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Classification of Lymphatic-system Malformations in Primary Lymphoedema based on MR Lymphangiography

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WHAT THIS PAPER ADDS

- A comprehensive classification of lymphatic-system malformation in primary lymphoedema is proposed and may lead to further study of the aetiology as well as rational treatment of the disease.

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ABSTRACT

Objectives: The study aims to investigate lymphatic-system malformations and proposes a classification of primary lymphoedema based on comprehensive imaging data of both lymph vessel- and lymph-node abnormalities.

Materials and methods: A total of 378 patients with primary lymphoedema of the lower extremity were examined with magnetic resonance lymphangiography (MRL) using gadobenate dimeglumine as contrast agent. Lymph vessels and drainage lymph nodes were evaluated, leading to the proposal of the classification of primary lymphoedema and the relative proportions.

Results: A total of 63 (17%) patients exhibited defects of the inguinal lymph nodes with mild or moderate dilatation of afferent lymph vessels. A total of 123 (32%) patients exhibited lymphatic anomalies as lymphatic aplasia, hypoplasia or hyperplasia with no obvious defect of the drainage lymph nodes. The involvement of both lymph vessel- and lymph-node abnormalities in the affected limb was found in 192 (51%) patients. The primary lymphoedema was classified as three major types as: (1) lymph nodes affected only; (2) lymph vessel affected only with three subtypes and (3) both lymph vessel and lymph node affected with subgroups.

Conclusions: A comprehensive classification of lymphatic-system malformation in primary lymphoedema is proposed, which clearly defines the location and pathologic characteristics of both lymphatics and lymph node and may lead to further study of the aetiology as well as rational treatment of the disease.

Primary lymphoedema is defined as oedema caused by lymphatic dysplasia and/or dysfunction due to congenital[1,2] or unknown factors. Primary lymphoedema occurs in 1 of every 10,000 people in the general population.[3] Patients with primary lymphoedema exhibit diverse clinical signs.[4] The disorder most commonly affects one lower extremity. Management of the individual patient has been hampered by difficulties in understanding the complex underlying pathophysiology and determining the prognosis. Kinmonth classified primary lymphoedema: (1) by the age at the time of onset; under this classification, the congenital type is relatively rare and presents at birth, while praecox is a more common type, developing during puberty, and the tarda type occurs after the age of 35 years and (2) by the abnormality of lymphatic vessels including aplasia, hypoplasia, hyperplasia and lymph-node fibrosis.[5] However, Kinmonth's classification is based on direct lymphangiography excluding patients for whom lymphatic cannulation is not possible. Furthermore, direct lymphangiography is limited to imaging part of the superficial lymphatic territory instead of mapping the entire lymphatic system. Kinmonth noted lymph-node abnormalities such as fibrosis in primary lymphoedema. However, X-ray imaging cannot clearly delineate nodal pathology.

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Recent improvements in imaging techniques have aided the study of lymphatic disease. Magnetic resonance lymphangiography (MRL) has emerged as a powerful imaging technique for the diagnosis of lymphatic disorders.[6–10]Dynamic and real-time observation of contrast enhancement in lymphatic vessels and drainage nodes with high-resolution images can provide comprehensive information concerning both the structural and functional abnormalities of the lymphatic system in primary lymphoedema and lymphoedema-related disease.[7] Intracutaneously injected paramagnetic contrast material was found to be easily absorbed by initial lymph vessels. As such, all patients including those with lymphatic aplasia were examined and included in the present study. We conducted repeated MRL examinations evaluating some patients twice or more to follow treatment outcomes and the course of the disease. Compared with commonly used lymphoscintigraphy techniques, MRL is more sensitive and accurate for outlining the morphological and structural changes to the lymphatic channel and lymph node.[11] In the current study, 378 patients with primary lymphoedema of the leg were examined using MRL. The lymph collectors and drainage nodes were studied as a whole system. The MRL data revealed lymphatic-system abnormalities that were more complex than those described in any previous report.[3–5] The current article summarises imaging results from 378 patients, and proposes a comprehensive classification system for lymphatic-system malformations in primary lymphoedema.

