Non-contrast Magnetic Resonance Lymphangiography: an emerging technique for the study of lymphedema

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ABSTRACT

Lymphedema (LE) is a chronic disabling disease, characterized by the accumulation of macromolecules and liquids in the interstitial space. Patients affected by LE should undergo appropriate imaging to confirm the diagnosis, to evaluate characteristics and the severity of LE and to allow for correct management and treatment plan. However, there is no consensus regarding the best imaging technique to study this disorder. We want to propose an overview of the studies published on Non-contrast Magnetic Resonance Lymphangiography, a relatively new technique for the diagnosis, assessment and management of lymphedema.

1. Introduction

Lymphedema (LE) is a chronic and progressive disease, characterized by the accumulation of macromolecules and liquids in the interstitial space, as a result of the impairment of the lymphatic system with respect to the formation and drainage of lymph [1,2]. It can affect any part of the body, but it is more common in the extremities, and is clinically characterized by chronic gross swelling of the affected limb, localized pain, atrophic skin changes and susceptibility to infections [3].

LE can be primary or secondary [4]; primary LE follows developmental abnormalities of the lymphatic system while secondary LE is the result of lymphatic vessels obstruction due to different conditions such as surgery, radiation treatment, trauma, pathological involvement of lymph nodes and infections [5,6].

Primary LE can be classified in: congenital, which is present at birth with a prevalence of 1.15/100,000 people and a predilection for women [4]; praecox, if LE appears during adolescence; or tarda, in case of late onset (after 35 years) of LE, which is uncommon and most frequent in female.

In developing countries, the most frequent cause of secondary LE is represented by Filariais, whereas in developed countries the commonest cause of secondary LE are lymphadenectomy and radiation therapy for cancer treatment [5].

LE is rarely fatal, but it is a disabling disorder that hugely affects the patients’ quality of life, causes significant morbidity and its management is very difficult.

Traditionally, LE has been commonly treated by a conservative approach, such as physiotherapy, lymphatic massage, wrapping and controlled compression [7].

However, in recent times, the implementation of new surgical techniques: the microsurgical lympho-venous shunts and lymph nodes autologous transfer have changed the therapeutic approach of this disorder. Lympho-venous shunt is the treatment of choice for hyperplastic LE, while lymph nodes transplantation is recommended for patients affected by aplastic or hypoplastic LE [8,9].

Investigation of LE is useful to provide differential diagnosis, to confirm the diagnosis, to assess the severity and extension of LE and to allow an adequate treatment planning.

Few imaging techniques can be used for LE evaluation. Lymphography has been the only available technique to study LE for a long time; it involves the injection of lipiodol ultra-fluid into a previously surgically exposed and canulated lymphatic vessel. This invasive technique required long acquisition times and was often burdened by allergic reactions and complications like pneumonia, and it was therefore abandoned [10].

Lymphoscintigraphy is performed by injecting intradermal Technetium 99 m sulfur colloid; the progression and the distribution of
the radio-labeled particles is evaluated by a gamma camera, but subdermal lymphatics cannot be assessed [11–13].

Another technique to detect lymphatic channels and evaluate patients with LE is indocyanine green (ICG) lymphography: ICG imaging is performed by injecting ICG into the interdigital web spaces; after 4 h, fluorescence images of lymphatic vessels can be obtained with a near-infrared camera device; the fluorescence images are digitalised for real-time display [14]. The main limits are: the long time after the injection needed to mark the lymphatic vessels and difficulty to clearly identify lymphatic vessels course in late-stage lymphedema [15].

Contrast-enhanced Magnetic Resonance Lymphangiography (CEMRL) is performed through subcutaneous injection of gadolinium-based contrast medium in interdigital web spaces of feet or hands [16]. It has been proved to be a safe technique, with high spatial resolution needed to mark the lymphatic vessels and diagnose dermal lymphatics [17].

However, CEMRL is limited by some issues: first, the procedure of injecting gadolinium chelates in the interdigital spaces is still off-label [21], it can cause patients’ discomfort and local reactions; moreover, due to the recent evidence of intracranial gadolinium deposition after contrast-enhanced MR imaging [22–24], the effort to use magnetic resonance imaging techniques that do not involve the administration of any contrast media, especially in younger patients, is increasingly pronounced.

