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Paediatric lymphoedema: An audit of patients seen by the paediatric and primary lymphoedema group of vascular European Reference Network (VASCERN)

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ABSTRACT

Little is known about the overall prevalence of lymphoedema in children and the types of paediatric lymphoedema seen by specialist centres. Therefore, this study was aimed to provide a profile of children with primary or secondary lymphoedema seen by the expert centres of the paediatric and primary lymphoedema working group (PPL-WG) of VASCERN and to compare the profile between the different countries.

A retrospective review of all children (aged up to 18 years) seen for the first time by the expert centres over one year (2019) was carried out. Lymphoedema-, patient- and genetics-related data was collected and described for the whole group and compared between the different European countries/UK.

In 2019, a total of 181 new children were seen by eight expert centres. For primary lymphoedema, the phenotype was based on the St George's classification of lymphatic anomalies. The percentages diagnosed according to each category were: 7.2% for syndromic lymphoedema, 2.8% for systemic/visceral involvement, 30.4% for congenital, 35.9% for late-onset lymphoedema and 19.3% for vascular/lymphatic malformations. 4.4% had secondary lymphoedema. Nearly 10% of all children had had at least one episode of cellulitis. The median delay from onset of symptoms to being seen by an expert centre was 2.4 years. In 44.4% of the children with primary lymphoedema a genetic test was performed, of which 35.8% resulted in a molecular diagnosis. Across the different centres, there was a wide variety in distribution of the different categories of paediatric lymphoedema diagnosed and the frequency of genetic testing.

In conclusion, this paper has demonstrated that there is a large delay between the onset of paediatric lymphoedema and the first visit in the expert centres and that an episode of cellulitis is a relatively common complication. Diagnostic variation across the centres may reflect different referral criteria. Access to genetic testing was limited in some centres. It is recommended that these issues are addressed in the future work of the PPL-WG to improve the referral to the expert centres and the consistency in service provision for paediatric lymphoedema in Europe.

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1. Introduction

The term primary lymphoedema covers a group of rare genetic conditions which lead to the abnormal development or function of the lymphatic system and presents clinically with chronic oedema. Secondary lymphoedema is chronic oedema, which arises from injury, e.g. surgery, trauma, malignancy or infection, to a previously normal lymphatic system (Executive Committee of the International Society of L, 2020). In children, secondary lymphoedema is also a rare disease. The specialist healthcare providers of the Paediatric and Primary Lymphoedema workgroup (PPL-WG) of VASCERN diagnose and treat adults and children with primary lymphoedema and also children with secondary lymphoedema (Jondeau et al., 2021). Paediatric lymphoedema (PL) is defined as having an age of onset up to and including 18 years.

A detailed algorithm classification (the St George's Classification for lymphatic anomalies) for primary lymphatic diseases based on the clinical features and the localization of the oedema and the accompanying characteristics (phenotype) was first developed in 2010 (Connell et al., 2010) and updated in 2013 (Connell et al., 2013) and 2020 (Gordon et al., 2020). The aim of this classification by phenotype was for diagnostic purposes and to facilitate research into the genetic causes of the different types. In this classification, primary lymphatic diseases are divided into five groups: 1) the syndromes, 2) lymphoedema with systemic or visceral involvement, 3) lymphoedema with a congenital onset (<1.0 year), 4) lymphoedema with a late onset (≥1.0 year) and 5) the vascular and lymphatic malformations. In the literature, there is little information about the prevalence rate of paediatric lymphoedema overall and of each of the different types. Specifically, the profile of patients with paediatric lymphoedema is not fully known and has not been compared previously across different European countries/UK.

The main common complication of both primary and secondary lymphoedema is the increased risk of the development of bacterial cellulitis in the affected area. There has been a misconception that cellulitis is rare in children with primary lymphoedema, but a recent publication has reported it to be a significant problem. The incidence rate of cellulitis among 128 children with lymphoedema was 4.2 episodes per 100 patient-years (Quere et al., 2018). In 29% of the cases, patients had a second episode, and 26% of that subgroup had three or more episodes. Cellulitis can be an unpleasant condition and may even lead to sepsis. It can also be responsible for worsening of the lymphoedema.

It is important that a child with a lymphatic disease receives a diagnosis as soon as possible after the occurrence of the symptoms. This not only facilitates prompt treatment to reduce the risk of progression of the lymphoedema (Executive Committee of the International Society of L, 2020), but also the identification of other clinical problems which may be associated with the diagnosis, e.g. in those with widespread lymphatic dysplasia (i.e. those with systemic/visceral involvement), syndromic primary lymphoedema and segmental overgrowth syndromes (i.e. vascular/lymphatic malformations) (Gordon et al., 2020). The specialist health care providers of the PPL subgroup of VASCERN recognise that - because primary lymphoedema in children is a rare condition - it is not commonly identified by general medical practice or paediatric services. This may lead to a prolonged delay between the onset of symptoms and the diagnosis being made. However, the delay between the onset of symptoms and the diagnosis has never been recorded.

The diagnosis of the lymphatic disease consists of a clinical examination to collect information about the age of onset, family history, distribution of the oedema, episodes of infection, BMI, skin problems, systemic involvement, associated problems and previous surgery (Damstra et al., 2021). Genetic testing is appropriate and helpful in the diagnosis and management of children with primary lymphatic disorders so, the patient may need be referred to a genetic specialist. This field is developing rapidly and a growing number of genetic causes are being identified each year (Gordon et al., 2020).

Different kinds of genetic testing can be applied:

- chromosomal abnormalities may be identified by karyotype/array CGH testing;
- germline mutations (by blood tests) may be investigated by single gene testing or lymphoedema gene panels or RASopathy gene panels where appropriate;
- somatic mutations (in tissue samples) may be identified by single gene tests or segmental overgrowth and RASopathy gene panels.

Currently, the number of children with primary lymphoedema who have genetic testing, the type of test carried out and the number in whom a pathogenic gene mutation/chromosomal anomaly is detected is unknown.

Therefore, the aim of this retrospective study was to describe the profile of children with primary and secondary lymphoedema seen by the various expert centres located in Europe and the UK, which comprise the VASCERN PPL group. A second aim was to compare these profiles between different countries and between the different categories of paediatric lymphoedema.

2. Methods

2.1. Patients

In this retrospective study, data of patients with paediatric lymphoedema were collected by the expert centres of the European Reference Network for rare vascular diseases (VASCERN), more specifically by the workgroup for Paediatric and Primary Lymphoedema (PPL-WG).

The following criteria were used for inclusion of patients in the data set: 1) Diagnosis of primary or secondary lymphoedema, based on clinical characteristics (see general patient pathway for paediatric and primary lymphoedema (Damstra et al., 2021); 2) The patient's age is ≤ 18 years; 3) The patient came to the expert centre for an initial consultation for lymphoedema in 2019 (this year was chosen as it was before the Coronavirus pandemic which affected referrals and investigations); 4) The patient was a new patient for the expert centre (i.e. came the first time to the centre).

2.2. Data collection

The health care providers were asked to provide information about their lymphoedema centre: the name, year of establishment, number of new lymphoedema patients seen per year and number of patient seen in follow-up per year, the proportion of primary/secondary lymphoedema, the number of children up to 18 years in the whole country, number of expert centres in the whole country, whether all paediatric lymphoedema categories are seen, the presence of a geneticist in the team and the reimbursement of genetic testing.

Between October and December 2020, an excel-file to collect the data regarding the characteristics of paediatric patients was made and discussed with the PPL-WG and then was sent to the health care providers of all expert centres. The health care providers were asked to search in their database/registry for all the patients complying the inclusion criteria. All study-specific patient information was collected retrospectively from the patient's medical file to complete the excel file.

For every included patient, the following information was collected:

- *Lymphoedema-related data*: type of lymphoedema (primary vs secondary), for primary lymphoedema, the category as defined in the St George's algorithm (Gordon et al., 2020): the syndromes, lymphoedema with systemic or visceral involvement, lymphoedema with a congenital onset (<1.0 year), lymphoedema with a late onset (≥1.0 year) and the vascular and lymphatic malformations (for every category: yes/no; type), region of swelling (extremities, with

distinction between upper and lower extremity, or trunk or genital or head/neck), history of cellulitis (yes/no),
- *Patient-related data*: gender (male or female), date of birth (DD/MM/YYYY), date of first consultation in the centre (DD/MM/YYYY), age of onset of lymphoedema (in months)
- *Genetics-related data*: family history (yes/no), genetic testing (yes/no; if yes: lymphoedema gene panel vs single gene test vs chromosomal karyotype/array CGH test; if yes: positive genetic test yes/no)

The whole dataset was reviewed by two of the authors (VK and ND) and any queries of classification were raised with each centre and amendments made if necessary.

2.3. Data analyses

SPSS version 28.0 was used to perform the data analyses.

Descriptive statistics, as number and proportions for discontinuous data and median, minimum and maximum and interquartile range for continuous data were used to give an overview of the characteristics of 1) all the included subjects with lymphoedema, 2) for each country separately and 3) for each PL category separately.

To compare the proportion of children between the different countries and between the different categories of paediatric lymphoedema a chi^2-test was used. To compare the median scores between the different countries and between the different categories a Kruskall Wallis test was applied.

3. Results

Eight expert centres provided data of patients with paediatric lymphoedema: one centre is located in Germany, one in the Netherlands, two in the United Kingdom, two in Belgium, one in Slovenia and one in France. Table 1 gives a summary of the other characteristics of the different expert centres that provided data.

3.1. Characteristics of all subjects with paediatric lymphoedema

Table 2 gives an overview of the lymphoedema-related, patient-related and genetic-related characteristics of all included subjects with paediatric lymphoedema (second column). In total, 181 children with lymphoedema were seen for the first time in the different expert centres in 2019.

The percentage in each category were:

- Syndromes – 7.2% (n = 13)
- Systemic/visceral involvement – 2.8% (n = 5)
- Congenital – 30.9% (n = 56)
- Late onset – 35.9% (n = 65)
- Vascular/lymphatic malformations – 18.6% (n = 34)
- Secondary – 4.4% (n = 8)

The number of patients with specific types of primary lymphoedema (with their Orphanet codes) is provided in Fig. 1.

Table 2 also shows that almost all patients had swelling of the extremities (n = 172, 95%), of whom 8 patients (4.7%) had swelling of the arm(s), 151 patients (87.8%) of one or both legs and 13 patients (7.6%) of arm(s) and leg(s). Less frequently was the trunk (8.3%), genital region (9.4%) and head or neck involved (6.6%).

Almost 10% of the subjects with PL had a history of cellulitis.

A slightly higher proportion of subjects with PL were female (58.6%). The median age of onset of the PL was 0.3 years. In more than half of the subjects occurred the lymphoedema within the first year after birth. However, the median age at the first consultation in the expert centre was at 8.5 years. The median delay between the onset of lymphoedema and the first consultation was 2.4 years.

In 33 of the children (19%), a family history of primary lymphoedema was reported (in 23 patients one parent was affected, in 5 patients a sibling and in 5 patients a more distant relative). In 67 subjects (44.4%) a genetic testing was performed. In the majority of the subjects

Table 1
Overview of the different expert centres of the European Reference Network for rare vascular diseases (VASCERN) –Paediatric and Primary Lymphoedema working group (PPL-WG).

