International Journal of Radiology Research
www.radiologyjournal.in
E-ISSN: 2663-4562, P-ISSN: 2663-4554
Received: 05-08-2020; Accepted: 20-08-2020; Published: 09-09-2020
Volume 2; Issue 2; 2020; Page No. 12-14

A rare manifestation of the neurofibromatosis type 1 involving the lower limb: Elephantiasis neuromatosa

Tushar Kalekar[1], Nikita Vinod Nemade[2*], Neeraj Surendra Patil[3]
[1-3] Dr. DY. Patil Medical College, Hospital and research Centre, Pimpri, Pune, Maharashtra, India

Abstract
Elephantiasis neuromatosa is one of the uniquemanifestations of neurofibromatosis type-1 (NF-1). Here is a case report of NF-1 presenting with elephantiasis neuromatosa of his lower limb. Radiological imaging helped in the perfect diagnosis as well as knowing the vasculature of a plexiform neurofibroma, which is necessary for further surgical planning.

Keywords: Elephantiasis neuromatosa, conventional radiography, magnetic resonance imaging, ultrasonography

1. Introduction
Neurofibromatosis type 1 (NF-1-Von Recklinghausen disease), is anautosomal-dominant inheritant syndrome. It is a neurocutaneous or phakomatosis syndrome interfering the development and growth of nerve cell tissues, with a prevalence of 1 in 3,000 births [1]. Pathologically, neurofibromas are of three types, the most common is localized neurofibroma, the least common is diffuse neurofibroma and the most pathognomonic lesion is plexiform neurofibroma [2]. Due to the long segment of a nerve trunk and its branches involvementPlexiform neurofibromatosis shows a characteristic "bag of worms" appearance on gross examination and cross-sectional imaging [3]. This may lead to gigantic hypertrophy of the skin, soft tissues and the underlying skeleton of a limb [4]. Because of such appearance, they are called as "elephantiasis neuromatosa" by Virchow [1].

2. Case Report
A 5-year-old male patient, known case of NF-1 came to our radiology department for imaging investigations of a large disabling right lower limb that had affected the patient's gait. It is gradually increasing in the size since childhood i.e. 2 months of his age, [Figure 1]. On local examination, marked soft tissue hypertrophy of the right leg extending from upper thigh up to the ankle is noted. The child does not have any neurological or visual complaints. On physical examination, multiple "café au lait" spots (>5 mm in greatest diameter) randomly distributed over the trunk was seen [Figure 2], with axillary freckling. Slit lamp examination of both eyes revealed normal study. Blood and urine tests (vanillylmandelic acid test) were all within normal limits. There was a family history of NF-1 in first-degree relatives.
Conventional radiograph showed soft tissue hypertrophy of the right leg. There is no thinning of cortices, bony erosion or periosteal reaction at present [Figure 3]. Radiograph of the skull revealed normal study [Figure 4]. Gray scale ultrasonography revealed a diffuse interdigitating network of elongated heterogeneous tumors along the long axis of the nerve. The lesions showed "target sign" appearances. However, the entering/exiting nerves could not be clearly seen [Figure 5] All the magnetic resonance imaging (MRI) sequences showeddiffuse elongated, extensive proliferation of all the neural elements in the entire lower limb involving femoral, tibial, fibular and sural nerves. The masses had a variegated appearance, ranging from nodular to thick irregular cords, few showing a branching pattern. The lesion showed mixedsignal intensity on T1W sequence [Figure 6] and heterogeneously high signal intensity on T2W/STIR sequences giving a "bag of worms" appearance – the characteristic of plexiform neurofibromatosis [Figure 7]. Vascular structures appeared normal. Underlying bones were normal. Screening MRI of the brain revealed normal study (not shown).
The patient has advised for cosmetic repair surgery of the right leg. Previously he was advised to use elastic compression bandages which showed mild reduction in the soft tissue swelling and hypertrophy over the period of 1 year. He is now advised for follow-up MRI brain scan to evaluate hamartomatous lesions in future period.

Fig 1: Photograph of the lower limbshowing limb enlargement, hypertrophy and disfigurement.

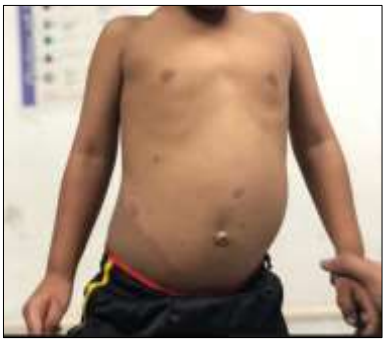

Fig 2: Photograph of the trunk showing multiple "café au lait" spots of variable sizes.

