



THE CHILD WITH NEUROFIBROMATOSIS TYPE 1 (NF1) — A GUIDE FOR HEALTH CARE PROFESSIONALS

“Neurofibromatosis” is actually a term that encompasses at least two distinct disorders, Neurofibromatosis Type 1 (NF1) and Neurofibromatosis Type 2 (NF2). Both NF1 and NF2 are genetically determined disorders. Generally, all affected members of a family have the same form of Neurofibromatosis. It is possible that other types of Neurofibromatosis exist but this has not yet been firmly established.

Neurofibromatosis Type 2 (NF2) affects 1 in 35,000 people. It is characterised by the appearance of benign tumours or lumps on the hearing and balance nerve (vestibular schwannomas), as well as other tumours of the nervous system. The features of NF2 are often not apparent at all in early childhood.

Neurofibromatosis Type 1 (NF1) is the more common disorder, affecting about 1 in 2,500 people throughout the world. Its major features are multiple flat brown skin patches that look like birthmarks (known as café au lait patches) and neurofibromas (fibrous lumps which grow on the nerve tissue). Because there are many nerves, it can affect other areas throughout the body, including in the brain and spinal cord. NF1 is a very variable condition and no two people will be affected in the same way. Some people go through life with only a few skin patches and perhaps a few bumps on the skin and are completely unaware that they are affected. Others can have major cosmetic or medical problems due to NF1 and these can begin at any time of life, even at birth. Such uncertainty can make it very difficult to know what to expect for a child with only café au lait patches.

The Diagnosis of Neurofibromatosis Type 1

The most common way for a person with NF1 to be diagnosed is by finding multiple café au lait patches. These patches must be at least 5mm in size to be counted in a child before puberty and at least 15mm after puberty.

Sometimes they are noticed at birth but more commonly they begin to appear in the first few months of life and can continue to increase in number for a period of several years. The café au lait patches in themselves are harmless. It is not unusual for them to be passed off as mere “birthmarks”. Indeed, anyone can have 1 or 2 café au lait patches without having NF1. The only significance of the café au lait patch is that it suggests the possibility that a person might have NF1, it does not prove it.

There are rare individuals who have as many as 6 café au lait patches but do not seem to have other features of NF1. It should be stressed that there is no connection between the number of café au lait patches on a person and the degree of severity of NF1. It does not matter if there are 6 patches or 600; the other features of NF1 will be the same.

The diagnosis of NF1 is considered to be established in anyone who has two features commonly looked for from the table below, for example: a child with more than 6

café au lait patches who also has Lisch nodules would be considered to be affected.

Although the presence of multiple café au lait patches strongly suggests the diagnosis of NF1, looking for these features involves doing a careful physical examination, including ophthalmology.

Diagnostic Criteria for Neurofibromatosis Type 1

- Six or more café au lait patches measuring at least 5mm before puberty or 15mm after puberty.
- Two or more neurofibromas or one plexiform neurofibroma (this is a large spreading type of lump).
- Freckles in the axillary (under the arms) or groin (skin-fold freckles).
- Lisch nodules on the iris of the eye (Lisch nodules are small lumps on the iris which are completely harmless to vision).
- Optic glioma. A growth on the nerve of the eye.
- Characteristic skeletal abnormality (bowing of shin bone, abnormality of orbit).
- A parent, brother, sister or child with NF1.

One problem with using these clinical diagnostic criteria is that many of these features of NF1 are age-related. Often they are not present in very young children with NF1 but only appear with time. Usually this can mean late childhood, around age 7-10, or even not until adolescence. Puberty is a particularly common time for other features of NF1 to appear.

As a result, it is often difficult to make a definite diagnosis of NF1 in a young child with multiple café au lait patches. There is a high chance that such a child is, in fact, affected but often it can take years before another feature of the disorder appears to confirm the diagnosis. It is common practice to re-examine such children, usually once a year, to look for the appearance of new signs of NF1 such as skin-fold freckles or Lisch nodules. If they are found the diagnosis is clear, if not, the question remains unsettled.

