

# Differences Between the Two Most Common Forms of Neurofibromatosis and the Importance of their Exact Diagnosis- a case report

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*Neurofibromatosis type 2 is a rare genetic disease with an autosomal dominant mode of transmission. It is characterized by many tumors in the central nervous system, where meningiomas and schwannomas are the most common. The hallmark of this disease is bilateral vestibulocochlear schwannomas. Although certain similarities with neurofibromatosis type 1 exist, neurofibromatosis type 2 is caused by a completely different gene mutation, producing a distinct clinical presentation and is monitored and treated differently. This paper will present the case of a 17-year-old boy misdiagnosed with neurofibromatosis type 1 at the beginning of his clinical workup. After taking a detailed patient history and an additional radiological examination, the correct diagnosis of neurofibromatosis type 2 was reached. The patient was operated on multiple times by experienced surgeons, which was thoroughly discussed at the pediatric oncology board. Neurofibromatoses come in many forms and are different diseases. Every diagnosis of neurofibromatosis should be made using defined diagnostic criteria to enable the correct treatment of the patient and preserve the patient's quality of life as much as possible.*

**Key words:** NEUROFIBROMATOSSES; FIBRINOGEN PETOSKEY

## INTRODUCTION

Neurofibromatosis type 2 is a tumour predisposition syndrome caused by pathogenic variants in *NF-2* (neurofibromatosis type 2) tumour suppressor gene. Although certain similarities with neurofibromatosis type 1 (NF1) exist, NF-2 is caused by different gene mutations, producing a different clinical presentation. The hallmark of NF-2 is bilateral vestibular schwannomas, along with meningiomas and schwannomas that appear throughout the entire neuroaxis. It is not uncommon for clinicians to confuse NF-2 with NF-1, hindering the treatment process and enabling disease progression. Here we present a patient with a previously neglected NF-2.

## CASE PRESENTATION

We present a case of a 17-year-old boy who came to the audiology clinic because of progressive deafness. During

the examination, he also complained of difficulties in walking and pronouncing words, with both symptoms lasting three months. In addition, the right side of his face appeared to be swollen. Further clinical examination revealed other comorbidities - lower cognitive ability, strabismus and a cataract in his left eye. According to the sparse information given by the patient's mother, his older brother and father died from a brain tumour. The patient was allegedly previously diagnosed with NF-1 but has never been further processed for this initial diagnosis. Due to progressing of neurological deficits and swelling of face, a diagnostic workup

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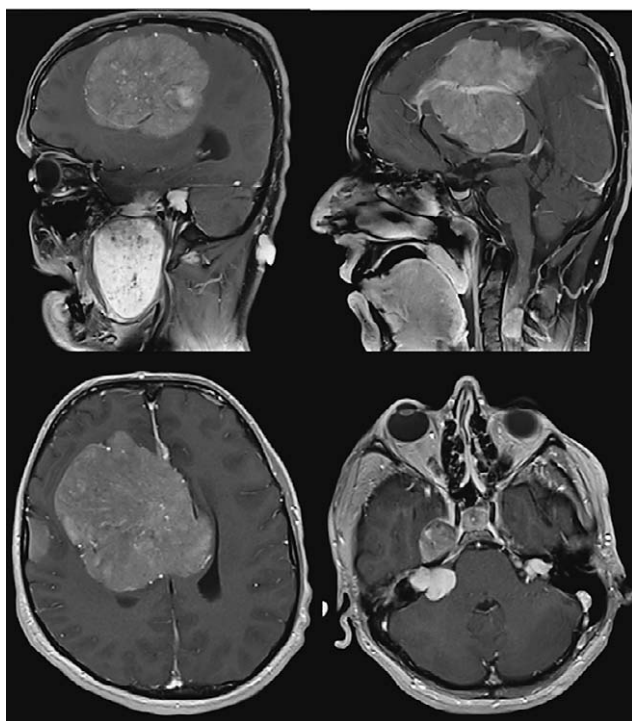


FIGURE 1. Preoperative images show a large frontotemporoparietal falcine meningioma, bilateral vestibulocochlear schwannomas, right pyramid apex meningioma and a large solid mass in the right parapharynx, all pointing to a high tumor load.

was started immediately, with computed tomography imaging showing multiple intracranial masses.

