Sleep Medicine 14 (2013) 754–762

Contents lists available at SciVerse ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder

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ARTICLE INFO

Article history:
Available online 7 March 2013

Keywords:
REM sleep behavior disorder
Parasomnia
Lewy body disease
Dementia with Lewy bodies
Parkinson's disease
Multiple system atrophy
Synuclein
Synucleinopathy

ABSTRACT

Objective: To determine the pathologic substrates in patients with rapid eye movement (REM) sleep behavior disorder (RBD) with or without a coexisting neurologic disorder.
Methods: The clinical and neuropathologic findings were analyzed on all autopsied cases from one of the collaborating sites in North America and Europe, were evaluated from January 1990 to March 2012, and were diagnosed with polysomnogram (PSG)-proven or probable RBD with or without a coexisting neurologic disorder. The clinical and neuropathologic diagnoses were based on published criteria.
Results: 172 cases were identified, of whom 143 (83%) were men. The mean ± SD age of onset in years for the core features were as follows – RBD, 62 ± 14 (range, 20–93), cognitive impairment (n = 147); 69 ± 10 (range, 22–90), parkinsonism (n = 151); 68 ± 9 (range, 20–92), and autonomic dysfunction (n = 42); 62 ± 12 (range, 23–81). Death age was 75 ± 9 years (range, 24–96). Eighty-two (48%) had RBD confirmed by PSG, 64 (37%) had a classic history of recurrent dream enactment behavior, and 26 (15%) screened positive for RBD by questionnaire. RBD preceded the onset of cognitive impairment, parkinsonism, or autonomic dysfunction in 87 (51%) patients by 10 ± 12 (range, 1–61) years. The primary clinical diagnoses among those with a coexisting neurologic disorder were dementia with Lewy bodies (n = 97), Parkinson's disease with or without mild cognitive impairment or dementia (n = 32), multiple system atrophy (MSA) (n = 19), Alzheimer's disease (AD)(n = 9) and other various disorders including secondary narcolepsy (n = 2) and neurodegeneration with brain iron accumulation-type 1 (NBAI-1) (n = 1). The neuropathologic diagnoses were Lewy body disease (LBD)(n = 77, including 1 case with a duplication in the gene encoding α-synuclein), combined LBD and AD (n = 59), MSA (n = 19), AD (n = 6), progressive supranulear palsy (PSP) (n = 2), other mixed neurodegenerative pathologies (n = 6), NBIA-1/LBD/tauopathy (n = 1), and hypothalamic structural lesions (n = 2). Among the neurodegenerative disorders associated with RBD (n = 170), 160 (94%) were synucleinopathies. The RBD-synucleinopathy association was particularly high when RBD preceded the onset of other neurodegenerative syndrome features.

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1389-9457/$ - see front matter
http://dx.doi.org/10.1016/j.sleep.2012.10.015

Conclusions: In this large series of PSG-confirmed and probable RBD cases that underwent autopsy, the strong association of RBD with the synucleinopathies was further substantiated and a wider spectrum of disorders which can underlie RBD now are more apparent.

1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by loss of normal skeletal muscle atonia during REM sleep with prominent motor activity and dreaming [1–5]. The parasomnia occurs more frequently in males, and usually begins manifesting after the age of 50 years [3–5]. RBD can occur without any coexisting neurologic disorders or findings (so-called idiopathic RBD or iRBD) and can be precipitated or aggravated by certain classes of medications, particularly selective serotonin or norepinephrine reuptake inhibitors [6,7]. RBD often is a manifestation of the state dissociation characteristic of narcolepsy [8]. Some cases of autoimmune and paraneoplastic encephalopathies, particularly in association with high titers of antibodies against proteins that form part of the voltage-gated potassium channel complex were identified over recent years [9]. RBD also can be triggered by structural brain lesions such as brainstem infarcts, tumors, vascular malformations, and demyelinating plaques associated with multiple sclerosis [10,11]; these accidents of nature have provided insights into the location of the networks implicated in human RBD. All structural lesions identified to date have been localized in the dorsal midbrain, pons, or medulla. Neuroimaging studies in the voltage-gated potassium channel complex–associated RBD cases show abnormalities in the mesial temporal lobe structures and usually not in the brainstem [12]. These unique cases underscore that the precise networks and neurotransmitter systems involved in human RBD remain unclear but most consistently relate to brainstem networks and their efferent or afferent connections.

