Paraparesis in a Young Adult: A Case Report on Neurofibromatosis-2

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Abstract

Background: Neurofibromatosis-2 (NF2) is a rare neurocutaneous syndrome that typically presents with hearing loss, tinnitus, or weakness associated with few subcutaneous nodules. In contrast to neurofibromatosis-1 (NF1), NF2 presents clinically with more central lesions rather than peripheral lesions. The presence of bilateral vestibular schwannomas through imaging studies distinguishes NF2 from other neurocutaneous syndromes.

Case: This is a case of an 18-year-old male who presented with lower paraparesis with associated hearing loss, cataract, and a few subcutaneous nodules. Centrally located lesions were suspected, thus brain and spine magnetic resonance imaging (MRI) were done revealing bilateral vestibular schwannomas and spine neurofibromas. The patient and family were advised for tumor surveillance, and apprised of surgical intervention once with brainstem compression symptoms.

Conclusion: NF2 is a rare debilitating disease that may lead to multiple neurologic deficits. The absence of recommended medical treatment and the multifocality of the tumors leave surgical resection a high-risk treatment option. Early recognition by tumor surveillance may give patients with NF2 a better prognosis and survivability.

Keywords: Neurofibromatosis, Schwannomas, Neurofibromas, Paraparesis, Bevacizumab

Introduction

Neurofibromatosis-2 (NF2) belongs to a group of neurocutaneous syndromes that includes neurofibromatosis-1 (NF1), and recently schwannomatosis. Among the three, NF1 is the most common, with an incidence as high as 1 in 2600 individuals. In contrast, NF2 occurs only in 1 in 25,000 individuals.[1,2] Schwannomatosis has the lowest incidence among the three. NF2 is a rare but debilitating disease that warrants early recognition.

NF2 is an autosomal dominant inherited syndrome that predisposes individuals to multiple tumors of the central nervous system. Patients with NF2 typically present at 20-25 years of age, half of the cases are sporadic and the other half occur in the presence of a family history. Males and females are equally affected.[3]

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Case Presentation

This is the case of an 18-year-old Filipino male student who had no known comorbidities and was admitted for the first time due to gradual bilateral leg weakness eventually resulting in paraparesis.

The patient noted onset of right-hand weakness with difficulty in writing four months before admission (*Figure 1*). A month later, this progressed to weakness on both legs, however patient was still ambulatory but with difficulty. Two months before admission, progression of weakness was then noted on both thighs with paralysis on both legs. The patient was already unable to ambulate with loss of bladder and bowel control. Consult was done with medications given, but with no relief. There was no history of recent vaccination, fever, diarrhea, cough, eye pain, back pain, or trauma. The patient was noted to have hearing impairment and cataract in the right eye since childhood with no interventions nor consults done. The patient and father noted a family history of weakness of an aunt on the maternal side, but with no consult done.

Upon examination, a few subcutaneous nodules were found on the forehead, right elbow, and right forearm (*Figure 2*). Muscle tone was spastic, with atrophic lower extremities, +3 patellar reflex, and positive Babinski sign bilaterally. Considerations at this time were NF1 versus NF2, multiple sclerosis, amyotrophic lateral sclerosis, and

