Neurofibromatosis Type 2: A Pandora's Box of Variable Presentations

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Abstract

Introduction Neurofibromatosis type 2 (NF2) also known as MISME syndrome stands for multiple inherited schwannomas, meningiomas, and ependymomas in the peripheral and central nervous system. It is a rare disorder of autosomal dominant inheritance due to mutations of a tumor-suppressor gene on the chromosome 22q12. Clinically, it is characterized by multiple benign tumors arising in both the central and peripheral nervous system, particularly from the bilateral vestibular nerve, in more than 90% of the patients, with more than two thirds of them developing spinal tumors.

Materials and Methods Here, we studied the variable presentations of cases of NF2, and thorough evaluation of patients was done by contrast MRI of brain and spine. Also, evaluation of ocular manifestations and cutaneous features was done in cases of NF2, and a follow-up was done for a period of 18 months with monitoring of cranial and spinal lesions.

Conclusion We studied the various presentations of NF2 and found that a significant proportion of the patients presented with nonvestibular tumors as the initial presentation, with bilateral cerebellopontine angle lesions being an incidental finding; also, the age of presentation in half of the patients was less than 30 years, and so we can conclude that in young patients with spinal tumors or multiple meningiomas, a thorough evaluation regarding family history and various features of NF2 should be done, so that early identification of the disease could be done and patients can be benefitted from timely interventions.

Keywords
- neurofibromatosis type 2
- MISME syndrome
- schwannoma

Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant syndrome predisposing to multiple benign tumors of the central and peripheral nervous system. The hallmark of this disease is the development of bilateral vestibular schwannomas, which occur in 90 to 95% of patients.[1-3] Spinal NF2-associated tumors include schwannomas of spinal nerves, meningiomas, and spinal cord ependymomas. Schwannomas of the spinal nerve root are frequently multiple, and they account for almost 90% of extramedullary spinal tumors.[4,5] Intradural, extramedullary spinal meningiomas are present in approximately 20% of patients.[1-4] These tumors, however, may not be distinguished radiologically or even at the time of surgery. Ependymomas account for more than 75% of intramedullary spinal cord tumors associated with NF2.[4,6-8] Their imaging evidence is found in 18 to 53% of patients, but they cause clinical symptoms in fewer than 20%.[4-6,9] Intramedullary astrocytomas of the spinal cord and intramedullary schwannomas have been rarely reported in NF2.[4-9] In contrast to sporadic tumors, the majority of NF2-related spinal tumors are asymptomatic during observation. Intracranial

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meningiomas are an important cause of morbidity and one of the presenting features in many cases of NF 2, so other than the vestibular tumors which are hallmark of NF2, nonvestibular tumors are an important entity and should be dealt with proactively to decrease the morbidity associated with cases of NF2.

Aim of Study

To provide an overview of various presentations of NF2 as per clinical and radiological characteristics, and to stress on the need for management of nonvestibular tumors in these cases.

Materials and Methods

Ten cases of NF2 were considered for the study, and all of them underwent contrast MRI of brain along with MRI of spine. A thorough ophthalmological evaluation for retinal hamartomas, optic nerve gliomas, and subcapsular lenticular opacities was done. The lesions were categorized as per spine and cranium for all the cases and were classified as NF2 as per baser criteria (►**Table 1**). Also, the age of presentation and presenting symptoms in these cases were noted and follow-up MRI of brain and spine for a period of 18 months were done for any increase in size of the lesions and development of new lesions.

Observations

We observed variable presentations of NF2 in our patients, and as per the baser criteria (►**Table 2**), they were labeled as NF2. It was observed that a significant (3 out of 5 patients) number of patients belonging to the younger age group (< 30 years) presented with symptoms other than classical symptoms of hearing loss, with variable presentations in the form of a case wherein patient presented with weakness of all four limbs; a case of absolutely asymptomatic for bilateral cerebellopontine (CP) angle lesions; a case with left CP angle space-occupying lesion (SOL) along with multiple meningiomas (►**Table 2**). Another important observation in our study was regarding spinal tumors;

Table 1 Showing baser criteria for classifying lesions as NF2

Feature	If present at or < 30 years of age	If present > age 30 years
First degree relative with NF2 diagnosed by these criteria	2	2
Unilateral vestibular schwannoma	2	1[a]
Second vestibular schwannoma	4	3[a]
One meningioma	2	1
Second meningioma (no additional points for > than two meningiomas)	2	1
Cutaneous schwannomas (one or more)	2	1
Cranial nerve tumor (excluding schwannoma one or more)	2	1
Mononeuropathy	2	1
Cataract (one or more)	2	0

[a]Points are not given for unilateral or second vestibular schwannoma if age is > 70 years.

