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THE ARTHROPOD-BORNE ONCHOCERCIASIS: IS IT DESERVED TO BE NEGLECTED?

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Abstract

Onchocerciasis a filarial parasitic nematode, also known as river blindness and Robles disease, is a neglected tropical disease infecting more than 18 million people mainly in sub-Saharan of Africa, the Middle East, South and Central America and many other countries. Disease infectivity initiates from *Onchocerca volvulus* (Filarioidea: Onchocercidae) transmitted by the blackfly, *Simulium* sp. which introduces the infective stage larva with its saliva into the skin. Within human body, adult females (macrofilaria) produce thousands of larvae (microfilariae) which migrate in skin and eye. Infection results in severe visual impairment or blindness for about 2 million, as being the world's second-leading cause of blindness after trachoma, as well as skin onchocercomata.

Key words: Egypt, Onchocerciasis, blackfly, General review, Recommendations

Introduction

Onchocerciasis is caused by the filarial nematode, *Onchocerca volvulus*. It is a major cause of both skin disease and blindness in endemic areas, known as "river blindness and Robles disease" because the blackfly vector for this infection breeds in areas near fast-flowing streams and rivers. Onchocerciasis can be a major cause of morbidity for individuals in endemic areas and can have major socioeconomic consequences (Taylor, 1990).

Epidemiology: Onchocerciasis is transmitted in limited areas of tropical Africa, Yemen, and Latin America. Humans are the only definitive host for *O. volvulus*, although there are a number of other species that infect only animals tell now. Approximately 18 million people are infected worldwide. More than 99% of symptomatic cases occur in sub-Saharan Africa, particularly in Nigeria and Zaire, It where 3 to 4 million infected individuals with skin disease, and 1 to 2 million with blindness or visually impaired. The disease tended to be found in rural areas (WHO, 1995). The visual impairment increase, in part, as the prevalence and intensity of infection in a community rises. In African endemic areas, the prevalence of infection can vary from village to village, but infection rates may be as high as 80 to 100% by the age of 20 in certain areas. Clinical manifestations become apparent later, with blindness peaking at 40 to 50 years of age. Hyperendemic regions were frequently depopulated because of high rates of ophthalmic complications. Neto *et al*. (2009) in Brazil reported that the prevalence of ocular lesions strongly correlated with the cutaneous nodules and eosinophilia, suggested that skin nodules might be an indication for an eye examination, since significant infection and onchocerciasis eye disease persisted in certain regions of Northern South America. There are two different strains of *O. volvulus* in Africa, one strain is transmitted by black flies that tend to breed in savannas; this strain is more commonly associated with ocular disease, even with only a moderate parasite burden and second strain is transmitted by vectors that breed in forests and generally was not associated with blindness (Higazi *et al*, 2005). Black flies are not efficient vectors; as 12 months in endemic areas is generally necessary to acquire infection, and as most helminthes, the worms do not replicate in humans, so an increase in adults burden requires additional exposure to a bite of an infective vector (Nguyen *et al*, 2005).

Life cycle: Humans are infected with *O. volvulus* by bite of the black fly; *Simulium* genus. The black fly transmits infective third stage larvae to humans, and these larvae are deposited into the host skin. Over a period of 6 to 12 months, the larvae mature into adult worms. Females measure 20 to 80 cm in length, live in subcutaneous or deeper intramuscular tissues surrounded by a fibrous capsule, whereas males measure 3 to 5cm and migrate between nodules to fertilize females. The prepatent period ranges from 10 to 12 months, the females begin to produce microfilariae. The *Simulium* female takes a blood meal from an infected human host, and ingests microfilariae. In the *Simulium*, the microfilaria enter the gut and thoracic flight muscles, progressing into the first larval stage, larvae mature into the second larval stage, and move to proboscis and into the saliva in its third larval stage. Maturation takes about seven days. When the black fly takes another blood meal, it passes the larvae into the next human's blood. In man, larvae migrate to the subcutaneous tissue and undergo two more molts, and form nodules as they mature into adults over 6 to 12 months. After maturing, males mate with females in subcutaneous tissue to produce from 1000 to 3000 microfilariae/day. The microfilariae migrate to the skin at daytime, and the vectors only feed in the day, so the parasite is in a prime position for the female fly to ingest it. Black flies take blood meals to ingest the microfilariae to restart the cycle. Adults can survive for up to 15 years, and microfilariae can survive for one to two years (Brattig, 2004).

