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Review

Fatal familial insomnia and Agrypnia Excitata: Autonomic dysfunctions and pathophysiological implications

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ABSTRACT

Fatal Familial Insomnia (FFI) is a hereditary prion disease caused by a mutation at codon 178 of the prion-protein gene leading to a D178N substitution in the protein determining severe and selective atrophy of mediodorsal and anteroventral thalamic nuclei. FFI is characterized by physiological sleep loss, which polygraphically appears to be a slow wave sleep loss, autonomic and motor hyperactivation with peculiar episodes of oneiric stupor.

Alteration of autonomic functions is a great burden for FFI patients consisting in sympathetic overactivation, dysregulation of its physiological responses and disruption of circadian rhythms. The cardiovascular system is the most frequently and severely affected confirming the increased sympathetic drive with preserved parasympathetic responses.

Sleep loss, autonomic and motor hyperactivation define Agrypnia Excitata (AE), which is not exclusive to FFI, but it has been canonically described also in Morvan Syndrome and Delirium Tremens. These three conditions present different pathophysiological mechanisms but share the same thalamo-limbic impairment of which AE is one of the possible clinical presentations.

FFI, and consequently also AE, is a model for the investigation of the essential role of the thalamus in the organization of body homeostasis, integrating both sleep and autonomic function control.

1. Introduction

Fatal Familial Insomnia (FFI) was first described by Lugaresi et al. (1986) as a hereditary, autosomal dominant and invariably fatal disease caused by a missense mutation at codon 178 of the prion protein gene (PRPN) co-segregating with methionine at Methionine (M) – Valine (V) polymorphic codon 129 on the mutated allele. The clinical hallmark of FFI is Agrypnia Excitata (AE), a syndrome characterized by a progressive and untreatable sleep loss with increasing difficulties in falling and remaining asleep both during the night and the day associated with 24-h motor and autonomic sympathetic overactivation and by a peculiar dream-like behavior known as oneiric stupor (OS) (Lugaresi et al., 2011). Pathologically, the thalamus, with severe but selective atrophy of its mediodorsal (MD) and anteroventral (AV) nuclei, appears to be the earliest and most severely affected brain structure in FFI (Kong et al., 2004). Thalamic lesions cause the loss of slow wave sleep (SWS) and the disconnection of the limbic cortical areas and the cortical and subcortical regions that also regulate autonomic functions, resulting in an increase of autonomic activation (Cortelli et al., 2006).

Agrypnia excitata is not exclusive to FFI but it has been also described in Morvan Syndrome (MS), an autoimmune limbic encephalopathy, and Delirium Tremens (DT), the well-known alcohol withdrawal syndrome (Liguori et al., 2001; Plazzi et al., 2002), suggesting as its origin an anatomic (FFI) or functional (MS, DT) interruption of the thalamo-limbic circuits regulating the sleep–wake cycle and the control of the autonomic nervous system (Lugaresi and Provini, 2001; Montagna and Lugaresi, 2002).

Of prominent importance is the role of the autonomic nervous system, permeating the clinical picture of FFI (and consequently of AE), a model disease for the investigation of the essential role of the thalamus for the central organization of body homeostasis integrating both sleep and autonomic function control (Benarroch and Stotz-Potter, 1998; Montagna, 2005).

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Table 1
Distribution of dysautonomic signs and symptoms in published cases of confirmed (genetically and/or pathologically) Fatal Familial Insomnia (FFI), divided by codon 129 genotype and listed by year of publication.

Author (year)	Country[a]	# of patients[b] (disease duration)	Hypertension	Blood pressure nocturnal non-dipping	Tachycardia	Breathing disorder	Hyperthermia	Hyperhidrosis	Gastrointestinal disorder	Genito-urinary disorder	Other dysautonomia
Homozygous for Methionine at Codon 129 (MM) - 85 patients (mean disease duration: 11.6 m)											
Chen et al. (2018)	CN	7 (13,6 m)[c]									(Unspecified dysautonomia)
Fukuoka et al. (2018)	JP	1 (16 m)	5 m		−	7 m (stridor)	5 m (remitting fever)	5 m			
Stevens et al. (2018)	US	1 (6 m)					3 m				
Yang et al. (2018)	KR	1 (13 m)									
(Lu et al., 2017)	CN	1 (20 m)						15 m	15 m (constipation)	15 m (retention)	
Sun et al. (2017)	CN	1 (11 m)	8 m	8 m	8 m	Onset (sleep apnea)	8 m		2 m (constipation)		
Wu et al. (2017)	CN	5 Cases:									
		# 1 (12 m)	+		+	−		+			
		# 2 (11 m)	+		−	−		+			
		# 3 (8 m)	−		+	(Irregular rhythm; stridor)		−			
		# 4 (10 m)	+		+	−		+			
		# 5 (18 m)	−		−	−		+			
Sun et al. (2015)	CN	1 (9 m – alive)									
Lee et al. (2014)	KR	2 Cases:									
		# 1 (9 m – alive)	9 m (fluctuation in blood pressure)		2 m	Onset (irregular nocturnal rhythm)		2 m			
		# 2 (27 m)									
Rupprecht et al. (2013)	DE	1 (5 m)									3 m (unspecified hyperactivity)
Frobose et al. (2012)	DE	1 (10 m)						Onset			
Shi et al. (2010)	CN	10 cases:									
and Shi et al. (2012)		# 1 (10 m)	7 m		−		2 m (evening pyrexia)	2 m			2 m (excessive salivation)
		# 2 (14 m)	7 m		7 m	Onset (nocturnal dyspnea; stridor)	(Evening pyrexia)	Onset			7 m (excessive salivation)
		# 3 (10 m)	−				−	+			
		# 4 (30 m)	−				(Evening pyrexia)	+			(Excessive salivation)
		# 5 (9 m)	−				(Evening pyrexia)	+			(Excessive salivation)
		# 6 (8 m)	+				(Evening pyrexia)	+			
		# 7 (8 m)	+				−	+			(Excessive salivation)
		# 8 (10 m)	−				(Evening pyrexia)	+			
		# 9 (8 m)	−				(Evening pyrexia)	+			(Excessive salivation)
		# 10 (7 m)	+				−	+			
Casas-Mendez et al. (2011)	SP	1 (15 m)				12 m (Biot's breathing)					(Unspecified dysautonomia)
Chang et al. (2011)	AU (VN)	1 (20 m)	Onset						Onset (constipation)		
Jansen et al. (2011)	EG	1 (7 m)	4 m	4 m							

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Table 1 (*continued*)

Author (year)	Country[a]	# of patients[b] (disease duration)	Hypertension	Blood pressure nocturnal non-dipping	Tachycardia	Breathing disorder	Hyperthermia	Hyperhidrosis	Gastrointestinal disorder	Genito-urinary disorder	Other dysautonomia
Saitoh et al. (2010)	JP	2 cases: # 1 (13 m) # 2 (14 m)			7 m		7 m (remitting fever)	7 m	7 m (constipation)	Onset (impotence)	
Zhang et al. (2010)	CN	1 (9 m)									(Unspecified dysautonomia)
Choi et al. (2009)	KR	1 (27 m – alive)									
Guerreiro et al. (2009)	MK	1 (not reported – alive)									
Oliveros et al. (2009)	SP	1 (7 m)				3 m (respiratory insufficiency)					
Raggi et al. (2009)	IT	1 (14 m)							10 m (incontinence)	10 m (incontinence)	
Friedrich et al. (2008)	DE	1 (15 m)								Onset (impotence)	
Haik et al. (2008)	FR	1 (6 m)	+	+	+		+				(Bilateral not responsive miosis)
Iriarte et al. (2007)	SP	1 (5 m)				4 m (nocturnal stridor)					
Yu et al. (2007)	CN	1 (12.5 m)	4 m		4 m						
Dimitri et al. (2006)	FR	1 (7 m)			4 m	4,5 m (irregular breathing)		2 m (nocturnal sweating)			
Schenkein and Montagna (2006)	US	1 (25 m)	18 m				5 m (fever spikes)	5 m			
Thomas et al. (2006)	DE	1 (6 m)				3 m (inspiratory disorder)					
Wermke et al. (2006)	DE	1 (not reported)									(Unspecified dysautonomia)
Spacey et al. (2004)	CN	1 (12 m)						9 m	9 m (constipation)	9 m (retention)	
Tabernero et al. (2000)	SP	2 cases: # 1 (10 m) # 2 (7 m)	−			7 m (irregular breathing; apnea)	7 m (fever)	7 m 3 m			Onset (amenorrhea) 7 m (non-responsive mydriasis) 3 m (bilateral miosis)
Almer et al. (1999)	AT	4 cases: # 1 (13 m) # 2 (11 m) # 3 (20 m) # 4 (18 m)			6 m	6 m (irregular breathing; dyspnea)	6 m 6 m +	6 m	Onset (constipation) Onset (constipation) +		6 m (recurrent flushes) 6 m (excessive salivation) −
Harder et al. (1999)	DE	5 (6.4 m)[c]									
Padovani et al. (1998)	IT	1 (11 m)	7 m		7 m		7 m (−) 11 m (fever)			10 m (incontinence)	
Rossi et al. (1998)	IT	1 (14 m)								Onset (loss of libido)	

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Table 1 (*continued*)