In this scenario, Non-contrast Magnetic Resonance Lymphangiography (NCMRL), a non-invasive imaging technique based on heavily T2-weighted sequences, able to highlight the signal of static or slow-moving fluid-filled structures, like lymphatic vessels, with a suppression of the signal intensity of the background tissues, could be an alternative safe and feasible technique for the diagnosis and treatment planning of LE.

In this article we want to propose a review of the Literature about NCMRL. A search of literature was conducted by searching PubMed (including Medline) and Science Direct to identify articles about lymphatic MRI. The PubMed database and Google search were conducted (including Medline) and Science Direct to identify articles about lymphatic MRI. The PubMed database and Google search were conducted using the search by key words as follows: lymphatic MRI, lymphatic Magnetic Resonance, MR lymphangiography, Magnetic Resonance Lymphangiography, non-contrast MR lymphangiography, unenhanced MR lymphangiography. Conference papers were outside the scope of the review.

2. NCMRL technique

2.1. MR equipment

NCMRL can be executed on a 3.0 T unit [25] but also on a 1.5 T unit [26–31].

At our Institution, MRI scans for LE assessment are performed with a 1.5-T scanner (Magnetom Avanto, Siemens Medical Solutions).

To study the thoracic duct, Takahashi et al. [26] used a quadrature detection phased-array coil; while a six-channel phased array body coil can be used for imaging the retroperitoneal lymphatic vessels [27,28], lower limb LE [29,30] and for the upper limb LE.

We did not perform imaging of retroperitoneal lymphatic vessels and thoracic duct; for LE of the lower limb, we use a phased-array 36-channel peripheral angiography coil and an 8-channel body coil (Siemens Medical Solutions; Fig. 1A), whereas, for the upper limb we use an 8-channel phased-array body coil (Siemens Medical Solutions; Fig. 1B).

2.2. Patient preparation

Patients are asked to suspend the lymphatic drainage for 48 h and the use of elastic stockings or bandages for 24 h.

To study retroperitoneal lymphatic vessels or lower limb LE, oral administration of pineapple juice 30 min before the examination can be considered to decrease the signal intensity of the bowel content, due to its content of manganese [29,32].

Fasting is not necessary but recommended for those patients who require a study of the upper limbs, in a prone position.

2.3. Patient positioning

Before positioning, it is important to explain in detail the diagnostic procedure and the need to maintain the position throughout the duration of the examination.

According to the patient’s size, the acquisition is usually performed in 3 or 4 steps to cover all the anatomical stations for both lower [29,30] and upper [31] extremities; for lower limbs, the anatomical stations are: 1: feet, ankle, lower leg; 2: knee, upper leg, lower thigh; 3: medial and proximal thigh; 4: inguinal and pelvic region, root of the thigh; while for the upper extremities, the anatomical stations are: 1: hand, wrist and forearm; 2: elbow, arm, shoulder; 3: axillary lymph nodes.

So far, the acquisition techniques described in the literature have provided for the acquisition of the entire limb also in secondary lymphedema, to accurately define the extent and severity of the disorder and to perform an optimal post treatment follow-up. In the future, it will be possible to evaluate, in agreement with the Clinicians, the hypothesis to perform more targeted examinations in patients with LE caused by lymph node dissection, to reduce the acquisition time.

2.4. Acquisition protocol

NCMRL technique is still evolving, but the principle of this examination is based on heavily T2-weighted sequences, resulting in a signal loss in tissue background, with highlighting of static fluids in lymphatic vessels [25–32], with a very long TR/TE, similar to that used in cholangiopancreatography or in MR urography. Acquisition parameters of non-contrast T2 MR lymphography sequences according to different authors and anatomical districts are listed in Table 1. Arrivé et al. applied at the end of the echo train a restore pulse to flip the transverse magnetization to the longitudinal direction to reduce the acquisition time [28,29,31].

