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Radiodiagnosis

NEUROCUTANEOUS MANIFESTATIONS OF NEUROFIBROMATOSIS TYPE-1: ROLE OF MULTIMODALITY IMAGING

Dr. Harmeet Kaur Assistant Professor, Department of Radiodiagnosis, Maharishi Markandeshwar Medical College & Hospital, Kumarhatti, Solan (HP)

Dr. Punit* Assistant Professor, Department of Orthopaedics, Maharishi Markandeshwar Medical College & Hospital, Kumarhatti, Solan (HP) *Corresponding Author

ABSTRACT Neurofibromatosis type-1 or Von Recklinghausen disease is a multisystem neurocutaneous disorder and the most common phakomatosis. One of the main characteristics of this disease is systemic and progressive involvement with impaired neurological functions. It is characterised by predominantly neurocutaneous features such as cafe-au-lait spots, axillary freckling, skeletal dysplasias, benign and malignant neurofibromas. We report a case of a 15-yr-old male patient who presented with multiple nodular lesions on both upper limbs and lower limbs, associated with sensory and motor weakness. Imaging findings revealed multiple cutaneous and subcutaneous neurofibromas involving peripheral and autonomic nerves presenting as soft tissue skin nodules clinically. We discuss the multimodality imaging findings of neurofibromatosis-1 in the present article and brief review of the available literature.

KEYWORDS : Neurofibromatosis type-1; neurofibroma; neurocutaneous manifestations; radiology.

INTRODUCTION:

Neurofibromatosis (NF) is a hereditary congenital disorder probably of neural crest origin that affects all 3 germinal layers. NF is not a single entity but a group of heterogenous neurocutaneous disorders involving both neuroectodermal and mesenchymal derivatives. Two types of neurofibromatosis are widely recognised: Type-1 and 2. Both types are inherited as autosomal dominant disorders with NF-1 having a penetrance of almost 100% and spontaneous mutation rate of about 50%.[1] With a prevalence of 1:3000-1:5000 individuals, NF-1 is over 10 times commoner than NF-2. NF-1 is diagnosed on the basis of well established diagnostic criteria. Prominent cutaneous manifestations include cafe-au-lait spots, freckling and cutaneous and subcutaneous neurofibromas. The diagnostic criteria for NF-1 are listed in Table I.[2]

Ÿ	Six or more cafe-au-lait macules (diameter > 5 mm in prepubertal patients and > 15 mm in postpubertal patients)
Ÿ	Two or more neurofibromas or one plexiform neurofibroma
Ÿ	Axillary or inguinal freckling
Ÿ	Optic nerve glioma
Ÿ	Two or more Lisch nodules (iris hamartomas)
Ÿ	A characteristic osseous lesion (sphenoid) dysplasia or cortical thinning of long bone, with or without pseudoarthrosis
Ÿ	First-degree relative (parent, sibling, or child) with NF-1

Table I : Criteria for NF-1 (two or more of the following)

CASE HISTORY:

A 15-yr-old male patient presented with multiple hyperpigmented macules and small nodular lesions all over his body. He also complained of pain, motor and sensory weakness in bilateral lower limbs with onset of limping in his right leg one year back. There was no history of seizures or neurological deficit. He had multiple soft to firm cutaneous nodules in bilateral upper and lower limbs, ranging from a few millimeters to several centimeters in diameter on examination. Multiple cafe-au-lait spots with diameter > 1.5 cms were also noted. Bilateral foot drop was seen with zero motor power in extensor hallucis longus and tibialis anterior muscles. Ophthalmological evaluation revealed multiple iris lisch nodules in both eyes without any visual impairment (Fig 1). ENT examination and nerve conduction study were unremarkable. He had positive family history with presence of cafe-au-lait spots and lisch nodules in his mother. He was referred to the radiology department for further imaging evaluation.