Germany	Netherlands	UK	UK	Belgium	Belgium	Slovenia	France
Established							
1979	2000	1990	1998	2010	2006	2002	1985
New lymphoedema patients every year							
1000	600	1450	1500	500	400	560	1100
Follow-up lymphoedema patients every year							
1500	1300	4000	1000	1400	1200	1320	5000
Primary/secondary							
15%/85%	20%/80%	15%/85%	20%/80%	25%/75%	20%/80%	15%/85%	25%/75%
Total number of children up to 18 years in the whole country							
13 677 902	3 400 000	12 664 275	12 664 275	2 365 000	2365 000	408 208	15 562 970
Number of expert centres in the whole country							
1	1	2	2	2	2	1	2
All five paediatric lymphoedema categories are seen							
Yes	No vascular malformations	Yes	Yes	No vascular malformations	No vascular malformations	Yes	No vascular malformations
Regarding genetic testing							
Work closely together with external genetic dpt	Geneticist is team member	Geneticist is team member	Geneticist is team member	Work closely together with internal and external genetic dpt	Work closely together with external genetic dpt	Work closely together with external genetic dpt	Work closely together with external genetic dpt
Is completely reimbursed	Is completely reimbursed if patient is referred by medical specialist	Is completely reimbursed as part of National Health Service	Is completely reimbursed as part of National Health Service	Is partly reimbursed	Is completely reimbursed	Is completely reimbursed	Is completely reimbursed if testing is performed in their hospital

Table 2
Overview of the patient characteristics for all included children with lymphoedema, with a comparison between the different countries.

Outcome	All children	Germany	Netherlands	United Kingdom	Belgium	Slovenia	France	P-value; comparison between countries
Number of children with paediatric lymphoedema first seen in the expert centre in 2019 Absolute Related to total number of children in the country (/100.000)	181 (100%) /	44 (100%) 0.32	12 (100%) 0.35	60 (100%) 0.46 Δ	14 (100%) 0.59	13 (100%) 3.18	38 (100%) 0.24	NA
Lymphoedema-related characteristics								
Category of primary/secondary lymphoedema								<0.001
Syndrome	13 (7.2%)	4 (9.1%)	2 (16.7%)	5 (8.3%)	2 (14.3%)	0 (0%)	0 (0%)	
Systemic/visceral involvement	5 (2.8%)	1 (2.3%)	0 (0%)	4 (6.7%)	0 (0%)	0 (0%)	0 (0%)	
Congenital	56 (30.9%)	19 (43.2%)	7 (58.3%)	14 (23.3%)	4 (28.6%)	2 (15.4%)	10 (26.3%)	
Late onset	65 (35.9%)	8 (18.2%)	3 (25%)	17 (28.3%)	5 (35.7%)	6 (46.2%)	26 (68.4%)	
Vascular/lymph malformations	34 (18.8%)	8 (18.2%)	0 (0%)	19 (31.7%)	2 (14.3%)	4 (30.8%)	1 (2.6%)	
Secondary	8 (4.4%)	4 (9.1%)	0 (0%)	1 (1.7%)	1 (7.1%)	1 (7.7%)	1 (2.6%)	
Region of swelling [a]								
Extremity/extremities	172 (95.0%)	41 (93.2%)	12 (100%)	56 (93.3%)	13 (92.9%)	12 (92.3%)	38 (100%)	0.602
Trunk	15 (8.3%)	11 (25.0%)	0 (0%)	2 (3.3%)	0 (0%)	2 (15.4%)	0 (0%)	<0.001
Genital	17 (9.4%)	7 (15.9%)	1 (8.3%)	6 (10.0%)	0 (0%)	0 (0%)	3 (7.9%)	<0.001
Head/neck	12 (6.6%)	3 (6.8%)	0 (0%)	2 (3.3%)	4 (7.1%)	2 (15.4%)	1 (2.6%)	<0.001
History of cellulitis								0.575
Yes	18 (9.9%)	4 (9.1%)	1 (8.3%)	7 (11.7%)	1 (7.1%)	3 (23.1%)	2 (5.3%)	
No	163 (90.1%)	40 (90.9%)	11 (91.7%)	53 (88.3%)	13 (92.9%)	10 (76.9%)	36 (94.7%)	
Patient-related characteristics								
Gender								0.748
Female	106 (58.6%)	25 (56.8%)	5 (41.7%)	34 (56.7%)	9 (64.3%)	9 (69.2%)	24 (63.2%)	
Male	75 (41.4%)	19 (25.3%)	7 (58.3%)	26 (43.3%)	5 (35.7%)	4 (30.8%)	14 (36.8%)	
Age at onset (y)[b]	0.3 (0.0–17.9; 10.6)	0.0 (0.0–15.6; 2.8)	0.0 (0.0–10.0; 3.9)	0.0 (0.0–16.0; 9.1)	0.0 (0.0–17.0; 13.3)	1.0 (0.0–16.0; 14.0)	10.3 (0.0–17.9; 12.1)	<0.001
Age of onset within first year	104 (58.4%)	32 (72.7%)	9 (75.0%)	38 (66.7%)	8 (57.1%)	6 (46.2%)	11 (28.9%)	<0.001
Age at first consultation (y)	8.6 (0.0–18.6; 12.9)	4.7 (0.0–16.4; 12.0)	5.1 (0.2–15.3; 8.2)	7.8 (0.2–17.9; 11.6)	8.2 (1.8–18.0; 13.5)	15.5 (0.6–18.6; 12.9)	13.3 (0.3–18.5; 9.2)	<0.001
Delay between onset and first consultation (y)[b]	2.4 (0.0–17.1; 5.3)	2.5 (0.0–15.5; 6.4)	0.8 (0.0–15.3; 5.1)	2.4 (0.0–17.1; 5.5)	2.1 (0.2–10.9; 3.7)	4.6 (0.6–15.5; 12.7)	1.8 (0.0–15.9; 15.0)	0.193
Genetic-related characteristics								
Family History								0.019
Yes	33 (19.0%)	8 (18.2%)	3 (25.0%)	14 (25.0%)	1 (9.1%)	3 (23.1%)	4 (10.5%)	
No	141 (81.0%)	36 (81.8%)	9 (75.0%)	42 (75.0%)	10 (91.9%)	10 (76.9%)	34 (89.5%)	
Missing	7	0	0	4	3	0	0	
Genetic testing								<0.001
Yes	67 (44.4%)	10 (55.6%)	11 (91.7%)	33 (57.9%)	7 (53.8%)	3 (23.1%)	3 (7.9%)	
No	84 (55.6%)	8 (44.4%)	1 (8.3%)	24 (42.1%)	6 (46.2%)	10 (76.9%)	35 (92.1%)	
Missing	30	26	0	3	1	0	0	
Type of genetic testing								0.110
Lymphoedema gene panel	52 (77.6%)	5 (50.0%)	9 (81.8%)	29 (87.9%)	4 (57.1%)	2 (66.7%)	3 (100.0%)	
Single gene test	10 (14.9%)	4 (40.0%)	1 (9.1%)	1 (3.0%)	3 (42.3%)	1 (33.3%)	0 (0.0%)	
Chromosomal test	5 (7.5%)	1 (10.0%)	1 (9.1%	3 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Result gene test								0.988
Positive	24 (35.8%)	4 (40.0%)	3 (27.3%)	12 (36.4%)	3 (42.9%)	1 (33.3%)	1 (33.3%)	
Negative	43 (64.2%)	6 (60.0%)	8 (72.7%)	21 (63.6%)	4 (57.1%)	2 (66.7%)	2 (66.7%)	

