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Advancements of Diagnosing the River Blindness

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A B S T R A C T
Riverblindness is also called onchocerciasis. It has historically been one of the leading causes of infectious blindness worldwide. It is endemic to tropical regions both in Africa and latin amercia and in the yemen. onchocerciasis is caused by infecrtion waith the filarial parasite onchocerca volvulus. The infection is spread through the bites of an insect vector, black flies of the genus simulium. in Africa , the major vectors are members of the sdamnosum complex, wahile numerous species serve as vectors of the parasite in latin amercia. It is a neglected tropical disease which is in disperate need of a therapeuhic revolution. Its pathology, whose symptoms are anchodermatitis, musculoskeletal pain and various stages of blindness , is a result of the deataha of the microfilariae in the sakin and eyes , the emergence of ivermectin rasistance inastifices the crucial need to identify new drug targets and agents that can effectively treat onchocerciasis.
Key words: Neglected tropical diseases, Onchocerciasis, Onchocerca volvulus, Ivermectin, Chitinaasae, Scaffold hopping.

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1. Introduction

Onchocerciasais is a disease produced by the infection waith the parasaitic nematodeco volvulus and transmitted through the bite of the black flies of the genus simulium. In latin amercia , the earliest programmes used a strategy of surgical removal of the adult parasites lodges in undetectable and in accessible areas of the body , the overall effect of this strategy on the prevalence of infection was relatively minor. The filariae causae dermatitis, subcutaneous nodules due to encapsulation of parasites in fibrous tissue and eye disease. The disease is transmitted by an insect of genus simulium at which breed in fast –flowing rivers and streams, leading to the name river blindness. The infected blackflies i.e.,

similium genus transmit larvae to humans by bring them.

Figure 1

Eye Infections:

Larvae migral;e to saubcutaneousa tissues where they become mature adults . gravid females produces prfoducses large numbers of microfilariae wahich migrate into the ocular tissues and die , causing small inflammatory lesians which leave scars. The accumulation of small scars in the cornea and the retina cause blindnesss. The drugs wahich kill microfilariae cause a marked inflammatory response known as the mazotti reaction and concurrent treatment with anti- inflammatory drugs is required to reduce the severity of this reaction. In contrast , dead microfilariae evoke punctuate heratitis, small cesians which consist of dead microfilariae surrounded by lymphocytes, eosinophills and local edeme. Ivermectin is currently being tested on patients and it has significant advantages.

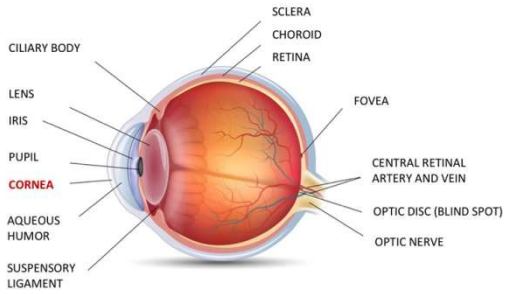

Fig 2 : Structure of Eye

Filarial Dermatitis:

Onchocerciasis is a filarial dermatitis principally affecting horses. Adult parasaites are located in nodules in connective tissue and can be asaymphomataic, microfilariae are kocated in the dermis,. Particularly of the ventral midline, are the source of the major lesions. Intermediate hosats, such as the simulidae (blackflies, gnats) and ceratopogonidae (biting midges), transmit the microfilariaea. In those horses with waith cutaneous inflammation attributed to microfilariae, dead or dying microfilariae induce the most intense inflammation and inflammation can be enhanced by microfilaricidal therapy. Ochengi in cattle has been studied as a model of human onchocerciasis in which it has been shown that selective antibiotic therapy against wolbachia results in reduced numbers of waolbachiasp, reduced numbers of adult ochengi and rteduced numbers of microfilaria, in equine onchocereciasis, clinical lesions related to microfilariae develop on the head , neck, medical forlimbs, ventral thorax, and abdomen and consist of patchy to diffuse alopecia, erythema, scaling, crusing and pigmentary changes.

