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TROPICAL FILARIAL PULMONARY EOSINOPHILIA (TFPE) WITH SPECIAL REFERENCE TO EGYPT: A MINI-REVIEW

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Abstract

Tropical filarial pulmonary eosinophilia (TFPE) is a clinical lymphatic filariasis (elephantiasis) manifestation caused by parasitic nematodes inhabiting the lymphatic and bloodstream. TFPE is an immune hyper-responsiveness to microfilariae that become lungs trapped in filariasis endemic tropical area especially among young adults, and four to seven times more common in males than in females.

Clinical manifestations usually start gradual. Symptoms include a dry, hacking, non-productive cough frequently paroxysmal and nocturnal, Asthma-like attacks associated with breathlessness and wheezing. Other symptoms include weight loss, fatigue, and malaise. But, dyspnea on exertion is relatively uncommon.

Key words: Lymphatic filariasis, Epidemiology, Vector, Pathogenicity, Treatment, Nursing role

Introduction

Tropical pulmonary eosinophilia (TFPE) can occur in any tropical area, but most commonly in filarial endemic regions like the Indian subcontinent, South East Asia (Rodhain and Rodhain-Rebourg, 1976), South Am erica, and Africa (Jha *et al,* 2022). Tropical filarial pulmonary eosinophilia is a clinical picture of lymphatic filariasis, a parasitic in fection caused by filarial nematodes (roundworms) inhabits lymphatic and bloodstream. Three species cause human lymphatic filariasis: *Wuchereria bancrofti, Brugia malayi,* and *B. timori* (Neva and Ottesen, 1978). Infection is transmitted by mosquito vector(s); humans are definitive hosts, TFPE is caused by an immune hyper-responsiveness to microfilariae trapped in lungs (Vijayan, 2007). A syndrome termed tropical eosinophilia, tropical pulmonary eosinophilia or TPE, or tropical filarial pulmonary eosinophilia or TFPE (Weingarten, 1943).

Epidemiology: TFPE can occur in any tropical area where filariasis and Culicidae mosquito occur, most commonly among young adults four to seven times more common in males than in females (WHO, 1992). WHO (1997) estimated that lymphatic filariasis affected over 120 million people in 72 countries throughout the tropics and sub-tropics of Asia, Africa, the Western Pacific, and parts of the Caribbean and South America. WHO (2022) added that LF impairs the lymphatic system and lead to huge enlargement of body parts, causing pain, severe disability and social stigma with a total 863 million people in 47 countries worldwide remain threatened by LF and require preventive chemotherapy to stop spread of this parasite. Lymphatic filariasis can be eliminated by stopping infection spread by preventive chemotherapy with safe medicine combinations repeated annually. More than 8.6 billion of the cumulative treatments were delivered to stop the infection spreading since 2000.

Review and General Discussion

The majority of cases of TFPE occur in endemic areas; cases in nonendemic settings have also been described. In a review of 17 cases observed in Toronto, all received an incorrect diagnosis at presentation (most often asthma), and a median of two consultations was required before the diagnosis was established (Boggild *et al,* 2004).

Pathogenesis: Pulmonary disease reflects a robust immunologic response against bloodborne microfilariae trapped in lung and reticuloendothelial organs (Ottesen and Nutman, 1992). TPE is an exaggerated immunological response to filarial antigens in adults in endemic areas, but uncommonly detected in children (Randev *et al,* 2018). TFPE develops in < 0.5% of patients with LF; explanation of this still unclear. The earliest histopathologic was histiocytic infiltration and a month later, an eosinophilic interstitial infiltrate developed (Islam *et al,* 1962). Tsanglao *et al.* (2019) in India reported that TPE must be suspected in patients from filaria endemic areas presented with cough, dyspnea or wheezing, high eosinophilia ($>3\times10^9$cells) with raised IgE level (>1000IU/ml). Also, sputum eosinophilia and chest pain due to rib fractures caused by vigorous coughing (Hayashi *et al*, 1996). But, early diagnosis and treatment prevented LF progression and risks (Mendoza *et al,* 2009). In chronic disease, there was eosinophil interstitial infiltration and increased pulmonary fibrosis, and microfilarial fragments identified in the biopsied lung or reticuloendothelial tissues (Jain *et al,* 2001).

