

LIMPRINT in Italy

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Abstract

Background: To define the profile of patients presenting with chronic edema (CE) in three centers in Italy (Lymphoedema IMPact and PRevalence INTernational).

Methods and Results: Data were collected in patients referred for CE between September 2016 and July 2017. A total of 1637 were recruited, 86.7% (1419) outpatients and 13.3% (218) inpatients with 80.6% (1319) female and mean age 54 years. Primary lymphedema occurred in 28.2% (461). In the 71.8% (1176) with secondary CE cancer occurred in 72% (846) and 28% (330) due to other causes. Data showed that 84.2% (226) had full upper body mobility, 15.5% (41) had limited mobility and 0.2% (2) had lost all mobility. Lower limb mobility status: 90.4% (1205) complete mobility, 8.4% (112) reduced mobility and 1.2% (21) wheelchair bound. Concurrent leg ulceration occurred in 32.9% (322) with 3.1% (51) having antibiotics. Treatment patterns varied with only 32.4% (530) receiving instructions in skin care, 61.2% (1002) multilayer compression and a further 67.8% (1110) compression garment with 17.6% (288) having sequential pressure therapy. Only 1.4% (23) had received psychological support. Out of the total 481/1637 (29.4%) were not prescribed any treatment. Only 50.4% (825) had access to subsidized treatments within the National and Regional Health Care System, whereas 49.6% (81) had to pay themselves with only half (50.9%) having access to treatment centers that were near their home.

Conclusion: Results from this study and active lobbying have led to changes in reimbursement of care for primary and secondary lymphedema in Italy; this has led to a much more optimistic picture for those affected.

Keywords: LIMPRINT, lymphedema, lymphedema, chronic edema, chronic edema, Italian prevalence

Introduction

LYMPHEDEMA IS A CONDITION that is poorly recognized and undertreated. Until recently it has been considered a rare disease and frequently defined as a complication of cancer and its treatment. Epidemiology was focused for many decades on those with breast cancer-related lymphedema leading to a very biased view on who was affected.^{1,2} However, it is now known that lymphedema is multifactorial and frequently affects both the lymphatic and venous system and is influenced by chronic inflammation and factors such as

hormonal influence on adipogenesis with a growing emphasis on genetic predisposition.³ Lymphedema has classically been defined as either primary in those with a congenital malformation or secondary due to damage of the lymphatics from trauma, including cancer treatment and other insults. However, taking a more global perspective lymphatic filariasis is the major cause with 40% of the 250 million predicted cases found in India and affecting the poorest populations.⁴

Lymphedema is a lifelong condition and there is increasing awareness of the impact that this condition plays on many aspects of daily life leading to deficits in health-related

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TABLE 1. EPIDEMIOLOGICAL DATA GENDER, CLASSIFICATION OF LYMPHEDEMA, AND FACILITY

| <i>Data collection period</i> | <i>Females</i> | <i>Males</i> | <i>Primary lymphedema</i> | <i>Secondary lymphedema</i> | <i>Outpatients</i> | <i>Hospitalized patients</i> |
|-------------------------------|----------------|--------------|---------------------------|-----------------------------|---|------------------------------|
| 1637 Patients | 1319 (80.6%) | 318 (19.4%) | 461 (28.2%) | 1176 (71.8) | 846 (72%) Cancer related 330 (28%) Other secondary | 1419 (86.7%) 218 (13.3%) |

quality of life and a risk of psychological problems such as depression and anxiety.⁵ The true impact on the patient and their family has not been adequately examined although early evidence would indicate that there are many social issues that patients face relating to employment and the ability to participate in activities of daily life.⁶ We are increasingly aware that if the condition is left untreated a spiral of complications such as recurrent cellulitis and loss of function may occur leading to further distress and potential disability.⁷

For the past decade the term chronic edema (CE) has been adopted as a public health term reflecting the many diverse populations that lymphedema can affect and includes both primary and secondary forms of lymphedema.⁸ The term is also a reflection of the growing recognition of the importance that the lymphatics play in all edemas irrespective of the underlying cause or concurrent risk factors.⁹

Within this study the following definition of CE was adopted:

Chronic oedema (CO) is a broad term used to describe edema that has been present for more than three months and involves one or more of the following areas: limbs, hands/feet, upper body (breast/chest wall, shoulder and back), lower body *(buttocks and abdomen, genital (scrotum, penis, and vulva), head, neck, or face.⁸

