INTRODUCTION (B)

Neurofibromatosis 1 is a common inherited autosomal dominant disease with a birth incidence of between 1 in 2,500 and 1 in 3,000 and a prevalence of 1 in 5000. The disease principally affects the skin and peripheral nervous system and about half the cases are the first in their family. The complications are manifold and may involve any of the body systems, the expression and severity of NF1 varies, even within families. Individuals with NF1 are at increased risk for the development of benign and malignant tumours. Mosaic NF1 occurs occasionally as a result of a somatic mutation in the NF1 gene, the proportion of the body affected depending on the time of mutation in embryonic development.

DIAGNOSTIC CRITERIA FOR NEUROFIBROMATOSIS 1 (B)

2 or more of the following are required:
- 6 or more café au lait macules (>0.5 cm in children and 1.5 cm in adults)
- 2 or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
- Axillary or groin freckling
- Optic pathway glioma
- 2 or more Lisch nodules (iris hamartomas seen on slit lamp examination)
- Bony dysplasia (sphenoid wing dysplasia, bowing of long bone +/- pseudarthrosis
- First degree relative with NF1

INITIAL DIAGNOSIS (C)

Initial referral should be to any clinician skilled in the diagnosis of NF1 (e.g. include geneticists, paediatricians, neurologists, dermatologists, general practitioners). The diagnosis is confirmed by:
- Detailed family history
- Examination of the skin
- Examination of the long bones and spine
- General physical and neurological examination
- Ophthalmology assessment and slit lamp examination (slit lamp is not necessary if diagnosis obvious from above criteria)

Note

Brain MRI is not a routine diagnostic test but benign developmental abnormalities (unidentified bright objects — UBO’s) are seen in the brain in children with NF1 especially between the ages of 8-16 years. The presence of UBO’s can help confirm the diagnosis in some cases. A neurofibromatosis co-ordinator should be consulted before undertaking brain magnetic resonance imaging in children for this purpose.

Mutational analysis may clarify the diagnosis in some cases.

Children with 6 café au lait patches alone and no family history of NF1 are likely to have NF1 and should be followed up as if they have the disease. (In some cases other signs of NF1 may not develop until late teens/early twenties. Slit lamp examination for Lisch nodules may be helpful in this group).

Children 4 years or older with 3-5 café au lait patches but no other signs of NF1 should be followed up in a specialist NF clinic, they may have a rarer form of NF.

ASSESSMENT AND MANAGEMENT OF CLINICAL PROBLEMS (C)

All adults and children with NF1 should be assessed at least once a year. Contact details for the general practitioner, named specialist or neurofibromatosis coordinator should be given to patients.

The following should be recorded at each visit:
- Development and progress at school (children)
- Fundoscopy and visual acuity (children)
- Height (children)
- Head circumference (children)
- Weight (children and adults)
- Pubertal development (children — for signs of delayed/precocious)
- Blood pressure (children and adults)
- Evaluation of spine (children and adults with known scoliosis or underlying plexiform neurofibromas).
- Evaluation of the skin (children and adults)
- System examination if specific symptoms
The Skin (B)

Neurofibromas are benign peripheral nerve sheath tumours that are focal (cutaneous/subcutaneous) or diffuse/nodular (plexiform) lesions.

Cutaneous neurofibromas
- Do not undergo cancerous change.
- Develop in teens/early twenties (and, occasionally, in early childhood)
- Vary in number amongst individuals.
- Cause itching that does not respond to antihistamines; individuals should avoid excessive heat and use emollients.
- Cause transient stinging
- Catch on clothing
- Produce cosmetic problems

Cutaneous neurofibromas can be removed if they cause any of the problems mentioned above. Individuals should be referred to surgeons skilled in the removal of neurofibromas, and plastic surgeons should be consulted for neurofibromas on the face and neck. There is no proven benefit of carbon dioxide laser treatment over surgical removal of troublesome neurofibromas, but laser may be help for some small lesions. There is a risk of hypertrophic scarring and of recurrence of neurofibromas after removal.

Subcutaneous neurofibromas
- Evident on palpation of the skin and may be tender to touch.
- Malignant change rarely occurs.
- If removal is contemplated, expert advice should be sought from NF1 specialists or soft tissue tumour/peripheral nerve surgeons as removal may result in neurological deficit.