Clinical manifestations: The onset of clinical manifestations is usually gradual. Symptoms include a dry, hacking, nonproductive cough frequently paroxysmal and nocturnal. Asthma-like attacks are associated with breathlessness and wheezing. Others are weight loss, fatigue and malaise, but dyspnea on exertion was relatively uncommon. Chest findings are minimal or absent in most patients. In some cases rhonchi, crepitations (especially over midzones & bases), and wheezing may auscultate. Lymphadenopathy, hepatomegaly and/or splenomegaly occurred in about 15% of patients (Freedman *et al,* 1994).

Diagnosis: The cardinal laboratory finding in TFPE is blood eosinophilia, usually above 3000/microl (Ong and Doyle, 1998). An elevation in serum IgE level frequently occurred often >1000 units/ml. Diagnosis is confirmed by marked elevations in filarial antibody titers, as MFs are generally neither detected in peripheral blood nor in circulating filarial antigen up to 50% (Lal *et al,* 1987).

Bronchoalveolar lavage showed an intense eosinophilic alveolitis in the active patients (Pinkston *et al,* 1987). Enlarged and tender lymph nodes, mainly in inguinal region, or lymphatic vessels inflammation in the extremities accompanied by MFs in midnight thick blood smears as diagnostic test in LF endemic areas (Wamae, 1994).

Chest X-ray showed increased bronchoalveolar markings, diffuse interstitial lesions (1 to 3mm in diameter), and/or mottled opacities (usually prominent in lower lung area), and hilar lymphadenopathy and pleural effusions are rare. The chest x-ray is normal in 20 to 30% of cases (Udwadia, 1975). Pulmonary function tests (PFTs) showed a predominantly restrictive pattern with mild to moderate airway obstruction, in few cases PFTs showed a predominantly obstructive pattern with a mild restrictive component (Brandao *et al,* 2009). Airway obstruction is reversible with bronchodilators (Molimard *et al,* 2005).

Differential diagnosis: TFPE differential diagnosis includes chronic eosinophilic pneumonia, drug hypersensitivities, military tuberculosis (Ray *et al,* 2012), fungal pneumonia (Azar *et al,* 2020), and pulmonary syndromes associated with other helminthes (Rocha *et al,* 1995). The *A. lumbricoides* in chest x-ray in pulmonary phase showed eosinophilia infiltration led to the Löffler syndrome (Pearson**,** 2020)**.** Mohamed *et al. (*2020) correlated between COVID-19 and Egyptian filariasis. *Toxocara canis* and/or *T. cati* caused dyspnea, high-grade eosinophilia, bilateral pulmonary nodules, common pulmonary cough and dyspnea symptoms mainly in bilateral pulmonary nodules image (Yoshikawa *et al,* 2011). *Strongyloides stercoralis* in chronic lung is the commonest extra intestinal organ in dissemination, with symptoms usually interpreted as a preexisting exacerbation condition more than a parasite (Davi dson *et al,* 1984), tuberculosis and strongyloidiasis must be markedly excluded as corticosteroid treatment, may lead to a fatal disse-

minated infection (Robinson *et al,* 1999). Also, pulmonary myiasis is an unusual zoonotic type with eosinophilic pneumonia (Morsy, 2014). *Trichomonas tenax* may colonize in airways during aspiration pneumonia causing pleural infection after a pulmonary abscess rupture with concurrent respiratory pathology or immunodepression (Porcheret *et al,* 2002), and *T. vaginalis* causes respiratory disease in newborns (Bruins *et al,* 2013).

Treatment: Standard one was diethylcarbamazine (DEC) given at 6mg/kg/day in 3 doses for 12 to 21 days (Thomsen *et al,* 2016), active against both MFs and worms, with a dramatic and rapid improvement in signs and symptoms in most cases. Restrictive and obstructive defects returned normal if given in the first infection few years, but a low-grade eosinophilic alveolitis may persist (Chitkara and Krishna, 2006). If DEC therapy was delayed, progressive interstitial fibrosis and irreversible impairment in pulmonary function could occur (Khalil et al, 2007).

