Neurofibromatosis type 1 (NF1)

Also known as Von Recklinghausen’s disease; Peripheral Neurofibromatosis; Von Recklinghausen’s Neurofibromatosis; Recklinghausen’s Phakomatosis; Multiple Neurofibroma.

**GP’s role**
- Where possible confirm or rule out a diagnosis in the parents of an affected individual using the clinical diagnostic criteria listed below. If unsure of a diagnosis, refer to Genetics Services (see Contacts, support and testing).
- Refer as appropriate to specialist paediatric or adult neurology, dermatology, ophthalmology and/or orthopaedic services.
- Refer to Genetics Services for discussion of prenatal genetic testing (see Contacts, support and testing).
- Refer family to relevant support groups (see Contacts, support and testing).

**Clinical features**
- NF1 is characterised by the development of multiple café-au-lait spots, inguinal/axillary freckling and multiple neurofibromas.
- Symptoms usually appear during childhood and may become more pronounced during puberty, pregnancy, or when hormonal changes take place.
- Range and severity of symptoms can vary greatly among affected individuals even between family members.
- Rate of progression is not predictable.
- Diagnosed when two of the following clinical features are present:
  > Six or more café-au-lait spots, >0.5cm diameter before puberty, or >1.5cm in adults
  > Two or more neurofibromas of any type or one plexiform neurofibroma
  > Freckling under the arms or in the groin area
  > Benign tumour of the optic nerve (glioma)
  > Two or more Lisch nodules (iris hamartomas)
  > A distinctive osseous lesion such as a sphenoid dysplasia or thinning of the long bone cortex with or without psuedoarthrosis
  > A 1° relative (parent, sibling or offspring) with NF1 by the above criteria

- Additional but not diagnostic features:
  > Precocious puberty or delayed sexual development may occur
  > About 50% have specific learning disabilities in reading, spelling or mathematics
  > Growth may be reduced
  > Macrocephaly
  > Scoliosis
  > Hypertension
  > Epilepsy
Neurofibromatosis

Genetics
- NF1 is caused by mutations in the NF1 gene that encodes a protein called neurofibromin, which functions as a tumour suppressor.
- Many different mutations in the NF1 gene have been identified in individuals with the condition.
- The condition follows a pattern of autosomal dominant inheritance.
- Approximately 50% of NF1 cases are inherited from a parent.
- About 50% are due to new mutations in the NF1 gene occurring randomly at or around conception for unknown reasons.

Prevalence
- NF1 affects about 1 in 3000 people.
- There is a wide range of severity of symptoms.
- Many people with the condition will only be affected mildly.
- For most people, NF1 does not significantly affect their health but for a few, NF1 can cause major health problems at certain stages of their lives.

Investigations
- Genetic testing is not needed to diagnose the condition after birth because most people with NF1 will have enough signs of the condition by age 5 years for a specialist to diagnose them with confidence.
- Genetic testing for NF1 is not widely available and is currently expensive, but it can be helpful in some situations, such as where prenatal diagnosis is requested.
- Prenatal genetic testing can be done where one of the parents is affected and wants to know if the fetus is affected, provided the specific NF1 mutation in the affected parent has been identified.

Management
- An annual review by GP for complications of the condition and for management advice (eg referral to plastic surgeon) should be undertaken.
- Be aware that:
  > Neurofibromas can cause cosmetic problems and wrap around or penetrate the nerves causing pain.
  > There is about a 5% increase in risk for various cancers, including brain tumour. Sometimes plexiform neurofibromas and, very rarely, simple neurofibromas can become malignant.
  > Hypertension is more common in NF1 patients than in the general population. At least annual blood pressure should be undertaken on all individuals with this condition. If hypertension is identified, then investigations for a secondary cause such as renal artery stenosis and phaeochromocytoma should be undertaken.
  > There is also an increased rate of scoliosis in NF1. This should be looked for and there should be a low threshold for referral to an orthopaedic surgeon for investigation and management. As with scoliosis in other conditions, it most commonly presents and progresses around the time of puberty.
- Areas of surveillance should include:
  > Ophthalmology for optic gliomas; growth of these is rare over 10 years of age.
  > Education, as specific learning disabilities in reading, spelling or mathematics may be present. Children also may have short attention span, low muscle tone, reduced co-ordination and emotional immaturity.
  > Monitoring of any rapid changes in the growth or symptoms of a neurofibroma.
Neurofibromatosis type 2 (NF2)

**GP’s role**
- Take and update the family history (see *Genetics in practice*).
- Inform adult patients with NF2 of the familial nature of the condition and risks to future children and relatives.
- Manage co-existent conditions.
- Provide referral as appropriate to neurology and ophthalmology specialists for assessment and surveillance.
- Provide referral to Genetics Services for discussion of predictive genetic testing (see *Contacts, support and testing*).