Materials and Methods

The present study included 378 patients diagnosed with primary lymphoedema (180 men and 198 women with a mean age of 33 years; range 5–77 years). Patients who had experienced adenolymphangitis, injury, tumour, radiotherapy or surgery before the onset of oedema were not included in the study. Of the selected patients, 297 exhibited unilateral lymphoedema, and 81 exhibited bilateral primary lymphoedema in lower extremities. The mean duration of disease across all patients was 12 years, ranging from 4 months to 55 years. Seven patients exhibited true congenital familial lymphoedema.

MRL was performed as described previously,[7,8] using a 3.0 T MR unit (Philips Medical System, Best, the Netherlands). First, three-dimensional (3D) heavily T2-weighted magnetic resonance imaging (MRI) was performed. After injection of the paramagnetic contrast agent gadobenate dimeglumine (Gd-BOPTA) into digital web spaces (0.7–0.8 ml/each point; MultiHance®; Bracco, Milan, Italy), 3D fast spoiled gradient-recalled echo T1-weighted images were acquired using a fat-saturation technique at consecutive time points for dynamic observation, Six consecutive inspections were performed in the leg, with each inspection taking 3 min. Five consecutive inspections were performed in the inguinal region and thigh each taking 3 min. Maximum intensity projection (MIP) reconstruction imaging was performed to map lymphatic vessels. Imaging of regional lymph nodes was acquired before and after contrast injection. The enhancement of contrast in regional lymph nodes was recorded and measured as the ratio of nodal/muscle signal intensity for direct comparison between bilateral inguinal lymph nodes. The lymph collectors and their drainage nodes were treated as a whole system in the analysis and classification of imaging data from primary lymphoedema limbs.

Results

After intracutaneous injection, the contrast was rapidly absorbed by the primary lymph vessels and transported with the lymph. The enhancement of lymphatic vessels and lymph nodes was inspected during the dynamic MRL and the drainage patterns of lymphatic vessels and nodes were clearly observed. Importantly, no enhanced lymph vessels were visualised in most contralateral healthy limbs. In some non-oedema limbs, weaker enhanced lymphatic channels were observed (Fig. 1(a)) and inguinal nodes were enhanced rapidly and completely (Fig. 2). Changes of the lymphatic system in primary lymphoedema can occur in the lymph vessels, the nodes, or both. The MRL findings regarding the lymph vessel- and lymph-node anomalies in 378 primary lymphoedema cases are summarised in Table 1.

Lymphatic anomalies

The number of lymphatic vessels ranged from 0 to numerous, and the diameter ranged from 0.5 to 8 mm in lymphoedematous limbs. The classification of lymphatic abnormality was determined mainly on the basis of the number and shape of the vessels. In cases of aplasia/hypoplasia, the peripheral vessels were either absent or severely hypoplastic in terms of number and size. In cases of