Author (year)	Country[a]	# of patients[b] (disease duration)	Hypertension	Blood pressure nocturnal non-dipping	Tachycardia	Breathing disorder	Hyperthermia	Hyperhidrosis	Gastrointestinal disorder	Genito-urinary disorder	Other dysautonomia
Will et al. (1998)	UK	2 cases:									
		# 1 (10 m)						Onset (nocturnal sweating)			
		# 2 (14 m)									
Zerr et al. (1998)	DE	6 cases:									
		# 1 (12 m)	Late phase				+	−	−		
		# 2 (16 m)	−				−	−	−		
		# 3 (9 m)	+				+	+	−		
		# 4 (not reported)	−				+	+	(Abdominal pain; diarrhea)		
		# 5 (9 m)	+				+	(Nocturnal sweating)	(Constipation)		
		# 6 (9 m)	−				+	(Nocturnal sweating)	−		
Colombier et al. (1997)	FR	1 (11 m)	8 m (24 h monitoring		8 m (24 h monitoring)	9 m (Biot's breathing)	8 m	9 m			8 m (sympathetic hyperactivity; vago-sympathetic disequilibrium)
Cortelli et al. (1997)	IT	7 Cases – 1 new [FFI-3] (10 m)									(Severe dysautonomia)
Gallassi et al. (1996)	IT	7 cases – 2 new:									
		# 1 [FFI-1 IV-43] (8 m)									(Severe dysautonomia)
		# 2 [FFI-2 IV-27] (8 m)									(Severe dysautonomia)
Nagayama et al. (1996)	JP	1 (6 m)			4 m	4 m (tachypnea)	4 m	4 m			
Reder et al. (1995)	US	1 (15 m)	12 m		12 m	13 m (paradoxical movements of vocal cords)	12-14 m (intermittent-steady pyrexia)		14 m (incontinence)	5 m (impotence) 14 m (incontinence)	
Medori et al. (1992)	IT	1 [FFI-2 IV-26] (8 m)	5 m	8 m (hypertension; reduced circadian variation of BP)	4 m	3 m (labored breathing; apnea)	4 m	3 m		3 m (impotence) 5 m (incontinence)	4 m (miosis)
Manetto et al. (1992)		7 cases – 4 new:									
		# 1 [FFI-1 IV-34] (7 m)									(Minimal dysautonomia)
		# 2 [FFI-1 IV-37] (18 m)									(Mild dysautonomia)
		# 3 [FFI-1 IV-75] (18 m)									(Mild dysautonomia)
		# 4 [FFI-1 IV-92] (7 m)									(Severe dysautonomia)
	IT	2 cases:									

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Table 1 (*continued*)

Author (year)	Country[a]	# of patients[b] (disease duration)	Hypertension	Blood pressure nocturnal non-dipping	Tachycardia	Breathing disorder	Hyperthermia	Hyperhidrosis	Gastrointestinal disorder	Genito-urinary disorder	Other dysautonomia
Lugaresi et al. (1986)		# 1 [FFI-1 IV-16/21] (9 m)	7 m	7 m (hypertension; abolition of circadian rhythm; altered reaction to pharmacological tests)	7 m	6 m (irregular breathing; tachypnea; apnea)	1-7 m (increased body core temperature; abolition of circadian rhythm)	1 m (orthostatic diaphoresis)	1 m (constipation) 7 m (incontinence)	Onset (impotence and loss of libido) 1 m (difficulty in micturition) 7 m (incontinence)	1 m (excess of salivation; rhinorrhea; lacrimation) 7 m (miosis; sympathetic hyperactivity; dysautonomia at cardiovascular reflexes)
		# 2 [IV-15/20] (7 m)									(Dysautonomia similar to #1)
Heterozygous for Methionine/Valine at Codon 129 (MV) - 18 patients (mean disease duration: 21.8 m)											
Pedroso et al. (2013)	BR (PT)	1 (12 m – alive)									
Baldin et al. (2009)	MA	1 (23 m – alive)				9 m (gasping breathing)		9 m		9 m (impotence)	
Synofzik et al. (2009)	DE	1 (24 m – alive)									(Moderate hyperhidrosis; hypertension in summer responsive to therapy)
Dauvilliers et al. (2004)	FR	1 (36 m)	−		−		18 m	18 m		18 m (impotence; dysuria)	
Marcaud et al. (2003)	FR	1 (13 m)	7 m		7 m			5 m			
Bar et al. (2002)	DE	1 (12 m)	9 m		9 m			9 m		Onset (impotence)	
Taniwaki et al. (2000)	JP	1 (12 m – alive)									
Harder et al. (1999)	DE	2 cases: # 1 (44 m)									
		# 2 (41 m)						Onset (nocturnal sweating)		21 m (incontinence)	
Brown et al. (1998)	US (UK)	2 cases: # 1 (9 m) # 2 (20 m)	+ +		+ +		+ +				
Zerr et al. (1998)	DE	2 cases: # 1 (10 m) # 2 (not reported – alive)	− −				− −	+ +	(Meteorism) −		
McLean et al. (1997)	AU (IE)	1 (21 m)									−
Silburn et al. (1996)	AU (IE)	2 cases: # 1 (13 m)	7 m		7 m		11 m (intermittent pyrexia)	7 m			
		# 2 (7 m)	3 m		3 m		3 m (intermittent pyrexia)	3 m			

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Country[a]	# of patients[b] (disease duration)	Hypertension	Blood pressure nocturnal non-dipping	Tachycardia	Breathing disorder	Hyperthermia	Hyperhidrosis	Gastrointestinal disorder	Genito-urinary disorder	Other dysautonomia
Perani et al. (1993)	IT	4 cases - 1 new [FFI-1 IV-80] (48 m – alive)									(Moderate sympathetic hyperactivity; preserved vagal function)
Cortelli et al. (1991)	IT	2 cases:									
		# 1 [FFI-1 V-58] (25 m)	15 m	20 m (hypertension; reduced circadian variation of BP, obliterated at 23 m)	15 m (tachycardia) 20 m (reduced circadian variation of HR, obliterated at 23 m)	20 m (irregular breathing; apnea)	Onset (fever)	Onset	20 m (incontinence)	20 m (incontinence)	Onset (excessive salivation; amenorrhea) 15 m (sympathetic hyperactivity; preserved vagal response at cardiovascular reflexes and pharmacological tests)
		# 2[FFI-1 IV-16] (32 m)		6 m (hypertension; reduced circadian variation of BP)	6 m (tachycardia; reduced circadian variation of HR)		6 m (intermittent fever)	6 m (intermittent sweating)			6 m (excessive salivation, sympathetic hyperactivity; preserved vagal response at cardiovascular reflexes and pharmacological tests)
Unspecified Polymorphism at Codon 129 (U) - 23 patients (mean disease duration: 11.9 m)											
Bian et al. (2018)	CN	6 (9 m)									(Unspecified dysautonomia)
Peng et al. (2015)	CN	1 (9 m)							Onset (constipation)		
Gistau et al. (2006)	SP	1 (13 m)	10 m		10 m		10 m	10 m		10 m (urinary retention)	
Spacey et al. (2004)	CN	1 (12 m)									
Tabernero et al. (2000)	SP	1 (5 m)				2 m (respiratory insufficiency)	2 m (fever)	2 m			Onset (amenorrhea) 2 m (bilateral late responsive miosis)
Brown et al. (1998)	US (UK)	2 cases:									
		# 1 (20 m)									
		# 2 (15 m)									
Zerr et al. (1998)	DE	1 (7 m)	–				–	+	–		
McLean et al. (1997)	AU (IE)	5 cases									
		# 1 (12 m)						Onset			
		# 2 (17 m)									–
		# 3 (20 m)									–
		# 4 (9 m)						8 m			
		# 5 (7 m)							(Diarrhea)		
Bosque et al. (1992)	US	1 (25 m)					Onset (fever)	Onset (nocturnal sweating)			
Julien et al. (1990)	FR	2 cases:									
		# 1 (8 m)									–
		# 2 (11 m)	10 m			Onset (nocturnal respiratory pauses)	10 m	10 m			10 m (miosis)

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Country[a]	# of patients[b] (disease duration)	Hypertension	Blood pressure nocturnal non-dipping	Tachycardia	Breathing disorder	Hyperthermia	Hyperhidrosis	Gastrointestinal disorder	Genito-urinary disorder	Other dysautonomia
Little et al. (1986)	UK	2 cases: # 1 (17 m) # 2 (12 m)				10 m (respiratory distress)					

Legend. m: months; +: symptom/sign present, but not better specified; −: symptom/sign searched and absent.

[a] Countries are indicated using ISO-3166 two letters Country Codes (ISO 3166 Maintenance Agency); if the descendancy of the patient is different from the nationality it is put in brackets.

[b] If the same case is described in more than one article information is referred to the first one describing it.

[c] Mean disease duration of the reported cases.

2. Fatal familial insomnia

2.1. Demographics

FFI typically appears between the fourth and sixth decade of life, most often between the ages of 51 and 60 years (Montagna, 2005), although early onset cases have also been reported (Almer et al., 1999; Harder et al., 2004; Rupprecht et al., 2013), up to 18 years of age (Dimitri et al., 2006). The patients' genotype of the unmutated allele of PRPN seems to influence both disease course and clinical presentation. FFI patients homozygous at codon 129 (codifying M also in the non-mutated allele at codon 129 of PRPN) have a more rapid evolution (11.6 ± 5.1 months) than FFI heterozygous patients (codifying V at position 129 of the non-mutated allele) who have a two- to three-fold longer disease duration (21.8 ± 12.8 months) (Table 1) (Montagna et al., 1998). Moreover, the short-evolution cases (M-M patients homozygous at codon 129) present the most typical features of the disease (Montagna et al., 2003).

