Clinical and ophthalmological manifestations in Neurofibromatosis Type1- An overview

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Abstract

Neurofibromatosis type 1 is an autosomal dominant, multisystem disorder affecting NF1 gene on chromosome 17. Ophthalmological manifestations of NF1 include lisch nodules, plexiform neurofibromas, malignant peripheral nerve sheath tumor, optic nerve glioma, choroid hamartomas, retinal tumors, congenital glaucoma and prominent corneal nerves. The diagnosis is based on the clinical features. Careful monitoring of the course of the disease along with management by multidisciplinary approach is necessary. Symptomatic neurofibromas and malignant peripheral nerve sheath tumors are treated by complete surgical removal. Optic nerve glioma treatment is not required as long as they are asymptomatic and clinically stable. The treatment of congenital glaucoma includes both medical and surgical therapy. Visual prognosis depends primarily on the presence or absence of optic pathway glioma or congenital glaucoma. Prenatal counselling is necessary as offspring of an affected individual has 50% risk of inheriting the autosomal dominant disease. This paper describes the variety of ocular and extraocular findings in NF1and the ophthalmologist's role in diagnosis and management of NF1.

Keywords: Lisch nodules, Optic nerve glioma, Neurofibromatosis type 1

Introduction

Phakomatoses is a neurocutaneous syndrome with autosomal dominant inheritance. Neurofibromatosis is a phakomatoses which primarily affects cell growth of neural tissue. It consists of two distinct genetic types and is characterized by occurrence of neuroectodermal tumors in multiple organs in both the types. These two forms of Neurofibromatosis (NF) are termed: Neurofibromatosis type-1 and Neurofibromatosis type-2.

Neurofibromatosis type 1 (NF1) previously known as vonRecklinghausen disease, is a multisystem disorder affecting 1 in 2600-3000 people.(1) This is an autosomal dominant (AD) disease with irregular penetrance and variable expressivity. The gene locus has been found in chromosome 17q11.(1) The clinical features commonly noted are skin pigmentation, Lisch nodules, and multiple benign neurofibromas, but may present with learning disabilities and skeletal abnormalities or central nervous system (CNS) tumors. The average life expectancy is reduced by 15 years in NF1 cases.(2)

Pathogenesis

The *NF1* gene protein product, neurofibromin, is a tumor suppressor expressed in many cells, primarily in neurons, glial cells, schwann cells and early in melanocyte development.(1) This protein is a regulator of ras guanosine triphosphatase activity (GTPase-activating protein, GAP). It acts as a regulator of signals for cell proliferation and differentiation by causing activation of GTPase which in turn inhibits the function of Ras and tyrosine kinase.(3) The functional loss of neurofibromin causes uncontrolled cell proliferation and thereby increases the risk for neoplasm. Schwann cells in neurofibromas, and melanocytes in café-au-lait macules (CALM) have a mutation in both *NF1* alleles.

Diagnostic criteria

National Institutes of Health (NIH) Consensus Conference in 1987 developed the criteria for diagnosis of NF1 for routine clinical use. Individual with presence of two or more of these manifestations fulfils the NIH diagnostic criteria.(4)

- Six or more cafe'-au-lait spots:
  - >5 mm in greatest diameter at prepubertal age and
  - >15 mm in greatest diameter in adults
- Lisch nodules in iris two or more in number
- Axillary or inguinal freckling
- Two or more neurofibroma of any type
- One plexiform neurofibroma
- Presence of optic nerve glioma
- A distinctive osseous lesion such as sphenoidal dysplasia or thinning of cortex of long bones with or without pseudoarthrosis.
- Presence of NF1 in first-degree relative.

NIH criteria are also useful for diagnosis in children above 4 years.

Natural History of Disease Manifestations

A. **Systemic features**:

1. **Cutaneous features**

a. **Café'-au-lait macules (CALM):** Cafe´-au-lait spots are usually the first manifestation of NF1to be observed. (Fig. 1). Nearly all affected

individuals develop multiple café au lait spots and by the age of 7 years 90% of cases have intertriginous freckling.[5] CALM are flat, uniformly brown with size varying from 0.5 to 12 cm. The colour is roughly two shades darker than the uninvolved skin. Histologically, CALMs have an increased number of melanocytes with increased concentration of melanin and giant melanosomes.

b. **Skinfold freckling:** Skinfold freckling (**Crowe's sign**) is very specific and considered as a pathognomonic sign. It mostly involves areas with minimal exposure to sunlight especially in axilla and groin.