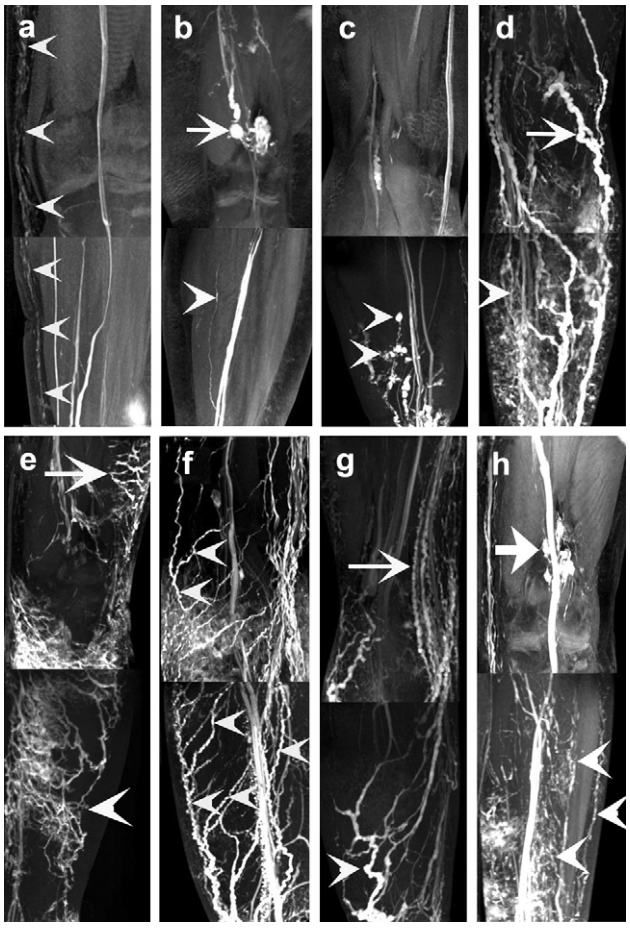

Figure 1. Composition images of MR lymphangiogram shows various lymphatic drainage pathways in primary lymphoedematous limbs. (a) A few weaker enhanced lymphatic vessels (arrowhead) in the inner side of lower limb of healthy volunteer. (b) Enhanced lymph vessels with cystic dilatation (arrowhead) in the distal part of the leg. (c) Numerous aberrant tortuous vessels with a mixture of larger (arrow) and smaller vessels (arrowhead). (d) A crisscross network of hyperplastic vessels in the thigh (arrow) and the calf (arrowhead). (e) Single deep lymph vessel (arrowhead) and popliteal nodes (arrow) were enhanced with absence of superficial lymph vessel. (f) Both superficial lymphatics (arrowhead) and deep lymph vessels and popliteal nodes (arrow) were involved. (g) Numerous hyperplasic lymph vessels with regular fold throughout the limb. (h) Treelike varicose lymph vessels in the calf (arrowhead) and channels with regular fold in the thigh (arrow).

