Teaching Course 1

**MDS-ES/EAN: Differential diagnosis of sleep related movement disorders - Level 3**

**REM sleep behavior disorder: Diagnostic criteria, EMG based accurate quantitative diagnostics, value and limitations of questionnaires for diagnosis and differential diagnosis**

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Carlos Schenck, Mark Mahowald and co-workers have been the first to describe REM sleep behaviour disorder in humans three decades ago, and they also coined the designation of this disorder.

Prevalence and implications

Although RBD is not a rare disorder, only few studies have addressed the prevalence of RBD in the general population. It reported that 0.38 % of the elderly cohort had PSG confirmed RBD (Chiu HF, Sleep 2000). A more recent series of Korean elderly reported a prevalence of 1.15 % idiopathic RBD in the elderly population, and 2.01 % for all types of RBD. Ohayon and co-workers used the Sleep Eval telephone interview in a large cohort of almost 5000 and reported a 2 % prevalence of violent or injurious behaviours during sleep (Ohayon and Schenck, 2010). In a sleep laboratory series of 703 consecutive patients, 4.8 % had REM sleep behaviour disorder (Frauscher B., Sleep Med. 2010) and importantly, several of these patients would not have been diagnosed by sleep history alone, only upon insistent questioning symptoms of RBD could be retrieved from history.

In a cohort of 110 healthy control patients, the prevalence of idiopathic RBD was 2 % (Mollenhauer, Neurology 2013). In PD, the prevalence in de novo patients was 25 % (Mollenhauer B. et al, Neurology 2013), and in clinically more advanced patients the prevalence ranged between 33 and 46 % (Wetter TC, Wien Klin Wochenschr 2001, Gagnon JF, Neurology 2002, Sixel-Döring F, Neurology 2011).
It is well known, that REM sleep behaviour disorder is associated with α-synuclein disorders, and may precede or follow the onset of α synuclein disease. The conversion rate of patients with initially idiopathic RBD is higher than 80 - 90 % to α-synuclein disease within the next one or two decades, which led to the consequence that patients with idiopathic RBD are now considered as having prodromal α-synuclein disease (Iranzo A, Lancet Neurol 2016), and PSG-proven diagnosis of RBD, has an extraordinarily high positive calculated likelihood ratio of > 130 as compared to a only moderate likelihood ratio of 2.3 for questionnaire based diagnosis (Berg, Postuma, MDS 2015).

**Diagnostic criteria for RBD**

The diagnostic criteria for REM sleep behaviour disorder according to the American Academy of Sleep Medicine comprise repeated episodes of sleep related vocalizations and/or complex motor behaviours. The behaviours need to be documented by polysomnography to occur during REM sleep, or are at least presumed to occur during REM sleep based on clinical history of dream enactment. In addition, it is required for diagnosis of RBD according to the ICSD-3 that polysomnographic recording is performed and demonstrates REM sleep without atonia, and that the disturbance is not better explained by another sleep disorder, mental disorder, medication or substance use (AASM ICSD-3, 2014).

**Questionnaires to detect probable RBD**

Several questionnaires and interview based instruments to detect RBD have been developed. The first was the RBDSQ developed in Marburg by Karin Stiasny-Kolster in 2007 (Stiasny-Kolster et al, 2007). In 2010, the REM sleep behaviour disorder questionnaire Hongkong followed (Li SX,
Sleep Med 2010). The Mayo sleep questionnaire, published by Brad Boeve in 2013, has an opening question for RBD and if this is answered positive, subsequent questions follow. The International RBD Study Group IRBDSG validated a single question for RBD (RBD1Q), which is worded: Have you ever been told, or suspected yourself, that you seem to act your dreams, while asleep (e.g. punching, flailing your arms in the air, making running movements, etc.)? (Postuma R, et al Movement Disorders 2012).

The Innsbruck REM sleep behaviour disorder inventory RBD-I is a 5-item questionnaire and also includes an RBD summary question. It was published in 2012, and systematically asks for violent/aggressive dream content, multiple vocalisations during sleep, movements and flailing or more extensive movements out of sleep, injury or near-miss injury of self or bed partner during sleep, and if behaviours are in line with dream content at least part of the time (Frauscher B., Movement Disorder 2012).

All those questionnaires have undergone validation studies and had sensitivities and specificities which looked acceptable, except a lower specificity in the control group with other sleep and neurologic disorders in the RBD SQ. However, in the course of the subsequent year, it became clear, that questionnaires alone for diagnosis of RBD may lead to false positives and false negatives, and that the application circumstances influence the outcome (Stiasny-Kolster Sleep Medicine 2015). In addition, it was shown that different questionnaires will give different prevalences of probable RBD (Mahlknecht P, Movement Disorders 2015) in the general population. It has also been shown, that administering an RBD questionnaire to a healthy population without further instructions can give up to 16 % false positives in otherwise healthy sleepers, who did not have RBD confirmed in subsequent sleep expert interview or polysomnography
(Frauscher B., JCSM, 2014). In addition, a follow-up study in the general population, were 437 participants aged over 60 years completed the RBDSQ twice in 2008 and 2010, showed that only 1.8% of this population screened positive on both occasions, while 6.6 vs. 4.3% screened positive only on one of the two assessments, so the congruence between both assessments was unexpectedly low. If this is related to fluctuation of RBD clinical expression over time, or a limitation of the questionnaire needs to be investigated by further studies (Stefani A., MDCP in press). In addition, the awareness of RBD may be low by the patients themselves (Fernandez-Arcos Sleep 2016) and improved if a bed partner participates in the interview.

