does the disease progress?

Initial symptoms of **Epilepsy with Progressive Mental Retardation (EPMR)** usually occur between the ages of 5 and 10 years. These are predominantly in the form of seizures though cognitive decline may

also present at a similar time. The seizure frequency will tend to increase until puberty, at which point cognitive deterioration will become more rapid. Behavioural changes may also be evident and can include episodes of irritability, restlessness and inactivity. These features may well continue into adulthood.

Epilepsy tends to be partially responsive to treatment, yet the number of seizures tends to decrease spontaneously after puberty, even without changes in treatment, and become relatively sporadic by the second-third decade of life. Cognitive decline continues with loss of speech reported in some cases. Motor function will also become impaired. In a number of cases, visual acuity is reduced (without evidence of retinal degeneration). The disease is termed as having a chronic course and survival beyond sixty years of age has been reported in some cases. In this respect, EPMR is very unusual amongst the NCLs of childhood onset.

In **Variant Late-Infantile CLN8 Disease** all children experience developmental delay before the onset of symptoms at 2 - 7 years of age. Myoclonic (rapid involuntary muscle spasm) seizures and an unsteady gait are commonly the initial symptoms, with other types of seizures presenting shortly afterwards. Cognitive decline and visual impairment usually occur with pronounced behavioural changes being frequently observed. Rapid disease progression with a loss of cognitive skills is generally experienced over a two year period from the time of diagnosis. By the age of 8 - 10 years severe deterioration of neurological and cognitive skills is apparent alongside medication-resistant epilepsy. Spasticity, dystonic posturing, tremors, and other extrapyramidal signs are all commonly seen.

In their second decade of life, children become unable to walk or stand without support. The life expectancy of children affected by this disease is not yet clear as the oldest known patients are now in their second decade and described as being in reasonably good health.

Are there any treatments?

Currently there is no cure for CLN8 disease or EPMR and therefore specialist symptom management and therapy is essential to assist in maintaining a good quality of life for children, young people and their families. Holistic support for parents, siblings and wider family members is extremely important throughout their journey.

Epilepsy can be difficult to treat and therefore attaining complete control of seizures is not always possible. Anti-epileptic drugs (commonly sodium valproate and clonazepam) will be necessary from the early stages of the disease process, however the response to these from variant late-infantile CLN8 patients is often poor after some initial benefit. Myoclonic (involuntary muscle spasms) seizures can be worsened with the use of medications such as lamotrigine.

Those diagnosed with EPMR may find clonazepam (best results), phenobarbitone and sodium valproate provide some levels of seizure control.

Various professionals including doctors, nurses, physiotherapists, occupational therapists, speech and language therapists are all likely to be involved in the care of children, young people and adults with CLN8 disease. They will work collaboratively and in conjunction with the family to provide a holistic approach to care.

Support and treatment will be needed for a range of issues including progressive difficulties with chewing and swallowing, oral secretions, motor disorder and sleep disturbance. Some individuals may even

require drug treatment for behavioural issues though this must be carefully balanced with seizure control. Attention to mobility, posture, skin and mouth care is essential and many will eventually require additional nutritional support that may include consideration of a gastrostomy.

What research is being done?

Research into possible methods for treating the disease is ongoing but at a very early stage. The use of anti-oxidants (high dosage of Vitamin E) has been tested in a few cases though its potential value remains unproven.

For updates and information regarding developments in research please visit the BDFA website: **www.bdfa-uk.org.uk** or contact the **BDFA Scientific Officer** via **0800 046 9832** email: **research@bdfa-uk.org.uk**

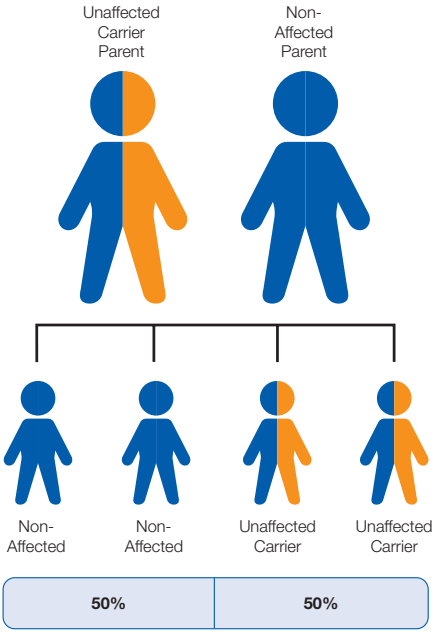
What are the genetic considerations?

The age that variant late-infantile CLN8 disease and EPMR is usually diagnosed means that some families will have younger siblings who may be affected but have not displayed any symptoms.

It may also be possible that older unaffected siblings are carriers of the disease and may want to understand how CLN8 disease may affect their family choices when they are older.