Other sequences can be associated in the examination: axial HASTE without fat suppression (TR: 1200 ms, TE: 114 ms, matrix: 176 × 256, flip angle: 180°, slice thickness: 6 mm) [28] or Iterative Decomposition of water and fat with Echo asymmetry and Least-squares estimation (IDEAL; acquisition plane: axial, TR: 4233 ms, TE: 76 ms, slice thickness: 6 mm, matrix: 320 × 192, FOV: 380 × 380) [29], this sequence, based on fat/water separation technique, provides contrasts of water and fat, in phase and out of phase and is used for the analysis of LE characteristics.

After performing a survey and calibration for all the anatomical stations previously listed, before the acquisition of the T2-lymphangiography sequence, we execute axial and coronal True Fisp sequences to assess the volumes of the affected and healthy extremity and to delineate the extension of LE, and axial T2 TSE to calculate lymph nodes number and size. Acquisition parameters of our protocol are listed in Table 2.

2.5. Post-processing and image analysis

After acquisition, the heavily T2-weighted 3D sequences source images are transferred to a dedicated workstation and elaborated with maximum intensity projection (MIP) reconstruction [26–32].

NCMRL allows the radiologist to obtain information regarding:

1. the symmetry/asymmetry of lower or upper limbs and, in case of asymmetry, if diffuse or segmental
2. the objective measurement of bilateral circumferential diameter of the affected and healthy limbs and of the subcutaneous fat thickness

3. the severity of LE that can be graded as absent, mild, moderate or severe [29,31]. LE was defined mild when: (a) the upper limit of subcutaneous infiltration was below the knee (when studying the lower extremities) or below the elbow (when studying the upper extremities), (b) the fluid infiltration of the subcutaneous tissue does not result in dimensional increase of the subcutaneous fat, (c) minimal epifascial fluid (thickness < 5 mm). LE was described as severe in the following cases: (a) when the subcutaneous infiltration is diffuse to the entire affected limb, (b) profuse fluid infiltration conditioning marked increase of the subcutaneous tissue thickness, (c) epifascial fluid thickness > 15 mm.

4. the presence of the honeycomb pattern [29,31], visible as trabecular/reticular structures in the subcutaneous fat

5. the thickening of dermis (dermis thickness > 2 mm)

6. any abnormalities in the muscle compartment, such as impaired/reduced tropism, atrophy, altered signal, fluid infiltration

7. the number of inguinal/axillary lymph nodes, their location and size

8. the appearance of loco regional lymphatic trunks [29]: aplastic, if no lymphatic trunk is visible; hypoplastic, if < 3 lymphatic trunks are recognizable; normal, when 3–6 lymphatic trunk are identifiable; hyperplastic, if > 6 lymphatic trunks are present or if their caliber is > 3 mm

9. the caliber [26] and dilatation of lymphatic vessels [28], presence of distal dilated lymphatic vessels (diameter > 1 mm) [29,31]

3. NCMRL indications

According to the studies reported in literature, NCMRL can be used with various purposes:

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NS = not specified in the article; TSE = Turbo Spin Echo.
3.1. Evaluation of the thoracic duct

Takahashi et al. [26], in a study on 113 patients affected by liver diseases or malignancy demonstrated that NCMRL with respiratory gating could visualize the whole thoracic ducts in 72.6% of cases and observed a significant dilatation of the thoracic duct in patient with alcoholic liver cirrhosis. The authors stated the utility of this technique for pre-surgical planning, but it has some limitations: the quality of the visualization of larger lymphatic vessels that can be dilated after thoracic duct ligation for gastric or esophageal surgery or can be injured during surgical interventions on pancreas, stomach or esophagus, resulting in abnormal dilatation of the abdominal lymphatic vessels with cystic appearance [28]. Another indication is the assessment of post-surgical abnormalities of lymphatic vessels that can be dilated after thoracic duct ligation for gastric or esophageal surgery or can be injured during surgical interventions on pancreas, stomach or esophagus, resulting in small lymphoceles [36].