For categorical data, number (%) is provided; for continues data, median (min – max; IQR) is provided.
Δ The calculation of the number of children related to total number of children in the country was based on the number of children with lymphoedema from England (n = 58) and the population of children in England (not the whole of the UK).
[a] Since a subject may have swelling at the level of different regions, the sum of the proportions is not equal to 100%.
[b] Data available of 178 subjects (data of 3 patients is missing).

a lymphoedema gene panel was performed (n = 52) and in a small number a single gene test (n = 10) or chromosomal test (n = 5) was carried out. Of the 67 genetic tests, 24 (or 35.8%) were positive and resulted in the identification of a pathogenic variant and a molecular diagnosis.

3.2. Comparison of characteristics of paediatric patient with lymphoedema between different countries

Table 2 gives also an overview of the number of children with paediatric lymphoedema first seen in the different countries in 2019 and provides the patient characteristics per country. The number of children with paediatric lymphoedema, related to the total number of children in the country ranges between 0.24/100 000 (in France) and 3.18/100 000 children (in Slovenia). The frequency of patients in the six categories of lymphoedema is significantly different between the different countries. Cases with systemic/visceral involvement were only reported by Germany and the UK (2.3% and 6.7% respectively). For the category congenital lymphoedema, higher proportions were reported in Germany and the Netherlands (43.2%–58.3%) than the other countries (15.4%–28.6%). For the category late onset lymphoedema, the proportion of cases was remarkably higher in Slovenia and France (46.2%–68.4%)

