Neurofibromatosis Type 1

Review Guidelines for Children with NF1

BASELINE ASSESSMENT AT DIAGNOSIS

At time of diagnosis, or possible diagnosis, ALL paediatric patients should be referred to a Genetics service, regardless of age. Those with complex medical problems should be referred to the nationally commissioned Complex NF1 Service. (**Please see attached referral criteria in appendix 1**). Annual review should be undertaken by the child's local paediatrician throughout childhood.

REVISED DIAGNOSTIC CRTIERIA FOR NF1

Legius E, Messiaen L, Wolkenstein P, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med. 2021;23(8):1506-1513. doi:10.1038/s41436-021-01170-5

A: Diagnostic criteria for child who does not have a parent diagnosed with NF1 if two or more of the following are present:

- Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in post pubertal individuals
- Freckling in the axillary or inguinal region
- Two or more neurofibromas of any type or one plexiform neurofibroma (PN)
- Optic pathway glioma
- Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CA's) defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/ near-infrared reflectance (NIR) imaging
- A distinctive osseous lesion such as sphenoid dysplasia,[b] anterolateral bowing of the tibia, or pseudarthrosis of a long bone
- A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present:

[a] If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1 but exceptionally the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.

[b] Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma

SIGNPOST FAMILIES TO NF CHARITIES

Nerve Tumours UK https://nervetumours.org.uk

Childhood Tumour Trust https://www.childhoodtumourtrust.org.uk/

Children's Tumor Foundation https://www.ctf.org

Neurofibromatosis Type 1
Annual Review Checklist - Children (0-16)

	WHAT TO LOOK FOR	WHEN TO REFER
GROWTH & PUBERTY	Record height, weight and head circumference (head circumference in children until 2/3yrs of age). Assess puberty	**Refer to paediatric endocrinologist if faltering growth/ delayed / arrested/ early onset puberty*. Consider brain imaging if OFC crossing centiles**
BLOOD PRESSURE	If BP high, repeat x 3 and if still high refer to paediatric nephrologist	**If still high refer to paediatric nephrologist for 24hr ambulatory BP monitoring and consideration of investigations to look for renal artery stenosis or phaeochromocytom**
SKIN	Neurofibromas – can be itchy, and sometimes tender or can bleed. May be cutaneous or subcutaneous. Plexiform neurofibromas – note location, appearance, size and hardness. Monitor large areas of café au lait pigmentation and/or excessive hair growth for development of a plexiform.	**Refer all children with plexiform neurofibromas. Rapidly growing, painful or changing lesions: URGENT REFERRAL to Complex NF1 Service or Specialist sarcoma team.**
SKELETON	Scoliosis– look for signs during entire growth period, and especially at puberty and during adolescent growth spurts. Pseudarthrosis – tibia most commonly affected but radius and ulna may be involved.	**Any curvature or bowing – REFER to NF1 specialist orthopaedic surgeon.**
EYES	Have regular ophthalmic reviews taken place for those aged 0-8 years? Is there any evidence of a squint, proptosis, or reduced visual acuity or change in visual behaviour?	**Refer all children to ophthalmology locally for regular eye check. Contact local ophthalmologist URGENTLY if there are concerns about the eye or visual symptoms.**
NEUROLOGICAL	Neurological symptom review, particularly ataxia, focal neurological deficit, seizures, headaches (new or unexplained) and visual disturbance.	**See below for brain imaging. Referral to local paediatric neurologist as per usual practice**
SLEEP	**Ask about sleep routine, delayed sleep onset and awakenings and day time somnolence**	**Advise re sleep hygiene. Consider melatonin. Local sleep clinic referral if issues persist**
DEVELOPMENT/ EDUCATION / BEHAVIOUR	Review development. Note ADHD, ASD and motor coordination difficulties are common in NF1 patients. Ask about educational attainment.	**Refer to local community paediatric services as per usual practice. Support those in school. Provide advice (see advice for teachers on Nerve Tumours UK website)**
MENTAL HEALTH	Ask about general emotional, social, psychological wellbeing in school age children	**Refer to school counselling/ local CAMHS as appropriate**

