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Magnetic Resonance Imaging Evaluation of Neurofibromatosis 1 and 2 Manifestations in Iranian Population

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Abstract **Introduction:** Neurofibromatosis type 1 (NF1) or von Recklinghausen's disease, is a rare multi-system genetic disorder caused by the mutation of a gene on chromosome 17 which is responsible for synthesis of a protein called neurofibromin and it can cause various neoplasms. Also, Neurofibromatosis type 2 (NF2) is a genetic disorder caused by mutation of Merlin gene, responsible for production of neurofibromin 2 or schwannomin, a cyto-skletal protein. In this study, authors plan to investigate the distribution of these neoplasms and their features on Magnetic Resonance Imaging (MRI). **Materials and Methods:** From July 2013 to October 2017, we have prospectively enrolled 36 patients with confirmed diagnosis of either NF1 or NF2 based on clinical criteria and post-operative histological examination, to our study and we have performed target-focused imaging, targeting mostly intracranial cavity and spine, and other organs based on patients symptoms to assess the prevalence of neoplasms associated with NF1 and NF2. Also, we have performed specific tests to determine and follow-up the complications of NF1 and NF2, being Electromyography (EMG) and Nerve Conduction Velocity (NCV) for possible spinal cord lesion evaluation and perimetry for evaluation of optic nerve and chiasma lesions in NF1, and audiometry for evaluation of acoustic neuroma and hearing disability in NF2 patients. **Results:** There were 36 patients, being 20 females and 16 males within 14-40 years old range. NF1 patients comprise 22 cases, being 12 females and 10 males with mean age of 25.7 years and NF2 patients comprise 14 cases, being 9 females and 5 males with mean age of 23.8 years. Perimetry showed affected visual field in 10 patients and neurological examination and EMG-NCV study revealed paresthesia and weakness in upper extremities in 6 patients. Also, audiometry revealed affected hearing pattern in 13 patients. MRI study in NF1 cases revealed Unidentified Bright Objects (UBO) in 15 cases, followed by optic nerve and optic chiasma glioma in 12 cases, spinal cord lesion being as cervical spinal neurofibromas in 6 patients and deep visceral and abdominal plexiform neurofibromas in 4 patients. Moreover, MRI examination in NF2 patients showed bilateral acoustic neuromas in all 14 cases, meningiomas in 9 cases and epenymoma in 2 patients. Also, histopathological examination of removed tissues in surgical candidates or patients with intermediate certainty of diagnosis, confirmed either neurofibromatosis. **Conclusion:** Although being rare, neurofibromatosis, whether type 1 or type 2, may cause devastating complications and sequel to the affected patients and in some instances; they may manifest themselves as uncommon lesions in neuro-imaging without other visible criteria for the disease. In this study, authors have investigated the possible lesions in association with NF1 and NF2, and incidental finings of these lesions in neuro-imaging or visceral imaging should prompt the suspicion for underlying phakomatosis such as neurofibromatosis.

Keywords: *neurofibromatosis, magnetic resonance imaging, optic nerve Glioma, Plexiform Neurofibroma, acoustic Neuroma*

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1. Introduction

Neurofibromatosis type 1 (NF1) or von Recklinghausen's disease, is a complex multi-system genetic disorder characterized by neuro-cutaneous manifestations such as café au lait spots and axillary freckles, as well as glioma of optic nerve and optic chiasma and skeletal dysplasia. [1] It is caused by mutation of NF1 gene which is responsible for production of neurofibromin protein which acts as a tumor suppressor. The incidence of NF is thought to be more than 1 in every 3000 births, with life expectancy of about 7.5 years less than general population due to its complications. [2] Gender affection is equal in male and female, due to autosomal dominant inheritance pattern, but certain complications such as scoliosis is seen more frequently in females. [3] NF1 differs from NF2 in which

