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# NEUROFIBROMATOSIS TYPE-2; A PATHOLOGICAL MECHANISM

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## ABSTRACT

Neurofibromatosis type 2 is an autosomal dominant multiple neoplasia syndrome. NF-2 disorder is developed mainly due to mutation in NF-2 tumor suppressor gene which is located on chromosome 22q12. Merlin, a type of protein is found to be the suppressor of tumor and after mutation in NF2 gene, Altered protein does not suppress the tumor activity and various types of complication like neurological complication which is associated with vestibular schwannomas, peripheral neuropathy, meningiomas, spinal cord ependymomas and opthalmological complication like cataract, epiretinal membrane and retinal hamartomas are generally seen. The multiple, progressive, and protean features associated with neurofibromatosis type 2 present substantial management challenges. Patients should be managed in specialty centres with skilled multi disciplinary team, consisting of a neurosurgeon, neurologist, geneticist, ophthalmologist, pathologist, radiologist, audiologist, and experienced nursing staff. In this review history of neurofibromatosis, pathogenesis of neurofibromatosis, structure of merlin protein, epidemiology, diagnosis and treatment of neurofibromatosis is reviewed.

**KEYWORDS:-** Merlin protein, Neurofibromatosis, Pathogenesis, Vestibular Schwannomas.

## INTRODUCTION

Neurofibromatosis is a autosomal dominantly inherited genetic disorder. It is firstly described by a German pathologist Friedrich Daniel Von Recklinghausen in 1982. It was described in a series of patient which has cutaneous lesion and tumor of peripheral and central nervous system. Neurofibromatosis is classified into three types of disease (1). Neurofibromatosis type1 (2). Neurofibromatosis-2. (3).schwannomatosis. Neurofibromatosis type 1 and 2 was differentiated in late 20$^{th}$ century and it was taken into consideration that these two disorder are different from each other and dominantly inherited genetic disorder.[1] Neurofibromatosis

type1 commonly called (von Recklinghausen's disease or peripheral neurofibromatosis) is now considered as one of the most common genetic disorder than neurofibromatosis, which occur in human with an incidence of 1/35000 individual.[2] Neurofibromatosis type 2 also known as (central neurofibromatosis or bilateral acoustic neurofibromatosis) disorder is a multiple neoplasia syndrome, it was firstly described in 1822 in a deaf patient with tumor in skull, dura mater and brain,[3] occur due to mutation in NF2 gene that leads to dysfunction in encode the protein merlin. NF2 occurs in 1/25000 live birth and it is inherited as an autosomal dominant trait.[4] Mutation in the NF1 gene and NF2 gene is mainly responsible for the development of these disorder.NF1 gene is located on chromosome 17q11.2, which is associated with encoding the protein called Neurofibromin. NF2 gene is located on the chromosome 22q12, which is associated with encoding the protein Merlin.[4] Neurofibromatosis type 2 show 100% penetrance by the age of 60 and has wide phenotypic variability.[5] Suspected patients was shown sign snd symptoms of development of lesions of nervous system, eye, ear and skin. Bilateral nerve schwannomas are the main characteristics of Neurofibromatosis type 2 patients. Patient can also develop schwannomas in other cranial, spinal, and peripheral nerve.

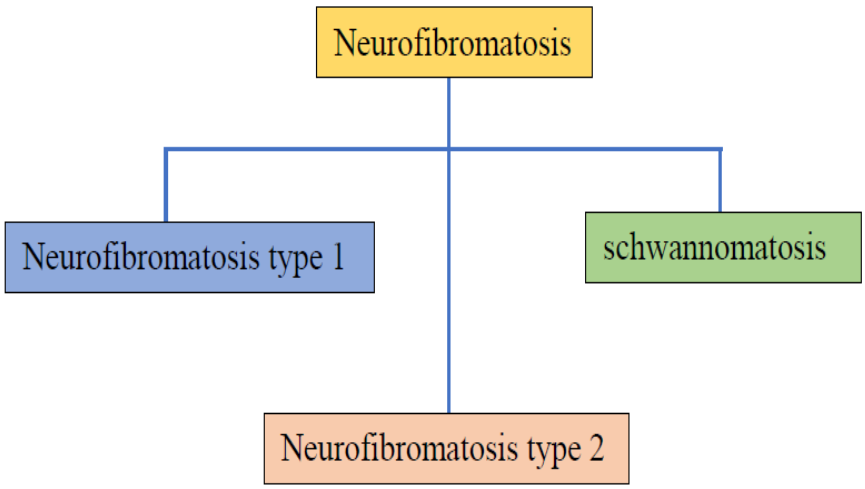


**Figure 1: Classfication of neurofibromatosis disorder.**

**History of neurofibromatosis**

Neurofibromatosis disorder was firstly described in 1822 in deaf person with characteristic symptom of tumor in the skull, dura mater, and brain[3] Neurofibromatosis type 1 and type 2 were not differentiated with each other and people use interchangable word for these two. In 1920, heritability of neurofibromatosis type 2 was described in three generation of family with characteristics symptoms of vestibular schwannomas.[6] In 1930 autosomal dominant

transmission was reported in family with 38 affected members across five generations.[7] In 1987 neurofibromatosis type 1 and type 2 were separated to each other through genetic linkage analysis.[8]