Recently, a multistep screening approach to search for iRBD has been suggested for prodromal PD in the general community. It includes a newspaper advertisement containing the single question screen for RBD published by the IRDB SG (Postuma, Sleep Med 2016). In this multistep approach study, screen-positive subjects underwent an interview based on the Innsbruck RBD inventory (Frauscher et al, 2012) administered by telephone interview. Those who passed both screens, underwent confirmatory polysomnography. With this strategy, the PPV of patients 66%, but this was out of 111 RBD screen positive participants, 36 had passed the secondary screen and 29 underwent full PSG (Postuma R et al, Sleep Med 2016)

**PSG Diagnosis of RBD**

While Mahowald and Schenck highlighted since the beginning the importance of PSG recording including EMG of the upper limbs to detect RBD, the older ICSD-2 criteria required only a more generic “excessive”
EMG activity in the submental channel or limbs. Later, the SINBAR group (Sleep Innsbruck Barcelona) performed a systematic study to access normative EMG values during REM sleep for the diagnosis of REM sleep behaviour disorder. For this study, 30 patients with REM behaviour disorder, and 30 matched controls underwent continuous surface EMG registration of 11 body muscles during polysomnography. The EMG activity during REM sleep was classified into tonic, phasic and any EMG activity by a blind rater and quantified for each muscle. In this study, it was shown that when a specificity of 100 % was targeted, the cut off for a diagnosis of RBD in the mentalis muscle alone was 18 %, and 32 % for the combination of any EMG activity in the mentalis muscle and phasic EMG activity in the flexor digitorum superficialis muscle. This gave a very high area under the curve of 0,998 %. Nevertheless, despite these quantitative EMG criteria, it should be emphasized, that a diagnosis of RBD requires additionally the presence of the other clinical criteria (behaviors and/or vocalizations).

A recent study in highlighted impressively the diagnostic advantages of performing polysomnography with EMG not only from the mental/submental muscles, but routinely including EMG from the upper limbs (flexor digitorum superficialis or biceps muscle) for a definite diagnosis of RBD, and the significant proportion of correct diagnosis who would have been missed, if submental muscle EMG alone would have been performed. The addition of arm EMG is technically not a challenge for PSG technicians who are used to record tibial anterior EMG (Fernandez-Arcos Sleep 2017).

Different other groups have used different approaches to quantify EMG activity during REM sleep. The original method based on submental EMG recording and dividing activity into tonic and phasic stems from Lapierre
and Montplaisir 1992. Zhang and co-workers included extensor of the forearms for quantified diagnosis of RBD (Zhang 2008). Other authors, including Bliwise, Consens and Eisensehr, proposed slightly different methods. The Mayo group recently confirmed the suitability of a SINBAR approach with a modified montage including “chin any” or tibialis anterior phasic EMG (Mac Carter Sleep 2014).

Another method that uses mental/submental EMG only is the REM atonia index RAI, which is somewhat the inverse figure of increased REM chin EMG activity index. It was first described and calculated by Ferri and coworkers, and later also used and validated by other groups (Mac Carter 2014). Ferri and co-workers also showed, that this approach has a good night to night stability (Ferri R, JCSM 2013).

In a recent study including 62 patients with Parkinson Disease, two visual methods, Montreal and SINBAR, and the automatic REM atonia index were compared. The REM atonia index had a 94,6 % sensitivity and 72 % specificity, and the authors concluded that RAI may be used as first line method to detect REM sleep without atonia in the diagnosis of RBD in patients with Parkinson Disease, together with visual inspection of video recorded behaviours, while the visual analysis might be used in doubtful cases (Figorilli, 2017).

In addition, because the visual and manual analysis of increased motor activity during REM sleep requires highly specific skills and is time-consuming and cumbersome, automatic detection several different approaches to detect REM sleep without atonia based on EOG and EEG has been proposed (Kempfner, 2012, Sissel Bisgaard 2015).
At present the only validated automatic analysis system for REM sleep without atonia that does not only include EMG quantification from the submental muscle, but also from the flexor digitorum superficialis muscle, and which is built-in into a commercially available PSG system, is supplied by OSG Belgium and has been validated (Frauscher B, Sleep 2014).

Implications for Diagnosis of RBD

In a situation, when a good polysomnography is still not readily available everywhere, has long waiting times, or seems too cumbersome, there may be a temptation to use a questionnaire based diagnosis of probable RBD only. However, the following should be kept in mind, at least for future studies of disease modifying substances to prevent the full clinical onset of neurodegenerative disease / α-synuclein disease in patients with still idiopathic RBD: The success of these future studies will depend on the fact if RBD has been diagnosed accurately and correctly or not. Fals positive and false negative diagnosis would confound the outcomes of any future treatment study. Therefore, a quantified and well ascertained PSG diagnosis of will help to advance the field of neurodegenerative research as a whole, and in the future hopefully also for the patients with IRBD.

Disclosure:
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Further reading:


