Neurological Cases Vol1 No1 APRIL 2014
ISSN 2374-3522 (PRINT) ISSN 2374-3530 (ONLINE) http://www.researchpub.org/journal/nc/nc.html

MISME Syndrome With Triple Tumors Affecting Cervical Spinal Cord

Xin Jin[1], *MD**, Junhua He[1], *MD*, Dingkun Wang[1], *MD*, Xinwen Zhang[1], *MD*, Ye Wu[1], *MD*, Hanjiang Liu[1], *MD*, Zhangyi Wu[1], *MD*, Jun Liu[2], *MD*, Jin Jun Luo[3], *MD, PhD**

Abstract — **MISME syndrome, a synonym of neurofibromatosis type-2 (NF2), stands for multiple inherited schwannomas, meningiomas, and ependymomas. It is an autosomal dominantly inherited disorder 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 vestibulocochlear nerve in more than 90% of the patients and more than two thirds of them develop spinal tumors, which are often devastating and difficult to manage. Simultaneous occurrence of triple tumors in an NF2 patient is rare. Furthermore, simultaneous occurrence of the triple tumors with histologic confirmation in a shared common location is not seen in the literature. We reported here a young woman with MISME syndrome with triple tumors affecting the cervical spinal cord in whom staging microsurgical resection intervention produced a clinically favorable outcome. Histological reports with immunochemical staining showed the presence of schwannomas, meningiomas, and ependymomas. We claimed that surgical debulking of these symptomatic craniospinal tumors is the treatment option of choice. Staging microsurgical techniques may reduce adverse outcomes.**

Keywords **-** craniospinal tumors; ependymomas, meningiomas, microsurgery, MISME syndrome, Neurofibromatosis type 2, schwannomas.

I. INTRODUCTION

Neurofibromatosis (NF) is an autosomal dominantly inherited syndrome. Based on its clinical and pathological features, NF is divided into two types: NF type-1 (NF1) and NF2. NF1, formerly known as von Recklinghausen disease, is caused by the gene mutations of neurofibromin on the long arm of chromosome 17 that is involved in the RAS pathway which plays a role in cell signaling. NF1 is one of the most common single-gene disorders affecting neurological function in humans[1].

NF2, also named as the MISME syndrome for "multiple inherited schwannomas, meningiomas, and ependymomas, is caused by mutations of a tumor-suppressor gene, the "Merlin" gene, on the chromosome 22q12[2]. NF2 is an uncommon genetic disorder with benign nervous system tumor development, so as named as MISME syndrome[3-9]. Although NF1 and NF2 are transmitted in an autosomal dominant pattern, up to 50% 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[9]. Both NF1 and NF2 affect men and women equally.

Common symptoms of NF1 include scoliosis, learning disabilities, vision disturbances, epilepsy and significant skin involvement. The diagnostic criteria for NF1 are: 1) Six or more café au lait macules (>0.5 cm in children or >1.5 cm in adults); 2) Two or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma; 3) Axillary or groin freckling; 4) Optic pathway glioma; 5) Two or more Lisch nodules (iris hamartomas seen on slit lamp examination); 6) Bony dysplasia (sphenoid wing dysplasia, bowing of long bone ± pseudarthrosis); 7) First degree relative with NF1[10]**.** The criteria are met in an individual if two or more of the features listed are present.

In contrast, the main manifestation of NF2 is symmetric multiple benign tumors involving the vestibulocochlear (cranial nerve [CN] VIII) nerves, which has been observed more than 90% patients[3-5]. At least two thirds of patients with NF2 develop spinal tumors, which are often devastating and difficult to manage[7]. Unlike NF1, NF2 is less likely to have skin lesions and not associated with neurofibromas. The diagnostic criteria for NF2 have been modified over time[11]. Most recent modified criteria for *definite* diagnosis of NF2 are: 1) Bilateral CN VIII schwannomas on magnetic resonance imaging (MRI) or computer tomography (CT) scan (no biopsy necessary); 2) First-degree relative with NF2; and 3) Either unilateral early-onset CN VIII schwannoma (age < 30 y) or any 2 of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity (juvenile cortical cataract)[10-13]. The criteria for *probable* diagnosis of NF2 are: 1) Early onset of *unilateral* CN VIII schwannomas on MRI or CT