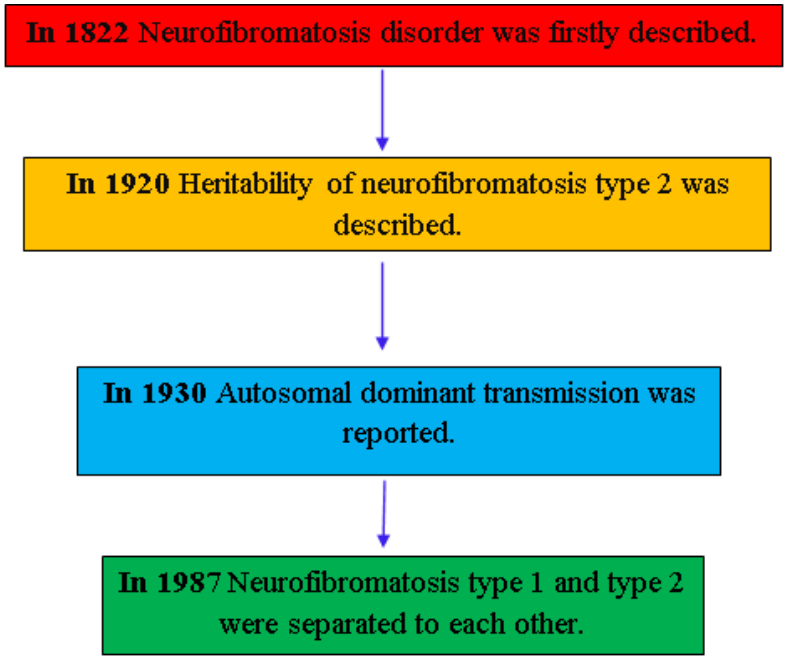


**Figure 2: This systematic diagram represent year in which these two disordered was separated with each other.**

**Pathogenesis of neurofibromatosis type 2**

NF 2 gene was identified as tumor suppresor in1993.This gene has 17 exon and associated with encoding the protein called Merlin (Moesin-ezrin-radixin like protein). Merlin is also known as schwannomin.[9] The main function associated with merlin protein is to supress the activity of tumor generation. Knudoson's two hit hypothesis of tumorigenesis, described that tumor formation initated when both alleles of tumor suppresor gene are inactivated.[10] Mutation in the gene are considered as major factor for inactivation of NF-2 gene. Mutation of gene can be due to de novo mutation of an allele or patient receive a mutated germline allele from their parents. De novo mutation of an allele occurs at the postzygotic stage of embryogenesis. So, after mutation in the NF-2 gene, tumor may be developed in many susceptible target organ (i.e Nervous system, eye, ear and skin).[11]

Major role of protein merlin is to supress the tumor formation and the mechanism by which merlin protein supress the tumor formation is interaction of merlin protein indirectly to it's membrane organization of protein (like CD44, epidermal growth factor receptor, layilin), cell to cell adhesion (like β catenin Є-cadherin β1 integrin, paxillin) and cytoskeletal architecture

(like βII spectrin, F-actin, Rho-guanosine triphosphatase) or through interaction with cytosolic protein (like phosphatidyl inositol 3-kinase enhancer long form, eukaryotic initiation factor 3 subunit c, transactivation responsive RNA binding protein, and Ral guanine-nucleotide dissociation stimulator). These interaction stop or reduce the regulation of various mitogenic signalling pathway like phosphoinostide-3 kinase (PI3K) and mitogen activated protein kinase (MAPK) signalling pathways.[12-16]