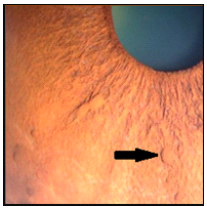

Fig.1: Slit lamp examination of the eyes shows dome shaped nodular lesions in the iris along its lower aspect s/o hamartomas/ lisch nodules (black arrow)

USG of the limbs showed multiple well marginated discrete as well as conglomerated nodular soft tissue lesions along the ulnar (Fig.2) and median nerves in the wrist, posterior tibial, peroneal nerves in the legs, also involving intercostals nerves in the thorax and sacral plexus in the pelvis. Nodules appeared predominantly hypoechoic with some of them displayed target appearance i.e. central hyperechogenicity with hypoechoic periphery. The involved nerves were thickened and showed fusiform enlargement. NCCT pelvis showed multiple soft tissue masses along the bilateral sacral foraminae, also causing their widening (Fig.3).

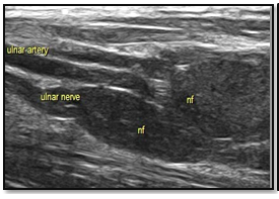

Fig.2: Longitudinal sonographic image of the forearm using linear probe showed multiple fusiform nodular hypoechoic lesions along the course of ulnar nerve with no separate visualisation of the involved nerve.

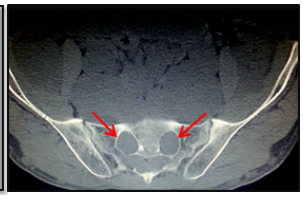

Fig.3: NCCT image of the pelvis revealed nodular soft tissue density masses in pre & paravertebral region and along bilateral sacral foraminae with their resultant smooth remodelling. (red arrows)

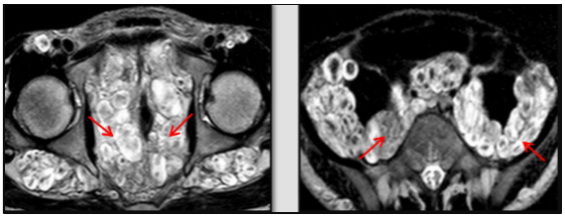

Fig.4&5: T2W axial images of the pelvis showing discrete nodular heterogenously hyperintense lesions along lumbo-sacral plexus involving femoral, obturator and sciatic nerves giving classical 'target appearance.' (red arrows)

In addition, skeletal survey including radiographs of chest, hands, spine and pelvis were done. X-ray thorax showed bilateral ribbon ribs and inferior rib notching (Fig.6). Mild scoliosis of upper dorsal spine was also noted. Our patient fulfilled four diagnostic criterias i.e. Six or more cafe-au-lait macules, multiple neurofibromas, lisch nodules and positive family history of the disease (mother). Histopathological examination of the nodules revealed spindle-shaped cells and pleomorphic fibroblast-like cells. Based on the clinical, radiological

and histopathological findings, the patient was diagnosed with Neurofibromatosis type -1.

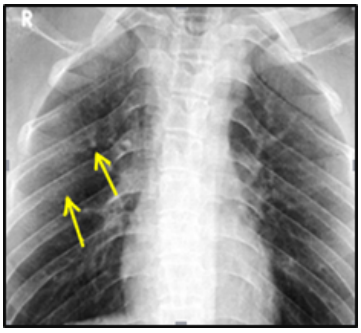

Fig.6: Radiograph of the thorax (AP) view showed ribbon ribs & inferior rib notching due to intercostal neurofibromas. (Yellow arrows)

DISCUSSION:

Neurofibromatosis is also known as congenital neuroectodermal dysplasia or neurocutaneous syndrome owing to predominant ectodermal involvement.[3] There is no ethnic or gender predilection. No specific risk factors for NF-1 have been reported. The pathogenesis of NF-1 is the loss of function of neurofibromin gene which is a tumor suppressor gene, located on the long arm of chromosome 17 (17q11.2).[4] It is expressed in many cells primarily in neurons, glial cells, schwann cells and melanocytes and inhibits uncontrolled cell proliferation. Schwann cells in neurofibromas and melanocytes in cafe-au-lait macules have a mutation in both NF-1 alleles, thus are abnormally proliferated in this condition.