Pathogenesis: *O. volvulus* adults reside in fibrous skin nodules where they are protected from the host immune response. The microfilariae, in contrast, are capable of moving through subcutaneous and ocular tissues. Although they provoke a minimal immune response while alive, on dyeing incite a clinical inflammatory response. *Wolbachia* sp. is endosymbiosis of adults and microfilariae, and are thought to be the driving force behind most of its morbidity. Dying microfilariae release *Wolbachia* surface protein that activatedTLR2 & TLR4, triggering innate immune responses and producing the inflammation and its associated morbidity (Baldo *et al*, 2010). The severity of illness is directly variable and depends upon the circulating microfiliaria number and the host immune response (Burnham, 1998). Some patients have a minimal immune response to parasite antigens, permitting microfilariae proliferation in the absence of symptoms (Prost *et al*, 1979). Others have a relatively robust immune response against circulating microfilariae (King and Nutman, 1991). Duration of infection may also play a role in degree of inflammatory response; it has been suggested that individuals with early *O. volvulus* infection mount a substantial cell-mediated immune response, while those with the chronic infection tend to have a blunted cellular immunity (Cooper *et al*, 2001). Patients with a significant cellular immune response, polyclonal B cell activation and hypergammaglobulinemia are common, as are nonspecific elevations in IgG & IgE. However, there was minimal evidence for the acquired immunity to *O. volvulus* in endemic areas (Kruppa and Burchard, 1999). Also, release of *Wolbachia*-derived antigens from dying adults and microfilariae can activate innate immune responses and may elicit inflammation in the skin and eye (Johnson *et al*, 2005). The heightened propensity for ocular disease due to the Savanna strain of *O. volvulus* relative to the milder Forest strain correlated with higher quantities of the *Wolbachia* DNA by PCR in the Savanna strain. Both *Wolbachia* and *Onchocerca* antigens appear to influence corneal inflammation, although dermatologic manifestations were attributable to *Onchocerca* antigens alone (Udall, 2007)

Clinical manifestations: The onchocerciasis manifestations include dermatologic ones (subcutaneous nodules and pruritic dermatitis) and ocular manifestations.

I- Subcutaneous nodules (onchocercomata)

are typically 0.5 to 3 cm in diameter; they usually contain one or two adult male and two or three adult female worms. Nodules are not associated with inflammation and do not usually cause significant symptoms. They typically appear over bony prominences and have an apparent predisposition for different anatomic sites depending upon the region in which the infection was acquired (reflecting the differences in vector biting habits in different regions). Infections acquired in Africa tend to cause nodules over the iliac crests and lower limbs, while those acquired in Latin America are more commonly associated with nodules on the head, neck, and upper extremities (Little *et al*, 2004). II- Dermatitis due to onchocerciasis is an intensely pruritic inflammatory papulonodular process that may affect up to half of individuals in endemic communities. Excoriation frequently leads to secondary bacterial infection. Subsequent lymphadenopathy can develop, most commonly in the inguinal region. Atrophic skin over the lymph nodes can become loose, leading to hanging folds of skin termed hanging groin. After prolonged enlargement and inflammation, the lymph nodes might become fibrotic, resulting in lymphatic obstruction and elephantiasis (Connor *et al*, 1985). The onchocerciasis dermatitis may be classified as follows: 1- Acute papular dermatitis manifests as small scattered pruritic papules, vesicles or pustules that may heal spontaneously in a few months or progress to one of the following categories. 2- Chronic papular dermatitis manifests with larger pruritic papules, often symmetrically distributed over buttocks, waist and shoulders. Hyperpigmentation and hyperkeratosis may develop in regions of chronic papular dermatitis. 3- Lichenified dermatitis (Sowda) manifests with hyperpigmented pruritic papules and plaques with associated edema and lymphadenopathy. A distinct form of lichenified dermatitis known as sowda (in Arabic, black or dark) is described in some regions, particularly Yemen and Sudan. Sowda is a localized form of lichenified dermatitis affecting one or multiple limbs; characterized by the dramatic skin disease and a brisk T-helper 2 (Th2)-type immune response with high IgE levels (Hoerauf *et al*, 2002). So, patients with sowda have a low microfilarial burden (microfilariae are usually absent in skin snips) and ivermectin therapy may be less effective in such patients. 4- Skin atrophy manifests with loss of skin elasticity and wrinkling of the skin; the resulting skin has the appearance of tissue paper. 5- Elephant skin or thickening of human skin associated with onchocerciasis. 6- Depigmentation manifests with loss of patches of skin with loss of pigment adjacent to areas of normally pigmented skin can result in a "leopard skin" appearance.

Ocular onchocerciasis: Onchocerciasis is a leading cause of blindness in the developing world. Individuals with blindness due to onchocerciasis have a fourfold increase in mortality and diminished life expectancy by 7 to 12 years. *O. volvulus* is the second commonest cause of blindness, after trachoma (WHO, 2014). Microfilariae cause ocular tissue inflammation leading to a reversible punctate keratitis known as snowflake opacity. Longstanding infection results in sclerosing keratitis, characterized by an inflammatory infiltrate beginning at the edge of the cornea and eventually involving the anterior chamber and/or the retinal epithelium. Posterior eye involvement, chorioretinitis, optic neuritis, optic atrophy, glaucoma and blindness may ensue. The slit lamp examination may show intraocular microfilariae, fluorescein angiography may demonstrate chorioretinal lesions (Egbert *et al*, 2005). In the ocular findings, differential includes infection with other microfilaria as *M. perstans, L. loa, O. gutturosa*, or *Dracunculus medinensis*, inflammatory lesions involving iridocyclitis includes systemic inflammatory etiologies as sarcoidosis, and other corneal degenerative/sclerotic diseases (Mcleod, 2008).

Onchocerciasis among visitors to endemic areas is relatively rare; if infection does occur it tends to manifest with pruritic dermati-

tis but without chronic skin changes or eye involvement. There may be an associated faint, nonspecific rash, but the chronic skin changes that are seen in endemic communities with high intensity of infection do not occur. Symptoms develop in a median period of 18 months from exposure time with range of three months to three years (Freedman, 2005).

