Great Ormond Street Hospital for Children NHS Foundation Trust: Information for Families

Megalencephalic leukoencephalopathy with subcortical cysts

Megalencephalic leukoencephalopathy with subcortical cysts (MLC1) is a very rare disorder affecting the 'white matter' of the brain, often leading to progressive loss of physical, and sometimes mental, skills over very many years. The name comes from the Greek and describes the features of the condition.

What is the cause?

MLC1 is a disorder mainly affecting the white matter (nerve fibres) of the brain. The white matter principally controls motor, rather than intellectual, function. The cause is a genetic mutation – the identified genes being MLC1 and MLC2A.

How is it diagnosed?

The diagnosis is made, initially, on the history of the child's symptoms; eventually an MRI brain scan shows abnormal swelling of the white matter (leukoencephalopathy) and cysts in the temporal or parietal areas of the brain which are characteristic of MCL1. These scan features, however, may not be apparent until several years have elapsed. The diagnosis can often be confirmed by genetic testing on a blood sample, although this may not be conclusive as there are likely to be other, as yet unidentified, causative genes.

Does it have an alternative name?

In the late 1990s, Dr Van der Knaap described the condition based on its features and the specific appearances of the brain scan. It was sometimes known as Van der Knapp Disease and Megalencephalic Leukoencephalopathy.

Is it inherited?

MLC1 is an autosomal recessive disorder; this means that both parents are carriers of the disease. Human beings have about 30,000 to 40,000 different genes, each of which has a function in making an individual person. The genes are arranged in pairs (one of the pair from each parent) on 23 chromosomes. Inevitably, some of these genes are faulty; a normal gene can overcome a faulty one, but if both genes in the pair are faulty, the genetic instructions cannot work. Most people carry different faulty genes but in MLC1 (and other recessive conditions) parents, though healthy themselves, carry the same faulty genes, and risk passing them on to their children. Each pregnancy carries

- a **25 per cent** chance of the child being **affected**
- a **75 per cent** chance of the child **not** being **affected**.

Is prenatal testing available?

If the genetic mutation has been identified in the affected child and parental DNA has been tested, prenatal diagnosis is possible.

How common is it?

It is estimated that the incidence in the UK is approximately 1:500,000.

How does the disease progress?

The infant will have no apparent problems in the first year but, if measured, the head size may be noted to be larger than expected (megalencephaly). Between the ages of two and ten years, the child shows signs of increasing unsteadiness (ataxia) usually followed by stiffness of muscle tone (dystonia) and involuntary writhing movements (athetosis) and, after very many years, progressive loss of mental skills.

As MLC1 is a relatively newly descibed condition, there is a lot still to learn about it but it is already clear that the features and prognosis are extremely variable.

Some children are wheelchair users in childhood or teenage years, others not until mid-adulthood. Many children will be prone to epileptic seizures and, as learning difficulties become more obvious, behaviour problems may also develop.

The children whose motor skills and balance are more severely affected are likely to have some slurring of speech (dysarthria) and incoordination of swallowing (dysphagia). In some children, mild head trauma may induce a sudden deterioration, often quite severe, usually followed by a slow improvement. In the most severe forms, where symptoms are worsening rapidly or in whom repeated set-backs are occurring, life expectancy can be significantly reduced. In these situations, the child or young adult is unlikely to be conscious of what is happening but family and carers will be aware of their increasing frailty so death would probably be anticipated and relatively peaceful when the time comes.

There is a recognised group of children who, despite initial gross-motor delay and increased head size, improve and stabilise (with or without a degree of disability) and the MRI features may also improve. These children have a different gene mutation: MLC2B.

Is there any treatment?

Although there is no treatment yet available that can stop the disease process, every effort is made to ensure that the child and young adult enjoy as much independence and life experiences as their friends. Help will be provided with mobility aids when necessary and any symptoms, including seizures, will be treated if and when they occur. In view of the risks associated with head injuries, it is prudent to take extra reasonable precautions to try to avoid these.

Is any research being done?

Research is progressing particularly in the genetic field and, with the identification of the MLC1, MLC2A and also MLC2B gene mutations, it is hoped that, in time, understanding of what the gene does will advance, with the eventual hope of gene therapy. Unfortunately this research is extremely complex and may seem very slow to the sufferer and their family. Your neurologist and information available from the support group can keep you informed of research progress.

Is there a support group?

The Climb National Information Centre for Metabolic Diseases can provide written information, telephone advice, support and contact (if wanted) with other families. Telephone their helpline on 0800 652 3181 or visit their website at www.climb.org.uk.

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