Multiple CNS Tumors in a Patient With Neurofibromatosis Type 2: Classical Presentation of a Rare Disease

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Abstract- Neurofibromatosis type 2 is a genetic autosomal dominant disorder caused by a spontaneous mutation in the gene located on chromosome 22 q11-13.1, which usually emerges in adolescence or early adulthood and is characterized by the development of bilateral vestibular schwannoma. We hereby report the classical case of Neurofibromatosis type 2 in a 25-year-old young male with multiple tumors associated with the disease. This patient presented to us with 3 years history of multiple painless nodules on his skin, facial weakness, left-sided progressive hearing loss, and 20 days history of weakness in the left lower limb. On Examination, he was vital with a GCS of 15/15. He was anemic with no jaundice. He had left inguinal lymphadenopathy along with multiple subcutaneous nodules on different areas, including the scalp, face, left mid-axillary line over the abdomen. He also had Right-sided facial palsy and horizontal nystagmus. CNS examination revealed an upgoing plantar on the left side, right facial nerve palsy, and bilateral vestibulocochlear nerve paralysis. Spine examination revealed spinal tenderness in the lower lumbar region. Superficial abdominal reflexes were absent. Upper limb and right lower limb power, tone, and reflexes were normal while the tone and power in the left lower limb were reduced power being ⅗. Reflexes were also exaggerated in the left lower limb. The right ankle showed swelling, most probably a plexiform neuroma. On investigations, he had normochromic normocytic anemia with mild leucocytosis. Platelets were normal. The rest of the biochemical investigations, including serum electrolytes, liver function tests, and renal function tests, were also normal.MRI brain and spine confirmed bilateral acoustic neuroma and multiple cranial and peripheral nerve tumors *i.e.*, classical presentation of a rare disease neurofibromatosis. He was referred to the neurology unit for further assessment and treatment.

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Introduction

Neurofibromatosis type 2 is a rare genetic autosomal dominant disorder, caused by a spontaneous mutation in the gene located on chromosome 22 q11-13.1. The estimated incidence of NF2 is 1 in 33,000 people worldwide. Therefore, it is important to report such cases so that its kept among the other differentials in patients with such an unusual presentation.

Case Report

25-year-old male patient from Kohat presented to the outpatient department of Medical "D" unit Khyber Teaching Hospital, Peshawar with 3 years history of multiple painless nodules on his skin, facial weakness, left-sided progressive hearing loss and 20 days history of weakness in the left lower limb. According to him, this weakness was of gradual onset associated with left lumbar pain. He denied any fecal or urinary incontinence. He had multiple visits to the local doctors in the last 3 years, where he was treated symptomatically. None of his family members had a similar illness or any other disease.

On Examination, he was vitally stable with a Blood pressure of 120/80 mm of Hg, a regular good volume pulse of 85/min and was afebrile. He was well oriented in time, place, and person with a GCS of 15/15. He was anemic with no jaundice. He had 2 palpable lymph nodes in the left inguinal region measuring 2x2 cm in size. He also had multiple subcutaneous nodules on different areas, including the scalp, face, left mid-

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axillary line over the abdomen, and right foot (Figure 1a, 1b).

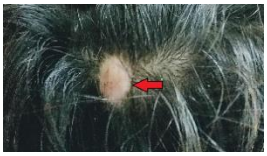

Figure 1a. An image of a subcutaneous nodule on the scalp of the patient

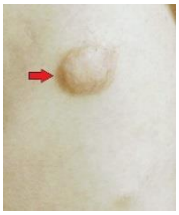

Figure 1b. An image of a subcutaneous nodule in the midaxillary line

These nodules were of different sizes, the largest one measuring roughly 3x3 cm in size. The nodules were painless, firm, mobile without any overlying skin changes.

He had Right-sided facial palsy and horizontal nystagmus, with the fast component to the left side. He had a dry coated tongue. Respiratory, cardiovascular, and gastrointestinal system examination was unremarkable. CNS examination revealed an upgoing plantar on the left side, right facial nerve palsy, and bilateral vestibulocochlear nerve paralysis. Spine examination revealed spinal tenderness in the lower lumbar region. Superficial abdominal reflexes were absent. Upper limb and right lower limb power, tone, and reflexes were normal while the tone and power in the left lower limb were reduced power being ⅗. Reflexes were also exaggerated in the left lower limb. The right ankle showed swelling, most probably a plexiform neuroma (Figure 2).

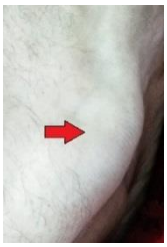

Figure 2. An image of a localized painless swelling on the right ankle most probably a plexiform neuroma

On investigations, he had normochromic normocytic anemia with a Hb of 11 gm/dL with mild leucocytosis. Platelets were normal. The rest of the biochemical investigations, including serum electrolytes, liver function tests, and renal function tests, were also normal. Investigations summarized in Table 1.

Magnetic resonance imaging of the brain and the whole spine showed bilateral acoustic neuroma, right frontal convexity meningioma, multiple cranial and spinal nerve schwannoma, and upper dorsal cord ependymoma (Figure 3a, b).

