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Review

The Relationship between Rem Sleep Behaviour Disorder and Parkinson's Disease Revisited – Are They One and the Same?

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Abstract

This paper reviews the relationship between RBD and PD and the pathophysiology. Most RBD patients develop PD within 14 years. PD pathophysiology is α-synucleinopathy with dopamine degeneration in nigrostriatal pathways. RBD pathology is poorly understood. Anomalies suggest RBD and PD are different, evidenced by smoking. RBD and PD are associated with glucocerebrosidase gene mutations (GBA gene), suggesting RDB with GBA gene mutation predicts PD. PET imaging, assessing vesicular monoamine transporter 2 (VMAT2), indexing nigrostriatal dopamine innervation, is lower in PD and RBD, in the putamen, ventral striatum and globus pallidus but not substantia nigra or subthalamus, compared with controls. VMAT2 may not contribute to pathophysiology of RBD in PD. Treatments for RBD and PD differ. PD with RBD had more depression, compared to PD without RBD. Only PD with RBD had statistically significant increased depression, compared with controls, and non-significant lowered cognition. PD patients, with and without RBD, had decreased ligand binding, compared to healthy controls, indicating no difference in VMAT2 within the caudate and

putamen. Research showed differences in cholinergic levels, noradrenaline and glucose metabolism for PD with and without RBD. RBD with PD, is multi-systematic, affecting regions beyond dopaminergic pathways. Treatment of RBD does not affects PD neurodegeneration. Researchers continue to search for neuro-protective intervention. There is a relationship between PD and RBD but it is not absolute. PD nigrostriatal degeneration is independent of RBD. Pathophysiological differences may explain why treatment of RBD does not alter its natural history.

Keywords
REM sleep disorder; Parkinson's disease; treatment; imaging; relationship; interaction; prodrome

1. Introduction

Parkinson's disease (PD), especially idiopathic PD, is said to have a prevalence of 1-2/1000 of the population, at any time, with the figure rising to ~1% of the population in the 60 plus age group [1]. During the life of the patient, the diagnosis of PD is determined by a clinical syndrome comprising at least 2 of 4 characteristics, namely bradykinesia, rigidity, tremor and gait instability [2, 3], although a revision of the diagnostic criteria has suggested that postural instability is no longer considered part of the diagnostic considerations [1] and there have been added supportive criteria, absolute exclusion criteria and red flags [1]. In either case, the definitive diagnosis remains a post-mortem diagnosis, based on neuropathological findings of α-synuclein-containing Lewy bodies and loss of dopaminergic neurons in the substantia nigra, following which many of the pre/ante-mortem diagnoses of PD have been brought into question [1].

Rapid eye movement (REM) sleep behaviour disorder (RBD) has been reported to have a prevalence of ~1% in the middle-to-older age group [4], similar to the prevalence of PD. While there is an unequivocal relationship between RBD and PD [5, 6] there is also an association between RBD and medications, such as antidepressants and antipsychotic agents [1]. RBD represents a parasomnia which is characterised by the acting out of dreams with a loss of the atonia that normally accompanies REM sleep [5, 7]. The American Academy of Sleep Medicine has created diagnostic criteria for the diagnosis of RBD, based on REM sleep without atonia being demonstrated on polysomnography (PSG) [8, 9]. Patients with RBD may present following self-injurious behaviour or having injured their bed-partners, without recollection of having done so or any memory of what took place [5, 6]. RBD patients are at risk of developing one of the neurodegenerative α-synucleinopathy diseases with >70% developing parkinsonism or PD or dementia within 12 years of their diagnosis [5]. It is argued that patients with RBD may develop accelerated disease progression of PD with more severe phenotype, than is the case for patients with α-synucleinopathy who do not have RBD [5].

The paper to follow will review the relationship between RBD and PD, trying to develop an understanding of how the two conditions interrelate and whether they are just expressions of a mutual pathology in which one is the prodrome for the other or if they have different underlying

pathophysiology and the exact relationship, that exists between the two, remains somewhat unclear.

2. The Relationship between PD and RBD

It is said that of those patients who present with RBD, a third will develop PD within 5 years of the diagnosis of RBD [10]. This figure may rise to as much as >90% after a period of 14 years, following the diagnosis of RBD [10] raising serious concern that RBD has an important role in the pathogenesis of PD or at least is a predictor of developing PD [10]. RBD is identified as being present in as much as half the PD population.