It is often asked: "If year after year no additional features appear, is there an age when the possibility of NF1 is ruled out?" At this point, there is no clear answer to that question. Most people with NF1 develop signs in addition to café au lait patches by puberty, but not necessarily all. There is no age when we can be sure that an individual having only multiple café au lait patches is not affected with NF1. However, if a child has **no** signs at all of NF by the age of 5, it is safe to assume that they will not develop the disorder.

There is currently no specific diagnostic test for NF1, particularly when a child presents with only multiple café au lait patches and no family history of the disorder. Sometimes further medical investigations may be done to determine if some other feature of NF1 is actually present.

In some cases it may be possible to offer mutation analysis to confirm a diagnosis of NF1 but, as yet, there is no blood test or laboratory test that can definitely **rule out** a diagnosis of NF1 in a child with only café au lait patches.

It is hoped that more universally effective and accurate testing will become available in the near future as we learn more about the NF1 gene.

Genetic Implications of Neurofibromatosis

NF1 is an autosomal dominant disorder due to an abnormality or change in the NF1 gene. An affected individual has a 50% chance of passing the abnormal gene copy to any child he or she might have. A child who inherits the abnormal gene will also have NF1. 50% of individuals diagnosed with NF1 are new or de novo mutations.

Many children diagnosed as having NF1 appear to be the only members of their families to have the condition, neither parent seems to be affected and no relative is known to have the condition.

There are two possible explanations for this situation: one is that one of the parents actually does have NF1, only its manifestations are so mild that he or she is unaware of being affected; alternatively, the apparently sporadic NF1 is due to the possibility that one parent is a germ line mosaic. In this case, neither parent will be affected and the risk to any further children they may have is similar to that of the general population.

At present the best way to resolve the issue is for parents to have a thorough examination looking for skin and eye signs. If neither parent is found to have features of NF1 the child is probably a new mutation. It is not impossible for the parents to have other affected children but it is unlikely, although they should be examined for signs of NF1 to be sure.

Regardless of whether an individual with NF1 is the first one in the family to be affected or whether the condition has been present for many generations, there is for everyone affected by NF1 a 50% risk of transmitting the condition to any child. However, there is no way to predict the degree of severity of the condition in offspring: severely affected parents may have mildly affected children and *vice versa*.

Genetic testing is currently available in some situations and this may then make it possible to offer a prenatal test. It is advisable to consult a doctor or genetic counsellor who can then provide additional information about the availability of such testing. If it is decided that a child has NF1 on the basis of a new mutation, it is natural to ask "How did this happen?"

Parents often wonder if there is something they did or did not do that caused this to happen. The cause of mutations in the NF1 gene is unknown. No environmental exposure has yet been implicated.

About Neurofibromatosis

NF1 is truly an unpredictable disorder. It varies widely in severity from one person to the next, even between two people in the same family. However, there are a few things that can be said with confidence. Firstly, severe complications of NF1 are by no means inevitable. Most individuals with NF1 live long and generally healthy lives and do not develop life-threatening complications.

Secondly, some complications of NF1 are apparent early in life. These include deformities of the leg bones or face, which are usually apparent in infancy. A child who is 5 years old and has only café au lait patches has escaped at least some of these severe complications of NF1. That is not to say that cosmetic or other severe problems cannot appear later on but major bone deformities associated with NF1 do not develop in an otherwise normal-appearing child with café au lait patches.

Thirdly, although there are many health complications that can occur in someone with NF1, it is rare for that person to have all the possible complications. However, some of the more rare complications that are associated with NF1 can occur at any stage during a lifetime, for example epilepsy or NF related blood pressure problems. Of course, the definition of what constitutes a "severe" problem can differ from one person to the next. Most people will experience some degree of cosmetic impact from the condition but in many cases this is not difficult to manage.

