LINKS BETWEEN PANS, POTS AND JOINT HYPERMOBILITY, HSD

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Outline

- Few words about history of CFS/ fatigue/ influenza
- About thinking
- Ambiome – microbiome - genome
- Autonomic nervous system
- Brain functioning: energetics and glymphatic flow
- Orexin
- Functional disorders - dysautonomia
- PANDAS/ PANS, BDD, POTS
- Hypermobility spectrum disorders
- Conclusions
- Future studies

Infections and encephalitides

- 1780-82 and in 1830-33 in Paris after influenza
- 1890-91 in Italy “La Nonna” – onset often around 9 (“nona”) days after infection
- Von Economy’s disease
- Encephalitis lethargica
- After the 1918 H1N1 epidemics

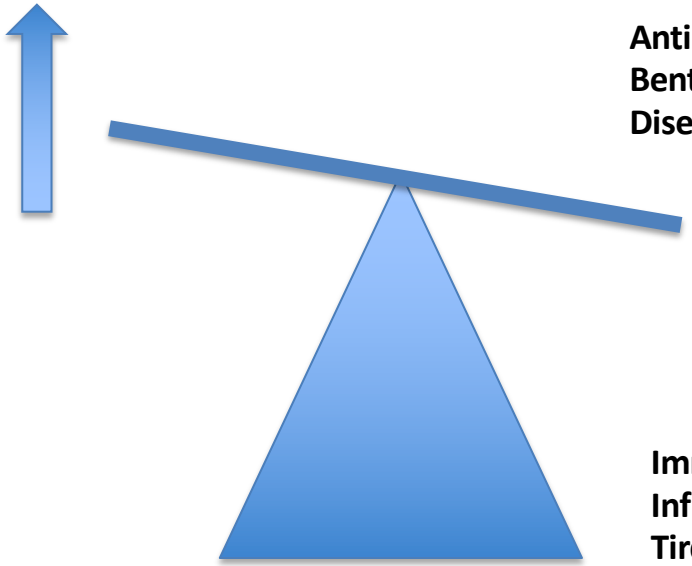
Medical thinking: dualism - monism

- Western philosophy
  - Descartes mind/ body dualism
  - Cartesian dualism
- Eastern philosophy
  - Substance dualism → a metaphysical line between consciousness and matter, where matter includes both body and mind
- Monism
  - Benedict de Spinoza
  - **Mind is in the brain**
    - Allan Hobson (Harvard) & Karl Friston (London) → Mind is electric
- Bayesian networks - Markov blanket
  - Parsimonian laws – Ockham's razor

Stressi, ”too much training”

Autonomic homeostasis

Sympathetic tonus ↗
Excessive sympathicotonia



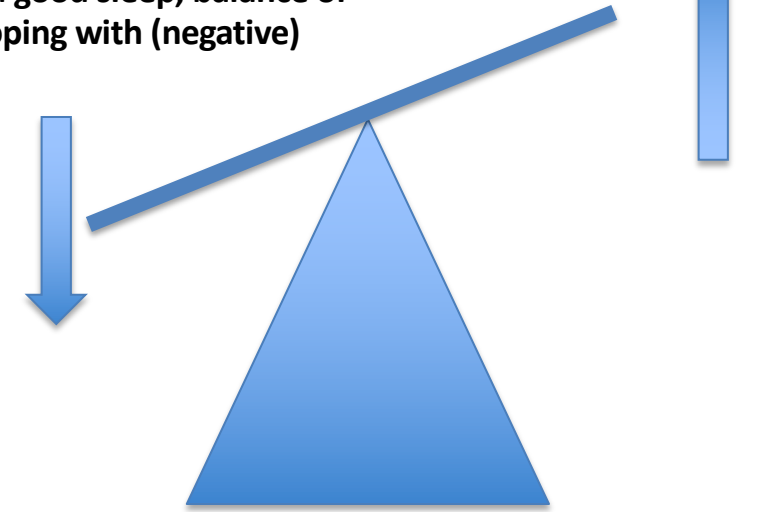
Anticholinerigc medications
Bentzodiazepines
Disease, poor sleep

Parasympathetic tonus ↘

Immunologcal resistance ↘
Inflammations ↗
Tirdeness, fatigue
Sleep disturbances, POTS, PANS…

Parasympathetic tone ↗
Porges ”double vagal system”
Vagus stimulation, nutrition

Proper use of time, relaxation, regular bed times, sufficient and good sleep, balance of exercise and rest, coping with (negative) stress



Sympathetic tone ↘

Resistance ↗
Inflammation ↘
Restorative sleep
- Better brain energetics
- Getting rid of waste product in the brain

Connections between CNS and gut role of the enterovisceral system

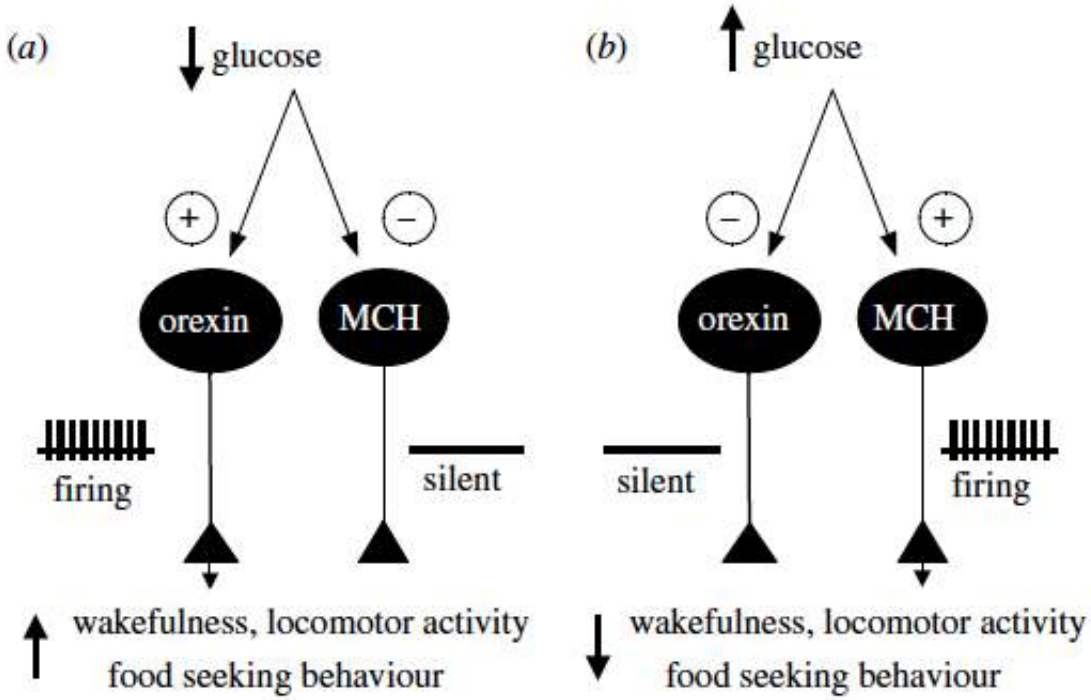
- Role of the vagal (parasympathetic) nervous system
  - Vagus nerve
- Enteric nervous system ← → brain: two-way connections
- Intestinal immune system
- Intestinal mucosa
- Gut microbiota