[1]Neurosurgery Department, Zhejiang Provincial Tongde Hospital, Hangzhou, Zhejiang, China.
[2]Pathology Department, Zhejiang Provincial Tongde Hospital, Hangzhou, Zhejiang, China.
[3]Departments of Neurology and Pharmacology, Temple University School of Medicine, Philadelphia, PA, USA.
*Correspondence to: Dr. X. Jin (e-mail: jinxintd@126.com) and Dr. J.J Luo (e-mail: jluo@temple.edu).

scan detected in patients younger than 30 years and 2) any of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity, multiple meningiomas (>2). Although CN schwannomas, except for CN VIII schwannomas, also occur spontaneously, they are relatively rare. Thus, the presentation of multiple CN schwannomas, or an unusual intracranial schwannoma, such as a single CN III (oculomotor), CN IV (trochlear), or CN VI (abducens) schwannoma, should prompt screening for NF2. Contrast-enhanced MRI of the brain and entire spine should be pursued[14-16] to detect small schwannomas, particularly of the CN and spinal nerve roots and intraparenchymal ependymomas[17]. MRI of high-resolution fast spin-echo (FSE) T2 and fluid attenuated inversion recovery (FLAIR) imagings can aid evaluation[18-20].

Although implicated by the name of MISME, simultaneous occurrence of the triple tumors in an individual can be rarely encountered. The occurrence of the triple tumors in a shared anatomic location, such as in cervical canal, is even rarer. To expand our knowledge, we presented a case of MISME syndrome affecting the cervical spinal cord in a young woman.

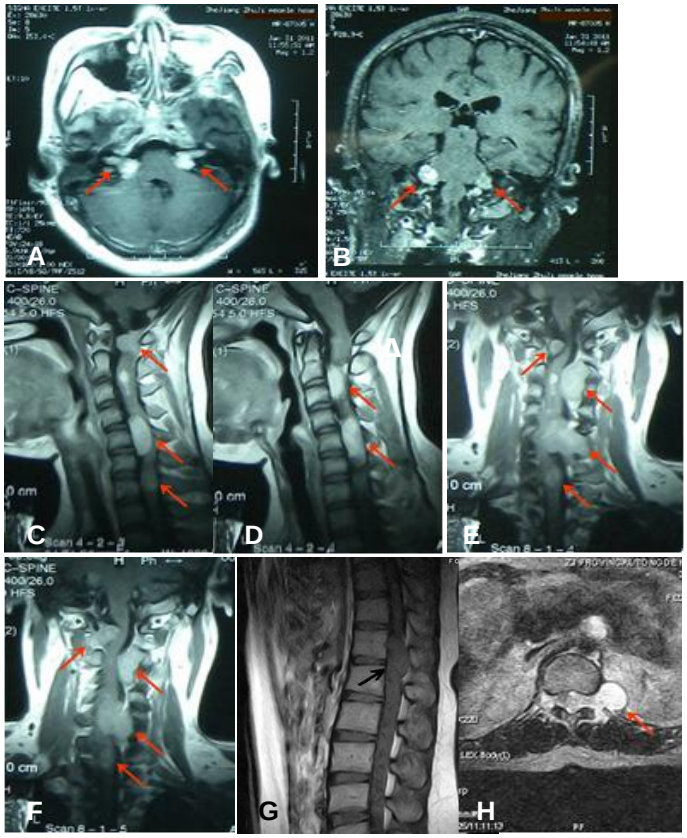

Fig. 1. Brain MRI with contrast of T1 weighed imaging (axial, **A** and coronal, **B**) shows bilateral vestibular schwannomas (arrows). Cervical spine MRI with contrast of the T1 weighted imaging (sagittal, **C, D** and coronal, **E, F**) shows multiple homogeneously enhanced well-defined solid mass lesions varying in sizes (arrows) at C1-C6 level intradural-extramedullarily and one at C6-C7 intramedullarily. Thoracolumbar spine MRI (**G:** T1 weighted sagittal image without contrast and **H:** T2 weighted axial image without contrast) shows a dumbbell shaped tumor at T12-L1 level. The left kidney was compressed by the tumor (**H**).