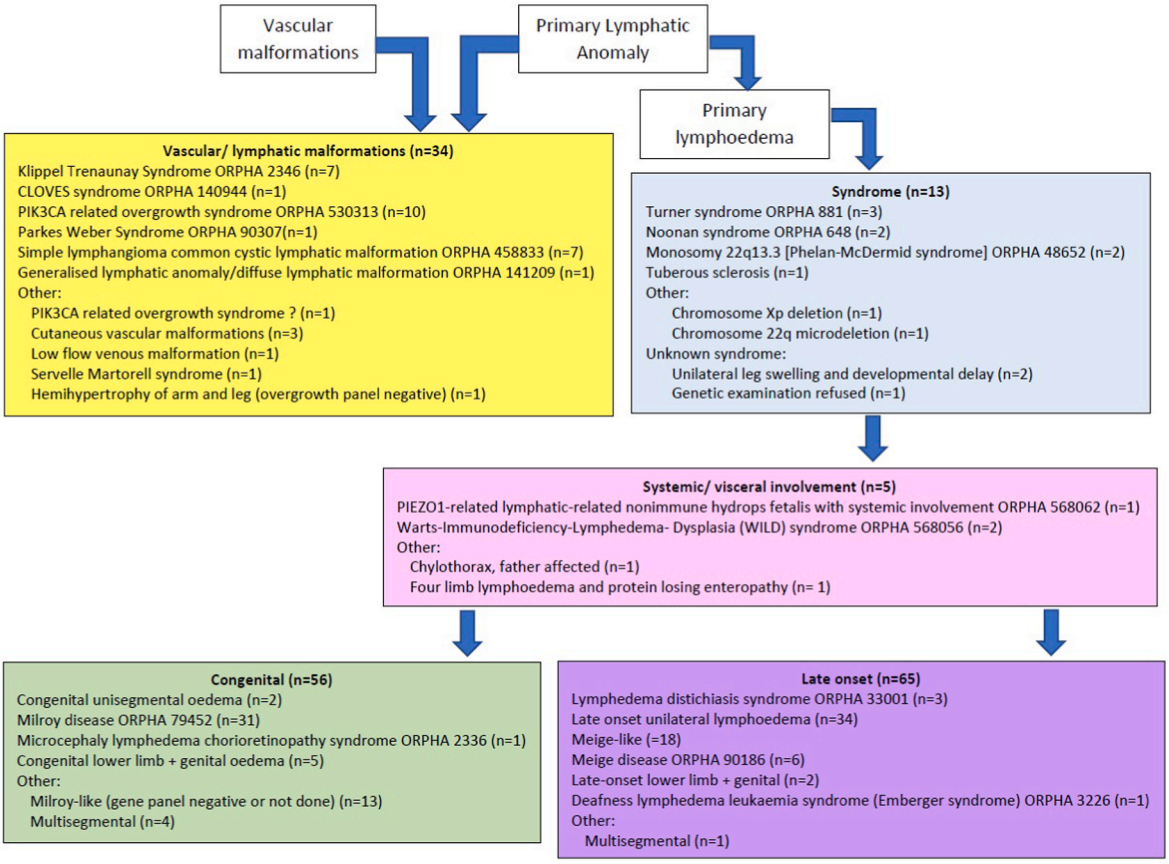

Fig. 1. Overview of the St-Georges Algorithm with the number of subjects in each category for every type of primary lymphoedema.

compared to the other countries (18.2%–35.7%). For the category vascular and lymphatic malformations, the Netherlands and France reported (almost) no cases (0–2.6%), whereas the other countries reported more cases (14.3%–31.7%). The proportion of syndromes and of secondary lymphoedema was low and comparable in the different countries. A significant difference in the frequency of swelling of the trunk, genital region and head/neck ($p < 0.001$) was found between the different countries. Germany and Slovenia reported more truncal swelling (25.0% and 15.4% respectively) than the other countries (0–3.3%). Germany, the Netherlands, the UK and France reported more genital swelling (7.9%–15.9%) than Belgium and Slovenia (0%). Slovenia reported more head/neck swelling (15.4%) than the other countries (0–7.1%). For the history of cellulitis, the proportions were comparable between the different countries.

The proportion of females and males was comparable between the different countries, as was the delay between the onset of lymphoedema and the first consultation in the expert centre. In contrast the age at the onset and the age of the subject at the first consultation was significantly different between the countries. The age at onset was much higher in France (10.3 years vs 0.0–1.0 years) and the age at first consultation was much higher in Slovenia and France (13.3–15.5 years vs 4.7–8.2 years), than the other countries.

Finally, the frequency of a family history of lymphoedema and the % of those who had genetic testing was significantly different between the countries. In the Netherlands, almost every child received a genetic test (91.7%), whereas in France genetic testing was performed in the minority of the children with primary lymphoedema (7.9%). In some centres, only limited genetic test data were available. When genetic testing was performed, in the Netherlands, UK and France, the majority was a lymphoedema gene panel (81.8–100.0%), whereas in the other countries these proportions were lower (50.0%–66.7%). Finally, the proportion of genetic tests that resulted in a positive result (i.e. a genetic cause was found) was comparable between the different countries (27.3%–42.9%).

3.3. *Comparison of the patient characteristics between the different categories of paediatric lymphoedema*

The region of swelling is significantly different between the different PL categories (see Table 3). Swelling of extremities was seen in (almost) all patients with a syndrome, congenital and late onset lymphoedema. Truncal swelling was more frequently seen in subjects with systemic/visceral involvement than in the other groups. Genital lymphoedema was most frequently seen in subjects with a syndrome or with systemic/visceral involvement. Head/neck lymphoedema were especially seen in subjects with vascular/lymphatic malformations and with secondary lymphoedema. The frequency of a history of cellulitis was comparable between the different paediatric lymphoedema categories.

The gender, age of onset, age at first consultation (and the delay between them) were significantly different between the categories. There were more female subjects reported in the categories ‘syndromes’, ‘systemic/visceral involvement’ and ‘late onset lymphoedema’. As expected, the age at the first consultation and the age at onset was the highest for the ‘late onset category’. In contrast, the delay between the onset and the first consultation was the highest in the ‘syndrome’ and ‘vascular/lymphatic malformations category’.

Finally, the frequency of family history, of genetic testing and of type of genetic testing was significantly different between the different categories. A family history was more frequently reported in subjects with ‘systemic/visceral involvement’ and with ‘congenital lymphoedema’. A genetic testing was also more frequently performed in these subjects and in subjects with a syndrome as well. A single gene test was more

Table 3
Overview of the patient characteristics per pediatric lymphoedema (PL) category.

Outcome	Syndrome (n = 13)	Systemic/visceral involvement (n = 5)	Congenital (n = 56)	Late Onset (n = 65)	Vascular/lymphatic malformations (n = 34)	Secondary (n = 8)	P-value
Lymphoedema-related characteristics							
Region of swelling							
Extremities	13 (100%)	4 (80%)	55 (98.2%)	65 (100%)	29 (85.3%)	6 (75%)	<0.001
Trunk	2 (15.4%)	3 (60%)	3 (5.4%)	2 (3.1%)	5 (14.7%)	0 (0%)	<0.001
Genital	3 (23.1%)	2 (40%)	7 (12.5%)	3 (4.6%)	2 (5.9%)	0 (0%)	0.001
Head/neck	0 (0.0%)	1 (20%)	2 (3.6%)	0 (0%)	4 (11.8%)	2 (25%)	0.001
History of cellulitis							0.719
Yes	1 (7.7%%)	0 (0%)	5 (8.9%)	6 (9.2%)	4 (11.8%)	2 (25.0%)	
No	12 (92.3%)	5 (100%)	50 (91.1%)	59 (90.8%)	31 (88.2%)	6 (75.0%)	
Patient-related characteristics							
Gender							0.019
Female	8 (61.5%)	3 (60%)	26 (46.4%)	49 (75.4%)	17 (50.0%)	3 (37.5%)	
Male	5 (38.5%)	2 (40%)	30 (53.6%)	16 (24.6%)	17 (50.0%)	5 (62.5%)	
Age at first consultation (y)	9.3 (0.7–16.0; 12.6)	0.8 (0.3–3.3; 1.8)	1.7 (0.0–16.1; 5.5)	14.5 (6.0–18.6; 4.5)	6.3 (0.3–17.6; 9.5)	7.1 (1.5–17.8; 9.5)	<0.001
Age of onset (y)[a]	0.0 (0.0–11.5; 1.8)	0.0 (0.0–0.1; 0.0)	0.0 (0.0–1.0; 0.0)	11.4 (1.0–17.9; 5.4)	0.0 (0.0–14.2; 0.0)	5.0 (0.0–16.0; 15.1)	<0.001
Age of onset <1 year [a]							<0.001
Yes	10 (76.9%)	5 (100%)	56 (100%)	0 (0%)	32 (97.0%)	2 (28.6%)	
No	3 (23.1%)	0 (0%)	0 (0%)	64 (100%)	1 (3.0%)	5 (71.4%)	
Missing	0	0	0	1	1	1	
Delay between onset and first consultation (y)	4.2 (0.7–15.5; 9.0)	0.8 (0.3–3.3; 1.8)	1.7 (0.0–15.9; 5.7)	2.0 (0.0–14.5; 3.4)	5.1 (0.3–17.1; 8.7)	2.1 (0.0–5.5; 3.8)	0.002
Genetic-related characteristics							
Family History							0.001
Yes	0 (0%)	2 (50%)	20 (37.0%)	10 (15.9%)	1 (3.0)	0 (0%)	
No	13 (100%)	2 (50%)	34 (63.0%)	53 (84.1%)	32 (97.0)	8 (100%)	
Missing	1	1	2	2	1	0	
Genetic testing							<0.001
Yes	9 (81.8%)	5 (100.0%)	26 (59.1%)	16 (27.1%)	11 (42.3%)	0 (0%)	
No	2 (18.2%)	0 (0.0%)	18 (40.9%)	43 (72.9%)	15 (57.7%)	6 (100%)	
Missing	2	0	12	6	8	2	
Type of genetic testing							0.003
Lymphoedema gene panel	2 (22.2%)	4 (80.0%)	21 (80.8%)	16 (100%)	9 (81.8%)	/	
Single gene test	5 (55.6%)	0 (0%)	3 (11.5%)	0 (0%)	2 (18.2%)		
Chromosomal test	2 (22.2%)	1 (20.0%)	2 (7.7%)	0 (0%)	0 (0%)		
Result gene test							0.564
Positive	5 (55.6%)	1 (20%)	10 (38.5%)	4 (25.0%)	4 (36.4%)	/	
Negative	4 (44.4%)	4 (80%)	16 (61.5%)	12 (75.0%)	7 (63.6%)		

For categorical data, number (%) is provided; for continues data, median (min – max; IQR) is provided.
[a] Data available of 178 subjects (data of 3 patients is missing).

frequently performed in the 'syndromes' group rather than a complete lymphoedema gene panel. The proportion of positive gene tests was comparable between the different groups.

4. Discussion

The data from this study of the profiles of children with primary and secondary lymphoedema seen by the European expert centres in 2019, when combined, allows comparison with previously published data on paediatric lymphoedema. Moreover, comparison of the profiles of individual centres across Europe can inform future developments of the PPL group of VASCERN.

4.1. Characteristics of all subjects with paediatric lymphoedema

The present study is the only study that has classified the types of paediatric primary lymphoedema using the St George's algorithm across different centres. Using the five broad categories of primary lymphoedema the largest number was that of late onset (35.9%) and the next largest was congenital lymphoedema (30.9%). Those with vascular and lymphatic malformations formed 18.8% of the patients seen, while those with syndromic conditions were 7.2% and those with systemic/visceral involvement represented 2.8%. These were broadly similar to those previously published by the St George's, London: 37% late onset, 21% congenital, 17% vascular and lymphatic malformations, 13% syndromic and 12% with systemic/visceral involvement (Gordon et al., 2020). Secondary lymphoedema was rare with only 4.4% of children having this. In previous studies the percentage with secondary lymphoedema was 2.8% (Schook et al., 2011) and 7% (Watt et al., 2017). As this paper is intended to focus on genetic causes of lymphoedema, this secondary group will not be discussed further here, except to note that there is growing evidence that there may be a genetic predisposition to some types of adult onset secondary lymphoedema such as that due to breast cancer treatment (Visser et al., 2019).

Table 4 shows some specific characteristics of children with primary lymphoedema in this study, in comparison with previous publications (Quere et al., 2018; Schook et al., 2011; Watt et al., 2017; Vidal et al., 2016; Todd et al., 2014). It should be noted that the age range which defines childhood varies across the publications but a number (including the present study) consider an upper age limit of 18 years as the definition. It is possible there may be differences in characteristics of patients older than this which have been included in some studies. The region affected by lymphoedema in the present study is comparable with the other studies. The vast majority of children had oedema of the lower extremity (range = 76–97%) with a much smaller percentage having upper extremity lymphoedema (range = 3.8–16.7%). Genital lymphoedema was quite common with a range of 6–18.1%. It should be noted that these numbers add up to greater than 100% for each study, as lymphoedema can occur in more than one site in each individual. Paediatric lymphoedema is more common in females than males and although there is some variation in results, most studies (including our study) suggest that around 60% of paediatric lymphoedema occurs in

Table 4
Comparison of characteristics of children with primary lymphoedema with other reports.

