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DIAGNOSTIC PROTOCOL FOR LYMPHOSCINTIGRAPHY IN NEWBORNS

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ABSTRACT

The purpose of this methods paper is to offer pediatricians and nuclear medicine physicians a diagnostic protocol for performing lymphoscintigraphy in newborns that may be useful for enhancing diagnosis and management of newborns with congenital lymphatic abnormalities. Indications for lymphoscintigraphy, choice of tracer, optimal dose, routes of administration, methods of data acquisition, timing, and interpretation of results for newborns are presented and discussed.

Lymphoscintigraphy is a minimally invasive technique that provides valuable morpho-functional information regarding the lymphatic system. It highlights the accumulation and transport of lymphatic fluid in the interstitial tissue, disturbances in which may cause swelling, most evident in the limbs (1,2). Early and precise diagnosis of lymphedema and other lymphatic disorders may prevent a range of complications that may lead eventually to extensive disability (3-5). Furthermore, lymphatic pathology can be specifically defined and distinguished from non-lymphatic causes of edema and effusion.

The introduction of new tracers, instrumentation, and approaches to therapy now allow Nuclear Medicine procedures to provide more accurate and therapeutically relevant information on superficial and deep lymphatic vessels. Recently, lymphoscintigraphy has been utilized in the evaluation of lymphedema by functionally highlighting the lymphatic outflow of any region of interest, up to the tributary lymph nodes of that region and beyond. Semi-quantitative evaluations, although technically difficult, can be important for recognizing early even pre-clinical stages of the disorder (1,6,7). Yet, the protocol for lymphoscintigraphy is not standardized and differs among diagnostic centers (6, and references therein, 8) with regard to choice of tracer, type and site of injection, use of dynamic and static acquisition, and the acquisition times themselves.

No literature is currently available regarding the standardization of lymphoscintigraphy in the field of neonatology and specifically in the special population of newborn infants with peripheral lymphedema and/or effusions. Thus, there is a need to standardize the guidelines for lymphoscintigraphy, especially with regards to tracer

characteristics, injection sites, image recording, and resulting drainage pattern of radiotracer particles. The aim of this paper is to define a protocol for the use of lymphoscintigraphy in newborns, by specifying choice of tracer, proper dose, modalities of administration, methods of data acquisition, both examination times and calculations of transport time, and lastly to indicate the main clinical disorders of the newborn for which lymphoscintigraphy would be applicable.

METHODS

Patients

The Neonatal Intensive Care Unit of the University of Genoa, Gaslini Institute, with the Nuclear Medicine Service of the San Martino Hospital of Genoa, and with the Section of Lymphatic Surgery and Microsurgery of the University of Genoa evaluated newborns affected by primary lymphedema of various etiologies, during the period from January 1998 to December 2002. A total of 22 patients (age range 2-7 months) were seen, and all patients underwent lymphoscintigraphy. These cases allowed us to establish a protocol for lymphoscintigraphy in newborns to evaluate both deep and superficial lymphatic circulation during the same session.

Patient Preparation

The parents or guardians are given information about the procedure itself and especially about the waiting time between injection(s) and lymphoscintigraphy, as well as the probable duration of the actual scan. Informed consent is obtained. A special explanation about the necessity of having a calm patient is important. Sedation is usually not required for a technically satisfactory examination, but in some patients who cannot or do not cooperate, mild sedation may be necessary. The safest drug is intranasal or per-rectal midazolam. Nevertheless, if sedation is used, it must follow local hospital guidelines. When sedation is employed, the newborn's oral fluid intake is limited so spontaneous micturition will not occur. Under such circumstances, a bladder catheter may be necessary. There are neither contraindications nor specific precautions to the imaging procedure, only to the sedation procedures.

There is no general agreement regarding stress lymphoscintigraphy. In adult examinations, stress maneuvers include walking, standing, limb massage, standardized treadmill exercise, bicycle exercise, repetitive squeezing of a rubber ball, and the use of a hand-grip exercise device. Massage, exercise, and standing, which enhance radiotracer transport from the injection site, have also been proposed. It is not possible to perform such maneuvers when evaluating a newborn. During several types of diagnostic procedures, a newborn needs to be restrained to limit spontaneous motor activity because movements may complicate lymph transport analysis and also interfere with obtaining good quality images. We decided not to perform a rigid bonding and rather, allowed limited movements. Following injection into the upper and lower extremities, a massage is carried out, lukewarm packages are positioned on the 4 inoculation sites, and the newborn is allowed spontaneous motor activity for 20 minutes. Finally, the newborn is restrained to obtain images.

