

Full constellation of clinical and radiological findings in a NF2 patient with overlapping NF1 features

Vivek Mohanty¹, Manoj Kumar Nayak²

From Junior Resident, ¹Department of Medicine, ²Department of Dermatology, All India Institute of Medical Science, Rishikesh, Uttarakhand, India

Correspondence to: Vivek Mohanty, Department of Medicine, Room No – 225, Building No – 84, All India Institute of Medical Sciences, Rishikesh - 249 203, Uttarakhand, India. E-mail: vivekmohanty.92@gmail.com

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ABSTRACT

Neurofibromatosis is a genetic disorder of the nervous system. Patients are classified on the basis of clinical features into two types – neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2). However, in most of the patients, all the clinical features associated with these disorders are not present. Furthermore, rarely some patients may have clinical features of NF1 overlapping with NF2. Here, we highlight an interesting case of a 24-year-old male with a history of recurrent seizures with intellectual impairment, progressive hearing, vision loss, and weakness of one side of the body. On physical examination, he had dermatological signs of NF1 in the form of café-au-lait macules and axillary freckling. Further examination revealed the presence of bilateral sensorineural hearing loss and posterior subcapsular cataract. Radiological investigation showed the presence of bilateral vestibular schwannomas and other features consistent with the diagnostic criteria of NF 2. The presence of these multiple findings along and an absence of family history made this case a rare presentation and diagnostic challenge.

Key words: *Ependymomas, Meningiomas, Neurofibromatosis 1 and 2, Schwannomas*

The neurofibromatosis including neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2) comprises a group of genetically distinct disorders of the nervous system which are characterized by a predisposition to nerve sheath tumors. NF2 is characterized by bilateral vestibular schwannomas, meningiomas, ependymomas, cataracts, and epiretinal membranes. The combination of complete hearing loss from vestibular schwannomas and blindness from bifacial weakness is a devastating potential outcome of NF2 [1]. NF2 is much less common than NF1, with a symptomatic prevalence of 1 in 210,000 [2]. Very rarely, the syndromes may overlap clinically [3].

Here, we highlight a case of NF2 having multiple nerve schwannomas, juvenile posterior lenticular opacities, ependymomas with overlapping features of NF1 in the form of axillary and peri-inguinal freckling, and café-au-lait macules with probable plexiform neurofibroma in spinal roots.

CASE REPORT

A 24-year-old male presented with chief complaints of seizures since 22 years of age in the form of right focal sensorimotor with impaired awareness, uprolling of the eyeballs followed by tonic-clonic movements of all four limbs, frothing, and post-ictal confusion. After the seizure episode, he started having hearing loss (right > left), which was progressive. Initially, the patient was unable to hear from a distance but now, he had difficulty in using

a phone. It was followed by progressive painless vision loss in the right eye with decreased mobility in the right eye. Since the onset of seizure, there was a gradual thinning of the right side of the body which started on the face. The patient became flat on the right side with eyes being more prominent, deviation of the tongue to the right side, and drooling of saliva from the angle of the mouth. It was followed by thinning of the right upper limb with weakness, and difficulty in taking arms above the head, difficulty in lifting weight and holding on objects.

It was followed by thinning of the left lower limb. Clothes became loose and slippage of slippers without knowledge. Since the onset of seizure, he was having progressive incoordination of the limbs during walking. It was associated with the swaying of the hands and smearing of the face. He had gradual progressive slurring of speech, not associated with any swallowing difficulty, nasal intonation, or nasal regurgitation. He is also complaining of pain abdomen which is colicky in nature and periumbilical which is also associated with altered bowel habits.

On examination, the patient was thin built with hemiatrophy of the right side of the face and right side of the body. The blood pressure was 126/84 mmHg in the right arm, supine position, pulse rate was 84/min, and respiratory rate was 16/min. The examination of the skin of the patient revealed bilateral axillary and peri-inguinal freckling, café-au-lait macules in the left thigh (Fig. 1a and b). There were no pallor, icterus, lymphadenopathy, or clubbing of the nails. Nervous system examination showed lower motor neuron type of the right hemiparesis, upper motor

neuron type of the right facial palsy, bilateral hearing loss, right visual loss with bulbar/pseudobulbar features, and cerebellar signs (Fig. 1c). Abdominal examination revealed swelling in the right lumbar region and epigastric region which was non-tender, with smooth margins, and not moving with respiration. Cardiovascular and respiratory system examinations were within normal limits with any appreciable murmurs or added breath sounds.

Contrast enhanced-magnetic resonance imaging brain with whole spine screening revealed multiple cranial nerve schwannomas, spinal ependymomas, multiple neurofibromas (most likely) with compression of cauda equina nerve roots, extra-adrenal paragangliomas, and neurofibroma adjacent to the right kidney with multiple peripheral nerve sheath tumor. T2 images showed a lesion in the falcine region with intense post-contrast enhancement like meningioma (Figs. 2 and 3). Ultrasound abdomen revealed a well-defined hypoechoic solid cystic lesion measuring 3×3.4 cm in the midline retroperitoneal location abutting laterally medial border of the middle and lower pole of the cortex of the right kidney and medially head of the pancreas. Ophthalmology review was done and the presence of posterior subcapsular cataract was diagnosed in the right eye of the patient.

The patient was diagnosed to have neurofibromatosis type 2 based on Manchester clinical criteria [4]. Neurosurgery consultation was taken in view of multiple cranial nerve schwannomas causing mass effect on the pons and medulla and also likely meningioma in the falcine region. The neurosurgeons planned for surgical resection of the cerebellopontine lesion and other schwannomas that were resectable. Surgery consultation was taken for extra-adrenal paragangliomas and they advised for close follow-up. The patient was being planned for follow-up of the right posterior cataract by the ophthalmology department. The patient was discharged and is in neurosurgery follow-up for surgical resection of the schwannomas. He is under regular monitoring for the extra-adrenal paragangliomas in the surgery department and for the posterior subcapsular cataract in the ophthalmology department.