Diagnosis: diagnosis of onchocerciasis depends upon a history of compatible epidemiologic exposure, clinical manifestations as described above, and supportive laboratory evidence of infection. The clinical picture may be difficult to distinguish from loiasis and from infections with *Mansonella* species. Infection with *Loa loa*, occurs frequently in certain endemic regions of Africa. Loiasis occurred only in western and central Africa and not commonly associated with severe disease in either residents or visitors to endemic regions and sometimes called "eyeworm" as the adult may be found migrating across the subconjunctiva of the eye. It is estimated that between 3 and 13 million people are infected. Infection appears to be occult in a large proportion of patients and remains undiagnosed; thus, the epidemiology of loiasis in many areas has not been clearly defined. The probability of infection increases with age in endemic regions, but the exact proportion of infected individuals varies from village to village depending upon vector abundance. Active infection is up to 40% of certain populations (Bakajika *et al*, 2014). The significance of infections with *Mansonella* sp. and frequency and severity of attributed symptoms are still debated (Mourembou *et al*, 2015). Non-specific laboratory findings in onchocerciasis patients may include the Ag-specific IL-5 response, peripheral eosinophilia and hypergammaglobulinemia (Hall *et al*, 1999).

A skin snip may be performed with a corneoscleral punch or with a small needle and disposable razor blade. It should be a bloodless specimen from the level of the dermal papillae, taken from areas of involved skin and from skin over each scapula, each iliac crest, and each calf. The biopsy specimen should be incubated in saline for up to 24 hours before examination for motile microfilariae. Staining the specimen may be required for species identification in endemic for other filarial species. The microfilariae have neither sheath nor nuclei in tails (Lipner *et al*, 2006).

Visualization of microfilariae by skin snip is a highly specific diagnostic tool, although this technique is inadequate for detecting early infection or infection with low worm burden. It takes approximately 18 months for the worm to mature and release enough microfilariae to be detectable by skin snip microscopy (Winthrop *et al*, 2006).

Slit lamp examination: Diagnosis of onchocerciasis can occasionally be made by visualizing microfilariae on slit lamp examination of the eye. Lesion may manifest as microfilariae visua-lized in anterior chamber or as punctate keratitis with or without inflammation, inflammatory punctate keratitis without visible microfilariae was insufficient for diagnosis (Enk *et al*, 2003).

Mazzotti test: Administration of diethylcarbamazine (DEC) to the onchocerciasis patients can lead to systemic reactions related to an inflammatory response to dying microfilariae. A 50 mg dose of DEC or a patch test using topical DEC can be given to people suspected of being infected. Pruritus would generally develop within three hours in infected individuals, although symptoms may be delayed for up to 24 hours. The test can be useful in both endemic areas and in expatriates suspected of being infected, with a sensitivity of >90%. However, the test can cause significant discomfort and can even be dangerous. Skin snips and ophthalmologic examination should be negative prior to performing the Mazzotti test, and it should only be performed in lightly infected patients to avoid severe reactions. Because of the symptoms it can invoke, but not recommended as a routine diagnostic test (Kilian, 1988).

Traditional serologic tests for antibodies

to *O. volvulus* use relatively crude antigenic extracts with significant cross-reactivity between other filarial and non-filarial parasites, and cannot differentiate between previous and active infection so are of limited utility in endemic areas. However, they can be useful for evaluation of travelers. Recombinant purified antigens ELISA and Western blot techniques improved the specificity of serology for the active onchocerciasis diagnosis (Luz *et al*, 2014). Other assays have been developed for detection of antibody subclass IgG4, since this subclass is may be a more specific marker of active onchocercal infection than total IgG with greater sensitivity than conventional skin snip examination (Lucius *et al*, 1992). The sensitivity of the ELISA test was 92% for serum and 86% for urine. In Cameroon, a urine and tear antigen detection dipstick test for the diagnosis of onchocerciasis was found to have sensitivity of 100% in urine and 92% in tears and specificity of 100% (Ayong *et al*, 2005).

PCR: Highly sensitive tests based upon DNA amplification, in Cameroon, samples of human serum, skin, and urine for the diagnosis of onchocerciasis (Vincent *et al*, 2000). Parasite DNA was detected in skin snips and urine by PCR, and results were compared with parasite antigen detection and serum concentrations of IgG4 antibodies. Boatin *et al*. (2002) found that PCR and a test based on the allergic reactions to topical application of diethylcar-bamazine (DEC) patch test proved more sensitive than low sensitive skin snipping. They added that DEC test might provide a good alternative to skin snipping alone for surveillance in low prevalence areas.

Radiology: Adult onchocerciasis sometimes can be identified on ultrasound examination of subcutaneous nodules. Nodules in deeper (e.g., nonpalpable) subcutaneous tissues can be also detected by ultrasonography (Udall, 2007). Removal and examination of the worms confirms the species diagnosis. Ultrasound may also be used as a new tool for the longitudinal observation of patients with onchocerciasis to monitor the viability of the adult worms after macrofilaricidal therapy (Mand *et al*, 2005).

Loaisis coinfection: In patients with onchocerciasis and *Loa loa* coinfection, onchocerciasis treatment with ivermectin therapy can facilitate entry of *L. loa* microfilariae to the central nervous system, leading to encephalopathy and potentially severe neurologic sequelae, and in a case, noontime blood should be taken to evaluate *L. loa* microfilariae prior to therapy (Kamgno *et al*, 2004).