Corticosteroid therapy was used as adjunctive therapy to reduce inflammation in acute setting but not definitive therapy for tropical filarial pulmonary eosinophilia, and must be confirmed by the randomized control studies (Mullerpattan *et al,* 2013). But, long-term therapy may be associated with more serious sequel, such as osteoporosis, aseptic joint necrosis, adrenal insufficiency, gastrointestinal, hepatic, & ophthalmologic effects, hyperlipidemia, growth suppression, and congenital malformations (Buchman, 2001). Relapses occurred up to 20% of patients within the first five years of DEC therapy (Cartel *et al*, 1990), treated with a repeated course of the same treatment regimen.

Although doxycycline (200mg/day for six weeks) has efficacy against adult filarial via its action on their *Wolbachia* endosymbionts (Fernando *et al,* 2011), but none evaluated DEC efficacy as either primary or adjunctive treatment for TFPE. Bronchospasm can generally be managed with bronchodilators, yet short-term corticosteroids may be necessary in severe cases. Four essential components of asthma management are patient education, asthma triggers control, monitoring for changes in symptoms or lung function, and pharmacologic therapy for both children and adults (Rank *et al,* 2013).

Southgate (1992) in England reported that low density of circulating MF often undetected by standard survey techniques occurs after anti-filarial drug administration and after vector control. But, detection by clinical, entomological or immunological methods was more sensitive than the usually employed parasitological techniques, due to extreme inefficiency of process transmissions. Stolk *et al.* (2005) in the Netherland analyzed series of MF counts from patients treated with a single dose of 400microg/kg ivermectin or 6mg/kg DEC (N= 23 in each with a year follow-up) by estimating microfilaricidal effect and reduction of MFs production. Ivermectin on average killed 96% and reduced production by 82%. DEC killed 57% and reduced production by 67%, with some patients very poorly responded. Strong reduction in overall MF production encouraged for LF control, but elimination diminished if part among population systematically responded poorly to treatment.

de Kraker *et al.* (2006) in the Netherland found that diethylcarbamazine-albendazole treatment of mf density dropped immediately, then slowly but steadily decreased further. But by ivermectin-albendazole treatment, mf densities immediately dropped to near-zero levels, followed by a small increase. For diethylcarbamazine-albendazole treatment average MF loss was about 83% (54% to 100% different studies) and worm-productivity loss was 100% (all studies). In ivermectin-albendazole, FM average loss was 98% to 100%, and worm productivity loss was 83% to 100%, with dose-dependent effects. Analysis estimation didn't depend on assumptions of worm lifespan or premature period and little on assumptions on MF lifespan. They concluded that the 2 therapies differed as to direct effect on MF, but both were highly effective against adults. Combined the-

rapies mass treatment caused high coverage with a large impact on LF transmission.

Ottesen (2006) in USA reported that in the past decade, treatment and control strategies for LF have undergone profound paradigm shifts-all due to a rapid increase in knowledge and understanding of LF as seen directly from a series of remarkable data by scientific and medical research communities. He added that a public health dimension focused on patients, supplements, predominantly patient-oriented to LF clinical approach. Gyapong and Twum-Danso (2006) in Ghana reported that by year 2004 end, almost half of the 83 endemic countries had initiated national programmes, providing mass drug administration to risky population of about 435 million. This remarkable achievement resulted from an enormous amount of technical, financial and political support by public and private sectors at community, national, regional and global level. Global program to eliminate lymphatic filariasis entered second quarter of operations, with substantial opportunities were taken and critical challenges were addressed. Ichimori *et al.* (2007) in Japan reported successfully eliminated LF and other parasitosis by community-driven, integrated nationwide campaigns during 1960s & 1970s. They added that the unique community-driven, by Japan-help approach of disease control and health improvement profoundly influenced PacELF activities with successful national disease-elimination model extended at regional level.

