Rare variant of misme syndrome – a case report with review of literature

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Abstract: MISME syndrome, also known as neurofibromatosis type-2 (NF2), stands for multiple inherited schwannomas, meningiomas, and ependymomas (MISME) 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 the peripheral nervous system, particularly from the bilateral vestibular nerve in more than 90% of the patients and more than two thirds of them develop spinal tumors. Simultaneous occurrence of bilateral vestibular schwanoma with cervical and lumbar ependymoma without neuro cutaneous marker with weakness of limb as initial presentation is rare finding in single patient. Here, we are reporting a rare case of MISME syndrome harbouring bilateral vestibular schwanoma with cervical and lumbar ependymoma tumors in a 45 year old male patient having no other lesion and neurocutaneous marker with weakness of limb as initial presentation without posterior subcapsular cataract.

Key words: Ependymoma, Meningioma, Neurofibromatosis type 2, MISME Syndrome, Schwannoma

Introduction

Neurofibromatosis (NF) is a syndrome of an autosomal dominant inheritance. NF is divided into two types: NF1 and NF2. NF1, formerly known as von Recklinghausen disease, is caused by mutations of neurofibromin gene on the long arm of chromosome 17. NF1 is one of the most common single-gene disorders affecting neurological function in humans (3).

NF2, also known as the MISME syndrome is caused by mutations of "Merlin" gene on the chromosome 22q12. NF2 is a rare genetic disorder with multiple benign nervous system tumors, so as named as MISME syndrome (1, 10, 12) Although NF1 and NF2 are associated with autosomal dominant inheritance, up to half of NF1 and NF2 patients are due to spontaneous mutation. The incidence is about 1 in 3500 live births for NF1 and 1 in 60,000 for NF2(5). It has no predilection for race, sex and ethnicity (2).

Although, simultaneous occurrence of the bilateral vestibular schwanoma with cervical and lumbar ependymoma in an individual can be uncommonly encountered, occurrence of

bilateral vestibular schwanoma with cervical and lumbar ependymomas with weakness of limb as initial presentation without posterior subapsular cataract in a single patient is a rare finding.

Case Report

A 45 yr old male patient presented to our outpatient department with the chief complaints of upper motor neuron type weakness of left side of upper limb and lower limb for 15 years, which was of insidious onset with initial progression and later non progressive course. His other complaints were hearing loss and tinnitus in the left ear for last 6 years, headache in left sub occipital region for 5 years, hearing loss with tinnitus in right ear for 2 yrs, swaying on either side while walking or difficulty in speech for last 6 months. There is no family history of similar disease which suggests that it is a sporadic case. Neurological examination revealed decrease in sensation on left side face with absent corneal reflex on left side left lower motor neuron type seventh cranial palsy(House and Brackmann grade 3),and bilateral sensory neural hearing loss(left>right) and left 9th and10th cranial nerve palsies. Motor examination revealed increase tone in all four limbs (Modified Ashworth Score -1). Power of the left side upper limb and lower limb was 4/5 and in right side upper and lower limb was 5/5 and it is non progressive in last 10 years. Deep tendon reflexes are 3+ in all four limbs; planter was extensor bilaterally. Sensations of touch and pinprick were decreased by 50% below C3 level.

Pure tone audiometry was suggestive of bilateral sensory neural deafness more on left side. Ophthalmic evaluation revealed bilateral mild papiloedema with no subcapsular lenticular opacities. Magnetic resonance imaging (MRI) of brain was showing a mass lesion present in left cerebellopontine angle (CP angle) cistern (Figure 1A). Mass was causing compression of brainstem. There is another smaller lesion on right CP angle cistern (Figure 1A). MRI of Spine revealed a well-defined intramedullary lesion at C3-C4 (Figure 1B) and another lesion at L1 region (Figure 1C).

We performed the microscopic subtotal excision of left CP angle lesion through retrosigmoid sub occipital approach as it was causing significant brainstem compression and planned right CP angle lesion for staged resection at later stage. As cervical and lumbar lesions were not causing progression of symptoms for years, we left it and follow up is planned. Histopathology report of left CP angle lesion revealed it was vestibular Schwannoma (Figure 3). Post-operative scan suggestive of near total excision of left CP angle lesion (Figure 2). There is no further deterioration of cranial nerve palsies post operatively.

