

Restless Legs Syndrome: Associated Conditions

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Clinical Definition

- Urge to move the legs with or without paresthesias
- Symptoms worse during inactivity
- Symptoms improve with activity
- Worsening of symptoms in evening and night



Secondary Causes of RLS

- Iron deficiency
- Renal failure
- Neuropathy
- Pregnancy
- Multiple sclerosis
- Essential Tremor
- Parkinson's Disease
- Others



Other RLS Associations

- Rheumatologic diseases
 - Sjogrens
 - Rheumatoid arthritis
 - fibromyalgia
- Peripheral vascular disease
- Celiac disease
- Obstructive sleep apnea

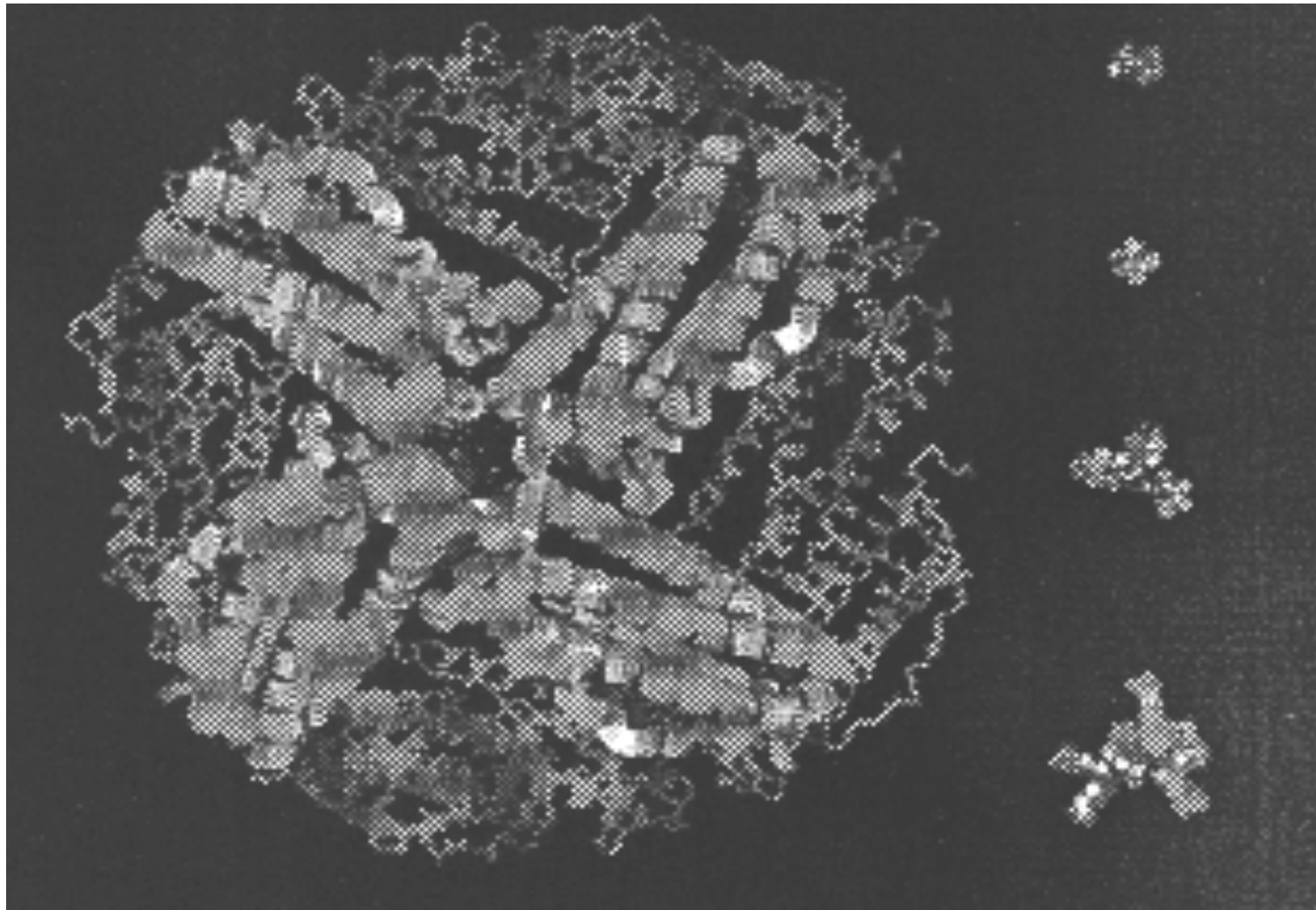
RLS and Systemic Iron Deficiency

Secondary and/or Primary?





Ferritin Model with other FE species





Measuring Serum Iron is Difficult

- Ferritin:
 - Acute phase reactant can be elevated for 6 weeks
 - Increased with age (should be greater than age)
 - Increased with decreased GFR (renal function)
- Iron:
 - 50% higher in AM compared to night
 - Increased after meal
- Iron binding percentage:
 - Formula with iron, TIBC, transferrin



Why Iron?

- Reduced brain iron is reduced in RLS
- We can't easily measure brain iron
- Iron regulation in brain very complex
- Blood iron probably not directly related to RLS symptoms, but if systemically low this may reduce brain iron



Serum Ferritin and RLS

- Late Onset of RLS (Non-familial)
 - Lower serum ferritin
 - Severity correlated with serum ferritin levels
- Early onset of RLS (Familial)
 - Normal serum ferritin
 - Severity not correlated with ferritin levels

