Muscular Dystrophy New Zealand

WHAT IS NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis type 1 (NF1) is an inherited condition causing tumours on nerve tissue anywhere in the body and a variety of other effects. It occurs in 1 in 3000 people and affects boys and girls equally.

FEATURES OF NEUROFIBROMATOSIS TYPE 1

In 1882 a German pathologist called Freidrich Daniel von Recklinghausen first characterised the tumours in neurofibromas which consist of mingling of nerve cells and fibrous tissue.The main features include six or more café au lait (CAL) spots on the skin, freckling in the armpits or groin area, brown spots on the irises (Lisch nodules) and lumps under the skin (neurofibroma). NF1 is sometimes referred to as von Recklinghausen syndrome. NF1 is usually is a fairly benign condition but occasionally can cause more serious complications most of which can be effectively treated especially if detected promptly. Informing NF families and their doctors about the condition in some depth will lead to the optimum management of the condition. Much research is going on into treatments for NF1 and some of the complications. Although the condition itself is not yet curable much can be done to allow youngsters growing up with NF1 to realise their full potential and lead active and fulfilling lives.

NF1 is very variable and for many people who have NF1 the problems are largely cosmetic but in about a third of cases more serious complications can occur. These include diffusely spreading deeper nerve growths (plexiform neurofibromas), curvature of the spine, bowing of the tibia in the lower leg, tumours of the optic nerve (gliomas) which often remain asymptomatic and severe hypertension. The hypertension can have rare causes which can be cured with surgical intervention. There is a small risk of malignant tumours in the central nervous system and the nerve sheath and occasionally elsewhere.

About 50% of people with NF1 have some learning difficulties, sometimes in specific areas, but the majority of affected children and adults have normal intelligence. If there are difficulties they may involve concentration, coordination, memory, visuo-motor and visuo-spatial skills, organising and processing and sometimes language. Behavioural problems can occur and children may experience significant self-esteem problems in adolescence which is exacerbated by the appearance of the neurofibromas.

There are two other forms of neurofibromatosis which are different from NF1 - NF2 and Schwannomatosis. NF2 usually first presents in teenage or early 20s with bilateral acoustic neuromas and is associated with a variety of benign brain and spinal tumours including meningiomas, cataracts and only occasional skin manifestations. Schwannomatosis is characterised by multiple schwannomas (benign nerve sheath tumor) of cranial, spinal and peripheral nerves which can be very painful but which are not associated with the ocular auditory or skin changes of NF2.

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CAUSE OF NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis is caused by mutations in the neurofibromin gene on chromosome 1. This protein is produced in many cells, including nerve cells and specialized cells surrounding nerves (oligodendrocytes and Schwann cells). Neurofibromin acts as a tumor suppressor, which means that it keeps cells from growing and dividing too rapidly or in an uncontrolled way. Mutations in the NF1 gene lead to the production of a nonfunctional version of neurofibromin that cannot regulate cell growth and division. This allows tumors such as neurofibromas to form along nerves throughout the body. It is unclear how mutations in the NF1 gene lead to the other features of NF1, such as café-au-lait spots and learning disabilities.

About 50% of cases are 'de novo' and caused by a spontaneous mutation in the gene, usually the paternal copy, and in these cases there is no family history of the condition. Occasionally in NF1 only a proportion of the body is involved - segmental NF – this is due to somatic mosaicism (different genetic information in the same tissue) so the mutation is only present in a proportion of cells.

Someone with NF1 has a 50% risk of passing on the condition each time they have a child. It is a very variable condition within as well as between families but does not skip generations. This means that children in the same family can have different presentations from each other and these may be different again from another unrelated family's presentation of the condition.

The reoccurrence risk for segmental NF will depend on whether the germ cells in the ovary or testes are involved. Genetic testing is possible but is usually only done if a family are considering prenatal or pre-implantation diagnosis or if an early definite diagnosis is critical and the person thought to be affected does not yet fulfil clinical criteria. In 90% of cases the mutation is a single letter change or a very small deletion or insertion in the NF1 gene. In 5% of cases a larger deletion has occurred involving the whole gene.

GENETICS

We each have two copies of the neurofibromin gene in each cell. To be affected with the condition only one copy needs to be defective. Around half of all people diagnosed with NF1 will have one parent who also has the condition. This type of inheritance pattern is called Autosomal Dominance. The other half are thought to have a new mutation (they are the first person in their family with the faulty gene).

DIAGNOSIS OF NEUROFIBROMATOSIS TYPE 1

The diagnosis of NF1 is clinical and is made when someone fulfils specific NIH clinical criteria for NF1. Some of these criteria are age dependent but by one year a child with a family history of NF1 can be usually be diagnosed, and by eight years when there is no family history.

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MANAGEMENT OF NEUROFIBROMATOSIS TYPE 1

Lifelong surveillance of blood pressure is very important in managing NF1Neurofibromatosis Type 1. Management also involves educating families with NF1 about their condition and what to look out for and report to their GP and an annual physical examination by a physician familiar with NF1. In childhood this would usually be their paediatrician.

Management would involve blood pressure monitoring, annual ophthalmic assessments, spinal checks and developmental assessment. Extra help in school may be needed to allow youngsters to fulfil their full potential.

Adults should see their GP annually for blood pressure monitoring and there should be a low threshold for thorough investigation of hypertension as there is an increased risk of not only essential hypertension but also renal artery stenosis and rare endocrine tumours called phaeochromocytomas.

Anyone with NF1 should report any rapid change in their lumps or onset of pain in them or any neurological symptoms promptly so that their doctor can organise appropriate imaging and specialist assessment. Routine imaging is not recommended.

A referral to a clinical geneticist shortly after diagnosis is strongly recommended to discuss the condition in more depth, consider rarer disorders which can be confused with NF1 and to offer assessment of other family members and discuss risks and options when planning a family. It is also very helpful for teenagers with NF1 to be referred again to genetics services just before they leave school for genetic counselling and advice.

OTHER INFORMATION

There are several drugs that are being trialed looking to treat various aspects of NF1 and NF2. A list of these and how far they are along in the clinical trial process is available at http://www.ctf.org/Research/Clinical-DrugPipeline.html

There is also an informative booklet created by the Children's Tumour Foundation called 'Newly Diagnosed with NF1 A guide to the basics' this is available here http://issuu.com/childrenstumor/docs/newlydiagnosedwithnf1guidefinal?e=11776789/7858308 or on the MDA website.

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WEBSITES

http://www.nfauk.org/ http://www.ctf.org/

This information has been adapted from the article written by Dr Alexa Kidd, Clinical Genetist, Canturbury Health Laboratories, for the Summer 2011 Issue of the MDA's InTouch Magazine