RBD associated with neurodegenerative disease was first appreciated over 15 years ago [13], and because RBD often precedes the onset of a slowly evolving neurodegenerative syndrome by years or decades [3,5,10,13–28], international attention has turned to view iRBD as a potential early clinical manifestation and biomarker of sorts of neurodegeneration rather than a curious parasomnia. Other features on PSG also can suggest an evolving neurodegenerative disorder such as laryngeal stridor and slowing of electroencephalogram activity [29–31]. If iRBD is a harbinger of parkinsonism, cognitive impairment, autonomic dysfunction, or some combination of these, at least in some individuals, one would hope that an intervention could be commenced and potentially delay the onset of these disabling features or prevent them from occurring altogether. Therefore, attention is focused on iRBD representing a "window of opportunity" with a glimpse of the future like few other neurologic or medical disorders can offer [26,27,32–34]. However, many questions remain.

Most studies based on clinically diagnosed cases have found that some neurodegenerative disorders are commonly associated with RBD and thus the rule, while others infrequently are associated with RBD, and hence the exceptions. Those commonly associated with RBD include multiple system atrophy (MSA) [1,2,5,14,15,23,25,29,35–46], Parkinson's disease (PD) with or without dementia [1,5,6,10,17,18,23,25,26,40,43,47–74], dementia with Lewy bodies (DLB) [10,21–27,75–85], and less commonly pure autonomic failure [40,86]. These disorders are collectively termed the *synucleinopathies* due to the presence of α-synuclein-positive inclusions in neurons or glia [87–90]. Yet several nonsynucleinopathy disorders also have been reported in association with RBD, namely spinocerebellar atrophy type 3 (Machado–Joseph disease) [91–94], progressive supranuclear palsy (PSP) [5,40,95,96], Guadalupian parkinsonism [97], Huntington disease [98], and Alzheimer's disease (AD) [26,99,100]. A single case of suspected corticobasal degeneration [101] was found to have REM sleep without atonia – the electrophysiologic substrate for RBD – but no history of dream enactment behavior. This case was considered representative of subclinical RBD. The clinically diagnosed cases therefore suggest that RBD often is (but not always associated with one proteinopathy – the synucleinopathies and less commonly associated with other proteinopathies; this is a phenomenon known in neurodegenerative disease circles as selective vulnerability. As disease-modifying therapies are being refined in the transgenic mouse models of neurodegenerative diseases to target proteinopathy pathophysiology, it will be critical for clinicians to accurately predict during life which proteinopathy is likely underlying any patient's features. Although clinicians make syndromic diagnoses in the clinic every day and infer which disease (and hence which proteinopathy) is underlying each patient's syndrome, this is an imperfect science and numerous examples abound in the literature on clinicopathologic inaccuracies. Assumptions often are made when the gold standard of neuropathologic examination rarely is or is never performed. Herein we describe the value of clinicopathologic correlations and the purpose of this large collaborative clinicopathologic analysis.

2. Design and methods

2.1. Case ascertainment

The International RBD Study Group initially convened in 2007 led by Professors Moller, Oertel and Stiasny-Kolster from the University of Marburg and includes investigators from many sites in North American and Europe who are devoted to clinical practice and research issues pertaining to RBD. Investigators at each site were contacted in March of 2012 and asked to query their local databases or recall specific cases they had followed with RBD from January 1990 to March 2012 through to autopsy. Colleagues at other sites in North America, Europe, and Asia who were not formally part of the consortium but had previously published on RBD also were contacted. Previously published cases were not excluded from our analysis, as the intention was to be as inclusive and as up-to-date as possible.

2.2. Data collection

A site leader at each site was designated and asked to provide basic demographic and clinical data on each autopsied case as well as with the neuropathologic diagnoses rendered by their local neuropathologist. Additional information such as which routine and immunohistochemical stains were used in the diagnostic evaluation also was included. The following data was requested for each case from each site leader:

- sex
- onset age of RBD
- method of determining diagnosis of RBD (PSG, history of recurrent dream enactment behavior, or questionnaire)
- onset age of cognitive impairment, if applicable
- onset age of parkinsonism, if applicable