Narcolepsy

I. S.M.C
Radisson Blu Hotel
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I. Defining the narcoleptic syndrome
   clinical features and diagnosis
   the role of investigations
   hypocretin (orexin) deficiency

II. Case history

III. “Secondary” narcolepsy

IV. Conclusions
The features of narcolepsy

**History**

**Gelineau 1880**

*“seized by somnolence”*

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**Rx for Narcolepsy**

- amyl nitrite
- apomorphine
- picrotoxin
- strychnine
- caffeine
- baths in the Seine
The features of narcolepsy
a syndrome of [REM] sleep dysregulation

- excessive daytime sleepiness * and sleep attacks
- cataplexy *
- sleep paralysis *, occasionally at sleep onset
- hallucinations (~visual) around sleep/wake transitions *

* tetrad described by Yoss and Daly 1957, fully present in ~ 20%
24-hour hypnograms in control and untreated narcoleptic patients

Adapted from Rogers et al. *Sleep*. 1994;17:590.
Clinical diagnosis of narcolepsy
nature of the sleepiness, beyond the Epworth...

- Need for sleep can be intense / irresistible
  - naps often occur in unusual places
    - ask about work, missing bus stops
  - “sleep attacks” may occur
    - no recollection of prior imperative to sleep
  - sleepiness worse if bored or unoccupied:
    - “do you regularly sleep as car passenger?”
    - “when was the last time you saw a film all the way through?”
  - naps typically short-lived (20 mins or less) and restoring dreams or hallucinations during daytime naps often reported
Clinical diagnosis of narcolepsy
nature of the sleepiness

- Total amount of sleep over 24h usually not that excessive
  overnight sleep typically fragmented or “destructured”
  often relatively refreshed on morning waking

- Complaints of poor memory / concentration very common
  even on *optimal* wake-promoting treatment:
  average attention/reaction time ≈ controls after 22h awake

- Automatic behaviours frequent
  in presumed “microsleeps”, eyes can be open
  losing items around house / inappropriate behaviours
Dear Sue

Happy New Year, I hope you had fun over the holidays.

As discussed previously I need to send you a bill which will be more than previously anticipated our time costs are £1,586.25 but I have discounted that to £1,400.00.

You have paid via standing order £675.00 of this which leaves £725.00 plus VAT to pay which equals £870.00.

As discussed you were going to double the standing order and then just pay it this way which is fine.

The reason for the increase is mainly the increase in the number of meetings that we have spent trying to decide the best way forward and hopefully I have tried to help you with that.

I trust you find this satisfactory.

With kind regards

Yours sincerely

Mrs J R Rhodes

Enc
Mrs S West
Home

JRR 5 January 2012

Dear Sue

Happy New Year! I hope you had fun over the holidays.

As discussed I need to send you a bill which will be more than previously anticipated Lift and cross our £18,0825 but have discussed that £14, Youd hae be £675 of standpoind er orde dr t, As discussed you were going to double yor tstding order tnatd just wpay which is h I kllwrer clwituewqf 454; dADEE ~###+fen

With kind regards

Yours sincerely
Overnight sleep in narcolepsy

- Sleep architecture usually dysregulated / “destructured”
  - frequent arousals, often with sleep maintenance insomnia
  - “sleep inertia” a major issue if deep non-REM sleep late in night

- Increased prevalence of all types of parasomnia
  - sleep-talking, sleep-walking, sleep-eating
  - REM sleep parasomnias (including REM sleep behaviour disorder)

- Restless legs syndrome (~20%)
  - also periodic limb movements

- Obstructive sleep apnoea
  - CPAP treatment poorly tolerated
  - hypnotics may help
REM sleep phenomena in narcolepsy

- Dreams at night particularly vivid or disturbing
  confusion with reality
  dreams well remembered
  delusional systems may develop

- Hallucinations, particularly when drowsy
  any modality, visual commonest
  broadly similar to parkinsonian hallucinosis
  e.g. “extra-campine” hallucinations, misperceptions

- Sleep paralysis in ~25%
  often at sleep onset
  may lead to “sleep phobia”

- Cataplexy
  ~rapid intrusion of REM sleep paralysis into wakeful state
  usually linked to emotional stimulus (or its anticipation)

“I’m tied up with rope, can’t breathe, shouting for help”
**Cataplexy**

- **highly specific symptom: “jelly episodes”, “cabbage attacks”**
  affects 2/3 of narcoleptics with a wide spectrum of severity