affected patients exhibit less cutaneous manifestations with higher incidence of meningiomas and acoustic neuromas (vestibular schwannoma) which is mostly bilateral. NF2 is caused by mutation of Merlin gene, responsible for production of neurofibromin 2 or schwannomin, a cyto-skletal protein. [4] NF2 or central neurofibromatosis is characterized by bilateral acoustic neuroma, meningiomas, juvenile cataracts and few cutaneous symptoms. [5] Its incidence is estimated about 1 in every 36000 births annually, with disease onset on early 20 years old. Both NF1 and NF2 exhibit various malignancies in both central nervous system and peripheral neuronal networks, which may be the first presenting symptoms. [6] In this study, authors plan to investigate the distribution of these neoplasms and their features on Magnetic Resonance Imaging (MRI).

2. Materials and Methods

Authors have enrolled 36 patients with confirmed diagnosis of either NF1 or NF2 based on clinical criteria and their imaging work-ups done under supervision of our neurology clinic of one of Tehran's private hospitals. The study period lasts from July 2013 to October 2017 with prospective design. We have excluded patients with history of intracranial malignancies, active malignancies and metastases, previous history of radiation therapy to skull or spinal column, active infectious processes in patients with underlying immune-compromised status, previous history of intracranial or spinal surgery, patients with underlying active collagen-vascular diseases and patients who refused to sign the written inform consent for enrollment in study and target focused MRI, have been excluded from the study. Thorough neurological and opththalmological and abdominal focused examination were performed on patients for detection of possible complications of their underlying neurofibromatosis and better direction of the authors to assess for target-focused MRI.We have performed target-focused imaging, targeting mostly intracranial cavity and spine, and other organs based on patients symptoms to assess the prevalence of neoplasms associated with NF1 and NF2. Also, we have performed specific tests to determine and follow-up the complications of NF1 and NF2, being Electromyography (EMG) and Nerve Conduction Velocity (NCV) for possible spinal cord lesion evaluation and perimetry for evaluation of optic nerve and chiasma lesions in NF1, and audiometry for evaluation of acoustic neuroma and hearing disability in NF2 patients. Patients entered to the study after collection of written informed consent authorized by ethics committee of our private hospital based on Helsinki Ethics Declaration.

3. Results

Authors have gathered demographic data, total patients being 36, 20 females (55.5%) and 15 males (44.5%) within 14-40 year old range. Patients who comprise NF1 group were consisted of 22 cases (61.1%), being 12 females (54.5%) and 10 males (45.5%) with mean age of 25.7 years. Also, patients who fulfill NF2 criteria were 14 cases (38.8%), comprised of 9 females (64.2%) and 5 males (35.8%) with 23.8 years as mean age. Perimetry evaluation for visual field of hidden and obvious blind spots and defects, exhibit visual field defect in 10 cases (27.7%). Also, due to upper extremities symptoms such as paresthesia and muscle weakness, authors have suspected possible spinal cord complications and EMG-NCV study revealed upper extremities involvement in 6 patients (16.6%), all of them being diagnosed with NF1. Since NF2 is mainly characterized by bilateral acoustic neuromas, authors have suspected patients with varying degrees of hearing defect secondary to lesions in their vestibule-cochlear nerve (cranial nerve VIII) nerve and thus audiometry examination revealed defects in hearing pattern of 13 patients (36.1%). NF1 MRI examination revealed non-specific white matter hyper-intensity on T2-weighted or fluid attenuated inversion recovery (FLAIR), know as Unidentified Bright Objects (UBO) in 15 cases (61.1%), followed by optic nerve and optic chiasma glioma in 12 cases (54.5%) as either unilateral or bilateral thickened optic nerve on T1-weighted and enhancement on T1-weighted imaging after contrast injection, spinal cord lesion being as cervical spinal neurofibromas in 6 patients (27.2%) being mostly intradural and extramedullary and abdominal plexiform neurofibromas in 4 patients (18.1%) being as large masses extended from neural foramina to retroperitoneal cavity visible as lobulated mass with neural foraminal origin on MRI. Moreover, MRI examination in NF2 patients showed bilateral acoustic neuromas in all 14 cases (100%) mostly as bilateral cerebellopontine angle with high signal intensity on FLAIR an enhancement with heterogeneity after contract injection on T1-weighted imaging, followed by 9 cases (64.2%) with meningiomas as: 5 patients with single lesion, 2 patients with 2 lesions and 2 patients with multiple lesions, mostly observed as iso-intense mass to grey matter on T1-weighted, homogenous enhancement after contrast injection on T1-weighted imaging and iso- to hyper-intense lesions on T2-weighted imagings. Also, MRI revealed ependymoma in 2 patients (14.2%) being as iso-to hypo-intense to white matter on T1-weighted and hyper-intense on T2-weighted imagings, with heterogenous enhancement on T1-weighted imaging after contrast injection. Also, histopathological examination of removed tissues in surgical candidates or patients with intermediate certainty of diagnosis, confirmed either neurofibromatosis.

