SHORT REPORT

REM sleep behaviour disorder differentiates pure autonomic failure from multiple system atrophy with autonomic failure

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Abstract

Ten patients with primary autonomic failure, followed up in a prospective clinical and laboratory study, were finally diagnosed as pure autonomic failure or multiple system atrophy with autonomic failure. Polysomnographic studies were performed in all patients. Whereas all four patients with multiple system atrophy complained of sleep related episodes suggesting REM sleep behaviour disorder (RBD) confirmed by polysomnography, RBD remained absent in the remaining six patients with pure autonomic failure. The data indicate that RBD is an important clinical feature, often heralding multiple system atrophy, but which is absent throughout the course of pure autonomic failure; its recognition can thus be useful in the prognostic evaluation of early primary autonomic failure syndromes.

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Primary autonomic failure syndromes comprise pure autonomic failure and multiple system atrophy with autonomic failure.[1] Pure autonomic failure is confined to the autonomic system, whereas multiple system atrophy with autonomic failure often, though not invariably, presents with autonomic failure but later becomes complicated with signs of CNS involvement such as parkinsonism and cerebellar ataxia.[1 2] Pure autonomic failure has a nearly normal life expectancy, whereas multiple system atrophy with autonomic failure has a much more severe prognosis. Differential diagnosis between the two conditions is therefore important, but often difficult especially in the early stages, when autonomic failure in multiple system atrophy may remain isolated in the absence of CNS involvement. In patients with primary autonomic failure, a follow up time of at least five years is required before a definite diagnosis is reached.[3] Moreover, there are no clearly differentiating laboratory tests as the early differential diagnostic value of supine plasma noradrenaline concentrations , which are often reduced in pure autonomic failure and normal or slightly raised in multiple system atrophy, is still debated.[1 4–6]

The vast majority (90%) of patients with multiple system atrophy have REM sleep behaviour disorder (RBD),[7] intense sleep related motor or verbal paroxysmal episodes occurring during REM sleep but without loss of muscle tone.[8] The episodes usually appear at least one hour after falling asleep, coinciding with REM sleep, occur intermittently during the night, are often more intense during the early morning hours, and are accompanied by the recall of vivid, fearful dreams. RBD represents the most common clinical sleep manifestation and polysomnographic finding in multiple system atrophy,[7] and often heralds the appearance of the other CNS symptoms by years.[7 9] RBD is attributed to involvement of the neural structures in the brain stem controlling muscle atonia during REM sleep.[8 10] As the brain stem remains largely spared in pure autonomic failure whereas it is severely involved in multiple system atrophy,[11] we ascertained whether RBD could distinguish patients with primary autonomic failure .

Material and methods

Ten de novo patients (seven men, three women, mean age 59.6 (range 40–67) years) with primary autonomic failure were enrolled in a prospective study to assess the evolution of the disorder. Possible orthostatic hypotension symptoms were blurred vision, dizziness, weakness, neckache, nausea, falls, or syncope appearing on assuming the erect posture. Other autonomic signs included, impotence, micturitional urgency, sphincter dysfunction and loss of sweating.

Patients underwent neurological examination, brain CT or MRI, tilting test, plasma noradrenaline concentrations supine and after 10 minutes of head up tilt test,[12] and videopolysomnography. They were followed up for a mean period of 4.8 (range 2–7) years and the examinations were repeated every year, until a conclusive diagnosis was reached. No patient was lost on follow up. Orthostatic hypotension was defined on tilting tests as a reduction of systolic blood pressure of at least 20 mm Hg or

diastolic blood pressure of at least 10 mm Hg not before the third minute and during 10 minutes of head up position at an angle of 65°.[1] Possible secondary causes of orthostatic hypotension were ruled out by appropriate tests.[13]

Videopolysomnographic recordings were performed with extended montages including EEG (C3-A2, C4-A1, O1-A2, O2-A1), right and left EOG, surface EMG from chin, intercostal, right and left tibialis anterior and right and left extensor digitorum communis muscles, microphone, nasal air flow, thoracic respirogram, ECG, and oxygen saturation. Paper speed was 10 mm/s and sleep stages were scored according to the criteria suggested by Rechtschaffen and Kales[14] with allowance for intermittent or sustained loss of REM atonia defining RBD.[15]

Results
At the first observation all patients had autonomic failure unassociated with signs of CNS involvement. A tilt test confirmed orthostatic hypotension (table) in all patients (mean decrease in systolic blood pressure 60.2 (SD 26.5) mm Hg; mean decrease in diastolic blood pressure 21.6 (SD 14.9) mmHg). Brain CT or MRI was normal in all the patients.

