

**DEBATE**

# Patients with idiopathic REM sleep behaviour disorder (iRBD) should be informed about the future risk of Parkinson disease

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## Aye

“Alan Alda was running for his life. The six time Emmy award winner was not on a movie set. He grabbed a big bag of potatoes and threw it at the attacker. Suddenly the scene shifted since his wife got awakened as she was just attacked with a pillow”. Years later, Alan was diagnosed with idiopathic Parkinson disease.

Idiopathic Rapid Eye Movement (REM) sleep behaviour disorder (iRBD) is defined by the International Classification of Sleep Disorders as having intermittent muscle activity during REM sleep, along with abnormal behaviours and actions related to dream content.<sup>1</sup> Although it affects only up to 0.5% of the general population, longitudinal studies show that 40-65% of patients with RBD will convert to idiopathic Parkinson disease over 10 years.<sup>2</sup> Further, up to 80% of patients with RBD, will be at risk for developing alpha synucleinopathies.

Polysomnography proven iRBD is the prodromal marker with the highest positive predictive value of idiopathic Parkinson disease.<sup>3</sup> It presents before significant irreversible neurodegeneration occurs in Parkinson disease. Therefore, the diagnosis of iRBD allows potentially beneficial life style changes such as selective increased consumption as in mediterranean diet and avoidance of exposure to pesticides and occupational solvents, to take place. Regular exercise which has been shown to elicit adaptive neuroplasticity in basal ganglia circuitries, can also be advocated.

Certain novel therapies are in the pipeline; already showing their potential to retard the progression of iRBD into synucleinopathies. A recent prospective cohort study showed that well-timed, long-term administration of melatonin is associated with reduced phenoconversion to parkinsonism and dementia.<sup>4</sup> The efficacy of idebenone, a potent antioxidant targeting mitochondrial dysfunction is currently being tested.

Disclosure of the future risk of parkinsonism is challenging, especially in the absence of definite disease-modifying therapies. Yet it will increase vigilance, facilitate early recognition of other non-motor symptoms, and reduce severe disability. On the other hand, being knowledgeable, may contribute to impaired quality of life (QOL), caregiver distress, increased institutionalization and overall increased patient related economic burden.

The decision of disclosure is governed by fundamental ethical principles. Patient's autonomy and veracity should be ensured. A recent study revealed that one-third of patients were not informed about the future risk of PD, but 90% would have liked to receive prognostic information.<sup>5</sup> Communications should be tailor made and can be started in broad terms, but should progress to more details based on the patients' needs and condition. The caring physician or neurologist should make a decision on the type and



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extent of information the patient would want to know, and at what time they would want greater details.

In conclusion, though disclosing the future risk of parkinsonism to patients with iRBD can be challenging, such disclosure is essential in order to respect the patient's autonomy and provide them with the necessary information to make informed decisions. Promising non-pharmacological and pharmacological treatment options are in the pipeline, providing hope for patients in delaying the onset of neurodegenerative diseases. Proper disclosure can lead to better outcomes for patients, their families, and the society.

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## Nay

"Should we tell what is coming *or* should we tell, what *might* be coming"

Uncertainty is the norm of the world; for most occasions the answer is a "might". To emphasize a fact beyond that uncertainty, which would possibly carry a significant emotional burden to a patient should always be guided by the pillars of ethics of medicine; autonomy, beneficence, non-maleficence and justice.

Here we stand before such a perplexity.

Rapid eye movement (REM) sleep behavioral disorder (RBD) is a parasomnia described in 1986. Which is characterized by vivid often unpleasant or combative dreams associated with simple and complex motor behavior during REM sleep. It can be idiopathic or secondary to narcolepsy, overt synucleinopathy, anti-IgLON5 encephalitis, LGI1 encephalitis or CASPAR2 encephalitis.

Cohort studies have noted an interesting association between the RBD and later development of Parkinson disease (PD). According to those studies the risk of developing an alpha synucleinopathy at 5, 10 and 14 years is shown to be 33% 75.5% and 90.9% respectively with a median conversion time of 7.5 years. The prevalence of alpha synucleinopathies shown to develop with RBD were dementia with Lewy bodies (44.6%) Parkinson disease (33.8%), multiple system atrophy (3%) and minimal cognitive impairment (18.4%).<sup>1,2</sup>

For PD, without a targeted disease modifying therapy (except physical exercise) at the moment, it is vital, that the precision of risk communication for its development be guided by combined risk scores using other biomarkers rather than a blanket warning of PD for all with RBD.<sup>2,3</sup> However, as much as it would increase the accuracy of prediction, these predictions

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may be time and resource consuming to be practical enough to be incorporated into general neurological practice.

To conclude, it is accepted that with the use of other biomarkers we *might* predict the development of PD with a higher probability. However, the availability and cost effectiveness of such screening is doubtful given that there is only symptomatic treatment at the moment. Given the uncertainty of developing the disease which also has a lengthy prodromal interval of 14.2+6.2 years, the emotional burden, discrimination and problems related to insurability must be strongly considered. Hence, maybe in a future where disease modifying treatment is available, the answer to the question might be otherwise.