Up to date, more than 70 affected families have been identified all over the world and in every ethnic group, with China presenting the absolute highest number of cases (> 25 kindreds) and Germany and Spain the highest prevalence in relation to their population (Cracco et al., 2018).

2.2. General features

2.2.1. Symptoms and signs

The clinical picture of FFI can be divided into three categories including sleep disorders, autonomic and classic prion disease neurological symptoms such as disorders of ocular movements, pyramidal signs, myoclonus, gait disturbances, apraxia and cognitive impairment (Cortelli et al., 2006; Cracco et al., 2018).

Changes in sleep with difficulties in falling asleep, early awakening and inability to take usual naps is one of the earliest features of the disease. At the same time, patients appear drowsy (with head and eyelid drops) during daytime and apathetic, though social behavior is preserved. Hypertension, slight evening pyrexia, a tendency to perspire, lacrimate and salivate, impotence and fluctuating diplopia accompany early insomnia in some cases. Sleep and autonomic alterations progressively worsen, patients become increasingly taciturn and appear indifferent to their surroundings and even their fate. When left alone, patients lap into a state of unresponsiveness showing peculiar motor behaviors during which they mimic daily-life activities, such as dressing, combing the hair, washing, and manipulating non-existent objects. If questioned, patients link these gestures to an oneiric scene, thus, the definition of “oneiric stupor” (Guaraldi et al., 2011; Lugaresi and Provini, 2007). Disturbances of gait (Cortelli et al., 2014), disequilibrium, dysmetria, spontaneous and evoked myoclonus and signs of pyramidal involvement such as deep hyperreflexia and Babinski's sign progressively appear. Later stages are characterized by ever-increasing oneiric stupors, inability to stand and walk, increasing dysarthria and dysphagia. Death supervenes for cardiorespiratory failure or intercurrent respiratory or systemic infections (Montagna et al., 2003).

Patients with 129MM genotype usually present sleep and vegetative disturbances as earliest symptoms, compared to 129MV who typically show visual symptoms and ataxia (Montagna et al., 1998). Throughout the disease course homozygotes tend to have more prominent insomnia, myoclonus, autonomic dysfunction, spatial disorientation, hallucinations and weight loss, while heterozygotes are more likely to demonstrate ataxia with equilibrium impairment and latero-retropulsion, dysarthria, seizures and bulbar symptoms (Cortelli et al., 2014; Cracco et al., 2018; Krasnianski et al., 2014).

2.2.2. Neurophysiological features

Longitudinal 24-h polysomnographic monitoring documents severe sleep fragmentation, reduction of total sleep time and a sleep-wake

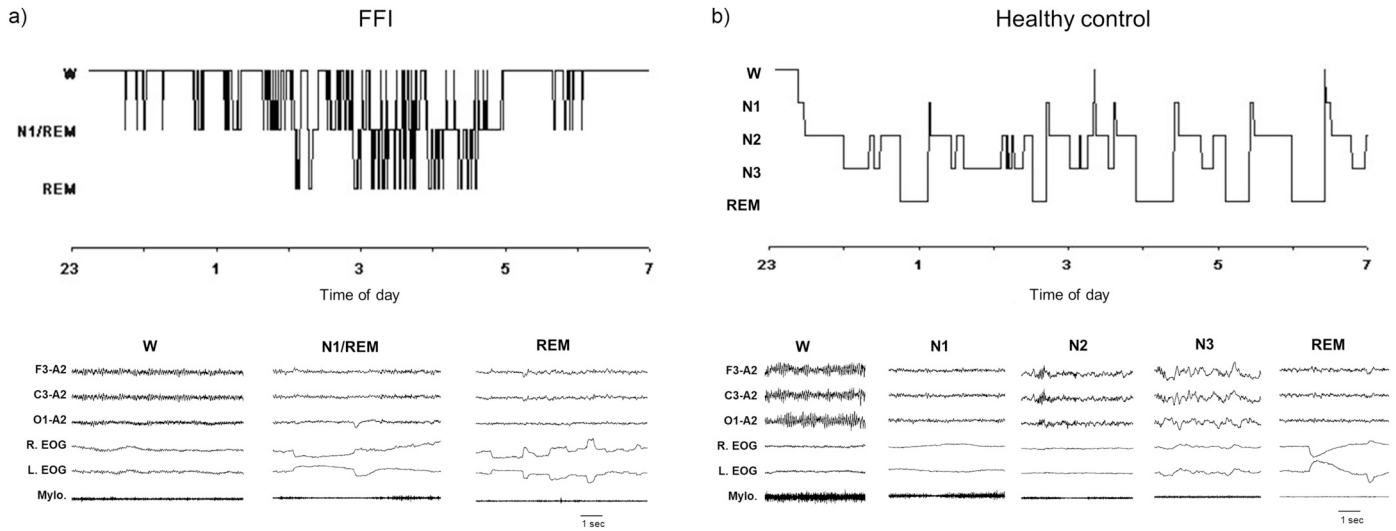

Fig. 1. Hypnogram (upper graph) and related excerpts of a polygraphic tracing (lower graph) in a patient with Fatal Familial Insomnia (FFI) (a) and in an age-matched healthy control individual (b). In the FFI patient the hypnogram continuously fluctuates between wake and subwakefulness (N1/REM) with short intrusions of REM sleep; the polygraphic excerpts show abolishment of spindle and delta sleep. EEG (F3-A2; C3-A2; O1-A2); R.: right; L.: left; EOG: electrooculogram; Mylo: mylohyoideus muscle.

cycle derangement with an early permanent and progressive reduction in sleep figures (spindles and K complexes) and deep sleep (delta sleep - slow wave sleep - SWS) (Sforza et al., 1995; Tinuper et al., 1989), more severe in the short disease course (Fig. 1). This derangement from physiological sleep, resulting from severe damage of the thalamic machinery, responsible for sleep generation, rules out the applicability of sleep scoring according to international criteria (Berry et al., 2017).

Subwakefulness is the predominant nocturnal and diurnal EEG and behavioral pattern consisting of stage 1 NREM sleep. This stage can be interrupted by sudden-onset episodes of rapid-eye-movement (REM) sleep with or without atonia lasting a few seconds or minutes (Lugaresi et al., 2011). This condition represents the neurophysiological substrate of dream enactment behaviors characterizing oneiric stupor, which can emerge from any of these stages.

The loss of sleep is associated with a loss of 24-h circadian motor rhythmicity documented by long-term actigraphic monitoring (Plazzi et al., 1997). Indirect calorimetry shows that energy expenditure is up to 60% more than in healthy controls (Plazzi et al., 1997), a feature associated with the severe metabolic exhaustion and cachexia in FFI patients (Montagna et al., 2003).

2.2.3. Neuropsychological features

Serial neuropsychological examinations document an early progressive impairment of attention and vigilance, whereas intellectual function remains substantially intact until the advanced stages of disease, resembling more a disturbance of consciousness (confusional state) rather than true dementia (Gallassi et al., 1996).

2.2.4. Neuroimaging

CT and MRI scans are unremarkable except for a mild cerebral and cerebellar atrophy in the most advanced disease stages. Serial PET (18 FDG-PET) scans invariably show an impaired thalamic metabolism from the early stages of the disease (Cortelli et al., 1997) or even several months before clinical disease onset in FFI mutation carriers (Cortelli et al., 2006). Although hypometabolism is invariably more pronounced in the thalamus, it extends to the mesial areas of the frontal lobe as the disease progresses, affecting the entire cortex and basal ganglia in the most advanced disease stages of long-evolution cases. The metabolic impairment prevails in the mesial areas of the frontal lobe in both short- and long-evolution cases (Cortelli et al., 1997).

2.2.5. Pathology

Bilateral thalamic degeneration (with neuronal loss and astrogliosis) is the invariable finding of FFI. The mediodorsal (MD) and anteroventral (AV) nuclei are the thalamic formations most consistently and most severely affected with neuronal loss often reaching 95–100% (Kong et al., 2004). Other thalamic nuclei are variably and less severely involved. The inferior olives undergo similar atrophy in most cases. The involvement of the cerebral cortex is directly related to disease duration: mild spongiform degeneration confined to the orbitofrontal cortex and anterior cingulate gyrus is commonly seen in short duration cases, whereas the cortical spongiform degeneration is widespread in cases of long duration. However, in accordance with PET findings, the cortical involvement is always most prominent in the corticolimbic regions regardless of the disease duration (Cracco et al., 2018; Kong et al., 2004; Parchi et al., 1998).

2.2.6. Prion protein analyses

Immunoblot analysis of the brain homogenates shows that, following deglycosylation, treatment with proteinaseK (PK), the protease-resistant (PK-res) fragment of the abnormal, disease-related prion protein (PK-resPrP^{Sc}), displays electrophoretic mobility corresponding to a relative mass of 19 kDa in FFI, and 21 kDa in $fCJD^{178}$ (Monari et al., 1994). Amino-acid sequencing of the PK-resPrP^{Sc} fragments isolated in the two diseases shows that the fragment N-terminus is aminoacid 97 in FFI and 82 in $fCJD^{178}$ (Parchi et al., 2000). These data show that the PrP^{Sc} species associated with FFI and $fCJD^{178}$, respectively, are cleaved by PK at distinct sites (97 and 82) generating fragments of different sizes. In turn the finding that PK cleaves PrP^{Sc} at distinct sites in FFI and $fCJD^{178}$ provides strong evidence that the conformation of PrP^{Sc} associated with these two diseases is different (Gambetti et al., 2003).

