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Review

Trachoma: Past, present and future

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Abstract

Purpose: To review the background, epidemiology and current management of trachoma in endemic areas and worldwide.
Methods: Review of literature.
Results: Trachoma is one of the leading causes of preventable blindness in developing countries. It was reported as one of the seven most neglected tropical diseases that can be prevented via drug administration. Its infliction is primarily aimed at those living in areas deprived of clean water and proper sanitation. It is estimated that trachoma is the cause of visual impairment in about 2.2 million people worldwide of which about 1.2 million are completely blind. With implementation of the SAFE (surgery, antibiotics, facial cleanliness, and environmental control) strategy with support from the International Trachoma Initiative (ITI) the incidence of trachoma has decreased significantly in the Middle East and North Africa region.
Conclusion: With the enhancement of socioeconomic and sanitary status of people, advent of new generations of antibiotics, training of expert ophthalmologists and eye care facilities the prevalence of trachoma is decreasing.

Keywords: Trachoma; *Chlamydia trachomatis*; Follicular conjunctivitis

Introduction

Trachoma comes from Greek word trachoma (τράχωμα) meaning "roughness". Trachoma was well known as an infectious ocular disease and documented as "ophthalmia". The history of this disease began as early as 8000 B.C. Taborisky and MacCallan believe Central Asia to be the origin.[1,2] Old documents refer to Chinese therapies (2600 B.C.) and Hippocratic Corpus, as well as works of several physicians; including Celsus (1st century A.D.), Discorides (40–91 A.D.), and Galen (129–216 A.D.). Trachoma was prevalent in Europe between 1200 A.D. and 1700 A.D.[2] Military activities helped the expansion of trachoma. In 1798, "Egyptian military ophthalmia" infected three thousand of Napoleon's troops in the Egyptian war, blinding many. Napoleonic Wars accelerated the spread of trachoma across Europe.[2] In 1810, British scientists proposed cleanliness, isolation, and improvement in the living conditions of soldiers as a measure to prevent the spread of trachoma.[3] A new source of infection emerged as immigrants moved to the new land, America, at the end of the 19th century. In 1897, trachoma was the first disease classified as a dangerous contagious disease by the U.S. government. Infected immigrants were sent back to Europe by the United States Public Health Service physicians.[4]

Because of the widespread distribution of trachoma, international organizations were allied to combat against this disease. Before World War II, La Ligue Contre Le Trachome and the International Organization against Trachoma were founded. Moreover, the World Health Organization (WHO) immediately after foundation classified trachoma as a dangerous disease for the human beings.[5]

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In 1954, T'ang and his colleagues from China cultured chlamydia trachomatis. At first, the causing agent of trachoma was believed to be a virus because of its small size and inability to culture, except in living cells.[6] By the 1970's, *Chlamydia trachomatis* deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) were found and because of susceptibility to antibiotics, it was assumed to be a bacterium.[7]

In the mid-20th century, the breakthrough of antimicrobials aided the development of trachoma treatment. In the early 1950's, both topical and oral tetracyclines were investigated. Topical tetracyclines were chosen as the most effective therapy and the treatment of choice till the late twentieth century as it had the fewest side effects. One dose of oral azithromycin therapy in the1990's became the preferred treatment for trachoma. With these new therapies available, trachoma became a more preventable epidemy.[8–10]

In this paper, we present the background knowledge for trachoma. To add the update, studies that were published between 2015–June 2016 were identified. The literature search was performed using Pubmed and Scopus databases with a search term of "trachoma". All original articles with English language were selected. The literature search revealed 36 articles. The relevant papers are discussed.

