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Rosacea: A Potential Risk for Parkinson's Disease Development

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Abstract

Rosacea and Parkinson's disease (PD) are two completely different pathologies, with different outcomes, that share a common interesting feature as their proposed originating factor. Both conditions show inflammation as a predominant aspect of their pathogenesis, having an important role in the excessive breakdown of connective tissue components. Metalloproteinases (MMPs) and Toll-like receptors (TLRs) are present in the skin and brain in physiological conditions, but can be significantly up regulated due to the disruption of normal signaling pathways, promoting an inflammatory cascade that results in the development of sustained inflammation. Recent evidence supports a link between these pathologies by showing an increased incidence of PD in patients with rosacea and a younger age at PD onset in these individuals, when compared to the reference population. In addition,tetracycline's anti-inflammatory properties shown in rosacea have been demonstrated in mouse models of neurodegenerative diseases like PD. Data from a Danish cohort study suggesting that the lack of rosacea disease severity-dependent association with the risk of PD is possibly due to the inhibition of the disease-severity effect by the treatment of moderate to severe rosacea with tetracycline may support this finding.

Keywords

Rosacea, Parkinson's disease, Matrix-metalloproteinases, Tetracyclines, Inflammation

Abbreviations

PD: Parkinson's disease; MMPs: Matrix-metalloproteinases; TLRs: Toll-like receptors

Introduction

Rosacea is a common, but often overlooked, benign chronic cutaneous disease of uncertain etiology that presents with many different clinical manifestations. Exact incidence data of rosacea are lacking because of difficulty in defining when the disease begins [1,2]. This condition is most frequently observed in fair-skinned individuals (skin phototypes I and II) of Celtic and Northern European origin. Adults over the age of 30 are the primary age group affected by rosacea, and the disorder occurs more frequently in women than in men (with the exception of phymatous rosacea where a vast majority of affected patients are adult males) [3-5].

The broad spectrum of rosacea includes a constellation of clinical symptoms and signs. These consist of facial flushing, the appearance of telangiectatic vessels and persistent redness of the face, eruption of inflammatory papules and pustules on the central facial convexities, and hypertrophy of the sebaceous glands of the nose with fibrosis (rhinophyma). Ocular changes are present in more than 50 percent of patients and range from mild dryness and irritation with blepharitis and conjunctivitis (common symptoms) to sight-threatening keratitis (rare) [6]. In 2002, the National Rosacea Society Expert Committee described based on distinct clinical patterns 4 rosacea subtypes: Erythematotelangiectatic (subtype I), papulopustular (subtype II), phymatous (subtype III), and ocular rosacea (subtype IV) [7].

A relatively high rate of rosacea (18.8%) was found among individuals with PD in 2001 by Fischer et al, while investigating the cutaneous manifestations of the disease [8]. Parkinson's disease is associated with numerous non-motor symptoms, some of which precede the motor dysfunction by more than a decade [9]. Among the cutaneous manifestations of PD, hyperhidrosis, facial flushing, seborrhea and seborrheic dermatitis are well recognized, the first two being considered manifestations of autonomic dysregulation in the skin. In a recent retrospective study, Tanner et al confirmed that seborrheic dermatitis was associated with an increased risk of PD. Fischer et al, noted an obvious symptomatic overlap between facial flushing that might occur in PD due to dysautonomia and facial flushing experienced by individuals with rosacea. They found that seborrhea is rare in treated patients with PD but that hyperhidrosis is common. Another study showed that hyperhidrosis and seborrhea progressed more than other non-motor symptoms after a new diagnosis of PD, despite often being overlooked in reviews [8,10]. In a nationwide cohort study of the Danish population, Egeberg *et al.* also observed a significantly increased risk of new-onset Parkinson disease in patients with rosacea. The incidence rates of Parkinson disease per 10,000 person-years were 3.54 (95% CI, 3.49-3.59) and 7.62 (95% CI, 6.78-8.57) in the reference population and in patients with rosacea, respectively. Of the 22,387 individuals who received a diagnosis of Parkinson disease during the study period, 43.8% were women, and 68,053 individuals (67.2% women) were registered as having rosacea years. Another important finding was a younger age at PD onset in these individuals, compared to the reference population. PD occurred approximately 2.4 years earlier in patients with rosacea (mean [SD] age, 73.7 [10.3] years) compared with the reference population (76.1 [10.2] years) ($P < 0.001$ for the difference). Among the rosacea subtypes, ocular rosacea showed a tendency toward an

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increased risk of PD (adjusted IRR, 2.03 [95% CI, 1.67-2.48]) [11].