→Implications also to nutrition, microbiota

→Use of antibiotics in PANS: benefits but also possible good or bad effects on gut microbiota → to be studied

Brain functions. Role of sleep

- Astrocyte-Neuron Lactate Shuttle by Magistretti and Pellerini
  - During slow-wave sleep → production of lactate in the astrocytes
  - Stimulants may ameliorate brain energetics
- Washing machine of the brain = glymphatic flow (Maiken Nedergaard)
  - During slow-wave sleep → elimination of harmofule metabolites that have accumulated in the brain
- Questions & hypotheses:
  - Problems in the brain energetics → fatigue and neuropsych symptoms
  - Problems in the glymphatic flow → fatigue and neuropsych symptoms



Burdakov et al. 2005

N.B. increase of glucose inhibits orexin → lower vigilance

Notions on NUTRITION. Low glycemic index, probiotics, sour foods …

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Cell Mol Neurobiol (2018) 38:385–391
https://doi.org/10.1007/s10571-017-0487-z

CrossMark

REVIEW PAPER

The Orexin System and Hypertension

Michael J. Huber[1] · Qing-Hui Chen[1] · Zhiying Shan[1]

(de Lecea 2012; Sakurai 2007, 2014; Tsujino and Sakurai 2009). Included in the range of functions that the orexins regulate is the central control of sympathetic nerve activity (SNA) and blood pressure. The anatomy of orexin-producing neurons in relation to regions of the brain involved in SNA and blood pressure control as well as functional in vivo studies, which support that the orexin system participates in SNA and blood pressure regulation, have recently been reviewed (Carrive 2013; Li and Nattie 2014).

N.B. Importance of proper salt and water balance

Na^+ ↗ → orexin ↗ → vigilance/ wake ↗ & BP ↗

Na^+ ↘ → orexin ↘ → vigilance/ wake ↘ & BP ↘, pulse ↗

→ symptoms of POTS and PANS get worse

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Functional disorder

Currently

- **Not a good term** as it is often misunderstood by both patients and professionals
- It may not be considered as an illness/ disease

  →Patients cannot have all social benefits that they should have
- Functional disorder = dysfunction of biological organs (brain, gut, bladder pain regulation etc) = “not functioning properly”

ICD-11

- → diagnostic codes for PANDAS (PANS) but there is controversy
  - For example in Denmark (and e.g. in Finland) some physicians recommend to use the diagnostic code **06C20** for all functional disorders including PANS, POTS, ME/CFS, fibromyalgia, irritable bowel syndrome, tension headache etc…

6C20 Bodily distress disorder

Parent

Disorders of bodily distress or bodily experience

Show all ancestors

Description

Bodily distress disorder is characterized by the presence of bodily symptoms that are distressing to the individual and excessive attention directed toward the symptoms, which may be manifest by repeated contact with health care providers. If another health condition is causing or contributing to the symptoms, the degree of attention is clearly excessive in relation to its nature and progression. Excessive attention is not alleviated by appropriate clinical examination and investigations and appropriate reassurance. Bodily symptoms are persistent, being present on most days for at least several months. Typically, bodily distress disorder involves multiple bodily symptoms that may vary over time. Occasionally there is a single symptom—usually pain or fatigue—that is associated with the other features of the disorder.

Exclusions

- Tourette syndrome (8A05.00)
- Hair pulling disorder (6B25.0)
- Dissociative disorders (6B60-6B6Z)
- hair-plucking (6B25.0)
- Hypochondriasis (6B23)
- Body dysmorphic disorder (6B21)
- Excoriation disorder (6B25.1)
- Gender incongruence (HA60-HA6Z)
- Sexual dysfunctions (HA00-HA0Z)
- Tic disorders (8A05)
- Feigning of symptoms (MB23.B)
- Sexual pain-penetration disorder (HA20)

Fink P, Schroder A. One single diagnosis, **bodily distress disorder**, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders. J Psychosom Res. 2010;68(5):415-26.

Comment: This code should not to be used for PANS or ME/CFS !

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Functional disorder

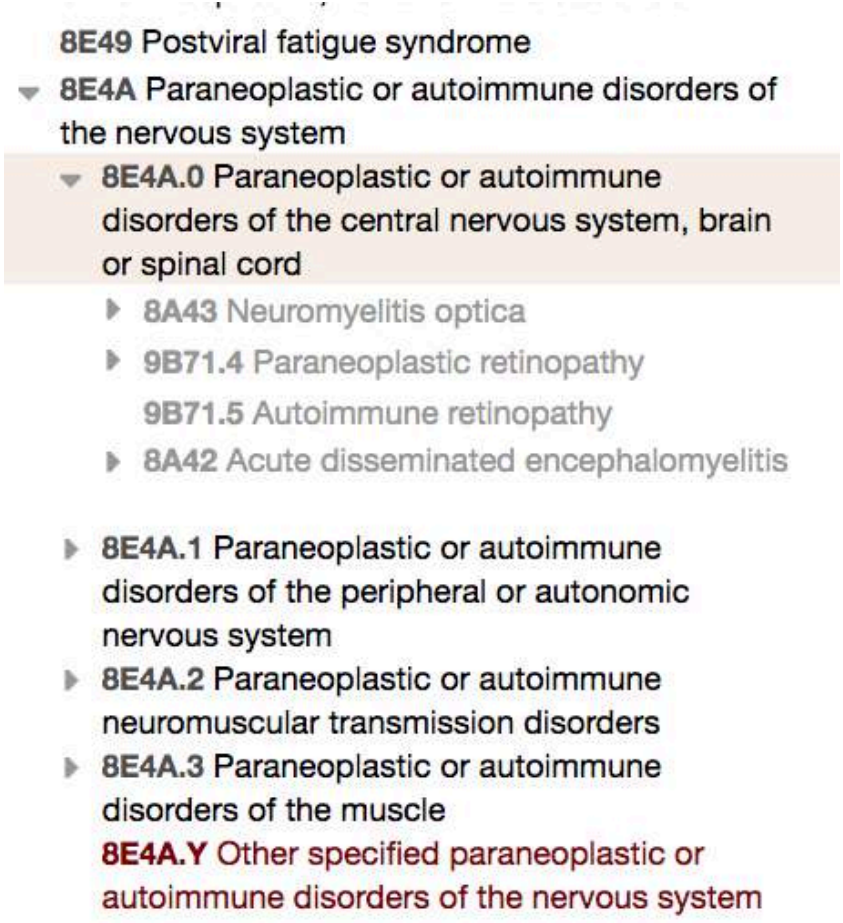
- Also understood as a Medically Unexplained Symptom (MUS), somatoform disorders – dissociative disorders – conversion
- **A much better alternative modern definition with analogies to computers is:**
  - **Structural disorder = Main board, hardware problem**
  - **Psychiatric disorder = Problem of CPU (Central Processing Unit)**
  - **Functional disorder = Software problem**
    - Dysfunction of a computer may be caused a computer virus or other “attack”