Distribution of Onchocerciasis:

The distribution of onchocerciasis is linked to the locatiaon of blackflies awhich are naturally found close to the fast running streamsa and rivers in the intertropical zones. Therefore , about 90% of the disease occurs in Africa. Onchocerciasais is also found in 6countries in latin amercia and in yemen in the arabin peninsula, where the disease is believed to be exported by the slave trade.

Fig 3: Schematic representation of River blindness

Consequences:

The death of microfilaria;ae is very toxic to the skin and the eye , producing terrible itching and various eye manifestations. After repeated years of exposure, these lesions may lead to irreversible biindness and disfigurative skin diseases sometimes named "leopard' skin , and "lizard ' skin.

Current Global Status &Impact:

A combination of vector control in West Africa , the use of vermectin, large-Scale community Directed treatment (comot) and the use of onchocerciasis transmission has allowed the continous annual treatment of more than 30 millian people. Interdruphion of transmission of o. volvulus and reduction of the burden of visual impairment and blindness has been achieved in most of the west African region and in sin latin amercian countries affected by this parasite, and in these areas onchocerciasis Is no longer a disease of public health importance. However , the skin disease, with its Adverse psycho-social and socio- economic effects, continues to be a problem in the Rest of Africa.

Life Cycle:

Humans are the sole definitive host. Infection occurs when a blackfly introduces an o. volvulus stage 3 larva into the host during a blood meal. The female nematode Develops to adulthood and permanently confined in a fibrous capsaule, whereas Male adults move freely throughout the skin and subcutaneous spaces. During adulthood The female worm migrate through the skin of the humam host, with particular affinity For the eyes sinc e it sheds hundreds of thousands of microfilariae measuring 220- 360 Micro metre. By undergoing autoimmune mechanisms, the inflammatory response Against dying microfilariae over years

of repeated infection causes the gradual and eventually blinding sclersoal opacification of the anterior eye by local inflammation And of the porterior eye. During a blood meal, the o.volvulus life cycle continues on Uptake of microfilariae by the blackfly. Once inside, the microfilariae penetrate the fly Gut and migrate to the thoracic flight muscles , where they develop to 3rd stage larvae and then find their way to the blackfly feeding apparatus. They then euter Another human host during a blood meal, thus completing the cycle. Microfilariae Persist in the human host for 3-5 years in contrast to the adult female worm life span, which is 2-15 yrs.

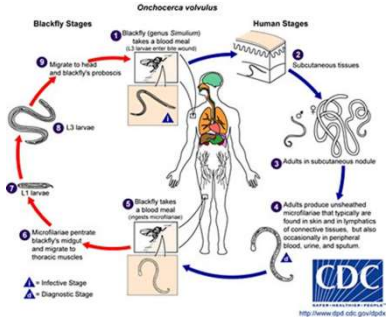

Fig 4: Life cycle of River blindness

Diagnosis and clinical management of Onchocerciasis:

Diagnosing onchocerciasis rellies an demonstration of chaararacteristic eye pathology or demonstration of MF awithin the sakin, PCR enamination of skin ships improves this situation , although sensitivity is still low in such persons, making this tool less Useful in endemic areas where ivermeetin has been asked to threat this disease for years skin patch testing with diethykarbamazine has been shown as a good alternative To skin snip evaluations in Africa. Advantages overe skin snip evaluation , although can Be operationally difficult fall off, patients must return in 24h. the sensitivity and specificity of the DEC path test is not yet clear although recent studies using newer Formulations suggest its utility in monitoring for infection within mass onchocerciasis treatment programs in Africa. A highly specific antigen detection test capable of diagnosing active infection has been reported in the literature, but to date, has received little evaluation. The development of a highly specific and sensitive test capable of determinis active onchocercal infection remains an imperative for public health campaigns seeking to control and eliminate this parasites.