There has been relatively little study into the prevalence and impact of CE although this area of research is now growing. The first research using the term CE was undertaken in a population in London (UK) in 2003 and reported a prevalence of 1.33 per thousand,⁸ and when repeated using the same methods in a similar population in Derby in the East Midlands (UK) in 2017 a prevalence of 3.93 per thousand population was recorded.¹⁰ It is not possible to claim that this threefold rise is a consequence of an overall increase in prevalence as it may be the effect of the condition being more known by health professionals in this area. Doubtless there are a myriad of reasons to explain this many of which have not yet been identified. What is clear is that it can no longer be defined as a rare disease but a complex one affecting a heterogenous population.

The issue of identification of patients in the health care system is compounded by the lack of professional knowledge causing many patients to remain undiagnosed and, therefore, "hidden." Frequently they only come to light when presenting with serious complications such as cellulitis or

leakage of lymphorrhea and have reached a late stage III (ISL classification). Parents of children with primary lymphedema also report a long delay of many years in obtaining a correct diagnosis in some countries, with a torturous journey of seeking the correct diagnosis and receiving incorrect information.^{11,12} Lymphoedema Impact and PRevalence INTer-national (LIMPRINT) has also shown that people are found in all parts of the health care system, including acute hospitals, specialist services, and social care settings.¹³⁻¹⁵ As there is a clear link to a sharp rise in CE prevalence in the very elderly it is likely that many are also "hidden" in the social care sector and the burden of management falls to families and carers. Undoubtedly, increasing age leads to the likelihood of patients having complex medical problems and receiving a polypharmacy of drugs that may also exacerbate the problem. Recent research undertaken in LIMPRINT has shown that cellulitis carries a lifetime risk of 37.4% in people with leg CE and has shown a close relationship to a concurrent chronic wound occurring in secondary lymphedema.⁷

Many important changes in the general population such as aging, reduced mobility, rising rates of diabetes and cardiovascular disease, and other comorbidities such as morbid obesity would indicate the likelihood that we will see an exponential rise in CE over the coming years. As we begin to unravel the complexity of the problem it becomes increasingly important to undertake research that can define the problem if we have hope to obtain funding and support for evidence-based care.

LIMPRINT was run under the auspices of The International Lymphoedema Framework (ILF), a charity whose aim is to improve the management of lymphedema. LIMPRINT is an epidemiology study designed to capture the size and impact of this condition in people identified in the health systems using a common methodology.

As one of the National Frameworks of the ILF, the Italian authors of this article who work daily with patients affected with lymphedema and dedicate themselves to research in the lymphological field saw the opportunity to join LIMPRINT and research the prevalence causes of lymphedema and different modalities of treatment of CE and the impact this has on health services within Italy, and as part of the greater international community. Their aim was to contribute to developing an awareness about the spread of lymphedema in the world and particularly to provide evidence to support the development and reimbursement of private and public health services for CE in Italy.

TABLE 2. AGE, LEVEL OF OBESITY, COMORBIDITIES, AND WOUNDS

| <i>Middle age</i> | <i>Normal weight</i> | <i>With associated obesity</i> | <i>With lymphatic ulcers</i> | <i>With diabetes</i> |
|-------------------|----------------------|--------------------------------|------------------------------|----------------------|
| 54 Years | 1285 (78.5%) | 352 (21.5%) | 322 (32.9%) | 111 (6.8%) |

The LIMPRINT study

The methods for development of the methodology and early results have already been published.¹⁶ In summary, LIMPRINT is a multisite epidemiological study that was undertaken in nine countries who are national framework members and at 40 sites within those countries. Data collection in Italy used the core tool that covers the following domains:

- Type of facility in which data are collected
- Level of obesity
- Relevant comorbidities
- Mobility status
- Classification of lymphedema
- Lymphedema history
- Cellulitis history
- Categories of treatment
- Site of swelling
- Wound area
- Access to treatment
- Subjective control of swelling.

Study setting

The study in Italy was conducted in three centers in the middle of Italy—Rome—Lazio, Terni—Umbria, and Ancona—Marche. Ethical approval for the study was obtained and staff involved in the study were trained in aspects of the data collection to ensure the quality of the data. The Italian study co-ordinator (M.C.) was supported by the LIMPRINT ILF team through regular steering group meetings to ensure support. Data were entered on to a secure electronic data system (ecrf) that included an audit facility that enabled the data to be checked centrally for accuracy by the ILF study monitor (S.M.). All patients referred or being treated for CE in the three sites were approached and asked to join the study by the team between September 2016 and July 2017. Over the recruitment time 1637 patients with a proven diagnosis of CE gave informed consent and were recruited and were seen in either an inpatient or outpatient facility.

