Curr Geri Rep (2016) 5:95–102
DOI 10.1007/s13670-016-0174-9

REM Sleep Behavior Disorder: a Prodromal Synucleinopathy

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Published online: 29 March 2016

Abstract Rapid eye movement sleep behavior disorder (RBD) is an abnormal condition that constitutes dream enactment behavior occurring during rapid eye movement (REM) phase sleep with loss of normal muscular atonia. Idiopathic RBD is a recognized risk factor for the development of alpha-synuclein neuropathology, often referred to as Lewy body disorders (LBD) like Parkinson disease, multiple system atrophy and dementia with Lewy bodies, with conversion rates of 80–90 % over a lifetime. In the past decade, studies have described multiple features of idiopathic RBD subjects that resemble patients with alpha-synucleinopathies, with specific abnormalities in olfaction, vision, gait, cognition, autonomic dysfunction, impaired cortical activity, and dopaminergic abnormalities in neuroimaging, leading to the idea that idiopathic RBD is a prodromal synucleinopathy that can precede neurodegenerative disease by decades.

This article is part of the Topical Collection on *Neurology of Aging*

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Keywords REM behavior disorder · Alpha-synucleinopathy · Neurodegenerative disease · Lewy body disorders · Parkinson's disease · Multiple system atrophy · Dementia with Lewy bodies · REM sleep without atonia · Parasomnia · Non-REM sleep · Polysomnography

Introduction

In 1986, Schenck and colleagues were the first to describe rapid eye movement (REM) sleep behavior disorder, commonly abbreviated as RBD. Most sleep parasomnias occur during non-REM (NREM) sleep, as such, one of the distinguishing features of RBD is that it is a REM sleep-parasomnia, characterized by a history of recurrent complex motor behaviors and/or vocalizations that emerge during a loss of normal REM sleep atonia [1]. The movements in RBD usually last less than 60 s, mirror dream content, and range from small hand movements to violent actions that typically involve limb flailing, grabbing, punching, kicking, running, jumping, and lurching out of bed. Often, these movements can result in injury to the patient or the bed partner [2]. Vocalizations might include orating, shouting, screaming, crying, singing,and swearing. As a special feature when awakening from one of these episodes, there is characteristically a rapid return to alertness and patients frequently describe vivid dreams. Behaviors depend on the amount of time spent in REM sleep leading to an increased occurrence in the latter half of the sleep period when REM sleep is more prevalent (which for most individuals is after 03:00). The frequency of RBD events can range from one every other month to multiple episodes per night and tend to become more aggressive over time.

Idiopathic RBD refers to RBD occurring in the absence of any other neurological disorder. Rarely RBD can be

caused by antidepressant medications (serotonin reuptake inhibitors, serotonin-norepinephrine uptake inhibitors, MAO inhibitors, and tricyclics), beta-blockers, withdrawal (alcohol and barbiturate), narcolepsy (orexin/hypocretin deficiency), and pontine lesions (vascular injuries or demyelinating disease). The diagnosis of RBD requires a clinical history of repeated episodes of sleep related motor behaviors plus REM sleep without atonia (RSWA) captured with polysomnography (Table 1).

Epidemiology

RBD affects approximately 0.5 % of the general population but seems to be more common in the elderly population with a prevalence range between 2 and 6 % [3, 4]. RBD is characterized by a strong male gender predilection with 82 % of the cases occurring in men and a male to female ratio of 9:1. Mean age of onset is 45–65 years but symptoms typically begin in late adulthood. In general, 4–5 years elapse between onset and diagnosis. As an under recognized condition, its diagnosis is usually challenging mainly as a result of the absence of a bed partner that will witness the patient sleep. In particular, women often have less injurious dream content, bringing less attention to sleep behaviors and the gender difference in life expectancy makes elderly women more likely to sleep without a bed partner and therefore less likely to look for medical attention; in many cases, RBD is found after referral to a sleep center for a different sleep disorder. Risk factors associated with the development of RBD include smoking, history of traumatic brain injury, lower education level, and exposure to pesticides [5].