Ref also to Philip Fischer, Mayo Clinic

As part of the pathophysiology: Dysfunction of thalamo-cortico-limbic connections

- **James-Lange theory→ no proper connection between thalamus and cortex** → no cortical (conscious) inhibition of the limbic system → **hypersensibility** of peripheral stimuli → worsening of symptoms
- **Canon-Beard theory→ no proper feedback connections between periphery and cortex** → no cortical (conscious) inhibition of the limbic system → **hypersensibility** of peripheral stimuli → worsening of symptoms

PANDAS (PANS) = **8E4A.0** in ICD-11



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POTS in ICD-11

- **8D89** Disorders of orthostatic tolerance
  - **8D89.0** Reflex syncope
  - **8D89.1** Syncope due to autonomic failure
  - **8D89.2** Postural orthostatic tachycardia syndrome
  - **8D89.3** Baroreflex failure
  - **BA21** Orthostatic hypotension
  - **8D89.Y** Other specified disorders of orthostatic tolerance
  - **8D89.Z** Disorders of orthostatic tolerance, unspecified

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Annual incidence of POTS

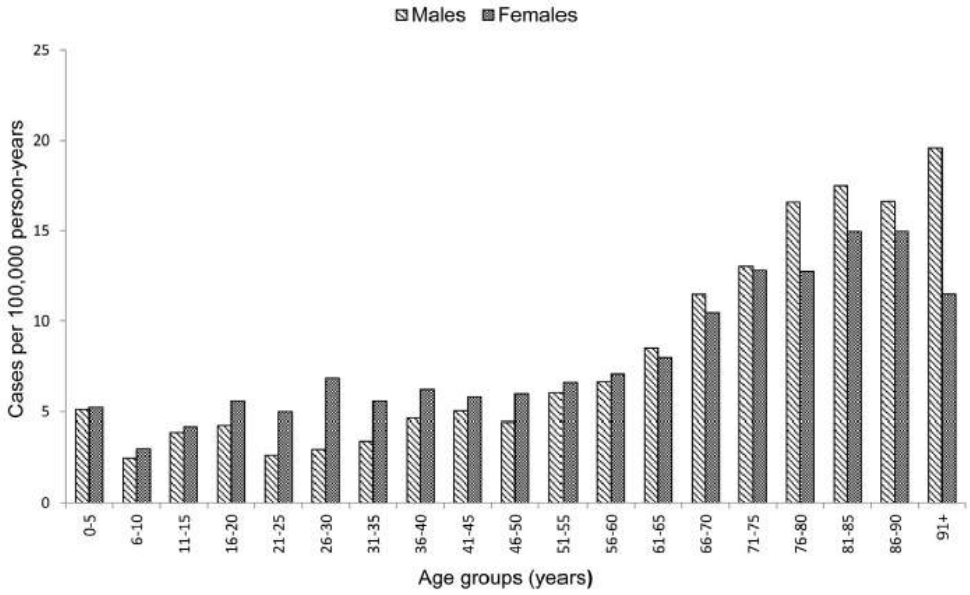

Fig. 3. Average annual incidence rate of postural orthostatic tachycardia syndrome (POTS) by age groups and sex during 2002–2012 in Finland.

72 cases of POTS diagnosed in 2002-2012
Incidence of POTS = 4.21/100 000 aged 11-15 years/ year
Skufca et al. 2017

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Year of diagnosis

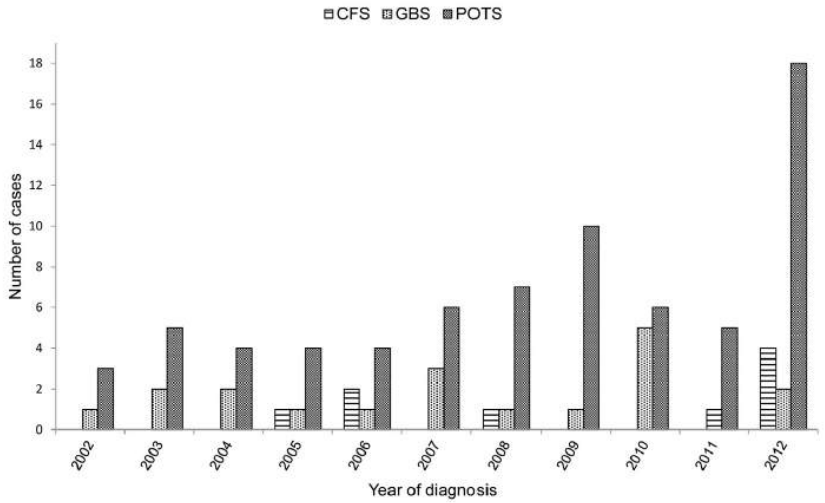

Fig. 4. Chronic fatigue syndrome/systemic exertion intolerance disease (CFS/SEID), Guillain Barré syndrome (GBS) and postural orthostatic tachycardia syndrome (POTS) in girls of age 11–15 years during 2002–2012 in Finland.