2.3. Dysfunction of the autonomic nervous system

Physiologic control of the autonomic system results from the balance between sympathetic and parasympathetic activity regulated by medullary reflexes and descending influences from the central autonomic network. This control allows the punctual regulation of visceral functions and processes controlling vital functions in response to internal and external demands with the final aim of maintaining body homeostasis (Benarroch, 1997).

Unbalanced autonomic functions with a prevalent sympathetic

activity are of utmost clinical relevance in FFI, not only for the signs and symptoms, but also for the related increased risk of mortality (Casas-Mendez et al., 2011; Dauvilliers et al., 2004; Montagna et al., 1994; Peng et al., 2015; Sun et al., 2017). Described as dysautonomia in more than 80% of patients reported in literature (Table 1), it could actually be a feature of all FFI patients, as some authors could not have specifically looked for it. To note, only three authors among reports on more than 120 patients explicitly state the absence of dysautonomia (Almer et al., 1999; Julien et al., 1990; McLean et al., 1997). Moreover, while cardiovascular and neuroendocrine (impaired) control have been analyzed in detail in FFI, the other autonomic features see sporadic and episodic description related to single case studies.

2.3.1. Cardiovascular

2.3.1.1. Blood pressure and heart rate. Cardiovascular signs and symptoms, clinically expressing as increased heart rate (HR) or elevated arterial blood pressure (BP), are recorded or measured in about 50% of patients. However, only few studies on BP and HR circadian rhythms are available, as longitudinal 24-h monitoring and precise evaluations are needed to document the severity of autonomic control disruption and its evolution throughout the course of the disease (Fig. 2) (Calandra-Buonaura et al., 2016).

Nocturnal BP fall is the first component of BP circadian rhythm to be markedly reduced or completely lost in FFI patients (Portaluppi et al., 1994a). However, at the early stage of the disease 24-h BP and HR profiles remain unchanged or mildly reduced in amplitude in their globality and patients are generally normotensive (Cortelli et al., 1999; Portaluppi et al., 1994a). As the disease progresses, the amplitude of circadian variations of BP and HR decreases further and patients develop full-blown and steady hypertension and tachycardia (Colombier et al., 1997; Portaluppi et al., 1994a), until complete obliteration of BP and HR rhythm profiles in the preterminal stage of the disease (Fig. 3a, black line and dots) (Lugaresi et al., 1986; Portaluppi et al., 1994a).

2.3.1.2. Hormonal and catecholamines circadian rhythms. In FFI early stages, although hormonal circadian rhythms are maintained, cortisol levels are already persistently increased, positively modulating vascular response to catecholamines and increasing sympathetic activity (Figs. 2 and 3b, gray shade). In later stages, further elevation in cortisol with normal adrenocorticotropin (ACTH) has been documented in association with a pathological nocturnal peak of cortisol and ACTH. In addition, norepinephrine (noradrenaline – NA) and epinephrine (adrenaline – A) levels elevation shows synchronism with the persistent tachycardia (Fig. 3a&b, black line and dots). Only the preterminal stage of the disease sees complete obliteration of the hormonal rhythms (Portaluppi et al., 1994a).

The circadian secretory patterns of somatotropin and prolactin (Portaluppi et al., 1995) are abnormal, negatively affecting menstrual cycle (Cortelli et al., 1991; Tabernero et al., 2000). Moreover, melatonin (MLT) secretion is reduced as most of the patients lack its physiological nocturnal peak, until the complete obliteration of its rhythm later on (Portaluppi et al., 1994b).

All these findings point to an impaired control of the cardiovascular system in FFI characterized by a higher sympathetic activity with preserved parasympathetic activity.

2.3.1.3. Physiological tests evaluating autonomic function. A sympathetic overactivity in FFI patients is also supported by the responses to autonomic functions tests (Colombier et al., 1997; Cortelli et al., 1991; Lugaresi et al., 1986). Already at early stage of the disease, although normotensive, patients usually present supine tachycardia and a high rise in NA at head-up tilt test. Later, with disease progression, patients can develop mainly systolic orthostatic hypotension, probably due to the deconditioning of patients, often bedridden at this stage, counterbalanced by a greater HR, plasma NA and A increase in response to orthostatism excluding sympathetic failure at this stage. At Valsalva Maneuver a prompt rise in HR during the hypotension phase, which is sometimes excessively marked (Colombier et al., 1997), is followed by a greater blood pressure overshoot with maintained compensatory bradycardia, which is maintained also during deep breathing test (Cortelli et al., 1991). In other cases BP is increased until no further change is seen during overshoot (Lugaresi et al., 1986), suggesting that the response to sympathetic stimuli, are not only increased but also not appropriately modulated (Cortelli et al., 1991), as it is also seen in cold pressure test where BP rise is conversely lower than normality (Colombier et al., 1997). Moreover, sympathetic overactivity is confirmed by abnormal diastolic BP rise at handgrip test (Cortelli et al., 1991) and by increased resting awake muscle sympathetic nerve activity (MSNA) (Donadio et al., 2009).

2.3.1.4. Pharmacological tests evaluating autonomic function. Infusing noradrenaline does not lead to a rise in BP, even if dosage is increased, in accord with the already markedly increased levels of catecholamines, which probably result in the downregulation of adrenoreceptors. On the other hand, atropine induces an abnormal rise in HR (Cortelli et al., 1991; Lugaresi et al., 1986) highlighting that, when parasympathetic tone is artificially withdrawn, an unrestrained sympathetic activity is exposed. Finally, although arterial hypertension can be controlled with beta-blockers in FFI patients (Bar et al., 2002; Synofzik et al., 2009), clonidine, a central sympathetic inhibitor, fails to obtain its full BP depressor and sedative effect, which is completely lost in patients with a longer duration of the disease (Cortelli et al., 1991) unveiling a refractory sympathetic dyscontrol.

2.3.2. Other dysautonomic features

2.3.2.1. Breathing. Autonomic dysfunction of breathing control is reported in about one fifth of literature cases (Table 1). Nocturnal breathing disorders have been described at onset in 4 patients, either as an irregular rhythm (Lee et al., 2014) or as respiratory pauses (Julien et al., 1990; Sun et al., 2017); in one case a respiratory noise functionally compatible with vocal cord adduction has also been clinically reported (Shi et al., 2010). Later on, patients develop diurnal alterations of breathing such as persistent tachypnea at rest (Lugaresi et al., 1987) and labored breathing. Terminal stages of FFI are variably characterized by respiratory failure, vocal cord adduction (Reder et al., 1995) or abnormal breathing rhythms (Biot's breathing) (Casas-Mendez et al., 2011; Colombier et al., 1997), which often require noninvasive ventilation (Casas-Mendez et al., 2011) or intubation (Fukuoka et al., 2018; Montagna et al., 1994; Montagna et al., 2003; Tabernero et al., 2000).

2.3.2.2. Body temperature. Increased body temperature has been observed in more than one third of FFI patients at early stages (Table 1), presenting as mild forms of evening pyrexia (Shi et al., 2010) or as more structured intermittent fever spikes without inflammatory correlates (Fukuoka et al., 2018; Silburn et al., 1996). As the disease progresses, the patients can experience a stabilization of the hyperthermia, which remains steady and difficultly treatable (Lugaresi et al., 1986; Reder et al., 1995). The circadian rhythm of body core temperature (BCT) is progressively severely disrupted during the disease course with a full suppression in advanced stages (Lugaresi et al., 1987; Montagna et al., 1994). As a matter of fact, FFI patients present higher mean BCT without any clear-cut fluctuations during the 24-h lacking the physiological nocturnal reduction (Fig. 2 and 3).

Hyperstimulation of sweating glands leads to hyperhidrosis, described in about 40% of the patients in the literature (Table 1). Frequently present at onset (Bosque et al., 1992; Harder et al., 1999), nocturnal or also diurnal (Cortelli et al., 1991; Frobose et al., 2012; McLean et al., 1997), intense sweating can be a steady condition or a part of an episodic “autonomic storm” (see Section 2.3.3) (Lugaresi et al., 1987).

