Acta Otorrinolaringol Esp. 2010;**61(4):**306–311

Acta Otorrinolaringológica Española

www.elsevier.es/otorrino

REVIEW

Neurofibromatosis type 2

Marta Pérez-Grau, Núria Miró, José Prades, Juan Vergés, Susana Lareo, and Francesc Roca-Ribas*

Unidad de Neurofibromatosis tipo 2, Servicio de ORL, Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona, Spain

Received December 3, 2009; accepted December 8, 2009

KEYWORDS
NF2;
Vestibular schwannoma;
Meningioma;
Brain stem implant

Abstract
Type 2 neurofibromatosis (NF2) is an invalidating, inherited, dominant, autosomal disease. It is commonly confused with type 1 neurofibromatosis, although the two disorders are different.
All subjects who inherit a mutated NF2 gene will develop the disease, which is characterised by the growth of schwannomas, generally affecting the vestibular nerve bilaterally, as well as meningiomas and other benign central nervous system tumours, before their third decade of life.
It is currently possible to identify the NF2 mutation in most affected families. Up to about 20% of NF2 patients with no family history, apparently sporadic cases, are actually individuals with mosaicism for this mutation.
Much of the morbidity from these tumours results from their treatment, which is primarily surgical. Small vestibular schwannomas can often be completely resected with preservation of both hearing and facial function. In case of large tumours it is possible to place a cochlear or brain stem implant during the schwannoma surgery.
Age at diagnosis, the presence of intracranial meningiomas and whether the patient was treated at a specialty centre or not have been cited as the strongest prognostic factors.

*Corresponding author.
E-mail address: 12226frs@comb.cat (F. Roca-Ribas).

0001-6519/$ - see front matter

PALABRAS CLAVE
Neurofibromatosis tipo 2;
Schwanoma vestibular;
Meningioma;
Implante de tronco

Neurofibromatosis tipo2

Resumen
La neurofibromatosis tipo 2 es una enfermedad invalidante que se hereda de forma autosómica dominante. A menudo se ha confundido con la neurofibromatosis tipo 1, aunque son patologías distintas.
Todos los sujetos que hereden una mutación en el gen de la neurofibromatosis tipo 2 (NF2) desarrollarán dicha enfermedad, caracterizada por el crecimiento de schwanomas, habitualmente vestibulares y de forma bilateral, así como meningiomas u otros tumores benignos del sistema nervioso central, antes de los 30 años de edad.
Actualmente, podemos identificar la mutación del NF2 en la mayoría de las familias afectas. Hasta un 20% de los pacientes afectos de NF2 sin historia familiar, aparentemente casos esporádicos, son en realidad individuos con mosaicismo para esa mutación.
La morbilidad de esos tumores es en gran medida debida a su tratamiento, que es principalmente quirúrgico. Cuando son pequeños, los schwanomas vestibulares se pueden resecar completamente con preservación tanto de la función auditiva como facial. En caso de tumores grandes se puede colocar un implante coclear o bien de tronco cerebral durante el mismo acto quirúrgico.
Los principales factores pronósticos son: la edad media al diagnóstico, la presencia de meningiomas intracraneales y si el paciente fue tratado o no en un centro especializado.

Introduction

Neurofibromatosis (NF) is a group of three related but genetically different disorders of the nervous system, which are inherited in an autosomal dominant pattern, and which cause cell tumours in the neuroglia.

Their prevalence is equal for both genders and they have no predilection for any race or ethnic group.

In the classification of the NF, we can differentiate:

- Type 1 neurofibromatosis or Von Recklinghausen disease (NF1)
- Type 2 neurofibromatosis (NF2)
- Schwannomatosis

History

The first case of NF2 was described in 1822 by a Scottish surgeon named Wishart. Later, in the nineteenth century, NF1 was defined by Von Recklinghausen.