2. **Neurofibromas:** Neurofibromas occur on the course of the peripheral and autonomic nerves. However, they never develop on pure motor nerves. Histopathology reveals units of proliferating axons, schwann cells, and fibroblasts, with each unit surrounded by a perineural sheath. They exhibit 'button-hole sign' that is invagination into skin occurs with pressure. It has been classified into following subtypes.

a. Discrete cutaneous

b. **Nodular plexiform:** It feels like 'bag of worms' on palpation. Eyelid involvement gives a characteristic 'S shaped ptosis.'

c. **Diffuse plexiform:** These infiltrate widely and deeply into surrounding structures.

The most frequent malignancy in NF1, the malignant peripheral nerve sheath tumor occurs in 8-12% of NF1 patients, and usually arise from pre-existing plexiform neurofibromas (PN).[6] Onset of pain or rapid growth in a stable PN is an indicator of malignant transformation. Pruritus is common in NF1 due to increased number of mast cells found in neurofibromas.

3. **Intracranial tumours:** Brain tumors more commonly occur in children and young adults with NF1 in the form of gliomas of the brainstem or cerebellum and have a less aggressive course.[7] It also occurs in at least 20% of cases who have optic nerve glioma or previously treated with radiation.[8]

4. **Neurologic/Psychologic:** Headaches, learning disabilities, attention deficit hyperactivity (ADH) disorder and seizures may occur. Most individuals with NF1 have normal intelligence, but in 50% to 75% cases learning disabilities can occur.[9] Social, behavioural and personality disorders are more marked in children with NF1.[10,11]

In at least 60% of T2-weighted MRI of the brain reveals an unidentified bright objects (UBOs), which are sometimes called "T2 hyperintensities" in cases of NF1, but the clinical significance is uncertain.[12] Presence of these may have a correlation with learning disorders in children but there are few evidence based studies to prove this hypothesis.

5. **Vasculopathy:** Essential hypertension commonly occurs in NF1. The other causes for hypertension are due to renal artery stenosis, coarctation of the aorta or pheochromocytoma; while in children it has a renovascular mechanism.[13,14] Cerebrovascular abnormalitiesmay present in as stenoses or occlusions of the internal carotid and cerebral arteries. Cerebral angiography shows "puff of smoke" (moyamoya) appearance which are the stenotic areas surrounded by small telangiectatic vessels.[15] Moyamoya develops more frequently in children with NF1 after cranial irradiation for primary brain tumors.[16]

6. **Endocrine disorder:** Precocious puberty and pheochromocytoma may occur in patients with NF1.[17]

7. **Skeletal abnormalities:** Dysplasia of long bones mainly affecting the tibia is seen in 1-4% of children. Sphenoid wing dysplasia (Fig. 2) and dystrophic scoliosis are other common musculoskeletal features in NF1.[18] Generalized osteopenia and frank osteoporosis are also more common in NF1.[19,20]

8. **Malignant tumors:** Patients with NF1 are 5-15% at risk of developing malignancy and most frequent neoplasm is malignant peripheral nerve sheath tumors.[6,21] These malignancies develop at a younger age and have a poorer prognosis. Other associated malignancies that occur in NF1are Juvenile myelomonocytic leukemia (JMML)and Gastrointestinal stromal tumors (GIST)[22,23] Risk of developing breast cancer is 3.5 to 5 fold, in women with NF1 above 50years.[24]

B. **Ophthalmological manifestations:** Ocular features of NF1 include lisch nodules, PN, optic nerve glioma, choroid hamartomas, retinal tumors, congenital glaucoma and prominent corneal nerves.[3,7,25] Loss of vision due to optic nerve glioma warrants early diagnosis of NF1.