Pathogenesis

Chlamydiae are obligate intracellular bacteria. Trachoma is caused by serotypes A, B, and C of chlamydia trachomatis. Ocular surface chlamydia infection causes a chronic inflammatory reaction, which is characterized by the presence of lymphocytic, monocytic, plasma cells and macrophages infiltrates. Prolonged inflammation induces conjunctival scarring as a result of recurrent and chronic conjunctival follicular reinfection.[11,12] During a chlamydial infection the normal architecture of the conjunctival epithelium is disrupted, the goblet cells are lost and the normal, loose, vascular subepithelial stroma is replaced with compact bands of type IV and type V collagen.[13]

Trachoma is a mucopurulent keratoconjunctivitis. There is a follicular and inflammatory response in the upper palpebral conjunctiva. The extraocular mucous membranes like nasopharynx can also be infected with *C. trachomatis*. Typical clinical manifestations in an endemic area seem sufficient for the diagnosis. However, laboratory tests are needed to confirm the diagnosis. Several different laboratory tests have shown promise in the diagnosis of trachoma. These tests are useful for diagnosis in areas with low prevalence or for research purposes. Cytologic tests either by Giemsa stain[14] or direct fluorescent antibody (DFA) tests[15] can detect the intracytoplasmic inclusions of *C. trachomatis*. *C. trachomatis* can also be cultured on several different cell culture systems.[16] The third method called enzyme immunoassay, takes advantage of binding of anti-chlamydia antibodies to certain chlamydial antigens.[17,18] Finally, nucleic acid detection is the newest and most sensitive test. It involves the identification of chlamydial DNA or RNA either by probing or amplification techniques. Nucleic acid amplification tests (NAATs) are currently used to assess the prevalence of trachoma infection and thus can be used to evaluate the success of control programs.[19,20]

Clinical presentation and classification

As previously noted, the physician can make the diagnosis of trachoma on the basis of clinical manifestations in endemic areas.

The differential diagnosis of trachoma include: allergic conjunctivitis, viral conjunctivitis, bacterial conjunctivitis and inclusion conjunctivitis.

Allergic conjunctivitis is the most common cause of a red itchy eye. Scant mucosal discharge and a papillary response on conjunctiva may also be found. Viral conjunctivitis presents with red eye and foreign body sensation. Tender preauricular lymph nodes may also be palpable on examination. Patients may express a history of upper respiratory tract infection. This is not usually present in trachoma. Bacterial conjunctivitis is characterized by a purulent discharge. In contrast to trachoma, follicular conjunctival reaction is rare.

Inclusion conjunctivitis or adult chlamydial conjunctivitis is a sexually transmitted disease caused by certain serotypes of *C. trachomatis*. It does not progress to trichiasis and scarring, in contrast to trachomatous conjunctivitis.

The WHO recommends a simplified grading system for trachoma. According to the WHO clinical disease grading of trachoma clinical manifestations are as below.[21–24]

Follicular trachoma (TF) is defined by the presence of at least 5 follicles (each at least 0.5 mm in diameter) on the central part of the upper tarsal conjunctiva. It is believed that the presence of follicles is an indicator of active disease. TF is most commonly found in 3–5 year old children. Follicles are dense collections of lymphocytes. Involution of follicles in limbal area may result in depressions that are called Herbert pits. These lesions are pathognomonic of past active trachoma.

Trachomatous inflammation-intense (TI) is the pronounced inflammatory thickening and papillary hypertrophy of the upper tarsal conjunctiva obscuring more than half of the normal deep tarsal vessels. Risk of significant conjunctival scarring and blinding disease increases after development of TI.

Trachomatous scarring (TS) is the presence of white lines, bands and sheets of fibrosis in the tarsal conjunctiva. TS is an indicator of past inflammatory disease and associated with the development of trichiasis and dry eye syndrome.

Trichiasis (TT), the blinding lesion that opacifies the cornea, is defined by at least one ingrowth of an eyelash touching the eyeball or evidence of recent eyelash removal. Trichiasis is the result of subconjunctival fibrosis over the tarsus. If TT is corrected in a timely manner, vision can be restored.

Corneal opacity (CO) is defined by the presence of easily visible corneal opacity over the pupil. The pupillary margin is blurred through the opacity. CO is the blindness stage of trachoma. Opacity includes pannus, epithelial vascularization, and infiltration.