Both were considered as part of the same illness for years. In 1987, it was finally recognised that they were two separate entities, and that the locations of their respective causative genes were on chromosomes 22 and 17.[1,2]

Incidence and prevalence

Initially, the incidence of NF2 was estimated at 1:30,000-40,000, with a prevalence of disease of approximately 1:200,000. However, recent studies suggest that the incidence of infants born with NF2 may be up to 1:25,000, and its prevalence higher than 1:80,000.[3]

The incidence is significantly higher than the prevalence of diagnosed cases because many cases do not meet the diagnostic criteria of the disease until after the third decade of life and others die before then.

Physiopathology

The manifestations of NF2 are the result of point mutations or deletions or large rearrangements of the *NF2* gene, located on the long arm of chromosome 22. This results in decreased production of the protein merlin or schwannomin, which acts as a tumour suppressor. A decrease in the function or production of this protein yields a predisposition to develop a variety of tumours of the central and peripheral nervous systems.[4]

The *NF2* gene is the only gene associated with NF2. Up to 50% of patients have no family history of NF2, so in those cases they are considered as presenting a *de novo* mutation.

NF2 is inherited in an autosomal dominant pattern. The *NF2* gene, like other tumour suppressor genes, requires the inactivation of both alleles for the loss of its function (Knudson's double impact model). Individuals who have a germline mutation require only a somatic mutation to lose full function of the gene.

Characteristics of the disease

The onset age for findings in patients with NF2 is usually around 18-24 years, although the range is from birth to 70 years. Almost all patients have developed a bilateral vestibular schwannoma at age 30. Apart from the vestibular schwannoma, patients with NF2 develop

schwannomas in other nerves (peripheral and cranial nerves), as well as meningiomas and, more rarely, ependymomas and astrocytomas. The most common ocular finding is a posterior subcapsular cataract, and this can be the first sign of NF2. During childhood it may be possible to detect a mononeuropathy, often in the form of facial paralysis or strabismus (by paralysis of the third cranial nerve).

The variable expression of NF2 between individuals explains the differences in size, location and number of tumours. Although these tumours are not malignant, their number and anatomic location lead to a significant morbidity and early death. Life expectancy is around 36 years, with an average survival from the time of diagnosis of 15 years; survival is improving with early diagnosis of disease and better treatment at specialised centres.[5,6]

This is considered a disease that starts in young adulthood. Consequently, NF2 may be underdiagnosed in children, in whom skin tumours and ocular abnormalities may be early clinical manifestations.[7]

Clinical manifestations

Vestibular schwannoma: early symptoms include tinnitus, hearing loss and impaired balance, usually with insidious onset. However, hearing loss may occasionally be of rapid onset, presumably due to vascular involvement of the tumour. It rarely causes facial paralysis, even if it is large. If left untreated, it will cause compression of the cerebellum and hydrocephalus. Schwannomas can also develop in other nerves, cranial and peripheral, being more frequent in sensory than in motor nerves.

Spinal tumours: up to two thirds of patients with NF2 develop tumours in the spinal cord and these are often the most difficult to handle. The most common are schwannomas, which usually originate in the intravertebral canal, in the dorsal roots.[8]

Up to 30% of patients may develop intramedullary tumours of astrocytoma or ependymoma type. Most spinally affected patients have multiple tumours, although many of them remain asymptomatic.

Meningiomas: approximately half of patients with NF2 develop meningiomas, most of them intracranial and mainly supratentorial.

Meningiomas in the orbit will cause vision loss due to optic nerve compression. Those originating at the base of the skull can cause neuropathy, cerebral compression and hydrocephalus.

A meningioma may be the form of presentation of NF2, particularly in childhood.[9]

Ocular affectation: one third of NF2 cases suffer unilateral or bilateral decrease of visual acuity. Posterior subcapsular opacity is the most common ocular finding, although it rarely progresses to a significant cataract. Such corneal opacities usually appear before the onset of the symptoms of vestibular neurinoma and can be observed in children.

More than 33% of individuals may suffer retinal hamartomas and epiretinal membranes.