Skufca et al. 2017

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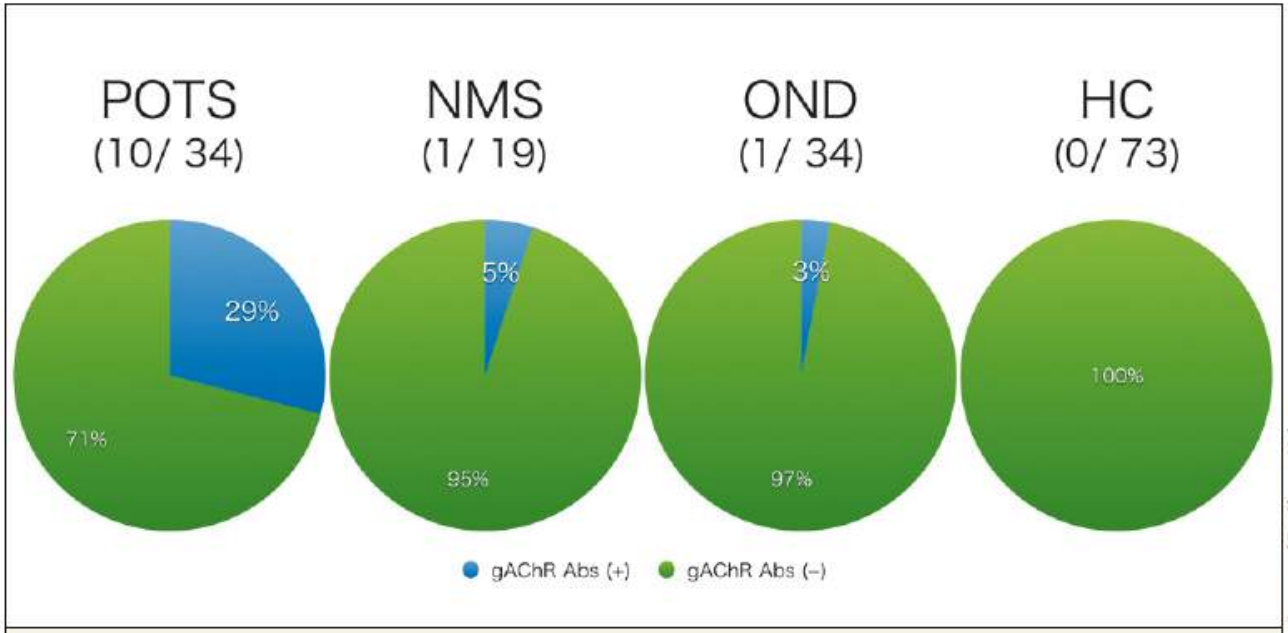


Courtesy of Dr. Shunya Nakane

AUTOANTIBODIES against anti-gAChR were detected in 29 percent, 5 percent, 3 percent, 0 percent (of samples from patients with POTS, neurally mediated syncope, other neurological diseases, and healthy controls, respectively.

Watari et al. Ann Clin Transl Neurol 2018

POTS = Postural Orthostatic Tachycardia Syndrome

- Risk factors
  - Caucasian
  - Prepuberty - puberty
  - Joint hypermobility
    - Over 40 % of subjects with joint hypermobility have POTS (Eccles et al. 2015)
  - High achievers
- Triggers
  - Infection, vaccination, traumatic event

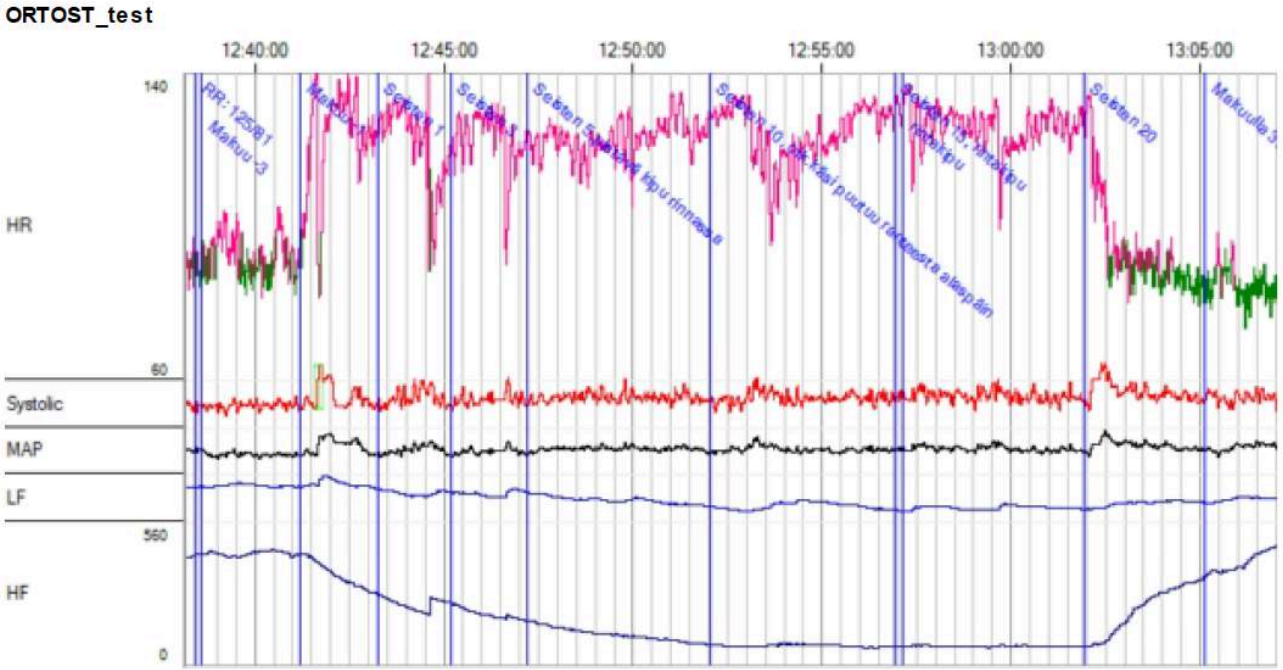
Clinical picture

- Variable symptoms
  - Symptoms related to dysautonomia
    - Dizziness, pains, palpitations, orthostatic intolerance, headache, wet and cold hands etc
    - Gastrointestinal symptoms
  - Motor symptoms and functional ”fits”
- Subjective symptoms, observed disorders and findings of neurological examination do not always fit
- Co-existence of different disorders is common

Diagnosing POTS in clinical practice

- **Clinical history**
  - Childhood, allergies, infections, vaccinations, symptoms indicating possible MCAD
- **Clinical examination**
  - Neurological status, mental status, Beighton, skin (Darier, dermographia,…)
- TILT test, Standing
  - Duration of test should be long enough: > 5 to 20 min (30 min)
- Tests of the ANS functioning including beat the beat EKG and BP, HRV
- dU-Na
- S-ferritin levels
- Neuronal antibodies, TPO, GPCR antibodies
- **Lumbar puncture**
- Brain imaging (MRI, PET)
- MCAD ? → S-tryptase, dU-Mhistamine, PGD2, FPD2U, 8674 B –KIT816