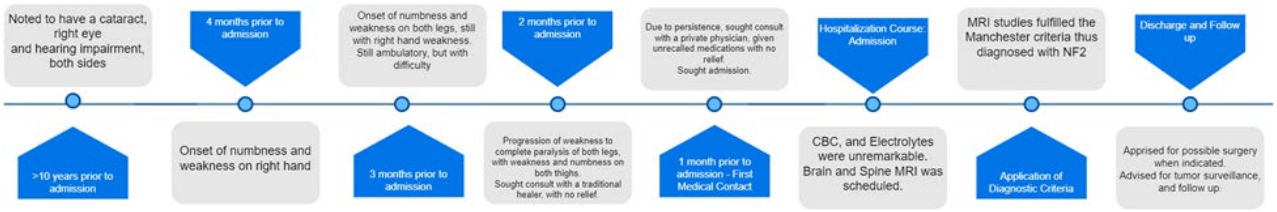

Figure 1. Chronology of Events

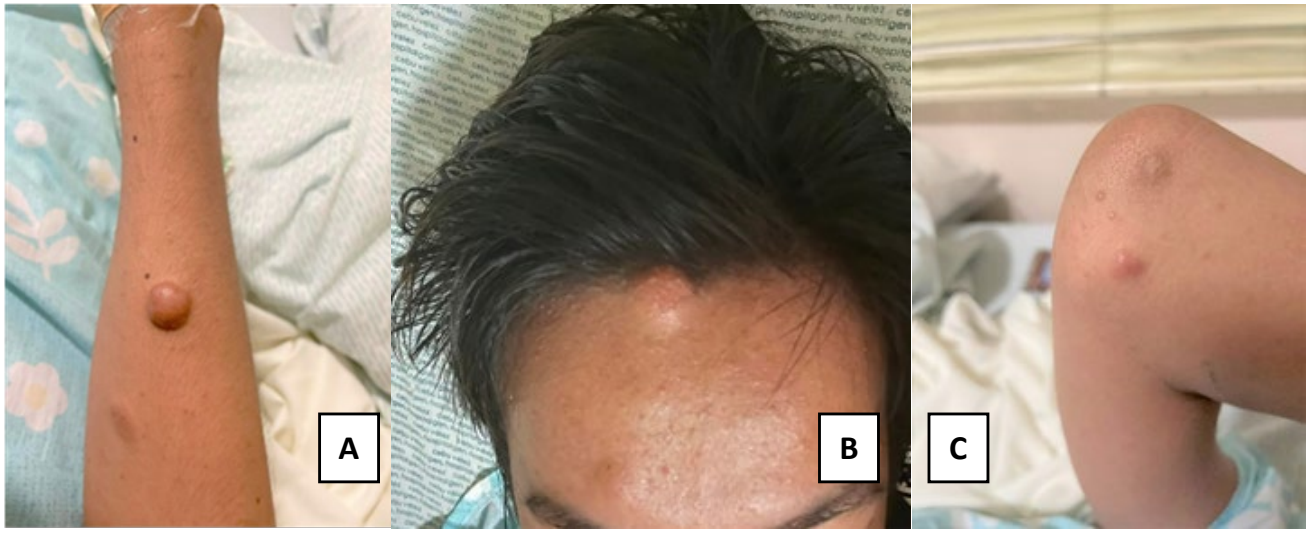

Figure 2. A. Nodule on right forearm 3 x 4 cm in diameter. B. Nodule on forehead 4 x 4 cm in diameter. C. Plaque on right elbow 1 x 2 cm in diameter

Guillain-Barre Syndrome. Laboratory work-up including complete blood count, serum potassium, and sodium were within normal limits. However, erythrocyte sedimentation rate and C-reactive protein were increased (*Table I*).

Cranial and spine magnetic resonance imaging (MRI) scan were done revealing multiple masses on the cerebellopontine angle signifying bilateral vestibular schwannomas, and multiple lesions on the neural foramina of the spinal cord signifying neurofibromas (*Figure 3*). Manchester criteria for diagnosis of NF2 were fulfilled (*Table II*). The patient and family were advised to watch out for brainstem compression symptoms, tumor surveillance, and possible surgical intervention.

Discussion

NF2 or the acoustic and central neurofibromatosis is a dominantly inherited syndrome that predisposes individuals to multiple tumors of the nervous system. Commonly, bilateral vestibular schwannomas at the cerebellopontine angle are found. Other tumor locations include intracranial and spinal meningiomas and other spinal tumors such as schwannomas or neurofibromas.[3]

Mutation in the tumor suppressor NF2 gene which produces merlin is responsible for the syndrome.[3] This leads to uncontrolled growth of fibroblasts, Schwann cells and other supportive tissues. The predominance of fibroblasts or Schwann cells is the basis for the diagnosis of a neurofibroma or schwannoma, respectively.[2]

These uncontrolled growths are responsible for the different clinical manifestations in NF2 including bilateral vestibular schwannomas, other cranial nerve schwannomas, spinal tumors and peripheral neuropathy. Due to the impingement of the 8th cranial nerve, patients manifest with hearing loss and tinnitus. Additionally, tumor growths in peripheral nerves lead to cutaneous or subcutaneous tumors, and lastly, ophthalmologic features such as cataracts and retinal hamartomas can also be present.[3] In our patient, vestibular schwannomas, spinal tumors, hearing impairment, a cataract, and subcutaneous tumors were noted.

The bilaterality of the vestibular schwannomas eventually leads to deafness. Additionally, the progression of tumor growth leads to poor balance, visual problems and muscle weakness which contribute to immobility as observed in our patient. With further tumor growth,

Table I. Laboratory Examinations

Parameter	Values	Reference Range
Complete Blood Count		
White Blood Cells, 10^3/uL	13.7	4-10
Neutrophils, %	77	47-80
Lymphocytes, %	18	13-40
Monocytes, %	3	2-11
Eosinophils, %	0.02	0-5
Basophils, %	0.211	0-2
Red Blood Cells, 10^6/uL	5.4	4.5-5.9
Hemoglobin, g/dL	15.0	13.5-17.5
Hematocrit, %	44.2	41-53
Mean Corpuscular Volume, fL	81	80-100
Mean Corpuscular Hemoglobin, pg	27	26-34
Mean Corpuscular Hemoglobin Concentration, g/dL	34	31-36
Platelets, 10^3/uL	345	140-440
Clinical Chemistry		
Sodium, mmol/L	140	136-142
Potassium, mmol/L	3.5	4.0-5.6
Immunology-Serology		
High Sensitivity C-Reactive Protein (HSCRP), mg/dL	1.64	<=0.5
Erythrocyte Sedimentation Rate (ESR), mm/hr	30	0-15

Table II. Manchester Criteria for Neurofibromatosis

Any of the following:	
1.	Bilateral vestibular schwannomas before age 70 years
2.	Unilateral vestibular schwannoma before age 70 years **and** first-degree relative (ascendant or descendant) with NF2
3.	Any two of the following: Meningioma, non-vestibular schwannoma, ependymoma, cataract; **and** First-degree relative with NF2 **OR** Unilateral vestibular schwannoma **and** negative *LZTR1* testing
4.	Multiple meningiomas **AND** Unilateral vestibular schwannoma **OR** Any two of the following: non-vestibular schwannoma, ependymoma, cataract
5.	Constitutional or mosaic pathogenic *NF2* gene mutation from the blood or by the identification of an identical mutation from 2 separate tumors in the same individual

impingement on lower cranial nerves such as CN 9 and 10 can lead to swallowing and speech problems.[4,5]

Evaluation for NF2 mutations is recommended for family members with the presence of any of the following: a first degree relative with NF2, multiple spinal tumors, cutaneous schwannomas, an apparently sporadic vestibular schwannoma in a patient < 30 years old or a solitary meningioma or non-vestibular schwannoma in a patient < 25 years old.[6,7] In this patient, genetic testing may be offered to immediate family members for early intervention in the presence of an NF2 mutation.

Genetic testing for the patient is not necessary for confirming the diagnosis, when clinical criteria is fulfilled. Clinical diagnosis of NF2 can be made in the presence of any one criterion in the Revised Manchester criteria (*Table II*).[8] The presence of bilateral vestibular schwannomas in a patient less than 70 years old was enough to fulfill the criteria in our patient thus genetic testing was not warranted

Management in NF2 begins with surveillance and follow-up. For young patients known to harbor an NF2 mutation, annual audiology, ophthalmologic evaluation, and cutaneous exam is recommended with Annual Brain MRI and Spinal MRI every 2 years beginning at 10 years old. Frequency can be reduced if no tumors are detected with initial imaging.[3] However, in patients in which characteristic tumors have been detected, tumor surveillance begins with a brain MRI every 6 months in the first year and then annually thereafter. Spinal MRI is also repeated after 6 months to assess tumor growth rate. Thus, our patient was advised for tumor surveillance and frequent follow-up.

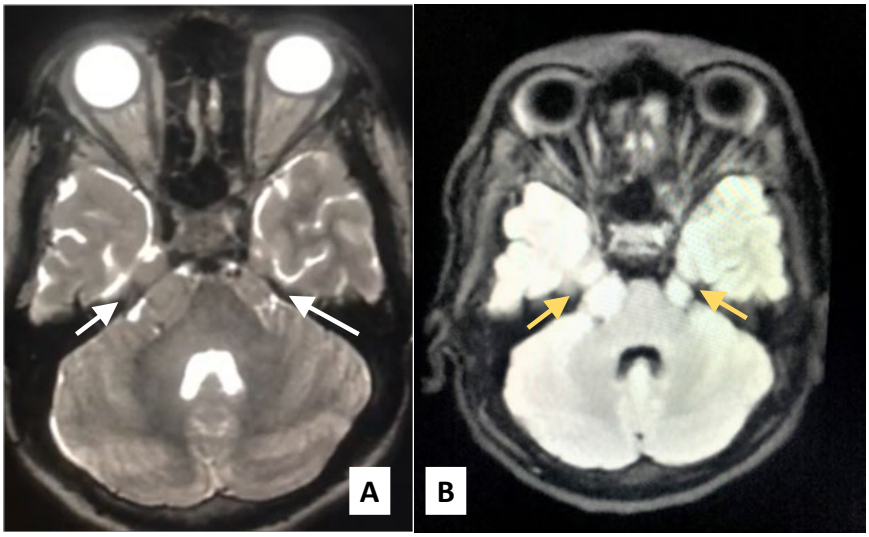

Figure 3. MRI showing multiple focal lesions in both cerebellopontine angle regions and pontomedullary cistern areas. Right: 1.1 x 1.8 x 1.3 cm Left: 0.8 x 1.6 x 0.6 cm. A. Brain MRI T2. B. Brain MRI T2 Flair

Surgical management for NF2 is expectant for large tumors or for patients showing signs of brainstem compression,

deterioration of hearing, and facial nerve dysfunction. Surgical management in patients with NF2 is more complex since the tumors are multifocal. The vestibular schwannomas may extend to the facial nerve and may risk resection of the facial nerve during surgery.[7,9] Indication for surgical management would include considerations for tumor size and symptoms of brainstem compression.[10] Patients with tumors > 3 cm with or without brainstem compression are advised for surgery, while patients with tumors < 3 cm without signs of brainstem compression are advised for tumor surveillance. In our patient, tumors were < 3 cm, thus tumor surveillance was advised. Recommendations for the excision of peripheral tumors, such as subcutaneous nodules, have not yet been established.

Current experimental studies are investigating bevacizumab as an option for medical management of NF2. Bevacizumab, an anti-vascular endothelial growth factor (anti-VEGF) drug typically used for cancers in the colon and breast as well as macular degeneration, may arrest both tumor progression and hearing loss in NF2 patients with vestibular schwannomas. Hearing improvement was noted in 56% of patients and decrease in tumor size in 47% of patients.[11] Indications for the use of bevacizumab include patients diagnosed with NF2 with vestibular schwannomas to radiographically reduce the size and improve hearing, or prolong time to hearing loss.[12] Recommended regimen would be intravenous bevacizumab 5 mg/kg every 2 weeks for at least 6 months then 2.5-5 mg/kg every 4 weeks as maintenance therapy thereafter.[13] High dose bevacizumab at 10 mg/kg/2weeks is not more effective than standard-dose bevacizumab for treatment in patients with NF2.[4]

Patients diagnosed with NF2 have an estimated survival of 15 years after diagnosis. Aside from brainstem compression due to tumor growth, immobility due to paralysis, vision, and hearing loss contribute to poor survivability. The average age of death of patients with NF2 is 36 years old.[3]

Conclusion

NF2 is a rare, but a debilitating disease that may lead to immobility, visual problems, and hearing loss leaving patients to have a poor quality of life. The multifocality of the tumors leaves surgical resection a high-risk treatment option. Early recognition by tumor surveillance and medical treatment may give patients with NF-2 better prognosis and survivability.

Informed Consent. Informed consent was obtained after a thorough explanation of the patient's condition, the rarity of the said condition, and the contribution it could make in the advancement in understanding NF2 by making a case report.

Conflict of Interest. The author declares that there is no conflict of interest regarding the publication of this paper.

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