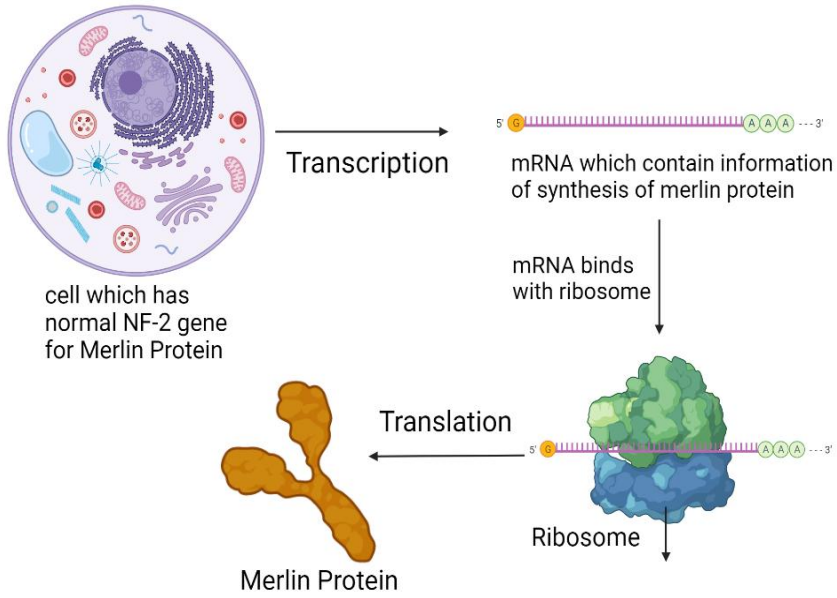


**Figure 3: Schematic diagram represent the Process of protein synthesis (Merlin protein).**

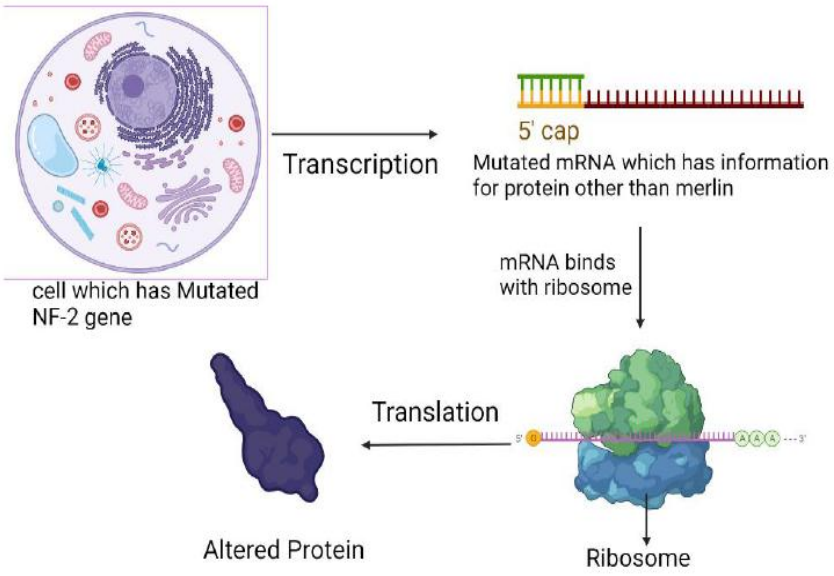


**Figure 4: Schematic representation shows that mutation in the NF-2 gene cause production of altered protein.**

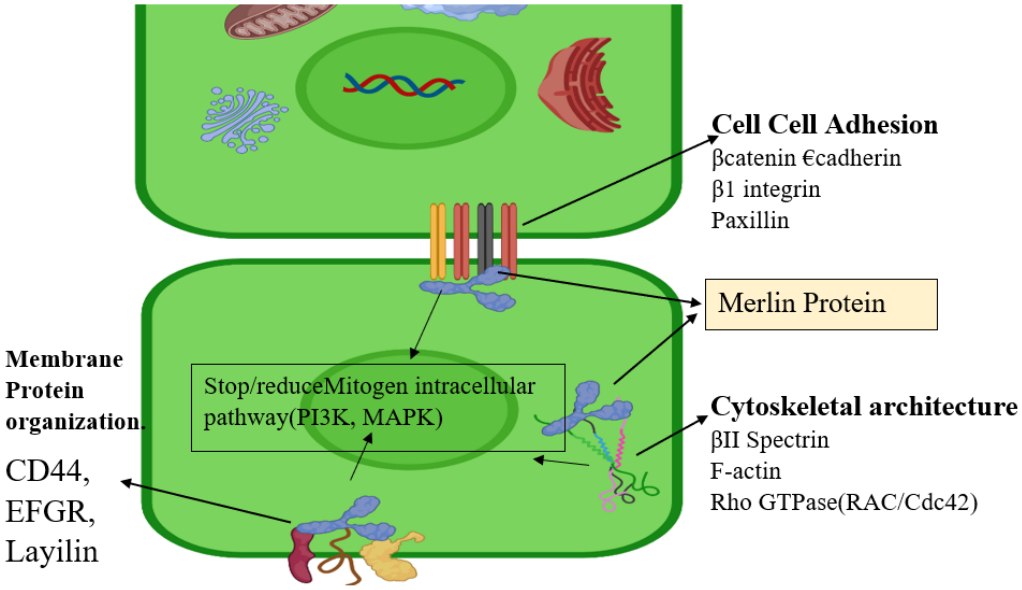


**Figure 5: Schematic representation Shows merlin protein interaction with different protein of cell that leads to stop in mitogenic signalling pathways.**

Severity of disease depends upon the site of mutation and types of mutation occur i.e in general, constitutional NF-2 non-sense or frame shift mutation occur then they cause severe disorder, whereas mis-sense mutation and inframe or large deletions are associated with mild types of disorder.[17] Splice site mutation are associated with variable disease severity. Although site of mutation also play a major role in severity of disease, if mutation occur b/w exon 1-5 then they cause more severe disease than mutation occur b/w exon 11-15.[18] Mortality rate of individual also related with types of mutation occur and site of mutation. Non-sense or frame shift mutation are having relatively high mortality rate than mis-sense mutation. Behaviour of specific tumor seems to vary independently of mutation type i.e it means types of mutation is also associated with types of tumor development.[19]

**Structure of protein merlin**

Merlin protein exist in individual in two isoform(I &II).[20] Out of two, only one isoform is responsible for tumor suppressing activity.[21] Merlin protein has a chain of 595 amino acid that is encoded by exon 1-15 and 17.[22] The merlin protein is composed of three domain: a tri-lobed amino terminal protein 4.1 ezrin-radixin-moesin(FERM) domain, an α-helical domain and a carboxy terminal domain.[23]

Phosphorylation of the protein is the main key regulator of tumor suppresor activity and merlin conformation. Phosphorylated merlin form a closed shape and dephosphorylation cause formation of open shape.[24] Open Shape is found to be active and closed shaped is

found to be inactive, phosphorylation at serine-518 amino acid is done by P21-activated kinases and cyclic AMP dependent-protein kinase A. This phosphorylation protect the intramolecular folding of protein.[25]

Dephosphorylation is done by myosin phosphatase-1 protein phosphatase-1δ. Dephosphorylation form closed structure of protein which is achieved by association of FERM domain with carboxyterminal domain. Closed form of protein is active in nature.[26]