3.2. Evaluation of retroperitoneal lymphatic vessels

NCMRL can be used to assess retroperitoneal lymphatic vessels, their anatomical variations or aneurysmal dilatation [27] and to diagnose and characterize abnormal conditions, such as retroperitoneal cystic lymphangioma [27], intestinal lymphangiectasia, lymphangioleiomyomatosis, post-surgical injury or dilatation [28].

Retroperitoneal cystic lymphangioma is a rare disorder, found predominantly in children, represented by uni or multilocular cysts containing lymphatic tissue in the wall [35], usually appearing as a cystic multiseptated mass with thin walls.

Intestinal lymphangiectasia is characterized by tortuous and markedly dilated lymphatic mesenteric vessels that can be well visualized on MR lymphangiography [28]; in lymphangioleiomyomatosis, NCMRL can show dilatation of the abdominal lymphatic vessels with cystic appearance [28]. Another indication is the assessment of post-surgical abnormalities of lymphatic vessels that can be dilated after thoracic duct ligation for gastric or esophageal surgery or can be injured during surgical interventions on pancreas, stomach or esophagus, resulting in small lymphoceles [36].

3.3. LE assessment

The diagnosis is LE is usually clinical, but NCMRL can be used to confirm the presence of a LE, which is visible as a fluid infiltration of the subcutaneous fat tissue, often visualized with a honeycomb pattern, associated with epifascial fluid collection [29], without any involvement of the muscular compartment (Figs. 2-6).

NCMRL can identify LE, assess its extent and grade its severity [29].

3.4. Differential diagnosis of LE

NCMRL allows a differential diagnosis between LE and fatty infiltration due to morbid obesity or lipoedema [29,33,34] and between LE and phlebedema: phlebedema is characterized by an involvement of the subfascial muscular compartment appearing as a dimensional increase, muscle edema or fatty degeneration [34]. LE is a disorder limited to the subcutaneous fat tissue and there is a saving in the involvement of the muscular compartment, also recently confirmed by a case series of 187 lower limbs LE [29] (Fig. 7).

3.5. Treatment planning of LE

There is no consensus about the imaging modality of choice for the evaluation of LE to establish the best treatment. X ray lymphangiography with oil-contrast injection has been abandoned, due to its invasiveness and possible complications [10,11]; lymphoscintigraphy can provide quantitative analysis of the lymph transport, but without a visualization of normal size lymphatic structures [12]. CEMRL demonstrated to have an excellent spatial resolution and can provide information regarding the anatomy of the lymphatic system and dynamic information of contrast medium transportation and nodal uptake [37]. This technique is useful for pre-surgical planning [13,14], but it has also some limitations: the quality of the visualization of larger lymphatic vessels (e.g. iliac trunks) is poorer than that of the distal lymphatic trunks [38] and the injected contrast medium is partially washed out through the circulatory system, thus causing an enhancement of the venous vessels that can be difficult to distinguish from the lymphatic structures [18]. In addition, a comparative study between CEMRL and NCMRL demonstrated a discrepancy in the assessment of number and caliber of lymphatics [39]: the authors hypothesized a reduced uptake of contrast medium in dilated lymphatic vessels caused by the raise in

![Fig. 2. Left lower extremity congenital LE. Coronal MIP reconstruction of lymphatic MRI showing left lower extremity congenital LE with characteristic epifascial distribution (arrows).](image-url)
Fig. 3. 70-Year old patient who underwent radical prostatectomy and lymphadenectomy for a carcinoma.

(A) True Fisp of the thighs.
(B) True Fisp of the legs.
(C) coronal MIP reconstruction of lymphatic MRI of the inguinal and iliac regions.
(D) inguinal axial T2 TSE.
Diffuse bilateral honey comb pattern of the subcutaneous fat tissue, which is markedly thickened (A, B, C) (arrows).
In MIP reconstruction (C), bilateral hypoplasia of left and right inguinal and lymphatic vessels; no inguinal lymph node is visible (D).