In an affected individual of NF-1, the criteria set by the NIH Consensus Conference are met.[2] (Table-1) Prominent neurocutaneous manifestations are cafe-au-lait spots, cutaneous and subcutaneous neurofibromas, iris hamartomas, axillary or inguinal freckling and optic gliomas. The earliest clinical finding usually seen in children with NF-1 is multiple cafe-au-lait spots. Cafe-au-lait spots are oval/round smooth bordered hyperpigmented flat macules. Hamartomas of the iris (lisch nodules) appear as reddish brown spots in blue or green coloured eyes and hypopigmented spots in brown eyes. Neurofibromas are benign nerve sheath tumours (NSTs) appearing as discrete swellings arising from peripheral nerves.[5] Generally, the cutaneous/dermal tumors are dome-shaped, soft, fleshy and skin-coloured to slightly hyperpigmented while subcutaneous ones are firm and nodular.

When the neurofibromas develop in the subcutaneous nerves, they may lead to chronic disabling pain and may degenerate into malignant peripheral NSTs. Spinal neurofibromas are a source of neural or spinal cord compression. These may cause radicular symptoms including pain, sensorymotor weakness and mononeuropathies.[6] Despite a considerable range of complications related to peripheral NSTs in NF-1, the prevalence of peripheral nerve involvement in NF-1 is considered rather low in large clinical studies, ranging from 0 to 4.3%. Other CNS manifestations of NF-1 are optic nerve glioma, UBOs, hydrocephalus and meningocoele which were not present in our case.
Ultrasound, CT and MRI can be useful in the noninvasive diagnosis and characterization of neurofibromatosis. Plain radiographs may detect a variety of subtle as well as obvious bony abnormalities like neural foraminal widening, thoracic scoliosis, posterior vertebral scalloping, tibial bowing, pseudoarthrosis and ribbon ribs. On ultrasound, most neurofibromas are hypoechoic, sometimes mimicking cystic lesions. However peripheral nerve continuity is diagnostic.[7]

CT has a role in the detection of thoracic, abdominal and pelvic complications of NF-1. CT scans demonstrate neurofibromas as hypodense solid fusiform masses in the distribution of nerves, with central areas of low attenuation and calcification. Low attenuation is due to myelin lipid content, fat entrapment and high water content in endoneurial myxoid tissue. These masses may present in the paravertebral region, abdomen, mediastinum, pelvis/ischiorectal fossae and limbs. Paraspinal neurofibromas are commonly dumbbell shaped /fusiform/spherical soft-tissue masses which may enlarge the exiting foraminae.

MRI is the most useful imaging modality to characterize tumour extent and suggest neurogenic origin due to its high contrast resolution and multiplanar capabilities.[8] PNSTs typically show T1 hypointensity & T2 hyperintensity or characteristic target sign with a central hypointensity surrounded by peripheral hyperintensity, oriented longitudinally along the nerve.[9]This sign is due to a dense central area of collagenous stroma. On post contrast images, they show heterogenous intense enhancement.

T2 high-signal intensities within the brain (globus pallidus and cerebellum) are recognized as UBOs on MRI, a common finding in children with NF-1.

CONCLUSION:

This article stresses upon the importance of multimodality imaging in patient with suspected neurofibromatosis. The proper clinical and genealogic analysis is important for the determination of the genetic risk and prognosis for the relatives of the proband. Life expectancy in NF-1 is approximately 8 years lower than the general population. Although there is a paucity of available medical treatments but ongoing trials hold promise in treating both cutaneous and non-cutaneous manifestations of NF-1.

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