RLS in Uremia (kidney failure)



RLS and Uremia

Author (year)	Cohort	RLS Diagnosis	# and % w/ RLS	RLS Predictors
Mucsi (2005)	HD	NIH Criteria	14% of 333	Assoc. with insomnia
Unruh (2004)	HD USA	“severe” RLS	15% of 894	Assoc. with increased mortality
Mucs (2004)	HD/PD Hungary		15%	NR
Gigl ¹ (2004)	HD/PD Italy	Written IRLSSG	21.5% of 601	Greater Duration of Dialysis
Bhowmik (2004)	India		1.5% of 65	NR
Takaki (2003)	HD Japan	IRLSSG (4/4) IRLSSG (≥2/4)	60 / 490 (12.2%) 112 / 490 (22.9%)	Hyperphosphatemia Stress
Goffredo (2003)	HD Brazil	IRLSSG Interview	/176 (14.8%)	Caucasion>Non-Caucasion
Bhowmik (2003)	HD India		6.6%	NR
Kutner (2002)	HD USA	IRLSSG Interview	308, 68% Caucasion 48% African	Caucasion> African American, no other significant predictors
Cirignotta (2002)	HD Italy	IRLSSG, Written /Interview	/127 (50%) /127 (33.3%)	NR

Author (year)	Cohort	RLS Diagnosis	# and % w/ RLS	RLS Predictors
Sabbatin³ (2002)	HD Italy	RLS question	257/694 (37%)	None
Miranda (2001)	HD Chile	Interview	43/166 (26%)	None
Hui (2000)	PD Hong Kong	Written question	124/201 (62%)	Insomnia
Virga (1998)	HD	“RLS”	(27.4%)	None
Collado-Seidel (1998)	HD Germany	IRLSSG (4/4) IRLSSG (≥3/4)	32/138 (23%) 44/138 (32%)	Inc. Parathyroid hormone
Winkelmann (1996)	HD USA	IRLSSG (3/4)	/204 (20%)	Dec. Hct poor sleep
Walker (1995)	HD Canada	ICSD	31/54 (57%)	Inc. BUN, p=0.04 Inc. Cr, p=0.08
Stepanski (1995)	PD	“Leg twitching”	26/81 (32%)	NR
Holley (1992)	HD / PD	“RLS”	30/70 (42%)	NR
Roger (1991)	HD / PD U.K.	“RLS”	22/55 (40%)	Hct, p=0.03 female
Bastani (1987)	HD	“RLS”	6/42 (17%)	NR
Nielson (1971)	None	“RLS”	43/109 (39%)	NR