4. Discussion

NF1 is one of the most common genetic disorders with autosomal dominant inheritance which is not limited to race or gender. This syndrome is caused by germ-line mutation in neurofibromin, which is included in RAS pathway and being considered of one of the RASopathy. [7] There are some well-known and less common manifestations of the disease, being cutaneous or sub-cutaneous development of neurofibromas, plexiform neurofibromas which complicates about 25% of NF1 patients and they are usually large and locally invasive masses and impose difficult management strategies. [8] Optic nerve and optic tract and optic chiasma tend to be complicated by gliomas, but with low grade and favorable prognosis, with pilocytic astrocytoma and low grade

astrocytoma being the most common. Malignant peripheral nerve sheath tumors (MPNSTs) may affect less than 15% of patients diagnosed with NF1, and they carry a poor prognosis for the affected patients. [9] Symmetric sensory-axonal neuropathy and poly-neuropathy associated with MPNSTs may affect about 1% of NF1 patients. [10] Gastrointestinal stromal tumors (GIST) results from activation of RAS-MAPK pathway and loss of heterozygosity in NF1, and every patient with known NF1 who presents with intestinal obstruction or gastro-intestinal bleeding should be listed as high suspicious to GISTs. Up to 30% of cases with NF1 have varying degrees of autism spectrum. [11,12] Also, learning disabilities with or without attention deficit hyperactivity disorder (ADHD) is reported to be as high as 40% in NF1 patients. [13] Bony abnormalities such as scoliosis, long bone intramedullary fibrosis, cortical thinning, vertebral ectasis, sphenoid bone dysplasia and higher incidence of osteoporosis is described in NF1 patients. [14] Other less common manifestation includes hypertension, pheochromocytomas, vascular lesions and stenosis, short stature, macrocephaly and Arnold-Chiari malformation type 1. [15] Diagnosis is based on 2 out of 7 criteria in the absence of alternative diagnosis, described as following: 1) Six or more café-au-lait spots or hyper-pigmented macules being 5 mm in diameter in pre-pubertal children and 15 mm post-pubertal, 2) Axillary or inguinal freckles (more than 2 freckles), 3) Two or more typical neurofibromas or one plexiform neurofibroma, 4) Optic nerve glioma, 5) Two or more iris hamartomas (Lisch nodules), 6) Sphenoid dysplasia or typical long-bone abnormalities and 7) First-degree relative with NF1. [16] Although the diagnosis of NF1 is clinical, but laboratory studies such as molecular testing of neurofibromin gene sequencing is helpful in patients with 1 criteria (such as multiple café au lait spots in absence of other findings). Also, imaging studies such as plain radiography and Computed Tomography (CT) scan and MRI may help for diagnosis of hidden criteria to naked eye. Brain MRI is the preferred method in evaluating patients with NF1 and should be considered in patients with history of increasing head circumference in an infant or young child, and in patients with suspicious history of decreased visual acuity or field and patients who suffers from headache. [17] Also, MRI is the preferred method of imaging in patients with upper limb weakness or tingling for assessment of possible underlying cervical spinal cord neurofibroma, with compressive effect on spinal cord or nerve roots and neural foramina, whether in cervical or in thoraco-lumbar area, for further evaluation of possible plexiform neurofibromas. [18] Moreover, diagnosis of NF2 requires at least 1 on of the following criteria: 1) Bilateral vestibular schwannomas; 2) A first degree relative with NF2 AND unilateral vestibular schwannoma OR any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities; 3) Unilateral vestibular schwannoma AND any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities and 4) Multiple meningiomas AND unilateral vestibular schwannoma OR any two of: schwannoma, glioma, neurofibroma and cataract. [19] Due to higher prevalence of acoustic neuromas and meningiomas and other intracranial lesions in NF2 patients, brain MRI is suggested in all of the patients with high suspicion to NF2. However, 3 dimensional volumetry of MRI is the preferred method for evaluation of acoustic neuroma's growth over time. [20] In this study, authors have investigated the prevalence of associated complications of NF1 and NF2 in Iranian population, using MRI as a target-focused method of imaging. Our findings raise the importance of further evaluation for underlying NF1 or NF2 in patients with such imaging findings.

