Osteoporosis

- There is an increased risk of osteoporosis and risk factors should be determined in adults, including diet exercise and age at menopause

Cardiovascular problems

Congenital heart disease

- Particularly pulmonary stenosis. Initial assessment should include a careful cardiology examination. If an unexplained murmur is present, referral for cardiology opinion and an echocardiogram should be made.

Hypertension

- Blood pressure should be checked annually and in adults should be less than 140/90 and less than 130/85 in individuals with end organ damage or diabetes mellitus. If blood pressure is found to be high during a clinic visit, it should be checked by the GP to verify findings.
- In children the blood pressure should be < the 95th percentile for age, height, and gender
- Consider **renal artery stenosis** in children, young adults and pregnant women, refractory hypertension in older individuals and those with abdominal bruit. A specialist centre should carry out an evaluation
- Consider **phaeochromocytoma** in individuals with refractory or paroxysmal hypertension, individuals with paroxysmal palpitations, headache, dizziness, or sweating and in pregnant women. Check plasma metanephrines. **Asymptomatic screening is not advised.**

N.B. Where there is a high index of suspicion refer to specialist centre for evaluation and management. In patients with phaeochromocytoma, **duodenal carcinoid** occurs at an increased frequency.

- Essential hypertension should be treated as in the general population

Glomus tumours

- Glomus tumours are small encapsulated tumours, mostly located in the nail beds of either fingers and/or toes. A purplish area may be visible around the nail bed
- Patients present with extreme localised pain which can mimic neurological pain and lead to unnecessary investigations for more proximal neurofibromas
- Excision of the tumour is an effective remedy

Gastrointestinal tumours

- Symptoms of bloating, pain, dyspepsia, constipation, bleeding or anaemia may indicate the presence of a **neurofibroma** or **GIST (gastro-intestinal stromal tumour)** in the digestive tract and should be investigated
- Patients are also at an increased risk of carcinoid tumours (usually in the duodenum).

Prenatal counselling

Prenatal and pre-implantation genetic testing is available for most families but the severity of the condition cannot be predicted within families. All individuals with NF1 should receive genetic counselling prior to conception.

Pregnancy

Liaison between obstetrician and NF1 clinician is important for patients with NF1 complications:

- Anticonvulsant medication needs careful monitoring. Patients on anticonvulsants need folic acid 5mg daily before conception if possible
- During pregnancy, skin neurofibromas may increase in size and number
- Need to be aware that cord compression may occur if spinal plexiform neurofibromas increase in size
- Consider renal artery stenosis or phaeochromocytoma as cause for hypertension (see above)
- Ensure that pelvic neurofibromas do not impede delivery
- Considerations with respect to spinal and epidural anaesthesia in pregnant women should form part of a discussion between the obstetrician and neurosurgeon

The baby requires assessment at birth for early complications and yearly review until disease status clarified. If there are no features by the age of 2yrs, NF1 is unlikely but one final review at 5yrs is advised.

Oral contraceptive pill

There is no current evidence to suggest that the oral contraceptive pill is associated with increased neurofibroma growth.

Transition

Transition care is an essential part of NF1 management. The aim is to support, educate, promote independence and ensure engagement with adult NF1 services. Transition care should be started at age 13-14 years and continue until transfer to the adult service at age 17 – 18 years.

The paediatric consultant and clinical nurse specialist should work with the child to introduce the adult team and gradually transfer to the adult service. If there is no adult specialist service available the GP should be informed with a copy of the guidelines.

Specialist Neurofibromatosis clinics

Multidisciplinary NF1 clinics evaluate, support and monitor NF1 patients to ensure a uniform approach and expert management.

They provide information about research to families and the professionals involved in their care. An increasing number of centres have specialist clinics – Nerve Tumours UK holds an up to date list of UK neurofibromatosis clinics.

There are two centrally funded specialist clinics for Complex NF1—see below for details.

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nervetumours.org.uk
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020 8439 1234

NTUK National Helpline

This is a part-time telephone service offering information and advice about Neurofibromatosis.

07939 046 030
Monday and Wednesday 9am – 5pm

helpline@nervetumours.org.uk

For more information follow us on social media:

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Useful Links

Nerve Tumours UK nervetumours.org.uk

The Genetics Interest Group www.gig.org.uk

Contact a Family www.cafamily.org.uk

National Neurofibromatosis Centres

Nationally commissioned to provide a service for patients with complex NF1 in England. Patients from elsewhere are seen but have to be funded.

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Clinical guidelines for the management of individuals with Neurofibromatosis Type 1 (NF1).

Introduction

Neurofibromatosis Type 1 (NF1) is a common inherited, autosomal dominant disease with a birth incidence of between 1 in 2,500 and 1 in 3,000(1). About half of the people with NF1 are the first in their family to be affected. The disease mainly affects the skin and nervous system. However, there are multiple complications and the severity and type of clinical problems can vary, 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 depends on the time of mutation during embryonic development.