***Linear growth deceleration or acceleration:** crossing at least 2 centiles on the growth chart over 6 months or more
Precocious puberty: Girls < 8 years (menarche < 9 years) and boys < 9 years
Delayed puberty: Girls > 13.4 years and boys > 13.8 years
Arrested puberty: Failure to progress through Tanner's staging if absence of breast development in girls at 14 years or menarche at 16 years and testicular enlargement in boys at 16 years

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MRI BRAIN IN CHILDREN WITH NF1

Routine brain MRI is NOT indicated in NF1

Image brain if:

- Focal neurological deficit (URGENT)
- New onset or unexplained headaches, worsening, changing (URGENT)
- Seizures
- Signs of raised ICP (URGENT)
- Concerns regarding growth and puberty
- Decline in visual acuity as defined by 2line Logmar change (URGENT)
- Transient ischaemic attack/ stroke like symptoms (URGENT)

SELUMETINIB FOR SYMPTOMATIC INOPERABLE PLEXIFORM NEUROFIBROMA (PN)

All patients with symptomatic PN should be referred to complex NF1 service

Patients will be assessed for eligibility for Selumetinib followed by discussion in the National MEK (mitogen-activated extracellular signal-regulated kinase) MDT

WHEN TO REFER TO SPECIALIST CENTRE?

According to complex NF1 criteria guidelines (See Appendix 1)

If medical complication not listed above requiring specialist advice

Diagnostic uncertainty where a diagnosis of NF1 remains a possibility (after review by regional geneticist)

Transition

RESOURCES

Guidelines for the diagnosis and management of individuals with neurofibromatosis 1 Rosalie E Ferner, Susan M Huson, Nick Thomas, Celia Moss, Harry Willshaw, D Gareth Evans, Meena Upadhyaya, Richard Towers, Michael Gleeson, Christine Steiger, Amanda Kirby
J Med Genet 2007;44:81–88. doi: 10.1136/jmg.2006.045906
http://dx.doi.org/10.1136/jmg.2006.045906

Annual review of children with neurofibromatosis type 1
Dunning-Davies B, Parker *Archives of Disease in Childhood - Education and Practice* 2016;**101**:102-111.
http://dx.doi.org/10.1136/archdischild-2014-308084

ERN GENTURIS tumour surveillance guidelines for individuals with neurofibromatosis type 1 Charlotte Carton,a,o D. Gareth Evans,b,q Ignacio Blanco,c,o Reinhard E. Friedrich,d,o Rosalie E. Ferner,e,q Said Farschtschi,d,o Hector Salvador,f,o Amedeo A. Azizi,g,p Victor Mautner,d,o Claas Röhl,h,r Sirkku Peltonen,i,j,o Stavros Stivaros,k,l Eric Legius,m,o and Rianne Oostenbrink,n,o, * On behalf of the ERN GENTURIS NF1 Tumour Management Guideline Group
eClinicalMedicine 2023;56: 101818
https://doi.org/10.1016/j.eclinm.2022.101818

Health Supervision for Children With Neurofibromatosis Type 1. Miller DT, Freedenberg D, Schorry E, Ullrich NJ, Viskochil D, Korf BR; COUNCIL ON GENETICS; AMERICAN COLLEGE OF MEDICAL GENETICS AND GENOMICS.. Pediatrics. 2019 May;143(5):e20190660.
https://doi.org/10.1542/peds.2019-0660

Neurofibromatosis Type 1
APPENDIX 1 - complex NF1 criteria

Criteria for referral to national complex neurofibromatosis 1 service

Two national complex neurofibromatosis centres:

1. Guy's and St Thomas' NHS Foundation Trust London: gst-tr.nfadmingstt@nhs.net
2. Manchester University NHS Foundation Trust: NF1.admin@mft.nhs.uk

Brain glioma / glial neoplasm

Any adult or child with brain or spine glioma or glial neoplasm (This is a diagnosis made by a neuro-radiologist)

Scan yearly for first 5 years after diagnosis and then long-term follow-up under complex NF1 (most gliomas that require treatment, do so in the first five years after diagnosis.