a. **Lisch nodules:** Lisch nodules are the most common ocular pathognomic markers for NF-1and usually do not cause any complication (Fig. 3). These are benign, yellow to brown colored, well-defined, dome-shaped elevations and histologically are melanocytic hamartomas. Lisch nodules are usually specific for NF-1 and mostly bilateral. They are usually not visible at birth and with age the prevalence gradually increases.[26] Kordić *et al* demonstrated incidence of lisch nodules to be 78% in 132 patients ranging from 0–16 years.[27]

b. **Plexiform neurofibromas:** PN infiltrate the orbit, temporal region or eyelids and can be vision threatening at times. Orbitotemporal neurofibromas can cause strabismus, ptosis, proptosis and change in globe length. Amblyopia may result secondary to ptosis and anisometropia.[26,28] Characteristic features of PN of the eyelid are thickening of upper lid, S-shaped ptosis and "bag of worm" like sensation. They may undergo malignant transformation to peripheral nerve sheath tumors.

c. **Optic pathway glioma (OPG):** Approximately 15-40% of children with NF-1have gliomas affecting the optic nerve, chiasma or optic tract.[29] Presence of bilateral optic nerve gliomas are almost pathognomonic feature of NF-1. These are locally invasive and slow growing tumors with low grade malignant potential and histologically are mostly pilocytic astrocytoma.[30] It presents mostly in first decade with decrease in visual acuity, painless proptosis, color vision defect, an afferent pupillary defect, strabismus, nystagmus and optic atrophy. A large lesion may cause compression of optic chiasma. Hypothalamic symptoms may also occur. Massive lesions may compress the third ventricle, resulting in obstructive hydrocephalus, headache, nausea, and vomiting.[31] Precocious puberty, especially in a child with NF1, should raise the suspicion of an OPG. Many NF1-associated OPGs are discovered incidentally when a brain MRI is ordered.

d. **Choroid hamartomas:** These are flat, ill-defined lesions and usually occur in the posterior pole. They contain neuronal and melanocytic components.

e. **Retinal tumors:** Astrocytic hamartomas, retinal capillary hemangiomas and combined hamartomas of the retina and retinal pigment epithelium are the common retinal tumors of NF1.

f. Absence of the greater wing of the sphenoid bone may lead to pulsatile proptosis.

g. **Glaucoma:** Congenital glaucoma is relatively rare and usually unilateral. Obstruction of aqueous outflow by neurofibromatous tissue in the angle is the primary pathology. Secondary angle-closure can also occur by forward displacement of the peripheral iris associated with neurofibromatous thickening of the ciliary body. Associated congenital ectropion uveae may be found. About 50% of patients have an ipsilateral plexiform neurofibroma of the upper eyelid or exhibit facial hemiatrophy. Retinal vasoproliferative tumours and neovascular glaucoma has also been found in NF1.[32,33,34]

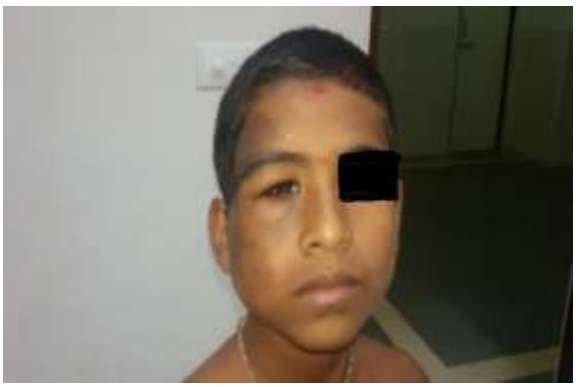

Fig. 1: A 10 year boy with multiple café-au-lait spots on right side of face and S-shaped ptosis

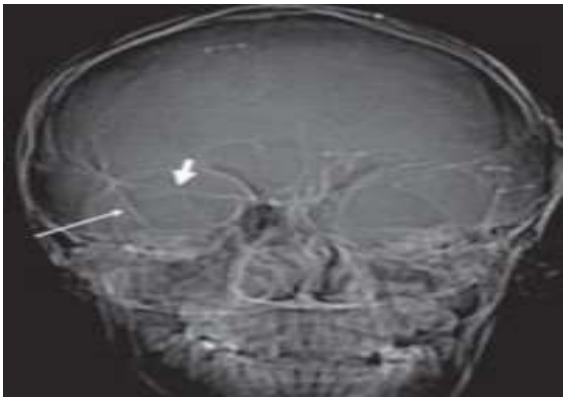

Fig. 2: Frontal computed tomography (CT) scan showing the bare orbit sign, with absence of the greater wing of the left sphenoid bone, in a patient with neurofibromatosis type 1. (Source: Radiopaedia.org)

