



MYTH OR SCIENCE: HOLIDAY ON PRESCRIPTION

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Insight

After living through the COVID-19 pandemic, we are all done with pandemics for the time being. However, a new pandemic might already be presenting itself – namely Parkinson's Disease. Although it is not an infectious disease that spreads as rapidly as COVID-19, the incidence of Parkinson's disease has been increasing exponentially in the past few years. The Radboud University Medical Center has a clinical expert centre aimed at treating Parkinson's disease and is on the frontiers of research in this field. Currently, no curative treatment is available, although the disease can be treated symptomatically with medication, and in some patients, surgery. One of the emerging theories is that stress worsens the symptoms of Parkinson's, which could mean that reduction of stress could improve the treatment of Parkinson's. But is this indeed true? Should

Parkinson's disease (PD) was firstly described in 1817 by British surgeon James Parkinson. Initially it was described as paralysis agitans; later, it was dubbed PD after James Parkinson[1]. James Parkinson described six patients presenting with PD's three main symptoms: bradykinesia, a resting tremor, and rigidity[2]. Bradykinesia refers to slowing and decreasing of repetitive movements, e.g. finger tapping. This can usually be seen clearly while testing coordination and movement during a neurological examination. Nonetheless, a variety of nonmotor symptoms occur as well, including autonomic dysfunction, mood disorders, and dementia[2].

PD is now known to be caused (amongst others) by a lack of dopamine in the basal ganglia[3]. The basal ganglia consist of multiple brain regions. One of those is the substantia nigra, which produces dopamine and is therefore important in PD[3]. Treatment of PD consists of the supplementation of dopamine, but the effect of levodopa can diminish with time[4]. In these patients or patients with severe symptoms, deep brain stimulation can be an option. It is important to know that both pharmacological and surgical treatment improve the motor symptoms, but do not affect the non-motor symptoms, i.e. depression, autonomic dysfunction, and dementia[4,5]. Recent studies suggest that stress can lead to an exacerbation of PD symptoms, which provides a possible new cornerstone to the treatment of PD. Could stress reduction strategies therefore help to improve the treatment of PD?

We have all experienced times of stress, whether it be to a smaller or bigger extent. Although most of us will not remember stressful times as particularly happy times, stress does have a function. Acute stress leads to the release of adrenaline, which stimulates the sympathetic nervous system[6]. The sympathetic nervous system regulates the 'fight or flight response'. Stimulation of the sympathetic nervous system leads to e.g. dilating of the pupils, increased heart rate, dilation of the bronchia, sweating, and inhibition of the gastro-intestinal system. This is particularly useful when you are being chased by a tiger, or, perhaps more realistically for most of us, trying to catch the train or aiming to finish a paper hours before the deadline. Furthermore, stress leads to an increase in the hypothalamic-pituitary-adrenal axis, which stimulates the secretion of glucocorticoids (cortisol) in the adrenal glands[7]. The secretion of cortisol leads to an increase in serum glucose, amongst others. This pathway is in essence regulated tightly, meaning that the increase in cortisol should be temporarily. However, in some cases, the stress may be chronic, resulting in a chronic increase in cortisol[7].

Multiple signs indicate that stress plays a role in PD. Firstly, psychological symptoms occur in a large number of patients with PD: 30-40% of patients develop depression, compared to 19.3% in the general population in the Netherlands[8,9]. 25-30% of patients struggle with anxiety, while 12.4% of adults in the Netherlands experienced an anxiety disorder in the past year[10]. This suggests that patients with PD are at least more susceptible to stress. Furthermore, stress can worsen motor symptoms, e.g. the resting tremor, and the response to medication can temporarily decrease in stressful times[9]. One study also showed that cortisone levels (an inactive form of cortisol) were increased in PD-patients, which suggests that the hypothalamic-pituitary-adrenal axis is upregulated in patients with PD[11]. This indicates that PD patients experience chronic stress.

Multiple theories exist that might explain the effect of stress in patients with PD. Van der Heide et al. provide a theoretical framework with three possible pathways[9]. Firstly, elevated glucocorticoids could lower the secretion of brain derived neurotrophic peptide, which could lead to hippocampal and prefrontal cortex atrophy and amygdala growth[9]. The amygdala is said to be our 'primitive' brain, responsible for emotional responses, whereas the prefrontal cortex is responsible for our cognitions, which allow us to take a step back and relativise[12]. You might therefore be able to imagine that it becomes more difficult to cope with stress if the amygdala takes the upper hand. This could explain the high prevalence of depression and anxiety amongst patients with PD. Secondly, increased glucocorticoid levels promote the secretion of pro-inflammatory cytokines, which could damage dopamine-producing cells in the substantia nigra, promoting the progression of the disease in this way[9]. Thirdly, the symptoms of PD manifest when more than fifty per cent of dopaminergic cells are lost[9]. This means that the loss of the first fifty per cent of dopaminergic cells must somehow be compensated within the brain, which is thought to occur in the striatal dopamine system. Stress might compromise this system, and thus lead to earlier clinical manifestation of PD.

But why is this so important? Although there is medication available that manages the motor symptoms of PD, the disease still carries a high amount of morbidity and decreases the quality of life of patients severely[3]. Its prevalence continues to increase rapidly - from 2.5 million people affected in 1990 to 6.1 million patients worldwide in 2016[13]. This number is even expected to increase further to 12 million patients worldwide in 2040[13]. Optimisation of the existing

treatment with stress-interventions, e.g. mindfulness, in addition to pharmacological or surgical treatments, could therefore potentially help a large number of patients.

Stress-management strategies, such as mindfulness, could therefore be implemented more widely in the future. However, their exact clinical effect on PD patients has not been fully elucidated yet. Nonetheless, could it be harmful to discuss the role of stress factors with your patients? Regardless of its clinical effect on PD, stress will not contribute to the patient's happiness.

Acknowledgements

RAMS would like to thank Rick Helmich, MD, PhD, neurologist at Radboud University Medical Center and associate professor, for providing the author of this author with feedback. Additionally, RAMS would like to thank Robbin Klamer, for proofreading and reviewing this article.

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