Case Report

Neurofibromatosis 2: rare constellation of findings with extensive cranial nerve involvement

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Abstract

In this report, we aim to present a sporadic case of a 17-year old female patient who presented to the Radiodiagnosis department in JSS Hospital, Mysuru, India with complaints of insidious onset of difficulty in walking, motor & sensory impairment, slurring of speech, difficulty in food ingestion, and hearing impairment. Magnetic resonance imaging revealed bilateral vestibular & non vestibular Schwannomas with extensive cranial nerve involvement, multiple spinal & falcine meningiomas, and cervicodorsal intramedullary ependymoma amongst other findings. These core features give rise to the acronym MISME, which describes Multiple Inherited Schwannomas, Meningiomas and Ependymomas. This case is being reported to highlight the rare constellation of multiple cranial nerve Schwannomas, meningiomas, ependymomas and other peripheral nerve sheath tumors in a single patient and will add to the evidence of MISME in world literature.

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Introduction

Neurofibromatosis 2 (NF2) is a rare autosomal dominant disorder characterized by the development of multiple central & peripheral nervous system tumors. The neoplasms include Schwannomas, meningiomas, and ependymomas and thus NF2 is also known as MISME, which stands for multiple inherited Schwannomas, meningiomas, and ependymomas. The presence of bilateral vestibular Schwannomas is a defining feature, and as many as 10% of patients with this tumor have neurofibromatosis type 2 [1–3].

Case report

The patient, who had no relevant family history, was apparently normal 7 years ago, after which she developed a gradually increasing swelling over the left side of neck after an episode of URTI. She had no history of fever or weight loss and no history of dysphagia/ear ache or ear discharge.

Her vital stats were normal. On examination, the swelling was single, circular, firm, non-tender, and fixed over the left submandibular region. There was no local rise of temperature
over the swelling, no palpable lymph nodes. USG revealed an abnormal heterogeneous mass lesion in the left submandibular region abutting the left CCA and IJV with no obvious encasement.

Over the course of 3 years, the patient developed similar swellings over the dorsum of hand and anterior abdominal wall.

On December 26, 2016, the patient underwent surgery and excision of the above-mentioned lesions were performed. The
biopsy findings of the lesions turned out to be Schwannomas with associated sialadenitis in the left submandibular gland.

Addressing the present day complaints, the patient underwent audiometry tests & was diagnosed to have moderate sensorineural hearing loss of both ears.

Patient was then subjected to MRI to assess extent of disease involvement. MRI was performed in a 3 Tesla Philips MRI machine.

MRI brain (Plain and contrast studies) and whole spine screening revealed bilateral vestibular & non vestibular Schwannomas involving all the cranial nerves except CN II, IV, & VI, multiple nonenhancing abnormal signal intensity foci involving right insular gyrus and bilateral white matter (which may suggest Neuronal migration disorder / Cortical dysplasia with unidentified bright objects), multiple ependymomas involving cervical and dorsal spinal cord, multiple spinal & fal- cine meningiomas, tumorlets in the cauda equina fibres, mul-

diple peripheral nerve sheath tumors in pre & para-spinal region, and visualized part of head & neck.

Discussion

NF2 is a rare autosomal dominant inherited condition, with an incidence of 1 in 33,000 to 40,000. It is characterized by the development of multiple neoplasms in central and peripheral nervous system [4]. In 1793, Tilesius recorded the first description of neurofibromatosis where he noted the cuta-neous lesions of molluscum fibrosum. In 1882, Von Reckling-hausen was the first to recognize the neural origin of the dis-
Fig. 9 – Axial – FLAIR sequence showing denervation atrophy of right tongue muscles.

ease where he described 2 patients with multiple skin and subcutaneous neurofibromas [5]. In 1987 NF was classified as 2 types (Type 1 & 2) based on their clinical and pathological features. NF type 1 caused by defect in neurofibromin gene which was located on the long arm of chromosome 17, whereas type 2 is caused by mutations in merlin gene, which is a tumor suppressor gene located on the long arm of chromosome 22 (22q12.2). This merlin gene maintains the cell connection of cytoskeleton with the plasma membrane, thereby controlling shape, motility of cell as well as growth regulation [4].

The diagnosis of NF2 is usually made in the second & third decades, mostly within 18-24 years of age. The patients with family history of NF2 should be screened as early as 10 to 12 years of age with annual MRI screening until 40 years of age.

In literature, almost 95% of cases of NF2 had vestibular Schwannomas, which is a definite diagnostic criterion for NF2 (as seen in this patient). 80% of patients developed tumors in other cranial nerves or meningiomas and two-third of patients developed spinal neoplasm [4]. Approximately 90% of patients suffer from ocular abnormalities like early cataracts (most common), retinal hamartomas, epiretinal membranes, and corneal lesions [4].

There are two phenotypes of NF2, namely the Wishart phenotype and the Feiling-Gardner phenotype. The Wishart phe-

Fig. 10 – (A) - Sagittal cut – T1- 3D sequence & (B) – Sagittal T2 sequence showing intramedullary hypointense lesion in cervical cord measuring 8.0 x 0.8 cm with peri & intratumoral cysts and hemorrhage – Ependymoma.

Fig. 11 – Sagittal cut – T1- 3D sequence showing few dural based lesions along the cervical cord, largest measuring 10 x 7 mm at C4 level – Meningiomas.
Fig. 12 – Sagittal cut – T2W – TSE - Multiple well-defined rounded lesions are seen along the cauda equina fibres -Tumorlets.

