Effects of noxious compounds in exhaled breath air as a potential mechanism causing “Red eye” in renal failure patients

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Received: 3 Nov 2007
Accepted: 18 Nov 2007
Published: 20 Nov 2007

Abstract
Renal failure can lead to the retention of nitrogenous waste products which affects almost all organ systems in human body and causes complex clinical manifestations. Eye can be one of these affected organs. “Red eye” is not an uncommon complication of renal failure. Over the past several decades numerous theories have attempted to describe the possible pathogenic pathways leading to the diverse ocular complications of renal failure. Some of the retained waste products in renal failure such as, nitric oxide, hydrogen peroxide and methylamines can be elaborated and exhaled via breath air. We hypothesize that the effects of these exhaled noxious compounds on the ocular surface over an extended period of time can be considered as another potential mechanism contributing to ocular manifestations, particularly the “red eye”, in renal failure.

Keywords
Red eye, Renal failure, Exhaled noxious compounds

Introduction
According to the research studies conducted in several countries, the prevalence of renal failure is higher than what has already been indicated, principally in the elderly (1-3). Other epidemiological studies have also revealed that renal failure is common in developing countries (4).

Normal functions of the kidneys can be affected by a variety of diseases and medical conditions resulting in elimination of GFR, perturbation of haemostatic state of water and electrolytes, reduction of hormone production, and retention of nitrogenous waste products (5-7).

Numerous experimental studies in different countries have been and are still being conducted in order to unfold the new aspects of renal failure’s implications on multiple organ systems such as gastrointestinal (8), oral cavity (9), pulmonary (10), cutaneous (11) and the other systems. The eye complications of renal failure have been the main subject of some other previous and ongoing research studies.

Some systemic diseases such as diabetes or autoimmune diseases leading to renal failure can also cause eye disorders as a part of their clinical manifestations. Additionally, several research studies have suggested hemodialysis as the main cause of some of the complicated eye disorders such as, increased IOP in patients with chronic renal failure (12).
“Red Eye”, with or without pain and irritation, is not an uncommon complication of renal failure (13). This symptom is thought to be triggered by chronic inflammation and metastatic calcification which is one of the most common complications of chronic renal failure (13-15). Several medical investigations have positively revealed the correlation between elevated calcium phosphate products and the development of band keratopathy (16-18).

A fraction of affected individuals can develop “red eye” in the absence of calcification due to chronic ocular irritation which can be caused by decreased lacrimation or blink reflex as well as chronic systemic inflammation (19,20). Prolonged exposure of the cornea and conjunctiva to these chronic ocular irritations can produce a reactive change mimicking those seen in common pinguecula (21).

Superior limbic kerto-conjunctivitis (SLK) is another kind of chronic ocular inflammation reported in some of the end-stage-renal disease (ESRD) patients undergoing hemodialysis which was first described by Bradley and Alexander (22) and later by Thygeson and Kimura (23). Common symptoms include burning, redness, gritty sensation and mucoid discharge associated with the conjunctival and corneal infiltration and inflammation (22-24). There is a case report describing endogenous endophthalmitis in a 57-year-old patient with ESRD (25).

Chronic renal failure has already been introduced as a risk factor for cataract (26). Two main theories suggested for cataractogenesis in CRF are: osmotic cataract—due to urea trapped in the lens—(27) and punctuate cataract—in the setting of hypocalcemic state, particularly in patients undergoing hemodialysis (28).

There are several case reports and research studies describing the possible correlations between the renal failure and a number of different retinal manifestations such as, retinal arteriolar calcification (29) and bullous exudative retinal detachment (30,31), as well as other ocular complications including optic neuropathy (32).

Eye and renal failure

Uremia refers to the complex and multi-organ clinical manifestations caused by accumulation of nitrogenous waste products due to renal failure (33). These waste products can be categorized into three main groups: 1. Urea and its subgroup known as the small water soluble compounds; 2. beta2-Macroglobulin and its subgroup known as the larger “middle molecules” compounds; 3. p-cresol and its subgroup known as protein bound compounds (34). Some of these uremic toxins can be exhaled through different mechanisms causing a fishy ammonia-like smell to the breath (35). This uremic feter is mainly attributable to the amines and more importantly, dimethylamine and trimethylamine (36). Increased level of some other gaseous compounds such as nitric oxide (37) and hydrogen peroxide (38) have also been traced in exhaled breath air of renal failure patients. All these volatile compounds have the potential ability to irritate the ocular surface and ultimately cause various ocular manifestations, especially the “red eye”.

Exhaled air analysis has attracted a great number of researchers as a challenging subject. The medical science has benefited from these studies in diverse aspects. However, experimental studies on the analysis of exhaled breath air, especially in uremic patients, are still lacking.

**Uremic breath and red eye, a new hypothesis**

Anchored in all the reviewed and above-stated studies, we hypothesize that ocular clinical manifestations and especially the “red eye” in renal failure may also be caused by eye exposure to the noxious volatile compounds existing in uremic breath. This hypothesis is also partially based on the idea derived from the theory presented by Hosseini et al (39), suggesting the noxious volatile compounds in exhaled breath air as the possible causes of the “red eye” in patients with H.pylori gastrointestinal infection.

Some of the volatile compounds in exhaled breath air of renal failure patients like, dimethylamine, trimethylamine, nitric oxide and hydrogen peroxide are able to affect the cornea and conjunctival epithelium by causing constant irritation and chronic reactive inflammatory response over an extended period of time. Particularly, this mechanism can be considered as an etiology of the “red eye” in the absence of ocular metastatic calcification.
According to several research studies, nitric oxide is thought to have the highest attribution to developing the “red eye” among all these gaseous compounds. Nitric oxide is an odorless and colorless gas and to some extent, it is soluble in water. This gas has been proved to affect the conjunctiva as a vasodilator (40). Research study conducted by Meijer et al (41) a guinea pig revealed the nitric oxide can play a significant role in stimulating and increasing the histamine-induced conjunctival vascular permeability. In addition, Astin et al’s (42) investigation on ocular hyperemia mediated by prostaglandin F2 alpha (PGF2 alpha) in the rabbit divulged that triggered synthesis of nitric oxide by PGF2 leads to ocular surface hyperemia.

With the purpose of attesting our hypothesis, we are proposing some possible methods:

1) Assessing and analyzing the exhaled breath air of renal failure patients divided into two groups according to the presence or absence of clinical or pathological ocular manifestations. The ultimate results can be utilized in a comparative study in order to disclose the correlation between the existence of noxious volatile compounds and the ocular complications.

2) Measuring the concentration of different exhaled noxious compounds in renal failure patients with the “red eye” and evaluating the characteristics of their ocular symptom to reveal the plausible attributions of these compounds to the occurrence and severity of the ocular manifestations.

3) Exposing the ocular surface of live subjects through an animal study to the breath air of uremic patients and assessing the possible ongoing and ultimate consequential ocular symptoms.

**Conclusion**

In this article we tried to raise a discussion about the possible pathophysiological factors causing the ocular complications in uremia. After a subtle review of all the available related research studies, we could not find any evidence indicating the correlation between exhaled noxious compounds in uremic breath and ocular manifestations.

The toxic effects of demethylamine, trimethylamine, nitric oxide and hydrogen peroxide on some live organ tissues have been revealed. These gaseous compounds have been detected in the exhaled breath air of uremic patients and most probably can affect ocular surface and trigger various ocular symptoms.

Further research and experimental studies are needed to discover the other possible implications of exhaled noxious compounds in diverse diseases and to open new chapters in diagnosis and treatment of ocular manifestations in renal failure.

**References**