

Chlamydia pneumoniae And Rosacea : A Possible Role In Etiopathogenesis Among Egyptian Patients

Protocol for thesis

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Introduction:

Acne rosacea is a chronic skin disorder that presents with symmetrical facial flushing and edema, leading to telangiectases that can later develop into papules, pustules, and persistent erythema. Tissue overgrowth of the nose (rhinophyma) also may occur. Conjunctival areas of involvement are known to occur, especially in the severest forms of acne rosacea. The prevalence of acne rosacea has been estimated to be about 10%, with women affected more often than men (*Berg & Liden, 1989*).

The exact cause of rosacea remains unknown. Several factors have been implicated in its pathogenesis; some are based on the evidence of scientific investigation, others on subjective observation. Proposed etiologic mechanisms can be grouped into the following categories: vascular abnormalities, climatic exposures, matrix degeneration, chemicals and ingested agents, pilosebaceous unit abnormalities and microbial organisms as *Helicobacter pylori* & *Demodex folliculorum* (*Crawford et al., 2004*).

Although the exact pathology of rosacea is still unknown, there is strong evidence that rosacea is primarily an inflammatory disease. Supporting the role for chronic inflammation is the host of elevated proinflammatory cytokines (TNF- α , IL-1B), matrix metalloproteinases (MMP-1, MMP-3, and MMP-9), nitric oxide (NO), and reactive oxygen species (ROS) that have been associated with rosacea in recent studies (*Kang et al., 2005 & Oztas et al., 2003*). Also, rosacea has been associated with elevated vascular endothelial growth factor (VEGF) (*Smith et al., 2007*). Indeed, the elevated cytokines, MMPs, VEGF, NO and ROS associated with rosacea, match closely with the known pathology of early gram-negative sepsis, an infection of the blood stream caused by toxin-producing bacteria. Also, it was found that vascular endothelial growth factor (VEGF) itself may be a key biomarker for sepsis (*Yano et al., 2006*).

While gram-negative bacteria such as *H. pylori* and even *Bacillus oleronius* (found in *Demodex folliculorum*) have been associated with rosacea in various studies, these bacteria have not been shown to enter the blood stream, and so not expected to produce pathology similar to early sepsis (*Rebora, 2002*). Looking at other inflammatory diseases for clues relating this pathology to associated gram-negative bacteria, one such pathogen, *Chlamydia pneumoniae*, stands out for its association with many inflammatory diseases, including atherosclerosis, multiple sclerosis, asthma, Alzheimer's and other inflammatory disorders (*Stratton, 2000*).

Persistent *C. pneumoniae* infection of epithelial cells has been shown to produce chronic blood vessel inflammation, resulting in production of a host of cytokines and growth factors such as those found in rosacea (*Blasi et al., 2004*). Additional studies suggest that chlamydiae, while classified as gram-negative bacteria due to their outer lipopolysaccharide coating, are actually a distinct group of eubacteria. It has a unique multi-form, intracellular and extracellular development cycle, allowing them to change between forms and promote the persistent infection that may lead to chronic inflammatory diseases (*Hogan et al., 2004*).

Another clue potentially linking rosacea with *C. pneumoniae* is recent studies in the anti-microbial peptides, cathelicidins, and their activity in rosacea. These studies have identified unusually high levels of kallikrein activated cathelicidins in rosacea and suggest that these two substances may be, in part, responsible for producing the papules and pustules associated with rosacea as well as in promoting the angiogenesis associated with the disease (*Koczulla et al., 2003 & Nizet & Gallo, 2003*). Some additional studies have shown that *C. pneumoniae* seems to evoke unusually high levels of cathelicidin activity and that endotoxins in general activate the kallikrein-kinin system (*Edfeldt et al., 2006 & Dela Cadena Raul et al., 1993*). However, cathelicidins seem to be ineffective in clearing *C. pneumoniae* infection. Potentially this is due to *C. pneumoniae*'s ability to revert between forms, effectively evading the immune response and this might explain the resulting ineffective but yet elevated levels of activated cathelicidins in rosacea patients (*Donati et al., 2005*).

In a trial to find a direct link between *Chlamydia pneumoniae* and rosacea, ***Fernandez-Obregon & Patton in 2007*** performed a pilot study on 10 rosacea patients. In this study *C.pneumoniae* antibodies were detected in the sera of 8 patients by immunofluorescence. However, immunohistochemistry of cheek biopsies revealed chlamydial antigen in 4 patients only. Other studies suggest that infection with *C. pneumoniae* can lead to pustular rashes (acute generalized exanthematous pustulosis) (***Manzano et al., 2006***)

A variety of treatments are available for rosacea, but unlike acne, which can be cured with isotretinoin, no rosacea treatments tend to be curative. Successful treatments of rosacea serve to reduce symptoms and the red facial appearance. Systemic therapy consists mainly of oral antibiotics. Effective therapy with oral use of tetracyclines or topical metronidazole achieves improvement in 80% to 90% of cases. Combining these modalities is often used to achieve a rapid response (***Wilkin, 1994***). Oral antibiotics, requiring frequent administration, introduce the possibility of poor compliance, and their long-term use carries the risk of uncomfortable side effects or other adverse reactions. Topical agents have been known to cause dryness and irritation in individuals with sensitive skin. Azithromycin, a second generation macrolide antibiotic given 3 times a week has been used successfully to treat acne (***Fernandez-Obregon, 2000***) and it has been used as a monotherapy in rosacea patients 3 times per week and the results show that it is safe and effective treatment for rosacea beside offering good compliance (***Fernandez-Obregon, 2004***).

Aim of the work:

The aim of this work is to investigate the role of *Chlamydia pneumoniae* in the etiopathogenesis of rosacea in Egyptian patients. Also, the proinflammatory cytokine TNF- α will be evaluated in a trial to find out if *Chlamydia pneumoniae* is actively involved in the inflammatory process in rosacea. Moreover, this study aims at examining the effect of antichlamydial antibiotic azithromycin on the proinflammatory cytokine TNF- α as an indicator of the active role played by *Chlamydia pneumoniae* in rosacea patients.

Subjects and methods:

Subjects:

The study will include 20 rosacea patients with variable disease stages and 10 age and sex matched healthy controls attending the Dermatology clinic, Ain Shams University Hospital.

Methods:

All cases will be subjected to:

- History taking
- General examination
- Dermatological examination and proper staging of the disease in rosacea patients
- Tissue biopsy for detection of Chlamydia pneumoniae antigen by PCR.
- Assessment of TNF- α mRNA by PCR in tissue biopsy
- Oral azithromycin will be given 3 times a week for a minimum of 4 weeks with assessment of clinical response.
- Another tissue biopsy will be taken after treatment for monitoring of chlamydial antigen and TNF- α mRNA after treatment.

This will be followed by data retrieval and statistical analysis.

The study will include

- Introduction
- Aim of the work
- Review of literature
- Subjects and methods
- Results
- Discussion
- Conclusion
- Summary
- References
- Arabic summary

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