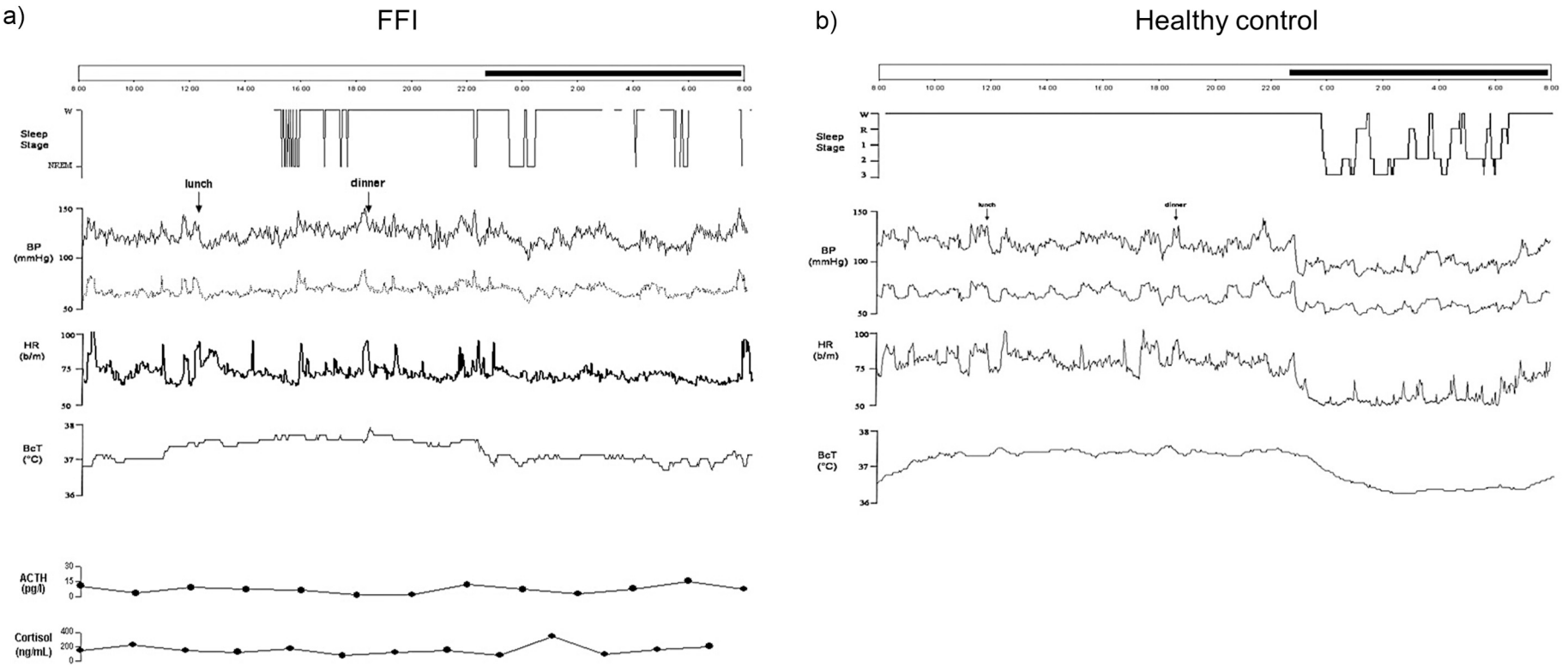

Fig. 2. Twenty-four-hour polygraphy in a patient with Fatal Familial Insomnia (FFI) (a) and in an age-matched healthy control individual (b) showing (from top to bottom) hypnogram and circadian rhythms of systolic and diastolic blood pressure (BP), heart rate (HR), body core temperature (BcT), adrenocorticotropin (ACTH) and of cortisol (FFI only). In comparison to the control, 24-h systolic and diastolic BP recordings lack the physiological nocturnal fall. The amplitude of HR circadian variation is markedly decreased; daytime HR peaks correspond to assumption of orthostatism. BcT nocturnal drop is impaired. Nocturnal pathological elevation of cortisol is independent of ACTH serum levels.

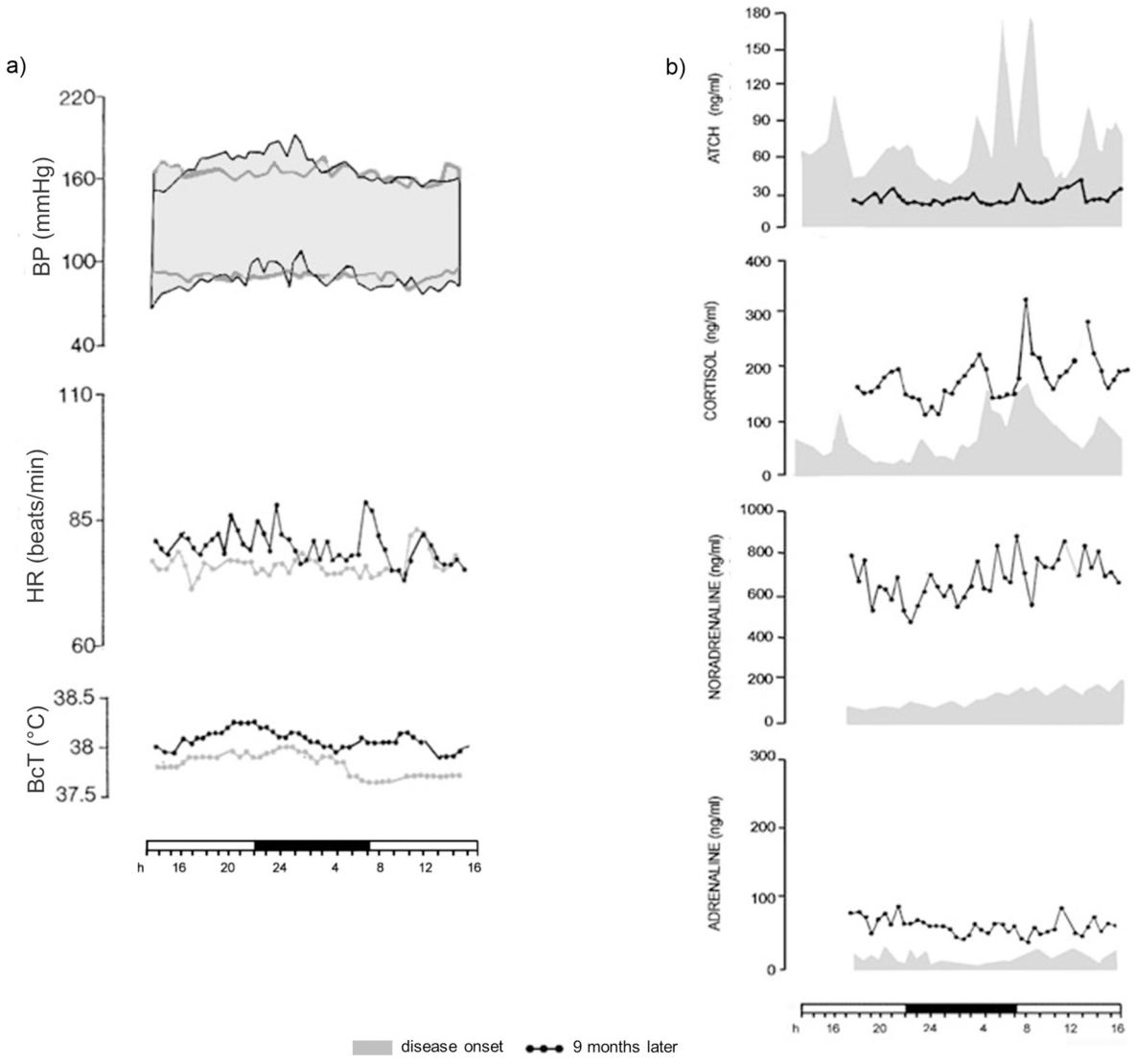

Fig. 3. Progressive disruption of 24-h rhythms of systolic and diastolic blood pressure (BP), heart rate (HR) and body core temperature (BcT) (a), adrenocorticotropin (ACTH), cortisol and catecholamines (b) during Fatal Familial Insomnia disease course. The gray line and shade represent values at disease onset, black lines after 9 months of disease. BP, HR, BcT, catecholamines and cortisol progressively set to higher levels.

2.3.2.3. Gastrointestinal. Decrease of gut motility due to sympathetic hyperactivity is probably the cause of constipation, generally reported among FFI patients, sometimes at onset (Almer et al., 1999; Peng et al., 2015). Gastrointestinal control impairment can manifest also as diarrheic syndrome (McLean et al., 1997) or meteorism (Zerr et al., 1998). When the disease reaches advanced phases (of neurodegeneration) dysregulation of sphincteric control, thus incontinence, can appear (Cortelli et al., 1991; Lugaresi et al., 1986).

2.3.2.4. Genito-urinary. Genito-urinary dysautonomia is frequent in FFI patients. When at onset it often presents as impotence in men and/or loss of libido in both sexes (Friedrich et al., 2008; Rossi et al., 1998; Saitoh et al., 2010), while urinary symptoms are less relevant at this stage, especially in short course MM patients.

In later stages, similarly to gastrointestinal alterations, the impairment of sphincteric control affects also micturition leading to incontinence (Cortelli et al., 1991; Harder et al., 1999; Lugaresi et al., 1986). Few cases, however, report the association of constipation and urinary retention (Lu et al., 2017; Spacey et al., 2004). This could suggest a dyssynergia of urinary sphincters more than a univocal insufficiency, probably related to a pathological adaptation to the underlying chronic sympathetic overactivity; however, urodynamic testing was never performed in these patients.

2.3.2.5. Salivation, lacrimation and pupillary tone. Excessive salivation and lacrimation can be found, either persistent (Lugaresi et al., 1986; Shi et al., 2012) or paroxysmal (Lugaresi et al., 1987).

Pupillary tone alteration, miotic (Julien et al., 1990; Medori et al., 1992) or mydriatic (Tabernero et al., 2000) and more frequently late- or non-responsive to light stimuli pupils (Haik et al., 2008; Tabernero et al., 2000) have been described.

2.3.3. FFI: a disease characterized by unbalanced autonomic control with sympathetic hyperactivation

To sum up, 1) the setting of BP, HR and temperature circadian rhythms to a higher level and their later disruption, 2) exaggerated NA and BP increase in response to physiologic stimuli (orthostatism and Valsalva respectively), 3) increased mean level of resting awake MSNA, 4) absent BP rise after NA infusion, 5) abnormal HR increase after atropine infusion and 6) reduced effects of clonidine, 7) increased paroxysmal or persistent sweating, salivation and lacrimation and 8) sphincteric dysregulation leading to complete insufficiency, point out

the presence of an increased sympathetic tone, responsive (even if only partially) to stimuli at early stages and completely dysregulated and unhinged in later phases in FFI patients. Hence, the sympathetic hyperactivation and the loss of its control, in terms of lack of any circadian rhythms and response to stimuli, are the two focal clinical points in FFI autonomic alterations. Illustrative of this condition are "autonomic storms", a possible event in FFI, characterized by a paroxysmal burst of sympathetic activity clinically translating into episodic hyperthermia, hypertension and tachycardia associated with excessive sweating, salivation and lacrimation which can precede short periods of SWS usually felt by patients as very restorative even if lasting only few minutes (Lugaresi et al., 1987).