Uremic RLS - Clinical

- 25%-30%
- Increased motor component
 - DWA = 78% vs 51%
 - PLMS = (mean) 119/hr vs 48/hr
- Not improved with dialysis
- Resolves with Transplantation
- Predicts mortality
- Similar treatment response

Neuropathy in RLS Patients
OR
RLS in Neuropathy Patients



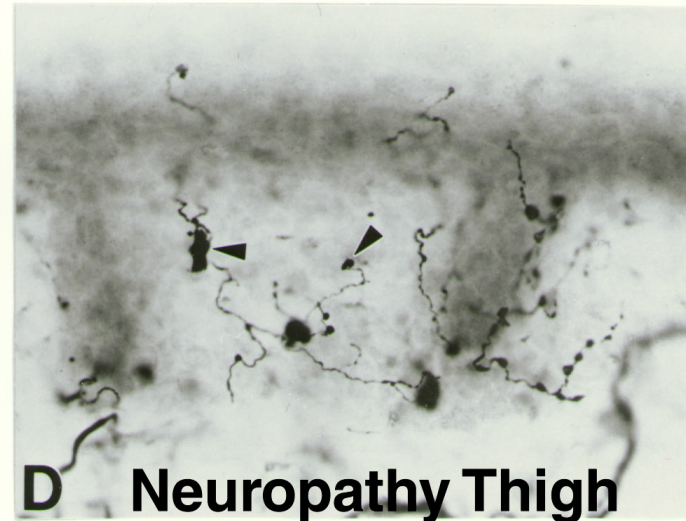
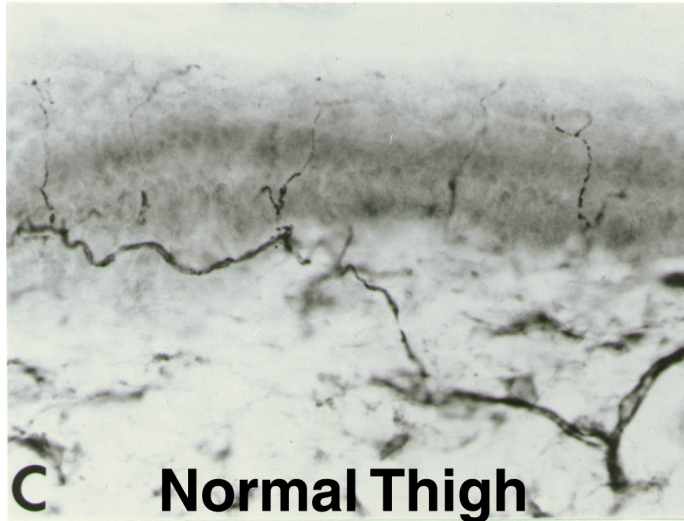


Neuropathy in RLS (Baylor College of Medicine)

- (+) Family history
 - 15/67 abnormal (22.4 %)
- (-) Family history
 - 22/31 abnormal (71.0 %)
- (P<0.0001)
- 4 nl EMG had ferritin <15



Normal vs SFSN: Thigh





Neuropathic RLS: Clinical

- Older age of onset
- More acute onset
- More rapid progression
- No family history
- Axonal
- May lack clinical neuropathy
- May also have neuropathic pain
- Similar treatment response ?