Fig. 13 – Sagittal cut – T2W – TSE - Few well defined rounded intermediate signal intensity lesions are seen along the exiting nerve roots of dorso-lumbar & sacral spine, largest measuring 44 x 26 mm at D12-L1 level -Schwannoma/Neurofibromas.

Fig. 14 – Sagittal cut – T2W – TSE - A well-defined T2 hyperintense lesion measuring 24 x 32 mm is seen in the left submandibular region -Schwannoma/Neurofibromas. A well-defined nodular T2 hyperintense mass lesion measuring 5.8 x 1.3 cm is seen in the left carotid space.

Fig. 15 – Sagittal cut – T2W – TSE - A well-defined intramuscular T2 intermediate signal intensity lesion measuring 24 x 12 mm is seen in the posterior paraspinal muscles at D10 level -Neurofibromas.
Fig. 16 – Axial cut – T2W – TSE - Well-defined lesion measuring 23 × 14 mm appearing hyper-isointense in left premaxillary region; Few well-defined ovoid lesions are seen in the muscles along the nape of neck - Schwannoma/ Neurofibromas.

Fig. 17 – Axial cut – FLAIR – Post-contrast sequence shows area of altered gyral signal intensity in the right insular cortex – Mineralization.

Fig. 18 – T2 sequence shows a parafalcine lesion measuring 9.5 × 6.0 mm in the right frontal lobe – Parafalcine meningioma. Also shows a well-defined cutaneous lesion in the right parietal region measuring 16 × 8 mm.

Fig. 19 – Post-contrast T1 sequence shows heterogeneously enhancing Parafalcine lesion measuring 9.5 × 6.0 mm in the right frontal lobe – Parafalcine meningioma. Also shows a well-defined homogeneously enhancing cutaneous lesion in the right parietal region measuring 16 × 8 mm.
Fig. 20 – GRE sequence shows significant blooming in the choroid plexus in the left temporal horn. Non-neoplastic choroid plexus calcifications in atypical locations (eg, temporal horn) are a rare manifestation of NF2 but can be striking.

Fig. 21 – Axial cut – NECT Figure sequence shows abnormal choroid plexus calcification in the left temporal horn.

Fig. 22 – HRCT Temporal bone – Axial cut - shows destruction of left jugular foramina & dilatation of right jugular foramina with loss of sitting duck sign. On HRCT temporal bone there is gross smooth dilatation of left foramen ovale, indicating extension of left trigeminal schwannoma along the mandibular nerve into the neck.

Fig. 23 – Coronal section - Bone window - shows destruction of left jugular foramina & dilatation of right jugular foramina.

Bilateral vestibulocochlear schwannomas are seen in > 90% cases of NF2. Most Schwannomas are well-delineated round or ovoid encapsulated masses that are attached to—but do not infiltrate—their parent nerves. There is evidence of previous literature documenting the occurrence of Schwannomas in other cranial nerves like Trigeminal, Oculomotor,

notype is more aggressive and characterized by multiple neoplasms in brain and spine, usually seen in patients <20 years of age. The Feiling-Gardner phenotype, on the other hand is less aggressive and is characterized by a single neoplasm in CNS, usually seen in patients >20 years of age.
is cervicothoracic region originating from dorsal root. Innumerable tiny schwannomas (tumorlets) throughout the cauda equina are seen in the majority of patients, including the case under discussion [6].

Meningiomas are seen in > 50% of NF2 patients, most commonly seen in the supratentorial location. Adult patients with NF2 have an average of three meningiomas. In spinal cord, Meningiomas are mostly seen in thoracic region. Multiple meningiomas are the second pathologic hallmark of NF2. They may be the presenting feature (especially in children). Meningiomas appear as unencapsulated but sharply demarcated masses [6].

Ependymomas are mostly seen in the intramedullary location of conus medullaris or cervical region [6].

Astrocytomas are mostly low grade [6].

Ocular lesions are seen in approximately 90% of NF2 patients, the most common and important clue for diagnosis being posterior subcapsular lenticular cataract. There can occur other lesions like retinal Hamartomas, epiretinal membranes, orbital meningiomas, and corneal abnormalities [4].

MISME syndrome, as previously explained, stands for Multiple Inherited Schwannomas, Meningiomas, and Ependymomas. There have been very few documented cases of simultaneous occurrence of all three tumors in the same patient. In this report however, we have presented a case of MISME syndrome with triple tumors extensively involving the central nervous system and multiple peripheral nerve sheath tumors.

Follow up

Surgical resection of the larger left vestibular schwannoma was done a few months following the patient’s visit to the Radiology department. On recent follow-up, it was noted that some of the patient’s symptoms had abated following the procedure. The patient is now closely monitored and further surgical treatment protocols are awaited for the patient.

Conclusion

Although the patient has no relevant family history, the myriad findings that have been mentioned in this case with the extensive cranial nerve involvement make for a classical and rare addition to the literature surrounding NF2.

Neurological examination and imaging of the central nervous system is the mainstay to establish a diagnosis of NF2. The disease, per se is not curable and management is limited to preservation of function as the patients have a lifelong propensity to develop new tumors or recurrence of old tumors. Treatment involves removal of only symptomatic lesions with regular surveillance for the other lesions. The spinal tumors are considered for removal only when there are signs of cord compression. Treatment options like Gamma Knife Radiosurgery have been considered the treatment of NF2-related vestibular Schwannoma owing to its good long-term tumor control rates of 87% at 5 years [3] Figs. 1–25.
Declaration of Competing Interest

The above-mentioned authors declare that we have no conflict of interest.

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