A minimum five year follow up (range 5–7 years) established that six patients had pure autonomic failure (four men, two women; mean age 58.8 (range 40–67) years). The other four patients developed unequivocal signs of CNS involvement within one to three years of follow up and were thus considered cases of multiple system atrophy with autonomic failure (table).

At first observation five of six patients with pure autonomic failure had extremely low supine noradrenaline concentrations, ranging from 16 to 187 pg/ml (normal values from 29 age matched healthy controls: 242 (SD) 100 pg/ml; range 108–500 pg/ml). A blunted noradrenaline head up tilt test response was found in five of six patients (table). No differences were detectable in systolic or diastolic blood pressure decreases on tilt testing between the two groups of patients. No patient with pure autonomic failure complained of sleep related motor or verbal

manifestations associated with fearful dreams, suggestive of RBD, throughout the follow up period. On polysomnography, all six patients with pure autonomic failure had a normal REM sleep pattern, with physiological REM atonia. Their sleep structure was characterised by a sleep efficiency ranging from 57 to 78% (mean 66%). Sleep stage percentages were stages 1–2 69.3% (range 54.8%-83%), slow wave sleep 8.4% (range 1.5%-20.2%), and REM sleep 15.6% (range 8.2%-25.3%). One patient had snoring with normal $HbSaO_2$ concentrations. Repeated polysomnography throughout the follow up ruled out a late appearance of RBD.

Four patients (three men, one woman; mean age 60; range 55–66 years) developed cerebellar or extrapyramidal signs within 1.7 (SD 0.9) years of follow up. In particular two patients presented with cerebellar and extrapyramidal signs, one with cerebellar signs and the other with parkinsonism with associated pyramidal signs. None of them responded to levodopa. Plasma supine noradrenaline concentrations were normal in two patients (226 and 229 pg/ml) and below the normal range in the other two (72 pg/ml in both), with a normal increase on head up tilting in two of four patients (table). All of them complained of possible RBD episodes since the ages of 40 to 60 (mean 51.5 years), with a frequency from two to three episodes a week to more than one episode every night. In three patients RBD episodes began one, four, and 20 years after onset of autonomic failure while in the fourth case they were concomitant with autonomic failure. In this group sleep efficiency ranged from 32% to 75%. Sleep structure was characterised by 74.7% of light sleep (range 66.6%-91.7%), 6.8% of slow wave sleep (range 1.7%-10.4%), and 15.6% of REM sleep (range 6.6%-23.4%). Videopolysomnographic recordings showed RBD in all of these patients since the first observation. Motor activity during the RBD ranged from a pronounced increase in myoclonic activity, with massive trunk and limb jerks, to complex oneiric behaviour with gesticulations, talking, yelling, fighting, or fleeing behaviour. One patient had eight apneas an hour with minimal $HbSaO_2$ at 88%. Two

Clinical and autonomic features of patients with autonomic failure

Patient no	Sex	Final diagnosis	Present age (y)	Follow up (y)	AF onset (y)	RBD onset (y)	C sign onset (y)	E sign onset (y)	SPD (mm Hg)	DPD (mm Hg)	Rest NA (pg/ml)	Tilt NA (pg/ml)	Δ NA (pg/ml)
1	M	PAF	67	5	52	—	—	—	−61	−24	38	60	+22
2	M	PAF	67	5	62	—	—	—	−85	−31	38	65	+27
3	M	PAF	46	6	37	—	—	—	−40	−20	37	144	+107
4	F	PAF	71	6	63	—	—	—	−76	−23	187	122	−65
5	F	PAF	74	7	56	—	—	—	−54	−15	24	24	0
6	M	PAF	55	5	46	—	—	—	−80	−35	16	27	+11
7	F	MSA	58	3	52	52	58	—	−27	0	72	126	+54
8	M	MSA	71	6	60	40	68	68	−106	−51	72	86	+14
9	M	MSA	61	3	55	54	56	56	−24	−6	229	402	+173
10	M	MSA	67	2	64	60	—	65	−49	−11	226	406	+180

