Neurofibromatosis type 2 – diagnosis, features and MDT approach

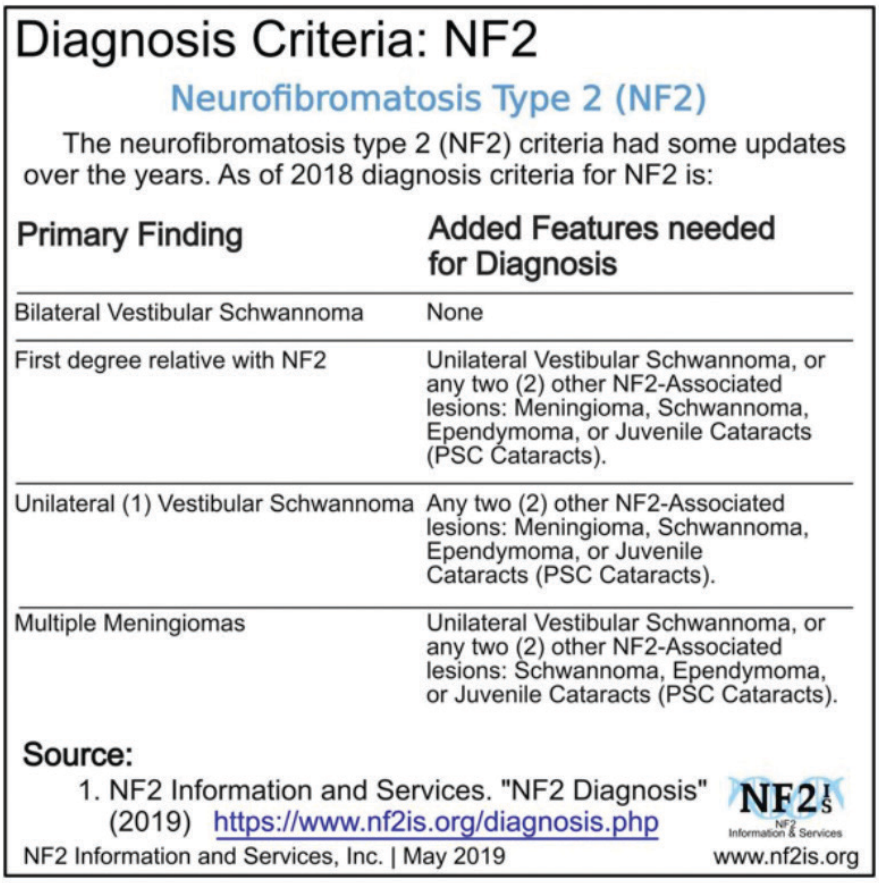
NF2 is a genetic condition caused by mutation in a single gene (*NF2* gene) on chromosome 22. The *NF2* gene provides instructions to produce a protein called merlin, also known as schwannomin. This protein functions as a tumour suppressor, preventing cells from growing and dividing too fast or in an uncontrolled way. Mutations in the *NF2* gene lead to the production of a non-functional version of the merlin protein that cannot regulate the growth and division of cells. The genetic fault will be present at birth, but signs of the condition do not usually appear until the teenage years, 20s or later. It can be passed on from a parent or it can start in a family with no previous history of the disorder. NF2 is a rare condition with a birth incidence of approximately one in 25,000–33,000 [1].

The main feature of NF2 is the growth of bilateral vestibular schwannomas. These are benign tumours that occur on the nerves for balance and hearing leading to the inner ear. Although these tumours are benign, they cause hearing and balance problems, usually resulting if untreated in complete loss of hearing. People with NF2 are at increased risk of developing other types of nervous system tumours as well. These are schwannomas of other nerves, meningiomas (benign tumours of the brain and spinal lining) and ependymomas of the brain or spinal cord. Juvenile cataract is a common eye issue at birth or shortly after for individuals with NF2. Children can also present with ophthalmic features such as reduced visual acuity from cataracts, retinal hamartoma, epiretinal membrane or optic nerve sheath meningioma. Other symptoms include squint, nystagmus and ptosis, with unexplained amblyopia being particularly common. Anyone diagnosed with or suspected of having NF2 is recommended to have an eye examination annually. It is also important to test vision and assess the health of optic nerve, to detect the presence of tumours.

Recent audit of ophthalmic manifestations of patient under the care the Manchester NF2 centre showed that 44% of patients were seen by ophthalmologists and nearly 85% of them had ophthalmic features, summarised in the table below (presented as a poster at NANOS 2021).

Ophthalmic feature	Percentage
Facial nerve palsy	30%
Cataract	13%
Ocular motility abnormalities (III, IV, VI)	10%
Combined hamartoma of retina and retinal pigment epithelium (RIPE)	6%
Visual pathway meningiomas	5%
Papilloedema	4%
Epiretinal membrane (ERM)	3%
Optic nerve glioma	<1%

The symptoms of NF2 can occur at any age, but they typically appear during adolescence or early adulthood. They can vary in presentation and severity depending on the exact location of the tumours. Early symptoms of NF2 include problems with hearing, balance and tinnitus. For tumours that occur outside of the hearing and balance nerves, symptoms might include weakness in the face, arms or legs, headaches and visual problems. If children present with ophthalmic features of NF2 an early referral needs to be made to NF2 service for further investigation. The diagnosis of NF2 is confirmed by a thorough clinical evaluation and specialised testing (i.e., magnetic resonance imaging (MRI), audiometry, vision test, etc). Molecular genetic testing for mutations in the NF2 gene is available for affected individuals who have a positive family history or if clinically indicated. A confirmed diagnosis of NF2 can be made if an individual has bilateral vestibular schwannomas (see table below).