Management and prevention

The WHO advocated a strategy for the prevention and treatment of trachoma to guide the international efforts to eradicate this blinding disease. This public health strategy is called "SAFE" which is a combination of the three elements of primary, secondary and tertiary prevention. It is proved that the SAFE strategy is highly valuable to treat and prevent trachoma. The components of SAFE are:

- Surgery
- Antibiotics
- Facial cleanliness
- Environmental improvements

The International Trachoma Initiative (ITI) was founded in 1998 to help the achievement of the WHO's target to eliminate blinding trachoma by 2020. ITI collaborates with governmental and nongovernmental organizations at the local, national and international levels to implement SAFE strategy for trachoma control.[23–27]

Surgery

Surgery is used to reverse the in-turned eye lashes of the patients with trichiasis or entropion and is of paramount importance to prevent blindness. It is a quite simple procedure and can be readily carried out in the community or at healthcare centers. Patients usually prefer a surgical procedure that can be performed in an outpatient setting. Eyelash removal can relieve the pain that is caused by rubbing the lashes over the eye but it does not restore vision. Unfortunately this procedure has a high recurrence rate. If TF reaches above 10%, surgery is recommended when district TT prevalence exceeds 0.1%.[23]

Antibiotic therapy

The introduction of antibiotics in the 20th century had a revolutionary impact on trachoma control and caused the elimination of trachoma in most developed countries by the 1950s and 1960s. The aim of antibiotic therapy is the reduction of infection burden in an affected community or treatment of an active disease. The administration of topical tetracycline ophthalmic ointment daily for a period of at least six weeks, or as an alternative, annual azithromycin tablets or liquid for infants can treat active infection.

The WHO recommends mass treatment with antibiotics in areas where the prevalence of active trachoma exceeds 10 percent among children aged between 1 and 9 years. When the prevalence of active disease is between 5 percent and 10 percent, either mass treatment or treatment of patients with active disease can be chosen.[24,28]

Azithromycin is currently the drug of choice for treatment of trachoma. Pfizer, the manufacturer of Azithromycin (Zithromax®) committed to providing this drug free of charge for trachoma control. To date, Pfizer's donation of Zithromax® through the ITI has reached millions of people in 19 countries. As of 2015, Pfizer has donated more than 500 million Zithromax® treatments.

Facial cleanliness

There is a strong correlation between trachoma and facial cleanliness as children with dirty faces can both transmit the disease if infected and catch it if not.[29] Ophthalmic and nasal discharges foster the proliferation and attraction of infective flies, while rubbing dirty eyes with cloth, sheets and mother's clothing, namely shawls, help transmit trachoma. Thus, it is strongly recommended that children should have clean faces as part of trachoma control program.[26]

Environmental improvement

It has been long known that the prevalence of trachoma in an area is related to the living conditions of inhabitants, access to clean water and availability of adequate sanitation.[30] Transmission of trachoma can be interrupted at the community level by improving the living standards of inhabitants and provision of an adequate supply of clean water.[31]

Any eradication program would fail without an acceptable level of sanitation, water disposal and water quality. To have a successful control program collaboration with other parts, such as education, water and sanitation is mandatory. Trachoma transmission is dependent on poor personal hygiene, fly density and its endemicity. Therefore, the SAFE strategy addresses poverty and development issues, aiming to improve the quality of life for millions of people in the world's poorest countries. Whenever TF prevalence exceeds 5% in children aged 1–9 years F and E components need to be implemented and district-wide distribution of antibiotics should be added in any district with a prevalence of TF higher than 10%.

All four above-mentioned components of the SAFE strategy are absolutely essential in any successful control program. Antibiotics and surgery minus hygiene and sanitation can merely remove symptoms and not the causes of the disease.[32] Improvement in domestic and personal hygiene holds great potential for sustainable elimination of trachoma, while treatment of active cases with antibiotics can cause the reduction of pathogen reservoir.