Note: The patient is given points, as shown in ►**Table 1**.
A definite diagnosis of NF2 is established if points are six or more.
A definite diagnosis is made of NF2 if constitutional pathogenic mutation of NF2 is detected.
If no constitutional pathogenic mutation of NF2 is found, then (i) A diagnosis of mosaic NF2 is established if mosaicism for a pathogenic NF2 mutation is found in blood or no detectable pathogenic NF 2 mutation is found in the blood, but the same pathogenic NF2 mutation is found in two separate NF2 associated tumors. (ii) Otherwise, a temporary diagnosis of possible NF2 is made pending further clarification. Clarification may occur if the patient is established to have a different condition (e.g., schwannomatosis or multiple meningiomas) by standard diagnostic criteria or if evolution of the patient disease over time permits establishing a diagnosis of NF2 pr mosaic NF2, according to the criteria mentioned above.

Table 2 Table showing age of presentation and various lesions classified as per cranium and spinal lesions

Cases	Age at presentation	Presenting symptoms	Radiological characteristics (cranial lesions)	Radiological characteristics (spinal lesions)
Case 1	45	Bilateral (left > right) with tinnitus on left side	Bilateral CP angle lesions (left > right)	Meningioma at L1 level, ependymoma intramedullary at C3-C4 level
Case 2	60	Bilateral (left > right) with tinnitus on left side	Bilateral CP angle lesions (left > right)	Absent
Case 3	20	Neck pain with weakness of right upper limb	Bilateral CP angle lesions (right > left)	Intramedullary lesion at C4-C5 level
Case 4	40	Right side hearing loss with tinnitus	Bilateral CP angle lesions (right > left)	Intradural extramedullary lesion at C3-C4 level
Case 5	35	Left side hearing loss with tinnitus	Bilateral CP angle lesions (left > right)	Absent
Case 6	24	Left side hearing loss	Bilateral CP angle lesion (left > right)	Absent
Case 7	24	Right side hearing loss	Right CP angle lesion with left trigeminal schwannoma	Intramedullary lesion at C2-C3 level, left paravertebral lesion at C6 level, multiple spinal cysts
Case 8	21	Headache with irrelevant talk	Right frontal convexity meningioma with multiple small intracranial meningiomas with left CP angle lesion	Meningioma at L1 level
Case 9	18	Weakness of all four limbs (upper > lower)	Bilateral CP angle lesion (left > right)	Intramedullary lesion at C3-C4 level (ependymoma)
Case 10	39	Right side hearing loss with tinnitus	Bilateral CP angle lesion (right > left)	Absent

Abbreviation: CP, cerebellopontine.

among 10 patients, 3 had intramedullary tumors, 3 had intradural extramedullary tumors, out of which 2 had tumors of the cauda equina (►**Table 2**; ►**Figs. 1–5**). With regard to the associated features of NF2, two patients had subcapsular lenticular opacities and both were above the age of 30 years, one patient had optic nerve glioma, one patient had retinal hamartoma, and two patients presented with neurofibromas (►**Table 3**).

Out of the 10 patients, 5 patients were above the age of 30 years, with all of them presenting with symptoms of hearing loss, which was attributed to their CP angle lesions (►**Table 2**). During the follow-up period, 4 out of the 10 patients underwent surgeries, 2 patients for the increase in size of the CP angle lesions and 2 for the spinal lesions presenting with cauda equina-like symptoms and therefore underwent emergency surgeries for the same (►**Table 4**). Various presentations according to the age groups are tabulated in ►**Table 5**.