Statistical analysis

Data analysis was performed by the study statisticians using Stata. Data from the three sites were pooled and results are presented as descriptive variables with *N* (%) for categorical variables.

Results

All patients seen were evaluated by a multidisciplinary team with lymphology experts before being entered into the study. Over the study inclusion period 86.7% (1419) were recruited in an outpatient setting and 13.3% (218) were seen as inpatients. Gender distribution showed a much higher proportion of females 80.6% (1319) and 19.4% (318) males. The mean age was 54 years. The underlying cause of primary lymphedema was reported in 28.2% (461) and secondary lymphedema 71.8% (1176). Further classification of secondary lymphedema into subcategories showed the predominance of a cancer-related condition with 72% (846) and 28% (330) other causes, for example, heart disease and neurological disorders (Tables 1 and 2).

TABLE 3. MOBILITY OF UPPER LIMBS (*N*=269)

| <i>Complete mobility</i> | <i>Limited mobility with paresthesia and hypo/anesthesia</i> | <i>Wheelchair</i> |
|--------------------------|--|-------------------|
| 226 (84.2%) | 41 (15.5%) | 2 (0.2%) |

Overall mobility status of the lower and upper body was assessed, including the range of movement of both the limb(s) affected by lymphedema and those unaffected. In the upper extremities the data showed that 84.2% (226) had full mobility, 15.5% (41) had limited mobility with accompanying paresthesia and hypo/asthenia. Of those 15.5%, 94% had CE secondary to oncological pathology. The remaining 0.2% (2) had lost all mobility in that limb (Table 3). The range of movement of lower limbs showed 90.4% (1205) had complete mobility, 8.4% (112) had limited mobility, and 1.2% (21) were wheelchair bound (Table 4). Of those with leg CE, 32.9% (322) suffered with concurrent leg ulcers with 3.1% (51) who had been treated or were presently being treated with broad spectrum antibiotic therapy for the treatment and secondary prevention of infectious complications.

In examining the data it emerged that a combined treatment for lymphedema is not homogenous: the evaluation of a multidisciplinary approach in the field of physical therapy showed that only 32.4% (530) of the patients received instructions and treatment for skin care. Furthermore, indication of the standard physical rehabilitation protocol (skin care, lymphatic drainage, bandaging, and physical exercise) leading to the prescribing of an elastic garment, was rarely found among the cases examined (Table 5).

The use of compression therapy was evaluated and showed that 61.2% (1002) had been prescribed multilayer bandaging as part of their treatment. However, this figure does not take into account patients unable to use this form of compression due to physical or psychological intolerance and who did not tolerate this intervention. In addition to this 67.8% (1110) were prescribed a compression garment with 17.6% (288) having undergone one or more cycles of sequential pressure therapy. Some had used or were using these pneumatic compression devices for self-treatment in the home. The impact on the patient's work and social life affected by lymphedema but only a small number 1.4% (23) had received psychological support. Out of the total cohort 481/1637 (29.4%) were not being prescribed any treatment at the time of recruitment. This will be influenced by those who were newly presenting to the specialist services. Results indicated that 50.4% (825) had access to subsidized treatments within the National and Regional Health Care System, whereas 49.5% (81) had to pay in full themselves for treatment (Table 6). Questions relating to access to treatment showed that only half (50.9%) had access to treatment centers that were near their home.

TABLE 4. MOBILITY OF LOWER LIMBS (*N*=1334: 322 BILATERAL)

| <i>Walk without support</i> | <i>Walk with support</i> | <i>Wheelchair</i> |
|-----------------------------|--------------------------|-------------------|
| 1205 (90.4%) | 112 (8.4%) | 21 (1.2%) |

TABLE 5. SPECIFIC PRESCRIBED THERAPIES

| | <i>Skin care</i> | <i>Bandaging</i> | <i>Manual lymphatic drainage</i> | <i>Pressotherapy</i> | <i>Physical exercises during treatment</i> | <i>Prescribed elastic garment</i> | <i>No indications</i> |
|--------------------|------------------|------------------|----------------------------------|----------------------|--|-----------------------------------|-----------------------|
| Number of patients | 530 (32.4%) | 1001 (61.2%) | 655 (39.4%) | 288 (17.6%) | 913 (55.8%) | 1109 (67.8%) | 481 (29.4%) |