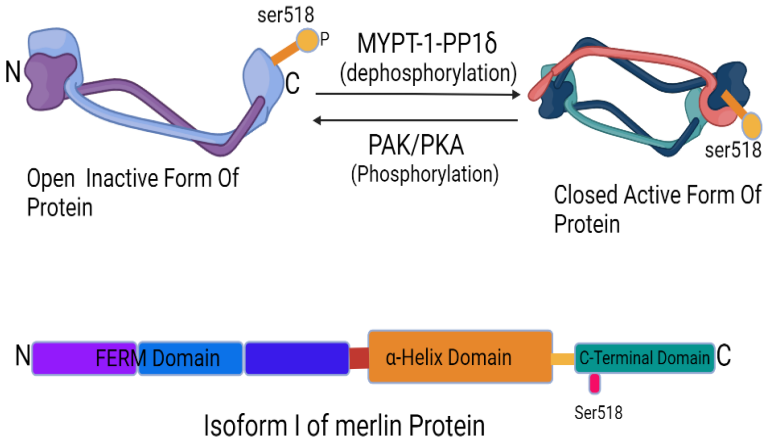


**Figure 6: schematic diagram shows the Phosphorylated and Dephosphorylated Structure of merlin protein and Isoform of merlin protein.**

**Epidemiology & Prevelance**

Application of modified diagnostic technique like MRI, Gene sequencing, and gene analysis method play very important role in the assesment of mutation in NF-2 gene which is important aspect in development of Neurofibromatosis type 2 disorder. The estimated incidence of neurofibromatosis type 2 disorder is around 1 in 37,000 per year with about half of affected individual represent the first case in the family as a result of new, dominant mutation. The disease prevelance rate is around 1 in 60,000.[27]

**Sign & Symptoms**

Suspected patient was showed sign and symptoms of development of lesions of nervous system, eye and skin. Bilateral vestibular nerve Schwannosis are the important charasteristics of NF type-2 disorder. NF type-2 patient can also develop schwannomas in other cranial, spinal, and peripheral nerve. Other nervous system tumors associated with this disorder include meningiomas, ependymomas, astrocytomas, and neurofibromas. But neurofibromas is mostly seen in NF type-1 patient, rather than NF type 2 patient. Peripheral neuropathies in

which tumor develop in nerve which is located outside of the brain and spinal cord is independently developed. Abnormalities in the eye can also be seen which include cataract, intracranial tumor and retinal hamartomas. Hearing loss is often unilateral initially, and can be accompained by tinnitus, dizziness, and imbalance.[28]

| Neurological lesions |
|---|
| Bilateral vestibular schwannomas |
| Other cranial nerve schwannomas |
| Intracranial meningiomas |
| Spinal Tumor |
| Extramedullary |
| Intramedullary |
| Peripheral Neuropathy |
| Opthalmological lesion |
| Cataracts |
| Epiretinal membrane |
| Retinal Hamartomas |
| Subcutaneous tumor |

| Cutaneous Lesions |
|---|
| Skin tumor |
| Skin plaque |
| Subcutaneous tumor |
| Intradermal tumor |