Management of Neurofibromatosis

There is no doubt that living with NF1 involves some degree of adjustment by affected individuals and their family members to both the possible medical problems; which have a potential to cause problems, and, to the uncertainty of when and whether they will occur.

There is currently no cure for Neurofibromatosis. A major goal of research is to continue to increase our knowledge of how the NF1 gene mutation affects the body and thereby develop effective means of therapy.

Until this is achieved (and progress **is** being made) medical management of NF1 is limited to the early detection of complications that can be treated. Treatment in this sense means thorough assessment of the skin manifestations and possible surgery or laser treatment to remove or reduce the size of neurofibromas.

Appropriate management of individuals with learning disabilities etc. is achieved with good communication between all professionals involved in that person's care. Anticipation of such problems and prompt intervention generally can improve the outcome of treatment.

It is recommended that a person with Neurofibromatosis has a complete medical check at least once a year. A paediatrician usually does this and from the age of sixteen these annual assessments can be done by the GP. The medical check generally consists of a medical history, physical (including blood pressure), neurological and eye examination.

Careful attention should be paid to any change in the skin manifestations of NF1, in particular of any growth or pain in a neurofibroma. The child's cognitive development and school progress should be discussed.

If the child complains of any unusual problems such as persistent severe headaches, vision changes or funny feelings in arms or legs these should be fully investigated and may include having a scan of the brain. Such scans are generally not carried out routinely unless there are signs or symptoms that indicate this should be done. However, some Doctors prefer to obtain as complete a picture as possible of how NF1 has affected an individual.

There is no single "correct answer" to this question. Probably more important than seeking a consensus on this issue, there should be an open discussion between Doctor and family about the risks and benefits of screening tests.

All this applies equally to a person with confirmed NF1 and to a child with multiple café au lait patches in whom the diagnosis is suspected but not confirmed. Such a child might well be at risk of developing NF1-related complications and so should be followed up just as though he/she has NF1.

Specific Complications of Neurofibromatosis

It should be remembered that severe complications in NF1 are rare. The majority of people with this condition do not have any problems at all.

Most newborn babies who have the NF1 gene mutation show few or no signs of the disorder. Café au lait patches are commonly noticed in the first few weeks of life or they may appear later. Their absence in a newborn that is at risk of inheriting NF1 from a parent does not mean that the baby has not received the NF1 gene.

By the first year of life the Café au lait patches are usually clearly visible. Sometimes a few freckles can be seen in the armpits or groins and, later, a few small neurofibromas may be noticed on the skin. The neurofibromas usually appear as small bumps on the skin that are soft to the touch and have a pink or purple hue.

They are not painful and rarely cause problems other than cosmetic ones. Young children usually do not have more than one or two small neurofibromas and might have none.

One exception is the plexiform neurofibroma. This is a neurofibroma that affects many branches of a nerve, usually a fairly large nerve. Occasionally, they are noticed in the newborn period, where they may appear as a soft swelling under the skin. Not finding a plexiform neurofibroma does not mean that one will not appear later in life. This is particularly true for those that are located deep under the skin, which may not be apparent until they have grown. Although they do not occur frequently, there are two types of bone deformity that are typical for NF1 and these generally are present from birth. One involves the long bones, most commonly the tibia.

Infants affected tend to have a bowing or curvature of the lower leg. Some degree of curvature is normal but an excessive degree indicates the possibility of tibial dysplasia. If tibial dysplasia is suspected, an X-ray is usually performed. If it is found, the child should be referred to an orthopaedic specialist. The abnormal region of the tibia is very prone to fracture and the fractures tend not to heal well. Orthopaedic care is usually directed towards prevention of fracture or management of fractures if they do occur.

The other unusual bone deformity is a bit of the sphenoid bone missing behind the orbit of the eye, detected by X-ray or scanning. It is not usual to do anything about the absence of the sphenoid bone itself.