Michael and Gambhir (2010) in UK reported a long-standing gap in LF epidemiology in effect of heterogeneous infection processes occurring in the major mosquito vector genera may have on parasite transmission and control. They concluded that the key finding in this work was filarial infection thresholds, system resilience, transmission dynamics and parasite response to control, were all influenced by the mosquito-vector prevailence.

da Silva *et al.* (2018) in Brazil reported that global program to eliminate LF caused extraordinary success to reduce transmission and preventing morbidity by massive drug administration (MDA) to population at-risk. In a study between 2007 & 2012, quantification of microfilaraemia (QMFF), circulating filarial antigen (CFA) and filarial IgG4 were assessed. CFA & IgG4 titres showed a significant annual drop in CFA (-0.290 OD) and IgG4 antibodies titres (-0.303 OD).

Ofanoa *et al.* (2019) in Tonga found that successfully LF elimination as a public health problem, acknowledged by WHO (2017). Tonga looks forward to work with stakeholders to eliminate LF transmission and reached zero incidence. Rojanapanus *et al.* (2019) in Thailand conducted over tyears 2002 to 2011 extensive MDA with the high coverage rates. By periodic and regular monitoring surveys. it delineated LF transmission areas at sub-village level and detected via its evaluation surveys-the Stop-MDA surveys & TAS, below transmission threshold rates that enabled its validation of LF elimination.

Melrose and Leggat (2020) reported that the deployment of US Armed Forces personnel into the central Pacific islands (highly-endemic LF), both Samoa and Tonga showed 1000s cases of the acute form and greatly reduced ability to carry out their mission. The major transmission factor was the aggressiveness and efficiency of *Ae. polynesiensis.* They successfully prevented the rapid resurgence of the *Aedes*-transmitted LF.

Al-Kubati *et al.* (2020) reported that Yemen in 2000 joined WHO global efforts to eliminate lymphatic filariasis as a public health problem by initiating a National LF Elimination Programme (NLFEP) that was fully integrated with National Leprosy Elimination Programme (NLEP), the Ministry of Public Health and Population. They reported that WHO (2019) validated Yemen as the second country in the WHO/EMRO to eliminate LF successfully as a public health problem. Ramzy and Al Kubati (2020) reported that EMR Countries in 2000, estimated risky population to be 12.6 million people, accounted for about 1% of the global disease bur-

den. Of the 22 EMR Countries, Egypt, Sudan and Yemen were LF endemic and the disease was suspected in Djibouti, Oman, Somalia and Saudi Arabia. After almost 2 decades, Egypt and Yemen were successfully validated by WHO as achieved elimination criteria in 2017 & 2019, respectively. But, Sudan in 2018 completed LF mapped up to 26.2% geographical coverage where mass drug administration required and scaled-up.

Pastor *et al.* (2021) in Brazil reported that tropical and subtropical LF affected about 67 million people worldwide requiring better diagnostic tools for prevention and effective control procedures. They added that studies focusing on antibody capture assays were based on 13 different antigens with at least six commercially available tests, with 5 proteins further used for the antigen capture tests development. They explored 5 antigens of SXP/RAL-2 family (BmSXP, Bm14, Wb-SXP-1, Wb14, WbL), others were BmShp-1, Bm33, BmR1, BmVAH, WbVAH, BmALT-1, BmALT-2, & Wb123 that developed high sensitivity and specificity tests with low costs to assist global program to eliminate LF.

Lupenza *et al.* (2022) in Tanzania reported that the National LF control program in 2000 used Mass drug administration (MDA) of Ivermectin and Albendazole to individuals aged 5years and above, gave a significant decline in LF transmission in Masasi District after seven rounds of MDA. However, the presence of individuals who are persistently non-compliant may delay elimination of LF in the District.