Diagnostic criteria for Neurofibromatosis Type 1

Two 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 1 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)
- Parent or child with NF1

Initial diagnosis

Initial referral should be to any clinician skilled in the diagnosis of NF1 (geneticists, paediatricians, neurologists, dermatologists). The diagnosis is confirmed by:

- Detailed family history
- Examination of the skin
- General physical examination including the long bones/spine and neurological assessment
- Ophthalmology assessment and slit lamp examination (slit lamp is not necessary if diagnosis is obvious from above criteria)

Routine brain scans are NOT recommended as part of the initial assessment unless neurological symptoms or clinical examination raises concerns.

Until recently, molecular testing has been used mainly for prenatal testing. However, genetic testing is now much easier and is being used to aid diagnosis when this is unclear.

Specific genetic changes associated with particular rare phenotypes have also been identified. Advice should be sought from a neurofibromatosis specialist or genetic clinic before genetic testing for the NF1 gene is undertaken.

Genetic testing

Children considered at risk of NF1 especially with 6+ café au lait macules or diagnosed with NIH criteria should ideally have genetic testing of the NF1 gene with an RNA-based approach and testing of SPRED1 if pigmentary features only.

Those testing negative who just have pigmentary features should be referred to clinical genetics for consideration of testing a panel of genes including, GNAS, MLH1, MSH2, MSH6, NF2, PMS2, PTPN11, SOS1, SPRED1 (if not already tested).

Assessment & management of clinical problems

All adults and children with NF1 should be assessed at least once a year. The key principles in managing NF1 are specific checks for age-related complications combined with patient education. Routine screening investigations in an asymptomatic patient are not recommended.

Contact details for the general practitioner, named specialist or clinic coordinator should be given to patients. The following should be recorded at each visit:

- Development and progress at school (children)
- Fundoscopy and visual acuity (done by a Paediatric Ophthalmologist until 8 years); after this, vision should be part of the annual check
- Height (children)
- Head circumference (children)
- Weight (children and adults)
- Pubertal development (children – for signs of delayed/precocious puberty)
- Blood pressure (children, and adults)
- Evaluation of spine (all children; adults with known scoliosis or underlying plexiform neurofibromas)
- Evaluation of the skin (children and adults)
- System examination if specific symptoms
- Risk factors for osteoporosis (adults)
- Individuals with severe kyphoscoliosis require a full respiratory assessment at diagnosis and if respiratory symptoms develop or worsen
- Evaluation of mood

The skin

Neurofibromas are benign peripheral nerve sheath tumours; there are three main types:

Cutaneous neurofibromas

- Do not undergo cancerous change
- Develop in teens/early twenties (and occasionally in early childhood)
- Vary in number between individuals
- Can cause itching which usually does not respond to antihistamines; individuals should avoid excessive heat and use emollients
- May cause transient stinging

- May catch on clothing
- Produce cosmetic problems
- NF1 patients benefit from referral to a plastic or dermatological surgeon for removal of these lesions
- Different treatment methods are used according to the size and site of the neurofibroma.

Subcutaneous neurofibromas

- Present in approximately 15% of patients
- 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

- Present in over half of patients & associated with major physical problems in about 6% of patients
- Grow along the length of a nerve and may involve multiple nerve fascicles and branches. The growth rate is unpredictable
- Facial plexiform neurofibromas (1-2% of patients) causing facial disfigurement develop during the first three years, if they are to develop at all

There is about a 15% lifetime risk of malignant change in plexiform neurofibromas. Individuals with NF1 should seek urgent ex – pert advice (preferably from a national NF1 centre) if the following develop in association with a plexiform or subcutaneous neurofibroma:

- Persistent pain for more than a month or nocturnal pain
- New or unexplained neurological deficit (weakness, tingling, numbness, difficulty with coordination or swallowing) or change in bladder or bowel function or breathing problems
- 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 because potentially they can **cause severe haemorrhage or encroach on vital organs. Expert advice should be sought before removal by experienced soft tissue tumour / plastic surgeons, preferably in a national NF1 centre.**

Vision

This includes:

Optic pathway gliomas (OPG)

OPG are pilocytic astrocytomas and often follow an indolent course in NF1. If children with NF1 are scanned, 15% will show changes compatible with an OPG but only one third of these will become symptomatic (5% of NF1 patients overall). No benefit has been shown from screening scans in asymptomatic children.

Ophthalmology Screening

- **Should be done 6/12 monthly for children up to the age of 4**
- **Every 12 months up to the age of 8**
- **Following the age of 8, they should be followed up by local opticians, with visual field testing where feasible**

As most of those that cause symptoms do so by the age of seven years, it is recommended that NF1 children have a check with a paediatric ophthalmologist once a year until they are eight years. This should include a baseline assessment of colour vision and visual fields as soon as the child can co-operate.