Trachoma in the Middle East and North Africa

The first country that was successful in eliminating trachoma in the Middle East and North Africa was Morocco. This was achieved through implementation of the SAFE strategy with support from the ITI. According to the WHO Global Health Atlas trachoma is highly prevalent in the Middle East and North Africa (MENA) region with more than half a million cases of trachoma occurring in this area. Yemen has the largest number of patients (204,000 cases), followed by Algeria and Iraq (roughly 140,000 cases each). Despite significant advances in the treatment of this disease in the modern era, trachomatous trichiasis is still a public health problem among some elderly populations in Oman,

particularly in women.[33] According to the latest WHO reports, Iran, Morocco, and Oman have been successful in achieving elimination goals in this area and have moved to the surveillance phase.[34]

Unfortunately, there is no document on true prevalence of Trachoma in Iran. However, it seems that trachoma was a major cause of visual impairment in this country in the early decades of the 20th century.[35] After the foundation of Farabi Eye Hospital by Professor Chams and colleagues and training of the first generation of ophthalmologists, the prevalence of trachoma decreased significantly.

A recent study in one of the epidemic parts of Iran, the city of Birjnad showed that trachoma was detected in 10% of the patients with chronic conjunctivitis. The results were similar for both sexes. Although the findings are hospital-based, the prevalence was not so high as to suggest prophylactic use of azithromycin (WHO protocol) for eradication of trachoma.[36] In a study in a deprived part of Iran, Sistan va Balouchestan corneal opacities were reported to be present in 14.9% of people with visual impairment.[37] The prevalence of trachoma in rural areas of Sistan va Balouchestan province of Iran has been investigated in a recent study. Results of clinical eye exams of 7912 participants were analyzed. The prevalence of TF and TT in this population was reported to be 0.59% and 0.02%, respectively. Thus, the authors concluded that Sistan va Balouchestan is not endemic for trachoma, despite previous belief.[38]

A study on causes of visual impairment showed that uncorrected refractive errors and cataract had a major role as causes of visual impairment in Tehran, the capital of Iran. Meanwhile corneal opacities due to all causes including trachoma, herpetic keratitis, trauma and chemical burns consisted of only 3.7 percent of causes of visual impairment in this population.[39]

The eye bank of the Islamic Republic of Iran reported that 3.3 percent of cases with corneal transplantation in a tertiary referral eye hospital in Iran were due to trachoma keratopathy which once again shows the decreasing prevalence of trachoma keratopathy.[40]

In conclusion, it seems that with the enhancement of socioeconomic and sanitary status of people and advent of new generations of antibiotics and training of ophthalmologists and eye care facilities, the prevalence of trachoma is decreasing, although not eradicated. In spite of this decrescendo pattern, it should be noted that the potentially blinding complications of trachoma need special and meticulous treatment plans.

Future directions

In 1998, the WHO called for an alliance for global elimination of blinding trachoma by the year 2020.[41,42] As previously noted, Iran is among the countries, along with Morocco and Oman, that have reported the achievement of elimination goals in the Middle East and North Africa along with Morocco and Oman.[34] However, a recent report showed that trachoma is still an ongoing health problem in certain areas of eastern Iran[43] despite many attempts to combat it. Several reasons have been suggested for this prevalence including interaction with Afghan people, water shortage and dust storms in these areas. It has been proven that trachoma is more prevalent in areas with malnutrition, poor hygiene and low living standards. Previous experiences have shown that trachoma cannot be successfully controlled without improvement in the environmental indices of living conditions, housing, diet, and sanitation. In fact, there are few diseases that show this degree of correlation with living conditions. Thus we believe that the solution of trachoma elimination in these areas lies in proper government health and welfare policies, funding from various sources and interaction with water and sanitation sector. With continued efforts in the more deprived parts of the country, we believe that trachoma will be eliminated as a blinding disease by the year 2020.

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