When only one parent is a carrier of the abnormal gene, and the other is non-affected, there is a 50% (1 in 2) chance that any child will be an unaffected carrier.

If parents are considering having additional children, they can access specialist advice and support from their local clinical genetics service following a referral from their GP. Prenatal testing may be possible in the early stages of any future pregnancy.



Is support available to families?

As soon as possible following a diagnosis of variant late-infantile CLN8 disease or EPMR, families should be offered support from various professionals attached to their local health, social, educational services and the BDFA Support & Advocacy Partner. Ideally a "Team Around the Child" will be formed, with one of the professionals appointed as a Keyworker for the family.

The child's needs should be discussed with the parents and assessed by the team. The team will work together to ensure that the child and family receive the ongoing care and support they need and that their choices are taken into account.

A child and family's needs will inevitably change as the disease progresses. As

such, it is often helpful if a clear process for regular planned reviews is identified and that a system is established for enabling additional reviews as and when they are deemed necessary. As the rate or pattern of the progression of the disease for each child remains uncertain, an individualised plan of care and support is essential.

The BDFA is able to provide various forms of holistic support and can be contacted via **0800 046 9832**
email: **support@bdfa-uk.org.uk**

How can families manage the financial challenges?

Caring for a child, young person or adult with variant late-infantile CLN8 disease or EPMR will bring additional financial challenges. It is vital that families are well informed about the full level of economic assistance available and the support that they are entitled to. They may well need help and guidance in accessing benefits and other sources of assistance.

The professionals and services supporting the family should provide advice and guidance. The BDFA can also support families with these issues in various ways, the Small Grants Scheme being one particular example.

What are the practical implications for the family?

As the illness progresses, specialist equipment and aids may become necessary and this is another area where the family will need help. Professionals will play a key role in ensuring that these and other items are provided in a timely manner following proper assessment of the individual's needs.

It is likely that over time some changes may be needed in the home environment to enable the family to appropriately care for someone with variant late-infantile CLN8 disease or EPMR. These may include installing ramps, widening doorways and providing suitable floor surfaces. A purpose-built wet room with a specialist bath or shower may eventually be needed and there are various other aspects that will require consideration.

There are grants and funds available to ensure that the work involved is affordable. An occupational therapist will consult on all aspects of any adaptations and assist the family in undertaking this process.

Will there be an impact on the child's education?

Education will continue to be important for the child and family and there will be many aspects that require consideration and significant assistance from those around them. "Statementing" was the process where the child becomes the subject of a Statement of Special Educational Needs. This was a formal document drawn up by the local Education Authority, based on advice from the health and other professionals involved. It describes the child's educational needs and makes recommendations for the appropriate educational provision and allocation of resources.

Education, Health and Care Plans have now replaced statements. All children and young people with an NCL diagnosis will require an Education, Health and Care Plan. These plans are personalised plans that should meet the education health and care needs of the child or young person.

It remains probable that many parents will continue to need guidance, understanding and support when trying to navigate the process of statutory assessment and the drawing up of the EHC Plan.

The BDFA has expertise in this field and can be approached by any parties seeking information or help.

The BDFA Educational Advisor may be able to provide specific support and can be contacted via **0800 046 9832**
email: **education@bdfa-uk.org.uk**

In what other ways can families be supported?

The realities of caring for an individual who has variant late-infantile CLN8 disease or EPMR can place enormous strain on a family, both physical and emotional. It will impact upon all members in numerous ways and so being made aware that support is available to groups and individuals to help with the challenges that will be faced is important. This support extends to wider family members and step-relatives.

There are several options to consider should families wish to explore ways of maximising the quality of the time they share with their children. Contacting a charitable wish-granting organisation may lead to them being able to create some valuable and significant memories.

Where can I get additional information and support?

The BDFA offers support to any family member, friend, professional or organisation involved in caring for a child with variant late-infantile CLN8 disease, EPMR or any other form of NCL throughout the UK. We provide informed guidance and assistance, actively seek to increase awareness of the diseases and facilitate future research to identify potential therapies and ultimately a cure.

We organise conferences, workshops and are able to arrange connections with other affected families. The BDFA also coordinates a Small Grants Scheme that can provide assistance for a range of needs.

The BDFA has a Support & Advocacy Partner who is able to assist with many of the issues highlighted in this document and can discuss each of them in greater detail and on a more personal basis.

They can be contacted via our Freephone Helpline: **0800 046 9832**
or email: **support@bdfa-uk.org.uk**

The BDFA can provide information on a number of local and national organisations who are also able to offer various forms of support and information that will be relevant to families. It may also be appropriate for a referral to be made to a local children's hospice service, as this can offer an additional experienced and skilled source of holistic support.

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