Methodology (Procedure), Radiotracers

A choice of Technetium-99m (99mTc) tagged tracers at a dose of 5MBq (0.135 mCi) in 0.3 ml each, includes colloidal particles with a diameter of 30-80 nm, particles of colloidal sulfurs with a diameter of 30-50 nm (Lymphoscint Solco®, Amersham Health), or 99mTc-microcolloidal sulfide (Lymphoscint, Namocool®; Solco Basel Ltd., Basel, Switzerland),with a particle diameter of less than 50 nm. Lymphoscint Solco® has a favorable particle size for scintigraphy, and

the labeled preparation is isosmolar to interstitial fluid, providing painless, subcutaneous administration. The radiotracers require an acid pH level for stability, which often causes the patient to experience a very brief burning sensation at the injection site.

Dose and Injection Site

To evaluate the superficial lymphatic circulation, three aliquots of tracer (0.1 ml each) are injected intradermally (epifascial) by a 25 gauge insulin needle into skin soft tissue above the second, third, and fourth metacarpal- and metatarsal-phalangeal joints of the hands and feet with 2 additional deep injections (subfascial) into each hand/foot. All injections are performed at the same time. The manufacturer's recommendations for the adult dose by single or multiple subcutaneous (interstitial) injection in current clinical practice range from 18.5-185 MBq (0.5-5 mCi) per injection site. Recommended volume per injection is 0.2-0.3 ml; a maximum volume of 0.5 ml per injection site should not be exceeded. Pediatric doses have not yet been definitively established. We followed the European Association of Nuclear Medicine recommendations to calculate the administered activity for the body weight, according to the following ratio (fraction of adult dose): 3 kg = 0.10; 4Kg = 0.14; 6 Kg = 0.19. There are no specific recommendations for the neonatal age. Subfascial injection of radiotracers is used to investigate the deep lymphatic system of the extremities, and combination with epifascial and subfascial route of administration produces a better differentiation of the various lymphatic features underlying extremity edema. We avoid local anesthetic agents (such as lidocaine) as they may alter local lymph dynamics. In our experience, however, the use of a superficial anesthetic cream has not produced any disturbance in lymph flow and can improve patient comfort. An iodine solution or alcohol swab is used to clean the injection site.

Parameters for Dynamic Acquisition (Imaging)

Images are recorded using high-resolution parallel-hole collimators with whole-body scanning mode, 10% window centered on the 140-KeV photopeak of 99mTc, a scan of 10 cm/min, and a dedicated computer. Data are displayed with the upper level set to show the small fraction of tracer that emigrates from the injection site to the nodes. The images are acquired with a gamma-camera to great field (Elscint APEX SP-6HR) with a collimator for low energies and high resolution (APC-45HR) (matrix 128 x 128; zoom 1; duration of each frame is 20 sec; duration of the acquisition is 10-15 min).

The gamma-camera is positioned as close as possible and anteriorly to the patient, who is in a supine position. The dynamic acquisition allows the visualization of the principal lymphatic channels and the first draining lymph nodes, which are the quantitative parameters in the transport index (TI). At the end of the dynamic acquisition, the study continues with the static images and uses the following parameters: matrix 256 x 256; zoom 1; duration of the acquisition 300 sec. Due to the small body dimension of neonates, it is possible to record data from all four injection sites at the same time. This allows reduction in exam time and the use of one side as control for patients with unilateral lymphedema.

Both the semi-quantitative and qualitative approaches to newborn lymphoscintigraphy have been taken into consideration. Semi-quantitative lymphoscintigraphy is considered by some a better technique than qualitative, in particular for detecting mild grades of lymphedema. Clearance rate and regional lymph node measurement are usually performed. Semi-quantitative evaluation of lymphatic drainage is established by a numeric index (transport index: TI) (9) calculated by the formula TI = K + D + 0.04T + N + V, where K is lymphatic transport kinetics (no delay, low grade delay,