	Schook (Schook et al., 2011) (n = 138)	Todd (Todd et al., 2014) (n = 455)	Vidal (Vidal et al., 2016) (n = 155)	Watt (Watt et al., 2017) (n = 86)	Quere (Quere et al., 2018) (n = 128)	Our study (n = 181)
Age limit for inclusion	Up to 21yr	Up to 18yr	Up to 18yr	?	Up to 25yr	Up to 18yr
Lymphoedema characteristics						
Syndrome	5%	20%	8%	19%	–	7.2%
Region of swelling						
Lower extremity	91.7%	76%	97%	94%	87.9%	90.6%
Upper extremity	16.7%	12%	9%	9%	3.8%	11.6%
Genital	18.1%	8%	6%	15%	8.3%	9.4%
History of cellulitis	18.8%	12.5%	14%	26%	29.7%	9.9%
Patient-related characteristics						
Gender (female/male)	59%/41%	58%/42%	70%/30%	60%/40%	61%/39%	59%/41%
Present at birth (%)	49%	51%	42%	58%	–	47.5%
Median age at onset (y)	0 (male) 10 (female)	–	4 (male) 10.7 (female)	–	–	0.0 (male) 1.0 (female)
Genetic-related variables						
Family history	7%	27%	18%	16%	–	19.0%

females and around 40% in males. The lymphoedema was described as familial in between 7 and 27% of cases and syndromic in 5–20%. Some of the differences may reflect the slightly different patient groups in each study. The lymphoedema was present at birth in between 42 and 58% of cases. The median age of onset seemed different in males from females with females tending to have a later age of onset. The number of children who had experienced cellulitis ranged from 9.9% in the present study to 29.7%. These figures emphasise that children with lymphoedema do indeed experience cellulitis and it is not an uncommon problem. It is not clear why there is such a range of incidence recorded but this may reflect that there could have been incomplete data in most studies which have been carried out retrospectively from case note review.

The median time between onset of symptoms and the first consultation at the expert centre was 2.4 years. It is well recognised that there can be a significant delay between the onset of symptoms and the diagnosis of primary lymphoedema in children so this figure will give a baseline, against which future improvements may be compared, as the work and influence of the PPL group progresses. Previous studies have shown variable results with an average time to diagnosis of only 9 months in one report (Watt et al., 2017) but a delay of over two years in referral to a specialist therapist in 45% children in another (Todd et al., 2014).

Genetic testing has become an important component of the diagnosis of the different types of primary lymphoedema and lymphatic and vascular anomalies. In our study 44.4% of patients had undergone genetic testing and of these 77.6% were lymphoedema gene panel tests, 14.9% were single gene tests and 7.5% were chromosomal tests. This is a rapidly evolving area and developments have occurred since the year when this study was carried out (2019) (Brouillard et al., 2021). A recent review suggests that in about 30% of patients with primary lymphoedema an underlying genetic defect has been discovered (Brouillard et al., 2021). In the present study 35.8% of all gene tests gave a positive result. This compares with 41% in the St George's audit (Gordon et al., 2020).

4.2. Comparison of the characteristic of the paediatric patient with lymphoedema between the different countries

The eight European expert centres in paediatric and primary lymphoedema (located in 6 different countries) taking part in the present study have some different characteristics (Table 1). For example, the oldest centre opened in 1979 and the youngest in 2010. It is already known from other studies that lymphoedema services can take some time to fully develop (Keeley et al., 2019). Nevertheless, in the present study, the proportion of patients with primary lymphoedema ranges from 15% to 25%, with the oldest service seeing 15% of its patients with primary lymphoedema and the youngest service seeing 25%. Therefore, the age of the service does not seem to be reflected adversely in the primary to secondary lymphoedema ratio here.

In order to determine whether the different centres in this study were seeing a similar proportion of children, the number of children seen for the first time by each centre in 2019 was compared with the country's population of children up to the age of 18 in that year (Table 2). The proportion of children seen with lymphoedema varied across the sites from 0.24 per 100 000 in France to 3.18 per 100 000 in Slovenia. This may reflect the fact that in countries such as France, Belgium and the UK, there is more than one specialist centre seeing children with lymphoedema, whereas in Slovenia there is only one expert centre. In addition, this proportion is probably an underestimate of the true prevalence, as not all children with lymphoedema may have been referred to the expert centres. In a UK study 40% were seen by expert centres, whereas 60% were seen by other lymphoedema services (Todd et al., 2014). There are no established accurate data on the prevalence of primary lymphoedema and its different subtypes in the literature (Brouillard et al., 2021). An often quoted figure comes from an old publication and suggests a prevalence of 1.15 per 100 000 of those with lymphoedema up to the age of 20 years (Smeltzer et al., 1985). This is similar to that found in the present study.

Furthermore, in some countries (such as in Slovenia, Germany and UK), the expert centres see children with vascular malformations as well whereas in others these patients go to a separate centre/department in the hospital. This pattern is confirmed in the variation between the numbers of patients seen in the category vascular/lymphatic malformations by the different expert centres (Table 2). Other differences in the proportion of children seen in the different categories of primary lymphoedema cannot be explained further. Because of these differences in the proportion of patients per category in the different countries, region of swelling (other than extremities), age at first consultation, median age of onset and family history is different between the different countries as well.

Finally, there was a very large range of the proportion of those who had genetic testing (from 7.9% in France to 91.7% in the Netherlands). Some of these differences can be explained by the different types of primary lymphoedema and lymphatic/vascular malformations seen by each centre, but may also be due to the lack of a clinical geneticist in the multidisciplinary team in all centres - except the centres in the UK (Table 1). The latter is significant, as it is now recognised that genetic testing is an important component of the accurate diagnosis of the different types of paediatric primary lymphoedema (Brouillard et al., 2021). Another explanation of the differences in genetic testing is the

difference in reimbursement of such testing between the different countries (Table 1).