II. Case Report

A 21-year-old woman presented for progressive hearing loss for 10 years, constant back pain for 2 years, weakness and stiffness in all four limbs for 8-months and inability to ambulate for 1 month. She also complained of constipation but no sphincter dysfunction. She was born blind in her left eye and found to have myopia in her right eye, legal deafness in her right ear and a hearing deficit (threshold >50dB) in her left ear. Neurological examination revealed weak muscle strength of 3/5 (Medical Research Council) in her left lower limb and 4/5 in all other limbs. She had spastic muscle tone in all four limbs with brisk tendon reflexes and bilateral positive Babinski signs. Sensory deficit with a bilateral C4 level and percussion pain on T12 spinal process were noted. Her breathing was fast and shallow.

MRI of the brain and cervical spine showed numerous well-defined mass lesions varying in size exhibiting isointense signal to gray matter on T1/T2 images and postcontrast enhancement. These masses resided in bilateral cerebellopontine angles (CPA) affecting acoustic nerves and cervical spinal cord at C1-C7 level intradural-extramedullarily and intramedullary (Fig.1A-F). MRI of thoracolumbar spine showed a dumbbell shaped mass extra-axially at T12-L1 level which also significantly compressed the spinal cord (Fig. 1G-H). Incident finding on the MRI showed the left kidney was compressed by the tumor (Fig. H) without clinical complaints nor laboratory evidence of kidney dysfunction. The clinical presentations and neuroimaging findings were consistent with the diagnosis of NF2[5, 10-12]. Interestingly, no mass was seen in the optic nerves on the brain MRI although the patient had visual deficits.

She underwent staging microsurgical debulking intervention. Initially, the intramedullar tumor at the C6-C7 and the intradural tumors at the C3-C6 levels, which badly compressed and displaced the cervical spinal cord, were removed completely (Fig. 2). The extradural segments of the masses, which encased the bilateral vertebral arteries at the level of C1-C2 and the left carotid artery at the level of C5-6, were subtotally resected (Fig. 2E and 2I). Pathology reports with histoimmunochemical staining showed spinal meningioma at C1-C2, schwannomas at C3-C4 and C5-C6 level, and ependymoma (WHO Grade II) intramedularlly at C6-C7 (Fig. 2).

Subsequently she underwent a secondary microsurgery to debulk masses on the bilateral vestibular and left facial nerves under the intraoperative monitoring with electromyography on facial nerve and brainstem auditory evoked potentials (Fig. 3A). Histologic exam showed schwannoma (Fig. 3B). During the operation, some tiny tumors of 1-2 mm in size rising from the facial, glossopharyngeal and hypoglossal nerves were observed, which were not seen on the brain MRI, suggestive of the limitation and low sensitivity of the MRI on the tiny sized tumors. Finally, she underwent a third operation 3 months later to relieve her back pain. The dumbbell-shaped tumor was completely removed (Fig. 1H and Fig. 3C). The compressed left kidney was also decompressed. Histological study showed schwannoma (Fig. 3D).