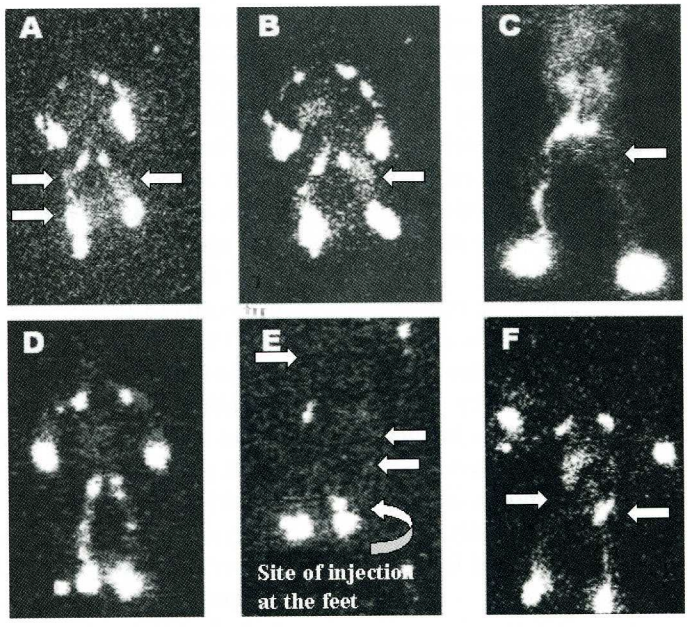

Fig. 1. Lymphoscintigraphy in newborns: Images and Transport Index (T.I.). Panel A: Dermal back flow (DBF) at the left lower limb and right delayed tracer drainage (arrows) in newborn affected by congenital leg lymphedema and chylothorax (T.I. 18). Panel B: Newborn with left leg lymphedema and a moderate quantity of chylous ascites. DBF at the left lower limb (arrow) (T.I. 18). Panel C: Absent visualization of left inguinal nodes in newborn (arrow) with peripheral left leg lymphedema, chylothorax and chyloperitoneum (T.I. 27). Panel D: Normal peripheral lymphoscintigraphic pattern in newborn with chylous ascites (T.I. <10). Panel E: Peripheral left leg and right arm congenital lymphedema. Absent visualization of right axillary (single arrow) and left inguinal nodes (double arrow) (T.I. 36) Panel F: DBF at the left thigh and absent visualization of right inguinal lymph nodes in newborn with peripheral leg lymphedema and chylous ascites (T.I. 27). A slight diffusion of the tracer is evident at the site of chylothorax and chyloperitoneum in all lymphoscintigraphic patterns.

extreme delay, lack of transport are 0, 3, 5, and 9, respectively), D is the distribution pattern of the tracer (normal, partial diffuse, diffuse, transport stop are 0, 3, 5, and 9, respectively), T is the time in minutes of tracer appearance in the lymph nodes (time in minutes to appear, no appearance is 9), V is the ratio between the visualization of lymph vessels and graft (nodes and vessels, respectively, clearly demonstrated, faint visualization, hardly recognizable, no visualization are 0, 3, 5, and 9, respectively). Each parameter ranges from 0 to 9, so total evaluation ranges from 0 (normal) to 45 (pathological). Transport index in healthy extremities has been found to be less than 10 (9-11).

Information about Previous Examinations Relevant to this Procedure

Previous lymphoscintigraphy scans should be available for review and to ensure that sufficient time has elapsed since the previous study (depending on the patient's chart and presentation). The most recent relevant radiographs and CT or MRI scans should also be available for comparison.

RESULTS

On the basis of the experience acquired through the collaboration of Neonatal Intensive Care Unit of the University of Genoa, Gaslini Institute, with the Nuclear

Medicine Service of the San Martino Hospital of Genoa, and with the Section of Lymphatic Surgery and Microsurgery of the University of Genoa in the evaluation of newborns affected by primary lymphedema of various etiologies, we have established a protocol that allows us to evaluate both deep and superficial lymphatic circulation during the same imaging session. Clinical examples of lymphoscintigraphy in newborns have been provided here and can be found also in an earlier article *(Fig. 1)* (12). The procedure was successful in obtaining high quality scintigraphic images of newborns. The images identified delayed tracer transport, dermal diffusion, and absence of lymph nodes on whole body images *(Fig. 1)*. Additionally, transport index values were calculated for all images (legend *Fig. 1*).