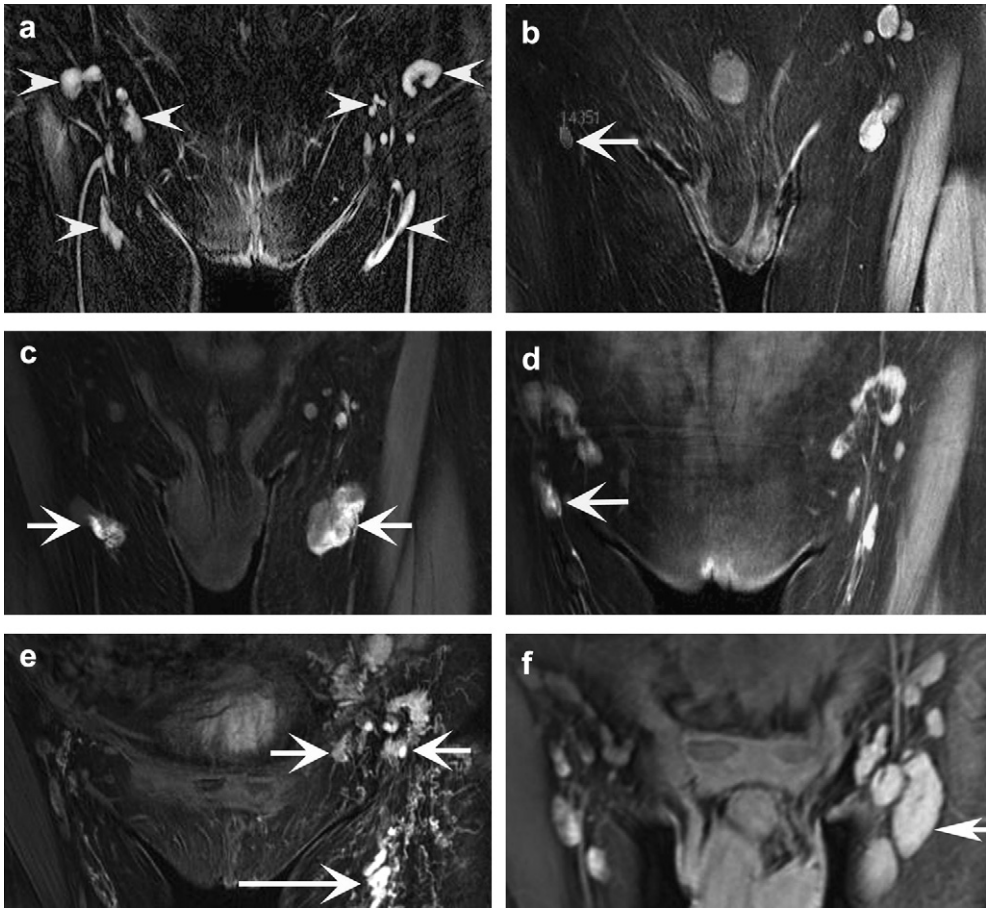

Figure 2. Diverse inguinal nodes abnormalities of primary lymphoedema displayed on MR Lymphangiogrames. (a). Imaging of inguinal lymph nodes (arrowhead) in healthy volunteer that were evenly enhanced and symmetry in shape and arrangement. (b) Single small node in a limb (arrow) with lymphatic hypoplasia and lymphoedema is compared with lymph nodes in a limb without lymphoedema. (c) Partially contrast-enhanced inferior inguinal nodes (arrow) in bilateral lymphoedema with secondary lymphatic dilatation. (d) Central part enhanced inferior inguinal node (arrow) compared with evenly enhanced contralateral healthy nodes. (e) Small nodes that are irregular shaped (small arrow) in a limb with lymphangiectasia (large arrow). (f) Enlarged inguinal lymph nodes (arrow) with homogeneous texture in the left side in contrast with lymph nodes of normal size in the right side.

hyperplasia, varicose lymphatic vessels were numerous, tortuous and dilated, and were observed in the limb and trunk. A total of 209 patients were diagnosed with lymphatic aplasia/hypoplasia. No superficial lymphatic trunks were visualised in the affected limbs of 70 patients. In 18 patients, only 1–2 deep lymph vessels were identified (Fig. 1(b)). A small number of superficial lymph vessels were visualised in 121 patients. Among these patients, the enhanced vessels stopped in the distal part (above the ankle) of the limb in nearly half of the cases (Fig. 1(c)). A total of 106 patients were diagnosed with lymphatic hyperplasia of the affected limbs, in which numerous aberrant tortuous vessels were strongly enhanced. The results revealed considerable variability in the sizes and distribution patterns of the lymphatic trunks (Fig. 1(d)–(g)). Both the superficial and deep lymphatic system were affected in 29 patients (Fig. 1(h)). Of these patients, 16 exhibited chylous reflux.

Table 1
MRL findings of lymph node & lymph vessel dysplasia in 378 patients with primary lymphoedema.

	No. of patients
Lymph node anomalies	272 (72%)
Lymph node affected only with nodal structural abnormal	63
Lymph node structural abnormal with lymphatic hypoplasia/hyperplasia	105 (77/28)
Lymph node hypoplasia with lymphatic hypoplasia/hyperplasia	77 (39/38)
Lymph node hyperplasia with lymphatic hypoplasia/hyperplasia	27 (8/19)
Lymphatic anomalies	315 (83%)
Lymphatic affected only	106
Lymphatic dysplasia with nodal abnormal	209
Lymphatic hypoplasia	209
No visualised superficial vessel	70
A few superficial vessels	121
Deep lymphatic visualised only	18
Lymphatic hyperplasia	106
Superficial vessel affected only	77
Both superficial & deep vessel affected	29
Chylous reflux	16

Lymph-node anomalies

Lymph-node abnormalities fell into three major categories, aplasia/hypoplasia, or hyperplasia or structural abnormalities. The common pathological features of affected lymph nodes included: significant increases or decreases in size and number (or total absence), irregular outline, heterogeneous texture and partial (marginal or central region) contrast enhancement (Fig. 2(b)–(f)). Of 378 patients, 272 showed morphological changes of the inguinal and/or iliac lymph nodes. Among 272 patients with severely affected nodes, 120 had never experienced cellulitis or lymphadenitis.