POTS in a patient with PANS: decrease of parasympathetic tone with ± changes in sympathetic tone



Mast cell activation

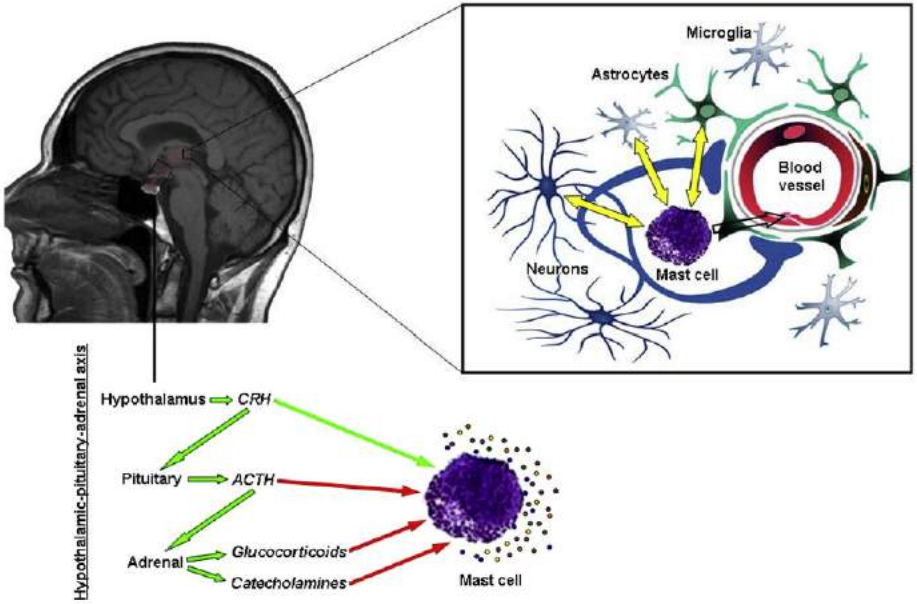


Fig. 1. Mast cell siting in the CNS. The highest densities of mast cells (MCs) in brain are found in the infundibulum, pituitary gland, area postrema, choroid plexus, hypothalamus, and thalamus (shaded red in the MRI picture). Emotional, physical, or inflammatory stress triggers corticotropin releasing hormone (CRH) secretion from the hypothalamus, in turn activating CRH receptors on MCs in the diencephalon and possibly also in the periphery. MC-derived neurosensitizing, proinflammatory, and vasoactive mediators can then induce central nervous symptoms in MCAD. In addition, the hypothalamic–pituitary–adrenal axis is activated, influencing the activation of MCs in the periphery (red arrows: inhibitory effects; green arrows: activating effects). Bidirectional interactions (yellow arrows) between MCs, microglia, astrocytes, and neurons in the central nervous system are depicted in the box. Upon stimulation MCs can release vasodilatory and inflammatory mediators (e.g., histamine, interleukin-6, vascular endothelial growth factor, tumor necrosis factor-α). As a result of dysregulation of this network by inappropriately activated MCs, neuroinflammation is induced. Histamine and proteases effect leakage of the blood–brain barrier at the tight junctions (black arrow), resulting in infiltration of circulating lymphocytes and also MCs by diapedesis. Focal brain inflammation can contribute to brain dysfunction, e.g., seizures, autistic behavior, hallucination, etc.

Afrin et al. 2015

JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Autonomic Nervous System Functioning Related to Nocturnal Sleep in Patients With Chronic Fatigue Syndrome Compared to Tired Controls

Maija Orjatsalo, MD[1,2]; Anniina Alakuijala, MD, PhD[1,2]; Markku Partinen, MD, PhD[2,3]

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Study Objectives: Autonomic nervous system (ANS) dysfunction is common in chronic fatigue syndrome (CFS). One of the main complaints in CFS is unrefreshing sleep. We aimed to study the nocturnal cardiac ANS in different sleep stages in patients filling the 2015 Institute of Medicine CFS diagnostic criteria.

Methods: In this case series study, the nocturnal heart rate variability and blood pressure (BP) variables in polysomnography were studied in groups of patients with CFS (n = 8) and tired controls (n = 8) aged 16–49 years. Five of the patients with CFS and controls were female. The heart rate variability and BP parameters and heart rate were studied in all sleep stages and wake.

Results: The amount of low-frequency oscillations of the electrocardiography R-R-intervals spectra (LF; predominantly reflects sympathetic activity) was higher for patients with CFS in all sleep stages compared to controls ($P < .001$). During wake, the amount of LF was lower for the patients with CFS ($P < .05$). The amount of high-frequency oscillations (HF; reflects parasympathetic activity) was lower in stage N3 sleep in the patients with CFS than for the controls ($P < .0001$), but, in total, HF was higher in patients with CFS ($P < .001$). Patients with CFS had higher overall nocturnal systolic and mean BP ($P < .0001$) and lower heart rate ($P < .0001$) than controls. No significant differences were found in sleep stage distributions.

Conclusions: The results suggest a nocturnal dysfunction of the cardiac ANS in CFS, presenting as lower parasympathetic tone in deep sleep and higher sympathetic tone asleep.

Keywords: autonomic nervous system, blood pressure, chronic fatigue syndrome, dysautonomia, heart rate variability, polysomnography, sleep, systemic exertion intolerance disease

Citation: Orjatsalo M, Alakuijala A, Partinen M. Autonomic nervous system functioning related to nocturnal sleep in patients with chronic fatigue syndrome compared to tired controls. *J Clin Sleep Med*. 2018;14(2):163–171.