Magnetic resonance imaging ensued for better visualization of intracranial and spinal masses, resulted with images showing many meningiomas and schwannomas (Figure 1). The biggest meningioma was situated bi-frontally, arising from the cerebral falx, with a diameter of 89 mm, creating significant compression on the brain. Multiple smaller meningiomas, around 10 mm in diameter, were situated in the right lower frontal sulcus, left middle frontal gyrus and right pyramid apex. Bilateral schwannomas of the eighth cranial nerves were also present. Smaller schwannomas of the CN V and CN III (cranial nerve) were present as well. Outside the head, the right parapharynx was shown to harbour an expansive solid process 72 x 58 mm in diameter pushing the surrounding structures of the neck, morphologically resembling a schwannoma. Multiple spindle-shaped solid masses were noticed surrounding cervical neural foramina, the largest measuring 32 x 27 x 20 mm at the C2/C3 level. Another mass measuring 26 x 15 mm in diameter was situated intradurally and extramedullary at C3/C4 level.

After seeing the MRI (magnetic resonance imaging) scans, we began suspecting that the patient's initial diagnosis of NF-1 was incorrect. Bilateral vestibulocochlear schwannomas are especially pathognomonic for NF-2, including the presence of multiple meningiomas and schwannomas. Ca-

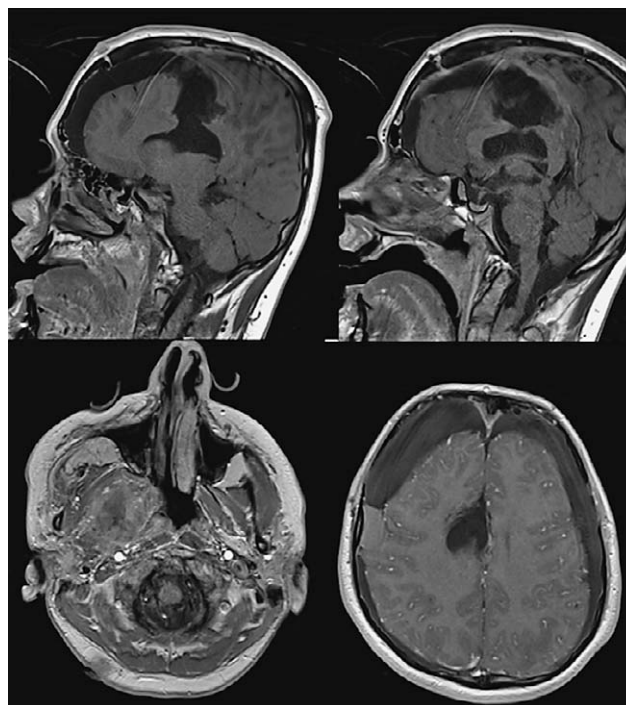


FIGURE 2. Postoperative images show gross total resection of the falcine meningioma and parapharyngeal mass.

fe-au-lait spots and neurofibromas were present. Subcutaneous neurofibromas were present in the back of the patient's neck, another common finding in NF-2 patients. The absence of Lisch nodules (pathognomonic finding for NF-1) also excluded the patient's primary diagnosis. In addition, ocular abnormalities, such as the cataract in our patient, also typically occur in NF-2 patients. We finally used the Manchester and Baser Paediatric Criteria to confirm our suspicions. All of the above findings led us to the patient's true diagnosis - NF-2. Still, the patient's life was endangered due to his many head, neck and spine tumours.

The large parafalcine brain tumour was the one that worried us the most. The patient underwent surgical resection, which took 11 hours and was successful (Figure 2). A pathohistological diagnosis confirmed the tumour was a Grade 1 meningioma. After the surgery, the patient developed cerebral salt-wasting syndrome. The complication was resolved. His neurological deficits started to decline slowly in the months following the first surgery. The second operation was a successful surgical resection of the large tumour of his right parapharynx, performed two weeks after his first surgery, with a pathohistological diagnosis confirming a schwannoma. During his second hospitalization to remove the spinal cord tumour, the patient went into a grand mal epileptic attack, which was susceptible to treatment. He was started on levetiracetam and did not have any subsequent epileptic attacks. The tumour at the C2/C3 level was successfully surgically resected, pathohistologically anal-

ysed and proven to be a schwannoma. An ophthalmologist confirmed the abnormalities of his left eye - anisocoria, strabismus and posterior cataract of his left eye.

The patient has lower cognitive abilities, but during his long hospital stay, even though he was scared and at times, distressed, he was always in contact and cooperative. Communication was sometimes difficult to establish due to his advanced hearing loss. An audiological examination confirmed deafness in his right ear and gradual hearing loss in his left ear. He was taught to read lips.

Next-generation sequence analysis was done, proving a pathogenic variant of the *NF-2* gene and *MET*, a known proto-oncogene. So far, there have been no published cases of connecting *MET* gene mutation with *NF-2*.

The patient was discharged with a scheduled neuroradiological screening in three months' time. The Tumour board will convene to consider possible chemotherapy. His neurological deficits were in decline and the patient finally went home to his family.