- **abrupt loss (~2 secs) muscle tone due to intrusion of REM paralysis**
  usually starts (and may remain) in jaw, face or neck
  head / facial jerking or bobbing common at onset

- lasts seconds (rarely minutes), awareness fully maintained (at start)

- usually occurs in relaxed environment, therefore rare to see in clinic
  uncommon in potentially risky activities (e.g. swimming or driving)

- **absent tendon reflexes during episodes**

- **emotion (or its anticipation) usually triggers episodes (laughter 80%)**
Examples of cataplexy

cataplexy in children (complete and partial)
Examples of cataplexy
cataplexy in adults (complete and partial)
Other symptoms in narcolepsy

- Metabolic abnormalities including appetite dysregulation
  - food cravings
    - especially carbohydrates at night
    - leptin deficiency and increased insulin resistance?
  - sleep-related eating disorder and nocturnal smoking
  - weight gain often concerning

- Psychiatric co-morbidity
  - (reactive?) mood disorder
  - “psychosis” with delusional component
Hypocretin (orexin) deficiency

- Hypocretin neurons (~50,000) in dorsolateral hypothalamus with widespread connections particularly to “arousal centres”

- HCT-2 receptor mutations in genetic canine narcolepsy over 19 dog breeds with sporadic narcolepsy genetically engineered rodents a good model

- Human narcolepsy due to destruction of HCT neurons monophasic autoimmune event? link to infections/vaccinations? CSF levels <110 pg/ml diagnostic
Normal function of hypocretin

Hypocretin stabilizes the hypothalamic sleep / wake switch:

activity $\uparrow$ if sleep drive high (also if hungry or expecting food)

Saper et al. Trends Neurosci 2001
Diagnostic criteria
ICSD-3 (2014)

- Narcolepsy Type 1
  daily imperative sleep >3 months
  at least 2 of:
  A  history of *typical* cataplexy
  B  positive MSLT findings:
     mean lat <8 min + 2 SOREM’s
  C  CSF Hypocretin (1) < 110pg/ml

previous overnight sleep needs monitoring

- Narcolepsy Type 2
  daily imperative sleep >3 months
  and …
  A  positive MSLT findings:
     mean lat <8 min + 2 SOREM’s
  B  not explained by other sleep disorder, medication etc.

MSLT: multiple sleep latency test; SOREM: sudden onset REM sleep (<15’

(1) Hypocretin levels are decreased in narcolepsy patients.
Epidemiology

- Accepted prevalence in western Europe is: > 1 in 3000
  - 20,000 narcoleptics in UK?
  - up to 75% undiagnosed??
- Roughly equal male-female ratio
- Peak incidence early teens, shortly before puberty
  - second smaller peak in early 40’s
- Link to vaccinations, notably Pandemrix in 2009
- Patient “journey” remains unpredictable
  - sleep education very variable in primary care
  - still few “sleep neurologists” (~ 20)
- Access to best proven treatments very variable....
- Patients (even on treatment) rarely fulfil true potential
Case example

- Ms EN, current age 35y
  - In Nov 2009 working as Local Councillor, had Pandemrix vaccination
    - within 3 months, unable to stay alert for more than ~3 hours
    - forced to stop work, couldn’t stay awake in meetings
  - “jelly attacks” when meeting friends unexpectedly
  - overnight sleep very fragmented, intrusive dreams, “misperceptions” occasional disabling “sleep drunkenness” on awakening

- started on Modafinil (600mg daily) and Dexamfetamine added (20mg)
  - reasonable response in daytime but nocturnal sleep still very poor
  - applying for Sodium Oxybate as part of DoH ex-gratia scheme
Hypothalamic pathology causing “secondary” narcolepsy

- Mr DS, current age 27
  - presented with headaches and hydrocephalus age 23
  - low grade glioma in tectal plate near IIIrd ventricle

- after neurosurgery, severe daytime sleepiness with sleep-wake dysregulation
  - vivid dreams, no cataplexy
after incident, severe sleepiness during day
SOREM in 4/4 naps on MSLT

fragmented nocturnal sleep with hallucinations and sleep paralysis but..

... depression cured!

Brain injury causing “secondary” narcolepsy in 48 yr-old depressive man (Mokhlesi, Lancet 2009)
Conclusions

- There’s more to narcolepsy than severe sleepiness - a syndrome of sleep-wake “dysregulation”
- If clinical doubt, history more useful than tests
- Cataplexy is the most specific symptom but it can be subtle and/or partial and ... ... it may be normal to “go weak with laughter”
- Most likely a monophasic auto-immune disorder triggered by non-specific immune response in genetically predisposed individuals?