The aim of this article is to briefly review the connection that could exist behind this potential risk, and how this could impact the future treatment of PD.

Pathogenesis

The exact pathogenesis of rosacea remains unclear. It is known that there may be a genetic component to the disorder. One of the proposed contributing factors is the dysregulation of the innate immune system, triggering the innate immune system leads to controlled increases in cytokines and antimicrobial peptides (AMPs) in the skin. These normal signaling pathways seem to be disrupted in patients with rosacea, which leads to an inflammatory response [7].

Well-characterized skin AMPs like Cathelicidin and LL-37 are activated by stratum corneum trypsin-like serine proteinases (TLSPs) of the kallikrein related peptidase family (KLK5)[12-14]. Activation entails either autoactivation and/or activation by other KLKs in a cascade-like manner, or removal of the profragment by enzymes such as Matrix metalloproteinases (MMPs) or other endopeptidases [15-17]. The expression of several MMPs, including MMP-2 and MMP-9, are increased in the skin of patients with rosacea [7].

Controlled breakdown of ECM (Extra cellular matrix) by MMPs plays an important role in detachment and migration of cells, as well as in tissue remodeling in several physiological situations. On the other hand, MMPs play a pathogenetic role in excessive breakdown of connective tissue components. MMPs are not constitutively expressed in the skin but are induced temporarily in response to exogenous signals, such as various cytokines or growth factors, cell-matrix interactions and altered cell-cell contacts [18,19].

Other common triggers for rosacea exacerbations include inflammatory reactions to cutaneous microorganisms, such as demodex folliculorum, ultraviolet (UV) light radiation, temperature changes, spicy food and alcohol (vascular hyperreactivity) [7].

Inflammation is a common feature shared by rosacea and PD in their proposed originating factors. Neuroinflammation is a predominant aspect of neurodegenerative diseases, manifested by glia activation and expression of pro-inflammatory mediators. Studies on animal models of PD suggest that sustained neuroinflammation exacerbates degeneration of the dopaminergic (DA) nigro-striatal pathway (substantia nigra pars compacta) [20].

In a similar way to the skin MMPs (MMP-2 and MMP-9) are expressed in the brain in physiological conditions, but can be significantly up-regulated in several brain pathologies. Data suggest that MMP-3 and MMP-9 released by injured neurons favors glia activation; glial cells in turn reinforce their reactive state via autocrine MMP release, contributing to nigro-striatal pathway degeneration [20]. MPTP mouse models of PD have shown that MMP-3 participates in the impairment of BBB integrity and T-leukocyte infiltration into the SN [21].

Some evidence could link Toll-like receptors (TLRs) modulations to both rosacea and human PD. TLRs typically identify and bind pathogen-associated molecular patterns (PAMPs) such as bacterial and viral derived carbohydrates, nucleic acids and lipoproteins. Increased levels of TLR2, which play a role in recognizing PAMPs, have also been found in lesional skin of patients with rosacea. Activation of TLR2 on keratinocytes leads to higher expression and activity levels of KLK5, leading to increased expression of LL-37 and its fragments [7]. Engagement of microglia with foreign substances results in activation mediated by TLRs [22]. More recently sterile non-pathogen related forms of inflammation in which endogenous disease-related signals (damage-associated molecular patterns; DAMPs) drive microglial activation have also been associated with TLRs [23]. Studies have recently shown that extracellular α-synuclein (α-syn) may act as a DAMP for microglia, increasing the expression of TLR1, TLR2, TLR3, TLR4 and TLR7, MyD88, MMP-9,TNF-α and IL-1β [24]. When a proinflammatory pathway is activated, microglia contributes to oxidative stress in the microenvironment through release of cytokines and reactive oxygen species that can adversely impact adjacent neurons [25].