**Clinical features**
- NF2 is a rare genetic condition that is primarily characterised by vestibular schwannomas.
- Symptoms may include:
  - Gradual hearing loss
  - Tinnitus
  - Balance problems
- The condition is diagnosed in individuals with one of the following:
  - Bilateral vestibular schwannomas
  - A 1° relative with NF2 and unilateral vestibular schwannomas or any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
  - Unilateral vestibular schwannoma and any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
  - Multiple meningiomas and unilateral vestibular schwannoma or any two of schwannoma, glioma, neurofibroma, cataract
- Café-au-lait spots may be present but are usually fewer in number than in NF1.
- Benign tumours may also occur in or around the spinal cord.
- Other tumours of the central nervous system may also develop including schwannomas, meningiomas, gliomas and rarely neurofibromas.
- Posterior subcapsular cataracts may develop at a younger age than would otherwise be expected, with symptoms including impaired and/or progressive loss of vision.
- Other features include:
  - Facial spasms
  - Generalised muscle weakness, numbness, pain, and/or partial paralysis
  - Difficulty swallowing and/or impaired speech
  - Other neurological problems including headaches and/or seizures
- Symptoms usually develop around the time of puberty or during early adulthood from the presence of benign tumours on both auditory nerves (acoustic neuromas/vestibular schwannomas) with 90% being symptomatic by age 45.
- Up to 30% of patients present in the first two decades of life with a non-vestibular tumour such as intracranial meningioma, astrocytoma or spinal tumour.
- 10% present under the age of 10 years. Early presentation with a non-vestibular tumour is an adverse prognostic indicator.
Genetics
- NF2 is caused by mutations in the NF2 gene that regulates the production of the merlin/schwannomin protein which functions as a tumour suppressor.
- Merlin/schwannomin is related to a class of proteins (ezrin-radixin-moesin proteins) that serve to link the internal, supportive system within a cell (cytoskeleton) to proteins in cell membranes.
- Many different mutations in the NF2 gene have been identified in individuals with the condition, and may contribute to the wide variability of symptoms and findings in affected individuals.
- The condition follows a pattern of autosomal dominant inheritance.
- Approximately 50% of NF2 cases are inherited and about 50% are due to new mutations in the NF2 gene.

Prevalence
- NF2 has an estimated birth frequency of 1 in 33,000 to 40,000.

Investigations
- Genetic testing is rarely required for diagnosis.
- The main utility for genetic testing of the NF2 gene is to enable predictive testing and to facilitate prenatal testing where this is requested.
- Following genetic counselling, genetic testing is first done on a family member with NF2 and germ-line mutations can be detected in about 60% of those affected. This can take some months. (See Contacts, support and testing).
- Once the family mutation has been identified, presymptomatic testing is then available to blood relatives and results are available in a much shorter time frame.

Management
- Early detection of vestibular schwannomas is associated with better outcome.
- The diagnosis is confirmed by a thorough clinical evaluation and specialised testing such as magnetic resonance imaging (MRI).
- Vestibular schwannomas are surgically removed when possible. The surgical procedure that is performed is based upon the size and precise location of the tumours.
- Radiation therapy may be considered for those who are not candidates for surgery.
- Tumour surveillance in carriers for an NF2 mutation, affected individuals and at-risk individuals.

Implications for other family members
- Testing for the NF2 mutation in asymptomatic family members can identify those who may be at risk of developing tumours and would benefit from regular screening.
- If a relative is found not to have inherited the family NF2 mutation then no further screening is necessary. The emotional and financial costs can therefore be avoided.
Bibliography


Neurofibromatosis Association of Australia (NFAA) Inc. http://nfaa.org.au