High-Resolution Ultrasonography in Leprosy: Value and Applications

Introduction

Leprosy continues to be prevalent in some of the countries of the world and India contributes over half of the world numbers.[1] Two key components of the disease are skin and nerve involvement. Diagnosis is based on the recognition of anesthetic skin lesions, identification of enlarged nerves, and the demonstration of the causative organism *M leprae*. With the integration of leprosy into the general health system, the clinical skill of recognizing skin lesions of leprosy and testing for anesthesia is declining. Skin smears to demonstrate *M leprae* is no longer a part of the leprosy control program. The palpation of nerves is a disappearing clinical skill, which is subjective and prone to inter-observer variability. At this juncture, the use of high-resolution ultrasonography (HRUS) for imaging peripheral nerves in leprosy has been ushered as a new diagnostic tool for their objective assessment.

The use of HRUS for nerves has many advantages in leprosy, apart from confirmation of their enlargement. While it is noninvasive and cost-effective in comparison with MRI of nerves, its wider availability, higher soft-tissue resolution, real-time and dynamic imaging, maneuverability[2] to examine the length of the nerve, and pinpoint the precise location of a nerve lesion make it a preferred option in leprosy. In addition to the measurement of the maximum cross-sectional area (CSA) of a nerve as an objective measure of nerve enlargement, its high resolution captures the morphological details of the nerve—the internal structure of individual fascicles based on echogenicity,[3] as well as the perineurium and the epineurium.[4] The use of color Doppler (CD) in addition enables the visualization of vascular channels and blood flow signals within the nerve.

The diagnosis of nerve swelling along the lateral popliteal nerve with the help of ultrasonography using a 5 MHz linear array real-time probe and a stand-off pad in the year 1987 was its first reported use in leprosy from France.[5] After a relative lull for more than a decade, with the advent of HRUS of 11–15 MHz, there was renewed interest in its potential role in leprosy.[6] Further work compared HRUS with nerve conduction studies where focal nerve thickening was detected in a proportion of the patients even in the absence of nerve conduction abnormalities.[7] A landmark case-control study established its use for all of the major nerves affected in leprosy and set a benchmark for its wider use in the diagnosis of all forms of the disease.[8] The technique was detailed in a review in *Clinics in Dermatology* on a special issue on leprosy.[9] This was further evaluated and substantiated by others in India[10,11] and different parts of the world.[12,13] Furthermore, nerve ultrasound has the potential to differentiate between hereditary, inflammatory polyneuropathies and axonal neuropathies or between different types of hereditary polyneuropathies.[14]

Key Applications of HRUS in Leprosy

While HRUS is useful for confirmation of nerve enlargement in all clinical types of leprosy, it is most valuable in pure neural leprosy (PNL) which is a diagnostic challenge in view of the absence of visible skin lesions and negative skin smears.[15] Ultrasonography has become a useful diagnostic tool to confirm PNL, circumventing the use of the invasive and potentially damaging tool of nerve biopsy for its definitive diagnosis.[16] The CSA of each individual nerve should be taken into consideration rather than an average CSA of all nerves since patients can present with thickening of only one or two nerves with all other nerves being normal in size. HRUS can help in the differentiation of leprosy from other neuropathies like ulnar nerve entrapment (UNE) where the nerve enlargement is found to be at the sulcus or just above the elbow, while in leprosy, it is more proximal, 3–4 cm above the elbow.[17] Other studies have detailed that the enlargement of ulnar nerve starts at the ulnar sulcus but is maximum about 4 cm above the medial epicondyle and reduces as we go further along the tract.[18] Studies are underway to decipher distinct patterns of nerve enlargement of other nerve trunks in leprosy as well. While all superficial nerves can be imaged, the best use of HRUS comes to the fore in the evaluation of median nerve which is commonly involved in leprosy but difficult to palpate and differentiate from the tendons at the wrist, its most superficial location. HRUS has also been used to diagnose and localize leprosy nerve abscess which is an often-encountered complication of leprosy.[19] Early recognition and treatment of neuritis especially in Type 1 reaction, where the inflammatory process can be intense and result in irreversible damage, is vital for the prevention of disability in leprosy. The edema of the nerve with an increase in CSA and often with hemodynamic changes during neuritis can be detected early by HRUS and CD.[20] The study of echogenicity and morphological changes in enlarged nerves during phases of neuritis would help to plan appropriate treatment measures, while the periodic follow up could serve as a prognostic guide for prevention/ management of nerve damage.[12,20]