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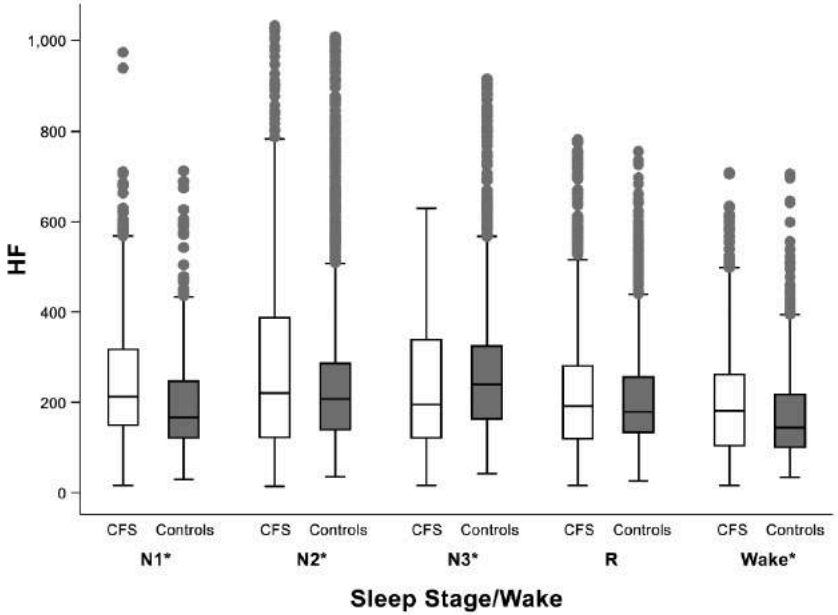
Figure 1—HF values in different sleep stages for chronic fatigue syndrome patients and controls.



The whiskers are adjacent lines, boxes are 25th to 75th percentile with median and the dots are outliers. * = $P < .0001$. CFS = chronic fatigue syndrome, HF = high-frequency components of the heart rate variability spectra.

Orjatsalo, Alakuijala & Partinen, JCSM 2018

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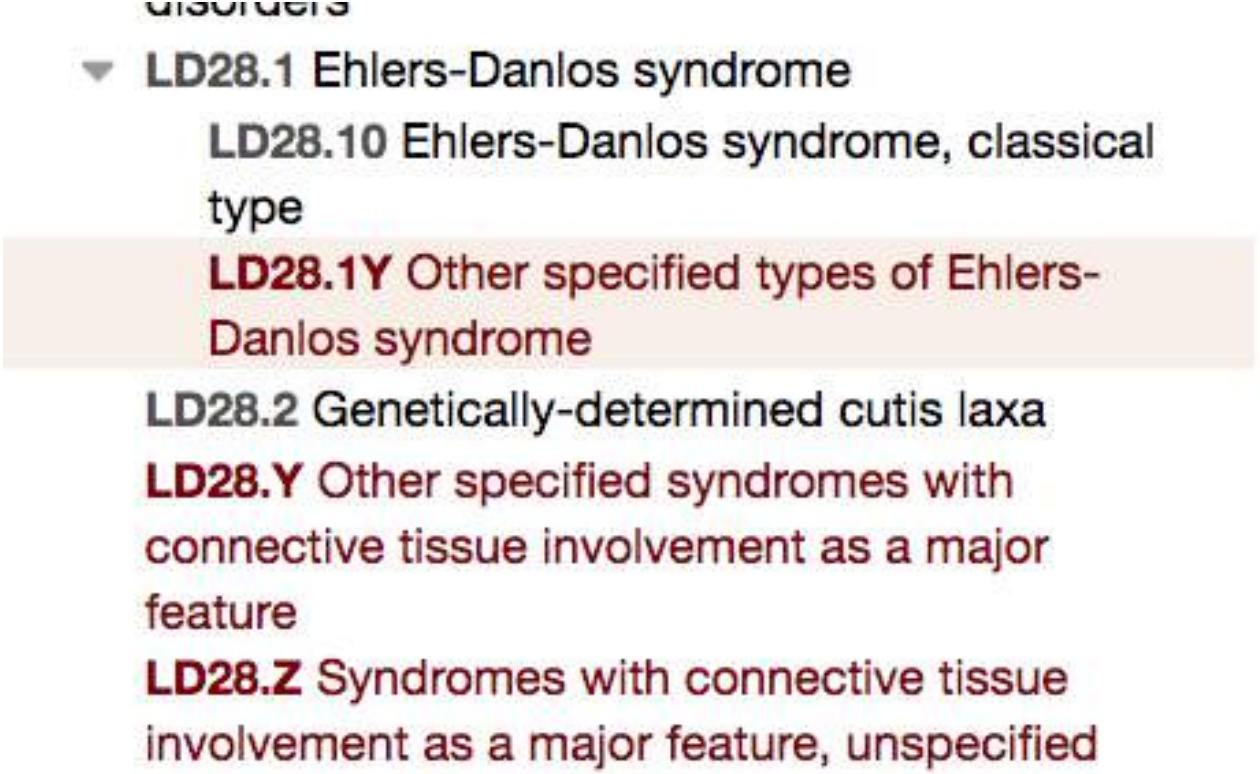
Hypermobility Spectrum Disorders in ICD-11



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Beighton-scale

	Right	Left
Small fingers >90°	0 / 1	0 / 1
Thumb	0 / 1	0 / 1
Elbow; hyperextension > 180° (>10°)	0 / 1	0 / 1
Knee; hyperextension >180° (>10°)	0 / 1	0 / 1
Hands ground	1	

Points 0-9; **hypermobility cut-points**:
≥ 6 in prepuberty
≥ 5 in puberty to 50 y
≥ 4 in people > 50 y

Malfait et al. 2017

TABLE III. The Five-Point Questionnaire. Adapted From [Grahame and Hakim, 2003]

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself "double-jointed"?

A "yes" answer to two or more questions suggests joint hypermobility with 80–85% sensitivity and 80–90% specificity

Malfait et al. 2017

Generalised joint hypermobility and neurodevelopmental traits in a non-clinical adult population

Martin Glans, Susanne Bejerot and Mats B. Humble

BJPsych Open 2017

Table 2 Demographics of the sample including prevalence of reported psychiatric disorders and hypermobility

	Females *N*=734	Males *N*=153
Age, mean (s.d.)	44.7 (10.4)	44.2 (11.0)
5PQ=0 (%)	237/734 (32.3)	67/153 (43.8)
5PQ=1 (%)	244/734 (33.2)	52/153 (34.0)
5PQ≥2 (%)	253/734 (34.5)	34/153 (22.2)
5PQ≥3 (%)	116/716 (16.2)	11/152 (7.2)
5PQ≥4 (%)	51/710 (7.2)	4/152 (2.6)
5PQ=5 (%)	10/709 (1.4)	2/152 (1.3)
Depression (%)[a]	143/728 (19.6)	14/153 (9.2)
Questionnaire version 2[b]	Females *N*=433	Males *N*=101
Anxiety disorders (%)[c]	11/430 (2.5)	1/100 (1.0)
Other psychiatric disorders (%)	10/430 (2.3)	2/100 (2.0)

a. ('Have you been diagnosed with depression?')
b. In a later stage of the study, a question about non-depressive psychiatric disorders was added. ('Have you been diagnosed with any other psychiatric disorder? If yes, which disorder?')
c. Anxiety disorders were identified by examining free text responses to the item 'other psychiatric disorder' independently by two of the authors. Missing data: 6 women did not respond to whether they had a history of depression. Out of the individuals completing the second version of the questionnaire, 3 women and 1 man did not respond to whether they had other psychiatric disorders. Regarding the 5PQ questionnaire 25 women and 1 man had one or more missing items.