**Opthalmological lesion**

**Cutaneous lesion**

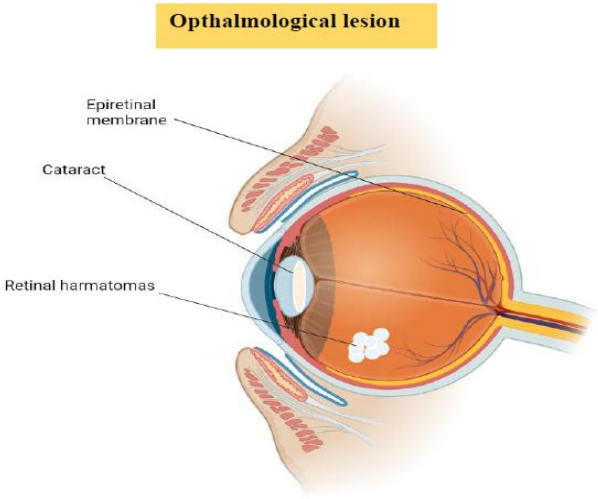


**Figure 8: This diagram demonstrate the different ocular lesion which is generally seen in NF-2.**

**Neurological lesion**

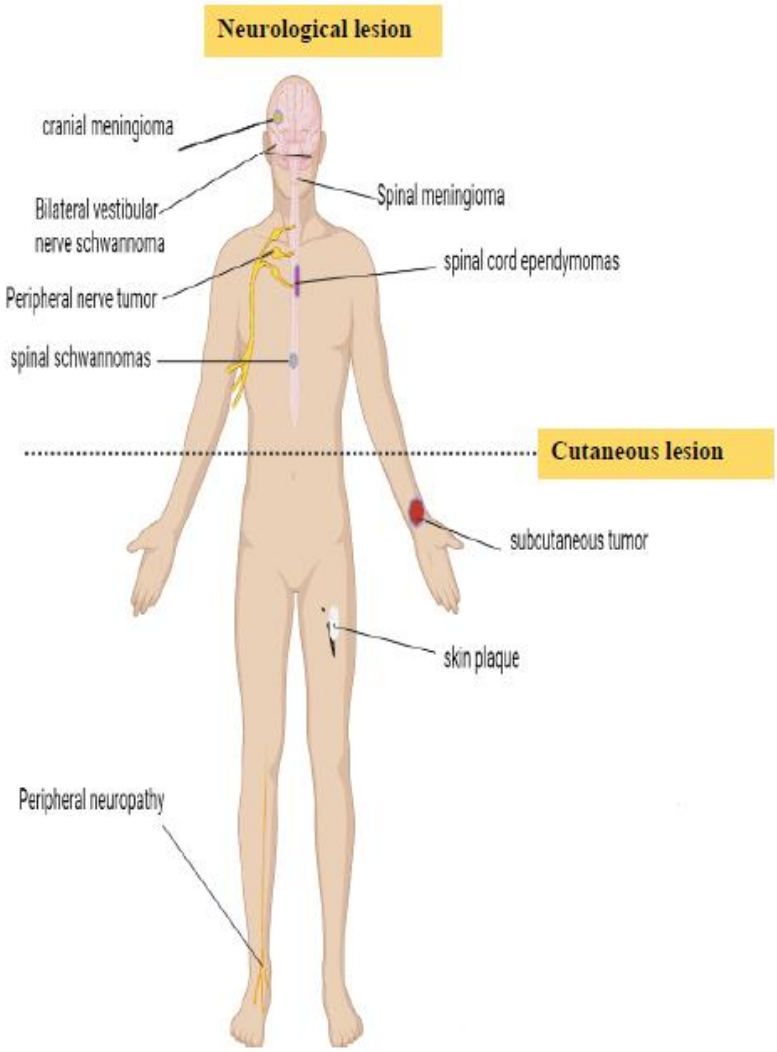


**Figure 7: Schematic diagram demonstrate the Different Neurological and Cutaneous lesion which is associated with NF-2.**

**Neurological description**

**1. Vestibular schwannomas**

Bilateral vestibular schwannomas are the characteristic features of neurofibromatosis type-2 disorde. It is identified in about 90-95% of neurofibromatosis patient.[29] More than 99% of vestibular schwannomas in NF-2 are benign and because of their location they represent a substantial cause of morbidity.[30] In the portion of cranial nerve VIII(vestibulocochlear nerve), generally sporadic vestibular schwannomas are more frequently originate but in this disorder it is noit present, only benign are observed.[31-32] Hearing loss and tinnituis are primarly symptom of NF-2 disorder and is present in 60% adult and 30% children population.it is found to be unilateral at onset of time.[33] In a retrospective study of auditory

analysis untreated ear will remain stable for upto 2-3 years, while some patient experience has to develop rapid hearing lossbut that is unrelated to tumor size or growthrate of tumor[34]. The tumor have highly variable growth rate and the rate of hearing loss often differe between ears of affected individuials.[35]

**2. Meningiomas**

Meningiomas is considered to ber second most common tumor that is associated with the patient on neurofibromatosis type-2 disorder. Generally two types of meningiomas tumor is seen, first one is intracranial meningioma, which is present in 40-60% of patient and second one is intradural extramedullary spinal meningiomas, that is present in about 20% of NF-2 patient.[36] Intracranial meningiomas are develop at a younger age and they are frequently multiple.[37]

Upto 20% children which has meningioma, they will have Neurofibromatosis type-2 disease. For better management, clinical screening and chekup is very necessary[38] The symptom produced in meningioma is depends upon size of tumor and their anatomical location. The presence of intracranial meningiomas is associated with a 2.5 fold rise in relative risk of mortality.[39]

**3. Spinal cord ependymomas**

Ependymomas is associated with spinal cord tumor. It account for more than 75% of intramedullary spinal cord tumor that is relatively associated with neurofibromatosis type-2 patient.[40] They are generally seen in 20-50% of patient but they having causing symptom in mostly 20% of patient[41] Intramedullary tumor occurs more frequently with non-sense or frame shift mutation in patient with NF type 2 disease. Sign & symptom related with spinal cord ependymomas depends upon their size and locatrion along the spinal axis. Patient with symptom at intramedulary spinal cord tumor is generally identified with recumbent backpain, weakness, sensory disturbance.[43]

**4. Peripheral neuropathy**

Peripheral neuropathy is developed in most of neurofiobromatosis patient during their life time. Many cases associated with tumor is responsible for compressing a nerve and some cases are not associated with tumor. A result of study showed that 65% of patient develop sign of neural dysfunction in the absence of compressive tumor.[44] Non tumor related peripheral neuropathy is unrelated to tumor in NF-2, came from report in which patient with

focal amyotrophy, distal symmetric sensorimotor neuropathy, or mononeuropathy multiples have been identified. Age of onset ranged from 7 to 41 years and the duration of symptoms ranged from 3 month to 50 years.[45]

**Ocular or opthalmological description**

In patient with neurofibromatosis type 2 disease, ocular lesion cataract, epiretinal membrane and retinal hamartomas can be seen. Cataract is usually seen in 60-80% of NF-2 patient[46] Cataract are identified in older person and it can be considered as specific to this disorder. Cataract interfere with vision in 10-30% of patient[47] Epiretinal membrane are translucent, semi translucent or whitish grey membrane with prominent whitish edges demarcating their borders. These membrane are not usually cause of visual activity loss[48] Retinal hamartomas are benign, glial tumor of the retinal nerve fiber layer that arise from retinal astrocyte. They are associated with NF-2 disease and identified in 6-22% of patient. They are frequently identified in the macula that frequent reduce the visual activity.[49]

**Cutaneous description**

Cutaneous manifestation includes skin plaque, subcutaneous tumor, and intradermal tumors.[50] These are present in about 70% patient of neurofibromatosis type 2 disease. Most skin tumor are schwannomas, neurofibromas and mixed tumor have been occasionally identified.[51]

Skin plaque is an elevated, solid, roughened, red area that are less than 2cm in diameter. It display slightly hyperpigmentation and hyper trichosis.[52] These are majorly identified in 40-50% of patient of under 10 years.[53]