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## Commentary

Parkinson disease (PD) affects 1-2 per 1000 of the population at any time. PD prevalence increases with age and PD affects 1-4% of the population above 60 years. Idiopathic Rapid Eye Movement (REM) sleep behaviour disorder (iRBD) affects only up to 0.5% of the general population, but longitudinal studies show that 40-65% of patients with iRBD will convert to idiopathic Parkinson disease over 10 years.<sup>1</sup> Further, up to 80% of patients with RBD, will be at risk for developing alpha synucleinopathies. In recent years however, several studies have used polysomnography (PSG) to diagnose RBD, finding a population prevalence of around 1% in the >50-60-year age group across Switzerland, South Korea and Spain.<sup>2-4</sup>

According to a meta-analysis including eight studies, the estimated prevalence of RBD in the PD population varies between 19 to 70%.<sup>5</sup> The co-occurrence of RBD and PD is important given the fact that RBD symptoms may precede by several years the onset of the motor features of PD. Therefore, idiopathic RBD is considered a pre-motor biomarker in PD.<sup>6</sup> The estimated risk of developing neurodegenerative disorders in patients with iRBD increases from 35% at 5 years to 73% at 10 years and to 92% at 14 years.<sup>7</sup> In a study including 100 PD patients, De Cock et al. reported 22% of cases in which RBD preceded PD, 23% of cases in which the parkinsonism and RBD developed simultaneously, while in the rest of the cases (55%), RBD occurred years after manifest parkinsonism.<sup>8</sup>

There is a debate that iRBD patients represent an earlier prodromal phase of the alpha-synuclein disorders, namely PD, Dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). As the PD/DLB prodrome is up to 20 years in duration,<sup>6</sup> and Parkinson is a slowly progressive neurodegenerative disease, patients at the time of their diagnosis will have already been suffering neurodegeneration over the prior decade(s), with loss of up to 60% of dopaminergic nigrostriatal projections at PD or DLB diagnosis. Arguably, as RBD subjects will be at a much earlier stage of disease, neuroprotective treatment strategies that aim to cure or even slow down disease progression should be targeted at this prodromal group. Others have argued that subjects who convert from RBD to PD are not typical of sporadic Parkinson disease. Evidence suggests that pathologically these PD subjects have alpha-synuclein pathology with a likely greater pathological burden than those who present without the RBD prodrome. The PD group of RBD subjects who convert to PD, or PD with concomitant clinical RBD episodes compared to those without RBD early on, is also more likely to have higher rates of cognitive impairment, depression, anxiety, autonomic dysregulation and other non-motor symptoms in the RBD-affected group.<sup>9</sup> It remains to be seen whether pharmaceutical or other interventions that improve sleep quality might in themselves modify or slow down established motor or cognitive progression.

Over the past 30 years, billions of dollars have been invested by the pharmaceutical industry in the search of a cure for PD, with 16 compounds all testing negative in completed large-scale trials.<sup>10</sup> The studies may have failed in part because intervention was attempted too late in the neurodegenerative cascade. Therefore, it can be argued that the time is now ripe for neuroprotective trials to focus on this promising prodromal group.

Options for treatment for RBD are poor, and are based on several small studies, which were mostly open label. Clonazepam starting at a dose of 0.25 mg nocte (increasing gradually to a maximum dose of 2.0 mg at a given point if tolerated) is probably more efficacious than melatonin MR (starting at 2 mg and increasing if tolerated to a maximum of 8-12 mg at a regular bedtime). However, both clonazepam and melatonin cause side effects including morning or daytime drowsiness, nocturnal confusion, and falls, so should be used with caution with specialist advice.

From above it is clear that iRBD is a prodromal feature of developing PD in a significant number. However, RBD is rare in the general population and it is rarely reported by patients and family members. In my experience of over 30 years RBD symptoms were not reported even by PD patients. Unless directly questioned the symptoms of RBD may not be volunteered. Is it practical to ask all patients visiting you of RBD symptoms? Some may think it is part of normal sleep, some may be sleeping alone and they may go unnoticed. This is more likely with different cultural backgrounds, educational levels and living standards. Falling off the bed, kicking the partner and injuries are possible consequences but how many would feel it important to report to a doctor if the person is otherwise normal, is uncertain.

Is it possible to screen populations for RBD or at least limit it to family members of PD patients? As there is no cure yet for PD and other synucleinopathies nor any well proven preventive methods, can we justify such costly screening methods? Also, it must not be forgotten that PD is a feared condition by the population and a warning that they are at a higher risk can cause much mental stress in the patient and family members. Therefore, if someone complains of sleep issues, we must take the opportunity and question on probable symptoms of RBD. If a diagnosis of RBD is made then treat RBD, being hopeful that it may prevent progression to PD, though we have no evidence for this yet. When informing individuals with RBD of the PD risk we should consider all these facts and decisions should be made on an individual basis. Suggested interventions are lifestyle changes such as selective increased consumption of dietary items and avoiding exposure to pesticides and occupational solvents. Regular exercise, which has been shown to elicit adaptive neuroplasticity in basal ganglia circuitries, can also be advocated. Screening all PD patients for RBD is justified, as the presence of RBD can increase morbidity and also because

it is known that such patients' PD symptoms progress rapidly and this knowledge will help to manage their treatment appropriately.

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