Audit of childhood lymphoedema in the United Kingdom undertaken by members of the Children's Lymphoedema Special Interest Group

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Key words

Children, congenital, phenotypes, primary lymphoedema

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Abstract

Childhood lymphoedema is a rare and poorly recognised condition with only a few specialist lymphoedema centres that have the experience of diagnosing and treating this group. The Children's Lymphoedema Special Interest Group (CLSIG) was formed in a bid to improve service provision and enhance practitioner knowledge and support. This innovative audit was undertaken to help establish clinical information about children with lymphoedema in the UK. This will help inform national service development and educational initiatives to improve recognition and management of childhood lymphoedema in the future.

Lymphoedema can be defined as a chronic swelling of one or more parts of the body due to a failure in lymph drainage. There is no curative treatment for this condition and the objective of Children's Lymphoedema Special Interest Group (CLSIG) is to raise awareness of the condition and promote effective treatment. Although the majority of referrals to lymphoedema services are for the assessment and management of adults with lymphoedema, babies and children with lymphoedema and congenital abnormalities, such as Milroy disease (an autosomal dominant congenital disease affecting the lower limbs), have been recognised since as far back as 1892 (Milroy, 1892).

Available evidence indicates that childhood lymphoedema is rare and there are few healthcare professionals with experience of diagnosing and treating lymphoedema in children (Mansour and Sharland, 1990; Todd, 2010a). The CLSIG) was formed in 2009 to gain more information about the number of children with this condition, to establish agreed methods of management and service provision, and to increase the knowledge of those providing this service. There are currently 20 members of the group with nineteen centres around the country contributing to the data collection for this study. Eight parents also participated. One of the initial objectives was to agree and set up an audit, which would capture information about children with lymphoedema in the UK. To the authors' knowledge, this is the first collaborative attempt that has been made to gain information about childhood lymphoedema from a national perspective. It is hoped that this evidence will help to inform service development and educational initiatives around the identification and treatment of childhood lymphoedema.

Method

The aim was to collect information about children and teenagers who had been given a diagnosis of lymphoedema and were living in the UK. Details about the lymphoedema of all children and teenagers in the UK up to the age of 18 years were eligible for inclusion.

The initial list of questions was agreed by multidisciplinary members of the group with the objective to collect descriptive data about the gender of the child, familial pattern of the condition, age of onset, site(s) of the body affected, as well as known episodes of cellulitis. Lymphoedema diagnosis and types of investigation, if available, were recorded, as were details of the type of professional who had referred the children to lymphoedema services.

No personal details were submitted regarding the children and each clinician had a unique identifying code known only to them, to which they added a number for each child that was submitted. The data collection forms were submitted either electronically or on paper to one of the authors who collated and analysed all data. The process of collecting data and the audit form were initially trialled by team members who submitted data between February and November 2010, at which point some minor revisions were made to the data collection form.

The second phase of audit collection was then commenced with the aim of collecting information on children who were not known to members of the CLSIG, but who were treated by other members of the British

Lymphology Society (BLS). A separate form was also developed for use by parents, as it was known that some children had been given a diagnosis of lymphoedema, but had not been referred on to a service for treatment. In order to target these groups, an invitation to participate in the audit was prepared and published in the newsletters of the BLS, as well the Lymphoedema Support Network (LSN) – the patient lymphoedema charity that supports most people and children/families with a diagnosis of lymphoedema.

Results

By February 2014, there were 455 children on the database. A total of 19 centres throughout the UK participated. The details of 8 children were entered by their parents. Sex was recorded in all cases and there were 265 female (58%) 190 male (42%) patients. The year of birth of each child ranged from 1992 to 2012, with the mode being 1997 (*Table 1a*).

The majority of children had one or two affected sites (84%) with two children having total body lymphoedema. Leg oedema (76%) was considerably more prevalent than arm oedema (12%), while 36 children had swelling in their trunk, 36 had genital oedema and 23 had facial oedema.