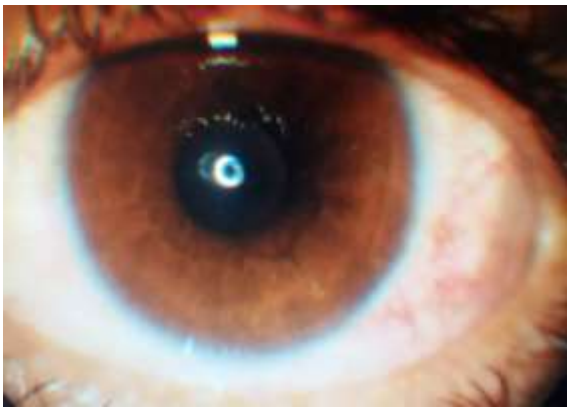

Fig. 3: Lisch nodules seen as yellowish, dome shaped lesions more marked in the lower iris between 5-6 clock hours

Investigations

These are advised in symptomatic cases and have an individualized approach.

- X ray of chest and long bones are done in cases of scoliosis or any skeletal abnormalities.
- CT scan of brain and orbit is helpful to rule out OPG and brain tumors. A typical fusiform appearance with kinking has been found on imaging. MRI which shows greater soft tissue definition is helpful in early detection of gliomas.[35]
- **Genetic testing** has increased our ability to make the diagnosis in uncertain cases or when prenatal or pre implantation genetic diagnosis is desired.

Management

NF1 is a multisystem disorder requiring management by multiple disciplines. Presence or absence of optic pathway glioma or congenital glaucoma is a visual prognosis indicator.[29,36] Genetic counselling plays an important role. It is essential to examine parents to determine whether they are affected

as half of all cases are familial. Along with physical examination looking for signs of malignancy, the social skills, learning ability and behavioural disorders must also be evaluated.[37]

Surgical indications of neurofibroma are those which are symptomatic, enlarging, or with signs of malignant transformation.[38] PN producing mechanical ptosis or cosmetic deformity are indications for surgical removal. However, due to the infiltrative nature of these lesions, complete excision is usually impossible and recurrence is quite common. The preservation of the nerve is a major challenge during surgery because neurofibromas are non- encapsulated tumors containing all nerve elements, i.e., axons, sheath cells, and connective tissues.[39,40,41] Radiotherapy is a contraindication due to risk of malignant transformation.[42] Sirolimus, an inhibitor of mTOR (regulator of cell growth in nervous system) plays a role in reducing pain associated with PN.[43] Imatinibmesylate has been demonstrated to reduce the size of a PN by interfering with c-kit receptor activity and thereby inhibiting stem cell factor's growth-potentiating effects.[44] Some recent studies have shown promising results with radiofrequency therapy for treatment of facial diffuse plexiform neurofibromas and café-au-lait spots.[45,46]

Medications that areused routinely for treatment of ADH disorder, depression, or anxiety are also effective in patients with NF1. Recently, improved cognition in NF1 has been reported in mice following treatment with lovastatin, an HMG-CoA reductase inhibitor.[47] However, Simvastatin (another HMG-CoA reductase inhibitor) failed to show any significant improvement after 3 months of treatment in the cognitive abilities of children with NF1, however this is still an ongoing area of investigation.[48]

Asymptomatic and clinically stable optic gliomas do not need treatment. For progressive optic pathway gliomas chemotherapy is considered as the treatment of choice.[49] Complete surgical resection has been reserved as a cosmetic palliative therapy for isolated optic nerve glioma in a blind eye. Radiotherapy is generally avoided as there are chances of inducing malignancy or Moyamoya syndrome.[42,50] However, in patients with postchiasmatic gliomas improvement in survival has been studied after radiation therapy.[51] Inhibitors of BRAF, MEK, and mTOR are already in clinical trials. Bevacizumab, has shown positive response in recurrent/refractory OPG[52] and are being evaluated in larger studies.

Medical therapy and surgical intervention (goniotomy, trabeculotomy, trabeculectomy, and aqueous shunting devices) may be necessary to treat glaucoma.