However, it can make the eye appear either bulging or sunken and even causes downward displacement of the eye. In addition, there can be a plexiform neurofibroma within the orbit and enlargement of the upper eyelid. This can be quite disfiguring and often tends to grow over the years.

Children with NF1 are often shorter than would be expected from the size of others in their family and their peers. The cause of this short stature is not known. They may have a larger head measurement than most children of a similar age. This generally does not cause discomfort to the child and is not usually linked with neurological problems.

The head grows at a faster rate than normal but at a steady, consistent rate. As long as this is the case it is not usually necessary to do an examination such as a scan. In rare instances the head growth may be associated with symptoms such as vomiting or severe or prolonged headache. In such cases a scan would probably be done to investigate the cause of such symptoms.

Brain tumours can occur at any point in life, including early childhood. One form of tumour that is particularly associated with early childhood is the optic glioma. This is a rare tumour of the optic nerve. Whilst these tumours are generally benign they can lead to loss of vision, pain, bulging of the eye or extend to affect other areas of brain function. Such

symptomatic optic gliomas are diagnosed by scanning and treatment depends on the location of the tumour.

Similarly, in some children with NF1, evidence of thickening of the optic nerve has been recorded. This represents an abnormality of the development of the optic nerve but there are no signs of the NF1 eye tumour. It is rare that this would require treatment.

The child with NF1 should not be treated as ill or as excessively fragile. There is no need to restrict activity unless there is known to be a particular complication of NF1 that would be prone to injury. It is also not necessary for parents to document every skin patch or bump. These can be checked during annual follow-up visits. The major things to be watching for are sudden changes in the size or appearance of a neurofibroma, unexplained pain or, as noted above, persistent or severe headaches.

It is recommended that all children with NF1 have an annual eye check to ensure early diagnosis of symptoms of optic glioma. Ideally up to the age of 7 this should be done by an Ophthalmologist and after that, annual checks at a good optician's.

As the child gets older, any of the features of NF1 mentioned above can begin to appear or continue to appear throughout the school age. Thus skin-fold freckles may increase, Lisch nodules may appear, plexiform neurofibromas may grow and neurofibromas may become visible on the skin.

Adolescence is generally a time of change and often this includes a change in the manifestations of NF1. Individuals who have not developed neurofibromas during childhood often begin to see skin neurofibromas during puberty. Pre-existing plexiform neurofibromas may grow at this time. Skin freckling can also increase. The cause of these changes is not well understood but it is thought that changes in hormones may be responsible. Similarly, the appearance or growth of neurofibromas is also seen in women with NF1 during pregnancy.

Learning and Behaviour

NF1 has an impact on the way that children and adults learn and perceive the world in which we live. The majority of children with NF1 have an intelligence that falls within the normal range, however, a significant proportion (up to 60%) experience difficulties that fall within the specific learning difficulty spectrum. For children with NF1, performance may fail to reflect their general intelligence.

The exact form of learning disability and degree of severity varies from child to child. Some experience difficulty with visual and spatial skills, some with speech and language, some with reading or maths or any combination of these skills. In addition some have difficulty focusing attention and it is recognised that some children will have ADD (Attention Deficit Disorder) or ADHD (Attention Deficit and Hyperactivity Disorder) that may benefit from a thorough psychological assessment.

The exact cause for the learning difficulties is unknown. It is not progressive: that is to say in general it does not get worse with time.

The management of learning disabilities in children with NF1 is the same as for any child with a learning problem. A thorough assessment of the child's skills and areas of weakness should be undertaken by all those involved in their care. An individual education plan should be drawn up to meet the child's identified special needs.

It is impossible to predict the course of NF1 in anyone with the disorder. Manifestations of NF1 generally do not disappear once they have developed, although café au lait patches sometimes fade in later life. Neurofibromas can appear at any time.

Although bone deformities are generally present from birth, cosmetic impairment from neurofibromas can develop at any time in life. Learning disabilities do not disappear in

adulthood but adults with NF1 and learning disability can lead productive lives if their learning problems were identified early and appropriate support provided.