Subcutaneous tumor developalong peripheral nerve and it is present in 45-50% of patient. Intradermal tumor are less frequently observed than other lesions of neurofibromatosis type 2 disorder. They are present in 40-45% of patient.[54]

**Diagnosis of neurofibromatosis type 2 disorder**

Diagnosis of neurofibromatosis disease is based on the clinical manifestation. Expert healthcare know about the family history of the suspected NF-2 patient, but many of the patient are without a family history of NF-2 but they have symptoms of this disease. They are identified by MRI (magnetic resonance imaging), by this method scanning of brain and spinal cord is done and determine the location of tumor. Vestibular schwannomas vividly enhance

and are best seen by high resolution contrast-enhanced, T1-weighted MRI. T2-Weighted or fluid-attenuated inversion recovery(FLAIR) MRI sequences are used to accurately quantify peritumoral oedema and cysts.[55]

Hearing test, vision test is also performed to identified symptoms related to the NF-2 disease. Genetic testing also provide evidence about the presence of NF-2 mutated gene.

**Management approach related to neurofibromatosis disorder**

The exact cure treatment for NF-2 disorder is still unknown. The symptoms of this disorder can be managed by several medicine like lapatinib, a tyrosine kinase that inhibit EGFR receptor, and a monoclonal antibody called bevacizumab that inhibit vascular endothelial growth.

Vestibular schwannomas tumor can be managed by complete surgical resection. Small vestibular schwannomas(less than 3 cm in diameter) is removed by surgery, they can preserve serviceable hearing and normal function of facial nerve. No direct genotype-phenotype association for hearing loss in neurofibromatosis type 2 has been established, and tumor size and growth rate do not predict hearing status; hence regional practice pattern and individual practitioner experience seems to most influence management of vestibular schwannomas in neurofibromatosis type 2.[56]

## CONCLUSION

Neurofibromatosis is an autosomal dominant multiple neoplasia syndrome, which is arised due to dysfunction of protein called Merlin. Various clinical characteristics emerges out which reduce the quality of life and increase complication in patient. Surgical management is used for the removal of several tumor, but the exact cure treatment for this disorder is still unknown. The development of novel therapy in future will give results in much more effective treatment.

## REFERENCES

1. Riccardi VM. Von Recklinghausen neurofibromatosis. N Engl J Med, 1981; 305: 1617-27.
2. Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, Rubenstein A, Viskochil D. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis, 1997; 2, 278: 51-7.

3. Evans DGR, Moran A, King A, Saeed S, Gurusinghe N, Ramsden R. Incidence of vestibular schwannoma and neuro fi bromato sis 2 in Incidence of vestibular schwannoma and neuro fi bromato sis 2 in the North West of England over a 10-year period: higher incidence than previously thought. Otol Neurotol, 2005; 26: 93–97.
4. McClatchey AI. Neurofibromatosis Annu Rev Pathol, 2007; 2: 191-216.
5. Evans DGR, Huson SM, Donnai D, et al. A clinical study of type 2 neuro fi bromato sis. neuro fi bromato sis. Q J Med, 1992; 84: 603–18.
6. Feiling A, Ward E. A familial form of acoustic tumour. BMJ, 1920; 10: 496–97.
7. Gardner WJ, Frazier CH. Bilateral acoustic neurofi bromas: a clinical 55 Gardner WJ, Frazier CH. Bilateral acoustic neurofi bromas: a clinical study and fi eld survey of a family of fi ve generations with bilateral deafness in thirty-eight members. Arch Neurol Psychiatr, 1930; 23: 266–302.
8. Rouleau GA, Wertelecki W, Haines JL. Genetic linkage of bilateral acoustic neuro fi bromato sis to a DNA marker on chromosome 22. Nature, 1987; 329: 246–48.
9. Rouleau GA, Merel P, Lutchman M, et al. Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fi bromatosis type 2. Nature, 1993; 363: 515–21.
10. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA, 1971; 68: 820–23.
11. Bianchi AB, Hara T, Ramesh V, et al. Mutations in transcript isoforms of the neuro fi bromato sis 2 gene in multiple human tumour isoforms of the neuro fi bromato sis 2 gene in multiple human tumour types. Nat Genet Nat Genet, 1994; 6: 185–92.
12. Ragge NK, Baser ME, Klein J, et al. Ocular abnormalities in neurofi bromato sis 2. fi bromato sis 2. Am J Ophthalmol Am J Ophthalmol, 1995; 1.
13. Ragge NK, Baser ME, Riccardi VM, Falk RE. The ocular presentation of neuro fi bromato sis 2. of neuro fi bromato sis 2. Eye, 1997; 11: 12–18.
14. Maccollin M, Mautner VF. The diagnosis and management of neuro fi bromato sis 2 in childhood. neuro fi bromato sis 2 in childhood. Semin Pediatr Neurol, 1998; 5: 243–52.
15. Mautner VF, Lindenau M, Baser ME, Kluwe L, Gottschalk J. Skin abnormalities in neuro fi bromato sis 2. abnormalities in neuro fi bromato sis 2. Arch Dermatol, 1997; 133: 1539–43.
16. Baser ME, Friedman JM, Aeschliman D, et al. Predictors of the risk of mortality in neuro fi bromato sis 2. of mortality in neuro fi bromato sis 2. Am J Hum Genet, 2002; 71: 715–23.