The median life expectancy of NF1 patients are generally 8 years lower than that of normal individuals. Malignancy and vasculopathy have attributed to the common causes of death.[53,54] Generally annual physical examination is recommended to monitor the disease progression. Kimberly et al recommended annual ophthalmologic examinations in children and less frequently in adults and regular developmental assessment in children. Regular blood pressure monitoring and magnetic resonance imaging was done in cases of suspected intracranial and other tumors.[55] To people who are undergoing family planning genetic counseling and chances of involvement of the offspring's should be explained.

Conclusion

In conclusion a multidisciplinary approach of evaluation and treatment often coordinated by a physician or a geneticist is required. The role of the ophthalmologist lies not only in diagnosis and prevention of visual loss but also in the recognition of rare systemic manifestations. Regular annual ophthalmological and systemic assessment is necessary for proper management of NF1. Genetic testing has increased our ability to make the diagnosis in uncertain cases, yet further research into genotype-phenotype correlations is needed. Although there is no specific medical treatment available at present but ongoing trials hold promise in treating both ocular and systemic manifestations of NF1 in future.

Reference

1. Wallace MR, Marchuk DA, Andersen LB, Letcher R, Odeh HM, Saulino AM, et al. Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. Science. 1990;249(4965):181–6.
2. Rasmussen SA, Yang Q, Friedman JM. Mortality in neurofibromatosis1: an analysis using U.S. death certificates. Am J Hum Genet 2001;68:1110 –1118.
3. Thomas L, Richards M, Mort M, Dunlop E, Cooper DN, Upadhyaya M. Assessment of the potential pathogenicity of missense mutations identified in the GT Pase-activating protein (GAP)-related domain of the neurofibromatosis type-1 (NF1) gene. Hum Mutat. 2012;33(12):1687–96.
4. National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, Md., USA, July 13-15, 1987. Neurofibromatosis. 1988;1(3):172–8.
5. DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics2000;105:608–614.
6. McCaughan JA, Holloway SM, Davidson R, Lam WW K. Further evidence of the increased risk for malignant peripheral nerve sheath tumour from a Scottish cohort of patients with neurofibromatosis type 1.J Med Genet. 2007;44(7):463–6.
7. Ullrich NJ, Raja AI, Irons MB, Kieran MW, Goumnerova L. Brainstem lesions in neurofibromatosis type 1. Neurosurgery 2007;61:762–766; discussion 766–767.
8. Sylvester CL, Drohan LA, Sergott RC. Optic-nerve gliomas, chiasmal gliomas and neurofibromatosis type 1. Curr Opin Ophthalmol 2006;17:7–11.
9. Hyman SL, Arthur Shores E, North KN. Learning disabilities in children with neurofibromatosis type 1: subtypes, cognitive profile, and attention deficit-