Treatment: The drug of choice for onchocerciasis is ivermectin (Plaisier *et al*, 1995). Ivermectin is a semisynthetic macrocyclic lactone derivative that appears to impair release of microfilariae from gravid female worms. It also may have some direct anthelminthic effects on adult worms, but does not eradicate infection (Duke, 2005). It should be given as a single dose 150 mcg/kg orally on an empty stomach with water. Treatment may be required for 10 years or more, even for travelers without ongoing exposure in endemic areas. a single dose after one week post reduced skin microfilarial counts by 85 to 95%, with prolonged suppression for at least a year (Alley *et al*, 1994). Adverse effects following ivermectin adminis-tration tend to occur as a result of the host immune response to released *Onchocerca* and *Wolbachia* antigens rather than as a result of drug toxicity (Keiser *et al*, 2002). Symptoms include fever, rash, dizziness, pruritus, myalgia, arthralgia, and tender lymphadenopathy occurs within three days of treatment. Symptoms incidence correlate with infection burden before treatment, which could be managed by analgesics and antihistamines (Njoo *et al*, 1995). In patients with onchocerciasis and loiasis coinfection, treatment of onchocerciasis with ivermectin therapy facilitates entry of *L. loa* microfilariae to the central nervous system, leading to encephalopathy and potentially severe neurologic sequelae (Bockarie *et al*, 1998).

Safety of ivermectin in young children (<15kg) and pregnant women remains to be established. Ivermectin has been inadvertently given to pregnant women during mass treatment programs; the rates of congenital abnormalities were similar in treated and untreated women (Pacque *et al*, 1990).

Diethylcarbamazine (DEC): is a potent microfilaricidal agent but is associated with numerous adverse effects including aggravation of ocular lesion, blindness, hypotension and death. DEC was used for treatment of onchocerciasis prior to the introduction of ivermectin. Doxycycline has activity against *Wolbachia*, the endosymbiotic bacteria within *Onchocerca* adults and microfilariae (Johnston and Taylor, 2007). Although it is not filaricidal for either adult worms or microfilariae, by targeting *Wolbachia* species it can reduce the burden of microfilariae in the skin. Patients with onchocerciasis, doxycycline (100 mg/day orally for 6 weeks) was followed by a single oral dose of ivermectin (150mcg/kg) resulted in up to 19 months of amicrofilaridermia and complete *Wolbachia* elimination (Hoerauf *et al*, 2003). Rifampin and Azithromycin used in vitro activity against *Wolbachia*, but not effective for onchocerciasis management (Richards *et al*, 2007).

Macrofilaricidal therapies: Suramin has activity against adult worms but has significant toxicity. Amocarzine has some reported macrofilaricidal activity, but with minimal clinical experience (Zea-Flores *et al*, 1991).

Removal of adult worms by nodulectomy, particularly in lightly infected individuals such as expatriates, but many deep embedded worms were undetected, so nodulectomy alone cannot be considered an effective strategy for cure (Ottesen, 1993).

Mass Control Programs: As to vaccine Steisslinger et al. (2015) reported that DNA vaccination with Ov-GAPDH has protective potential against filarial challenge infection in the mouse mode. Thus, to prevent onchocerciasis relies on black fly vector control and mass chemotherapy programs.

The largest mass control program has been the Onchocerciasis Control Program, an international partnership initiated in 1974 which implemented mass ivermectin treatment and aerial insecticide spraying of rivers with black fly larvicidal agents in West Africa (Hopkins *et al*, 2005). The aerial spraying ended in 2002 but mass treatments are still needed (Osei-Atweneboana *et al*, 2007). Because the adult worms can live for 15 years or more, ivermectin distribution need to be sustained for a minimum of 10 to 15 years to achieve eradication (Taylor *et al*, 1990).

The safe ivermectin greatly reduces the burden of microfilariae in skin and eye tissues and effective for mass chemotherapy (Peters and Phillips, 2004). In control programs, ivermectin is administered once yearly. However, the ocular microfilaria load falls at a slower rate than skin microfilaria load; ocular loads can return to 30% of pretreatment levels at one year. Administration of ivermectin every six months resulted in greater reductions in microfilarial loads than annual treatment (Awadzi *et al*, 1999).

It is possible that more frequent treatment could provide additional benefit. In a study of 657 patients with onchocerciasis, those who received treatment three times yearly had fewer remaining female worms than those treated once yearly (Gardon *et al*, 2002).

In the regional countries:

In Kuwait: Abdul-Salam and al-Taqui (1995) over a period of 14 months, the blood of 284 camels were examined, of these 32 (11%) were found infected with the microfilaria in all months except summer, July to September, and February. The peak (27%) was in June at the end of spring. They suggested that harsh environmental conditions in Kuwait during summer either arrest development of microfilariae or influence their diurnal distribution in camels' tissues. Hira *et al*. (2008) described zoonotic filariasis in two patients from Kuwait; one with *Onchocerca* spp. and one with *Dirofilaria* spp. The

first was a 12-year-old Kuwaiti woman who had visited Saudi Arabia, initially reported ocular symptoms. She later reported a nodule that appeared in the suprapubic area, which was resected. This patient represented the 15th reported case of zoonotic onchocerciasis in a country that is not endemic for human onchocerciasis. The second was a 34-year-old Indian woman from Kuwait City, reported a moving object in her left eye. A live worm was extracted and identified as an immature female *Dirofilaria* (*Nochtiella*) *repens*.

In Libya, only Crosskey and Ashford (1981) reported *Simulium* s. l.

In Saudi Arabia, Cheema *et al*. (1984) reported that 125 of 478 (26.2%) camels were infected with onchocerciasis and prevalence rates in local and imported camels were 93/272 (34.2%) and 32/206 (15.5%), respectively. Infection was characterized by hard nodules in the connective tissue around the nuchal ligaments and in the subcutis. The nodules consisted of cavities containing live, degenerate or dead microfilariae, inflammatory cells, fibrosis and calcification. *O. fasciata* microfilariae were concentrated in the skin over the head and neck regions and often caused mild non-suppurative dermatitis. Nasher (1986) reported *O. fasciata* in subcutaneous nodules of anterior parts of Camelus dromedarius (nuchal ligaments, neck, and shoulders) infection ranged between 2 &29, with a mean of 10.8 nodules/ camel. He added that infection rate was 59%, they did not exhibit any apparent disease. Hussein and el Sammani (1990) found that for the release of *O. raillieti* microfilariae from skin snips and for their subsequent in vitro maintenance, Tyrode's solution containing 20% equine serum and antibiotics was the best medium tested, followed by phosphate buffered saline proved useful. A temperature 7-12^{o}C lower than that of host's body favored microfilariae release from skin snips. Microfilariae were best maintained at 4-10^{o}C, when they remained alive for up to 5 days. *O. raillieti* microfilariae had an evening periodicity which could be related to a possible vector's peak of feeding activity.

Siddiqui and al-Khawajah (1991) mentioned that Sowda, localized asymmetrical onchocerciasis lesion was endemic in Yemen and Southern Saudi Arabia characterized by hyperpigmented lichenified papular lesions on one leg with intense pruritus and enlargement of femoral and inguinal lymph glands. They reported that in the long standing human cases did not show elephantiasis of the leg or genitalia. Microfilaria appeared to be scarce and adult worms could not be detected clinically or by the ultrasonography (except in one case).

Ghandour *et al*. (1991) reported that 192 male camels young, adult and old were examined for *O. fasciata* infection. The overall prevalence rates were 10.9 & 33.3%, respectively. The prevalence rate was higher in young and adult camels than in old ones. An increase in size and weight of nodules was reported with an increase in age of the camels. Nodules varied in diameter from 2 to 36 mm and in weight from 0.5-5.0g. The overall percentage of soft viable and calcified nodules was 42.5 & 57.5%, respectively. The viability of worms decreased, but calcification increased with increased age of the camels. By SEM, four levels of degeneration and calcification of worms were described. Omar and Raoof (1996) in Abha Province reported *O. fasciata* by histochemical investigated suggested that it lacks a classical, mammalian-type respiratory pathway and that oxidative phosphorylation is of no importance as an energy generating pathway in this essentially anaerobic parasite.

Helmy and Al Mathal (2003) diagnosed three patients referred from Dermatology Out-patients Clinics, King Abdulaziz University Hospitals, as Sowda (chronic hyperactive form of *O. volvulus*). The patients came from Asir Region in the Southern of the Kingdom. There was extensive follicular hyperplasia of the regional lymph nodes in two cases only. The skin snips taken of three patients were positive and urine of one pa-

tient was positive. Six months after the onset of treatment in the Specialized Hospital, skin snips and urine samples were negative.

In Yemen, Anderson *et al.* (1973) reported onchocerciasis with reference to sowda. Omar *et al*. (1979) **in a** pilot study in the south-western region of the Yemen Arab Republic reported microfilariae in 61 persons examined in eight. A single larva of *S. damnosum* was collected in Wadi-Barakani, and numerous larvae and pupae of *S. ruficorne* & *S. hargreavesi* were taken in fast-flowing streams in four localities. By SEM and histochemical examination the microfilariae and adults belonged to *O. volvulus*, which were typically as those in Liberia, West Africa. al Qubati *et al*. (1997) reported that ivermectin (Mectizan) chosen as a control strategy plan in onchocerciasis was active during 3 months for the less on clinical and histological data. After a short increase of itching and oedematous skin aspects clinical signs decrease. Some patients notice an itching rebound after 90 days. Histologically, localized ingratiates, presence of mononuclear cells and melenin loaded histiocytes and eosinophils decreased. The rythm cure has to be studied on a longer period but 3 to 6 months repetition between oral treatment with 200 micrograms/kg dose during two years could be effective

Connor *et al*. (1983) reported that Sowda is an unusual form of onchocerciasis in the Yemenites that differed from African onchocerciasis. They added that Clinical and pathological studies on 18 patients in North Yemen, the most striking clinical features were swollen, darkened, pruritic, papular skin changes that were usually limited to one leg, more rarely to one arm, and large soft regional lymph nodes and dermal changes were deeper and more diffuse than in African onchocerciasis, with many large fibroblasts and plasma cells and that the microfilariae of *O. volvulus* were much rarer in skin from Yemenites with sowda. When they treated the patients with diethylcarbamazine, the dermatitis became suddenly worse as the microfilariae degenerated and provoked acute inflammation, but dermatitis decreased after several days after treatment. Enlarged lymph nodes from sowda showed follicular hyperplasia, in contrast to follicular atrophy and perivascular fibrosis characteristic of lymph nodes from cases of African onchocerciasis. Richard-Lenoble *et al*. (2001) stated that the geophysics of the north Yemen, associating a north-south directed mountainous fish bone (rising in more of 2,000 meters), to numerous rivers or "wadis" is convenient to the development of *Simulium* shelters, main vectors of *Onchocerca* sp. They identified as microfilaria type *Onchocerca* but not belong to species *volvulus*, or to species *ochengi*. They added that the clinical picture of sowda be the result of developing onchocerciasis of animal origin and not identified as to day. They distinguished 2 kinds of answers based on the clinical origin of the snip-tests: the first one concern 3 patients with numerous dermal microfilariae but without any clinical sowda and corresponding to microfilaria *O. volvulus* type but different from the forest or savannah strains found in sub-Saharan Africa. The second one corresponds to 2 patients with less than 5 microfilariae in their snip-test, showing the typical clinical picture of sowda. Büttner and, Rácz (1983) reported 14 subcutaneous nodules from five patients with severe localized onchocerciasis, one patient with a mild dermatitis and two men with the generalized form, with median worm burden were two filariae/patient. Ten nodules contained adult parasites with an average sex ratio of 1.6 for female to male worms. Onchocercomata of the two patients with severe localized onchocerciasis comprised one or two pairs of microfilariae producing worms whereas the microfilaria load in these patients' skin was less than 100 000 microfilariae. One nodule contained no intact microfilariae but more than 10 000 small granulomas with all stages of degenerating microfilariae whereas the density of 0.08 live microfilariae per milligram in the skin near

to the nodule was very low. They concluded that patients with severe localized onchocerciasis possessed the capacity naturally to kill microfilariae as many degenerating microfilariae were surrounded by eosinophils or macrophages or which lay in small abscesses with neutrophil leucocytes or in small granulomas.Abdel-Hameed *et al.* (1987) reported a case of Sowda with microfilariae in the lymph nodes.. They concluded that the Yemeni case contrasted with African onchocerciasis, where the lymph nodes tend to be atrophic and microfilariae are usually present.

In Israël, Beaucournu-Saguez *et al*. (1976) described *Simulium* (*W.*) *golani* Beaucournu-Saguez and Braverman as n. sp. in the Golan region (35 degrees 42' E, 32 DEGREES57' N). It was related to *Simulium* (*W.*) *paraequinum* Puri 1933 but was distinguished by the morphology of pupal respiratory filaments and structure of male genitalia. Oshry *et al*. (1995) presented a 31-year-old male Ethiopian immigrant with ocular onchocerciasis. In Ethiopian population the various manifestations of the disease in all its stages can be found. Patient was treated with oral Ivermectin, once a year, the safest of known medications. The need for early detection and treatment is emphasized because of the potential for ocular destruction. Pressman *et al*. (1998) described an 11-year-old girl, a new immigrant from Ethiopia, who had a firm mass in her left thigh, caused by *O. volvulus*. It was completely excised. This is a very rare condition in Israel, which must be considered in patients coming from endemic areas. Rozenman *et al*. (1984) reported a 15-year-old boy with onchocerciasis had severe generalized pruritus of five months' duration, who emigrated to Israel one year earlier. A biopsy specimen of an area of depigmentation on the right thigh disclosed microfilaria of *O. volvulus*. They concluded that discovery of an unusual disease in a nonendemic area is an example of the increased complexity of differential diagnosis resulting from the ease of travel from one geographic region to another. Enk *et al.* (2003) stated that since 1992, approximately 9,000 immigrants arrived from the Kuwara province of northwest Ethiopia where onchocerciasis was endemic. They examined 1,200 recent immig-rants residing at the Mevasseret Zion immigration center outside Jerusalem. They found that by skin examination in 83 patients, the commonest was chronic papular onchodermatitis about 46 patients (55%); depigmentation and atrophy in 13 (15%) and 12 (14%), respectively. In 40 patients (48%) living microfilaria were detected in skin snips. Of 65 patients, 45 (66%) had ocular complaints. The corneal abnormalities were found in 55/130 eyes (42%), active anterior segment intraocular inflammation and live microfilariae were in 4 eyes (3%) and lens changes in 16 eyes (1%), eleven eyes (9%) showed retinal or choroidal changes. They concluded that onchocerciasis skin and eye manifestations were prevalent among symptomatic Ethiopians who immigrants.

Baum *et al*. (2014) carried out a retrospective study of 27 Ethiopian immigrants to Israel were all positive skin snip test or by IgG4 of onchocerciasis in 14 patients. The commonest presentation was a combination of lichenified onchodermatitis with atrophy and depigmenta-tion (36%), eosinophilia and elevated IgE were common. They concluded that Immigrants from endemic regions presenting with pruritic diseases, especially those with a clinical picture suggestive of atopic dermatitis, should be evaluated for possible onchocerciasis infection