5. Conclusion

Although being rare, neurofibromatosis, whether type 1 or type 2, may cause devastating complications and sequel to the affected patients and in some instances; they may manifest themselves as uncommon lesions in neuro-imaging without other visible criteria for the disease. In this study, authors have investigated the possible lesions in association with NF1 and NF2, and incidental finings of these lesions in neuro-imaging or visceral imaging should prompt the suspicion for underlying phakomatosis such as neurofibromatosis.

References

[1] Dugoff, L., Sujansky, E., "Neurofibromatosis type 1 and pregnancy," *American Journal of Medical Genetics Part A*, 66(1). 7-10. 1996.

[2] Rodriguez, F.J., Perry, A., Gutmann, D.H., O'neill, B.P., Leonard, J., Bryant, S., Giannini, C., "Gliomas in neurofibromatosis type 1: a clinicopathologic study of 100 patients," *Journal of Neuropathology & Experimental Neurology*, 67(3). 240-9. 2008.

[3] Stevenson, D.A., Schwarz, E.L., Viskochil, D.H., Moyer-Mileur, L.J., Murray, M., Firth, S.D., D'astous, J.L., Carey, J.C., Pasquali, M., "Evidence of increased bone resorption in neurofibromatosis type 1 using urinary pyridinium crosslink analysis," *Pediatric research*, 63(6). 697. 2008.

[4] Evans, D.G., "Neurofibromatosis 2 [Bilateral acoustic neurofibromatosis, central neurofibromatosis, NF2, neurofibromatosis type II]," *Genetics in medicine*, 11(9). 599. 2009.

[5] Harris, G.J., Plotkin, S.R., MacCollin, M., Bhat, S., Urban, T., Lev, M.H., Slattery, W.H., "Three-dimensional volumetrics for tracking vestibular schwannoma growth in neurofibromatosis type II," *Neurosurgery*, 62(6). 1314-20. 2008.

[6] Aboukais, R., Baroncini, M., Zairi, F., Bonne, N.X., Schapira, S., Vincent, C., Lejeune, J.P., "Prognostic value and management of spinal tumors in neurofibromatosis type 2 patients," *Acta neurochirurgica*, 155(5). 771-7. 2013.

[7] Diggs-Andrews, K.A., Brown, J.A., Gianino, S.M., Rubin, J.B., Wozniak, D.F., Gutmann, D.H., "Sex is a major determinant of neuronal dysfunction in neurofibromatosis type 1," *Annals of neurology*, 75(2). 309-16. 2014.