ISSN 2374-3522 (PRINT) ISSN 2374-3530 (ONLINE) http://www.researchpub.org/journal/nc/nc.html

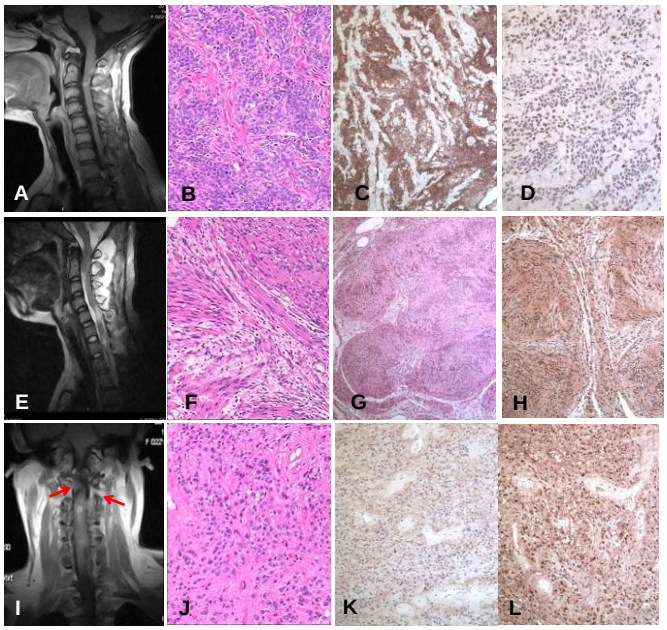

Fig. 2. MRI of cervical spine 3 months post-operation shows the postsurgical changes (**A:** sagital T1 weighted imaging; **E:** sagital T2 weighted imaging and **I:** coronal T1 weighted imaging). The previously demonstrated intradural tumors (see Fig. 1C-1F) disappeared except the extradural remnant at the C1-C2 level (I: arrow). A well decompressed cervical spinal cord is shown. Microphotos of histological and immunochemical staining show meningioma resected from the C1-C2 (**B:** H&E staining; **C:** EMA staining and **D:** Progesterone Receptor staining); schwannomas resected from C3-C4 and C5-C6 (**F:** H&E staining; **G:** Verocay body and **H:** S100 protein staining) and ependymoma (WHO Grade II) resected intramedullarily from C6-C7 (**J:** H&E staining, **K:** GFAP staining and **L:** S100 protein staining).

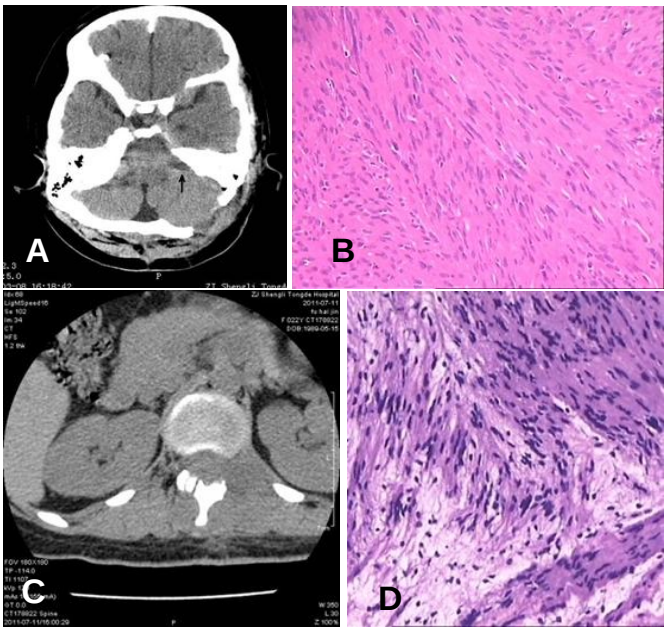

Fig. 3. **A:** Brain CT without contrast shows the postoperative changes in left CPA with disappearance of the left vestibular schwannoma (arrow). **B**: Histological examination shows vestibular schwannoma (H&E staining). **C:** CT without contrast of lumbar spine at T12-L1 level shows the disappearance of the dumbbell-shaped tumor (see Fig. 1H). **D:** Histological examination shows schwannoma (H&E staining).

Follow-up at 6 months after the operation, her symptoms were significantly improved. She regained her muscle strength significantly (4^{+}/5 in all limbs) and was able to ambulate without assistance. Her back pain was completely relieved, however, her hearing deficits and left facial palsy remained. No genetic study was performed.