A total of 51.2% of the children [n=233] presented with lymphoedema from birth (*Table 1b*), with the numbers steady throughout the rest of the years. Most cases were diagnosed within the first year (*n*= 35) or at the age of 12 years (*n*=27).

One aspect of the audit was to record the number and type of investigations that the children had undergone prior to diagnosis. In total, there were 30 different types of investigations carried out (*Table 2*). Genetic testing, lymphoscintigraphy, blood tests, and Magnetic Resonance Imagery (MRI) scans were the most common.

Table 3 shows that the majority of children had undergone only one investigation. One-hundred-and-one (22%) children had no investigations carried out. Forty (40%) of these were assessed at a highly specialised centre, whereas 61 (60%) were assessed elsewhere.

Family history

In order to determine whether the lymphoedema was hereditary or not, family history of swelling was noted in all cases (*Table 4*). A total of 332 (73%) had no family history of swelling, leaving 123 (27%) citing family involvement. Ten of these replied "yes", but did not number or identify the family members involved. Data from the remaining 445 are shown in *Table 4*. In most cases where there was a family history of swelling, the nuclear family members were affected — mother (24%), father (16%), sister (14%) and brother (11%).

Lymphoedema diagnosis was given in 193 cases (*Table 5*). These diagnoses were grouped where possible, into the current classification and diagnostic algorithm (Connell et al, 2013). Most were diagnosed with congenital lymphoedema (33.7%). Syndromic diagnosis was recorded in 38 cases (19.7%), with the majority being Turner syndrome (*n*=16). Other syndromes identified in individual children included 22q11.2 deletion syndrome, De Novo chromosomal abnormality, chromosome 1p deletion, Jarmas syndrome, and Nemo mutation. Klippel Trenaunay Weber Syndrome (KTS) was the most common in the disturbed growth classification.

Information regarding the incidence of cellulitis was recorded in all cases. A total of 398 (87.5%) of the group had never experienced an episode of cellulitis. Of the remaining 57 (12.5%) children who had suffered from cellulitis, 23 (40.3%) reported recurrent attacks.

It was possible in 383 cases (84%) to calculate the approximate waiting time from diagnosis to the point when the child was referred to a treatment service. Sixty-one children (16%) waited less than 6 months and a fifth of the group had accessed treatment within 1 year. Although the majority of the group (55%) were referred to a service within 2 years from the onset of oedema, 28.7% waited between 2–10 years and 16%

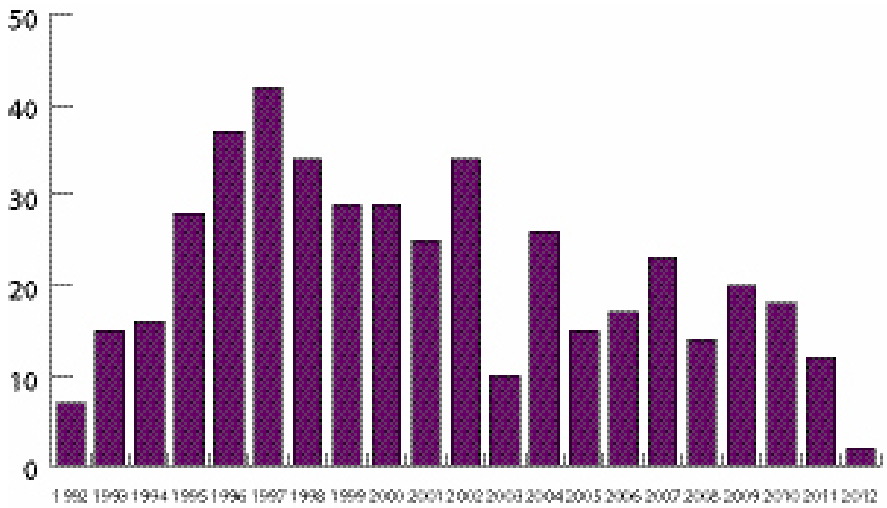

Table 1a. Number of children born in each year.

