



Prolactin and Prolactin-inducible protein (PIP) in the pathogenesis of primary acquired nasolacrimal duct obstruction (PANDO)

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ABSTRACT

Primary acquired nasolacrimal duct obstruction (PANDO) is a syndrome of unknown etiology, predominantly affecting post-menopausal females, characterized by progressive inflammation, fibrosis and subsequent obstruction of the nasolacrimal duct. Numerous factors have been proposed as possible etiologic factors and include anatomical configuration, ocular and nasal infections, peri-lacrimal vascular disorders, hormonal influence, lacrimal drainage lymphoid tissue, gastroesophageal reflux disease, topical medications, swimming pool exposure, smoking, genetic factors, autonomic and lysosomal dysregulation. The authors hypothesize Prolactin (PRL) and Prolactin-inducible protein (PIP) play a role in the etiopathogenesis of primary acquired nasolacrimal duct obstruction.

Introduction

Primary acquired nasolacrimal duct obstruction (PANDO) is a syndrome of unknown etiology, predominantly affecting post-menopausal females, characterized by progressive inflammation, fibrosis and subsequent obstruction of the nasolacrimal duct [1–3]. The resultant clinical manifestations include epiphora and discharge, occasional development of lacrimal sac mucocele or acute dacryocystitis [2]. Numerous factors have been proposed as possible etiologic factors and include anatomical configuration, ocular and nasal infections, peri-lacrimal vascular disorders, hormonal influence, lacrimal drainage lymphoid tissue, gastroesophageal reflux disease, topical medications, swimming pool exposure, smoking, genetic factors, autonomic and lysosomal dysregulation [1–7]. Prolactin receptors have been identified in the epithelia and submucosal glands of the lacrimal sac and nasolacrimal ducts [6]. They have been proposed as possible extra-pituitary sites of prolactin synthesis. Significant proportions of Prolactin-inducible protein (PIP) has been detected in lacrimal sac extracts [7].

Hypothesis. Prolactin and Prolactin-inducible protein play a role in the etiopathogenesis of primary acquired nasolacrimal duct obstruction.

Evaluation of hypothesis

Prolactin

Prolactin (PRL) is a pituitary hormone secreted by the lactotrophs and its main function is during pregnancy and lactation and contributes to the development of mammary glands, synthesis of milk and its maintenance [8]. However, PRL is known to be synthesized in extra-pituitary sites and has a significant immunomodulatory role. Cells of the immune system produce PRL, express PRL receptors (PRLR) and also respond to it, suggesting an autocrine or paracrine mechanism [6,9,10]. PRL acts as a cytokine and inhibits the negative selection of autoreactive B-lymphocytes. Conversely PRL stimulates the proliferation of lymphocytes and modulates thymic actions [9]. Apart from lymphocytes, PRLR have also been noted in macrophages and fibroblasts [10,11]. PRL can enhance or inhibit pro-inflammatory mechanisms in a specific manner and hence maintains a crucial pro and anti-inflammatory balance. Hence, it would not be surprising that PRL has been linked to numerous auto-immune disorders like rheumatoid and psoriatic arthritis [10,11]. In addition, PRL has demonstrated tropic action on lacrimal glands and regulates its secretion and protein content [12]. In animal experiments, PRL has been shown to restore the lacrimal gland cholinergic neurotransmitter receptors [13] and also augment the effects of testosterone [14].

Hormonal influence as a factor in PANDO was mainly proposed

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because of the female predilection and more so in the post-menopausal age. Ali et al [6] performed a qualitative hormonal profiling of the entire lacrimal drainage system in female and male subjects with PANDO and cadaveric controls. They studied expression of estrogen alpha (ER α), estrogen beta (ER β), aromatase (CYP19), testosterone (TSTR), progesterone (PGR), oxytocin (OXTR), prolactin (PRL), and somatostatins 1 to 5. They found that PRL receptors expression to be prominent in the lacrimal sac and NLD epithelia and also the sub-mucosal glands but the canalicular epithelium showed minimal expression. Interestingly, this expression was less prominent in normal post-menopausal females as compared to normal males of comparable age. The diseased samples of PANDO showed reduced expression in the epithelia and absence in the submucosal glands. This possibly gives an indirect evidence that reduced expression of PRL may predispose the nasolacrimal duct obstruction. The hypothesis can thus be that reduced PRL may hamper the physiological functions of the lacrimal epithelia and its submucosal glands, disturbs the cholinergic interactions, and facilitates an imbalance of the pro and anti-inflammatory modulatory effects. The possibility of local hormonal microenvironments in the lacrimal drainage, independent of the systemic levels have been hypothesized earlier [6]. Since all these may be local effects, it can lead to regional inflammation and such recurrent attacks may predispose the nasolacrimal ducts to an obstruction and subsequent clinical syndrome of PANDO.

Prolactin-inducible protein (PIP)

Prolactin-inducible protein is a single polypeptide chain expressed in salivary, sweat and lacrimal glands [15]. PIP is upregulated by Prolactin and androgens. It has versatile functions in reproductive and immune systems [16]. PIP is also overexpressed in malignancies and is being investigated as a potential biomarker for tumor detection and progression [15,16]. Interestingly, it is also being considered as a good biomarker for the corneal disease, keratoconus [17] and has also been hypothesized in the pathogenesis of dacryoliths [18]. It can bind to many bacterial species and inhibit their proliferation. It can also bind to CD4 cells, Fc portion of immunoglobulin G and zinc alpha-2 glycoprotein [7]. Its abundance in mucosal tissues suggests a role in mucosal immunity [15]. Immune dysfunctions have been demonstrated in PIP knock-out mice. Lacrimal drainage system (LDS) has a large mucosal surface and hence the presence of PIP is not surprising. It is possible that PIP in part protects the LDS from continuous onslaught of bacteria from ocular surface and also mediates local immune responses. Disorders in PIP synthesis and regulation can be intricately associated with PRL and can potentially predispose the LDS to infections and inflammations. These may in turn make the narrow and vulnerable NLD to repeated attacks, healing by fibrosis and subsequent obstructions and clinical syndrome of PANDO.

Current challenges and consequences of the hypothesis

Linking prolactin and PIP to PANDO would need extensive targeted investigations. It is yet to conclusively demonstrate local synthesis of PRL and PIP and whether the source is the LDS cells themselves or immune cells, as has been demonstrated in autoimmune diseases. Site-specific molecular interactions of PRL and PIP in NLD is to be ascertained. Animal experiments of the LDS involving PIP knock out mice would give insights into clinical pathophysiology. It is important to remember that hormonal influences are at most grossly involving the NLD and not lacrimal sac. Is this because of narrower dimensions of NLD or are the lacrimal sac effects being missed is yet to be deciphered. The lead of PRL and PIP in etiopathogenesis of PANDO is promising but may only partly explain the causative mechanisms involved unless all the interacting molecular pathways are deciphered. The discovery of molecular mechanisms in PANDO will have a massive impact on the way we treat them. It would not be audacious for us to believe that

PANDO would one day have a medical treatment and there may even be preventive strategies in the future.

Conclusion

The presence of Prolactin receptors in the LDS and isolation of PIP from lacrimal extracts opens up exciting avenues to explore the pathogenesis of PANDO.

Conflict of interest statement

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.02.051>.

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