Malignancy

It must be recognised that some complications of NF1 can be life threatening. The most frightening to many people is cancer. Neurofibromas are not cancerous growths; they do not spread through the body even though they can appear in many places on the skin. Neurofibromas do grow but not all growth indicates malignancy. In some individuals, however, a cancer may develop within a neurofibroma. A deep-seated lump or a plexiform may become painful at rest or grow rapidly. Any change in the appearance of such a lump should be investigated swiftly.

This is most unlikely to happen with the small skin neurofibromas but seems to be more likely to occur in the plexiform neurofibromas. Likewise, plexiform neurofibromas grow and are occasionally painful if bumped or otherwise traumatised. The signs of malignancy would be the appearance of pain in what was a previously painless mass as well as some sudden growth. The pain is more likely to occur spontaneously, without any evidence of injury to the mass.

Malignancy related to NF1 is estimated to occur in up to 10% of affected individuals. It can be treated, usually with a combination of surgery, radiation and chemotherapy. The outcome depends largely on how early the cancer is detected.

In addition to malignancies, the possibility of tumours in the brain and spinal cord must be considered. These, too, occur in relatively few individuals with NF1, although the risk to people with NF1 of developing a brain tumour is higher than the risk to the general population. They are usually detected after symptoms such as headache, vomiting, seizures, visual disturbance or behavioural changes are apparent. There might be an abnormality noted on neurological examination. The tumour would show up on a scan. Sometimes the tumour will be biopsied. There may be a range of treatment that can be offered: surgery, radiation therapy or chemotherapy. **It should be stressed that not all headaches in individuals with NF1 means that a brain tumour is present.**

Ordinary headaches, tension headaches and migraines are at least as common in individuals with NF1 as in the general population. Individuals are advised that persistent or especially severe headaches should be reported to a doctor.

When to tell a child about Neurofibromatosis

One of the most common and difficult questions asked by parents of children with NF1 is when and how to explain the disorder to the child. For advice on this please refer to the fact sheet "Talking to Children about Neurofibromatosis" published by the Neurofibromatosis Association.

Should teachers be told about Neurofibromatosis in a child?

Parents often ask whether the school or child's teachers should be informed that their child has NF1. This is a matter for the parents to decide. It is their choice. A concern often raised is that this can result in the child being labelled and that this could have a negative effect on the child.

However, informing the school teachers and having a frank discussion with the child's teachers can often correct common misconceptions about NF1 and lead to early detection and treatment of learning problems related to the condition.

Sources of Support

The diagnosis of Neurofibromatosis can be a great shock and cause much emotional distress. In addition, getting the support and information needed can become difficult. It is therefore important to maintain open communication with all the health professionals who are involved in the care of the child with NF1.

The Charity was set up in 1981 by families with NF to help others. It has a network of Specialist Advisors, based at some regional genetics centres, providing advice and support to anyone affected by NF, as well as families, friends and professionals involved in their care.

The Neuro Foundation has a Telephone Helpline which is available on Tuesdays and Wednesdays. The number is listed below together with details of our website, where further information is available.

Produced
with financial
support from



The Neuro Foundation has taken reasonable care to ensure that the information contained in its publications is accurate. The Neuro Foundation cannot accept liability for any errors or omissions or for information becoming out of date. The information provided is not a substitute for getting medical advice from your own GP or other healthcare professional.

**The Neuro Foundation,
HMA House, 78 Durham Road,
London SW20 0TL**

T: 020 8439 1234

W: www.nfauk.org

E: info@nfauk.org

Telephone Helpline: 07866 946334 (Tuesdays and Wednesdays ONLY)

The Neuro Foundation is the working name of the Neurofibromatosis Association, a Registered Charity No. 1078790 and SC045051 and a Company Limited by Guarantee registered in England and Wales, No. 03798407 Updated 07/09