At the time of diagnosis of PD, it has long been accepted that post-mortem findings indicate confirmation of the presence of advanced degeneration, within the nigrostriatal dopaminergic system, with an estimated loss of between 50-70% of the dopaminergic terminal loss within the putamen [11].

The pathophysiology of RBD is less well understood but the hypothesis is that inhibitory projection from the pontine sublaterodorsal nucleus to the spinal cord degenerates which results in withdrawal of the normal paralysis of skeletal muscles that occurs during REM sleep [7]. RBD does not always precede PD and may occur at the onset of the PD or the diagnosis of PD may pre-empt the diagnosis of RBD [12]. There has been conflicting evidence of the relationship between RBD and PD progression with a considerable number claiming that there was enhanced progression if both co-existed [6, 13-15] and there being evidence which refutes this phenomenon [16].

There are some fascinating anomalies which suggest that RBD and PD lack the common link which some might suggest. The first of these is the relationship to smoking. RBD is said to be more common in those who are, or were, smokers [4, 17] while smoking appears to have a protective effect on the evolution of PD [18].

RBD is associated with mutations in the gene encoding for the lysosomal enzyme glucocerebrosidase (GBA gene). There is also an association between mutations of the GBA gene and PD [19]. This common association suggests that a patient who has both RDB and GBA gene mutation has a much greater predictive risk of developing PD and the combination of both RBD and the GBA gene mutation may offer significant predictive value for anticipating the development of PD [20].

RBD is recognised to have a prodromal association with both PD and PD plus (namely dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA)) with the vast majority having an α-synucleinopathy [21]. There is a strong association between RBD and neurodegenerative disease, especially PD, in which the first manifestations of PD may be the RBD, necessitating careful follow-up of any patients presenting with RBD [22]. What is unclear is if those with RBD and PD have greater affected denervation of striatal dopamine when compared with PD patients who do not exhibit RBD [23].

Valli et al [23] explored this issue of denervation of striatal dopamine, looking at the availability of vesicular monoamine transporter 2 (VMAT2), which provides an index of nigrostriatal dopamine innervation, is lower in those with combination of PD and RBD than it is with healthy controls, within the putamen, ventral striatum and globus pallidus but not within the substantia nigra or subthalamus [23]. When compared with those who had PD without RBD, VMAT2 and striatal dopamine denervation, in general, may not be a significant contributor to the pathophysiology of

RBD in PD patients [23]. The treatment of RBD and PD are quite different (such as Clonazepam or Melatonin for RBD [24] compared with levodopa, MAO A&B inhibitors, dopamine agonists, entacapone and device assisted treatments for PD [25, 26] respectively).

As reported by Valli and colleagues [23] and supported by others [10, 27, 28], neuroimaging studies report consistent striatal dopamine transporter (DAT) depletion in 20–40% of PSG confirmed idiopathic RBD patients (without PD), relative to healthy controls, particularly within the putamen. The decline of striatal DAT has been demonstrated from healthy controls to sub-clinical RBD (REM sleep without atonia on PSG, but without abnormal nocturnal behaviours) to manifest RBD to PD [29, 30]. This pattern of decreased striatal DAT also is found in patients with PD and probable RBD where they show greater DAT depletion in the caudate and putamen, compared to PD patients who do not have probable RBD [31, 32]. It follows that DAT imaging may contribute a role in detecting RBD and in those who have PD with probable RBD.

Continuing the message from Valli et al [23] and others [33, 34], VMAT2 is an integral membrane protein responsible for moving monoamine neurotransmitters, including dopamine, from the cytosol to the synaptic vesicles [33]. VMAT2 is sensitive to changes in vesicular dopamine concentration [34] and it is argued that quantifying VMAT2 levels allows a more accurate measurement of the dopaminergic terminal integrity when compared to measuring DAT levels [35].