Diagnosis Criteria: NF2

Neurofibromatosis Type 2 (NF2)

The neurofibromatosis type 2 (NF2) criteria had some updates over the years. As of 2018 diagnosis criteria for NF2 is:

Primary Finding	Added Features needed for Diagnosis
Bilateral Vestibular Schwannoma	None
First degree relative with NF2	Unilateral Vestibular Schwannoma, or any two (2) other NF2-Associated lesions: Meningioma, Schwannoma, Ependymoma, or Juvenile Cataracts (PSC Cataracts).
Unilateral (1) Vestibular Schwannoma	Any two (2) other NF2-Associated lesions: Meningioma, Schwannoma, Ependymoma, or Juvenile Cataracts (PSC Cataracts).
Multiple Meningiomas	Unilateral Vestibular Schwannoma, or any two (2) other NF2-Associated lesions: Schwannoma, Ependymoma, or Juvenile Cataracts (PSC Cataracts).

Source:

1. NF2 Information and Services. "NF2 Diagnosis" (2019) https://www.nf2is.org/diagnosis.php

NF2 Information and Services, Inc. | May 2019

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Several different types of mutations of the *NF2* gene have been identified in individuals with the disorder, e.g., deletions, missense, splice site, nonsense and frameshift mutations. The presentation of NF2 can be extremely variable and studies have determined genotype-phenotype correlations with truncating pathogenic variants (nonsense and frameshift) cause more severe disease courses than missense mutations, splice site mutations, or large deletions [2,3].

In some individuals with NF2, the disorder is inherited from an affected parent. Subsequent transmission is in an autosomal dominant pattern. Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary to cause a disease. The abnormal gene can be inherited from either parent. The risk of passing the abnormal gene from affected parent to offspring is 50% for each pregnancy and screening for NF2 can start at birth. The risk is the same for males and females. More than 50% of NF2 cases have no family history of the disease [4]. In such cases, NF2 is caused by a new gene mutation. A considerable proportion of NF2 patients, particularly milder cases, have mosaic disease, in which only a proportion of cells contain the mutated NF2 gene. The initiating mutation occurs after conception. The proportion of cells affected depends on how early in development the mutation occurs [4]. If a mosaic parent passes on NF2 to their child, that child will have full blown NF2 with more severe disease than their parent. However, the risk to a child of patients with mosaic NF2 is much less than 50%. Genetic counselling is recommended for people with NF2 and their family members.

The specific treatment approach for NF2 depends on the type and location of the tumour as well as an individual's age and general health. Surgery, stereotactic radiosurgery and bevacizumab therapy are available for the management of intracranial and spinal tumours. Cochlear implantation and auditory brainstem implantation are offered if indicated [5]. Regular monitoring is required for all affected individuals. Individuals identified as at risk are also to be offered annual magnetic resonance imaging (MRI) beginning at approximately age 10 to 12 years and continuing until at least the fourth decade of life in addition to regular hearing evaluations. Pre-symptomatic genetic testing is an integral part of the management of NF2 families. Prenatal diagnosis and pre-implantation genetic diagnosis is possible [4]. Earlier diagnosis and better treatment lend itself to improved survival in those affected.

Due to the complex nature of the disease, the management of NF2 requires highly skilled multidisciplinary approach. In England NF2 patients are manged through specialised service commissioned in 2010 by NHS England. There are four main centres – Manchester, Oxford, Cambridge and London, each having associated satellite centres. Each centre has a core multidisciplinary team (MDT) consisting of genetics, otolaryngology, neurosurgery, paediatrics, neurology, ophthalmology, audiology, radiology, psychology, physiotherapy, specialist nurses and administrative staff. In addition, the core team has access to plastic surgery, peripheral nerve surgery and adult and paediatric oncology. There are weekly multidisciplinary clinics, each with six to eight patients. Each patient is discussed during a team meeting and the management decisions that are made are then discussed with the patients. All patients are reviewed at least annually and have close monitoring of disease progression using MRI. Audiological assessments are also part of the annual review.

NF2 clinical nurse specialists have a pivotal role in supporting patients through their NF2 journey. Patients face various co-morbidities in their lifetime such as progressive hearing loss, visual impairment and neurological disability. The genetic implications can be far reaching for them and their family. Management is not just focused on medical or surgical interventions but is around providing best quality of life and helping them adjust to a diagnosis of NF2 and all this entails. There are NF2 specialist nurses linked to all four main centres across England, they also work closely with satellite centres providing services to NF2 patients and their families in accordance with the national guidelines and national service standards. The NF2 specialist nurse coordinates patient care between multiple clinicians and locations, they support patients with the management of their disease by providing expert advocacy for newly diagnosed patients or those in acute need. The role of NF2 specialist nurse extends to the wider community such as schools, colleges and workplace and are a point of contact when needed. Furthermore to their role, the NF2 specialist nurse builds a good professional rapport with their named patients and families, helping them with decision-making around complex treatment requirements, empowering patients to live independently and providing access to social, psychological and other support services where it is required.

NF2 is a life-limiting and life spoiling condition. Early diagnosis and multidisciplinary management play a vital role in improving life expectancy and quality of life of affected individuals.

References

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AUTHOR

Jincy Kurian,

Clinical Nurse Specialist Neurofibromatosis Type 2, Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Saint Mary's Hospital, Manchester, UK.

SECTION EDITOR

Ali Yagan,

Consultant Ophthalmic Surgeon, Neuro-ophthalmology and ocular motility, Manchester Royal Eye Hospital, UK.

E: ali.yagan@mft.nhs.uk