Peripheral immunological challenges and chronic inflammatory diseases influence the pathogenesis and progression of PD. The communication between the immune and the nervous system is very fluid, cytokines being the main mediators of inflammation in both brain and periphery [26]. In vivo studies have demonstrated that the serum and cerebrospinal fluid of PD patients have higher levels of IL-1β, TNF-α, and IL-2 and also CD4+ and CD8+ T lymphocytes, indicating peripheral activation of lymphocytes [27-31]. Several studies support a role for the adaptive immune system in PD etiology and progression. The presence of cytotoxic T lymphocyte (CD4+ and CD8+) has been described to infiltrate the substantia nigraof patients and animal PD models [32-34]. In resemblance to MMPs, the influx of these peripheral cells into the brain parenchyma could indicate a BBB dysfunction in PD patients [35,36]. In this way the adaptive immune system might modulate microglia activation in PD pathogenesis [37].

Neurodegenerative disorders seem to share a common pathway with the presence of misfolded proteins in the central nervous system. Clinically, PD can often be difficult to distinguish particularly early in the course of the disease when potential disease modifying agents may be more likely to be effective. A wide distribution outside the CNS is reported for α-syn. The clinical manifestations of PD have been associated with the distribution of the α-syn and tau pathology as well as the time of evolution. Rodríquez-Leyva *et al.*, found the presence of both α-syn and p-tau in the skin of PD patients. In contrast to previous reports that looked for α-syn expression in nervous peripheral terminals from somatic or autonomic fibers in the skin of PD patients, they found it not only in the nervous tissue, but also in the keratinocytes of the epidermis [38].

A Link between Treatment Strategies

The use of tetracyclines for the treatment of rosacea has been a common practice for more than a decade owing to its non-antibiotic actions [39,40]. Recent hypothesis attributed this feature to its capacity to ameliorate the inflammatory response through normalization of cathelicidin processing [41]. Tetracyclines have been shown to inhibit white cell movement during inflammation, lymphocytic proliferation and arachidonic acid production from cell membrane components [42-48]. Proteolysis inhibition mediated by MMPs which are secreted by activated neutrophils plays an important role on its anti- inflammatory effect [49,50]. Inhibition of MMP-2 and MMP-9, which break down the basement membrane of the capillary vessels, promotes integrity of the capillary wall, reduces sensitivity to vasodilatory stimuli, prevents capillary leakage, improves the integrity of connective tissue, and downregulates cytokines (e.g., TNF-α and IL-1β) that assist in erythema and inflammation associated with rosacea [51,52]. Tetracyclines have also been shown to impair angiogenesis by the inhibition of MMPs and may accelerate nitric oxide (NO) synthase degradation, which may prove beneficial in rosacea, as excess NO promotes vasodilation and inhibition of extracellular matrix synthesis [53,54]. Tetracyclines can affect molecular signaling pathways, resulting in decreased transcriptional activity for several MMPs, which can reduce the MMP-mediated extracellular matrix breakdown [55-57]. Doxycycline, a semi synthetic second-generation tetracycline, exhibits superior pharmacokinetic properties and lesser toxicity than first-generation tetracyclines[58]. They also possess antiangiogenic and anti-inflammatory properties that make it a promising therapeutic option in the treatment of rosacea.

Similar results have been observed in the use of Tetracyclines in in vitro and in vivo models of neurodegenerative diseases, such as PD, where neuroprotective abilities are conferred by suppressing matrix MMPs induction via both anti-apoptotic and anti-inflammatory mechanism [59]. Since PD etiology and pathogenesis remain unclear, levodopa replacement serves as the main therapy. However, it cannot prevent the progression of dopamine (DA) neuron degeneration [60]. Doxycycline high lipid solubility results in good brain penetration

and its protective effect has been demonstrated in different models of brain injury. In addition to MMP suppression it has been suggested that doxycycline might provide neuroprotection for PD by promoting the decrease of microglial activation, depression of oxygen radical release from polymorphonuclear neutrophils, inhibition of nitric oxide synthase and reduction of cleaved caspase-3 protein and proinflammatory cytokines (TNF-α and IL-1β) expression [59,61]. It has also been described a significant reduction in the expression of MHC II after the use of doxycycline, suggesting that doxycycline can play a neuroprotective role in down regulating the microglia MHC II [60]. Recent animal models of PD, like the lipopolysaccharide-PD or the 6-hydroxydopamine (6-OHDA) model, have demonstrated that doxycycline prevented dopaminergic neuron death by its anti-inflammatory and immunomodulatory properties.