Both intraorbital and intracranial tumours will produce a decrease in visual acuity and diplopia.

Monopolyneuropathy: especially during childhood, mononeuropathy is associated with NF2. It can often take the form of facial paralysis with only partial recovery, or else strabismus (due to paralysis of the motor oculi externus (MOC) or drooping foot or hand).[10]

A progressive polyneuropathy may appear in adults. This would not be directly related to the tumour masses.[11]

Cutaneous affectation: skin exploration is an aid in the diagnosis of NF2, although cutaneous findings are more subtle than those of NF1. Up to 70% of patients may present skin tumours. The most common lesion type is that resembling intradermal plaques with more pigmentation than the surrounding skin and often with an excessive hair growth, but they may also present subcutaneous schwannomas.

Diagnosis

In 1988, the NIH published a consensus about the diagnostic criteria for NF2,[12] which is clinical and from which only one criterion is required for diagnosis:

1. Bilateral Schwannomas of the eighth cranial nerve diagnosed by MRI or CR (biopsy is not necessary)
2. First-degree relative having NF2 and:
   a) Unilateral schwannoma of the eighth cranial nerve, with early onset (age <30 years)
   b) Two of the following:
      - Meningioma
      - Glioma
      - Schwannoma
      - Children with posterior subcapsular lenticular opacity (juvenile cortical cataract)
3. Unilateral schwannoma of the eighth cranial nerve diagnosed by CT or MRI with early onset (detected in a patient under 30 years) and 2 of the following:
   a) Meningioma
   b) Glioma
   c) Schwannoma
   d) Juvenile cortical cataract
4. Multiple meningiomas (>2) and:
   a) Unilateral schwannoma of the eighth cranial nerve
   b) 2 of the following:
      - Glioma
      - Schwannoma
      - Juvenile cortical cataract

Although schwannomas of the cranial nerves are relatively rare (with the exception of eighth cranial nerve schwannoma), they also occur spontaneously. Therefore, any patient presenting schwannomas in multiple cranial nerves, a rare intracranial schwannoma or a schwannoma of a single cranial nerve, third (MOC), fourth (pathetic), or sixth (motor oculi externus) should prompt a screening for NF2.

In addition, differential diagnosis should be considered in patients with multiple extra-axial tumours of the brain or spinal cord, regardless of whether they are meningiomas or schwannomas.

Molecular genetics diagnostic testing for NF2

At present, the molecular genetics diagnosis of NF2 is handled by analysing point mutations through the complete sequencing of the coding and intronic regions of the molecular *NF2* gene, and the detection of large deletions or rearrangements using the MLPA technique.

Chromosomal analysis: chromosomal abnormalities associated with NF2 have been reported, so chromosome analysis is recommended. Nevertheless, it is important to note that chromosomal abnormalities are usually not large and rarely does this study enable determination of the alteration responsible for the NF2.

Fluorescent *in situ* hybridisation analysis (FISH): it can detect small deletions that affect multiple exons of the *NF2* gene or the entire gene.

In patients without a family history (*de novo* cases), the detection rate of mutations in the *NF2* gene is low, approximately 50%. One of the reasons that might explain this low rate of detection of mutations in the germline is the presence of mosaicism. Recent studies show that up to 25%-33% of individuals with NF2 due to a *de novo* mutation present mosaicism.[13]

Identifying these patients with mosaicism for the *NF2* gene can be complex, given that:

- They generally have an incomplete phenotypic expression. Consequently, they frequently do not present bilateral vestibular schwannomas.
- The study of the *NF2* gene in the germline based on DNA extracted from peripheral blood lymphocytes does not usually find the mutation responsible for the symptoms; the genetic analysis of tumour tissue is required to diagnose the presence of mosaicism.

Differential diagnosis

NF1: although the two diseases are clinically distinct and are caused by mutations on different chromosomes, there is still confusion between NF1 and NF2:

- Patients with NF2 do not have the same cognitive problems that have been observed in NF1. Neither do they have Lisch nodules or "milk & coffee" skin blemishes.
- In NF2, schwannomas rarely became malignant and progress to neurofibrosarcoma.