2.4. Sporadic familial insomnia

Patients sharing clinical and histopathologic features with FFI, without any PRNP mutation or any positive familial history, have been ascribed to the clinical definition of Sporadic Fatal Insomnia (sFI) (Abu-Rumeileh et al., 2018; Montagna et al., 2003), often referred to as the thalamic form of sCJDMM2 (Hayashi et al., 2015; Iwasaki et al., 2017; Moda et al., 2012).

The sFI clinical and histopathologic phenotype appears to be more variable than that of the FFI variant linked to the 129 homozygous genotype (Cracco et al., 2018; Montagna, 2005). Consequently, although many symptoms of sFI overlap with those observed in FFI, insomnia has not been a prominent symptom in many cases of sFI (only 29% of patients at onset) (Puoti et al., 2012), unless specifically investigated (Moda et al., 2012). This is true also for autonomic symptoms, reported only in half of the illustrated cases (Table 2) and in one third of the recently reviewed European patients (Abu-Rumeileh et al., 2018). Impaired breathing control and genito-urinary symptoms are the most frequent, while cardiovascular ones, heralding features of FFI, are described in just one patient with hypertension. On the one hand, this outcome is predictable since the specific FFI mutation D178N is likely to impose more constraints on the initial spontaneous conversion to a prion-like conformation of the mutated PrP compared to the presumably idiopathic conversion (Collinge and Clarke, 2007; Imberdis and Harris, 2016). On the other, autonomic symptoms may not have been the main focus of these reports and therefore not searched in detail. Several cases have been generically described as "with dysautonomia", which probably, if specifically investigated, could have been more frequent in sFI patients (Abu-Rumeileh et al., 2018).

Other symptoms overlap with those observed in FFI such as cognitive decline and/or ataxia (42%) at disease onset and cognitive impairment, ataxia, insomnia and myoclonus in the more advanced stages. Moreover, symptoms characterizing atypical parkinsonian syndromes, such as oculomotor symptoms, dyskinesia, and parkinsonism are often present in sFI at presentation (Cracco et al., 2017; Parchi et al., 1999b).

Eventually, although the phenotypic similarities to FFI outweigh the features shared with any of the sCJD subtypes, the absence of pathognomonic clinical signs, the young age at onset, and the relatively low sensitivity of classical diagnostics make the clinical diagnosis of sFI challenging (Abu-Rumeileh et al., 2018).

3. AGRYPNIA EXCITATA in other neurological disorders

The clinical hallmark of FFI, Agrypnia Excitata is a definite clinico-neurophysiological condition characterized by: 1) slow wave sleep loss with disruption of the physiological sleep-wake cycle, 2) a day and night, motor, sympathetic and aminergic overactivity and 3) peculiar episodes of oneiric stupor (Lugaresi and Provini, 2001; Lugaresi and Provini, 2007; Lugaresi et al., 2011; Montagna and Lugaresi, 2002; Provini, 2013), which must be fulfilled to make the diagnosis.

1. Disruption of the sleep-wake cycle consists in: a) the disappearance of spindle-delta activities, b) REM sleep fails to stabilize, appearing only in short recurrent episodes or mixed with stage 1 NREM sleep. Behaviorally, the mixture of stage 1 and REM sleep results in a state of somnolence or mental confusion accompanied by hallucinations, delirium and oneiric stupor (Guaraldi et al., 2011).
2. Twenty-four-hour diurnal and nocturnal (circadian) motor, sympathetic and aminergic overactivity are fundamental signs of AE. Of particular interest is the steady higher secretion of NA during both day and night in opposition with reduced MLT levels and the absence of its nocturnal peak. This inverse correlation between the circadian secretion of NE and MLT could constitute a biological marker of AE (Lugaresi et al., 2011).
3. Oneiric stupor, the third characteristic sign of AE, consists in the recurrence of stereotyped gestures mimicking daily-life activities (Fig. 4). OS should not be confused with REM Sleep Behavior Disorder (RBD), real enacted dreams, appearing during REM sleep without atonia. Moreover, while OS are clinically reported by patients as a single oneiric scene, RBD are enactments of a true dream in which emotions and memories are transformed into a fantastic movie-like plot (Provini and Tachibana, 2019).

Outside FFI, Agrypnia Excitata has been canonically observed in other diseases presenting different pathophysiological mechanisms, such as Morvan Syndrome (MS) and Delirium Tremens (DT).

3.1. Morvan Syndrome

Diffuse muscle contractions (myokimias and cramps), associated with acute insomnia, anxiety and profuse perspiration characterize the syndrome first described by Morvan (Morvan, 1890). In most cases, MS resolves in a few weeks or months, but in others the progressive worsening of symptoms leads to a confusional-oneiric state preceding death by months or more seldom years, as described by Liguori et al. (Liguori et al., 2001). MS is usually an autoimmune disease presenting serum antibodies against voltage-gated K^+ channels (VGKC) and may have a paraneoplastic origin (Liguori et al., 2001; Vincent et al., 2004).

3.1.1. Neurophysiological features

Fisher-Perroudon et al.(Fischer-Perroudon et al., 1974), using polygraphic techniques, showed for the first time in an MS patient the complete absence of sleep four months prior to demise. This finding was subsequently confirmed by others (Cornelius et al., 2011; Liguori et al., 2001; Murri et al., 1976).

Serial polysomnographic recordings in MS usually document a complete absence of spindles and delta activity with the predominance of a state intermediate between stage 1 (dominant theta activity and slow eye movements) and REM sleep (transient reduction of muscle tone or REM discharges), resembling the state of "subwakefulness" described in FFI patients, interspersed with intrusions of more definite REM epochs (Fig. 5, middle graph) (Provini et al., 2011).

3.1.2. Autonomic and hormonal findings

Hyperhidrosis is present in almost every patient described in literature. Tachycardia, fluctuations in blood pressure with hypertensive crisis are also commonly reported (Abou-Zeid et al., 2012), while laboratory examinations reveal increased and disrupted hormonal rhythms and altered responses to physiological stimuli (Liguori et al., 2001).

Twenty-four-hour plasma levels of NA can be up to two-fold higher than in healthy controls, without any physiological nocturnal decrease (Liguori et al., 2001) or even with an increased nychthemeral secretion (Spinazzi et al., 2008). Blood levels of ACTH and cortisol are reported to be slightly raised at night with preserved physiological early morning increases. Melatonin levels are lower than normal in the absence of any circadian rhythm. Prolactin and growth-hormone levels are negatively affected too (Liguori et al., 2001).

Plasma NA, already increased at supine rest, presents an abnormal

Table 2
Distribution of dysautonomic signs and symptoms in published cases of confirmed (genetically and/or pathologically) Sporadic Familial Insomnia (sFI), divided by pathological peculiarity (Cracco et al., 2018) and listed by year of publication.

Author (year)	# of patients (disease duration)	Hypertension	Blood pressure nocturnal non-dipping	Tachycardia	Breathing disorder	Hyperthermia	Hyperhidrosis	Gastrointestinal disorder	Genito-urinary disorder	Other dysautonomia
sFI cases with typical pathology - MM2-thalamic										
Cracco et al. (2017)	4 (24 m)[a]									
Grau-Rivera et al. (2016)	1 (24 m)					20 m (fever)				
Hayashi et al. (2015)	1 (16 m)									
Blase et al. (2014)	1 (35 m)				35 m (respiratory failure)			5 m (incontinence)	5 m (incontinence)	
Moda et al. (2012)	2 (27 m)[a]									
Moody et al. (2011)	1 (22 m)									10 m (anisocoria)
Capellari et al. (2008)	1 (24 m)				(Sleep apnea)				(Incontinence)	(Unspecified autonomic hyperactivity)
Iwasaki et al. (2006)	2 (31 m)[a]									
Hamaguchi et al. (2005)	5 (39 m)[a]									(Unspecified dysautonomia in 2 cases)
Yamashita et al. (2001)	1 (73 m)					Onset (fever)				
Parchi et al. (1999a)	5 cases:									
	# 1 (18 m)								5 m (impotence)	
	# 2 (15 m)				15 m (respiratory insufficiency)	15 m (fever)				
	# 3 (24 m)									
	# 4 (15 m)									
	# 5 (17 m)								13 m (incontinence)	
Mastrianni et al. (1999)	1 (16 m)				10 m (loss of cough reflex)					1 m (heat intolerance) 6 m (excessive lacrimation)
Kawasaki et al. (1997)	1 (53 m)								10 m (neurogenic bladder)	Onset (photophobia) 14 m (orthostatic hypotension)
sFI cases with atypical pathology - MM1, MM1 + MM2, other										
Iwasaki et al. (2017)	1 (5 m)									
Fernandez-Vega et al. (2015)	1 (27 m)									
Saito et al. (2011)	1 (32 m)								24 m (retention)	
Priano et al. (2009)	1 (10 m)	8 m			Onset (obstructive sleep apnea) 8 m (irregular breathing with desaturations)	8 m				
Mehta et al. (2008)	1 (42 m)									
Hirose et al. (2006)	1 (30 m)						10 m			10 m (unspecified dysautonomia in addition to hyperhidrosis)
Piao et al. (2005)	1 (29 m)									

Legend. m: months.
[a] Mean disease duration of the reported cases.