III. Discussion

We presented here a rare case of MISME, or NF2, with pathologically confirmed triple tumors affecting the cervical spinal cord in a young woman, in whom microsurgical debulking interventions resulted in a favorable outcome. To our knowledge, this is the first report of MISME syndrome, or NF2, with pathologically confirmed triple tumors affecting cervical spinal cord after PubMed search.

The average age of the onset of clinical manifestations in individuals with NF2 is 18 to 24 years[9]. Clinical studies have shown that NF2 patients have 90–95% chances to suffer from bilateral vestibular schwannomas and 70% of a variety of spinal neoplasms[15]. Radiological studies with pathological confirmations have shown schwannoms in 83% cranial and 75% spinal cord tumors while meningiomas in 75% cranial[21] and 20% intradural extramedullary spinal cord tumors[4], which is associated with significant morbidities[7]. The most common spinal tumors are schwannomas, which usually originate within the intravertebral canal on the dorsal root and extend both medially and laterally, taking the shape of a "dumbbell", as also seen in our patient [Fig. 1G and 1H]. Schwannomas can develop along the course of cranial, spinal and peripheral nerves. Although meningiomas are benign, they may be difficult to completely resect, as seen in our patient with meningiomas encasing the bilateral vertebral arteries. The exact incidence of ependymomas in NF2 is unclear but likely to be low[14]. Ependymomas are relatively rare tumors, accounting for only 4% to 6% of primary central nervous system neoplasms. About one-third of all ependymomas arises within the spinal canal and represents the most common (approximately 40%-60%) intramedullary spinal neoplasm in adults[22-24]. NF2 associated with spinal ependymomas usually have an indolent course and approximate three-fourth of them were asymptomatic[25], therefore, they can be either observed or treated with surgical excision[26]. The constellations of clinical presentation, neuroimaging and surgical findings in our patient fulfilled the diagnostic criteria for NF2, or MISME. Histologic studies confirmed the diagnosis. Surgical removal is the option of treatment choice and can produce a satisfactorily clinical outcome[25]. In our patient, we successfully resected most of the cervical tumors and produced a favorable improvement without causing neurologic deficits.

Vestibular schwannomas affecting young patients with NF2 may cause significant hearing loss, facial palsy and brain stem dysfunction. A chance to preserve hearing exists only if the maximal hearing loss is less than 30 dB preoperatively because surgical intervention may also adversely add risks[27]. Our patient who failed to salvage hearing function after operation was primarily due to her advanced disease course with multiple schwannomas involving the CN VIII. Early intervention may be needed to achieve the best outcomes in preserving facial and

auditory functions. Cochlear implants, vibrant sound bridge, bone anchor hearing aid and auditory brainstem implant, which are the alternative ways to salvage sensorineural hearing loss, are clinically available[28-31]. Early resection of the tumors may be warranted for symptomatic tumors. Complete resection of meningiomas, schwannomas and ependymomas can be achieved but at times may be a procedure challenge. The strategy with gradient priorities using staging microsurgical techniques to debulk tumors in different locations may be carried out, and should be individualized depending on patient's age, overall clinical status, and ease of respectability[25]. Microsurgical techniques and intraoperative monitoring may help to reduce adverse outcomes. If a complete resection is infeasible, stereotactic radiotherapy, and possibly gene therapy, may be beneficial in improving quality of life and prolonging life span.

IV. Conclusions

MISME syndrome, or NF2, is a rare clinical condition. MISME with pathology confirmed triple tumors involving the cervical spine is rare and not seen in the literature. The features of multi-tumors involving the brain and spinal cord imply a clinical management challenge. Surgical debulking on symptomatic craniospinal tumors is the treatment option of the choice. Staging microsurgical techniques may reduce adverse outcomes. The strategy for the treatment must be individualized.

References

1. Costa RM, Silva AJ. Molecular and cellular mechanisms underlying the cognitive deficits associated with neurofibromatosis 1. J Child Neurol 2002;17(8):622-6; discussion 627-9, 646-51.
2. Striedinger K, VandenBerg SR, Baia GS, McDermott MW, Gutmann DH, Lal A. The neurofibromatosis 2 tumor suppressor gene product, merlin, regulates human meningioma cell growth by signaling through YAP. Neoplasia 2008;10(11):1204-12.
3. Asthagiri AR, Parry DM, Butman JA, Kim HJ, Tsilou ET, Zhuang Z, et al. Neurofibromatosis type 2. Lancet 2009;373(9679):1974-86.
4. Patronas NJ, Courcoutsakis N, Bromley CM, Katzman GL, MacCollin M, Parry DM. Intramedullary and spinal canal tumors in patients with neurofibromatosis 2: MR imaging findings and correlation with genotype. Radiology 2001;218(2):434-42.
5. Mautner VF, Baser ME, Thakkar SD, Feigen UM, Friedman JM, Kluwe L. Vestibular schwannoma growth in patients with neurofibromatosis Type 2: a longitudinal study. J Neurosurg 2002;96(2):223-8.
6. Holland K, Kaye AH. Spinal tumors in neurofibromatosis-2: management considerations - a review. J Clin Neurosci 2009;16(2):169-77.
7. Dow G, Biggs N, Evans G, Gillespie J, Ramsden R, King A. Spinal tumors in neurofibromatosis type 2. Is emerging knowledge of genotype predictive of natural history? J Neurosurg Spine 2005;2(5):574-9.
8. Harada H, Kumon Y, Hatta N, Sakaki S, Ohta S. Neurofibromatosis type 2 with multiple primary brain tumors in monozygotic twins. Surg Neurol 1999;51(5):528-35.
9. Evans DG. Neurofibromatosis type 2 (NF2): a clinical and molecular review. Orphanet J Rare Dis 2009;4:16.
10. Stumpf DA, Alksne JF, Annegers JF. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol 1988;45(5):575-8.
11. Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 1997;278(1):51-7.
12. National Institutes of Health Consensus Development Conference Statement on Acoustic Neuroma, December 11-13, 1991. The Consensus Development Panel. Arch Neurol 1994;51(2):201-7.
13. Mautner VF, Tatagiba M, Guthoff R, Samii M, Pulst SM. Neurofibromatosis 2 in the pediatric age group. Neurosurgery 1993;33(1):92-6.
14. Gillespie JE. Imaging in neurofibromatosis type 2: screening using magnetic resonance imaging. Ear Nose Throat J 1999;78(2):102-3, 106, 108-9.
15. Mautner VF, Tatagiba M, Lindenau M, Funsterer C, Pulst SM, Baser ME, et al. Spinal tumors in patients with neurofibromatosis type 2: MR imaging study of frequency, multiplicity, and variety. AJR Am J Roentgenol 1995;165(4):951-5.
16. Egelhoff JC, Bates DJ, Ross JS, Rothner AD, Cohen BH. Spinal MR findings in neurofibromatosis types 1 and 2. AJNR Am J Neuroradiol 1992;13(4):1071-7.
17. Beges C, Revel MP, Gaston A, Brugieres P, Meder JF, Martin N. Trigeminal neuromas: assessment of MRI and CT. Neuroradiology 1992;34(3):179-83.
18. Allen RW, Harnsberger HR, Shelton C, King B, Bell DA, Miller R, et al. Low-cost high-resolution fast spin-echo MR of acoustic schwannoma: an alternative to enhanced conventional spin-echo MR? AJNR Am J Neuroradiol 1996;17(7):1205-10.
19. Chen SL, Liu C, Liu B, Yi CJ, Wang ZX, Rong YB, et al. Schwannomatosis: a new member of neurofibromatosis family. Chin Med J (Engl) 2013;126(14):2656-60.
20. Tryggvason G, Barnett A, Kim J, Soken H, Maley J, Hansen MR. Radiographic association of schwannomas with sensory ganglia. Otol Neurotol 2012;33(7):1276-82.
21. Nunes F, MacCollin M. Neurofibromatosis 2 in the pediatric population. J Child Neurol 2003;18(10):718-24.
22. Waldron JN, Laperriere NJ, Jaakkimainen L, Simpson WJ, Payne D, Milosevic M, et al. Spinal cord ependymomas: a retrospective analysis of 59 cases. Int J Radiat Oncol Biol Phys 1993;27(2):223-9.
23. Schild SE, Nisi K, Scheithauer BW, Wong WW, Lyons MK, Schomberg PJ, et al. The results of radiotherapy for ependymomas: the Mayo Clinic experience. Int J Radiat Oncol Biol Phys 1998;42(5):953-8.
24. Tihan T, Chi JH, McCormick PC, Ames CP, Parsa AT. Pathologic and epidemiologic findings of intramedullary spinal cord tumors. Neurosurg Clin N Am 2006;17(1):7-11.
25. Plotkin SR, O'Donnell CC, Curry WT, Bove CM, MacCollin M, Nunes FP. Spinal ependymomas in neurofibromatosis Type 2: a retrospective analysis of 55 patients. J Neurosurg Spine 2011;14(4):543-7.
26. Aguilera DG, Mazewski C, Schniederjan MJ, Leong T, Boydston W, Macdonald TJ. Neurofibromatosis-2 and spinal cord ependymomas: Report of two cases and review of the literature. Childs Nerv Syst 2011;27(5):757-64.
27. Samii M, Matthies C, Tatagiba M. Management of vestibular schwannomas (acoustic neuromas): auditory and facial nerve function after resection of 120 vestibular schwannomas in patients with neurofibromatosis 2. Neurosurgery 1997;40(4):696-705; discussion 705-6.