2. Clinical Presentation and Pathogenesis

Onchoceerciasis most commonly presents as a difuse popular dermatitis, often with Intense pruritis. These recently infected patients tend to demonstrate a strong TH' type Immune response. In patients with chronic disease, however, the cutaneous Manifestations can be differentiated across a spectrum , from pruritic lichenification are Associated with strong lelper lymphocyte (TM2) response, whereas depigmentation has Been shown to correlate with a wilder TM2 reactivity exposure to mchocerca break Down products induces a strong eosinophilic response as well. Subdermal nodules Called "onchocercomata" which are most easily seen over borny prominces, are Another commonly reported manifestation of onchocerciasis. The value and reliability Of verbal diagnosis by eliciting a history of nodules in areas where the disease is highly endemic have been described elsewhere. In Africa, onchocercomata are often Found over the bony prominces of the torso and hips, whereas in southamercia , where it is sometimes called "robies disease", the predominant strains typically produce Nodules in the head and shoulders. The presence of onchocercomata does not correlate With microfilarial load. This is not thought to result from vertical transmission but, Rather , from stimulation of a fetal shift towards a TH2 response to onchocercal Infection that , an exposure later in life , favours tolerance of the presence of o.volvulus and paradoxically, more. Severe dermatological symptoms.

Onchocerciasis and HIV Infection:

Of exposed to HIV, especially the macrophase tropic, HIV-1, patients with onchocerciasis have a greater like- lihood of converting to HIV positivity than do those without onchocerciasis. HIV infection may worsen the severity of onchodermatitis, although this aspect of the relationship has not been well studied. Recent work by reaffirms That is safe to include HIV - infected patients in mass treatment populations.

Differential Diagnosis:

The differential diagnosis of the diffuse popular dermatitis seen in acute onchocerciasis is exclusive and may include food allergies , leprosy, pinta, syphilis, vitaminA deficiency, And yaws. Also, certain parasitie infestations can resemble onchocerciasis. Other onchocerca species-onchocerca gutturosa , in most cases- have been found to infect Humans, but only 6cases of infection have been reported ,without evidence of transmission . Rarely, o.volvulus infection can mimic dracunculiasis. The subcutaneous filiria emerging at the skin in 3documated cases.

Lateral Flow immunoassay Distick Diagnostic:

Janda says onchocerciasis monitoring and evaluation are especially necessary steps For people leading elimination efforts. The current gold standard for detecting the Parasitic worms is a "skinsnip" biopsy. However , snips are generally insensitive Indicators of infection, and the sensitivity of the skinsnip decreases and the densivity of micrtofilaria in between past and current infections. The key to the essay success was in the making of designer antibodies to detect a

unique biomaker that only shows up when a human host has metabolized a worm Neurotrausmitter called tyramine. Humans then secrete this biomaker in unique. A negative on the 'Dipstick' test shows a colored line in the test. Unlike the skin snip biopsy , janda says this non- invasive test is the tirst to use a metabolite produced by adult worms.

Hapten and testline conjugate synthesis:

Production of mAbs for NATOG detectionrequires the synthesis of a small Molecule hapten. Due to the number and variety of glucuronidated compounds Present in nrine, it was vital to obtain mABs with highly selectivity for NATOG However , mAbs raised against small molecule carbohydrates often have low affinity. In addition, the selection of an 'immunobgically silent" linker becomes increasingly More difficult to achieve as the size of the carbohydrate epitope becomes smaller, Resulting in immune dominount responses directed toward the tether and not the compound of interest. For preferential binding of the test line, limiting the sensitivity of the LFJA. The hapten was designed with a simple modification to The amide to append a thiol linking site while maintaining the lore NATOG Structure.

Health Care Professionalisms Diagnose Onchocerciasis in this Way: Clinical presumptive diagnosis is made if the patient lives or visits areas where the disease is endemic and has characteristic skin or eye changes described above. Definitive diagnosis is simply done by seeing adult worms in excised skin nodules, eye lesions, or by finding microfilariae in skin shavings or punch biopsies of the skin. In addition, an immunological test for antibodies developed against the parasites early in the infection is useful to determine if a person is infected before microfilariae are detectable. This test is available from the CDC. It is important to obtain a definitive diagnosis so that appropriate treatment can be started (see treatment section below). Onchocerciasis is a type of filariasis that does not respond well to some other drugs used to treat other similar filarial diseases. Diethylcarbamazine, a commonly used drug that is a derivative of piperazine, actually has been linked to severe and sometimes fatal patient reactions when used to treat onchocerciasis. A new drug capable of killing the adult worms of onchocercias is is under study for use in humans. It's named moxidectin but has not yet been approved for use in humans for treatment of onchocerciasis.