Pathophysiology

REM sleep is controlled mainly by nuclei in the medulla oblongata and pons of the brainstem. Currently, the proposed pathophysiology of RBD is thought to be associated with dysfunction in the activation of the reticular formation neurons by the cholinergic system, a positive feedback interaction that produces the onset of REM, which is in turn terminated by the inhibitory activity of REM-off aminergic neurons, with orexin, a hypothalamic neuropeptide that regulates wakefulness, arousal, and appetite, providing stability to NREM/REM sleep phases. Anatomically, RBD constitutes a brainstem nuclei dysfunction involving the pontine REM-on (pre-coeruleus and sublateraldorsal nucleus) and REM-off (ventral lateral portion of the periaqueductal gray matter and lateral pontine tegmentum). The sublateraldorsal nucleus likely represents the common pathway that projects directly to the spinal interneurons causing inhibition of skeletal muscle activity in REM sleep or indirectly through the magnocellular reticular formation [6]. Supratentorial influences on both the locomotor generators and muscle atonia are also occurring [7].

Table 1 Criteria for RBD diagnosis by The International Classification of Sleep Disorders—third edition (*ICSD-3:2014*)

A. Repeated episodes of sleep-related vocalization and/or complex motor behaviors.
B. These behaviors are documented by polysomnography to occur during REM sleep or based on the clinical history of dream re-enactment are presumed to occur during REM sleep.
C. Polysomnography recording demonstrates REM sleep without atonia (RSWA).
D. The sleep disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance abuse.

Diagnosis

The diagnosis of RBD requires a complete physical and neurological exam to identify contributing comorbid conditions and medicines, as well as detailed inquiries about sleep-wake times, sleep quality, duration, and excessive daytime sleepiness. Neuropsychiatric health and history should be evaluated and performance on a bedside cognitive test like the Montreal Cognitive Assessment documented. Health practitioners are advised to inquire about recurrent dream enhancement behaviors not only with the patient but also with their bed partners. Screening surveys are available and include REM Sleep Behavior Disorder Single-Question Screen-RBD1Q (sensitivity 94 %, specificity 87 %) and REM Sleep Behavior Disorder Screening Questionnaire-RBDSQ (sensitivity 96 %, specificity 56 %). If RBD is suspected, patients should be referred for a video recorded nocturnal polysomnography (PSG) with a dedicated RBD montage, as part of the requirements for definitive diagnosis. A single night PSG can miss up to 20 % of RBD cases [1]. On the other hand, if REM sleep without atonia (RSWA) occurs during a single night PSG but is not associated with abnormal motor behavior, the clinical history and documentation of dream enactment behavior can secure the diagnosis. The pursuit of additional testing such as a neurocognitive battery or neuroimaging should be based on clinical findings. After a confirmed RBD diagnosis by PSG, health care practitioners should direct the patient for management and follow-up to either a sleep specialist or neurologist.

Relationship of RBD with Neurodegenerative Disease

A growing body of clinical studies have proposed that idiopathic RBD is a risk factor for the development of alpha-synuclein mediated neurodegenerative disease (or Lewy body disease), with an estimated rate of conversion over a lifetime of 81–90 % [8]. The Lewy body diseases (LBD) are classified as alpha-synucleinopathies based on a shared neuropathology and some degree of overlapping symptomatology and include Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). The neuropathological hallmark is a lesion composed of fibrillary aggregates of insoluble alpha-synuclein protein in selective populations of neurons and glia, forming inclusions, Lewy bodies, and Lewy neurites. RBD is widespread among these patients with a prevalence of 30–50 % in PD [9], 80–95 % in MSA [10], and 50–80 % in DLB [6]. Less frequently, RBD has been associated with other neurodegenerative diseases, like progressive supranuclear palsy, frontotemporal dementia, Parkinsonism of Guadalupe, amyotrophic lateral sclerosis, Alzheimer's disease, spinal cerebellar ataxia, Huntington disease, and myotonic dystrophy.

Importantly, among the non-synucleinopathies, patients tend to develop RBD concurrently or after the onset of the disorder whereas in alpha-synucleinopathies RBD typically presents as a prodromal condition years or decades before the symptomatic onset of the core diagnostic features of PD, DLB, and MSA. The fact that RBD regularly occurs in alpha-synucleinopathies and rarely in other neurodegenerative diseases is supported by the concept of early involvement of the brainstem neuronal networks that control REM sleep, with a temporal sequence that begins in the medulla and eventually ascends to more rostral structures, compromising the SLD (sublaterodorsal nucleus) and leading to RSWA and RBD [6, 11].