## DISCUSSION

*NF-2* is a genetic disease affecting approximately 1 in 25 000 people (1). The pathogenic variants are found on chromosome 22q12 in all patient's cells, although mosaics do exist. The mutated protein in *NF-2* is merlin (sometimes called schwannomin), a tumour suppressor protein with a suggested role in the communication between surface signalling and cytoskeleton matrix. Consequently, tumours associated with *NF-2* are meningiomas, schwannomas and spinal cord ependymomas. Meningiomas occur mostly intracranially and cause significant morbidity and mortality in this patient population (2). Ocular abnormalities like cataracts, epiretinal membranes and retinal hamartomas are also pathognomonic for *NF-2* (3). Cafe-au-lait spots, although often mentioned, are not necessarily present in these patients. Neurofibromas are often subcutaneous with a predilection for the head and neck region (as in our patient). Manchester Criteria, as well as Baser Paediatric Criteria should be used to confirm the diagnosis.

It is not uncommon for clinicians to confuse *NF-2* with *NF-1*. These diseases regrettably share the same name, even though their etiology, clinical presentation and life expectancy are entirely different. Differentiation of these disorders is not simply an academic exercise - the natural history and treatment of these and other forms of neurofibromatosis differ (4). As mentioned, a mutated gene is found on chromosome 22 in *NF-2* (or chromosome 15 in *NF-1*). Clinical presentation of *NF-2* involves many schwannomas and meningiomas (whereas *NF-1* is known to cause optic pathway gliomas

and specific, potentially malignant-turning plexiform neurofibromas). We deem especially important to recognize that even though disease burden is different in every patient and can be quite extensive (as was in our case), *NF-1* and *NF-2* differ in the malignancy and treatment susceptibility of their associated tumors. The main predictors of survival in *NF-2* have proven to be age at the time of diagnosis, intracranial meningioma status and access to specialty centres (5).

Conclusively, every patient suspected of these diagnoses should be evaluated using the Manchester and Baser Paediatric Criteria to establish the diagnosis, starting with adequate treatment methods and regularly scheduled radiological screening. Furthermore, it is worth noting the existence of many other, less common types of neurofibromatosis. (4). Naturally, a genetic analysis should be done, especially since the recent discovery of a possible diagnosis overlapping between *NF-2* and schwannomatosis (6), along with genetic counselling of the family.

Treatment relies on surgical removal of growing tumours and careful surveillance by scheduling regular patient screenings (7). Radiation therapy is commonly avoided in this patient population (unless surgery is contraindicated) due to the fact that loss of the *NF-2* tumor suppressor gene predisposes patients to the malignant transformation of a radiated tumour. Additional use of other drugs is still under discussion and requires further clinical trials (8,9).

In our case, contacting the patient's family proved difficult, and information about the family history we managed to obtain was done so through the patient's grandmother. It is essential to remember that these genetic diseases pose a psychological burden for the whole family. Therefore, a healthcare professional should try as much as possible to establish a meaningful relationship with the family. Moreover, children and adults suffering from similar diseases are sometimes overmedicalized (10), which is another affliction of these patients.

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## SAŽETAK

# Razlike dviju najčešćih oblika neurofibromatoza te važnost ispravne dijagnoze istih – prikaz slučaja

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*Neurofibromatoza tipa 2 je rijetka genetska bolest s autosomno dominantnim tipom nasljeđivanja. Karakterizira je prisustvo mnogih tumora središnjeg živčanog sustava, među kojima su najčešći meningeomi i švanomi. Obilježje ove bolesti su bilateralni vestibulokohlearni švanomi. Iako postoje određene sličnosti s neurofibromatozom tipa 1, neurofibromatoza tipa 2 je uzrokovana potpuno drugačijom genetskom mutacijom, izaziva posebnu kliničku sliku te se nadzire i liječi sasvim drugačije. Prikazujemo slučaj 17-godišnjeg dječaka koji je na početku kliničke obrade bio pogrešno dijagnosticiran kao slučaj neurofibromatoze tipa 1. Uzimanjem detaljnije anamneze i statusa pacijenta te daljnjom radiološkom obradom određena je ispravna dijagnoza neurofibromatoze tipa 2. Bolesnik je operiran 3 puta od strane iskusnih kirurga te je njegov slučaj temeljito diskutiran na pedijatrijskom onkološkom odboru. Neurofibromatoze postoje u raznim oblicima te se vode kao različite bolesti. Svaka dijagnoza neurofibromatoze treba biti postavljena korištenjem definiranih dijagnostičkih kriterija kako bi se omogućilo ispravno liječenje bolesnika te što dulje očuvanje njegove kvalitete života.*

**Ključne riječi:** NEUROFIBROMATOZA; FIBRINOGEN PETOSKEY