Fig. 4. Left leg congenital LE in a 14-year old girl.
(A) Coronal MIP reconstruction of the lower legs.
(B) Coronal True Fisp of the lower legs.
(C) Volume rendering calculated with ITK SNAP open source software.
Left leg LE with epifascial distribution (A). True Fisp sequence (B) can be automatically segmented through ITK SNAP open source software or other images analysis software to objectively calculate the volumes of healthy and affected limbs and to monitor treatment results.
the endolymphatic pressure.

In this context, NCMRL is starting to present itself as an optimal imaging technique for LE treatment planning [32]. In their study on 187 primary lower limb LE, Arrivé et al. [29] demonstrated an excellent correlation between the LE grading and characteristics of lymphatic trunks and the capacity of this examination to differentiate the type of LE in aplastic, hypoplastic or hyperplastic in order to choose the correct surgical strategy.

3.6. Follow up after treatment

There is no reliable method for follow-up LE after treatment. NCMRL, as a noninvasive technique, can be used to objectively evaluate the results of LE therapy. Arrivé et al. [31] reported a first experience on 15 patients affected by secondary LE following breast carcinoma treatment. They performed a pre-treatment NCLMR of the upper limb and a second examination at least 6 months after lymph node transplantation. In the presurgical MR they assessed: the severity of LE, the involvement of the muscular compartment, the evidence of distal dilated lymphatic structures; in the follow-up MR, they evaluated: the visualization of the transplantation site, the visualization of transferred lymph nodes and the LE severity in comparison with the previous MR (stable, reduced or increased). According to their experience, NCMRL can be used as an objective reproducible imaging examination to establish the course of LE after surgery.

4. Limitations and strengths

NCMRL has some limitations. First of all, diagnostic experiences with this relatively new technique are few: more investigations with larger patient case series are still needed to validate the use of this examination, to accurately determine the areas of application, and maybe even to improve the technique.

Secondarily, non-contrast lymphangiography cannot depict normal

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**Fig. 5.** Primary tarda LE in a 38 year old woman.
Bilateral LE of the lower third of the legs with epifascal distribution (A) (arrows).
Hyperplasia of inguinal lymphatic vessels on both sides (B) (arrow head).

**Fig. 6.** Primary LE in a 10 year old female child.
LE of the right leg (A), more represented at the ankle level (B) (arrow).
or hypoplastic lymphatic structures [30], only when the lymphatic fluid is impaired, the vessel is dilated and filled with stagnated lymph, and it becomes visible on NCMLR.

Third, because of the absence of contrast medium, NCMLR does not provide functional information about the timing of the lymphatic drainage or the nodal uptake, unlike CEMRL.

Moreover, NCMLR has limited spatial resolution, therefore CEMRL results to be the best technique for the evaluation of distal lymphatic vessels; however, NCMLR seems to be superior for the analysis of proximal lymphatic trucks, such as inguinal and iliac [29].

Although so far not reported by the studies in the literature, we must also consider as a limitation the possibility of confounding influence of fat; therefore, according to our experience, the sequences without fat saturation are useful for an optimal evaluation of the extension of size increase of the involved limbs and to obtain reproducible measurements, especially useful in the follow-up of treatment. On the other side, the heavily T2-weighted sequences, resulting signal loss in tissue background, with highlighting of static fluids, allow the visualization of epifascial fluid components and lymphatic vessel. The most important advantage of this technique is the non-invasiveness and the non-need to administer contrast medium: this means great benefits for allergic patients and for pediatric patients, who can safely undergo this type of examination, and no risk related to gadolinium deposition. Moreover, the absence of contrast medium results in lower costs, when compared to CEMRL. Another advantage against CEMRL is the short acquisition time: in at least half an hour patient positioning and imaging acquisition of the whole lower limbs are performed, while for CEMRL a total average examination time of 1 h and 15 min for the lower limb is expected [17] and faster acquisition time means further cost reduction.

5. Conclusion

NCMLR is a non-invasive imaging technique, useful for the analysis of LE.

It seems to be a valuable tool in the diagnosis and the surgical planning of LE, providing helpful anatomical information on the type of LE, on the lymph nodes number and the sites suitable for nodal transplantation and LE follow up after surgery.

Further studies with more extensive cases are necessary to validate this technique.

Declarations of interest

None.