17. Parry DM, MacCollin MM, Kaiser-Kupfer MI, et al. Germ-line mutations in the neuro fi bromato sis 2 gene: correlations with disease severity and retinal abnormalities. Am J Hum Genet, 1996; 59: 529–39.
18. Baser ME, Kuramoto L, Woods R, et al. The location of constitutional neuro fi bromato sis 2 (NF2) splice site mutations constitutional neuro fi bromato sis 2 (NF2) splice site mutations is associated with the severity of NF2. is associated with the severity of NF2. J Med Genet J Med Genet, 2005; 42: 540–46.
19. Baser ME, Makariou EV, Parry DM. Predictors of vestibular schwannoma growth in patients with neuro fi bromato sis type 2. schwannoma growth in patients with neuro fi bromato sis type 2. J Neurosurg, 2002; 96: 217–22.
20. Bianchi AB, Hara T, Ramesh V, et al. Mutations in transcript isoforms of the neuro fi bromato sis 2 gene in multiple human tumour isoforms of the neuro fi bromato sis 2 gene in multiple human tumour types. Nat Genet Nat Genet, 1994; 6: 185–92.
21. Sherman L, Xu HM, Geist RT, et al. Interdomain binding mediates tumor growth suppression by the NF2 gene product. tumor growth suppression by the NF2 gene product. Oncogene Oncogene, 1997; 15: 2505–09.
22. K, Heiska L, Gronholm M, Renkema GH, Carpen O. Cyclic AMP-dependent protein kinase phosphorylates merlin at serine 518 AMP-dependent protein kinase phosphorylates merlin at serine 518 independently of p21-activated kinase and promotes merlin-ezrin independently of p21-activated kinase and promotes merlin-ezrin heterodimerization. heterodimerization. J Biol Chem J Biol Chem, 2004; 279: 18559–66.
23. Kissil JL, Johnson KC, Eckman MS, Jacks T. Merlin phosphorylation by p21-activated kinase 2 and eff ects of phosphorylation on merlin by p21-activated kinase 2 and eff ects of phosphorylation on merlin localization. localization. J Biol Chem J Biol Chem, 2002; 277: 10394–99.
24. Jin H, Sperka T, Herrlich P, Morrison H. Tumorigenic transformation by CPI-17 through inhibition of a merlin transformation by CPI-17 through inhibition of a merlin phosphatase. phosphatase. Nature, 2006; 442: 576–79.
25. Shaw RJ, Paez JG, Curto M, et al. The Nf2 tumor suppressor, merlin, functions in Rac-dependent signaling. functions in Rac-dependent signaling. Dev Cell Dev Cell, 2001; 1: 63–72.
26. Rong R, Surace EI, Haipek CA, Gutmann DH, Ye K. Serine 518 phosphorylation modulates merlin intramolecular association and phosphorylation modulates merlin intramolecular association and binding to critical eff ectors important for NF2 growth

suppression. binding to critical eff ectors important for NF2 growth suppression. Oncogene Oncogene, 2004; 23: 8447–54.

27. Antinheimo J, Sankila R, Carpén O, Pukkala E, Sainio M, Jääskeläinen J. Population-based analysis of sporadic and type 2 neurofibromatosis-associated meningiomas and schwannomas. Neurology, 2000; 54: 71–76.
28. Parry DM, Eldridge R, Kaiser-Kupfer MI, Bouzas EA, Pikus A, Patronas N. Neuro fi bromato sis 2 (NF2): clinical characteristics of 63 aff ected individuals and clinical evidence for heterogeneity. Am J Med Genet, 1994; 52: 450–61.
29. Mautner VF, Lindenau M, Baser ME, et al. The neuroimaging and clinical spectrum of neuro fi bromato sis 2. and clinical spectrum of neuro fi bromato sis 2. Neurosurgery Neurosurgery, 1996; 38: 880–86.
30. Baser ME, Evans DGR, Jackler RK, Sujansky E, Rubenstein A. Neurofibromato sis 2, radiosurgery and malignant nervous system tumours. fi bromato sis 2, radiosurgery and malignant nervous system tumours. Br J Cancer Br J Cancer, 2000; 82: 998.
31. Brackmann DE, Fayad JN, Slattery Iii WH, et al. Early proactive management of vestibular schwannomas in neuro fi bromato sis management of vestibular schwannomas in neuro fi bromato sis type 2. Neurosurgery, 2001; 49: 274–83.
32. Khrais T, Romano G, Sanna M. Nerve origin of vestibular schwannoma: a prospective study. schwannoma: a prospective study. J Laryngol Otol J Laryngol Otol, 2008; 122: 128–31.
33. Nunes F, MacCollin M. Neuro fi bromato sis 2 in the pediatric population. population. J Child Neurol Child Neurol, 2003; 18: 718–24.
34. Masuda A, Fisher LM, Oppenheimer ML, Iqbal Z, Slattery WH. Hearing changes after diagnosis in neuro fi bromato sis type 2. Hearing changes after diagnosis in neuro fi bromato sis type 2. Otol Neurotol Otol Neurotol, 2004; 25: 150–54.
35. Baser ME, Mautner VF, Parry DM, Evans DGR. Methodological issues in longitudinal studies: vestibular schwannoma growth rates in issues in longitudinal studies: vestibular schwannoma growth rates in neuro fi bromato sis 2. neuro fi bromato sis 2. J Med Genet J Med Genet, 2005; 42: 903–06.
36. Patronas NJ, Courcoutsakis N, Bromley CM, Katzman GL, MacCollin M, Parry DM. Intramedullary and spinal canal tumors MacCollin M, Parry DM. Intramedullary and spinal canal tumors in patients with neuro fi bromato sis 2: MR imaging fi ndings and in patients with neuro fi bromato sis 2: MR imaging fi ndings and correlation with genotype. correlation with genotype. Radiology Radiology, 2001; 218: 434–42.