Valli et al [23] used PET imaging in PD patients with, and without, probable RBD as compared with age-matched healthy controls. They, hypothesized that PD with probable RBD would have greater dopamine denervation, with decreased VMAT2 availability, in striatal regions (including the caudate, putamen, and ventral striatum) relative to PD without probable RBD and healthy controls, consistent with reductions of the DAT reported in the striatal regions of PD patients with probable RBD [23]. In addition to severity of PD, they also looked at measures of depression and cognition, comparing the 3 groups, and found that patients with PD and probable RBD had higher depression scores, as compared to PD patients without RBD, but only the combined group of PD and RBD had statistically significant evidence of elevated levels of depression, compared to healthy controls ($p = 0.03$) and non-statistically significant lowered measures of cognition [23]. Both groups of PD patients, with and without RBD, had decreased ligand binder, compared to healthy controls, indicating that the lower VMAT2 availability was PD dependant rather than related to RBD [23]. This supported earlier findings, by Kotagal et al [36], who used the same ligand, looking at PD patients with and without RBD, and found no difference in VMAT2 levels within the caudate and putamen.

Katagal and colleagues [36] did show a difference in cholinergic levels, when comparing PD patients with and without RBD. Using a different ligand, Sommeraurer et al showed a difference between PD patients with and without RBD for noradrenaline levels [37] while Arnaldi and colleagues [31] showed a difference between the groups for glucose metabolic activity. This suggests that RBD pathophysiology in patients with PD is multi-systematic impacting on brain regions beyond being restricted to the dopaminergic pathways. These combined findings suggest that VMAT2 and general striatal dopamine denervation may not be a significant contributor to the pathophysiology of RBD in patients with PD. As suggested by Valli, following their sophisticated PET studies, there needs to be more research to better define the contributing factors in the neural chemistry mechanisms which underpin the association of RBD in patients with PD and the evolution of the two conditions [23].

There is no convincing evidence that symptomatic treatment of RBD affects the neurodegenerative outcomes and hence the development of PD [38] and any hypothesis that RBD

itself accelerates neurodegeneration, maybe via interruption of normal sleep patterns, lacks sufficient supportive evidence [38]. While depression and anxiety are said to be predictive of PD, in population studies, evidence questions whether the expression, of either anxiety or depression, has any effect on the rate of conversion to PD, in patients with anxiety and/or depression and RBD [39]. Acknowledging the high conversion rate, from isolated RBD to a diagnosis of one of the α-synucleinopathies, be it PD, DLB or MSA [5], the lack of cause and effect, regarding progression of nigrostriatal degeneration regarding PD, with or without RBD, is still something for which there remains significant debate. Researchers are still searching for a possible intervention for patients with RBD, to alter the natural history of PD, in those patients with RBD but at this stage the evidence is sparce [40, 41]. There is no debate that the concurrence of the two conditions, namely RBD and PD, has a negative impact on the quality of life for the patient, especially in the non-motor effects attributed to PD [42] but, at this stage, any form of intervention is basically designed for symptomatic relief rather than benefiting the long-term outcome and prognosis.

Thus far in this discussion, there has been an emphasis on the differences between RBD and PD but there is a body of opinion that seeks to identify biomarkers that may predict the conversion from RBD to one of the α-synucleinopathies [43, 44]. The argument being proffered is that the identification of such biomarkers, which may define disease progression, would "*monitor treatment response once disease-modifying therapies become available*" [43]. It was further argued that identifying of biomarkers could provide an indication of disease subtype and predict which form of α-synucleinopathy patients, with isolated RBD, might develop [43, 44]. Amongst these, it has been argued that *"…the most promising neuroimaging biomarker in idiopathic RBD to aid the prediction of phenoconversion is striatal presynaptic striatal dopaminergic dysfunction…*" [44] although such biomarkers remain to be properly identified and their relevance confirmed.

3. Conclusions

From the above interrogation of the literature, there appears to be a definite relationship between PD and RBD but the relationship is far from absolute. The degenerative processes, affecting the nigrostriatal system, in patients with PD, appear to be independent of the RBD and appear to be an expression of the PD alone, although debate persists. There are differences in the pathophysiology, as shown with PET cerebral imaging which may serve to explain why the treatment of RBD, a possible prodrome to PD, does not affect the natural history of the PD. While they can, and often do, occur concurrently, the approach to management is diagnostic specific and does not reflect a mutually effective remedy. There is need to further explore the relationship and to better understand the underlying pathology in which RBD frequently heralds to propensity to PD.

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Competing Interests

There is nothing to declare.

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