Multiple Sclerosis

CNS autoimmune myelin lesions
separated by space and time



Multiple Sclerosis

	Prevalence	Comment
Zambrano (2008) U.S.	84/251 (33.5%)	Not assoc. with age, sex, MS type
Manconi (2007) Italy	51/156 (32.7%)	-Primary progressive -MS first in 91.5%
Gomez-Choco (2007) Spain	18/135 (13.3%) MS 11/118 (9.3%) control	Diagnostic criteria less clear
Auger (2005) Canada	75/200 (37.5%) MS 16/100 (16%) control	Written questionnaire



Multiple Sclerosis

- Autoimmune condition where body “attacks” myelin in the brain and spinal chord
 - Women>men
- Multiple studies show higher rates of RLS in people with MS
- Correlates with more progressive course and spinal chord lesions



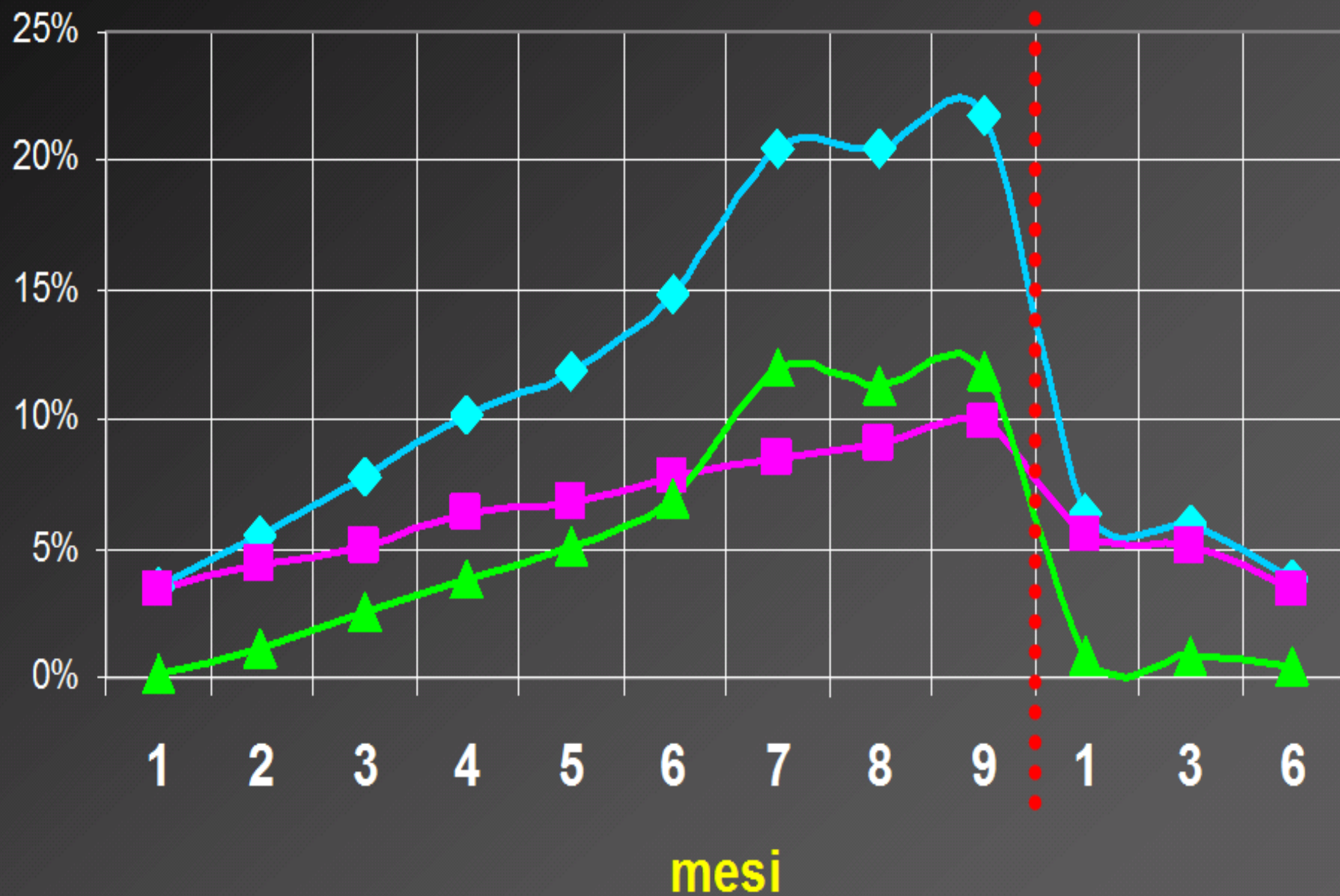
The Italian Case Control RLS in MS Study (Manconi et al,)