4.3. Comparison of the patient characteristics between the different categories of paediatric lymphoedema

The detailed diagnosis by Orphanet code for pooled data from all the expert centres is shown in Fig. 1. In each broad category, there are a significant number in the undiagnosed/'other' diagnosis section, indicating that an Orphanet coded diagnosis was not available for all patients. Sometimes this could have been because the phenotype was evolving and a final pattern had not been established. On other occasions it may be that genetic testing was not available (perhaps because the child's family did not wish to pursue it) or that the phenotype did not fit a known syndrome. Furthermore, Orphanet codes are not available for all categories described in the St George's algorithm (Gordon et al., 2020).

Pooled patient characteristics from all centres were also compared with the different broad categories of paediatric lymphoedema (Table 3). Typically, syndromic lymphoedema may be more common in females, because of the lymphoedema associated with Turner syndrome (Atton et al., 2015). In addition, late onset primary lymphoedema, e.g. Meige lymphoedema, seems to affect more females than males, but the reason for this and the genetic cause of Meige lymphoedema is not yet known (Gordon et al., 2020). It should be stressed that the term "congenital" describes a category in the algorithm, and that lymphoedema in children placed in other categories may still be present at birth, e.g. in Turner syndrome which is included in the syndromic category.

Differences in age of onset, age at first consultation and family history are again to be expected given the different presentations/genetic causes of the different groups. The delay between onset and first consultation ranges from 0.8 years for those with systemic/visceral involvement (but $n = 5$) to 5.1 years for those with vascular/lymphatic malformations. The latter may simply be due to a delay in referral to the expert centre as patients may present to other centres first. Furthermore, the final diagnosis may take time to be confirmed. Knowledge is evolving rapidly in this group and diagnosis often requires a tissue biopsy for genetic testing for somatic mutations. In addition, in some cases a pathogenic mutation may not be detected on the first biopsy due to low frequency in the cells. This may require repeating the biopsy and/or different testing with a greater read depth. Finally, it is not uncommon for some of these cases to be labelled as Klippel Trenaunay syndrome initially and that the final diagnosis of *PIK3CA* related overgrowth spectrum (PROS) may not be made until the child is seen in an expert centre and investigated in further detail.

4.4. Strengths of the study

This is the first study of the patients seen by the European expert centres for paediatric lymphoedema, which are members of the PPL-WG of VASCERN. Another strength was that the St George's diagnostic algorithm and revised Orphanet codes were used to describe the profile of the patients by diagnostic category.

4.5. Limitations of the study

The study was a retrospective review of patient databases and records, so there may be incomplete or incorrect data. Furthermore, not all expert centres, which are members of the VASCERN PPL-WG were able to take part. Ethical committee regulations in Finland did not allow the Helsinki centre to share their data with the PPL group.

5. Conclusions/recommendations

The structure and organisation of the expert centres for paediatric lymphoedema seems to vary from country to country:

1. In some countries, there is just one expert centre, but in others, there is more than one expert centre. If only one health care provider represents a country, as proposed by the European Reference Network, we recommend setting up a well-functioning expert network within countries where there is more than one expert centre/lymphoedema clinics. This would facilitate delivering the aims of the ERN in developing and providing consistent care for rare diseases across all European countries. Such a network already exists in France and in the UK.
2. Currently in all expert centres, patients are referred internally from other departments in the hospital, but also externally from other hospitals and first line health care providers. Our results demonstrate that the interval between the onset of primary lymphoedema and the first contact in an expert centre is > 2 years and is similar in the different centres. Furthermore, not all children with primary lymphoedema are referred to the expert centres and remain under the care of general lymphoedema clinics. Therefore, we recommend that referral pathways to the expert centres are formalised in each country to ensure that as many children as possible are assessed in these centres and that the children are referred as soon as possible after the onset of the lymphoedema.
3. The results support the need for a consistent approach to assessment and investigations of children with primary lymphoedema, including genetic testing to be available to each expert centre. Therefore, we recommend the involvement of a clinical geneticist in the expert centres to work as part of the multidisciplinary team of each centre. Currently this is not uniformly available across the expert centres, although clinical geneticists are core members of the clinical teams in the two UK centres and in the Netherlands and one will join the team in Slovenia in 2022. This approach should lead to improved diagnosis and outcomes for patients but will also result in more accurate data being recorded in disease databases and registries. Moreover, at this moment genetic testing is not fully reimbursed. As a consequence, some parents and their children with primary lymphoedema refuse genetic testing. Therefore, we recommend to obtain full reimbursement of genetical testing in all European countries.

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Nele Devoogdt: Formal analysis, Methodology, Supervision, Writing – original draft. **Malou Van Zanten:** Data curation, Methodology. **Robert Damstra:** Writing – review & editing. **Kirsten Van Duinen:** Data curation. **Janine L. Dickinson-Blok:** Writing – review & editing. **Sarah Thomis:** Data curation. **Guido Giacalone:** Data curation. **Florence Belva:** Writing – review & editing. **Sinikka Suominen:** Writing – review & editing. **Heli Kavola:** Writing – review & editing. **Michael Oberlin:** Data curation. **Jochen Rossler:** Writing – review & editing. **Tanja Planinsek Rucigaj:** Data curation. **Katie Riches:** Data curation. **Sahar Mansour:** Data curation, Conceptualization. **Stéphane Vignes:** Data curation. **Vaughan Keeley:** Formal analysis, Conceptualization, Methodology, Supervision, Writing – review & editing.

Data availability

The authors do not have permission to share data.

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