SURGICAL CHALLENGES IN LYMPHATIC FILARIASIS

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INTRODUCTION

For more than 43 million Africans infected with the Wuchereria bancrofti, the risk of developing lymphedema of the limbs and genitalia, hydroceles, and chyuria is significant. It is estimated that as many as 10 million men in Africa suffer from hydroceles caused by lymphatic damage associated with filarial infection. Ninety percent of infections worldwide are caused by Wuchereria bancrofti. Brugia malayi and Brugia timori are responsible for the other 10%, but are not known to cause urogenital disease and are not found in Africa. Recent reports by the Global Alliance for Elimination of Filariasis (GAELF) and the World Health Organization (WHO) cite 83 countries endemic for filariasis. Thirty nine of these are in Africa (Table 1) (Fig. 1). In addition, the economic burden of the disease is staggering. It has been estimated at US $1 billion/year in India. Surgeons are frequently consulted for cases of hydroceles, severe lymphedema, and chyuria. Yet most surgeons are unaware of current public health programs in their regions and are not actively working in coordination with program managers to bring their skills to bear. New insight into the basic science of lymphatic filariasis (LF) and surgical options will give the surgeon a broader set of skills to deal with these interesting and complex cases. Collaboration with program managers in the Global Program for Elimination of Lymphatic Filariasis (GPELF) in endemic areas can allow surgeons to greatly impact the successful elimination of filariasis as a public health problem in the foreseeable future.

HUMAN / MOSQUITO / PARASITE / BACTERIA: A COMPLEX INTERACTION

The direct cause of lymphatic filariasis is infection by the adult parasites and microfilariae of Wuchereria bancrofti or Brugia malayi. W. bancrofti is this parasite which causes the lymphangiectasia responsible for genital pathology. The adult female W. bancrofti is a pale,
threadlike nematode measuring 6-10 cm in length and 0.2 mm in width. The male is smaller, at 4-6 cm in length and 0.1 mm width.\(^{3,4}\)

Transmitted primarily by mosquitoes of the species Coquex, Aedes and Anopheles, its range is in tropical and subtropical zones.\(^6\) Mosquitoes deposit the larvae on the host skin adjacent to the puncture site (the larvae are too large to be transmitted through the mosquito’s proboscis), and the third stage larval (L3) parasites migrate through the venous system and lungs to eventually take up residence in the lymphatics. In adolescent and adult men, there is a preference for the lymphatics of the spermatic cord. There they form nests occupied by male and female worms, and produce the first stage larvae or microfilariae by viviparous reproduction. These larvae migrate from the lymphatics to the peripheral blood where mosquitoes ingest them. In the mosquito, the developing microfilariae become third stage larvae, L3. With a lifespan of 5-10 years, adult worms are more resistant to anti-inflammatory agents than are microfilaria. Microfilaria may live up to several months. The diurnal periodicity of microfilaria distribution in the blood stream is not related to discharge from the mature female, but instead relies on a circadian rhythm, which is not well understood.

Recent reports have implicated Wolbachia sp, an endosymbiotic bacterial parasite of the filarial worm as a cause of human disease. Wolbachia is known to exist in many species of insects, worms, and arachnids. It is known to profoundly affect the productive success of insects and arachnids.\(^5,7\) It has been found in W. bancrofti in many regions which have been studied, Wolbachia influences the reproductive behavior of many of the infected species, and it seems to correlate with human pathological manifestations of filariasis.\(^8,9\) Reports suggest that medical treatment with antibiotics directed to Wolbachia may actually decrease filarial burden.\(^9,10\) It is not certain whether this is because treating the bacteria changes the reproductive activity of the worms or whether there is some more direct action. The direct role of Wolbachia in lymphatic filarial disease in humans is unknown. However, Wolbachia surface protein (WSP) has been detected in patients with active disease. In a study in Haiti it was shown that anti-Wolbachia surface protein (anti-WSP) was more predictive of morbidity than filarial infection status\(^6\) leading the authors to speculate that the inflammatory response seen as after treatment with antifilarial drugs may be related to exposure to WSP. Since the Wolbachia organism lives within the filarial parasite, it is thought that the damage to humans may be related to exposure at the time of the death of the worm.