AF onset=age at onset of autonomic failure; RBD onset=age at onset of RBD; follow up=duration of observation from first presentation at our Institute until final diagnosis; C sign onset=age at onset of cerebellar signs; E sign onset=age at onset of extrapyramidal signs; SPD=systolic blood pressure decrease (mm Hg) on tilt test at the first observation; DPD=diastolic blood pressure decrease (mm Hg) on tilt test at the first observation; rest NA=noradrenaline concentrations at rest (supine) at the first observation (normal values from 29 age matched healthy controls: 242 (SD 100) pg/ml; range 108-500 pg/ml); tilt NA=norepinephrine concentrations after 10 minutes head up tilt at the first observation (normal values from 29 age matched healthy controls: 441 (SD 147) pg/ml; range 246-836 pg/ml); ΔNA=difference in noradrenaline concentrations between 10 minutes head up tilt and baseline values at the first observation (normal values from 29 age matched healthy controls: 199 (SD 77 pg/ml) range 111-366 pg/ml).

patients had snoring, two laryngeal stridor, and one periodic limb movements during sleep accompanied by EEG arousals.

Discussion

Our study indicates that, within the primary autonomic failure syndromes, RBD is confined to multiple system atrophy, and probably represents a tell tale sign of extensive pathological involvement of the brain stem, which is absent in pure autonomic failure. Neuropathological degeneration in pure autonomic failure remains confined within the peripheral autonomic system, especially the postganglionic sympathetic neurons, with limited brainstem involvement.[11] On the contrary, the pathology of multiple system atrophy is characterised by widespread involvement of the peripheral, autonomic, and central nervous systems.[11 16 17] Damage to the REM sleep atonia cells of the pons probably represents the pathological change causing RBD in multiple system atrophy.[7] In three of four patients with multiple system atrophy RBD heralded onset of autonomic failure, confirming previous data in the literature.[7 9] A delayed emergence of the parkinsonian signs or other signs of multiple system atrophy in patients with RBD has already been described.[7 9 18] However, in patient 8 RBD preceded the appearance of autonomic failure by 20 years, a long time delay compared with the other cases (one and four years). In our previous multiple system atrophy material, RBD preceded the other signs of multiple system atrophy by one to 19 years, whereas in the literature the longest delay reported is three years.[9] The rather long gap between RBD and onset of autonomic failure in patient 8 remains puzzling, but it is noteworthy that this patient also displayed a rather slow progression of the other signs of multiple system atrophy. Future studies with more patients with RBD may clarify this issue, which implies that in some cases multiple system atrophy may have a quite prolonged disease course.

RBD split our autonomic failure population in two, without overlap, and therefore seems to have a good diagnostic specificity. Even though ours is a small series, RBD had more diagnostic specificity than the supine noradrenaline concentrations, which showed partial overlap between the two groups of patients. Furthermore, the finding of a plasma noradrenaline response to head up tilting similar to that in normal subjects in three out of 10 patients is in keeping with previous data,[19] suggesting that measurement of the change in plasma noradrenaline with postural stimulation may be misleading in autonomic failure. In fact, increases in plasma concentrations of the neurotransmitter can occur after a reduction in its plasma clearance.

Alongside RBD, breathing disorders during sleep such as laryngeal stridor were found in multiple system atrophy in patients with autonomic failure, but not in all of them or in the early stages. Changes in sleep structure were non-specific and did not differentiate the two groups.

In conclusion, RBD is an important clinical sign in autonomic failure, and when present RBD most probably heralds multiple system atrophy. Clinical and polysomnographic investigation for this peculiar sleep related disturbance may improve the differential diagnosis in patients presenting with isolated autonomic failure.

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