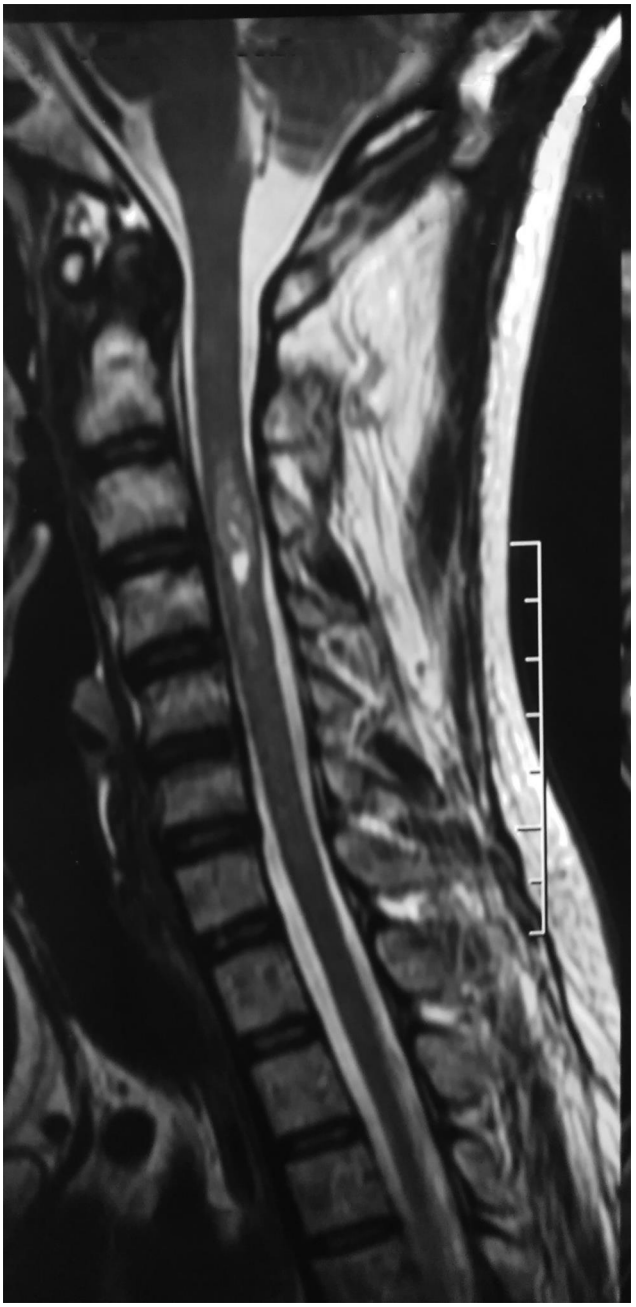

Fig. 1 Cervical intramedullary lesion with L1 intradural extramedullary lesion.

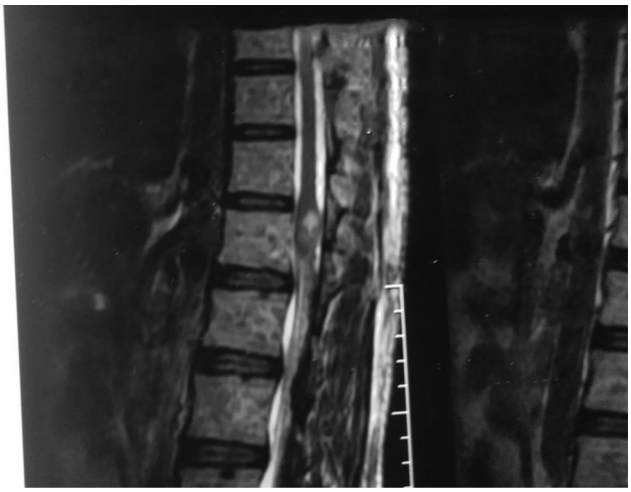

Fig. 2 L1 intradural extramedullary lesion.

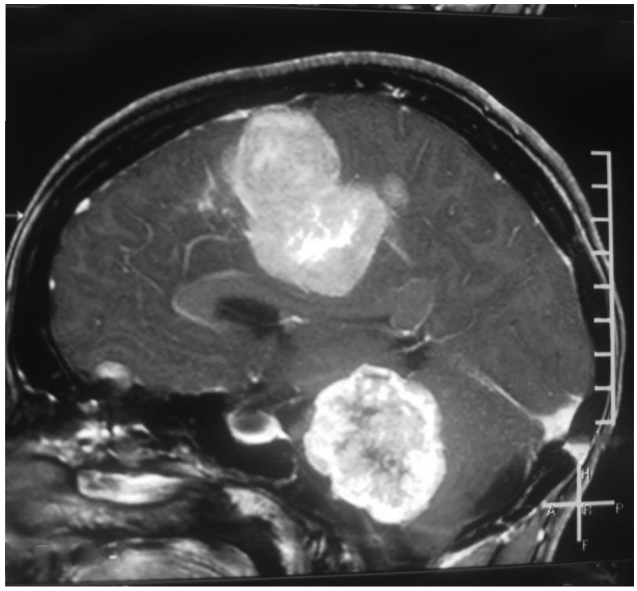

Fig. 3 Cerebellopontine angle lesion with multiple menigiomas.