Table 3 The association between self-rated neurodevelopmental symptoms (i.e. ADHD, autism spectrum disorder (ASD) and clumsiness) and self-reported generalised joint hypermobility (GJH) traits in a non-clinical adult Swedish population

Neuro-developmental traits		Hypermobile[a]	Not hypermobile	*t*	d.f.	*P*
ASRS total score, mean (s.d.)	Men (*n*=152)	25.2 (9.36)	23.8 (8.11)	0.82	150	0.41
	Women (*n*=730)	25.9 (8.20)	25.3 (7.90)	0.97	728	0.33
AQ-10 total score, mean (s.d.)	Men (*n*=144)	10.2 (3.89)	9.14 (3.35)	1.46	142	0.15
	Women (*n*=701)	8.46 (3.31)	8.47 (3.35)	–0.04	699	0.97
				χ^2	d.f.	*P*
Clumsiness, (yes/no)[b]	Men (*n*=152)	33 (3/30)	119 (7/112)	0.43	1	0.51
	Women (*n*=717)	247 (34/213)	470 (80/390)	1.28	1	0.26

ASRS, Adult ADHD Self Report Scale, continuous scoring method (0–4 on each item).
AQ-10, Autism quotient abridged 10-item version, continuous scoring method (0–3 on each item).
a. Endorsement of two or more items in the 5PQ.
b. Clumsiness defined as reported performance below average in physical education in school at age 12 years ('In elementary school (when you were about 12 years), did you perform worse than average in physical education (i.e. ball games, coordination, agility)?'). A yes response suggests clumsiness, whereas a no response does not.

- No statistically significant differences

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In children 17.1 % have Beighton≥6

TABLE 2 Beighton score for both participant groups

Beighton score	Physiotherapy group (n = 32), n (%)	School group (n = 41), n (%)
9	0 (0)	2 (4.9)
8	2 (6.3)	1 (2.4)
7	0 (0)	1 (2.4)
6	5 (15.6)	3 (7.3)
	Cut-off for GJH using Beighton score ≥6/9	
5	1 (3.1)	1 (2.4)
4	9 (28.1)	9 (22.0)
3	3 (9.4)	3 (7.3)
2	7 (21.9)	8 (19.5)
1	0 (0)	2 (4.9)
0	5 (15.6)	11 (26.8)

GJH, generalized joint hypermobility

Moore et al. 2018

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PLOS ONE

RESEARCH ARTICLE

Hypermobility of joints in dancers

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N= 77 Jazz dancers

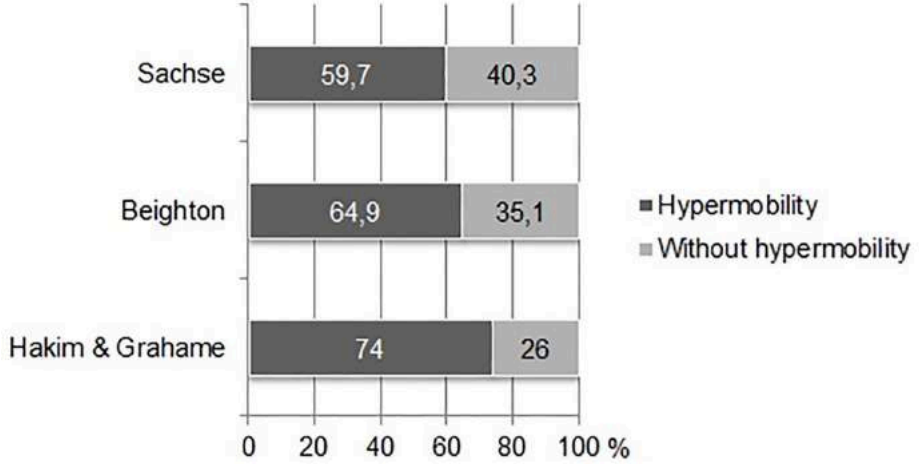

Fig 2. Percentage frequency distribution of JHS prevalence, according to Sachse, Beighton, and Hakim & Grahame.

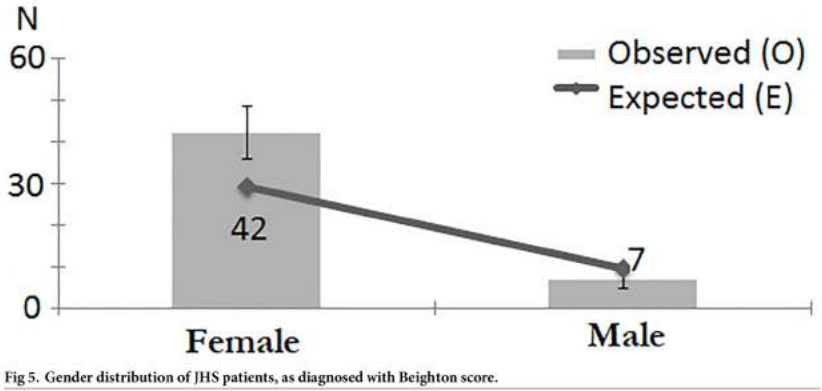

Fig 5. Gender distribution of JHS patients, as diagnosed with Beighton score.

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frontiers in
NEUROSCIENCE

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Neurovisceral phenotypes in the expression of psychiatric symptoms

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This review explores the proposal that vulnerability to psychological symptoms, particularly anxiety, originates in constitutional differences in the control of bodily state, exemplified by a set of conditions that include Joint Hypermobility, Postural Tachycardia Syndrome and Vasovagal Syncope. Research is revealing how brain-body mechanisms underlie individual differences in psychophysiological reactivity that can be important for predicting, stratifying and treating individuals with anxiety disorders and related conditions. One common constitutional difference is Joint Hypermobility, in which there is an increased range of joint movement as a result of a variant of collagen. Joint hypermobility is over-represented in people with anxiety, mood and neurodevelopmental disorders. It is also linked to stress-sensitive medical conditions such as irritable bowel syndrome, chronic fatigue syndrome and fibromyalgia. Structural differences in "emotional" brain regions are reported in hypermobile individuals, and many people with joint hypermobility manifest autonomic abnormalities, typically Postural Tachycardia Syndrome. Enhanced

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Table 2 | Summarizes extra-articular disorders associated with joint hypermobility with example references.