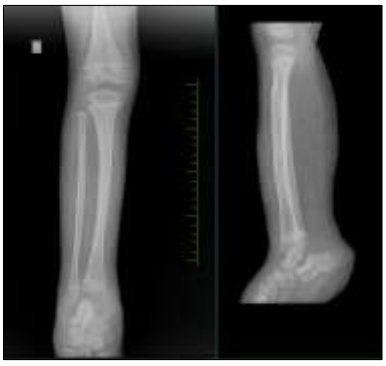

Fig 3: Radiograph of the right leg showing soft tissue hypertrophy.

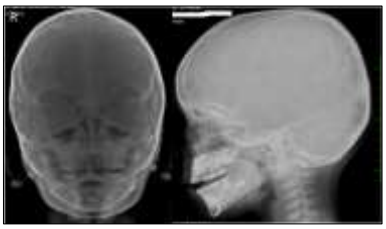

Fig 4: Radiograph of the skull- Normal.

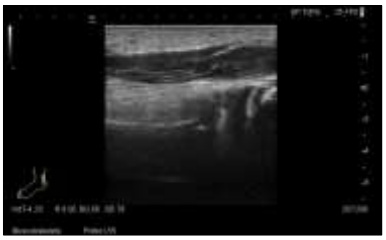

Fig 5: Ultrasonography revealed a diffuse interdigitating network of elongated heterogeneous tumors along the long axis of the nerve on longitudinal section, and "target sign" on transverse scan.

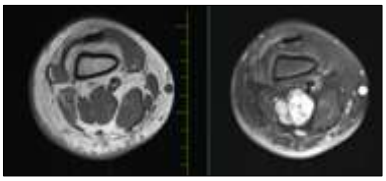

Fig 6: (T1 and T2FS axial images) - mixedsignal intensity on T1W sequence and heterogeneously high signal intensity on T2W sequences giving a "bag of worms" appearance.

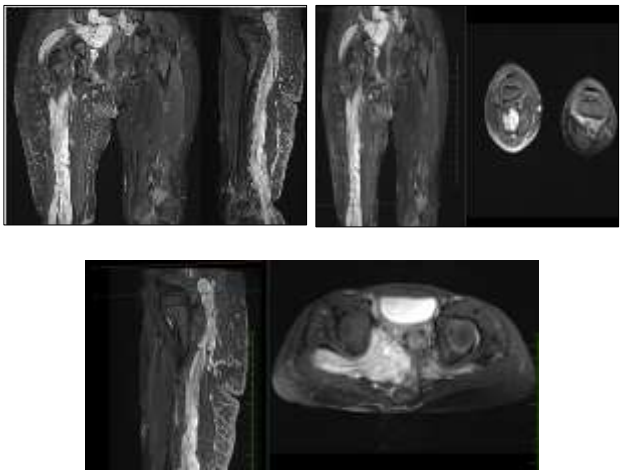

Fig 7: (A, B and C-T2 STIR COR and SAG images) - showeddiffuse elongated, extensive proliferation of all the neural elements in the entire lower limb involving femoral, tibial, fibular and sural nerves. The masses had a variegated appearance, ranging from nodular to thick irregular cords, few showing a branching pattern.

3. Discussion

NF-1 is a phakomatosis syndrome with chromosomal defect in the long arm of chromosome 17q11.21. Various skin lesions and peripheral or central nervous system neoplasms are seen. The diagnostic criteria were given by National Institutes of Health (NIH) in 1987. These well-recognized diagnostic criteria are neurofibromas (two or more simple, or one plexiform neurofibroma), café-au-lait spots (six or more, >5 mm in greatest diameter in children and >15 mm in adults), Lishhamartomas in iris (two or more), axillary or inguinal freckling, skeletal abnormalities (sphenoid dysplasias or cortical thinning, with or without pseudoarthrosis), optic glioma and first-degree relative with NF-1. Presence of two or more of these seven criteria establishes the diagnosis of NF-1. In our patient, three of the seven diagnostic features were present [5].

Plexiform neurofibroma has prevalence of 26% in patients with NF-1.It usually presents at birth or early childhood. They are unencapsulated, poorly circumscribed tumors that diffusely infiltrate the nerve and the adjacent fat and muscle. Therefore they are usually unresectable, where tumor resection is impossible without sacrificing the nerve tissue. Fusiform enlargement of multiple nerve fascicles and branches is characteristic. Plexiform neurofibromas contain a mixture of Schwann cells, fibroblasts, reticulin and collagen fibers and a loose mucoid matrix interspersed between the axons of the parent nerve. They typically affect the trunk and extremities, but may also involve the head-neck and bladder. Associated bone dysplasia is often encountered secondary to chronic hyperemia or as part of the mesodermal dysplasia. Such tumors give rise to a variety of problems, including disfigurement and functional impairment [6].