Schwannomatosis: defined as multiple neurilemomas and schwannoma, but with no vestibular schwannoma. Affected individuals develop intracranial tumours of the nerve roots or peripheral nerves. One third of patients with schwannomatosis suffer segmental disease.

Unilateral vestibular schwannoma: this is a common tumour in the general population, approximately 5%-10% of all intracranial tumours and the vast majority of cerebellopontine angle tumours.

In vestibular schwannomas, 5% are bilateral and associated with NF2, while 95% are unilateral in individuals without a genetic predisposition to develop the disease.

The risk that a unilateral tumour is the first manifestation of NF2 is related to the age of the patient. Subjects under 30 years with a symptomatic vestibular neurinoma have a high risk of developing a contralateral neurinoma and NF2 should be ruled out. In addition, 6% of individuals apparently suffering from isolated vestibular schwannoma present mosaicism for the NF2 gene mutation.[14]

Meningioma: on rare occasions, patients have been described with multiple meningiomas with an autosomal dominant inheritance pattern, but without an associated vestibular schwannoma.

Typically, multiple meningiomas can be observed in elderly patients. Upon finding a single meningioma in an individual younger than 25 years, a possible NF2 should be ruled out.

Cowden disease: this is associated with multiple meningiomas, neurofibromas and hamartomas, including Lhermitte-Duclos disease (cerebellar gangliocytoma). However, it is not associated with schwannomas of the eighth cranial nerve.

Meningiomatosis and multiple meningioangiomatosis.

Gorlin syndrome: associated with meningiomas, astrocytomas and medulloblastomas, but not with schwannomas.

Evaluation of patients diagnosed with NF2

The following evaluations are recommended for establishing the extent of the disease in an individual diagnosed with NF2:

- Cranial and spinal MRI.
- Hearing evaluation, including BAEP.
- Ophthalmologic evaluation.
- Cutaneous test.

Patients with NF2 should be evaluated and treated at a specialised centre for NF2, with experience in the management of the various complications of the disease.[15]

Genetic counselling

All patients suffering from NF2 should be referred to genetic counselling units to receive appropriate attention. These units meet the needs presented by patients with NF2 and their families regarding the possibilities of developing or transmitting the disease, about its prognosis and options for its management, treatment and monitoring, as well as the benefits, risks and limitations of a genetic study.

Approximately 50% of individuals with NF2 have an affected parent, and 50% have NF2 as a result of a *de novo* mutation.

Between 25%-33% of individuals who are *de novo* cases (with no family history of NF2) present mosaicism for the NF2mutation.[16,17]

We recommend evaluation of the parents of a subject with an apparently *de novo* mutation, with a thorough medical history. In addition, if there is any suspicion of NF2, we advise performing an MRI. One parent may be excluded if their offspring has mosaicism, but the absence of the mutation detected in the child does not rule out the possibility of mosaicism in the parent. As the age of onset of

symptoms remains constant in each family, it is usually not necessary to carry out controls on asymptomatic parents.

Each of the descendants of a person with NF2 has a 50% chance of inheriting the mutation and, therefore, of presenting the disease.

Individuals with somatic mosaicism and bilateral vestibular tumours have less than a 50% chance of having an affected child.[18] If the mutation is detected in the tumour DNA but not in leukocyte DNA, the risk for the offspring is less than 5%.

Family planning: genetic counselling should be offered to all young adults affected or at risk. The identification of the mutation in the *NF2* gene responsible for the disease makes it possible for different family planning options to be considered.

Prenatal diagnosis: prenatal diagnosis in cases with a 50% risk for NF2 can be carried out through DNA analysis of foetal cells obtained by chorionic villus biopsy.

Preimplantation diagnosis: this is the determination of the mutation in the embryo at the morula stage before implantation in the womb. It requires approval by the National Commission on Assisted Reproduction.