DISCUSSION

The diagnosis of neurofibromatosis is based on Manchester criteria [4]. About 50% of the patients of NF2 have no family history [5]. The NF2 gene has been mapped to chromosome 22. It is a tumor-suppressor gene spanning 110 kb and its protein product, named merlin or schwannomin, has been found to mediate communication between the extracellular milieu and cytoskeleton [6-8]. Loss of heterozygosity of chromosome 22q (LOH 22q) has been detected in many specimens of NF2-related tumors, including acoustic schwannoma and meningioma [6-8]. The mean age of onset in 58 individuals was around 20.3 years; initial symptoms resulted from vestibular schwannomas (44.4%), other CNS tumors (22.2%), skin tumors (12.7%), and ocular manifestations including cataracts and retinal hamartomas (12.7%) [2]. Café-au-lait macules can be seen frequently in NF2 patients, but they are not as prominent as they are in NF1 and are



Figure 1: Clinical features of the patient (a) axillary freckling; (b) café-au-lait macules; (c) hemiatrophy of the right side of the face

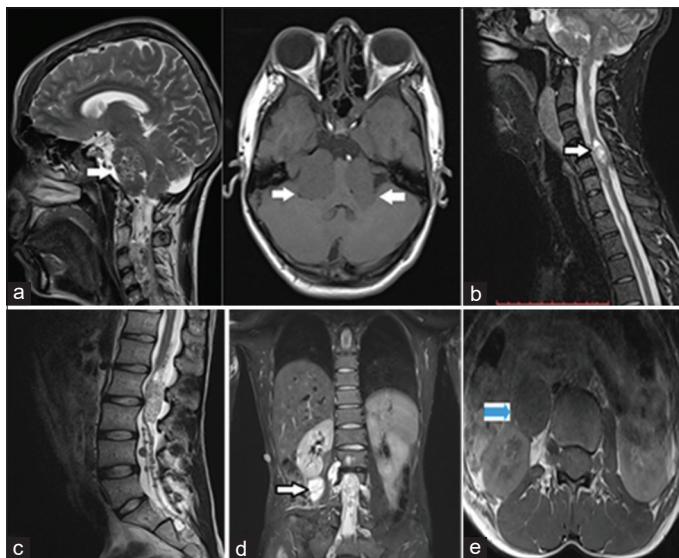


Figure 2: (a) T2 axial and T1 coronal images showing cerebellopontine angle tumor suggestive of vestibular schwannomas; (b) T2 sagittal view showing intraspinal ependymoma; (c) T2 sagittal view lumbo-sacral spine showing multiple neurofibromas; (d) T2 coronal view showing neurofibroma adjacent to the right kidney; (e) T2 axial view showing neurofibroma adjacent to the right kidney

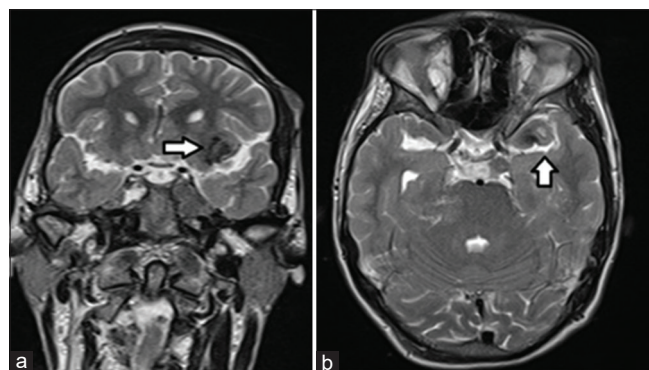


Figure 3: T2 coronal and axial view showing lesion with post-contrast enhancement suggestive of meningioma

not associated with other pigmentary abnormalities, for example, skin-fold freckling [9].

Schwannomas and meningiomas are relatively common, as seen in our patient, but glial tumors, including astrocytomas and ependymomas, occur much less common [9]. Several authors have studied a series of cases to try to define the incidence of the tumors in cases of NF2. Mautner *et al.* studied 48 patients

with NF2, in which the prevalence of findings was vestibular schwannomas (CNVIII) in 46 (96%), spinal tumors in 43 (90%), posterior subcapsular cataracts in 30 (63%), meningiomas in 28 (58%), and trigeminal schwannomas in 14 (29%) [10]. Wayman *et al.* [11] reported cranial MR of 11 patients. In their series, all patients had acoustic schwannomas, 8 had other cranial nerve tumors (5 multiple and 3 single), and 6 had meningiomas (4 multiple and 2 single) [11]. Patronas *et al.* [12] studied a series of 49 patients with NF2 with spinal MRI, which demonstrated spinal cord and/or canal tumors in 31 (63%). Twenty-six patients (53%) had intramedullary lesions, 27 patients (55%) had intradural extramedullary tumors, and 22 patients (45%) had at least one tumor of each type [12]. Our patient had multiple cranial nerve schwannomas, meningioma in the falcine region, spinal ependymomas, multiple neurofibromas with cauda equina root compression, dermal neurofibroma, and extra-adrenal paraganglioma with posterior subcapsular cataract.

CONCLUSION

We can say that there was a full constellation of signs and radiological findings in this NF2 patient, an absence of family history, hemiatrophy of one side of the body whose association is uncommon with NF2, and overlapping features of NF1 which is a rare presentation and led to a diagnostic challenge.

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