- N: MS=861, controls=649, 25 centers
- MS Age 41.2(10.6) y, Duration 10.4 y [1-46]
 - Relapsing remitting 75.4%
 - Primary progressive 5.8%
 - Secondary progressive 18.8%
- RLS at least 2/week
 - 19.0% vs 4.2%
- Risk factors
 - Primary progressive, older, longer MS duration, global disability



Prevalence of RLS in Pregnancy

Authors	N° cases	Prevalence
Ekbom	486	11.3%
Jolivet	100	27.0%
Ekbom	202	12.4%
Goodman et al	500	19%
Suzuki et al	16.528	19.9%
Manconi et al	606	26.6%
Hubner et al	501	12%



—◆— tot RLS —■— pre RLS —▲— new RLS



Treatment of RLS in Pregnancy

- Pergolide B
- Pramipexole/Ropinirole C
- Levodopa C
- Oxycodone B
- Methadone B/D
- Codeine C
- Propoxyphene C/D
- Benzodiazepines D/X
- Gabapentin C

Restless Legs Syndrome and Parkinson's Disease



	Population	RLS in PD	Risk Factors	Relative Age of Onset	Comment
Gomez-Esteban (2007)		25/114 (21.9%)	Female		Not assoc. with daytime sleepiness
Ondo (2002)	U.S.	63/303 (20.8%)	Reduced serum ferritin	PD first in 85%	Older age of onset/less family history
Driver-Dunckly (2006)	U.S. STN DBS	6/25 (24%)	NR	NR	Improved with STN DBS
Peralta (2005)*	Austria	28/113 (24%)	Younger age Lower "on" H&Y	PD first in 83%	RLS symptoms during "wearing off"
Simuni (2000)*	U.S.	42/200 (21%)	"fluctuators" (P=0.14)	PD first in 93%	RLS undiagnosed in 59%
Braga-Neto (2004)	Brazil	45/86 (49.9%)	Duration of PD, but not age	NR	Not associated with daytime sleepiness
Chaudhuri (2006)	U.S. and Europe	46/123# (37.4) Controls (28.1)		NR	Part of a non-motor survey
Kumar (2002)	India	21/149 (14.1%) Controls (0.9%)	NR	NR	RLS Dx based on a single question
Krishman (2003)	India	10/126 (7.9%) Controls (1.3%)	-Older age -Depression	NR	
Nomora (2005)	Japan	20/165 (12%) Controls (2.3%)	Younger age	PD first in 95%	RLS worsened PSQI
Tan (2002)	Singapore	1/135 (0.6%) Controls (0.1%)	---	---	"Motor restlessness in 15.2%



PD / RLS Conclusions

- Symptoms of RLS are common in PD
- RLS does not contribute to PD sleepiness
- RLS/PD: associated with lower serum ferritins
- PD symptoms precede RLS symptoms unless there is a (+) family history of RLS
- RLS does not become PD
- Idiopathic RLS may prevent PD



RLS and Essential Tremor

- 33/100 patients presenting with ET had RLS
 - 58% of these + family history of RLS
 - IRLRS = 16.8 ± 8.1
 - Only predicted by + family history of RLS
- 1/68 patients presenting with RLS had tremor >1
 - “trace” tremor in about 50%



Medications

- Anti-histamines
- Dopamine blockers
- Anti-depressants



Conclusions

- “Secondary” RLS Exists
- The Relationship Between Primary and Secondary RLS is Unclear
 - Exacerbating of Underlying Disease
 - Distinct Independent Diseases