On ultrasound, these masses are usually hypoechoic, well defined and elliptical, oriented along the long axis of the nerve. Posterior acoustic enhancement is very common (70%). Color Doppler reveals variable vascular patterns, ranging from moderate, irregular central to predominantly peripheral vascularity. Some may not have any demonstrable vascularity [7]. MRI reveals large conglomerate masses consisting of innumerable neurofibromas,

diffusely thickening the involved nerve and often extending into the nerve branches. This tumor has a locally aggressive behavior, but the infiltrative pattern is not indicative of malignancy and has no histologic evidence of anaplastic or mitotic features [8]. The typical pattern on MRI is relatively low signal intensity or signal intensity similar to that of muscle with T1-weighting and signal intensity greater than that of fat with T2-weighting. The hyperintense pattern on T2WI reflects the high water content of the myxoid matrix [2]. Three signs have been noted as diagnostic aids on MRI [9], but they are also seen on ultrasound [3]. The "target sign" is characteristic of benign neurofibroma. The target appearance represents a geographic difference between the histologic zones of the neurofibroma. The high signal intensity seen in the peripheral zone is likely related to the high water content of the myxomatous tissue and the central low signal intensity is probably related to T2 shortening caused by the dense fibrocollageneous tissue. The fascicular sign refers to fascicular bundles in neurogenic tumors showing speckled appearance due to the presence of both high and low signal intensity. The split-fat sign is the presence of fine rind of fat at the periphery of the masses, and it represents the slow-growing nature of the tumor. The tumor usually exhibits avid contrast uptake but has a heterogeneous appearance on ultrasonography and MRI, owing to the presence of cysts, hemorrhage or necrosis [3, 9, 10]. CT of plexiform neurofibromas shows large multilobulated low-attenuation masses, usually within a major nerve distribution [4]. MR or CT angiography is mainly used to assess the vascular supply of the tumor and abnormal tumor vessels and to locate vessels suitable for preoperative intra-arterial embolization [4, 5]. Large and diffuse masses may cause venous obstruction and hypertrophy of the feeding vessels. Post-contrast images may also show the extensive capillary pooling of contrast throughout the soft tissue mass corresponding to the plethora of abnormal vessels in "the hemangio-neurofibroma" and the large ectatic veins, which is a pathognomonic finding of a hypervascularised plexiform neurofibroma [4].

The radiological modalities most often used in analyzing neurofibroma include CT and MRI. Ultrasound and color Doppler has a very limited role in the evaluation of a large mass, extending outside the range of the probe. Although CT is rarely helpful in making a specific diagnosis, it can provide a precise evaluation of the bone lesion and the extent of the soft tissue lesion; however, it is by far inferior to MRI in soft tissue contrast resolution and the visualization of tissue planes. Dynamic contrast-enhanced 3D MR or CT angiography represents a recent advance in imaging with rapid acquisition of high-quality angiographic images that permit a free choice of imaging planes and phases delineating the arterial and venous supplies, visualization of the abnormal changes of the vasculature in the affected limb, important landmarks in surgical planning. It should be emphasized that MRI and MR angiography may assist not only in the correct diagnosis of neurofibroma but also in imaging the vasculature of a plexiform neurofibroma, which is essential for proper surgical planning.

Treatment of diffuse and progressive plexiform neurofibroma is primarily surgery. However, complete resection of the tumor is not possible because of marked entanglement of the tumor with the nerves. Improved understanding of the molecular and cellular biology of the cells involved in the formation and growth of neurofibromas has led to development of other forms of treatments, including drug therapies, whose role is yet to be defined [10].

The common differential diagnosis in this case is other soft tissue tumors causing elephantiasis, such as filariasis, macrodystrophia lipomatosa, lymphangiomatosis, vascular malformation such as hemangioma and massive subperiosteal hematoma.

4. Conclusion

There are many imaging modalities available today to study the peripheral nerves. However MRI, cross sectional imaging, and angiography (CT or MRI) help in the correct diagnosis of neurofibroma or plexiform neurofibroma and is helpful for the surgical planning.

5. Acknowledgements

I would like to express my sincere gratitude to my advisor Prof. Dr. V. M. Kulkarni for the continuous support.

6. References

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