Greene *et al.* (2022) in USA identified the Wb-bhp-1 encoded a *W. bancrofti* homologue of Bm R1, *B. malayi* protein used in the *Brugia* rapid antibody test for brugian filariasis with a single exon that encodes a 16.3 kD protein (Wb-Bhp-1) with 45% amino acid identity to BmR1. They added that immunohistology showed that anti-Wb-Bhp-1 antibodies primarily bind to Mf. Plasma from 124 of 224 (55%) MF individuals had IgG4 antibodies to Wb-Bhp-1 by ELISA. They concluded that Wb-Bhp-1 a novel antigen useful for serologic diagnosis of bancroftian filariasis, but needed to assess its value for monitoring the success of filariasis elimination programs Supali *et al.* (2019) in Indonesia compared the impact of annual and semi annual mass drug administration (MDA) on the prevalence of *Brugia timori* and *W. bancrofti* in Flores Island. They added that model-adjusted prevalence estimates showed that apparent differences in treatment effectiveness were driven by differences in baseline prevalence and that adjusted prevalence declined more rapidly in the semiannual treatment group. They concluded that the annual MDA reduced Mf prevalence to less than 1% in areas with low to moderate baseline prevalence. Semiannual MDA was useful in rapidly reducing Mf prevalence in the area with higher baseline endemicity.

Nursing interventions role, Dean (2001) reported that the International Skin Care Nursing Group (ISNG) is an active member of the WHO's efforts to eliminate LF as a world health problem. In early 2000s, ISNG had resources to fund a project team who worked within WHO programme to mobilise the nursing response, which still exists as a netwo rk supporting nurses who have an interest in the skin health. Byrne and Collins (2015) in USA reported that by using evidence and assessment skills, nurses and advanced practice nurses assess, diagnose, and treat LF child. They added that nurses can assist nursing students, nurse practitioner students, and faculties to promote sustainability benchmark of nursing leadership in global health. Also, Mag (2018) in Philippines reported that for nurse to manage filariasis must: 1-Monitor client's vital signs especially temperature, 2-Assess skin color and integrity as to wounds, bleeding, or any skin changes, 3- Assess for any discomfort and pain, 4- Provide wound care, 5- Elevate affected body area to reduce swelling, 6- Give ordered medications and discuss them to client, 7- Provide support to perform basic activities, 8- Encourage a motion range and simple exercises of affected extremities to stimulate lymphatic flow,

9- Recognize client's self-esteem needs, and
10- Provide health teaching and information for continuity of care.

In Egypt, Makhlouf *et al.* (1989) in Assiut City ddemonstrated the MF in a stray cat. Weil *et al.* (1999) in a longitudinal study for MF and filarial antigenemia infection in villages near Cairo, among 1,853 subjects >9 years of age were 7.7% & 11.2%, respectively. But, MF counts and antigen levels over one-year period were significantly lower in older people due to develop partial immunity to LF by time with rates of 1.8% & 3.1%, respectively. They added that MF and parasite antigen levels were significantly reduced by diethylcarbamazine therapy, but many of them refused treatment, and most treated people were still infected a year later. Incident infections approximately balanced infections lost to produce an apparent state of dynamic equilibrium. Farid *et al.* (2001) reported that PCR based assay proved a dependable epidemiological LF tool in villages and for application in LF control programmes in endemic areas. Ramy (2002) recommended PCR-based assays to detect filarial infections in mosquitoes (particularly for xenomonitoring of elimination campaigns). El Setouhy and Ramzy (2003) mentioned that WHO (1997) called to eliminate lymphatic filariasis based on rounds of mass drug administration of an annual single-dose of combined drug regimens for 5-6 consecutive years. They added that Egypt and Yemen have active national LF elimination programs but, elimination activities in Yemen were still restricted to certain identified endemic regions. Hassan *et al.* (2005) reported a high prevalence (38%) of asymptomatic MF patients by night blood smear examination, and that MF DNA was in 91/655(13.9%), *C. pipiens* with high MF rates in indoors collections with significant risk factors of transmission. El-Bahnasawy *et al.* (2013) stated that filariasis mass drug administration were gained only with applyi ng feasible friendly vector control measures. Ramzy *et al.* (2019) reported that LF was in Egypt since ancient times and by 1930s was recognized as major public health problem in the Nile Delta caused by *W. bancrofti* and *C. pipiens* the vector. Thus, wide mass DEC treatment and intensive vector control by the Ministry of Health and Population, LF infection rate declined in 1960s. In 2000, Egypt was among the countries to join WHO global efforts to eliminate LF by initiating a national elimination programme (NLFEP), and Egypt was validated (WHO 2017) as the first country in the Eastern Mediterranean Region to successfully achieve LF elimination.