Treatment and morbidity/mortality

Vestibular schwannoma: hearing loss due to a schwannoma of the eighth cranial nerve is the morbidity most frequently associated with NF2.

The treatment of these schwannomas is eminently surgical. When the vestibular tumours are small (<1.5 mm), they can be completely resected while preserving hearing and facial function; if the tumours are large, often a debulking is all that is possible without damaging the facial or cochlear nerve. However, there is currently a tendency towards open surgery, because cochlear implants (or, in case the cochlear nerve has to be sacrificed, brain stem implants) can be placed during the same operation.

Conventional external radiation therapy is contraindicated in cases of malignant transformation of the tumours.[19]

An alternative to surgery is stereotactic radiosurgery in selected patients (those with very aggressive tumours or patients who refuse a surgical intervention) and with worse outcomes in patients who suffer from unilateral vestibular schwannoma.[20]

The treatment of hearing loss should include patient referral to an audiologist and for lip-reading training, as well as hearing aids like cochlear implants or brainstem implants.

Other tumours, such as meningiomas and ependymomas, cause symptoms by mass effect on surrounding structures and are sometimes excised. Nevertheless, serial MRI scans are generally performed to monitor these tumours, since surgery may produce sequelae years before they occur with their natural evolution.

Despite the different types of tumours found in NF2, their malignant transformation is rare and may be iatrogenic in many patients.

The age of death is variable in patients with NF2 and many patients have a relatively normal life cycle.

The prognostic factors for mortality risk are: age at diagnosis, the presence of intracranial meningiomas, and whether the patient was treated at a specialised centre or not.[21,22]

Monitoring

The following should be performed in patients with a confirmed genetic mutation for NF2 or those with a genetic status that has not been clarified by molecular analysis:

1. MRI at 10-12 years of age, which must be repeated annually at least until the fourth decade of life.
2. Auditory evaluation including BAEP, which will be useful for detecting an impairment of the auditory nerve function before changes are observed on the MRI scan.
3. Annual routine eye examination.

Conclusions

NF2 is a debilitating disease, largely unknown in the medical community.

If NF2 is suspected, the patient should undergo a cranial and spinal MRI, a hearing evaluation (including BAEP), a complete ophthalmological evaluation and a skin test.

These patients should be referred to genetic counselling units to undergo genetic analysis, to receive information on this disease and its treatment options and for the early detection of possibly affected offspring.

It is important to refer these patients to specialised centres where they can be treated by multidisciplinary units including specialists accustomed to the disease.

Conflict of interests

The authors declare no conflict of interests.

Acknowledgements

We thank Dr. I. Blanco Guillermo, Director of the Genetic Counselling Program on Cancer at the Institut Català d'Oncologia.

References

1. Seizinger BR, Rouleau GA, Ozelius LG, Lane AH, Faryniarz AG, Chao MV, et al. Genetic linkage of von Recklinghausen neurofibromatosis to the nerve growth factor receptor gene. Cell. 1987;49:589-94.
2. Rouleau G, Seizinger BR, Wertelecki W, Haines JL, Superneau DW, Martuza RL, et al. Genetic linkage analysis of bilateral acoustic neurofibromatosis to a DNA marker on chromosome 22. Nature. 1987;329:246-8.
3. Evans DG, Moran A, King A, Saeed S, Gurusinghe N, Ramsden R. Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought. Otol Neurotol. 2005;26:93-7.
4. Gutmann DH, Sherman L, Seftor L, Haipek C, Lu KH, Hendrix M. Increased expression of the NF2 tumor suppressor gene product,