**DIAGNOSIS**

The most common screening test for microfilaria is the night blood smear. Microfilaria are most commonly active at night and can be detected on thick smear in microfilaraemic patients. The ICT is a more expensive serology test used in mapping and population studies. However, the ICT antibody test for the adult worm is known occasionally to be negative even when adult living worms have been confirmed to be present with ultrasound and surgery.\(^{12,13}\) Adult parasites of W. bancrofti prefer to occupy the lymphatic vessels of the spermatic cord rather than the lymph nodes in adult men where lymphangiectasia may be detected by ultrasound. Characteristic filarial dance sign has been detected in men, women, and children infected with adult worms.\(^{4,14-18}\) It is the primary diagnostic test to confirm the presence of living adult worms in the lymphatics of the spermatic cord in adult men and the lymph nodes of children.\(^{15}\) Adult worms are detected by the filarial dance sign in up to 80% of infected men\(^4\) and 45.5% of infected women.\(^{17}\)

**PATHOLOGY**

The experience with naïve human hosts shows that initial infection causes an intense inflammatory reaction, particularly in the lymph nodes. The inflammation causes temporary obstruction, which later re-canalizes.\(^{18-20}\) Studies have shown that the damage to lymphatics is not primarily inflammatory but instead secondary to an alteration of the microenvironment of the lymphatic vessel resulting, ultimately, in lymphangiectasia.\(^{21-23}\) Immune tolerance may be acquired in utero in children of infected mothers.\(^24\) With the variations in reproductive activity of the worms, humans carrying living adult parasites may be asymptomatic without microfilariaemia, asymptomatic with microfilariaemia, or symptomatic with acute and chronic disease.\(^{12,25}\) The mechanism by which the parasite influences its microenvironment to cause the dilation of the lymphatics is unknown. However, it does not appear to be caused by a chronic inflammatory process.
Fig. 2: Algorithm for the management of scrotal swellings
While the adult worms are living, the endothelium of the lymphatics shows no sign of inflammation in most cases. The lymphangiectasia is a generalized phenomenon in the lymphatics and causes lymphatic dysfunction in many parts of the body as can be demonstrated by lymphangiogram. Ottesen notes that lymphangiectasia may be a response to a diffusible factor affecting the endothelium and eventually the vessel wall. Morbidity does not necessarily correlate with immunological markers for disease. In a study of 121 patients with hydroceles in an endemic area of Haiti, Addiss et al. found that only 39% were positive for microfilaria. The circulating filarial antigen (from the adult worm) was identified in 43% of microfilaria-negative men with hydrocele. The hydrocele volume was inversely proportional to blood filarial density. In another study, hydroceles were found to correlate; findings may correlate more closely with anti-Wolbachia surface protein.

Among the most distressing problems in symptomatic patients are periodic “acute attacks” characterized by localized pain and fever. Filariar adenolymphangitis (FADL) is caused by the death of an adult worm from natural causes or drug treatment, such as diethylcarbamazine (DEC). The characteristics of the attack, either adenitis or lymphadenitis, depend on where the dead parasites lodge. Patients with scrotal disease may experience an erythematous, indurated, tender spermatic cord accompanied by malaise or a headache. Orchalgia or orchitis, epididymitis or funiculitis may also occur. The inflammatory response is characterized by infiltration of the lymphatic walls by neutrophils, eosinophils and macrophages. The degenerating worms may become the focus of microabscesses and localized obstruction of the lymphatic channel. There, they may become calcified in the later phases of decomposition. Hydroceles occurring after “acute attacks” usually resolve spontaneously.

Acute dermatolymphangitis (ADLA) occurs due to secondary infection of damaged superficial lymphatics, frequently by beta hemolytic streptococci. Chronic manifestations in the scrotum include a “puffy” or spongy skin of the scrotum or sometimes an extraordinarily thickened, subcutaneous tissue. In these patients, the testis, epididymis, and cord may remain largely intact. Lymphoscintigraphy can help to assess the extent of the disease both superficially in the deep systems in these cases.