As to LF vector(s), family Culicidae includes mosquitoes, a word derived from the Spanish meaning little flies. Family includes 2 sub-families Culicinae (Linnaeus 1790) and Anophelinae (Meigen 1818). Culicinae contains 33 genera. Mosquitoes of medical and economic importance are *Culex*, *Aedes*, *Haemagogus*, *Psorophora, Mansonia, Sabethes* and *Anopheles* (Stone, 1977). Harbach (1988) identified twenty species of *Culex* in southwestern Asia and Egypt. They were *C. pipiens*, *C. quinquefasciatus*, *C. vegans*, *C. torrentium*, *C. decens*, *C. antennatus*, *C. univittatus*, *C. perexiguus*, *C. theileri*, *C. laticinctus*, *C. mattinglyi*, *C. simpsoni*, *C. sinaticus*, *C. duttoni*, *C. sitiens*, *C. poicilipes*, *C. mimeticus*, *C. bitaeniorhynchus*, *C. tritaeniorhynchus* and *C. pseudovishani*.

Culex pipiens plays the main role in LF transmission as in Lybia (Vermeil, 1953), Saudi Arabia (Sebai *et al*, 1974), Egypt (Harb *et al*, 1993) and Qatar (Mikhail *et al,* 2009) and Rift Valley fever (El Gebaly, 1978), West Nile virus (Wilson, 1991), Sindbis fever in Saudi Arabia (Wills *et al*, 1985) and Egypt (Monath, 1991) and causes biting nuisances (Morsy *et al*, 2003). Hassan *et al.* (2002; 2003) reported that *C. pipiens* complex from indoors of HCVpatients or among same organs of symbiotic and aposymbiotic ones fed on HCV positive blood by an artificial membrane, HCV-RNA was detected in heads of the in-door symbiotic ones at 3 & 6 hrs post-feeding. HCV was detected at 3rd day & 8th day in gut. HCV transmission by mosquito didn't yet prove, but paves the way to study *C. pipiens* gut-bacteria as anti-HCV agent. The *Culex* commonest Egyptian

species were *antennatus, perexiguus, pipiens, poicilipes, pusillus, quinquefasciatus, thelerei* & *univittatus* (Kirkpatrick, 1925; Gad, 1963; Rifaat *et al,* 1971; Harbach *et al*, 1988; Farid *et al*, 1997), with *C. pipiens* complex allover Egypt (Mohamad *et al,* 1981; Morsy *et al*, 1990,2004; Mostafa *et al*, 2002; El-Bashier *et al*, 2006). Rifaat *et al.* (1971) in laboratory conditions found that *C. antennatus* transmitted filariasis.

Conclusion and Recommendations

Lymphatic or bancroftian filariasis, a parasitic disease caused by *W. bancrofti*, was identified as the second-leading cause of permanent and long-term disability, with about 50 million people in Egypt and sub-Saharan Africa represented aparently one-third of all cases worldwide. Cardinal TFPE laboratory data are blood eosinophilia >3000/microl & elevated serum IgE often >1000 units/ml. Diagnosis can be confirmed by filarial antibody titers elevations. Microfilariae are generally not detectable in peripheral blood.

For TFPE treatment, DEC (6mg/kg/day in 3 doses for 12 to 21 days) was recommended. Bronchospasm can be managed with bronchodilators but, in severe cases, short-term corticosteroids. For mosquito-vector control insecticides used must be friendly environmental safe ones, whether in- or outdoors in spraying or as repellents

In all countries, with the marked civilization and establishing modern houses, roads' network, agricultural and industrial projects mainly in newly the reclaimed areas, but the mosquitoes are still common worldwide playing role in the transmitting risky zoonotic diseases and as annoying blood suckers.

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