Plexiform neurofibromas
- Grow along the length of a nerve and may involve multiple nerve fascicles and branches
- They may be nodular and multiple discrete tumours may develop on nerve trunks. Associated bony and soft tissue hypertrophy can occur. The growth rate is unpredictable.
- Facial plexiform neurofibromas causing facial disfigurement develop during the first three years if they are to develop at all.
- There is about a 10% lifetime risk of malignant change in plexiform neurofibromas, most common in the 2nd and 3rd decades.
- Individuals with NF1 should seek urgent expert advice if the following develop in association with a plexiform neurofibroma.
- Persistent pain for more than a month
- New neurological deficit
- Change in texture from soft to hard
- Rapid increase in size

Symptoms may arise from a plexiform neurofibroma that is not visible or palpable. Removal of benign plexiform neurofibromas may be very difficult due to impingement on surrounding structures and nerves and their vascular. Expert advice should be sought before removal by experienced soft tissue tumour/plastic surgeons.

Vision (B)

Visual problems include
- Glaucoma
- Sphenoid wing dysplasia resulting in proptosis/exophthalmos/enophthalmos
- Plexiform neurofibroma involving eyelid, orbit
- Optic pathway gliomas (OPG)
- OPG are pilocytic astrocytomas that occur predominantly in children under 7 years and are often indolent tumours. Manifestations include optic atrophy, decreased vision colour vision, pupillary and visual field, abnormalities, squint, proptosis, hypothalamic disturbance.
- Young children do not complain of visual impairment and parents need to be informed of the possible problems.
- Children under 16 years need annual visual assessment by an ophthalmologist.
- Visual acuity can be assessed at developmental age 3 years.
- Colour vision can be assessed at developmental age 7 years.
- Visual fields can be assessed at developmental age 8 years.
- Brain MRI screening for OPG is not indicated as treatment is not required in the absence of progressive visual disturbance or proptosis. Expert advice should be sought for the management of OPG.
- Adults should be assessed by an optician every two years (and by an ophthalmologist if there are specific problems).
**Cognitive problems and behavioural difficulties (B)**

Cognitive problems are common in NF1 and may take the form of IQ in the low average range (IQ < 70 is rare) or specific learning problems including clumsiness, reading/writing difficulties, visual spatial problems and attention deficits. Behavioural difficulties include sleep disturbance and poor interpretation of social cues. There is an increased frequency of attention deficit hyperactivity disorder.

- A detailed developmental assessment should be performed as soon as possible and definitely before school. Enquire about school progress during yearly assessment
- Close liaison between school, educational psychologists, occupational therapists and clinicians.
- Question adults about literacy skills and refer to adult literacy classes if appropriate

**Neurological problems (C)**

- Cerebrovascular disease
- Malformations (including aqueduct stenosis)
- Tumours (cerebral and optic pathway gliomas, ependymoma, medulloblastoma, NOT vestibular schwannomas)
- Epilepsy particularly complex partial seizures
- Pressure on peripheral nerves, spinal nerve roots, spinal cord from plexiform neurofibromas
- Neurofibromatous neuropathy (mild symmetrical distal tingling numbness or weakness)

Neurological examination should be undertaken during annual assessment. Any unexplained neurological signs/symptoms warrant referral to adult/paediatric neurologist.

**Urgent advice should be sought if individuals experience acute/progressive sensory, motor deficit, incoordination or sphincter disturbance. Headaches on waking, morning vomiting and altered consciousness are suggestive of raised intracranial pressure.**

**Psychological problems (C)**

Psychological problems arise from cosmetic problems caused by neurofibromas and from the complex and unpredictable nature of the disease. Symptoms of anxiety and depression should be treated with counselling or antidepressants. Nf.1 family support coordinators, counselling, psychiatric advice and a support agency such as “Changing Faces” may all play a role managing psychological problems

**Malignancy (B)**

There is an increased risk of malignant peripheral nerve sheath tumour, rhabdomyosarcoma (especially pelvic), leukaemia, phaeochromocytoma, optic pathway and cerebral gliomas (see above).

**Orthopaedic problems (C)**

- Bowing of long bones +/- pseudoarthrosis presents in infancy and will not develop de novo once the child is fully mobile
- Scoliosis may be idiopathic or dystrophic. It can be associated with underlying plexiform neurofibroma and in severe cases result in respiratory compromise. Dystrophic curves are associated with additional kyphosis and onset is earlier than in idiopathic cases
- Spine should be checked once a year in children with Nf.1. Individuals with scoliosis should be referred for orthopaedic assessment.