Of 272 patients, 63 exhibited more severely affected nodes than vessels, with moderate dilatation of the vessel without obvious

changes in number and shape and could not be included in the hypoplasia or hyperplasia groups. Interestingly, malformations of lymphatic vessels were not always concordant with those of the lymph nodes. Among 77 patients with hypoplasia of the inguinal lymph nodes of the affected limbs, 38 exhibited hyperplasia of the efferent lymph vessels. In contrast, among 27 patients with hyperplasia of the inguinal lymph nodes eight exhibited lymphatic hypoplasia. The coincidence of hypoplasia of lymphatic vessels and lymph nodes of the affected limbs was observed in 39 patients. Evidence of abnormalities in both lymphatic vessels and drainage lymph nodes, exhibited as hyperplasia, was observed in 19 patients. The iliac lymph-node abnormalities were commonly seen in the lymph node and lymphatic hyperplasia groups.

Classification of lymphatic-system anomalies

In summary, the MRL findings of lymphatic-system anomalies in primary lymphoedema were divided into three major patterns. Evident defects of the inguinal lymph node with moderate dilatation of afferent lymph vessels were observed in 63 patients (17%). Lymphatic anomalies, including lymphatic aplasia, hypoplasia or hyperplasia with no obvious defect of the drainage lymph nodes, were observed in 106 (28%) patients. Abnormalities of both lymph vessels and lymph nodes in the affected limb were exhibited in 209 (55%) cases. Based on these results, we propose the following classification of lymphatic-system abnormalities in primary lymphoedema using MRL imaging:

(1) Only lymph nodes affected, with nodal structural abnormalities,
(2) Only lymph vessels affected:
  (a) lymphatic aplasia/hypoplasia and
  (b) lymphatic hyperplasia
(3) Lymph vessels and lymph nodes affected, with subgroups:
  (a) lymphatic and nodal aplasia/hypoplasia,
  (b) lymphatic aplasia/hypoplasia + nodal hyperplasia,
  (c) lymphatic aplasia/hypoplasia + nodal structural abnormalities,
  (d) lymphatic and nodal hyperplasia,
  (e) lymphatic hyperplasia + nodal aplasia/hypoplasia and
  (f) lymphatic hyperplasia + nodal structural abnormalities.

Clinical data regarding this MRL classification are presented in Table 2. We found no clear difference between groups regarding the onset time of lymphoedema. The frequency of tarda development of lymphoedema was 40% (26/63) in the lymph node affected-only group, followed by 29% (36/124) in the nodal abnormal/lymphatic-hyperplasia group, 10% (9/85) in the nodal abnormal/lymphatic-hypoplasia group and 8% (9/106) in the lymphatic affected-only group. The tarda type thus appeared to be relatively common in lymph node-related lymphoedema. There was no significant difference in the severity of disease between the lymphatic/node hypoplasia and hyperplasia groups. In general, oedema became more extensive and tissue fibrosis progressed as the course of the disease progressed in all groups. The seriousness of oedema and fibrosis appears to be more relevant to the course of the disease than the type of lymphatic-system malformations involved. Oedema in the ankle and foot was most common in the lymphatic hypoplasia-only group. Oedema in the thigh and/or extragenital sites and/or buttocks and lower abdomen wall were more common in the inguinal lymph node aplasia/hypoplasia and node affected-only types.