What about Egypt, Khalil (1939) pointed out that the case of *Onchocerca* reported as" filaria in the macula "by Barrada in 1935 and by Wilson, 1934, as "onchocerciasis of the macula" appeared in the literature as two separate cases based on the same case. He reported an onchocerciasis patient from Belbeis City who never left Sharkia Governorate. Besides, one species of Simuliidae was reported in Egypt (Steyskqal and el-Bahy, 1967). El-Massry and Derbala (2000) exam-

ined 3376 imported and 200 local Egyptian camels for O. fasciata from September 1997 toAugust, 1998. They found that imported camels had the higher infection rate (2.75%) mainly on both abdominal sides, hind limbs (concentrated in thigh region) and fore limbs particularly on the shoulders and nuchal ligament while local ones showed no palpable or detected nodules. This distribution varied according to the degree of infection

Biswas and Yassin (2013) reported a 19-year-old Egyptian male studying and living in Pittsburgh, PA, USA, for 18 months suffered from a month-long irritation and right eye watering without any visual loss. An ophthalmologist prescribed topical steroids for possible allergic conjunctivitis, which did not resolve his irritation. Patient's recent traveled in a trip to New Delhi, India, and Siwa oasis (West of Egypt) more than a year prior to this presentation. He has never had any pets such as dogs and cats. Ophthalmologic examination revealed a subconjunctival nodule (1.5×1 cm) only in the medial aspect of the right eye. The patient underwent surgical exploration of the nodule under local anesthesia, which revealed 12 dead and living worm fragments, each about 1 cm in length & 0.2-0.3 mm in thickness. Serology showed a positive IgG4 for filariasis, CBC was normal and the peripheral blood smear was negative for eosinophilia or microfilaria. The histopathological examination showed adult *Onchocerca* sp. based on specific morphologic features. There was no evidence of microfilaria in the uteri. The CDC confirmed the diagnosis, and the patient was treated with ivermectin (100 mg/kg) once and has had no further recurrence of his symptoms after two years of follow-up.

The zoonotic onchocerciasis: Genus *Onchocerca* contains one human parasite; *O. volvulus*, which is the filaria responsible for the neglected onchocerciasis or the river blindness (Otranto and Eberhard, 2011). Other species affect cattle, horses, deer, pet animals…etc. are: 1- *O. armillata*, 2- *O. cervicalis*, 3- *O. dukei*, 4- *O. fasciata*, 5- *O. flexuosa*, 6- *O. gibsoni*, 7- *O. gutturosa*, 8- *O. jakutensis*, 9- *O. linealis*, 10- *O. lupi*, 11- *O. ochengi*, 12- *O. ramachandrini*, 13- *O*. sp. '*bushbuck*', 14- *O*. sp. '*Siisa*' and 15- *O. tubingensis*.

Several *Onchocerca* species are agents of zoonoses. In dogs, cases of ocular onchocerciasis were reported in Central Europe mainly Germany, Hungary, Portugal, Switzerland (Eckert, 1993), and in Southern Greece and Portugal (Otranto *et al*, 2013).

Cello (1971) reported that the microfilariae *O. cervicalis* were capable of producing a variety of lesions in the equine eye, by dead, rather than living ones. He added that clinical features are conjunctiva, cornea, uveal tract, lens and retina. *Onchocerca* sp. was normally found in Caucasian wolves (Burr *et al*, 1998) morphologically indistinguishable from *O. lienalis* (Sréter-Lancz *et al*, 2007).

As to human ocular onchocerciasis, Hira *et al*. (1994) stated that 13 previous cases have been reported from the United States, Canada, Switzerland, Hungary, Russia, and Japan. The species involved in these infections were tentatively identified as *O. gutturosa*, *O. cervicalis*, *O. reticulate*, and *O. dewittei japonica* on the basis of morphologic features. Koehsler *et al*. (2007) reported the14th case identified *O. jakutensis* by molecular techniques in a patient from the United States who had traveled throughout Europe.
Fukuda *et al*. (2008) in Japan reported that microfilariae of *O. dewittei japonica* (causative agent of zoonotic onchocerciasis in Oita, Kyushu) from wild boar (*Sus scrofa*), *O. skrjabini* and *O. eberhardi* from sika deer (*Cenus nippon*), *O. tienalis* from cattle, and an unnamed *Onchocerca* sp. from wild boar, were injected intrathoracically into newly-emerged black flies species to identify the potential vector(s). *O. dewittei japonica* microfilariae developed to the infective larvae in *Simulium aokii*, *S. arakowae*, *S. bidentatum*, *S. japonicum*, *S. quinquestriatum*, and *S. rufibasis* and development of infective larvae of *O. skrjabini*, *O. eberhardi*, and the

unnamed *Onchocerca* sp. occurred in *S. aokii, S. arakawae,* and *S. bidentatum*, and *O. lienalis* microfilaria occurred in *S. arakawae*. They proposed a key to identify *Onchocerca* infective larvae found in Oita. They reconsidered the identification of three types of infective larvae from *Simulium* species captured at cattle sheds: the large type I larvae that may be an unidentified species; the small type III identified as *O. lienalis* might include *O. skrjabini* too; the intermediary type II that may be *O. gutturosa*, or *O. dewittei japonica*, or the unnamed *Onchocerca* sp. of wild boar.

Labelle *et al*. (2011) in USA by clinical, histopathologic, and molecular diagnosis reported two domestic short hair cats with *O. lupi* causing episcleritis and orbital cellulitis.

Eberhard *et al*, (2013) reported that zoonotic onchocercosis was attributed to species primarily of cattle (*O. gutturosa*), horses (*O. cervicalis*), the European deer (*O. jakutensis*), and the wild boars (*O. dewittei japonica*), which were localized in subcutaneous tissues, muscular fasciae, or cervical ligaments, whereas in humans, *O. gutturosa* and *O. cervicalis* caused an ocular localization.