While making a definitive diagnosis of leprosy, there is also a need to be aware of the ultrasonographic features of the nerve in diseases like diabetes and other neuropathies in order to differentiate them from leprosy. Studies suggest that nerve stiffness tends to increase in the setting of peripheral neuropathy, regardless of etiology, consistent with loss of more compliant myelin and replacement with connective tissue.[21] During recent years, ultrasound elastography (UE), a relatively new imaging technology to quantify tissue stiffness, has been gaining the interest of researchers and healthcare professionals since its introduction by Ophir and colleagues in 1991.[22] It has evolved considerably and found application in many clinical disciplines over the past decade.[23] The two most commonly used elastographic techniques are strain elastography (SE) and shear wave elastography (SWE). Published evidence shows clearly that UE can assist in the diagnosis of many types of peripheral neuropathies, such as carpal tunnel syndrome and other entrapment neuropathies, diabetic peripheral neuropathy, and peripheral neuropathy associated with other systemic diseases, sometimes at the stages at which the condition is still asymptomatic.[24] While UE is still a subject of ongoing research, it can be an additional useful tool for peripheral nerve elasticity evaluation in leprosy, as already been reported from a study on median nerves.[25]

Future Use of HRUS in The Leprosy Program

HRUS of peripheral nerve is already accepted as a vital tool in the objective evaluation of nerve thickening and diagnosis of leprosy.[26] Nonetheless, studies are needed to arrive at definite cut off values based on normative data for each of the commonly affected nerves in leprosy in different racial populations. There is also a need for arriving at a consensus on radiological grading of loss of nerve fascicular architecture. Supplementary research work to evaluate and standardize the usefulness of UE imaging techniques in leprosy should be done with a similar objective. With the use of more modern imaging techniques, it is now possible to further quantitate the changes in the architecture of the nerve accurately and objectively.[27,28] Newer techniques like *Diffusion Tensor Imaging Tractography* are being combined with MRI imaging techniques in the nerve to study details of myelin discontinuity, demyelination, and remyelination.[29] Similar advanced ultrasound-based imaging techniques could be developed, standardized, and applied with the same objective.

As the Global leprosy program is aiming for 90% reduction in rate per million of new cases with grade-2 disability in its strategy for 2021-2030 (WHO global leprosy strategy draft for 2021-2030), it would be useful to include the use of HRUS of nerves for early detection of neuritis in its strategy for managing leprosy and its complications to prevent new disability as an optional diagnostic tool. It is especially relevant as this global strategy is planned for next 10 years, we can expect the wider availability of HRUS across India and world over this period. While awaiting the global program to include it, it will be a proactive initiative by National Leprosy Eradication Program (NLEP) if they were to include the use of HRUS in the Indian national leprosy strategy, as a welcome measure to identify and prevent neuritis and its sequel which is disability.

Training programs for young dermatologists were taken up by IADVL to increase the awareness on the versatility and value of this technique in leprosy and it was well appreciated.[30] From the papers presented by postgraduate students and young dermatologists at national and regional meetings of IADVL and IAL as well as at the International Leprosy Congress in Manila in 2018, it is becoming obvious that more and more dermatologists, leprologists, neurologists, and radiologists are recognizing the value of this technique. In a country like India where dermatologists from medical institutes and colleges have been shown to play a significant role in the diagnosis and treatment of leprosy,[31] one can foresee the wider use of this imaging technique. In addition, greater availability of HRUS facilities in general and the promise of hand-held portable HRUS sonography devices[32] in near future could soon enable imaging of nerves in leprosy to become a point-of-care diagnostic technique. It could potentially be a prognostic technique helping to chart specific measures to prevent neuritis and disability. Such being the case, the inclusion of the use of imaging of nerves in the national strategy for NLEP is only a step away.

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