[8] Aylsworth, A., Carey, J.C., Korf, B., Marks, J., Pyeritz, R.E., Rubenstein, A., Viskochil, D., Gutmann, D.H., "The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2," *American Journal of Ophthalmology*, 124(5). 718-9. 1997.

[9] Ferrari, A., Bisogno, G., Macaluso, A., Casanova, M., D'angelo, P., Pierani, P., Zanetti, I., Alaggio, R., Cecchetto, G., Carli, M., "Soft-tissue sarcomas in children and adolescents with neurofibromatosis type 1," *Cancer*, 109(7). 1406-12. 2007.

[10] Listernick, R., Ferner, R.E., Liu, G.T., Gutmann, D.H., "Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations," *Annals of neurology*, 61(3). 189-98. 2007.

[11] Yamamoto, H., Tobo, T., Nakamori, M., Imamura, M., Kojima, A., Oda, Y., Nakamura, N., Takahira, T., Yao, T., Tsuneyoshi, M., "Neurofibromatosis type 1-related gastrointestinal stromal tumors: a special reference to loss of heterozygosity at 14q and 22q," *Journal of cancer research and clinical oncology*, 135(6). 791-8. 2009.

[12] Seddighi, A.S., Seddighi, A., Behrouzian, S., Nikouei, A., "Simultaneous Presentation of Cerebellopontine Angle Pleomorphic Xanthoastrocytoma and Malignant Melanoma in a Known Case of Neurofibromatosis 1; Probable Role of BRAF Gene: A Case Report and Review of Literature," *International Journal of Cancer Management*, 10(7). 2017.

[13] Garg, S., Green, J., Leadbitter, K., Emsley, R., Lehtonen, A., Evans, D.G., Huson, S.M., "Neurofibromatosis type 1 and autism spectrum disorder," *Pediatrics*, 132(6). e1642-8. 2013.

[14] Seitz, S., Schnabel, C., Busse, B., Schmidt, H.U., Beil, F.T., Friedrich, R.E., Schinke, T., Mautner, V.F., Amling, M., "High bone turnover and accumulation of osteoid in patients with neurofibromatosis 1," *Osteoporosis international*, 21(1). 119-27. 2010.

[15] Kumar, K.H., Shaikh, A., Sandhu, A.S., Prusty, P., "Neurofibromatosis 1 with pheochromocytoma," *Indian journal of endocrinology and metabolism*, 15(Suppl4). S406. 2011.

[16] Boyd, K.P., Korf, B.R., Theos, A., "Neurofibromatosis type 1," *Journal of the American Academy of Dermatology*, 61(1). 1-4. 2009.

[17] Denckla, M.B., Hofman, K., Mazzocco, M.M., Melhem, E., Reiss, A.L., Bryan, R.N., Harris, E.L., Lee, J., Cox, C.S., Schuerholz, L.J., "Relationship between T2-weighted hyperintensities (unidentified bright objects) and lower IQs in children with neurofibromatosis-1," *American Journal of Medical Genetics Part A*, 67(1). 98-102. 1996.

[18] Seddighi, A., Nikouei, A., Seddighi, A.S., Zali, A.R., Tabatabaei, S.M., Sheykhi, A.R., Yourdkhani, F., Naeimian, S., "Peripheral nerve injury: a review article," *International Clinical Neuroscience Journal*, 3(1). 1-6. 2016.

[19] Matsuo, M., Ohno, K., Ohtsuka, F., "Characterization of early onset neurofibromatosis type 2," *Brain and Development*, 36(2). 148-52. 2014.

[20] Ruggieri, M., Gabriele, A.L., Polizzi, A., Salpietro, V., Nicita, F., Pavone, P., Platania, N., Milone, P., Distefano, A., Privitera, G., Belfiore, G., "Natural history of neurofibromatosis type 2 with onset before the age of 1 year," *Neurogenetics*, 14(2). 89-98. 2013.