MANAGEMENT

The pillars of management of lymphatic filariasis morbidity are both medical and surgical. From the medical perspective, the guiding principle is to eliminate the production of microfilaria, which are ingested by mosquitoes and carried to re-infest new hosts. This can presumably be accomplished by sterilizing the adult worms, by killing them, by killing microfilariae, or by killing Wolbachia. It has been shown in Haiti that even in the microenvironment of neighbourhoods, infected households can contribute to re-infection of neighbours after initial successful medical therapy. This means that the entire population of an endemic area must ingest the antiparasitic drugs. In some places, this works by spiking the table salt with DEC. However, in regions where W. bancrofti is co-endemic with onchocerciasis, DEC is not recommended because of possible adverse consequences of death in living adult worms. In these regions, including most of sub-Saharan Africa, ivermectin must be used instead to reduce morbidity. Albendazole is also given along with these other drugs to potentiate the effects. With DEC and Albendazole treatment, it is not unusual for patients to develop temporary, painful scrotal or other nodules and fever, which occur with the death of the worms. Transient hydroceles may also form shortly after treatment. Additionally, some patients/parasites are resistant to DEC and Albendazole. It is helpful that other medications or combinations of these may exist for successful treatment.

Recent reports suggest that treatment with doxycycline may be beneficial in LF. An 8 week course of 200 mg/day can bring down the detected microfilaria to 50% in 3 months and almost 0 in 6-12 months. The rationale for giving this is that doxycycline kills Wolbachia, an endosymbiont of the worm. Killing the Wolbachia seems to render the worms sterile. Additionally, doxycycline seems to ultimately eliminate the worms, at least by decreasing the number of worm nests in serial ultrasound studies of a cohort of patients.

Personal hygiene is critical to care of patients with clinical manifestations of lymphatic filariasis, including elephantiasis of the extremity or of the genitalia. Regular bathing, antibiotics when necessary, and local care are critical to the outcome of any medical treatment. Local support groups, known as “Hope Clubs”, lend much support to patients in communities,
especially with edema of the limb. In many cases, the patient cannot adequately clean the limb on his or her own, and requires family and community assistance.

**HYDROCELE / CHYLOCELE**

Western textbooks do not address the pathology of the lymphatics associated with filarial-related hydroceles. On physical examination, a hydrocele associated with scrotal lymphangiectasia or nodules of the cord in an endemic area is highly suggestive. One method of subclassification describes the filarial hydrocele as containing a clear or yellowish fluid without leukocytes. In contradistinction, a chylocele contains milky chyous fluid. On aspiration, this fluid will not usually contain microfilariae unless contaminated by blood during the procedure. Recommendations from the WHO informal consultation on surgical management of filariasis speak against the Lord-type plication of the tunica vaginalis for patients with LF. A vertical incision is recommended in order to preserve the already-damaged superficial lymphatics of the skin and subcutaneous tissues. Prior to surgery for a presumed hydrocele, it is necessary to ensure that all superficial skin inflammation, bacterial and fungal infection has resolved. Aspiration and drainage are not recommended and injection of sclerosing agents is contraindicated. The recommended algorithm for identifying and triaging scrotal swellings is shown in Fig 2.

Chylocele is most often associated with long-standing disease characterized by acute and chronic inflammation, thought to be secondary to the original lymphatic pathology. The lymphatics draining the tunica vaginalis are damaged and chyous fluid leaks into the sac. Aspiration of a chylocele also may reveal leukocytes characteristic of acute and chronic inflammation. Frequently, the testis and epididymis are severely inflamed and necrotic.