Audiometry was suggestive of bilateral sensorineural hearing loss.

Based on the symptoms, clinical examination, and radiological imaging, he was diagnosed as a case of Neurofibromatosis type 2.

Initially, he was started on symptomatic treatment, including management of neuropathic pain, multivitamins, and IV fluids. After the confirmation of diagnosis, the patient and the family was counseled regarding the disease prognosis, and he was referred to the neurosurgeon for further assessment and management.

Table 1. Laboratory investigations

Reference ranges	Parameters	Patient's values
12-15gm/dl	Hemoglobin	11 gm/dl
4000-11000/cm mm	White cell count	10,000/cm mm
	CRP	Negative
1.2-3 mmol/L	Urea	1.65 mmol/L
0.8- 1.3 mg/dL	Creatinine	0.65 mg/dL
135-145 mmol/L	Serum Sodium	138.8 mmol/L
3.5-5 mmol/L	Serum Potassium	5 mmol/L
95-105 mmol/l	Serum Chloride	96 mmol/l
2-20 micromol/L	Total bilirubin	3.7 micromol/L
50-100 U/L	Alkaline phosphatase	90 U/L
<20 mm/1st hour	ESR	20 mm/1st hour
	Echocardiography	Normal ECHOCARDIOGRAPHIC study
	Hepatitis B/ Hepatitis C/ Human Immunodeficiency virus serology	Negative by ELISA

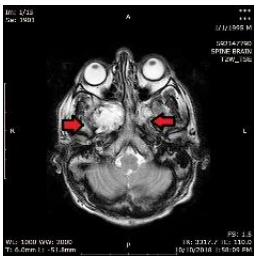

Figure 3a. Multilobulated enhancing masses in bilateral CP angle cisterns measuring 2.3x2.9cm suggesting acoustic neuroma. Nodular enhancing lesions in internal acoustic meatus most probably small schwannoma

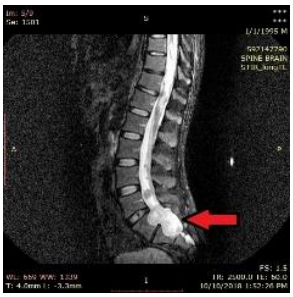

Figure 3b. Multiple enhancing extramedullary intradural masses in spinal canal suggesting spinal nerve schwannoma, largest one measuring 5x3cm seen in the sacral canal at S1, S2

Discussion

Neurofibromatosis is an autosomal dominant genetic disorder in which numerous neurocutaneous changes are seen. Two types of neurofibromatosis have been described: type 1 (NF1) and type 2 (NF2). However, the terms and entities like segmental neurofibromatosis (NF3) and familial café au lait spots (NF4) have also been described by some authors (1). NF1 is the most common among neurocutaneous

syndromes, with the incidence rate higher than NF2, *i.e.* 1 per 3.000-3.500 births, while the rate for NF2 is 1 per 50.000 births. The spontaneous mutation is the cause of about 50% NF1 and 10% NF2 (2,3). Neurofibromatosis type 2 is characterized by the development of bilateral vestibular schwannomas. The first probable case report of neurofibromatosis type 2 was that of Wishart in 1820 (4). Multiple intracranial tumors were present in this patient without any reported cutaneous features and were, therefore, quite different from those patients reported by von Recklinghausen in 1882 (5). This observation led to the recognition of NF2 as a separate clinical entity. The diagnosis of neurofibromatosis type 2 is based upon these features:

1. Bilateral vestibular schwannomas (or acoustic neuromas) of nerve VIII, confirmed by MRI, CT, or histological examination.

2. A first-degree relative with NF2 and unilateral tumor of nerve VIII;

3. A first-degree relative with NF2 and any two of the following tumor types: neurofibroma, meningioma, schwannoma, glioma, or juvenile posterior subcapsular lenticular opacity (6). Ferner *et al*., (7) gave three sets of diagnostic criteria for NF2 which includes;

1.Bilateral vestibular schwannoma (VS) or family history of NF2 plus Unilateral VS or any two of meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities. 2.Unilateral VS plus any two of meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities

3.Two or more meningioma plus unilateral VS or any two of glioma, schwannoma, and cataract. There are two forms of NF II (8).

The Wishart-Phenotype which is characterized by multiple cerebral and spinal lesions in people younger than 20 years and usually has a rapid progression of the tumors. People with NF II who develop single central tumors with slow progression after the age of 20 are thought to have the Feiling-Gardner-Phenotype. Usually spontaneous mutations are responsible for these disorders. The genes affected by these mutations are located on chromosome 22 q11-13.1. The NF2 gene product called schwannomin or merlin (595 amino acids) causes suppression of neoplasm formation. Merlin is responsible for regulating multiple proliferative signaling cascades such as receptor tyrosine kinase signaling, p21-activated kinase signaling, RAS signaling, MEK-ERK cascade, and MST-YAP cascade (9).

Merlin's deficiency can result in unmediated progression through the cell cycle due to the lack of tumor suppression, mainly because of the cell to cell junction disruption, sufficient to result in the tumors characteristic of Neurofibromatosis type. The nature of

gene mutation determines the severity of the clinical course (2).