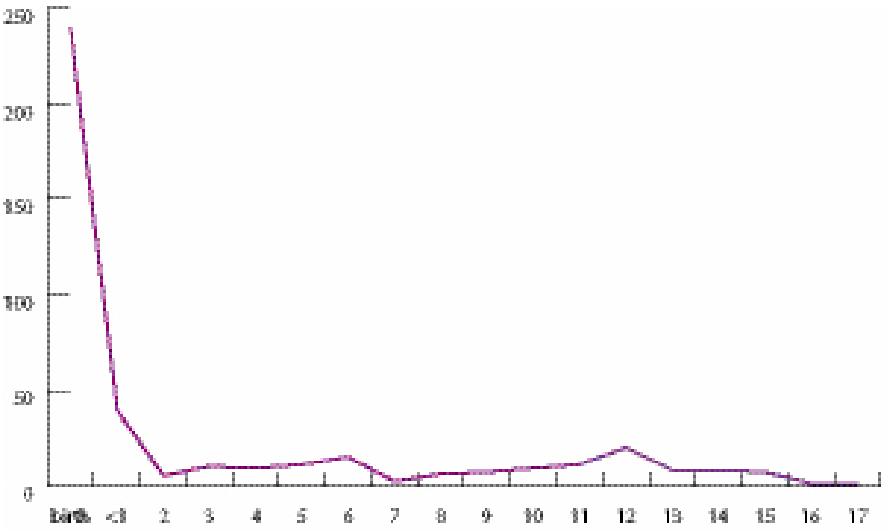

Table 1b. Age of onset of swelling.

waited between 10–17 years to be seen by a lymphoedema practitioner.

The referring medical speciality was recorded in 265 cases (58%). The majority of children were referred to services by secondary care consultants, predominately from paediatric services (n=85 [18.6%]). Other specialities who were recorded as frequent referrers included plastic surgery (*n*=36), dermatology (*n*=30), vascular (*n*=14), oncology (*n*=9), rheumatology (*n*=11). Forty-two children (9.2%) were referred by their General Practitioner. Children were infrequently referred by a wide range of other professionals including genetics, palliative care, endocrinology, other lymphoedema clinicians, orthopaedics, physiotherapist, health visitors, gastroenterology, occupational therapy, and urology.

Discussion

This work was designed and undertaken by a multidiscisplinary group of healthcare professionals involved in treating childhood lymphoedema. The condition is not common in children and at the time of undertaking this audit there was little collective information about the young people who are referred to paediatric lymphoedema services (Todd, 2010b; Connell et al, 2013).

Each CLSIG member submitted information on the type of lymphoedema on each child in their care. The member was responsible for anonymising the data by giving each child an individual code which was not passed on. All information was collated and analysed on a central database.

A total of 455 children's data were collected. From a population of approximately 11.5 million children in the UK (Office for National Statistics [ONS], 2011; National Records of Scotland, 2013) this gives a prevalence rate of 4/100,000. However, as with other prevalence studies, this is likely to be an underestimation. The results indicate that more females are affected than men, with a ratio of 6:4. More than half of the total number presented with swelling from birth (53%). There was a steady accrual in incidence during years of development (median of six new cases per year) with peaks at one, 11 and 12 years of age (14, 11 and 18 new cases, respectively). The graph in *Table 1* showing the year of birth of the children does not reflect the trend in numbers of children being born in these years (ONS, 2011). There is a slow

Table 2. Range of investigations carried out.

Investigations	No	%
Genetic Testing	151	22
Lymphoscintigraphy	110	16
Bloods	91	13
Doppler	50	7
Ultrasound	83	12
Scan (MRI/CT/Duplex)	126	18
X-Ray	18	3
ECG	11	2
Endoscopy	9	1
Biopsy	7	1
Venogram	6	1
Renal investigation	6	1
MRI angiogram	2	<0
Sigmoidoscopy	2	<0
Colour duplex ultrasound	1	<0
Cardiac assess	1	<0
Groin dissection	1	<0
EEG	1	<0
MR venogram	1	<0
Barium meal	1	<0
TOTAL	**678**	**97%**

Table 3. Number of investigations each child underwent.