**LYMPH SCROTUM, PENILE DERMATO-LYMPHANGIOPATHY AND LYMPHEDEMA OF THE LABIA**

“Lymph scrotum” is perhaps the most crippling complication of lymphatic filariasis in men. It is almost always seen in patients who have a history of multiple acute attacks due to bacterial and/or fungal superinfection and who have chronic lymphangiectasia. It may be seen after surgery for chylocele or hydrocele, and represents the dermatological manifestation of pathological lymphatic drainage. Patients experience continuous dripping of milky lymphatic fluid from “blisters” on the surface of the scrotal skin. Some patients wear cloth coverings with plastic backing to blot the fluid. Others fashion cups and other contrivances to catch it. In these patients the skin of the penis is often also involved in the process including the entire shaft but limited by the corona of the glans. Principles of effective surgery for lymph scrotum and lymphangiectasia of the penis include complete scrotectomy and removal of the shaft skin and subcutaneous tissue. The scrotum may be covered by a mesh skin graft and the penile shaft with a full-thickness skin graft after the patient has received effective antibiotic treatment and has stabilized the inflammatory process. Lymphedema in the setting of LF has been successfully treated with nodovenous shunts pioneered in India. Although long-term success can be achieved, treatment must be done at a tertiary hospital with the capability for microvascular surgery.

**CHYLURIA AND HEMATURIA**

Chyluria in patients with LF is often intermittent and related to diet and other factors. It is caused by rupture of the small lymphatics of the collecting system, and is possibly related to secondary infection. Hematuria often accompanies chyluria, but must be evaluated in its own right to exclude other common pathology associated with hematuria in adults. Chyluria frequently responds to a diet emphasizing high protein and low fat. For intractable cases, various surgical techniques have been advocated including retrograde ureteral irrigation with AgNO3 or provodone iodine, or laparoscopic or open disruption of the lymphatics surrounding the affected kidney. Of these, irrigation with 0.2-5% provodone iodine has been effective without the risk of silver deposits in the kidney. However, such irrigations may need repetition multiple times. Hematuria and proteinuria are seen in up 40% of microfilaricmic patients but not in those without microfilaremia. Gross and microscopic hematuria due to LF responds to medical treatment with DEC within two weeks of treatment.

**SURGICAL CHALLENGES**

There is great need for surgeons to contribute experience in a prospective manner for LF. For example, it is not known what the best
types of surgery are for filarial hydroceles. The WHO consultation report of 2002\textsuperscript{36} was the result of the pooled experience of the consultants. Yet there has not been a prospective study to compare the various published techniques in patients with documented LF. This is particularly important, as conditions in operative theatres vary greatly, especially in developing countries. In some settings diathermy is available. In others it is not. The techniques appropriate for a district hospital will differ from those available in a tertiary setting. The availability of perioperative antibiotics, analgesics, and anesthetics may vary as well. For chyluria, cystoscopy is considered to be optimal for diagnosis and treatment. Yet basic endoscopy is not universally available, nor is retroperitoneoscopy in most surgical settings. Developing the optimal surgical treatments for patients in developing countries with limited resources continues to challenge surgeons. There is a dearth of published research addressing these topics but an opportunity to bring new light to the problems.

CONCLUSION

The ambitious program set out by the World Health Assembly (WHA 50.29) for elimination of LF worldwide depends on an educated medical community and an educated public\textsuperscript{34}. In endemic areas, partners in the Global Alliance are initiating local village and urban programs for education, such as “Hope Clubs”. Patients learn not just from health care providers, but also from each other. Surgeons both from temperate climates and tropical regions must become educated about the pathophysiology of lymphatic filariasis in order to care for their patients and to prevent harm from foreseeable complications of surgery. Patients with LF must be considered to have a life-long disease requiring management even after all evidence of active infection has resolved. Surgeons can become advocates for their patients by assisting in the management of their overall disease in addition to the conditions for which they originally seek treatment.

REFERENCES

6. Wolbachia website: www.wolbachia.sols.uc.edu


Internet Resources:
www.filariasis.org
www.wolfchilla.sois.ug.edu.au
www.filariasis.net

Other Resources: World Health Organization Regional Office for Africa (AFRO) Medical School C Ward Parirenyatwa Hospital P.O. Box BE 773 Belvedere Harare Zimbabwe
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