Discussion

NF2 is a hereditary tumor predisposing syndrome that leads to the development of multiple intracranial and spinal tumors. About 60% of NF2 patients had single or multiple spinal tumors.[3,4,6,10] It is believed that in NF2 patients, spinal tumors besides meningiomas are associated with disease severity.[11] In the present study, patients with spinal tumors had a lower age at initial presentation of the disease. We found that patients with spinal tumors had an early presentation, and this could emphasize aggressive course of disease and increased morbidity. In contrast to intramedullary tumors, which are associated with less favorable functional prognosis after surgery, extramedullary tumors provide the

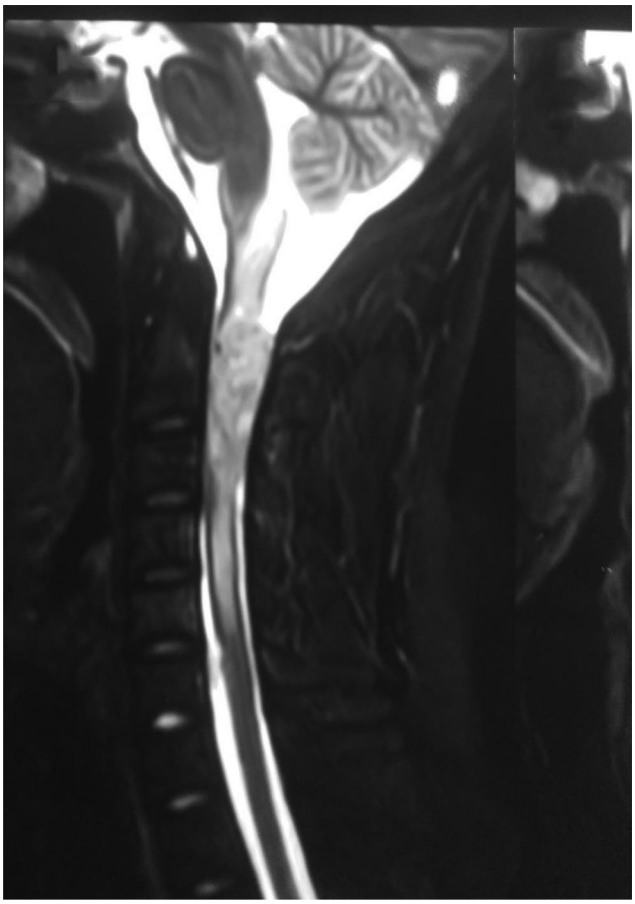

Fig. 4 Cervical intramedullary lesion.

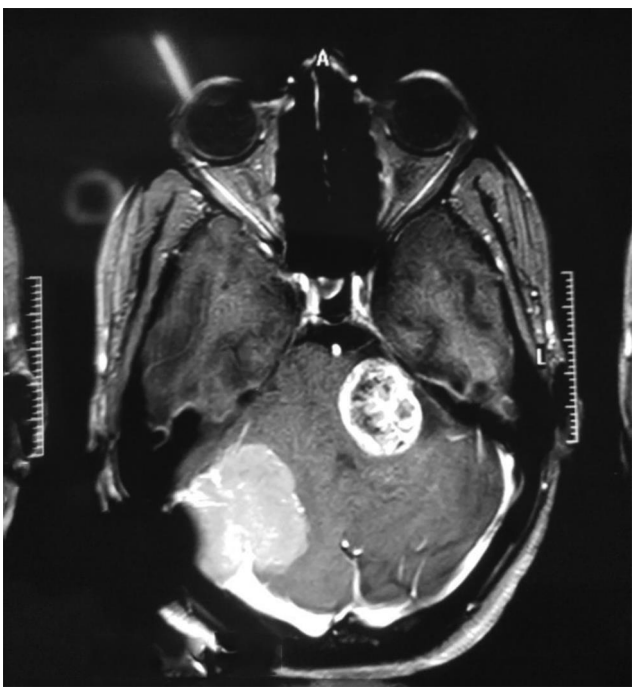

Fig. 5 Right cerebellopontine (CP) angle lesion with left trigeminal schwannoma.