Discussion

Findings from this study contribute new knowledge of the impact of CE on patients and health services in Italy. A high proportion of women were reported to be affected in Italy and this compares with data from a larger study using the same methods services ($n=8140$) in the United Kingdom, France, Italy, and Turkey.¹⁴ The mean age of 54 in Italy is considerably younger than those seen in specialist services in the United Kingdom who also found much higher levels of obesity and morbid obesity compared with the Italian population in whom only 19.7% were obese. This is not surprising as the United Kingdom has the highest rates of morbid obesity in the population (27%) compared with only 10% in Italy. Mobility was much less affected in the Italian study with >84% having full mobility compared with two thirds reporting reduced mobility in the wider study group. The number of patients with primary lymphedema was significantly higher in Italy (28.2%) than the number reported in the combined study (16%), but had a similar rate to those in Turkey. The reasons for this are unclear, but it may reflect patterns of diagnosis and use of investigations or that services are treating a different patient group in Italy compared with other centers. Italy and the United Kingdom reported a similar rate of leg ulceration compared with other centers such as Turkey, although this will be influenced by the larger number of breast cancer patients seen in the Turkish sites. Cancer was a common cause of secondary CE in Italy in a similar distribution in France, Italy, and Turkey (80%) compared with only 35% in the U.K. services.

This study offers new insight into the effects of access to treatment with more than half reporting either having no access to treatment or that who would have to travel a long distance for care. At the time the study was undertaken only half of those affected could have their treatment paid for by the health services with the remainder having to pay themselves. Other studies report the insidious effects this may have on families.¹⁷ A study undertaken in France, which has a public health care system, showed that the out-of-pocket costs are a burden to families on low income who may be unable or unwilling to allocate their scarce funding on aspects of treatment such as compression therapy.¹⁸

It is increasingly recognized that different models of specialist's services for lymphedema have emerged across the world and despite attempts to standardize what constitutes an expert center there is a huge diversity in care provision. It is suggested that services that have been in operation for longer periods of time have evolved in the types of patients that are referred and treated. An example of this can be seen in the United Kingdom in which services in the past were largely focused on patients with cancer-related lymphedema.¹⁴ However, with time the focus has changed to include primary patients and those with a range of secondary CE not related to cancer. Different models of care have also evolved around areas of medical interest in lymphedema such as rehabilitation, dermatology, and vascular disease. The growing recognition of the complexity of the populations is leading to increasing emphasis on the importance of interdisciplinary services that can provide comprehensive diagnosis, treatment, and follow-up. There is increasing evidence of the important link with other services such as wound care and the requirement to develop pathways of care that support people in primary care. Service provision requires a clear understanding of the different types of patients who require treatment and robust epidemiology to show the number of people affected in the health system so that care can be organized and reimbursed appropriately.

Conclusion

This study aimed to identify the profile of patients seen within specialist CE services in Italy. The study findings support the diverse population of people affected and the deficits that still exist in effective care delivery. It emerges that in Italy, despite the noteworthy advances in welfare and social security legislation obtained in recent times, the number of sick people who must take care of themselves at their own expense remains high. The authors will continue to work hard to complete this difficult and troubled journey. However, in Italy, it is important to underline that during the time that the LIMPRINT study was in progress in the country new directives issued by the government in September 2016 regarding assistance to patients with primary and secondary lymphedema, and a further directive in January 2017 naming

TABLE 6. POSITIVE/NEGATIVE WELFARE (AVAILABILITY OF PUBLIC SANITARY SYSTEM)

| | <i>Treatments within the National and Regional Health Care System</i> | <i>Patients paying in full for various treatments</i> | <i>Presence of treatment centers close to home</i> | <i>No treatment centers close to home</i> |
|--------------------|---|---|--|---|
| Number of patients | 825 (50.4%) | 812 (49.6%) | 804 (49.1%) | 833 (50.9%) |

primary lymphedema as a rare disease (thus having dedicated protection) have revolutionized and are revolutionizing the “public” role in this branch of medicine. Lymphedema patients begin to be better and more widely assisted throughout the country. Probably repeating the same study at the current time in Italy would provide a substantially different and more positive perspective for lymphedema patients.

Author Disclosure Statement

No competing financial interests exist.

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