An estimated risk of conversion has been calculated using case series and cohort studies. Case series have reported that approximately half of the patients convert to a neurologic disorder within 10 years [12, 13], whereas several longitudinal studies have projected the risk of developing an alpha-synucleinopathy to be: 10–41 % at 5 years, 40–76 % at 10 years, and up to 80–90 % between 14 and 16 years after the onset of RBD symptoms. The majority of the patients in these cohorts developed PD, followed by DLB, mild cognitive impairment (MCI), and MSA (Table 2). This finding might be explained by the greater incidence of PD and DLB in the older population. Research has shown that MCI (a transitional stage of dementia [14]) when present with RBD frequently evolves to PD or DLB [15]. In a pivotal longitudinal observational study of idiopathic RBD patients, 82 % developed a defined Lewy body disease, with the few who remained in a neurological disease free state, all had decreased striatal dopamine uptake. The rate of neurological disease free state was 7.5 % at 14 years, and in the cases where the definitive diagnosis of dementia was made post-mortem, brain tissue specimens showed the presence of Lewy body pathology in 97 % of the cases [16••].

In an attempt to characterize the features of RBD patients who convert, one recent multicenter study assessed different risk factors and concluded that the patients who develop neurodegenerative disease tend to be older, have prodromal autonomic and motor symptoms, and report a positive family history of dementia, neither gender, caffeine consumption, smoking, or alcohol exposure predicted conversion [17••].

Recent clinical studies suggest that prior to the emergence of a distinct synucleinopathy, RBD patients may already manifest subtle motor and cognitive deficits, including loss of visuoconstructional skills (visual perception, visual learning and color identification), cognitive impairment (impaired attention, executive function, and learning), rigidity, mild tremor and gait abnormalities (postural instability, freezing of gait, decreased walking velocity), and hyposmia and autonomic dysfunction (urinary incontinence, erectile dysfunction, and constipation) [6, 17••, 18–20, 21•, 22, 23, 24•]. Post-mortem studies have also described diffuse Lewy body pathology in the brainstem of RBD patients [25, 26]. Some of these features and deficits have been used to predict conversion; specifically, one study showed that decreased olfaction at baseline could predict a 65 % 5-year risk to develop a neurodegenerative disease compared with 14 % of those with normal olfaction at baseline [27]. Furthermore, a 10-year prospective study suggested that the risk of developing a defined neurodegenerative synucleinopathy based disease was associated with advanced age, olfactory loss, abnormal color vision, and subtle motor dysfunction and that the use of these prodromal markers are associated with increasing the risk of conversion by 200 % [28]. Taken together, these findings challenge the concept of idiopathic RBD and suggest that RBD may not be truly idiopathic, but in most cases, an early clinical manifestation or a prodrome of an evolving neurodegenerative disease, which might present years later with the symptom that meets the diagnostic criteria for alpha-synucleinopathies.

RBD and Dementia with Lewy Bodies

Cognitive impairment with concomitant (or within a year) Parkinsonism, hallucinations, and delusions with a variable pattern of fluctuating cognition, attention, and alertness clinically characterizes Dementia with Lewy bodies (DLB). Currently, RBD is a suggestive feature for the diagnostic criteria of DLB [29]. In the setting of dementia, the presence of RBD often indicates Lewy body pathology, and virtually, all RBD patients