Table 3 Showing associated manifestations in cases of NF2

Cases	Ophthalmological manifestations (subcapsular lenticular opacities, retinal hamartomas, optic nerve gliomas)	Cutaneous features (neurofibromas)
Case 1	Absent	Absent
Case 2	Absent	Absent
Case 3	RETINAL HAMARTOMA IN LEFT EYE	Absent
Case 4	Absent	Neurofibromas in left parapharyngeal and submandibular space
Case 5	Subcapsular lenticular opacities bilaterally	Absent
Case 6	Absent	Absent
Case 7	Absent	Left paravertebral neurofibroma
Case 8	Optic nerve glioma in right eye	Absent
Case 9	Absent	Absent
Case 10	Subcapsular lenticular opacities	Absent

Abbreviation: NF2, neurofibromatosis type 2.

possibility of full recovery after surgical treatment. Our study confirms higher percentage of NF2 patients with intramedullary tumors with an early age of presentation. This proves that intramedullary tumors in NF2 patients are associated with disease severity. We also found that intramedullary tumors in all patients were located in the cervical spine, which is consistent with previous reports. This predilection of ependymomas for cervical cord and craniomedullary junction (CMJ) is different from that for patients with sporadic tumors, which are more commonly located within the brain and less common in the cervical cord.[12,13] Moreover, spinal ependymomas in NF2 patients are usually multiple and present with typical appearance of a "string of pearls" in neuroimaging. In our analysis, it was found that the presence of tumor-associated cysts and young age as the initial symptoms of NF2 may be associated with tumor growth, the occurrence of clinical symptoms, and the need for surgical intervention in patients with intramedullary tumors. However, due to small numbers of patients in our series, no meaningful conclusions can be drawn. The majority of our patients were asymptomatic for the intramedullary tumors suggesting that most NF2 patients with ependymomas can be safely monitored without indication for surgical treatment. It should be noted, however, that even a nongrowing, asymptomatic intramedullary spinal tumor in a patient with NF2 may be an indication for surgery. Aboukais et al[10] reported that in their three symptomatic patients operated for intramedullary tumors,

Table 4 Showing operative interventions, disease progression and biopsy of various lesions

Cases	Operative interventions (on presentation)	Biopsy of lesions	Follow-up at 6 months	Follow-up at 18 months
Case 1	None–asymptomatic for spinal lesions and no hearing loss on audiometry, so kept on follow-up.	Left CP angle lesion–schwannoma	No significant increase in size of spinal lesions, increase in size of left CP angle lesion with decreased hearing–underwent retrosigmoid suboccipital craniotomy with excision of left cp angle lesion	No sgnificant increase in size of spinal lesions and right CP angle lesion and is asymptomatic for spinal lesions.
Case 2	Had severe sensorineural hearing loss on audiometry, underwent retrosigmoid suboccipital craniotomy and excision of left CP angle lesion	Left CP angle lesion–schwannoma spina lesion at L1–meningothelial meningioma	No significant increase in size of right CP angle lesion, spinal lesion at L1 increased, causing cauda equina-like symptoms, so underwent laminectomy with excision of lesion.	No increase in size of right CP angle lesion
Case 3	Underwent C3-C5 laminectomy with tumoral decompression, was on follow-up for bilateral CP angle lesions	Spinal lesion at C3-C4–ependymoma	No significant increase in size of bilateral CP angle lesions, no new spinal lesions	Asymptomatic for CP angle lesions and no new spinal lesions
Case 4	Underwent right retrosigmoid suboccipital craniotomy with excision of right CP angle lesion, spinal lesion was asymptomatic and of small size so was kept on follow-up for the same	Right CP angle lesion–schwannoma	No significant increase in size of spinal lesion and left CP angle lesion	No significant increase in size of spinal lesion and left CP angle lesion
Case 5	Underwent left retrosigmoid suboccipital craniotomy with excision of left CP angle lesion	Left CP angle lesion–schwannoma right CP angle lesion–schwannoma	No significant increase in size of right CP angle lesion, no spinal lesion	Increase in size of right CP angle lesion, so underwent right retrosigmoid suboccipital craniotomy with tumoral decompression of right CP angle lesion and sent for stereotactic radiosurgery for residual lesion
Case 6	Underwent left retrosigmoid suboccipital craniotomy with excision of left CP angle lesion	Left CP angle lesion–schwannoma	No significant increase in size of right CP angle lesion, no spinal lesion	No significant increase in size of right CP angle lesion, no spinal lesion
Case 7	Underwent right retrosigmoid suboccipital craniotomy with excision of right CP angle lesion, left trigeminal lesion most likely schwannoma was small, so kept on follow-up	Right CP angle lesion–schwannoma	No significant increase in size of left trigeminal lesion, no spinal lesion	No significant increase in size of left trigeminal lesion, no spinal lesion
Case 8	Underwent craniotomy with excision of right frontal convexity meningioma on follow-up for spinal and left CP angle lesion	Right frontal SOL–meningothelial meningioma spinal lesion at L1–meningothelial meningioma left CP angle lesion–schwannoma	Spinal lesion at L1 increased, causing cauda equina-like symptoms underwent laminectomy with excision of SOL, also developed hearing loss on left side, so underwent retrosigmoid suboccipital craniotomy withexcision of left CP angle lesion	No significant increase in size of other cranial lesions and no new spinal lesions
Case 9	Underwent laminectomy C3-C5 level with excision of intramedullary SOL on follow-up for CP angle lesions	Intramedullary SOL–ependymoma	No significant increase in size of bilateral CP angle lesions, no new spinal lesions	No significant increase in size of bilateral CP angle lesions, no new spinal lesions
Case 10	Underwent right retrosigmoid suboccipital craniotomy with excision of right CP angle lesion on follow-up for left CP angle lesion	Right CP angle lesion–schwannoma	No significant increase in size of left CP angle lesion, no spinal lesions	No significant increase in size of left CP angle lesion, no spinal lesions

Abbreviations: CP, cerebellopontine; SOL, space-occupying lesion.

Table 5 Showing frequency of various manifestations according to age groups

Various manifestations	Age < 30 years (number of patients)	Age > 30 years (number of patients)
Hearing loss	2/5	5/5
Spinal tumors	4/5	2/5
Ocular manifestations	2/5	2/5
Cutaneous features	1/5	1/5

neurological recovery was only partial in two patients and absent in one. In contrast, no postoperative worsening was reported for the three asymptomatic patients with tumor growth. This suggests that growing tumors should be considered for surgery before clinical symptoms appear. Therefore, our treatment strategy in all cases of spinal cord tumors must assume strict clinical and radiological monitoring, considering surgery in any case of documented tumor growth before the onset of neurological symptom. Much has been written about the management of vestibular tumors in NF2 patients, but quite a significant number of NF2 cases present with either nonvestibular cranial tumors or spinal lesions as the presenting complaint, so management of these tumors is also equally important. One of our patients presented with headache and irrelevant talk, and on imaging, had a large right frontal convexity meningioma with multiple small intracranial meningiomas in addition to an asymptomatic left CP angle lesion, so she underwent surgery for meningioma causing symptoms. Meningiomas in NF2 are removed for cortical compression causing neurological deficit or seizure activity. Hydrocephalus is treated with either direct tumor removal or ventriculoperitoneal shunt before definitive surgery. Two of our patients had meningiomas at L1 level, and they underwent surgery, as there were cauda equina lesions and they had developed urinary abnormalities. Operative interventions, biopsy of various lesions, and follow-up of the patients were done up to 18 months (►**Table 4**) and is still on, with two patients having spinal lesion at L1 level during the follow up in spite of maximum efforts of strict monitoring, which they did not comply with and reported late at their usual follow-up. They turned up only when initial symptoms appeared with cauda equina-like symptoms on presentation; subsequently, urgent surgery was carried out, with almost complete bladder control achieved at 3 months postsurgery. This further emphasizes the strict monitoring and follow-up needed in cases of NF2 to catch these cases early and prevent the significant neurological abnormality that it can lead to.

Conclusion

NF2 is not a curable disease, and this disease spectrum has variable presentations, as seen in our study. Therefore, it is imperative to address early the lesion causing the patient to be symptomatic. Our study emphasizes that the spinal lesions and related cranial tumors in cases of NF 2 should be dealt with proactively, considering the development of new tumors and recurrences are more frequent in cases of NF2, and early surgery is advocated in these related tumors if the presenting symptom is related to these tumors and also in cases of incidental detection of bilateral CP angle lesions. A reasonable follow-up is warranted, considering the slow growing nature of these tumors.

Conflict of Interest
None declared.

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