Fig. 4. Frame sequence of an oneiric stupor episode in a patient with Fatal Familial Insomnia. The patient performs gestures such as pointing at something and manipulating an inexistent object, quietly mimicking usual daily life activities.

increase in orthostatism; the appearance of numerous extrasystoles makes it almost impossible to measure HR response to further testing (Liguori et al., 2001; Spinazzi et al., 2008). After plasma exchange treatment, autonomic responses remain pathological, but to a lesser extent, allowing us to highlight the absence of HR adjustment during Valsalva maneuver and deep breathing test (Liguori et al., 2001). Moreover, MSNA showed that sympathetic activity was much more elevated than in controls during resting wakefulness in two MS patients (Donadio et al., 2009).

3.1.3. Neuropathology

Brain examination is grossly unremarkable. In the case described by Liguori et al. MS patient's serum IgG link predominantly with rat brain hippocampus and thalamus on indirect immunohistochemistry; thalamus and striatum are the areas of substantial leakage of IgG on direct immunohistochemistry (Liguori et al., 2001).

3.1.4. Pathogenesis

It has been suggested that the VGKC antibodies may act on the peripheral nervous system as well as centrally, crossing the blood–brain barrier and binding predominantly to thalamic and striatal neurons (Abou-Zeid et al., 2012; Liguori et al., 2001). Recent studies documented that the target autoantigens are generally not VGKC proteins, but neuronal proteins that interact functionally and structurally with a specific subset of VGKC complexes (Cornelius et al., 2011). Nonetheless, it should be emphasized that, regardless of the different molecular pathogenetic mechanisms, the VCGK complex autoimmune disorders typically share sleep disturbances and the accompanying state of motor and autonomic activation related to a dysfunction of thalamo-limbic circuits (Irani and Vincent, 2016).

In agreement with clinical findings, experimental laboratory data have shown that sub-families of VGKCs are involved in wake–sleep cycle regulation (Cirelli et al., 2005; Espinosa et al., 2004; Espinosa et al., 2008). In fact, not only VGKC mutated flies (Cirelli et al., 2005) and Kv3.1-Kv3.3 VGKC subunits-knocked-out mice (Espinosa et al.,

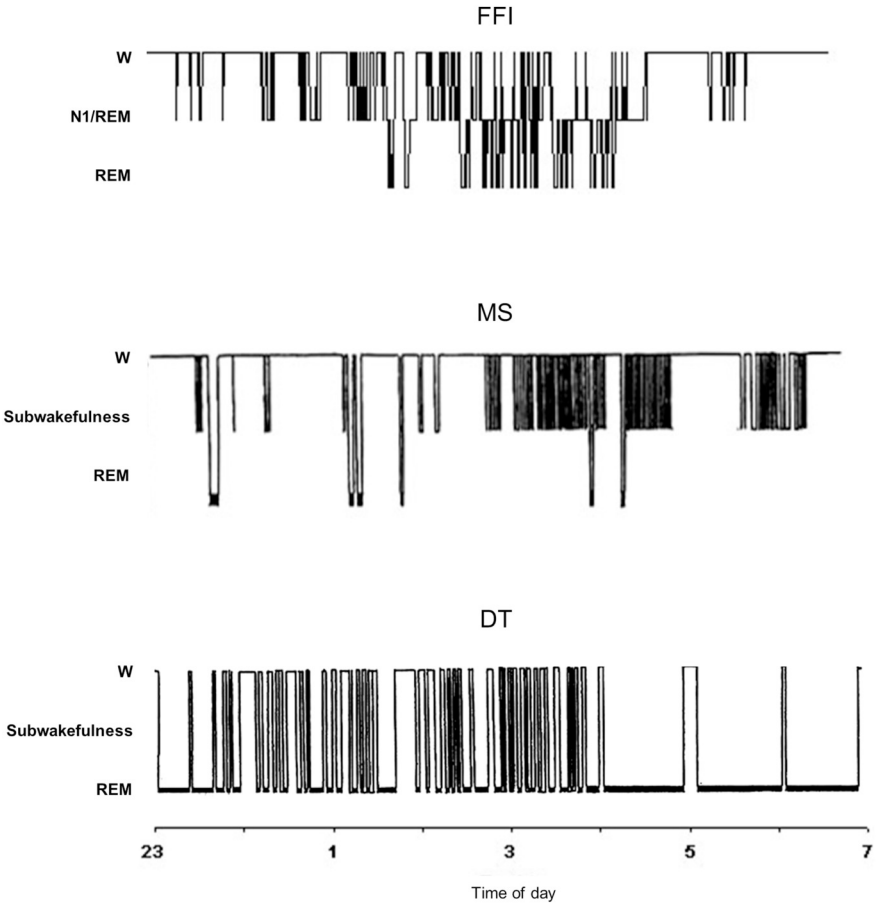

Fig. 5. Hypnograms in a patient with Fatal Familial Insomnia (FFI – upper graph) and in patients with Morvan Syndrome (MS – middle graph) and Delirium Tremens (DT – lower graph). Deep sleep is absent in all the three conditions; N1/REM-Subwakefulness and REM sleep episodes are the only stages recorded.

2004) present a marked reduction in sleep time, but also these same subunits are particularly expressed in mice's thalamic reticular nucleus, which plays a crucial role in synchronized sleep generation (Espinosa et al., 2008).

3.2. Delirium tremens

Alcohol withdrawal syndrome (AWS) arises within 48 h after the last drink in alcohol abusers. The signs and symptoms of AWS consist of tremors, nausea, perspiration attacks, anxiety, motor agitation, and insomnia. Unless prompt appropriate treatment is given, AWS may develop into a fluctuating disturbance of consciousness accompanied by hallucinations, delirium, and dream enactment with motor agitation and severe autonomic signs (profuse perspiration, tachycardia, and hyperventilation), an acute psychotic state commonly termed delirium tremens (DT) (Provini et al., 2008).

In a typical case of DT Plazzi et al. (Plazzi et al., 2002) described a confusional-oneiric state consisting of hallucinations and violent dream enactment, but also calmer gestures mimicking daily-life activities, such as shaving or hair combing and reported by the patient as such. These episodes persisted throughout night and day, thus representing episodes of oneiric stupor.

3.2.1. Neurophysiological features

Twenty-four-hour polysomnographic recordings document a marked reduction or even a total disappearance of spindle and delta sleep (Plazzi et al., 2002). Wake and sub-wake EEG features mixed with intrusion of REM sleep become the dominant polygraphic and behavioral condition (Fig. 5, lower graph), as already described both in FFIs (Montagna et al., 2003) and in seminal works on AWS by Japanese authors (Kotorii et al., 1980; Tachibana et al., 1975).

3.2.2. Autonomic findings

Autonomic dysfunction such as profuse perspiration, tachycardia, and hypertension is particularly common in patients with DT (Kotorii et al., 1980; Plazzi et al., 2002; Tachibana et al., 1975), who present also with increased cortisol and plasma catecholamines levels (Montagna and Lugaresi, 2002).

3.2.3. Pathogenesis

The clinical and polysomnographic features of the acute DT are similar to those of FFI and MS. A dramatic change in Gamma-AminoButyric Acid (GABA) inhibitory synapses, down-regulated by the longstanding alcohol abuse, together with the up-regulation of the *N*-methyl D-aspartate (NMDA) glutamatergic receptors (McKeon et al., 2008; Plazzi et al., 2002) are probably the cause of the disorder (Lugaresi et al., 2011).

3.3. Other conditions

3.3.1. Mulvihill-Smith syndrome

The Mulvihill-Smith syndrome is a rare clinical condition (11 cases identified up to date) characterized by progeria-like aspect, multiple pigmented nevi, lack of facial subcutaneous fat, microcephaly, low stature, and mental retardation (Baraitser et al., 1988; Passarelli et al., 2018).

In 2005 Ferri et al. reported the case of a 25-year-old woman with Mulvihill-Smith syndrome and negative genetic analysis for PRNP mutations who underwent two overnight video-polysomnographies (vPSGs) (Ferri et al., 2005). The recordings showed three different conditions in the absence of any physiological sleep stages: A) a state with closed eyes, desynchronized EEG activity, presence of eye movements similar to those recorded during wakefulness, irregular breathing, heart arrhythmia and afinalistic movements of the upper limbs and hands, often simulated the movements needed to button up a shirt; B) slow waves mixed with desynchronized EEG activity, low chin muscle tone, presence of slow eye movements, heart arrhythmia, regular breathing and absence of motor activity; C) central apnea episodes, heart rate arrhythmia, desynchronized EEG activity, high chin muscle tone, rapid eye movements and afinalistic movements similar to stage A.

In this case (Ferri et al., 2005) the lack of a 24-hour recording fails to record a pervasive condition persisting night and day; in addition, no specific data on autonomic hyperactivation are given, as arrythmias could be secondary to central apneas (Ratz et al., 2018).

3.3.2. Creutzfeldt–Jakob disease VV2

Sporadic Creutzfeldt–Jakob disease (CJD) of the VV2 subtype (sCJDVV2) shares not only the prion etiopathology with FFI, but also the 19 kDa PrP^{Sc} isoform deposition (type 2) (Parchi et al., 1999b). These patients, however, are homozygous for valine at polymorphic codon 129 and do not carry any mutation in PRNP gene.