Investigations	No	%
None	101	22%
1	171	38%
2	85	19%
3	64	14%
4	25	5%
5	4	1%
6	4	1%
7	1	0%
TOTAL	**455**	**100%**

Table 4. Number of family members with lymphoedema.

Number of family members with lymphoedema	No	%
0 family members	332	75%
1 family member	55	12%
2 family members	42	9%
3 family members	7	2%
4 family members	9	2%
TOTAL	**455**	**100%**

decline in total birth rates until 2009 and a sharp increase in 2010. The majority of children had one or two affected sites and lower-limb oedema was more frequently reported than upper-limb.

There are a limited number of equivalent studies to provide comparative data. Dale (1985) reported on a study of 312 patients with primary lymphoedema at a single site between 1965 and 1980. He described a gender ratio of three females to one male. The slight increase in male incidence described here may reflect the inclusion of secondary lymphoedema and also a change in referral pattern over the last thirty years.

Dale described a prevalence of primary lymphoedema as 1 in 6,000. A population prevalence of 1.15 per 100,000 has also been recorded (Smeltzer et al, 1985). There is a view that reported prevalence is an under estimation of true numbers (Moffatt et al, 2003). Up to the present time, literature is based on single centre studies, which may contribute to an ascertainment bias.

There were a total of 30 different investigations recorded in the audit. Despite the wide variety of investigations listed, 22% of the children had undergone no investigations at all. A total of 60.3% of these were referred from non-specialist centres and the lack of investigation may be the result of referring practitioners assuming the lymphoedema is Milroy, thus avoiding the need for further investigation. A total of 39.6% were assessed at a highly specialised lymphoedema centre where the extensive knowledge and experience in lymphoedema would have allowed an accurate diagnosis without investigation in some cases.

The most common investigations included MRI scans, blood tests, lymphoscintigraphy and genetic testing. Increasing ability to identify types of lymphoedema through molecular genetic testing has led to a greater understanding of Milroy disease and lymphoedema distichiasis syndrome (Connell et al, 2013). In this audit, there was a family history of lymphoedema in 123 cases (27%), indicating the probability of a hereditary condition. For most of the children in this audit, family history was not discolosed. It has been noted that the presentation of a swollen leg in a child presents a difficult diagnostic problem (Wright and Carty, 1994). A number of potential causes need to be excluded and this may be reflected in the variety of investigations that have been recorded.

Lymphoscintigraphy is recognised as providing the most effective investigation for lymphoedema (Damstra et al, 2008). Although not always necessary as part of the clinical investigation in children, it is of value in cases of uncertainty surrounding the extent of lymphatic abnormality (Bellini et al, 2008). MRI is of value in the differential diagnosis of tissue hypertrophy. It is also considered useful in diagnosing infants and young children when the more invasive lymphoscintigraphy investigation is inappropriate (Browse et al, 2003). Routine blood tests are used to identify other systemic causes of oedema such as hypoproteinaemia.

In this audit, classification was based on phenotype (Connell et al 2013) that is the result of careful assessment of personal and family history and physical examination (Damstra and Mortimer, 2008). The presence of syndromic diagnosis and vascular malformations were also recorded. Congenital lymphoedema was the most common cause of swelling (33.7%) with the majority of these given a diagnosis of Milroy disease. This figure is slightly higher than that of a recent unpublished audit of 254 children attending a highly specialised lymphoedema centre, which found 31% were diagnosed with congenital lymphoedema (*Table 6*).

There is anecdotal evidence among lymphoedema specialists that non specialists are prone to assuming that the term 'Milroy' is synonymous with primary

Table 5. Recorded diagnoses (n=193).