28. Odat HA, Piccirillo E, Sequino G, Taibah A, Sanna M. Management strategy of vestibular schwannoma in neurofibromatosis type 2. Otol Neurotol 2011;32(7):1163-70.

29. Roehm PC, Mallen-St Clair J, Jethanamest D, Golfinos JG, Shapiro W, Waltzman S, et al. Auditory rehabilitation of patients with neurofibromatosis Type 2 by using cochlear implants. J Neurosurg 2011;115(4):827-34.

30. Lustig LR, Yeagle J, Driscoll CL, Blevins N, Francis H, Niparko JK. Cochlear implantation in patients with neurofibromatosis type 2 and bilateral vestibular schwannoma. Otol Neurotol 2006;27(4):512-8.

31. Bento RF, Brito Neto RV, Tsuji RK, Gomes MQ, Goffi-Gomez MV. Auditory Brainstem Implant: surgical technique and early audiological results in patients with neurofibromatosis type 2. Braz J Otorhinolaryngol 2008;74(5):647-51.

Questions *(please choose a single answer)**:***

1. MISME syndrome, or NF2, is an inherited disorder with:

   A. Autosomal dominant pattern.
   B. Autosomal recessive pattern.
   C. X-linked dominant pattern.
   D. X-linked recessive pattern.

2. MISME syndrome, or NF2, is caused by the gene mutation involving:

   A. 17q11.
   B. 22q12.
   C. 13q14.
   D. Xq23.

3. Patients of NF2 are less likely to have:

   A. Skin neurofibromas.
   B. Bilateral CN VIII Schwannomas.
   C. Optic gliomas.
   D. Juvenile posterior subcapsular lenticular opacity (juvenile cortical cataract).

4. MISME syndrome commonly includes all the following tumors EXCEPT:

   A. Schwannomas.
   B. Medulloblastoma.
   C. Ependymomas.
   D. Meningiomas.

5. The following statements on NF2 are correct except:

   A. The incidence is about 1 in 60,000 live births.
   B. The average age of the onset of clinical manifestations in individuals with NF2 is 18 to 24 years.
   C. Clinical studies have showed that NF2 patients have 90–95% chances to suffer from bilateral vestibular schwannomas.
   D. At least two thirds of individuals with NF2 develop spinal tumors.
   E. The diagnostic criteria include 6 or more café au lait macules (>0.5 cm in children or >1.5 cm in adults).

Answers: 1: A; 2: B; 3: A; 4: B 5: E.