Condition	References
Attention deficit hyperactivity disorder	Koldas Dogan et al., 2011
Anxiety	See later review, e.g., (Martin-Santos et al., 1998)
Asthma	Morgan et al., 2007
Carpal tunnel syndrome	Aktas et al., 2008
Chiari malformation type I	Milhorat et al., 2007
Chronic constipation	De Kort et al., 2003
Chronic fatigue syndrome	Nijs et al., 2006
Chronic regional pain syndrome	Stoler and Oaklander, 2006
Crohn's disease	Vounotrypidis et al., 2009
Developmental co-ordination disorder	Kirby and Davies, 2007
Fecal incontinence	Arunkalaivanan et al., 2009
Fibromyalgia	Ofluoglu et al., 2006
Functional gastrointestinal disorder	Zarate et al., 2010
Headache attributed to spontaneous cerebrospinal fluid leakage	Schievink et al., 2004
Hiatus hernia	Al-Rawi et al., 2004
Mitral valve prolapse (MVP)	Yazici et al., 2004
Migraine	Bendik et al., 2011
New daily persistent headache	Rozen et al., 2006
Pelvic organ prolapse	Lammers et al., 2012
Postural tachycardia syndrome	Mathias et al., 2012
Psychological distress	Baeza-Velasco et al., 2011
Rectal evacuatory dysfunction	Mohammed et al., 2010
Somatosensory amplification	Baeza-Velasco et al., 2011
Urinary stress incontinence	Karan et al., 2004

Extra-articular disorders associated with joint hypermobility, adapted from Castori (2012).

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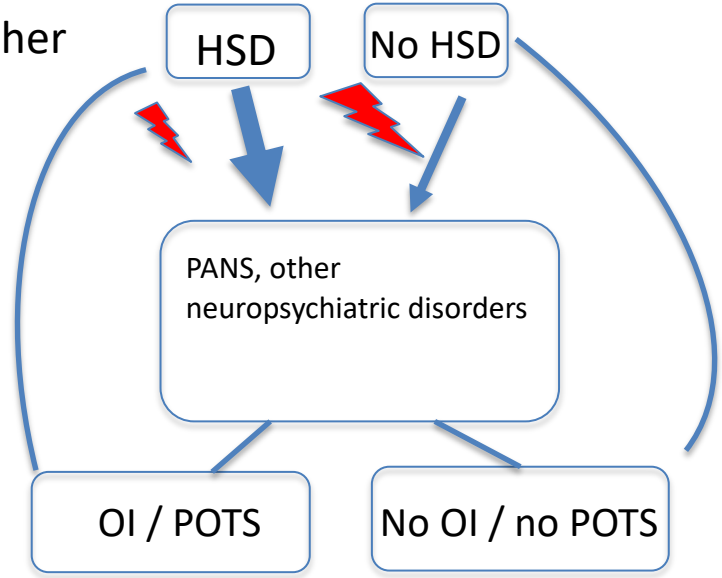
Genetics
- HSD; HLA-, other

Triggers



Treatment according to etiology and symptoms and degree/ type of OI and of the concomitant psychiatric symptoms and other diseases, such as MCAD

Markku Partinen

Evolution of PANS / POTS

- Genetic susceptibility (HLA, microbiome, autopathia, HSD/ EDS)
- early environment (infections, development of microbiome) & low sense of coherence →
- immunological trigger (infection, any trauma) & affected BBB → dysfunction of glial cells →
- brain energetics (mitochondria, pyruvate cycle, ANLS) affected + inflammation → glymphatic flow affected
- neuronal dysfunction & dysautonomia → symptoms of PANS & POTS →
- resting, horizontal position, lying, lack of exercise → deconditioning, sodium-balance affected, worsening of salt balance → worsening of symptoms… & worsening of muscle energetics & worsening of dysautonomia
- pains, neurological symptoms…

Conclusions and Questions

- **PANS, POTS and joint hypermobility link with each other**
- Symptoms are variable. The most disabling symptoms differ between patients
- Autoimmune-mediated
- Genetic susceptibility probably exists
- POTS may be mainly a problem of parasympathetic (vagal) tone? – cf. Porges
- About origins of POTS/ dysautonomia/ PANS
  - Risk factors of POTS and PANS: Caucasian, high achiever (sympathicotonia), joint hypermobility
  - Genetic susceptibility + a traumatic event disturbing ANS control
    - **Trauma may be: microbial attack, other immunological attack, physical trauma, mental trauma**
    - **A function may be disturbed without any structural (anatomical) damage**
      - **Compare to a software problem in a computer**

A lot needs to be done/ studied

- Autonomic tone and autonomic Abs in PANS vs controls
- Genetic studies
- Experimental studies – animal models
- Autoantibodies
  - Finding the epitopes → immunoadsorption ?
- RCTs on treatment / rehabilitation
  - Antibiotics, anti-inflammatory medications, immunomodulatory therapies
  - Increase of parasympathetic tone and/or decrease of sympathetic tone
  - Different forms of CBT as part of treatment and rehabilitation
  - SSRI, SNRI - action also on synaptic rewiring
- Epidemiological studies
  - Prevalence and incidence of PANS and POTS in populations
    - < 10 yrs, 10 to 17 years, 18 to 39 years, 40 + years

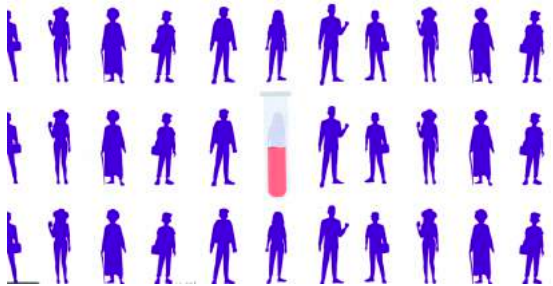
FinnGen – a study to examine sleep and health

Hanna Ollila

10% of population
Current N = 200 000 (target = 500 000 000)

6M individuals

REGISTRY DATA:
(Autoimmune) encephalitis N= 281
Narcolepsy N = 1271
Hypersomnia N = 136
Fibromyalgia N = 29 620
ME/ CFS N = 1 000 – 5 000 ?
POTS N = 72
PANS N = 50 – 200 ?



Comment: Final number of true diagnoses needs still to be verified

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