Syndromic	**No (%) 38 (19.7%)**	**Disturbed growth/ cutaneous manifestations/ vascular anomalies**	**No (%) 55 (28.5%)**	**Late onset (l/o)**	**No (%) 19 (9.8%)**	**Congenital**	**No (%) 65 (33.7%)**	**Others**	**No (%) 16 (8.3%)**
Turner	16	KTS/?KTS	18	Meige/ ? Meige	10	Milroy/? Milroy	50	Primary l/o	6
Noonan/? Noonan	10	Vascular malformation	31	Meige like	4	Congenital l/o	2		
Unknown	2	Others	6	distachiasis/ ?distachiasis	5	Milroy-like	10		
Others	10					VegFR3 abnormality	3	Primary l/o praecox	10

*Some of the data had a question mark against the diagnosis and some did not – these were combined

Table 6. Comparative audit data from highly specialised lymphoedema service (Mansour, 2014).

	Syndromic	Disturbed growth	Late onset	Congenital	Systemic	Others
Unpublished audit	18%	19%	28%	31%	4%	0%
This audit	19.7%	28.5%	9.8%	33.7%	0%	8.3%

lymphoedema and this may account for the slightly higher figure in this audit. Although the characteristics of Milroy were originally described in 1892, it was only in 1998 that the causative gene was first located (Ferrel et al, 1998). Syndromic primary lymphoedema accounted for 19.7% of the children, 42% of which had Turner syndrome — a chromosomal abnormality affecting females in which all or part of one of the sex chromosomes is absent. One of the common features of this condition is lymphoedema of the hands and feet (Ranke and Saenger, 2001). Of the vascular abnormalities, Klippel Trenaunay Weber syndrome was most frequently recorded with 10 cases. In addition to capillary and venous anomalies, the abnormal development of lymph vessels results in swelling of the affected limb (Gloviczki and Driscoll, 2007). There is a vast difference between these figures and those of the unpublished audit (*Table 6*). This variation in results is likely to be the result of the more accurate diagnostic facilities in the highly specialised centre.

Cellulitis (infection of the skin and tissues) is a common complication of lymphoedema (British Lymphology Society, 2013). It is believed that patients with primary lymphoedema are more likely to suffer cellulitis than patients with secondary lymphoedema. Ranges in populations that include patients with primary lymphoedema vary from 23% to 32% (Mortimer, 2000). This audit shows that 12.5% (n=57) of the children suffered from cellulitis, more than a third of which reported experiencing recurrent episodes. This however would suggest that children are less likely than adults to suffer from cellulitis.

Waiting times for referral to a treatment site has been highlighted as a major source of stress for families (Todd et al, 2002; Moffatt et al, 2010). Of the 383 children who had waiting times data recorded, only 16% waited less than 6 months for referral whilseover a half the children (55%) were seen by a treatment service in less than 2 years from the time of diagnosis. However, a delay in referral of 10–17 years from onset of swelling was reported by 16% of respondents.

Previous studies have asserted that lack of clinical and service location knowledge is responsible for referral delay, but the lack of available services for treating children may also have contributed to this situation. It is hoped, however, that the establishment of the CLSIG will improve clinical knowledge and lead to better referring practice.

From the wide range of medical specialities referring to lymphoedema services, it would appear that there is no clear diagnostic route for children suspected of having lymphoedema. This poses challenges in terms of raising awareness and establishing effective referral guidelines. The small number of cases and specialist nature of the treatment precludes the provision of care for children across all existing lymphoedema clinics. A network of regional centres has been proposed and this has been reflected in the existing network of children's services that make up the network of the CLSIG. Currently, there are plans to develop an assessment and onward referral pathway to aid in the diagnosis and treatment planning for children with lymphoedema. There are also plans to establish national protocols of care for children with lymphoedema.

Conclusion

This article is based on an audit of children's services in the UK and has been undertaken as a collaborative enterprise by members of the CLSIG. Some 455 cases were reported by a total of 19 centres and 8 parents. The audit has indicated the common features, causes and characteristics of the children referred, together with the clinical phenotypes seen. There was a wide range of medical investigations used across the population and a number of specialities were involved in the initial diagnosis of the child. Almost half the children in the study had to wait for over 2 years to be referred to a children's lymphoedema service for treatment. This study provides some indication of the nature of the difficulties faced by children with lymphoedema. It will also form a basis for the development of education strategies and ongoing service development.

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