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Original Research Article

Neurofibromatosis Type 1 in a Pediatric Patient Presenting with Neurological and Behavioral Symptoms: A Case Report

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Abstract:

Von Recklinghausen or Neurofibromatosis1 is a neurocutaneous syndrome affecting both the integument and central nervous system (CNS) of varying severity. It occurs due to mutation of the NF1 gene. Here, we report a case of 13-year-old boy, second born of non-consanguineous marriage, who presented with complaints of tingling sensation of over the limbs for the past one-year, poor scholastic performance and behavioral problems. There was no significant family history neither any similar complaints in either of the parents or older sister. A delay in attaining developmental milestones were noted by mother at 3 years of age. Various examinations revealed multiple café au lait spots all over the body, shagreen patch over the neck. Lisch nodules in bilateral eyes with multiple neurofibromas over both arms. Neuroimaging of brain and spine showed characteristic findings specific for Neurofibromatosis 1. The child was treated with Gabapentin with regular multisystemic follow-up.

Keywords: Neurofibromatosis Type 1, Von Recklinghausen disease, Pediatric neurocutaneous syndrome, Café au lait spots, Developmental delay, Behavioral problems.

Introduction

Neurofibromatosis is a neurocutaneous autosomal dominant disorder characterized by tumors on the nervous system, skin and result in other systemic abnormalities. Three types are known: neurofibromatosis (NF) 1 and 2, and schwanomatosis, all of which are considered distinct entities as they are clinically and genetically distinct diseases.[1]

NF1 also known as peripheral neurofibromatosis, or von Recklinghausen neurofibromatosis is a rare disorder with incidence of 1: 3000 live births caused by loss of function mutation in the NF 1 gene; of which 50 % is inherited and 50% are de novo gene mutation.[2] The pathogenic gene is found on chromosome 17. It regulates the production of neurofibromin.NF1 does not skip generations.

This multisystem disorder is characterized by multiple café au lait spots, intertriginous freckling, multiple benign cutaneous neurofibroma detectable by simple visual inspection and learning and /or behavioral issues.[3] NF1 are associated with plexiform neurofibroma as well but are mostly internal and not suspected clinically. NF1 has an equal predisposition for male and female with no preference for race or etjnicity. It is a progressive disease. Clinical features are evaluated, and symptoms are addressed but currently there is no definitive treatment for NF1.

Case Presentation: A 13-year-old presented to our hospital with complaints of tingling/pulling sensation of both arms and legs on and off in the past 1 year which had increased in severity in the last one week prior to presentation.

He has a history of delayed attainment of developmental milestones: it was first noticed by mother at 3 years of age that the child had delayed speech. The patient attained social smile at 6 months of age, head control at 7 months of age, walking with support at 2 and ½ years of age and speaking bisyllables at 3 years of age.

At 4 years of age mother noticed behavioral abnormalities such as not sitting quietly even when instructed, inattentiveness, easily distracted, meddling with objects at home, constantly climbing furniture, interrupting others when conversing.

He also had a history of temper tantrums and breath holding spells. He had a surgical history of laparoscopic orchidopexy for Right undescended testis at 5 years of age. He also had two episodes of loss of consciousness at 10 years of age. He also has a history of very poor scholastic performance. This boy is a second born child born of non-consanguineous marriage. No similar complaints were found in either of the parents or older sibling.

On examination the patient appeared thin, poorly nourished and underweight (Figure 1). He had pallor with dental caries and hyperpigmentation over the hard palate. clinical findings included prominent forehead, hypertelorism, pointed chin, high arched palate. (Figure 2) Simian creases in both palms. Notable clinical findings include Multiple subcutaneous nodules/ swellings were noted over the chin, cervical regions and arms; multiple café au lait spots: more than seven in number over shoulder, trunk, lower and upper limbs with size ranging from 1.5 cm to 8.5 cm which had increased with age. Shagreen patch over the left cervical region and axillary freckling. Multiple subcutaneous nodules were palpable over the occipital region. (Figure 3,4)