Table 2 Cohort Studies

Study	iRBD Patients (*N*)	Conversion Rates	Average Follow-up (years)	Latency (from onset of symptoms)
Schenck et al. 1996 [60]	29	38 % to Parkinsonism (definitive PD: 8 and probable PD: 3)	5	12.7
Schenck et al. 2003 [61]	29 (follow-up)	65 % to Parkinsonism and/or cognitive impairment	12	N.A
Iranzo et al. 2006 [12]	44	45 % to neurodegenerative disease (PD: 9, DLB: 6, MSA: 1, and MCI: 4)	5.1	11.5
Iranzo et al. 2008 [62]	44 (follow-up)	64 % to neurodegenerative disease (PD: 10, DLB: 8, MSA: 1, and MCI: 9)	6.8	N.A
Postuma et al. 2009 [13]	93	28 % to neurodegenerative disease (PD: 14, DLB: 7, AD: 4, and MSA: 1) Estimated risk: 17.7 % at 5 years, 40.6 % at 10 years, and 52.4 % at 12 years (Follow-up data determined that AD patients were in fact DLB)	5.2	7.2
Wing et al. 2012 [63]	91	21 % to neurodegenerative disease (PD: 8 and dementia: 11) Estimated risk: 8.5 % at 5 years and 38.1 % at 10 years	5.6	N.A
Iranzo et al. 2013 [16••]	44 (Follow-up)	82 % to neurodegenerative disease (PD: 16, DLB: 14, MSA: 1 and MCI: 5) Estimated risk: 34.8 % at 5 years, 73.4 % at 10 years, and 92.5 % at 14 years	10.5	12
Schenck et al. 2013 [8]	26 (follow-up)	80.8 % parkinsonism or dementia (PD: 13, DLB: 3, MSA: 1, unspecific dementia: 1, AD: 2) (In the AD, patient's autopsy confirm AD plus LBD)	16	14.2
Iranzo et al. 2014 [64]	174	37.4 % to neurodegenerative disease (PD: 22, DLB: 29, MSA: 2, and MCI: 12) Estimated risk: 33.1 % at 5 years, 75.7 % at 10 years and 90.4 % at 14 years	4	11
Postuma et al. 2015 [17••]	279	33.3 % to neurodegenerative disease (PD: 39, dementia: 47, and MSA: 7) Estimated risk: 25 % at 3 years and 41 % at 5 years (28 of the dementia patients met the criteria for probable DLB)	3.8	7

PD Parkinson's disease, *MSA* multiple system atrophy, *LBD* Lewy body disease, *DLB* dementia with Lewy bodies, *MCI* mild cognitive impairment, *N.A* no data is available

with MCI will subsequently develop DLB [30]. Olfaction, in particular odor identification, has been shown to predict conversion to DLB in RBD patients [31], the same way that sniffing sticks have been reported to predict the conversion of RBD patients to Dementia with Lewy bodies, with 82.4 % accuracy [32]. In the DLB population, the presence of RBD is associated with earlier onset of Parkinsonism and visual hallucinations [33].

RBD and Multiple System Atrophy

MSA is a rapidly progressive neurodegenerative disease characterized clinically by autonomic and urogenital dysfunction, with variable expression and severity of Parkinsonism, cerebellar, and corticospinal dysfunction. Most recent consensus criteria subtype the syndrome of MSA by the predominant clinical feature of Parkinsonism to MSA-P and the predominant features of cerebellar dysfunction to MSA-C [34]. A distinct neuropathology of glial intracytoplasmic inclusions composed of conformational changed alpha-synuclein is widespread in MSA with cell loss in the striatonigral and olivopontocerebellar areas of the brain, brainstem, and spinal cord. Brainstem neuronal-glial cell loss in the cholinergic pedunculopontine and laterodorsal nuclei in MSA is thought to lead to RBD. The presence of RBD in the MSA population is unrelated to age, disease severity, clinical subtype, or disease duration [35].

RBD and Parkinson Disease

The combination of RBD, hyposmia, and impaired color identification has been hypothesized to predict a more rapid conversion to PD [27]. RBD has also been proposed as a prodromal marker for Parkinson's disease for research purposes [36]. One study in particular showed that the presence of RBD in PD can predict the development of dementia in 5 years [37] and another study concluded that the severity of RBD defined by increased percentage of tonic chin EMG activity during REM sleep predicts progression to PD [38].

The presence of RBD in PD patients is associated with the non-tremor dominant subtype of PD, a greater disease burden with more rapid motor and cognitive decline as evidenced by mild cognitive impairment, higher Hoehn and Yahr stage, poor quality of life scores and motor function, gait freezing, higher incidence of orthostatic hypotension, hallucinations, constipation, falls, and higher average dosages of levo-dopa [6, 39–41]. RBD in PD patients has been correlated with age, dementia, dyskinesia, depression, and hyposmia [23]. In PD, the brain structures that modulate REM sleep (gigantocellularis reticular nucleus, subceruleus region) are damaged. It is postulated that during PD with RBD, motor commands from the cortex bypass both basal ganglia modulation (dysfunction as a result of PD) and SLD/SC (pre-coeruleus and sublateraldorsal nucleus) inhabituation (dysfunctional due to RBD), thus enabling movements [42].

Neuroimaging of RBD

In the last 5 years, an impressive range of imaging techniques has been used to understand the structural and functional neural differences between RBD and other Parkinson and related disorders. Mapping of whole-brain white matter using diffusion tensor imaging (DTI) has demonstrated significant microstructural changes in right substantia nigra (SN), the olfactory region, the left temporal lobe, the fornix, the internal capsule, the corona radiata, and the right visual pathway of RBD patients [43]. Another combined DTI and structural MRI study reported decrease in white matter integrity in the tegmentum, rostral pons, and pontine reticular formation along with increase in gray matter densities in both hippocampi of RBD patients [44].

A structural T1-weighted MRI study demonstrated reduced volume of putamen bilaterally in RBD [45] compared to age-matched controls and early PD patients. Another structural study found reduced thalamus bilaterally in PD patients with RBD compared to PD patients without RBD and to controls [46]. A focus on MRI measurement of the olfactory bulbs and olfactory sulcus depth in RBD patients showed reduced bulb volume but not sulcal depth compared to controls, and olfactory discrimination thresholds were negatively correlated with bulb volume but not sulcal depth [47]. Other MRI studies in smaller samples report abnormalities in the ponto-mesencephalic tegmental region [48] and dorsomedial pons [49]. A recent study linked patterns of frontal lobe cortical thinning with phonetic-fluency (a frontal function) and low cerebrospinal fluid total alpha-synuclein in RBD and non-demented PD patients [50]. In individuals with DLB, those with probable RBD showed less severe Alzheimer-related pathology in the medial temporal lobes, whereas absence of probable RBD was characterized by Alzheimer-like atrophy MRI patterns (e.g., greater atrophy of temporal-parietal cortices, hippocampus, and amygdala) and increased phosphorylated-tau burden [51].

A study employing neuromelanin-sensitive imaging focused on the locus coeruleus, a brainstem region implicated in blocking muscle tone during normal REM, and found reduced signal intensity in PD patients with RBD compared to PD patients without the sleep disorder [52]; furthermore, the reduced signal correlated with the percentage of abnormally increased muscle tone during REM sleep. Functional connectivity assessed by functional MRI during the resting state has demonstrated reduced correlations between left SN and left putamen in RBD versus controls, but the correlations were higher compared to early PD patients [53•]. In the same study, elevated correlations between right SN and right precuneus compared to both controls and patients with PD. More recently, strongly negatively functional connectivity was reported between left SN and bilateral hippocampus in RBD patients [54]. A functional single-photon-computed tomography study on a small set of patients sought to understand which regions are activated during RBD during actual REM episodes and found that in RBD patients and PD patients with RBD neural activity bypasses the basal ganglia [55].

Taken together, these imaging findings show overlapping neural changes with the cortical and subcortical regions in addition to structural and functional alterations in PD and other PD related disorders occurring in RBD. These results also reveal neural alterations unique to RBD including midbrain, visual cortical pathways, and regions like the hippocampus that are implicated in higher cognitive functions.

Management and Treatment

There are two critical management goals in the treatment of RBD patients: (1) establishing a safe sleeping environment for the patient and the bed partner and (2) decreasing the intensity of unpleasant behaviors/vocalizations in the RBD patient. Patients with RBD are at risk for sleep-related injuries with an incidence around 55 %. Safety is a primary concern and securing the bedroom environment becomes a priority. Methods of self-protection like placing a mattress on the floor next to the bed, padding corners of furniture, removing sharp

objects or breakable objects on night stands, removing knives and weapons, securing windows and doors or using window protection, and removing furniture from the room are advised to be the first measures to take [56].