In Italy, Otranto *et al*. (2012) stated that Other *Onchocerca* species were sporadically reported as zoonotic agents. Cases of canine onchocerciasis caused by *O. lupi* are on the rise in the United States and Europe. Its zoonotic role was ascertained in a single case from Turkey. They reported *O. lupi* infesting human eyes in two patients, one from Turkey and second from Tunisia. In the first case, diagnosed was based on *O. lupi* morphology at the gross examination, histological analysis and anatomical description, as well as molecularly confirmation. They concluded that *O. lupi* infestation is not an occasional finding but must be considered in the differential diagnosis of other zoonotic helminths causing eye infestation as *D. immitis* and *Dirofilaria repens*. Both cases came from the areas where canine onchocerciasis were not previously reported in the literature, suggesting that an in depth appraisal of the infestation in canine populations is necessary.

Eberhard *et al*. (2013) mentioned that zoonotic onchocerciasis (*O. lupi*) was reported from the North American continent, the West Coast of the United States and from Europe. They added that other zoonotic species were *O. cervicalis, O. gutturosa*, and *O. dewittei.* There have been reports of cryptic infections with *O. lupi* presenting with subconjunctival nodules from Europe as well as (Sréter *et al*, 2002). *O. lupi* seemed to be the commonest zoonotic species affecting the eye and aberrant infections occurred in joints, head soft tissues, foot, abdomen, shoulder, and cervical spine (Hira *et al*, 2008).

Ilhan *et al*. (2013) in Turkey reported a 28-year-old male who displayed a painless, immobile mass under the conjunctiva, measured 10×12 mm in size. Pathological examination of the surgically excised tissue was suggestive of infection by a filarial nematode. The parasite was identified as *O. lupi* through molecular analysis. They added that all previous cases reported of *O. lupi* in both humans and dogs were more symptomatic than that patient, *Onchocerca* infection should not be ruled out during the differential diagnosis of the subconjunctival and orbital cystic mass in instances where there is little to no inflammation.

Several *Onchocerca* species are agents of zoonoses. Among the 15 clinical cases of zoonotic onchocerciasis reported worldwide (Uni *et al*, 2010), the species identified were *Onchocerca gutturosa* and *Onchocerca cervicalis* (Faísca *et al*, 2010), affecting cattle and horses, respectively, *Onchocerca jakutensis* from the European deer (Koehsler *et al*, 2007) and in half of the human cases.

O. lupi was recognized parasite causing nodular lesions associated with ocular disease (i.e., conjunctivitis, ocular swelling, photophobia, lacrimation, discharge, exophthalmia) in zoonotic potential dogs (Sréter *et al*, 2002) but only recently been reported in

one patient from Turkey (Sréter and Széll, 2008). Zoonotic human ocular cases in are increasingly being reported worldwide, including Iran and Tunisia cau-sed by *O. lupi* (Mowlavi *et al*, 2014), Turkey (Otranto *et al*, 2012). In addition, *O. lupi* infection was recently diagnosed near the spinal canal in a 22-month-old child from Arizona, USA (Biswas and Yassin, 2013).

Conclusion

The parasite *Onchocerca volvulus* is well-known in its endemic areas in South and Central America and West Africa. It is transmitted to man by *Simulium* flies and causes systemic infection with skin, lymphatic and ophthalmic manifestations and can cause blindness (river blindness). Onchocerciasis is an infectious disease caused by the filaria. Very little is known regarding onchocerciasis imported from the endemic to non-endemic areas. Ivermectin, a relatively safe and low-cost treatment, should be considered even in the absence of a proven disease. On the other hand, zoonotic ocular onchocerciasis due to many non-human *Onchocerca* species is worldwide documented even from pet dogs and cats.

Recommendations

General onchocerciasis symptoms include severe itching, bumps under the skin, blindness and thus reducing the patient's ability to work and learn. There are no vaccines or medications available to prevent *O. volvulus* infection. The best prevention efforts include the personal protection measures against the biting of insect-vector (CDC, 2016). Consequently, to present onchocerciasis in man and/or animals and its risky complications, the following is suggested.

1- There must be urgent entomological surveys for members of genus *Simulium* in particular on the Egyptian borders. It is a day-bite insect-vector.

2- The dermatologists should keep in mind onchocerciasis dermatitis, sowda, particularly over buttocks, waist and shoulders; meanwhile the ophthalmologists should take into consideration the onchocerciasis blindness or river blindness in differential diagnosis of eye disease.

3- The veterinarians must consider zoonotic onchocerciasis in the skin and eye of farm and pet animals.

4- The owners of pet animals must consult the veterinarians if they notice eye complications.

5- Clinicians and veterinarians are requested to put the worm or microfilariae they could extract in a labeled specimen tube of normal saline or 70% ethanol and refer to a reference parasitologist for species identification to pave the way for feasible control measures.

6- Last but not least, there must be regional collaboration or working groups especially with the African countries under the umbrella of the WHO and/or CDC to stop spreading of the risky filarial parasite. This could be by annual or semi-annual scientific meeting to exchange the information and experience.

7- On the other hand, the health education cannot be neglected. Besides, promoting the behavior in the design of preventative interventions.

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