merlin, impairs cell motility, adhesion and spreading. Hum Mol Genet. 1999;8:267-75.
5. Baser ME, Friedman JM, Aeschliman D, Joe H, Wallace AJ, Ramsden RT, et al. Predictors of the risk of mortality in neurofibromatosis 2. Am J Hum Genet. 2002;71:715-23.
6. Evans DG, Baser ME, O'Reilly B, Rowe J, Gleeson M, Saeed S, et al. Management of the patient and family with neurofibromatosis 2: a consensus conference statement. Br J Neurosurg. 2005;19:5-12.
7. Ruggieri M, Iannetti P, Polizzi A, La Mantia I, Spalice A, Giliberto O, et al. Earliest clinical manifestations and natural history of neurofibromatosis type 2 (NF2) in childhood: a study of 24 patients. Neuropediatrics. 2005;36:21-34.
8. Dow G, Biggs N, Evans G, Gillespie J, Ramsden R, King A. Spinal tumors in neurofibromatosis type 2. Is emerging knowledge of genotype predictive of natural history? J Neurosurg Spine. 2005;2:574-9.
9. Perry A, Giannini C, Raghavan R, Scheithauer BW, Banerjee R, Margraf L, et al. Aggressive phenotypic and genotypic features in pediatric and NF2-associated meningiomas: a clinicopathologic study of 53 cases. J Neuropathol Exp Neurol. 2001;60:994-1003.
10. Evans DG, Birch JM, Ramsden RT. Paediatric presentation of type 2 neurofibromatosis. Arch Dis Child. 1999;81:496-9.
11. Sperfeld AD, Hein C, Schroder JM, Ludolph AC, Hanemann CO. Occurrence and characterization of peripheral nerve involvement in neurofibromatosis type 2. Brain. 2002;125:996-1004.
12. National Institutes of Health Consensus Development Conference. Statement on neurofibromatosis. Arch Neurol. 1987;45: 575-9.
13. Moyhuddin A, Baser ME, Watson C, Purcell S, Ramsden RT, Heiberg A, et al. Somatic mosaicism in neurofibromatosis 2: prevalence and risk of disease transmission to offspring. J Med Genet. 2003;40:459-63.
14. Evans DG, Ramsden RT, Gokhale C, Bowers N, Huson SM, Wallace A. Should NF2 mutation screening be undertaken in patients with an apparently isolated vestibular schwannoma? Clin Genet. 2007;71:354-8.
15. Baser ME, Friedman JM, Evans DG. Increasing the specificity of diagnostic criteria for schwannomatosis. Neurology. 2006;66:730-2.
16. Evans DG, Ramsden RT, Shenton A, Gokhale C, Bowers NL, Huson SM, et al. Mosaicism in neurofibromatosis type 2: an update of risk based on uni/bilaterality of vestibular schwannoma at presentation and sensitive mutation analysis including multiple ligation-dependent probe amplification. J Med Genet. 2007; 44:424-8.
17. Kluwe L, Mautner V, Heinrich B, Dezube R, Jacoby LB, Friedrich RE, et al. Molecular study of frequency of mosaicism in neurofibromatosis 2 patients with bilateral vestibular schwannomas. J Med Genet. 2003;40:109-14.
18. Evans DG, Wallace AJ, Wu CL, Trueman L, Ramsden RT, Strachan T. Somatic mosaicism: a common cause of classic disease in tumor-prone syndromes? Lessons from type 2 neurofibromatosis. Am J Hum Genet. 1998;63:727-36.
19. Baser ME, Evans DG, Jackler RK, et al. Neurofibromatosis 2, radiosurgery and malignant nervous system tumours. Br J Cancer. 2000;82:998.
20. Rowe JG, Radatz MW, Walton L, Soanes T, Rodgers J, Kemeny AA. Clinical experience with gamma knife stereotactic radiosurgery in the management of vestibular schwannomas secondary to type 2 neurofibromatosis. J Neurol Neurosurg Psychiatry. 2003;74:1288-93.
21. Baser ME, Friedman JM, Aeschliman D, et al. Predictors of the risk of mortality in neurofibromatosis 2. Am J Hum Genet. 2002;71:715-23.
22. Asthagiri AR, Parry DM, Butman JA, Kim HJ, Tsilou ET, Zhuang Z, et al. Neurofibromatosis type 2. Lancet. 2009;373:1974-86.