Manifestations of OPG include optic atrophy, decreased colour vision, pupillary & visual field abnormalities, squint, proptosis and hypothalamic disturbance. Young children do not complain of visual impairment and parents need to be alert to possible eye problems such as bumping into things or failure to pick up small toys. Expert advice should be sought for the management of OPG.

In children with no visual problems, vision should be assessed annually by an optician or orthoptist from eight to sixteen years.

All NF1 patients need to be advised to seek urgent assessment if they develop visual symptoms, although this may be problematic in early childhood.

Glaucoma (in early childhood)

Congenital Sphenoid wing dysplasia resulting in proptosis/exophthalomos/enophthalmos

People with sphenoid wing dysplasia and one of the above need assessment by an experienced craniofacial team

Plexiform neurofibroma involving eyelid orbit

Cognitive problems & behavioural difficulties

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, autism spectrum disorders and developmental coordination disorders.

- A detailed developmental assessment should be performed as soon as possible and definitely before school
- Enquire about school progress and general behaviour during yearly assessment
- Close liaison between school, educational psychologists, occupational therapists and clinicians is required
- Assessment for Special Educational Needs (and/or statement) should be carried out if appropriate
- Question adults about literacy skills and refer to adult literacy classes if appropriate by age 7 years or if diagnosed later, a baseline neurocognitive psychology assessment should be considered by the appropriate psychologist including frontal executive function/ behaviours. There should be a low threshold for additional educational support including application for an Education Health Care assessment, in particular in anticipation of any school transition (e.g. primary to secondary school).
- Referral to a Child & Adolescent Mental Health Service (CAMHS) may be warranted

Neurological problems

- Tumours (**cerebral, spinal and optic pathway gliomas**, NOT vestibular schwannomas or meningiomas). Individuals with low grade gliomas require at least yearly MRI for 5 years and then monitor clinically
- Malformations (including **aqueduct stenosis**)
- **Epilepsy**, particularly complex partial seizures
- Cerebrovascular disease
- **Pressure on peripheral nerves, spinal nerve roots, spinal cord from plexiform neurofibromas**
  - **Neurofibromatous neuropathy (mild symmetrical distal tingling, numbness or weakness)**
  - **Multiple sclerosis**
  - **Neurovascular complications**

Aqueduct stenosis, Epilepsy, Multiple sclerosis and cerebrovascular disease should all be managed as in the general population.

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

The most common findings on brain MRIs are focal areas of signal intensity on T2 weighted images (FASI). They are most commonly seen from 8-16 years and tend to disappear in adulthood. They have no association with other CNS pathologies, nor is there clear correlation with learning problems.

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

Psychological problems

Psychological difficulties including social/generalised anxiety and mood disorders are common in NF1. The symptoms may arise from **cosmetic problems** caused by neurofibromas and from **the complex, variable and unpredictable nature of the disease**. Symptoms should be carefully evaluated and referral to Psychiatry or Psychology may be warranted.

Support Specialists and other support organisations may all play a supportive role in managing psychological problems.

Anxiety and depression

The presence of anxiety disorders and depression can add to the burden of illness, and affect symptom presentation. Treatment of these conditions is tailored to the individual usually with a combination of pharmacological and/or psychological therapies. Care should be taken to differentiate from adjustment disorders, cognitive impairment, demoralisation, or other physical manifestations of NF1.

Malignancy

People with NF1 have an increased risk of malignant peripheral nerve sheath tumour, cerebral and spinal gliomas and phaeochromocytoma (rare in children). Children are also at risk for developing rhabdomyosarcoma (especially pelvic), juvenile myelomonocytic leukaemia.

Malignant peripheral nerve sheath tumours (MPNST)

Assess with history and clinical examination annually for typical signs of MPNST.

- Any neurofibroma with rapid growth, or increased pain or change to hard texture, neurological deficit (including motor, sensory, coordination difficulty, swallowing, breathing or sphincter impairment).

Symptomatic plexiform neurofibromas require investigation with MRI/FDGPET CT/PETMRI, and referral to the national NF1 centres is advisable.

Follow-up should be tailored to the individual in people with persisting symptoms /high risk for MPNST if negative PET or negative biopsy. They will require discussion in the national complex NF1 service.

Whole body MRI

Consider a baseline Whole Body MRI between the ages of 16 to 20 years to assess internal burden could be potentially useful and should be particularly considered in whole gene deletion patients and patients with a high subcutaneous nodular burden. They may also be useful for assessing women who are considering pregnancy when considering epidural/spinal intervention.

Breast cancer in women

Women age 30-50 years should be advised of increased breast cancer risks of 4 – to 5 – fold under 50 years (not substantially increased thereafter). Access to extra breast screening is according to guidelines for moderate (20%) lifetime risk or high risk if there is additional family history of breast cancer.

Orthopaedic problems

Bowing of long bones +/– pseudarthrosis

- Presents in infancy and if not present once the child is fully mobile will not develop at all.

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
- The spine should be checked once a year in children and teenagers with NF1 until they have finished growing
- Individuals with scoliosis should be referred for spinal orthopaedic assessment