3. Treatment

Treatment is done by giving the patient ivermectin, an antiparasitic drug once or twice per year for about 10-15 years (the life span of adult worms). This antiparasite drug is effective in killing the microfilariae but does not kill the adult worms. The mature worms may remain alive for 10-15 years in the patient. Most clinicians recommend that subcutaneous nodules should be excised, if possible, thereby removing the adult worms that may reproduce more microfilariae over time. Some clinicians recommend that after ivermectin treatment, patients may benefit from a six-week dose of doxycycline antibiotic. Doxycycline damages and kills *Wolbachia*bacteria that are inside the microfilariae and adult worms, resulting in the death of microfilariae and ineffective microfilariae produced by the surviving adult worms. This may slow or halt further disease development.

The use of diethylcarbamazine (a treatment used before ivermectin became available) is contraindicated. It may cause severe or fatal patient reactions in individuals with onchocerciasis. The standard treatment for onchocerciasis is ivermectin (150-µ g/kg given orally ever 6 to 12 months). Ivermectin is a highly lipophilic, 16-membered macrocyclic lactone from *Streptomyces avermitilis* . Single-dose ivermectin effectively kills microfilariae by blocking postsynaptic, glutamate-gated chloride ion channels, inhibiting transmission, and paralyzing the nematode. It also appears to enhance immune responses against *O. volvulus* in the treated host .Other than a significant oncogenic effect on adult female worms, ivermectin has little macrofilaricidal effect; therefore, it controls but does not cure the disease. One year after receipt of ivermectin treatment, skin microfilarial densities regain at least 20% of pretreatment levels, requiring repeated treatments for the lifespan of the adult worm A 15-month study showed that ivermectin is actually more effective at preventing further reactive onchocercal skin lesions than at clearing extant lesions. Effective ivermectin treatment apparently requires a robust immune response. Administration of single doses of 150 µ g/kg every 3 months has been recommended on the basis of evidence of decreased rates of posttreatment reactions (e.g., edema, pruritis, and backache) over time, compared with yearly dosing. This is thought to be due to decreased numbers of microfilarae dying and releasing their antigens after more frequent treatments.

High-dose ivermectin (800 µ g/kg) was shown to be no more effective than administration of the 150 µ g/kg dose, and high doses may be harmful. In 2003, Awadzi et al. reported that coadministration of ivermectin and albendazole, although apparently safe, did not lead to prolonged or enhanced amicrofilaridermia.

Presently, the only approved medication with a significant effect against adult worms is suramin, but toxicity, inconvenience (twice-daily injections administered for several weeks), and availability only through the Centers for Disease Control and Prevention (in the United States) virtually eliminate its clinical utility for treatment of onchocerciasis. A promising new drug, moxidectin, has been shown to have significant macrofilaridical activity in animal studies, is safe for use in humans, and has already undergone phase II trials.

Adverse Effects of Ivermectin:

Skin reactions after receipt of ivermectin treatment are commonly reported in persons with high microfilarial densities. After receipt of ivermectin treatment, circulating eosinophil counts decrease, and IL-5 and eosinophil-derived neurotoxin levels increase, showing a statistically significant correlation with clinical reaction scores. The physiologic enzyme tryptase, released from mast cells, can be used as a marker of degranulation. Cooper et al showed that plasma tryptase levels increase 12 h after microfilarial

killing with ivermectin, preceding adverse symptoms, which start 24 h and peak 36 h after receipt of ivermectin treatment. This increase correlated with clinical reaction scores, markers of eosinophilic sequestration (decreased peripheral blood eosinophilia and increased plasma IL-5 levels), and activation of degranulation (increased plasma eosinophil-derived neurotoxin levels). Reactions could be associated with lipopolysaccharide-like endotoxins released by *Wolbachia* symbionts or by hypersensitivity to true parasite antigen.

Burchard et alfound a statistically significant correlation between ivermectin treatment and protein-leaking glomerular disturbances 5 days after administration of treatment. Total urinary protein excretion was significantly higher in patients with high microfilarial densities (>80 microfilariae per mg of skin). However, the change was minor and deemed to be clinically negligible. No statistically significant association between onchocerciasis and autoimmune glomerular or tubular disorders was demonstrated.