In 2009 La Morgia et al. (La Morgia et al., 2009) described the case of a 77-year-old male with a 3-month history of dysarthria and rapidly progressive gait ataxia, a 2-month history of daytime hypersomnolence with complex “oneiric” behaviors and a subsequent pathologic confirmation of a sCJDVV2 with prevalent thalamic degeneration. An overnight vPSG disclosed a complete loss of SWS and alternating epochs of wakefulness and N1 NREM sleep interspersed with bursts of REM sleep. Subcontinuous motor activity characterized by myoclonic jerks or complex quasi-purposeful behaviors mimicking everyday activities, fixed HR and irregular breathing were also recorded. For the following two weeks the patient underwent a prolonged actigraphic monitoring that showed almost continuous motor activity, while autonomic hyperactivity was not evaluated over the 24-h period. Neuropathological examination disclosed moderate to severe spongiform degeneration and gliosis, associated with mild to moderate neuronal loss in the thalamus with PrP^{Sc} type 2A deposition.

3.3.3. Whipple disease

Whipple disease (WD), an infection caused by Tropheryma whippelii, usually occurs with gastrointestinal and rheumatologic symptoms. Oculomasticatory myorhythmia (OMM), which is characterized by pendular vergence oscillations of the eyes at 1 Hz and synchronous with rhythmic contractions of masticatory muscles, is pathognomonic for WD. Hypothalamic dysfunction, supranuclear ophthalmoplegia, sleep and daily movement disorders, are also reported and may represent the only manifestations of the disease in rare cases (Louis et al., 1996; Schwartz et al., 1986).

In a seminal work, Voderholzer et al. showed a total abolition of the sleep–wake pattern during a serial overnight vPSGs associated with lack of the usual nocturnal increase of melatonin secretion in a patient affected by WD with neurological involvement (Voderholzer et al., 2002).

In 2013 Calandra-Buonaura et al. reported the case of a 33-year-old man with WD (Calandra-Buonaura et al., 2013) and features highly suggestive of Agrypnia Excitata as documented by a 24-h vPSG. A severe reduction of total sleep time and the absence of spindles, K-complexes, slow-wave and also REM sleep were documented with the recordings of only two phases: wake and stage 1 NREM sleep. Behaviorally, the patient presented with OMM during both wake and sleep and a subcontinuous motor activity characterized by quasi-purposeful gestures mimicking daily life activity resembling oneiric stupor (Guaraldi et al., 2011). Dysautonomic features were also present such as diaphoresis, increased heart rate (HR) (> 100 beats per minute) and mean body core temperature (38.6 °C). Subsequently, with antibiotic treatment and disease resolution, a gradual normalization of sleep, cardiovascular and temperature cycles' physiology with disappearance of OMM and oneiricisms was observed.

The case reported by Calandra-Buonaura et al. (Calandra-Buonaura et al., 2013) fulfilled completely the diagnosis of AE as documented by the absence of physiological sleep, autonomic hyperactivation and persistent oneiricisms during 24-h videopolygraphic recording.

4. FFI and Agrypnia: the role of the thalamus in autonomic control and body homeostasis

4.1. The central autonomic network

The areas of the central nervous system controlling autonomic functions form a network distributed throughout the neuroaxis. First described by Benarroch (Benarroch, 1993), the central autonomic network (CAN) exerts both tonic and reflex control of visceral functions and integrates the autonomic output with endocrine and motor responses during complex adaptative behaviors (Benarroch, 1997).

CAN structures have neurochemically complex reciprocal interconnections; converge somatic, visceral and humoral information; integrate control of autonomic, endocrine, behavioral motor and antinociceptive responses and show a state–dependent activity, including the sleep-wake cycle (Benarroch, 1997).

Several nuclei of the thalamus have connections with areas of the central autonomic network: the paraventricular nucleus (PVT) projects to the medial prefrontal cortex and receives multimodal visceral and somatosensory inputs; the mediodorsal (MD) nucleus is connected with several limbic areas involved in autonomic control (Benarroch and Stotz-Potter, 1998).

4.2. The thalamus and autonomic dyscontrol in FFI and AE

Post-mortem examination (Lugaresi et al., 1986; Manetto et al., 1992) and positron emission tomography (Cortelli et al., 2006; Cortelli et al., 1997; Perani et al., 1993) indicate that the mediodorsal and the anteroventral (AV) nuclei of the thalamus are selectively affected in FFI, with sparing of the hypothalamus and brainstem autonomic areas. Evidence of thalamic dysfunction is also present in AE as demonstrated in MS and DT (Lugaresi et al., 2011). While AV projects primarily to areas involved in learning and visuo-spatial memory (i.e. the “posterior” limbic circuit), the MD nucleus is the most likely candidate to be involved in the mechanisms of autonomic hyperactivation, and a general overactivation of homeostatic control, in FFI (Benarroch and Stotz-Potter, 1998).

From the autonomic point of view, the MD nucleus presents reciprocal connections with hypothalamus, amygdala and prefrontal cortex (Benarroch, 1993). Its medial region is connected with various limbic areas involved in the control of autonomic functions such as anterior cingulate gyrus and insular cortex, while its most central part, immediately adjacent to the PVT, receives inputs from the infralimbic area, amygdala and lateral preoptic area, and to some extent, the dorsomedial nucleus of the hypothalamus (Benarroch and Stotz-Potter, 1998). Functionally speaking, the MD nucleus serves as an integral relay between the inhibitory effect of the cortex, integrating instinctive, emotional and cognitive inputs, and the hypothalamus, organizing biologic rhythms, endocrine and autonomic functions (Benarroch, 1993; Benarroch and Stotz-Potter, 1998). Thus, the disconnection caused by MD degeneration/dysfunction results in a functional imbalance of an unbridled and activated hypothalamus, leading to the increase of autonomic activation, with tachycardia, tachypnea, systemic arterial hypertension, hyperthermia and a rise in circulating catecholamine levels typical of AE (Lugaresi et al., 1998; Montagna, 2005). Indeed, the flattening of circadian rhythmicity is a consequence of autonomic hyperactivation, as in a system oscillating between two extremes, the amplitude of oscillations diminishes as the axis of equilibrium shifts towards one end (Lugaresi et al., 1998). Autonomic hyperactivity (increase in BP and tachycardia) can be reproduced in anesthetized and conscious rats by injections of the gamma-aminobutyric acid antagonist bicuculline into the medial portion of the MD nucleus of the thalamus (Stotz-Potter and Benarroch, 1998). In addition, thalamic neurons showing phasic neuronal activity related to systolic BP and thought to be involved in the integration of afferent baroreceptor information have been identified in humans. Their derangement may contribute to cardiovascular disturbances (Oppenheimer et al., 1998).

4.3. The thalamus and sleep in FFI and AE

From a broader perspective, the thalamus is fundamental to govern the sleep–wake cycle in terms of both wake promotion with thalamo-cortical loops (Lugaresi et al., 2011) and slow-wave sleep onset and continuity by means of its MD nucleus allowing extra thalamic connections for the reticular nucleus (Lugaresi et al., 2004; Montagna, 2005), original generator of sleep spindles (Steriade et al., 1993). Spindling and SWS invariably disappear in FFI and AE, independent of their etiology, as the thalamus is the structure most severely impaired or damaged and thalamo-cortical and cortico-thalamic circuits are deeply involved by the pathological processes (Lugaresi et al., 2011). REM sleep, on the contrary, continues to be present or even becomes overrepresented (as in DT) because its pontine generator is undamaged and transmission of the signal originating from the REM-on system to the forebrain follows extrathalamic pathways, as originally proposed by Jouvet (Jouvet, 1962) and since confirmed (Lu et al., 2006; Saper et al., 2010). Somnolence and stupor are the consequences of long-lasting and severe sleep deprivation. However, it cannot be excluded that the pathologic process affecting the thalamolimbic system may also have an impact on wake-promoting thalamo-cortical loops, as suggested by the fact that, in FFI, continuous somnolence and the inability to sleep appear together at disease onset (Lugaresi et al., 2011).

4.4. Conclusion: from homeostasis to allostatic overload

We can hypothesize that thalamic lesions introduce a *diaschisis* (from the classical Greek διά – dia = throughout, and σχίζω – schizò = to separate – “separated throughout”) between limbic regions involved in instinctive behavior and those cortical-subcortical areas (basal forebrain, hypothalamus, brainstem) that promote sleep, allowing for a functional imbalance to arise in the form of sympathergic and motor activation and loss of deep sleep (Lugaresi et al., 1998).

FFI, caused by degeneration of medial thalamo-limbic structures, mechanistically involved in deep sleep production and autonomic balance, is a basic disorder of the control of body homeostasis, traditionally defined as a steady state in which all physiological parameters operate within normal values. This condition can be better explained in light of past and recent evidence with the more dynamic process of allostasis whereby an organism maintains physiological stability by changing parameters of its internal milieu by matching them appropriately to environmental demands (McEwen, 1998; McEwen, 2017; Sterling and Eyer, 1988). When repeated allostatic responses are activated (e.g. during stressful situations) and real or interpreted threats to homeostasis initiate consecutive activation of sympathetic drive and glucocorticoid secretion, the body starts to experience the “wear and tear” of allostatic load (McEwen and Stellar, 1993). At its extremes, dysregulation of allostatic responses, often in response to chronic stressors, leads to the overtly pathologic condition of allostatic overload (Juster et al., 2010), where sympathetic and neuroendocrine overdrive, similarly to sympathetic hyperactivity of FFI, lead to a condition of disease. In light of this, FFI could represent also a natural model where patients experience a maximal allostatic overload of exclusive internal origin due to the maladaptive effect of thalamic lesions on the equilibrium of the central autonomic network regulation.

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