DISCUSSION

Diagnosis and management of a newborn affected by primary lymphedema is a challenge (13-17,19) and currently relies on history and physical exam. A newborn presenting with lower extremity edema and a family history of lymphedema is easier to diagnose than one with no family history. Initially, the edema is soft and pitting, but over the course of months and years, the swelling becomes hard and "non-pitting," and the skin thickens from the overgrowth of connective and adipose tissue accompanying lymphostasis. Since the cutaneous lymphatics are not functioning adequately, the local immune response is impaired, and recurrent skin infections may occur, leading to further damage to the lymphatics and worsening of lymphedema. Early diagnosis during the neonatal age is important to prevent the rapid evolution of lymphedema. Lymphoscintigraphy offers objective evidence to distinguish lymphatic pathology from non-lymphatic causes of extremity edema (7,8,16). Delay, asymmetric or absent visualization of regional lymph nodes, dermal "backflow," asymmetric visualization of lymphatic channels, collateral lymphatic channels, interrupted lymphatic structures, and abnormal lymph nodes in the deep lymphatic system are the main criteria used to define lymphatic dysfunction. Borderline cases may occur in the newborn. In these cases, quantitative analysis may increase the sensitivity and specificity of lymphoscintigraphy in the early diagnosis of lymphatic disorders of the newborn (18,19).

The characteristics of the ideal tracer for lymphoscintigraphy are highly dependent on colloid particle size and stability (19,20). There has to be homogeneous dispersion of small particles (diameter <100 nm) for the colloid to migrate from the injection site to the lymphatic channels and lymph nodes. Larger particles (500-2,000 nm) remain trapped at the injection site, while smaller particles (approximately 5 nm) penetrate through the blood capillary barrier, and lead to possible misinterpretation of the scintigraphic pattern. Due to the reduced size of newborn lymphatic vessels as compared to adult vessels, the choice of particle size is extremely important. Newborns may present with congenital lymphedema. In these cases, emphasis should be placed on rapid visualization of the lymphatic vessels rather than the lymph nodes. In this view, the optimal range of particle size is generally skewed toward the lower end of the useful range for colloids. On the basis of our experience, we found that the optimal size is below 30-50 nm, in order to ensure rapid lymphatic drainage. This dimension allows good transport and minimizes significant entrapment at the injection site.

Lymphoscintigraphy of the extremities is generally performed by injecting the tracer in the interdigital space of the hands and feet (6,21,22). Intradermal or subdermal-subcutaneous injections are often defined as synonymous. However, these terms are not totally interchangeable from the standpoint of lymphatic drainage. The very limited tissue space of the hands and feet in the newborn may generate further confusion

between intradermal and subdermal injection. The epifascial lymphatic circulation constitutes the superficial lymphatic system, whereas the subfascial circulation is the deeper system. Therefore, on the basis of the present protocol, full evaluation of lymphatic circulation, which is especially useful in the congenital form of lymphedema, requires both epifascial and subfascial tracer injections to be performed. In our experience with congenital lymphedema of the newborn, we have found that, although tracer drainage is faster through the superficial system than the deep one, performing the visualization of the deep system first is preferable. The pattern of deep lymphatic circulation is predictable since the subfascial lymphatics are represented by relatively few, large vessels that follow the general path of the major blood vessels in the extremities. On the other hand, the pattern of the superficial lymphatic circulation is more variable and is usually represented by more abundant lymphatic vessels. When lymph flow and pressure are within physiologic limits, the superficial and deep lymphatic systems are quite independent, usually with very little or no exchange of lymph between them in either direction. If significant lymph stasis occurs, the deep lymphatic system may shunt towards the superficial lymphatic vessels. This important diagnostic clue could easily be missed when there is persistent visualization of the superficial lymphatic system by prior injection of radiocolloid.

Although several methods have been reported for the semi-quantitative assessment of lymphoscintigraphic patterns, a description of the findings is usually sufficient for the general interpretation of lymphoscintigraphic patterns. The combined evaluation of the epifascial and subfascial lymphatic system allows the detection of abnormal communication between the two systems, i.e., such as altered lymph flow patterns (6,21-23).

In conclusion, lymphoscintigraphy is very useful in evaluating primary lymphedema of the newborn and related lymphatic disorders, both to obtain an etiologic diagnosis and also for important physiologic and anatomic information for treatment including preoperative planning. The procedure is relatively easy to perform, safe, reliable, minimally invasive, and only slightly discomforting for the patient compared to conventional contrast lymphangiography, which is difficult to perform and may be potentially dangerous. Indications for this diagnostic tool encompass all types of primary lymphedema and lymphangiodysplasias such as peripheral lymphedema, congenital chylothorax, chylous pericardial effusion, and chylous ascites, as well as the lymphangiectasias (intestinal, pulmonary, or affecting other organs), either alone or in combination. The presence of these conditions "in utero" or of non-immune hydrops fetalis are further indications to perform lymphoscintigraphy as soon after birth as possible.

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