Ivermectin is a potent P-glycoprotein inhibitor ,and as such, it has been shown to be very safe in mammals, whose γ - amino butyric acid (GABA) receptors and neurons lay behind a blood-brain barrier ,Care should be taken in patients with active meningoencephalitis or other states associated with a weakened blood-brain barrier. Seizure associated with ivermectin treatment, which was been rarely reported, may be due to the drug passing the blood-brain barrier in susceptible individuals, but it should be noted that epilepsy need not be a contraindication to mass treatment programs. Over the course of large-scale, international treatment programs, there have been no reports of worsened epilepsy after receipt of ivermectin treatment.In addition to epilepsy, some experts believe that onchocerciasis can also cause ⩾ 1 of a loosely defined group of growth retardation syndromes.This has not been thoroughly disputed or validated. Because of the rarity of growth retardation syndromes among populations from areas where onchocerciasis is endemic, the safety of ivermectin therapy for patients with growth retardation syndromes cannot be assumed, and such patients are referred to clinics for proper diagnosis and treatment.

Ivermectin Resistance:

As ivermectin continues to be used in both animals and humans, resistance presents another challenge to global eradication efforts. Keddie et al. maintained there may not be preexisting resistance genes among O. volvulus populations, slowing the development of ivermectin resistance. However, a study by Ardelli et al. suggests that the genetic heterogeneity of O. volvulus is higher than previously thought. They believe that resistance alleles do preexist, that mass ivermectin treatment is rapidly transforming the population genetics of O. volvulus, and that clinical resistance is imminent. Indeed, parasites from ivermectin-treated patients demonstrate decreased diversity at many genetic loci for P-glycoprotein, suggesting changes in allelic patterns that may lead to resistance. Although ivermectin resistance has been reported in 4 species of nematode parasites that generally do not affect humans,it has not yet been unequivocally demonstrated in O. volvulus.

4. New Directions in Therapy

A new approach to therapy targets endosymbiotic *Wolbachia* bacteria. In 2000, a landmark study first showed that doxycycline cleared *Wolbachia* bacterial endosymbionts from the endodermis and uteri of adult female worms, leading to unusually extensive worm sterility not seen in other antifilarial treatments. In a nonrandomized, placebo-controlled trial involving humans, doxycycline (100 mg per day for 6 weeks), followed by a single 150-μ g/kg dose of ivermectin, resulted in up to 19 months of amicrofilaridermia, as well as 100% elimination of *Wolbachia*species from worms that were isolated and tested immune histologically. The effect on microfilaridermia is thought to result from a complete block of embryogenesis for at least 18 months. In contrast, ivermectin only works against late-stage developing microfilariae still in the uterus, and it has little or no effect on early-stage embryos. The authors suggest that infected patients who permanently leave areas of endemicity should be offered, in addition to ivermectin, a 4– 6-week course of doxycycline (100– 200 mg per day) to achieve long-term amicrofilaridermia. PCR-detectable presence of *Wolbachia* species may remain and could signify the presence of dormant but viable bacteria ,but these bacteria appear unable to repopulate the worms up to 18 months after treatment. More research is needed to secure this conclusion.

Hoerauf et alrecommend concurrent administration of ivermectin with doxycycline therapy, as well as administration of another ivermectin dose 6– 8 months later to eradicate microfilariae too immature to be sensitive to the initial microfilaricidal treatment. However, caution should accompany the concurrent use of ivermectin and doxycycline, because these agents have not been formally studied for interactions. An easy way to circumvent the potential for interactions is to delay doxycycline therapy until several days after administration of an ivermectin dose.

5. Conclusion

Onchocerciasis continues to be a problem in Africa and Latin America. With the recent discoveries in doxycycline-mediated eradication of Wolbachia species, health care providers now have another option for treating this historically devastating disease. As research and development in DNA-based and antigen-based means of diagnosis continues, physicians will soon have an array of effective and convenient tests at their disposal to diagnose the disease and test for cure. Still, global efforts and further research are needed to control the disease worldwide.

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