hyperactivity disorder. Dev Med Child Neurol 2006;48:973–977.
10. Prinzie P, Descheemaeker MJ, Vogels A, et al. Personality profiles of children and adolescents with neurofibromatosis type 1. Am J Med Genet A 2003;118:1–7.
11. Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. Neurology 2005;65:1037–44.
12. Lopes FerrazFilho JR, Munis MP, Soares Souza A, Sanches RA, Goloni-Bertollo EM, Pavarino-BertelliEC. Unidentified bright objects on brainMRI in children as a diagnostic criterion for neurofibromatosis type 1.PediatrRadiol 2008;38:305–10.
13. Fossali E, Signorini E, Intermite RC, et al. Renovascular disease and hypertension in children with neurofibromatosis. Pediatr Nephrol 2000;14:806–10.
14. Han M, Criado E. Renal artery stenosis and aneurysms associated with neurofibromatosis. J Vasc Surg 2005;41:539 –543.
15. Cairns AG, North KN. Cerebrovascular dysplasia in neurofibromatosis type1. J Neurol Neurosurg Psychiatry2008;79:1165–70.
16. Ullrich NJ, Robertson R, Kinnamon DD, et al. Moyamoya following cranial irradiation for primary brain tumors in children. Neurology 2007;68:932–938.
17. Vicha A, Musil Z, Pacak K. Genetics of pheochromocytoma and paraganglioma syndromes: new advances and future treatment options. Curr Opin Endocrinol Diabetes Obes2013;20(3):186–91.
18. Elefteriou F, Kolanczyk M, Schindeler A, Viskochil DH, Hock JM, Schorry EK, et al. Skeletal abnormalities in neurofibromatosis type 1: Approaches to therapeutic options. American Journal of Medical Genetics, Part A. Vol. 149. 2009;2327–38.
19. Vitale MG, Guha A, Skaggs DL. Orthopaedic manifestations of neurofibromatosisin children: an update. Clin Orthop Relat Res.2002;401:107–118.
20. Lammert M, Kappler M, Mautner VF, et al. Decreased bone mineral density in patients with neurofibromatosis 1. Osteoporos Int 2005;16:1161–66.
21. Friedrich RE, Hartmann M, Mautner VF. Malignant peripheral nerve sheath tumors (MPNST) in NF1-affected children. Anticancer Res 2007;27:1957–60.
22. Yoshimi A, Kojima S, Hirano N. Juvenile myelomonocytic leukemia: epidemiology, etiopathogenesis, diagnosis, and management considerations. Paediatr Drugs 2010;12(1):11–21.
23. Kramer K, Hasel C, Aschoff AJ, Henne-Bruns D, Wuerl P. Multiple gastrointestinal stromal tumors and bilateral pheochromocytoma in neurofibromatosis. World J Gastroenterol 2007 Jun 28 [cited 2016 May 31];13(24):3384–7.
24. Sharif S, Moran A, Huson SM, et al. Women with neurofibromatosis 1 are at a moderately increased risk of developing breast cancer and should be considered for early screening. J Med Genet 2007;44:481- 484.
25. Bottillo I, Ahlquist T, Brekke H, Danielsen SA, van den Berg E, Mertens F, et al. Germline and somatic NF1 mutations in sporadic and NF1-associated malignant peripheral nerve sheath tumours. J Pathol 2009;217(5):693–701.
26. Cassiman C, Legius E, Spileers W, Casteels I. Ophthalmological assessment of children with neurofibromatosis type 1. Eur J Pediatr 2013;172(10):1327–33.
27. Kordić R, Sabol Z, Cerovski B, Katusić D, Jukić T. Eye disorders in neurofibromatosis (NF1). Coll Antropol 2005;29 (Suppl 1): 29–31.
28. Savar A, Cestari DM. Neurofibromatosis type I: genetics and clinical manifestations. Semin Ophthalmol 2008;23(1):45–51.
29. Listernick R, Charrow J, Greenwald MJ, Esterly NB. Optic gliomas in children with neurofibromatosis type 1. J Pediatr 1989;114(5):788–92.
30. Rodriguez FJ, Perry A, Gutmann DH, O'Neill BP, Leonard J, Bryant S, et al. Gliomas in neurofibromatosis type 1: a clinicopathologic study of 100 patients. J Neuropathol Exp Neurol 2008;67(3):240–9.
31. 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.
32. Hood CT, Janku L, Lowder CY, Singh AD. Retinal Vasoproliferative Tumor in Association with Neurofibromatosis Type 1.J Pediatr Ophthalmol Strabismus 2009.
33. Shields JA, Pellegrini M, Kaliki S, Mashayekhi A, Shields CL. Retinal vasoproliferative tumors in 6 patients with neurofibromatosis type 1. JAMA Ophthalmol 2014;132(2):190–6.
34. Chiu S-L, Chen S-N, Chen Y-T, Chen P-J. Coats disease and neovascular glaucoma in a child with neurofibromatosis. J Pediatr Ophthalmol Strabismus 2011;48 Online: e1–3.
35. Avery RA, Dombi E, Hutcheson KA, Acosta MT, Baldwin AM, Madigan WP, et al. Visual outcomes in children with neurofibromatosis type 1 and orbitotemporal plexiform neurofibromas. Am J Ophthalmol 2013;155(6):1089–94.
36. Erb MH, Uzcategui N, See RF, Burnstine MA. Orbitotemporal neurofibromatosis: classification and treatment. Orbit 2007;26(4):223–8.
37. Tonsgard JH .Clinical Manifestations and Management of Neurofibromatosis Type 1 2006.Semin Pediatr Neurol 13:2-7.
38. Valeyrie-Allanore L, Ismaïli N, Bastuji-Garin S, Zeller J, Wechsler J, Revuz J, et al. Symptoms associated with malignancy of peripheral nerve sheath tumours: A retrospective study of 69 patients with neurofibromatosis 1. Br J Dermatol 2005;153(1):79–82.
39. Fadda MT, Giustini SS, Verdino GG, Bartoli DD, Mustazza MC, Iannetti GG, et al. Role of maxillofacial surgery in patients with neurofibromatosis type I. J Craniofac Surg 2007;18(3):489–96.
40. Prada CE, Rangwala FA, Martin LJ, Lovell AM, Saal HM, Schorry EK, et al. Pediatric plexiform neurofibromas: Impact on morbidity and mortality in neurofibromatosis type 1. J Pediatr 2012;160(3):461–7.
41. Serletis D, Parkin P, Bouffet E, Shroff M, Drake JM, Rutka JT. Massive plexiformneurofibromas in childhood: natural history and management issues. J Neurosurg2007;106(5 Suppl):363–7.
42. Evans DGR, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet 2002;39(5):311–4.
43. Hua C, Zehou O, Ducassou S, Minard-Colin V, Hamel-Teillac D, Wolkenstein P, et al. Sirolimus improves pain in NF1 patients with severe plexiform neurofibromas. Pediatrics 2014;133(6):e1792–7.
44. Robertson KA, Nalepa G, Yang F-C, Bowers DC, Ho CY, Hutchins GD, et al. Imatinibmesylate for plexiform neurofibromas in patients with neurofibromatosis type 1: a phase 2 trial. Lancet Oncol 2012;13(12):1218–24.