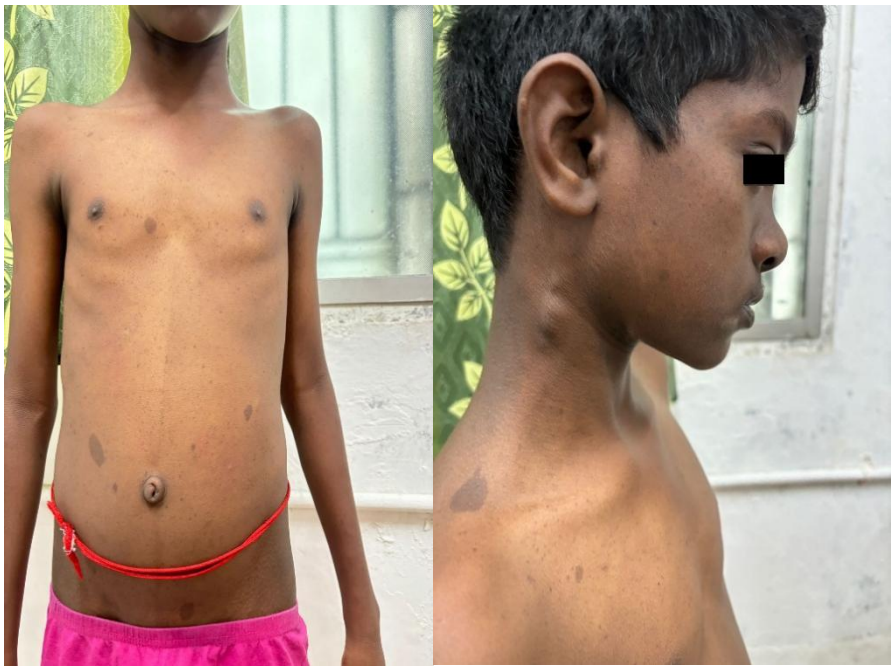

Figure 1 and 2:

Figure 3 and 4:

He was categorized as stage 3 under the Tanner staging of Sexual Maturity Rating (SMR). Neurological examination was normal with no organomegaly.

All lab investigations were normal.

MRI Brain and Spine demonstrated:

- Diffuse T2 FLAIR hyperintensities in deep white matter of bilateral cerebral hemispheres, dentate nucleus, right gangliocapsular region and splenium of corpus callosum.
- Linear t2 FLAIR hyperintense lesions over subgaleal plane of the right occipital region with 9th, 10th, and 11th nerve roots enlarged.
- Hyperintense nodules are seen involving subgaleal plane of cranium.
- Multiple fusiform hyperintensities along the entire spine in the region of the neural foramen with extraforaminal extension into paravertebral and presacral regions.

All of the above features were suggestive of Neurofibromatosis type 1.

Ophthalmic evaluation showed Lisch nodules in bilateral eye.

Otolaryngology evaluation was found to be normal.

Neurosurgery evaluation suggested nil intervention with regular follow up. Child was found to have intellectual disability disorder (IDD) according to Binet Kamat test where he got the mental age of 8 years and 2 months with IQ of 59 (38 – 63) which indicates mild level of deficit in intellectual functioning. Patients were advised to undergo vocational training, to switch to NIOS Syllabus and get a disability certificate.

Paediatric neurologist opinion was taken and was advised to get an ultrasound abdomen with renal artery Doppler. He also started on Tablet Gabapentin 100mg 1 tablet to be taken morning and night for 1 week followed by 1 tablet to be taken at night till next review.

Ultrasound KUB and renal Doppler showed no abnormalities. Patient was advised yearly assessments of ophthalmic examination, neurological, blood pressure monitoring and scoliosis evaluation.

Patient visited the paediatrics opd for review after two months in view of persistent pain in the upper limbs. Patient was started on Tablet Tryptomer 10 mg at night and the dose of Gabapentin 100mg was increased to three per day. Both the medications were advised to be continued followed by a follow-up after three months.

Discussion:

NF1, the most common form of neurofibromatosis, represents monogenic disorder with autosomal dominant inheritance presentation with a strikingly high rate of de novo mutations. These de novo mutations are found to be responsible for the sporadic appearance of NF1.[2] Penetrance is complete or at least nearly so by the age of 5 years but the expressivity may vary even within the same consanguinity. There is no gender, race or ethnic predilection. {3,4} With lifetime risk of 59.6% [5] for malignancy, lifelong surveillance of NF1 patients is justifiable [1]

Now, knowledge regarding germline mutations in genes encoding products of the RAS/mitogen-activated protein kinase (MAPK) pathway has expanded. These are called as RAS opathies, and first one to be identified was NF1.[6] Seven clinical diagnostic criteria were suggested by the US NIH Consensus Development conference. To confirm the diagnosis at least TWO criteria should be met. [7]

Table 1:

National institutes of health (NIH) Diagnostic Criteria for Neurofibromatosis 1(NF1) and Other Common Findings	
The diagnosis of NF! Is made, if >= 2 of the following are met.	
1.	>= 6 CALM's of > 5 mm (prepubertal) and > 15 mm (post pubertal) in greatest diameter
2.	>= 2 neurofibromas of any type or >= 1 plexiform neurofibromas
3.	Freckling in the skin folds like the axillary or the inguinal regions
4.	Glioma of the optic pathway
5.	>= 2 Lisch Nodules / iris hamartoma
6.	Distinct osseous lesions (sphenoid dysplasia or thinning of long bone cortex)
7.	A NF1 diagnosed first degree relative as per above mentioned clinical criteria

CALM: café au lait macules; PNs: Plexiform Neurofibroma; CNs: Cutaneous neurofibroma

Some of the clinical manifestations of NF1 are age dependent (i.e., neurofibromas), particularly sporadic cases (no parents with NF1). Therefore, diagnosis is not easy in early childhood.

The order of appearance of the skin manifestations are CALMs, axillary freckling, lisch nodules, and CNs or subcutaneous neurofibromas or PNs. Therefore, NF1 penetrance is often suggested by CALMs, which are hyperpigmented skin lesions.

Although the classical criteria is largely used and agreed upon, new cutaneous and extra-cutaneous features have been described. For example, the presence of unidentified bright objects on imaging – hyperintense lesions on T2-weightedbrain magnetic resonance imaging (MRI) scans representing aberrant gliosis; pathognomic of NF1.

Patients with somatic/segmental NF1 have only a specific area of the body affected with neither of the parents being affected.[8]

There is an overlap between phenotypic presentations in patient's withNF1 gene mutations like neurofibromatosis-Noonan syndrome such as short stature, ocular hypertelorism, low-set ears and down slanting palpebral features. [9]

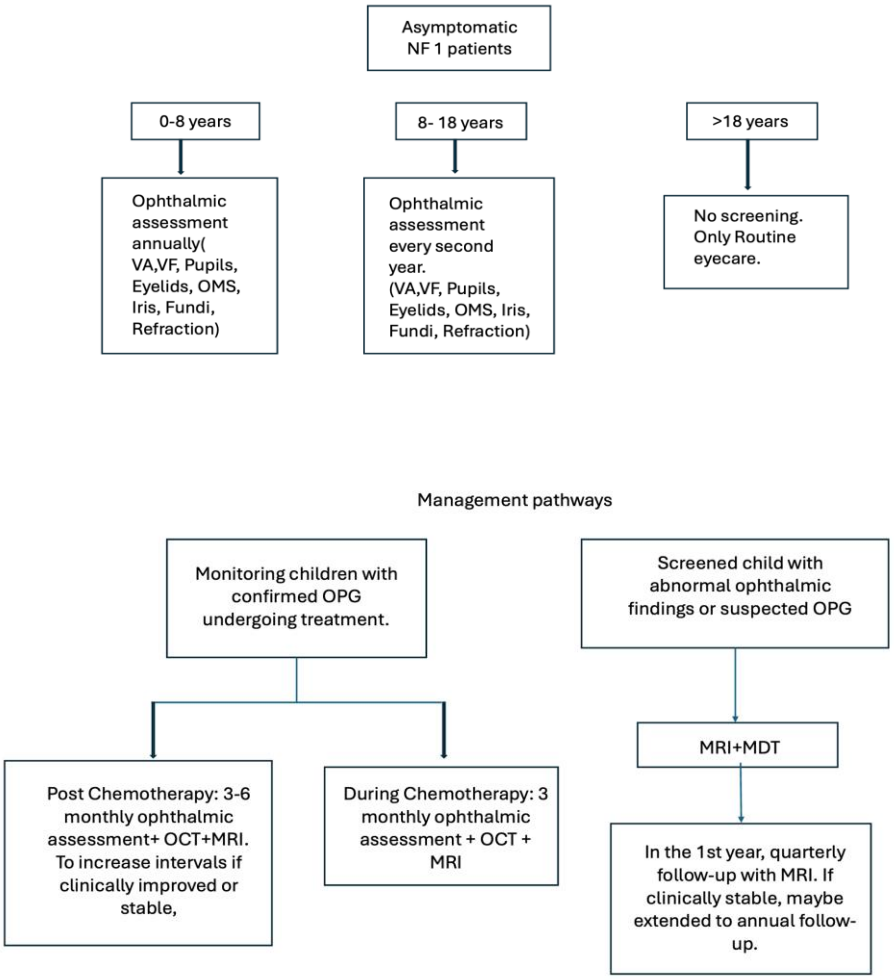

Figure 5: Proposed Screening Guidelines and Management pathways of patients with NF1.

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