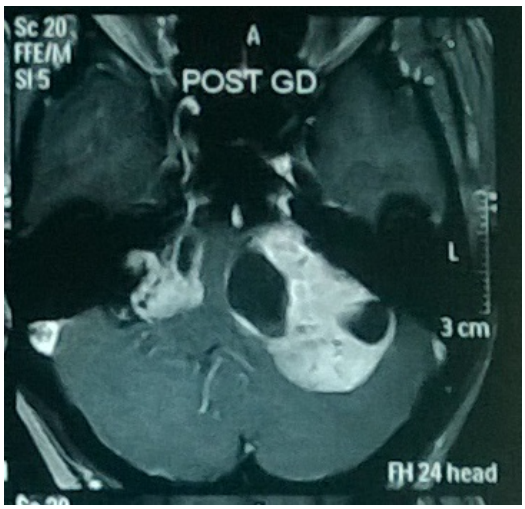

Figure 1A

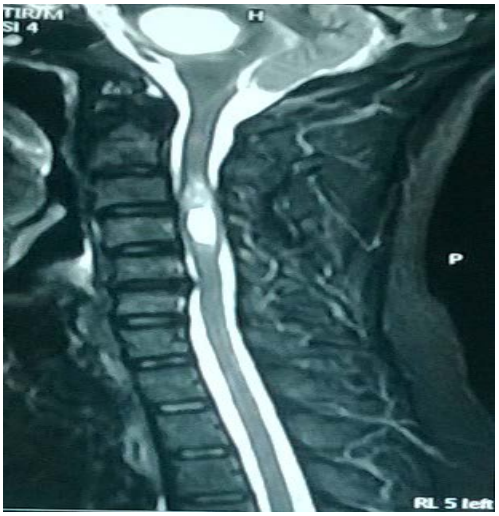

Figure 1B

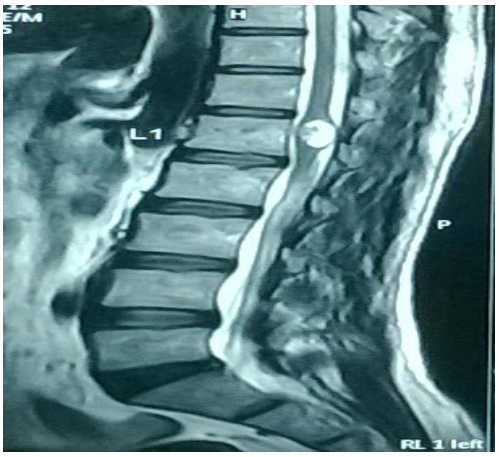

Figure 1C

Figure 1A - Showing mass lesion in both CP angle region with heterogeneous contrast enhancement and brain stem compression on left side. **Figure 1B and 1C** - Showing mass lesion at C3-C 4 and L1 level

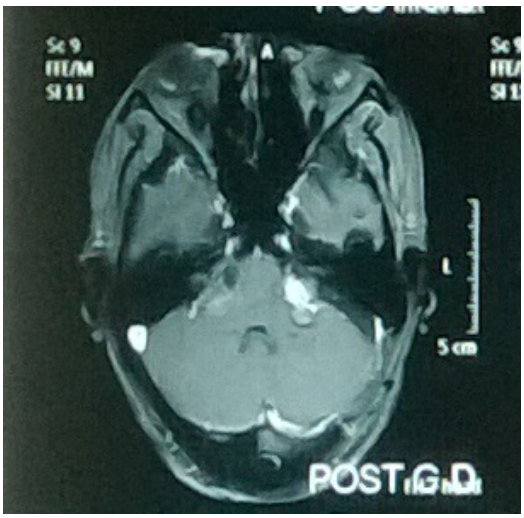

Figure 2 - Post-operative image suggestive of near total excision of left CP angle lesion

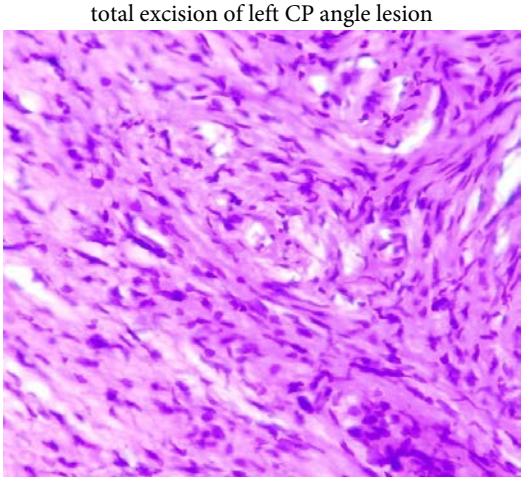

Figure 3 - Histopathology suggestive of schwanoma

Discussion

MISME Syndrome is synonymous with Neurofibromatosis (NF) type 2 Neurofibromatosis is a condition with autosomal dominant inheritance characterized by presence of multiple spaces occupying lesion in central and peripheral nervous system. The first probable reported case of neurofibromatosis type 2 was that of

Wishart in 1820 (18). This patient had multiple intracranial tumours with no cutaneous features and was, therefore, different to those patients reported by von Recklinghausen in 1882 (17), whose principal features were nodular skin lesions with no intracranial tumours. Later authors reported cases of neurofibromatosis type 1 with intracranial tumours and neurofibromatosis type 2 with cutaneous features (9, 4). In reporting a large family with neurofibromatosis in 1930, Gardner and Frazier (6) suggested that bilateral acoustic neuromas represented a separate central form of von Recklinghausen neurofibromatosis.

NF was classified as two types based on their clinical and pathological features (9). NF 1 caused by defect in neurofibromin gene which is located on long arm of chromosome 17, whereas NF 2 caused by mutations in merlin gene located on long arm of chromosome 22. This merlin gene is a tumor suppressor gene, which maintains cell connection of cytoskeleton with the plasma membrane, there by controls shape, motility of cell as well as growth regulation (5). It has almost 90% clinical penetrance rate.

The diagnosis of NF2 usually made in 2nd and 3rd decades of life, mostly 18 to 24 yrs of age (5). Diagnostic criteria which confirms diagnosis of NF2 is A) Bilateral 8th cranial nerve schwannomas on imaging or B) First degree relative with NF2 and unilateral 8th cranial nerve schwannoma at <30 yrs or any two of following: Glioma, Neurofibroma, Schwannoma, Meningioma, Juvenile posterior subcapsular lenticular opacity. The criteria for presumptive or probable diagnosis of NF2 are A) unilateral 8th cranial nerve Schwannoma <30 yrs and: Glioma, Schwannoma, Meningioma or posterior subcapsular cataract or cortical cataract. B) Multiple Meningiomas (Two or More) and unilateral vestibular Schwannoma <30 yrs or at least one of Glioma, Schwannoma, Juvenile posterior subcapsular cataract (7, 14, 15)

Almost more than 90% cases of NF2 will develop bilateral 8th cranial nerve schwannomas. In literature occurrence of schwannomas from other cranial nerves like Trigeminal, Occulomotor, Trochlear and Abducens nerves have been described previously. The most common type of spinal tumor in NF2 is schwannomas. Most common site is cervico thoracic region originating from dorsal root. 50 to 75% of NF2 patients develop meningiomas, most commonly in supra tentorial location.

Histopathologically mostly they are fibroblastic type. In spinal cord, meningiomas are mostly seen in thoracic Region. Ependymomas are seen in intramedullary location of conus medullaris or cervical region. Approximately 90% of NF2 patients had ocular lesions.

Neurological examination and imaging of craniospinal axis is crucial to establish a diagnosis. Mautner et al published a case series of 48 NF2 patients regarding their prevalence of various lesions in 1996(13). He concluded that 46 patients had 8th cranial nerve schwannomas (96%, 43 bilateral and 03 unilateral), 43 patients (90%) had Spinal tumors, 30 patients (63%) had posterior subcapsular cataracts, 28 patients (58%) had meningiomas, and Trigeminal schwannomas

were present in 14 (29%) patients. MR imaging of brain and spine with contrast is the investigation of choice in NF2 patients. NF2 patients should be managed by multidisciplinary approach which includes a neurologists, neurosurgeons, neuroradiologists, ophthalmologist, geneticist, audiologists and otologists. Every child with family history of NF2 should be screened with imaging of brain and spine as early as possible from 10 to 12 years with annual scans until 4th decade.

Management in NF2 patients is preservation of function rather cure as they have lifelong tendency to develop new tumors and or recurrences. NF2 related 8th cranial nerve schwannomas are difficult to manage as they are often large by the time they are diagnosed and tend to behave aggressively. Symptomatic Vestibular schwannomas should be treated early to preserve auditory and other cranial nerve functions. There are various modalities for treatment of vestibular schwannomas in NF2. Single or multiple fraction stereotactic radio surgery advocated at some centres with good local control and low incidence of side effect. Regardless of approach all centers agree that intervention should be done only if there is documented tumor growth or progressive hearing loss. Surgical options include radical resection, partial removal and decompression. We prefer a suboccipital retrosigmoid approach with goal of preserving facial nerve and hearing. There was significant brainstem compression in our case on one side so we did subtotal removal of mass lesion to relive compression from brainstem. We planned staged resection for the contalateral tumor. Early surgery is advocated if vestibular tumor is less than 1.5 centimetres (cms) in diameter to preserve hearing and facial nerve function. If size is more than 1.5 cms it is preferred to wait until there is motor dysfunction due to brainstem compression. Cochlear implants, hearing aids and auditory brainstem implants are alternative modes of treatment for complete hearing loss (16, 11). Menengioma in NF2 are removed for cortical compression causing neurological deficit or seizure activity. Surgical removal of intramedullary spinal tumor is recommended only when there are sign of spinal cord compression. Hydrocephalus is treated with either direct tumor removal or ventriculoperitoneal shunt before definitive surgery.

Conclusion

MISME syndrome, or NF2, is not a curable disease. Limited usefulness of adjuvant therapy leaves surgery as primary treatment to alleviate symptoms. Surgery should be limited to removal of tumour that are causing symptoms. Surgical approaches to tumors of NF2 is generally similar to the approach of same tumor in patients without NF2. However, the decision of when to operate and what level of aggressiveness is required, is often of critical importance in NF. Even though the relentless progression of disease may be discouraging many times, ability of neurosurgical procedures to alleviate symptoms and improve quality of life is significant.

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