37. Nunes F, MacCollin M. Neuro fi bromato sis 2 in the pediatric population. population. J Child Neurol Child Neurol, 2003; 18: 718–24.
38. Evans DGR, Birch JM, Ramsden RT. Paediatric presentation of type 2 neuro fi bromato sis. neuro fi bromato sis. Arch Dis Child Arch Dis Child, 1999; 81: 496–99.
39. Baser ME, Friedman JM, Aeschliman D, et al. Predictors of the risk of mortality in neuro fi bromato sis 2. of mortality in neuro fi bromato sis 2. Am J Hum Genet, 2002; 71: 715–23.
40. Lee M, Rezai AR, Freed D, Epstein FJ. Intramedullary spinal cord tumors in neuro fi bromato sis. tumors in neuro fi bromato sis. Neurosurgery, 1996; 38: 32–37.
41. Rennie ATM, Side L, Kerr RSC, Anslow P, Pretorius P. Intramedullary tumours in patients with neuro fi bromato sis type 2: Intramedullary tumours in patients with neuro fi bromato sis type 2: MRI features associated with a favourable prognosis. Clin Radiol, 2008; 63: 193–200.
42. Patronas NJ, Courcoutsakis N, Bromley CM, Katzman GL, MacCollin M, Parry DM. Intramedullary and spinal canal tumors MacCollin M, Parry DM. Intramedullary and spinal canal tumors in patients with neuro fi bromato sis 2: MR imaging fi ndings and in patients with neuro fi bromato sis 2: MR imaging fi ndings and correlation with genotype. correlation with genotype. Radiology Radiology, 2001; 218: 434–42.
43. Ferrante L, Mastronardi L, Celli P, Lunardi P, Acqui M, Fortuna A. Intramedullary spinal cord ependymomas – a study of 45 cases with long-term follow-up. Acta Neurochir(Wien), 1992; 119: 74–79.
44. AD, Hein C, Schroder JM, Ludolph AC, Hanemann CO. Occurrence and characterization of peripheral nerve Occurrence and characterization of peripheral nerve involvement in neuro fi bromato sis type 2. involvement in neuro fi bromato sis type 2. Brain, 2002; 125: 996–1004.
45. Kilpatrick TJ, Hjorth RJ, Gonzales MF. A case of neuro fi bromato sis 2 presenting with a mononeuritis multiplex. J Neurol Neurosurg Psychiatry, 1992; 55: 391–93.
46. Shaw RJ, Paez JG, Curto M, et al. The Nf2 tumor suppressor, merlin, functions in Rac-dependent signaling. functions in Rac-dependent signaling. Dev Cell Dev Cell, 2001; 1: 63–72.
47. Bouzas EA, Parry DM, Eldridge R, Kaiser-Kupfer MI. Visual impairment in patients with neuro fi bromato sis 2. impairment in patients with neuro fi bromato sis 2. Neurology, 1993; 43: 622–23.

48. Meyers SM, Gutman FA, Kaye LD, et al. Retinal changes associated with neuro fi bromato sis 2. with neuro fi bromato sis 2. Trans Am Ophthalmol Soc Trans Am Ophthalmol Soc, 1995; 93: 245–57.
49. Ragge NK, Baser ME, Klein J, et al. Ocular abnormalities in neurofi bromato sis 2. fi bromato sis 2. Am J Ophthalmol Am J Ophthalmol, 1995; 120: 634–41.
50. Mautner VF, Lindenau M, Baser ME, Kluwe L, Gottschalk J. Skin abnormalities in neuro fi bromato sis 2. abnormalities in neuro fi bromato sis 2. Arch Dermatol, 1997; 133: 1539–43.
51. Wiestler OD, Von Siebenthal K, Schmitt HP, Feiden W, Kleihues P. Distribution and immunoreactivity of cerebral micro-hamartomas in bilateral acoustic neuro fi bromato sis (neuro fi bromato sis 2). in bilateral acoustic neuro fi bromato sis (neuro fi bromato sis 2). Acta Neuropathol, 1989; 79: 137–43.
52. Martuza RL, Eldridge R. Neuro fi bromato sis 2. (Bilateral acoustic neuro fi bromato sis). neuro fi bromato sis). N Engl J Med, 1988; 318: 684–88.
53. Ragge NK, Baser ME, Riccardi VM, Falk RE. The ocular presentation of neuro fi bromato sis 2. of neuro fi bromato sis 2. Eye, 1997; 11: 12–18.
54. Mautner VF, Lindenau M, Baser ME, Kluwe L, Gottschalk J. Skin abnormalities in neuro fibromatosis 2. abnormalities in neuro fi bromato sis 2. Arch Dermatol, 1997; 133: 1539–43.
55. Sobel RA, Wang Y. Vestibular (acoustic) schwannomas: histologic features in neuro fi bromato sis 2 and in unilateral cases. features in neuro fi bromato sis 2 and in unilateral cases. J Neuropathol Exp Neurol J Neuropathol Exp Neurol, 1993; 52: 106–13.
56. Brackmann DE, Fayad JN, Slattery Iii WH, et al. Early proactive management of vestibular schwannomas in neuro fi bromato sis management of vestibular schwannomas in neuro fi bromato sis type 2. Neurosurgery, 2001; 49: 274–83.