Egeberg *et al.*, found no rosacea disease severity-dependent association with the risk of Parkinson disease when moderate to severe rosacea was defined by initiation of treatment with tetracycline. To explain this result, the authors hypothesized that a disease-severity effect might be blunted by the treatment of moderate to severe rosacea with tetracycline [11].

Discussion

Gender is an established risk factor for the development of PD, with the male-to-female ratio being approximately 3:2. Studies have found that TLR gene polymorphisms in females can make them less susceptible to PD. This finding can also reveal that the pathogenesis of male and female PD might be different; females are less likely to develop PD and there is evidence that estrogen in the female could help to reduce the dysfunction of dopaminergic neurons in PD patients [62]. Egeberg *et al.*, found that a considerable percentage of women were diagnosed with PD (43.8%) [11]. The potential risk for PD development in patients with rosacea could impact this male-to-female ratio, since rosacea occurs more frequently in women.

The increased risk of PD in patients with ocular rosacea described by Egeberg *et al.*, was proposed due to the high proportion of patients who had received prescriptions of hypromellose eye drops, which are used for ocular rosacea [11]. To this date it is not clear the exact pathogenesis of rosacea and whether the mechanisms of action are the same for all the types of rosacea. This finding should be considered as a result of the available data, and further investigation should be done in order to determine whether there is an association of PD with ocular problems.

Recent studies on MMPs showing the role that these enzymes could play in the shift of a beneficial response into a pathological chronic state in these two conditions support the need for further investigation for a better understanding of how the unbalance of the delicate equilibrium between activation and inhibition results in the expression of the disease. Re-establishment of this equilibrium could be a therapeutic strategy aimed at modulating inflammation. Although specific MMP inhibitors have been developed, indiscriminate block of this enzymatic activity is a dangerous ground, since MMPs play different roles depending on the type of pathology and time of activation. Therefore it would be important to define the perfect timing at which beneficial effects can revert into detrimental, complicating the efforts of treatment with MMP inhibitors.

The implication of TLRs in the development of disease in rosacea and PD described to date could help to clarify the pathogenesis of these two conditions. Similarly to MMPs, TLRs play a role in acute inflammation which can be protective, but prolonged inflammation cause progressive toxicity and cellular damage. Further studies are warranted to investigate the temporal expression of these receptors in leukocytes and the contribution that this has to pathology, which in turn could lead to the discovery of biomarkers as well as the development of anti-inflammatory therapeutic strategies specific for these receptors.

Data from Rodríquez-Leyva *et al.* study suggest that we may be able to study the pathophysiology of neurodegenerative diseases through an analysis of skin [38]. These results add to previous findings suggesting that the skin reflects clinically suspected brain pathology. Immunohistochemical analysis of α-syn and p-tau in the skin could be used to distinguish PD, though not as a unique and reliable peripheral biomarker in clinical routine. Further, because of the ease of obtaining 4 mm punch biopsies, these techniques could be added to the analysis of α-syn in body fluids and peripheral tissues as a potential biomarker for PD.

The particular ability of Tetracyclines to reduce the inflammatory response, believed to be the cause for its effectiveness in the treatment of rosacea, and the results from recent studies demonstrating a hypothetical "protective effect" by reducing the risk of PD in patients with rosacea undergoing treatment with tetracycline could become a major field of investigation with the aim of unifying grounds on the causative and/or aggravating elements underlying these pathologies. The potential clinical utility of the neuroprotective effects of Tetracyclines is still a matter of debate, results from recent studies have been disappointing, indicating only moderate neuroprotective effects at best, which have also been associated with significant side effects in some instances. The discussion surrounding the therapeutic efficacy of minocycline in animal and cell models of other neurodegenerative diseases, as well as in patients, has met with significant disagreement [63,64]. Further studies are strongly needed to establish the most appropriate timing and dosage, as well as the indications for which Tetracyclines could be effective and safe. While there are limitations in the translation of results from rodents to humans, these findings nevertheless hold the prospect that the readily available, inexpensive and in terms of risk, safe drug doxycycline, could be used for the treatment of PD [41].

Conclusion

There is a potential link between rosacea and PD. Emerging findings from the basic pathogenesis of both diseases and data suggesting that the skin reflects clinically suspected brain pathology, makes us believe that rosacea could be a new biomarker of PD. This is an area that needs additional research. Although Tetracyclines may be promising in the treatment for PD, targeted highly specific therapies could lead to additional treatment strategies that could change the course of PD.

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