Discussion

Primary lymphoedema is typically managed as a chronic lymphoedema without consideration of its background as a congenital vascular malformation.[12] The present report summarises diverse lymphatic and lymph-node malformations in 378 patients with primary lymphoedema based on high-resolution MRL images. The classification proposed in the current report covers three major types of lymphatic-system malformation in the disease as follows: only lymph nodes affected, only lymph vessels affected and both lymph vessels and lymph nodes affected. These types contain respective subtypes. This updated classification system clearly defines the location and pathological characteristics of the disease to provide a clear and more useful definition. Therefore, the proposed system is likely to be more convenient and understandable for clinical workers and patients, and to facilitate investigations into the respective aetiologies of the pathological changes in the vessels and nodes involved in the disease.

The current results revealed that the malformations of lymph vessels were not always concordant with those of the lymph nodes in primary lymphoedema. The lymph vessel and node may be affected together or alone, and may express different types of anatomical anomalies. The latter category is not included in Kinmonth's classification.[5] Some patients with hyperplasia of the lymphatic vessels of the affected limbs were found to exhibit an absence of drainage lymph nodes, and some with hyperplasia of the inguinal lymph nodes exhibited few afferent lymph vessels. The diverse morphological anomalies of the lymphatic system, and the discordance of pathological changes between lymph vessels and nodes, indicate the complexity of the pathoaetiology of the disease. Recent studies with newly discovered molecules have revealed that the process of lymphatic-vasculature development involves three

Table 2
Clinical data between the MR lymphangiographic classifications.

	Lymph node affected only	Lymphatic affected only		Lymph node abnormal/lymphatic hypoplasia			Lymph node abnormal/lymphatic hyperplasia		
		Aplasia/hypoplaisa	Hyperplasia	Nodal hypoplasia	Nodal hyperplasia	Nodal structural anomalies	Nodal hypoplasia	Nodal hyperplasia	Nodal structural anomalies
No. of patients	63	85	21	39	8	77	38	19	28
Male:female	(35:28)	(31:54)	(13:8)	(16:23)	(3:5)	(31:46)	(21:17)	(13:6)	(17:11)
Congenital	12	21	7	14	2	14	7	6	3
Praecox	26	57	11	17	4	37	25	13	22
Tarda	25	6	3	8	2	26	6	0	3
Unilateral	47	59	18	34	8	51	31	17	23
Bilateral	16	26	3	6	0	16	7	2	5
Infection									
No	41	45	7	19	4	34	18	9	6
Few	13	23	7	8	2	18	10	3	9
Frequent	9	17	7	12	2	25	11	7	13

stages:[13,14] (1) lymphatic specification and budding, and formation of primary lymph sacs, the mutual development of the lymphatic vasculature and the lymph nodes then stops, and both structures develop independently of each other; (2) lymphatic sprouting and blood–lymphatic vascular separation; and (3) the remodelling and maturation of the initial lymphatic-vessel network into lymphatic capillaries and lymphatic collecting vessels. The heterogeneous phenotype of lymphatic-system abnormalities in primary lymphoedema may result from events occurring at different stages of embryonic development of the lymphatic system.[13,15,16] For example, hypoplasia of lymph vessels may result from a failure or lack of endothelial budding. The hyperplasia of both lymphatic channels and drainage nodes is likely to result from an event occurring during lymphatic specification and budding, or at the stage of the formation of primary lymph sacs before the separation of lymphatic vessels and lymph-node development.

In conclusion, the current report proposes a novel classification based on high-resolution MRL that covers three major types of lymphatic-system malformation in primary lymphoedema. This new classification system may be helpful in further studies focussed on the development of more appropriate target-oriented treatment.

MRL is a relatively new approach. We made the comparison of MRL with lymphoscintigraphy in our previous study;[11] the data are not included in the present report. The reproducibility of MRL in evaluating lymphatic disorders will further be demonstrated in a separate paper.

Ethical Approval

None.

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Conflict of Interest

None.

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