**Cardiovascular problems include (C)**

- Congenital heart disease
- Carry out careful cardiological examination and if unexplained murmur refer for cardiology opinion and echo

**Hypertension**

- Blood pressure should be checked annually and should be less than 140/90 and less than 130/85 in individuals with end organ damage or diabetes mellitus. If blood pressure found to be high during clinic visit it should be checked 3 times in 1 month to verify findings
- Blood pressure should be checked once in upper and lower limbs to look for aortic coarctation
- Consider renal artery stenosis in children, young adults and pregnant women, refractory hypertension in older individuals, and those with abdominal bruit. Evaluation should be carried out by a specialist centre
- Consider phaeochromocytoma in pregnant women, individuals with refractory or paroxysmal hypertension, individuals with paroxysmal palpitations, headache, dizziness, or sweating.
- A clinician should check 24 hour urinary catecholamines only if a phaeochromocytoma is suspected.

*N.B. If there are associated symptoms, ensure that urine collection taken when symptomatic. Where there is a high index of suspicion refer to specialist centre for evaluation and management. Treatment involves alpha and beta blockade before surgery. In patients with phaeochromocytoma, duodenal carcinoid may also occur.*

- Essential hypertension should be treated as in the general population.
Contact the Neurofibromatosis Association

The association welcome enquiries from patients, their families, health professionals or anybody with an interest in or who require information / literature on Neurofibromatosis.

The Neurofibromatosis Association of Ireland
Carmichael Centre,
North Brunswick Street,
Dublin 7.
24 Hour Help Line 01– 8726338
Fax: 01– 8735737
E-mail: nfaireland@eircom.net
Web Site: http://www.nfaireland.ie

Family Support
Dr. Ann Murray
Ms. Therese Buckley R.G.N, R.M, P.H.N.

Neurofibromatosis Association Services
⇒ 24–hour Help Line
⇒ Literature: CD–ROM on Nf.1, Book’s, leaflets, Video, Clinical Guidelines for Management of individuals with neurofibromatosis 1.
⇒ Information Service to Patients, Doctors and schools.
⇒ Family support & counselling
⇒ Bi–monthly Newsletter - Neuro News
⇒ Information evenings
⇒ Home / Hospital visits
⇒ Introduction / referral to other services
⇒ Awareness / Education Programme
⇒ Respite Weeksends
⇒ Advocacy

Clinical Guidelines Endorsement
I am delighted to support and endorse the new clinical guidelines for the management of Neurofibromatosis 1 (NF.1). The leaflet and CD-ROM will be of great help to the many different health professionals who are involved in the care of people with NF.1. Such guidelines are best tailored to suit the particular needs and circumstances of people with NF1.

The National Centre for Medical Genetics is delighted to be associated with the Neurofibromatosis Association of Ireland. The NCMG has a wealth of experience with neurofibromatosis and sees many families with the condition around Ireland. The NCMG holds genetic clinics in Dublin, Cork, Limerick and Galway and is happy to see families with NF1, with a referral from their own doctor.

Professor Andrew Green
Director
The National Centre for Medical Genetics

The guidelines were written by Dr Rosalie Ferner1 Consultant Neurologist, Guy’s Hospital, London, Mr Nick Thomas1 Consultant Neurosurgeon, Kings College Hospital, London, Ms Linda Partridge1 Support Services Manager, Neurofibromatosis Association UK, and Mr Richard Towers2 Neurofibromatosis Specialist Adviser, Guy’s Hospital, London. They were edited by Dr Susan Huson1 Consultant Clinical Geneticist, Oxford Radcliffe Hospital., Dr Celia Moss1 Consultant Paediatric Dermatologist, Birmingham Children’s Hospital, Professor Gareth Evans1 Consultant Clinical Geneticist, St Mary’s Hospital, Manchester, Mr Tim Morley1, Consultant Orthopaedic Surgeon, London and Professor Charles French-Constant1 Consultant Clinical Geneticist, Addenbrookes Hospital, Cambridge.

These guidelines have been circulated compliments of the Neurofibromatosis Association of Ireland to all health professionals Consultants, Hospital Doctors, G.P’s, Public Health Nurses also to NF. patients and their families.

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