Clinicians and other health care providers should try to identify and treat comorbid sleep disorders that can exacerbate the RBD symptoms. To our knowledge, no randomized, double blind, controlled studies have been performed for RBD treatment. Currently with a B level of evidence, the first line treatment includes melatonin (6–15 mg) and clonazepam (0.25–4 mg). Both therapies suppress RBD behaviors (dream enactment behaviors and unpleasant dream recall) in the majority of patients during the first week of treatment; however, melatonin has a better side effect profile [57]. Melatonin, a naturally occurring brain "sleep hormone" or neurohormone produced by the pineal gland can restore REM sleep circadian rhythm by synchronizing sleep timing or regulating light–dark cycles with other physiologic and biologic rhythms through melatonin receptor activation. When taken at bedtime, melatonin can improve RBD symptoms and restore REM sleep atonia [21•]. Response rates range from 75 to 83 %, and it is generally well tolerated with minimal side effects that can include morning headache, sleepiness, and delusions/hallucinations. The US Food and Drug Administration categorizes melatonin as a dietary supplement and it is available as an OTC immediate release formulation, but it is recommended that a pharmacist or physician be aware of possible interactions with other medicines when melatonin is prescribed as a sleep aid. Ramelteon or brand name Rozerem is a melatonin analog that works at selective melatonin receptors and has been shown to be effective in improving RBD symptoms [58].

The beneficial effect of clonazepam, a long-acting benzodiazepine, is thought to be related to its GABAergic activity that depresses motor reflexes at the spinal cord level, thereby reducing muscular activity. Studies have shown clinical efficacy ranging from 80 to 90 %, reports of complete benefit in 79 % and partial in another 11 %. It is recommended to start low and slow, starting at 0.25 to 0.5 mg at bedtime and increase to 1–2 mg as needed. In the use of clonazepam for the reduction of RBD, women tend to require higher dosages than men. Clonazepam treatment has long-term benefits especially in reducing the more violent behaviors. Treatment with clonazepam should be continued indefinitely as relapse occurs swiftly if discontinued. Side effects include sedation, confusion (especially in older patients), memory disturbance, gait abnormalities, and impotence. Before using clonazepam in patients clinicians should rule out obstructive sleep apnea, a commonly occurring sleep disorder and frequently associated with RBD, as clonazepam may worsen sleep apnea, especially if untreated. A combination of melatonin and clonazepam can also be effective therapy in the treatment of RBD symptoms. Other drugs reported to improve RBD and considered level C evidence include pramipexole, levo-dopa, donepezil, and rivastigmine and with even more limited research support, zopiclone, carbamazepine, desipramine, clozapine, and sodium oxybate [59].

Patients with RBD that do not respond to medical management are at serious risk of self-injurious behavior or injury to a bed partner. The brain can respond to auditory stimuli during REM sleep, so educating bed partners or roommates to verbally direct behavior (if not too violent or aggressive) during a dream enactment episode may be helpful with medically refractory RBD patients. A sleep aid device described as an alarm system that provides calming instructions to patients when they become active has been shown to effectively redirect behavior.

Conclusions

RBD is a relatively common parasomnia in the older population, characterized by dream enactment behavior and RSWA. Clinical, cognitive, imaging, and neuropathological data support the concept of RBD as a prodromal synucleinopathy, and therefore, a clinical predictor of emerging synuclein mediated neurodegenerative diseases like DLB, PD, and MSA, with conversion rates over time greater than 80 %. To date, the mechanisms for conversion remain unclear and neuroprotective interventions that could halt progression to a neurodegenerative disorder have remained elusive.

Patients identified with RBD should be made aware of the risk of developing a neurodegenerative disease and be monitored for early markers of Parkinsonian disorders including changes in olfaction, autonomic dysfunction, vision, subtle motor function disturbances, and specifically the presence of mild cognitive impairment. In our experience, we would advocate that RBD be actively screened in the late adult population, accurately diagnosed using video polysomnography and effectively treated. The correct diagnosis is extremely important due to the emotional burden of having RBD and the resulting disruption and poor quality of sleep produced. The patient with RBD should be introduced to the concept of having a diagnosis that may represent a prodromal synucleinopathy. Education on sleep hygiene that fosters good sleep quality should be provided as well as prescribed measures that are known to reduce the risk of Parkinsonian disorders.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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