The symptoms of NF2 usually emerge in adolescence or early adulthood, more commonly by the age of 20 years and includes bilateral vestibular schwannomas (or acoustic neuromas) along with progressive hearing loss, tinnitus, vertigo, and headaches. The patient can have facial nerve paralysis in advanced stages. Apart from these symptoms, other tumors like an acoustic neuroma and other CNS tumors in various sites within the brain and spinal cord (*e.g.*,

meningiomas, ependymomas, astrocytomas) can also occur.

Schwannomas of other cranial nerves like trigeminal nerve, facial nerve can also be seen. It can also lead to ocular conditions such as cataracts, opacification of the lens, *etc.* Skin changes presenting as spots similar to those occurring in NF1, but less numerous and smaller, may be absent. Typically no Lisch nodules are observed. In neurofibromatosis type 2, it has been reported that the prevalence rate of acoustic neuroma is 90%, neurofibroma of the skin 90%, neurofibromas of the cranial nerves and meningiomas are 50%, neuromas of spinal nerves and of peripheral nerve stem 40%, and ependymomas in 20% of cases (2,10,11).

Neurofibromatosis type 2 can be diagnosed by clinical assessment, family history, histopathological examination, radiological assessment, genetic counseling to establish NF2 incidence among first-degree relatives, and prenatal testing. Unfortunately, Neurofibromatosis type 2 is an incurable condition (2,4). Surgical removal of the tumors is one of the treatment options.

Several different surgical techniques are there for the removal of acoustic neuroma (12). For hearing loss, cochlear implants are used. However, the severity of damage to the cochlear nerve by schwannoma often precludes the use of cochlear implants. In these cases, the brainstem implant can help in the recovery of hearing loss.

More importantly, those diagnosed as having neurofibromatosis type 2 should have regular follow up at specialist centers as the timing and type of surgery, particularly for vestibular schwannoma, is critical (13).

Regular neurological examinations and scans should be performed at least annually, depending on the severity of the condition in the individual. In cases of unilateral vestibular schwannomas, brain stem evoked responses should be measured annually

An annual assessment of tumor size is also required. Genetic counseling is also important for assessment and screening of relatives at risk.

Neurofibromatosis type 2 can be diagnosed by clinical assessment, family history, histopathological examination, radiological assessment, genetic counseling to establish NF2 incidence among first-degree relatives, and prenatal testing. Although the disease is incurable, but an early diagnosis can lead to some improvement in the quality of life by offering different surgical treatment options. Also, it's of great importance to regularly monitor the patients and disease progression through annual screening scans and examinations in such patients.

References

1. Krzystolik K, Cybulski C, Sagan L, Nowacki P, Lubiński J. Endolymphatic sac tumors and von Hippel-Lindau disease – case report, molecular analysis and histological characterization. Folia Neuropathol 2009;47:75-80.
2. Santos CC, Miller VS, Roach ES. Zespoły nerwowo-skórne. In: Bradley WG I, Daroff RB, Fenichel GM, Jankovic J, eds. Neurologia w praktyce klinicznej. Lublin: Wydawnictwo Czelej, 2006:2229-68.
3. Ward BA, Gutmann DH. Neurofibromatosis 1: from lab bench to clinic. Pediatr Neurol 2005;32:221-8.
4. Wishart JH. Case of tumours in the skull, dura mater, and brain. Edinburgh Med Surg J 1982;18:393-7.
5. Von Recklinghausen F. Uber die multiplen Fibroma der Haut und lhre Beziehung zu den multiplen Neuromen. Berlin: A. Hirschwald, 1882.
6. Neurofibromatosis. Conference Statement. Arch Neurol 1988;45:575-8.
7. Ferner RE, Huson SM, D. Gareth R. Evans. Neurofibromatoses in clinical practice. London: Springer, 2011:191.
8. Walter J, Kuhn SA, Brodhun M, Reichart R, Kalff R (June 2009). "Pulmonary meningioma and neurinoma associated with multiple CNS tumours in a patient with neurofibromatosis type 2". Clin Neurol Neurosurg 2009;111: 454-9.
9. Okada, Tomoyo; You, Liru; Giancotti, Filippo G. Shedding light on Merlin's wizardry. Trends Cell Biol 2007;17:222-9.
10. Sagar SM, Izrael MA. Pierwotne i przerzutowe guzy układu nerwowego. In: Hauser SL ed. Harrison. Neurologia w medycynie klinicznej. Vol. II: Lublin: Wydawnictwo Czelej, 2008:433-51.
11. Omeis I, Hillard VH, Brain A, Benzil DL, Murali R, Harter DH. Meningioangiomatosis associated with neurofibromatosis: report of 2 cases in a single family and review of the literature. Surg Neurol 2006;65:595-603.
12. Jean Régis, Pierre-Hugues Roche. Modern Management of Acoustic Neuroma. Switzerland: Karger Publishers, 2008:191.
13. Evans DGR, Ramsden R, Huson SM, Harris R, Lye R, King TT. Type 2 neurofibromatosis: the need for supraregional care? J Laryngol Otol 1992;107:401-6.