DNET (dysembryoplastic neuroepithelial tumour)

Any adult or child with the above to be followed long-term by national service until a diagnosis has been made on histology (DNET cannot be distinguished reliably from glioma on brain MRI)

Aqueduct stenosis

This could be caused by a glioma, web or periaqueductal proliferation of glial cells.
NF1 patients may remain stable for many years and then deteriorate acutely with hydrocephalus

Optic pathway glioma

Children with OPG

1) All children with OPG for 2 years after diagnosis (most children with OPG who need treatment will do so in the first 2 years after diagnosis) / or children with OPG and deteriorating vision / precocious puberty / abnormal visual examination
2) OPG and significant learning problems
3) Not possible to test vision due to developmental or cognitive problems
4) Treated with chemotherapy
5) Treated with radiotherapy
6) Referred for second opinion
7) Any other neurological or ophthalmological problem that threatens vision or overlaps with neurovascular or inflammatory disease

Adults with OPG

1) Treated with chemotherapy
2) Treated with radiotherapy
3) Significant learning problems
4) Any other neurological or ophthalmological problem that threatens vision or overlaps with neurovascular or inflammatory disease or demyelination

The service works closely with regional neuro-oncology teams to ensure NF1 patients entered into relevant clinical trials.
Please let us know about any children with NF1 and OPG so we can ensure their long-term outcome is recorded

Multiple sclerosis

(There is an increased frequency of all types of multiple sclerosis in NF1 and clinical signs of NF1 and multiple sclerosis overlap).

Patients will be followed by both NF1 and MS specialists
Radiologically isolated demyelination
(50% risk of developing MS)
Clinically isolated syndrome

Vasculopathy

Includes intracranial e.g.moya moya, aneurysm, haemorrhage, vascular malformation, renal artery stenosis

Cord compression / cauda equina compression caused by neurofibromas

(Many patients do not require intervention despite neuroimaging findings. The cord compression is normally in the high cervical cord).
The complex NF1 service is involved in decision making about timing of surgery. Patients are followed-up, unless they have had surgery and do not have significant deficit

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APPENDIX 1 - Complex NF1 criteria

Criteria for referral to national complex neurofibromatosis 1 service continued

Symptomatic neurofibromas

1) Neurofibromas that cause one or more of persistent pain/nocturnal pain, rapid growth, change in texture or new or unexplained neurological deficit and require FDG PET CT. N.B. The decision to undertake PET imaging and the interpretation of results is a complex issue. To avoid unnecessary radiation, we recommend that patients with symptoms are referred to the national centers prior to PET imaging

2) Symptomatic neurofibromas causing significant
a) Neurological deficit
b) Impaired respiratory function
c) Impaired sphincter function
d) Haemorrhage
e) Severe infection
f) Limb overgrowth, extensive internal neurofibromas/ extensive neurofibromas involving the skull base/ face
g) Symptomatic neurofibromas that are not operable and are being considered for MEK inhibitors

Atypical neurofibroma (atypical neurofibromatous neoplasm of uncertain biologic potential)
People with previous resection of neurofibroma(s) reported to be atypical on histology by expert pathologists (these are associated with increased risk of future MPNST)

Neurofibromatous neuropathy
People with this axonal neuropathy have an increased risk of developing malignant peripheral nerve sheath tumour

Malignant peripheral nerve sheath tumour
Any past history or current history of MPNST (People with past history of MPNST are at increased risk of developing new MPNST)

Gastrointestinal stromal tumour (GIST)
These tumours may present with abdominal pain, change in bowel habit or haemorrhage

Sarcoma
Including bone sarcoma and rhabdomyosarcoma

Other Tumours
Phaeochromocytoma
Breast cancer < 50 years (increased risk in NF1 and requires screening from 40 years)
Cancer of colon, thyroid, lymphoma, leukaemia, melanoma other malignancy – increased risk

Pseudarthrosis of long bone
Adults and children seen once by Complex NF1 service to ensure no other bone dysplasia/ adequate vitamin D and referral to specialist pseudarthrosis team / adult rehabilitation team

Unusual NF1 phenotype
Legius syndrome
Kyphoscoliosis causing respiratory impairment
Spinal phenotype
Whole gene deletion – increased risk of malignancy

Genetic Counselling for people with mosaic NF1
Patients with mosaic NF1 should first have RNA based mutation analysis via the Manchester lab. If the results are normal they are then eligible for skin biopsy from café au lait macules (for melanocyte culture) or neurofibroma removal (for Schwann cell extraction and culture). The specific tissues are necessary to identify the causative mutation for genetic counselling.
Contact Dr Emma Burkitt Wright (Manchester) or Dr Dragana Josifova (GSTT).