45. Baujat B, Krastinova-Lolov D, Blumen M, Baglin a C, Coquille F, Chabolle F. Radiofrequency in the treatment of craniofacial plexiform neurofibromatosis: a pilot study. Plast Reconstr Surg 2006;117:1261–8.
46. Yoshida Y, Sato N, Furumura M, Nakayama J. Treatment of pigmented lesions of neurofibromatosis 1 with intense pulsed-radio frequency in combination with topical application of vitamin D 3 ointment. J Dermatol 2007;34(4):227–30.
47. Li W, Cui Y, Kushner SA, Brown RA, Jentsch JD, Frankland PW, et al. The HMG-CoA reductase inhibitor lovastatin reverses the learning and attention deficits in a mouse model of neurofibromatosis type 1. Curr Biol 2005;15:1961–7.
48. Krab LC, de Goede-Bolder A, Aarsen FK, Pluijm SM, Bouman MJ, van der Geest JN, et al. Effect of simvastatin on cognitive functioning in children with neurofibromatosis type 1: a randomized controlled trial. JAMA 2008;300:287–94.
49. Fisher MJ, Loguidice M, Gutmann DH, Listernick R, Ferner RE, Ullrich NJ, et al. Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. Neuro Oncol 2012;14(6):790–7.
50. Ullrich NJ, Robertson R, Kinnamon DD, Scott RM, Kieran MW, Turner CD, et al. Moyamoya following cranial irradiation for primary brain tumors in children. Neurology 2007;68(12):932–8.
51. Miller NR, Iliff WJ, Green WR. Evaluation and management of gliomas of the anterior visual pathways. Brain 1974;97(4):743–54.
52. Packer RJ, Jakacki R, Horn M, Rood B, VezinaG, Mac Donald T, Fisher MJ, Cohen B. Objective response of multiply recurrent pediatric low-grade gliomas to bevacizumab and irnotecan. Pediatr Blood Cancer 2009;52:791–795.
53. Evans DGR, O'Hara C, Wilding A, Ingham SL, Howard E, Dawson J, et al. Mortality in neurofibromatosis 1: in North West England: an assessment of actuarial survival in a region of the UK since 1989. Eur J Hum Genet2011;19(11):1187–91.
54. Masocco M, Kodra Y, Vichi M, Conti S, Kanieff M, Pace M, et al. Mortality associated with neurofibromatosis type 1: a study based on Italian death certificates (1995-2006). Orphanet J Rare Dis 2011;6-11.
55. Jett K, Friedman JM. Clinical and genetic aspects of neurofibromatosis 1. Genet Med. 2010;12(1):1–11.