NARCOLEPSY

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DEFINITION

Narcolepsy is a chronic sleep disorder that exhibits excessive uncontrollable daytime sleepiness. There are three subtypes:

Type 1 narcolepsy with cataplexy
low hypocretin (orexin) level in hypothalamus causing changes between wake, REM sleep, and non-REM sleep,
OR

cataplexy with excessive daytime sleepiness

Type 2 narcolepsy without cataplexy
excessive daytime sleepiness but no muscle weakness, less severe and have normal hypocretin

DEFINITION

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- Type 3 Secondary narcolepsy
  underlying causes such as an head injury, a brain tumor, multiple sclerosis, encephalitis. Symptoms are as classic in type 1, plus more severe, and sleep for long periods -→ > 10 hours/night.

CAUSES

1. Autoimmune disorders- loss of the hypocretin-secreting neural cells which attacked by the immune system because of a combination of genetic and environmental factors, especially when cataplexy is present.

2. Family history- Most cases are sporadic but up to 10% having family with similar symptoms and is associated with HLA complex genes on chromosome 6.

3. Brain injuries- trauma, tumors, number of surgeries, radiation dose, ventricular shunt, BMI, and other diseases that mentioned above under the third subtype secondary narcolepsy.

RISK FACTORS

- An inherited genetic fault-strong genetic component with genetic marker HLA-DQB1*06:02
- Hormonal changes, including those that take place during puberty or the menopause.
- Major psychological stress.
- A sudden change in sleep patterns.
- An infection, such as swine flu or a streptococcal infection.
- Having the flu vaccine Pandemic.

PRESENTATIONS

Classic main symptoms

- Excessive daytime sleepiness
  Sleep attack is usually the first symptom. This episode mostly occurs during boring activities, but can occur at any time.

- Hallucinations while falling asleep or waking up
  Often occur along with sleep paralysis.
  - hypnagogic
    just before falling sleep, or

  - hypnopompic
    just before awakening

PRESENTAIONS

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- Cataplexy
  1. Loss of muscle tone following a strong emotional stimulus, present as knees buckle, jaws sage, eyelids droop, head drop, or complete loss of muscle control.
  2. Only occurs in some patients.

- Sleep paralysis

  A short period of inability to move or speak while falling asleep or upon waking.

  -mimics the paralysis that occurs during a REM sleep.

  -not everyone with sleep paralysis has narcolepsy.

- Other symptoms

  Fatigue, depression, difficulty concentrating, memory problems, periodic leg movements and sleep apnea.

DIAGNOSIS

A) Screening to evaluate for narcolepsy:

a. Epworth Sleepiness Scale
measure dose or sleep in 8 situations. An ESS score >10 suggests excessive daytime sleepiness. High level of sleepiness (16-24) indicates significant sleep disorders.

b. Swiss Narcolepsy Scale (SNS), <0 suggestive type 1 narcolepsy
consider using SNS if ESS score >10. It assesses five symptoms that can be used to screen for the presence of narcolepsy with cataplexy.

DIAGNOSIS

2) Diagnostic testing:
Overnight polysomnography (PSG) followed by a multiple sleep latency test (MSLT).

Criteria of Type 1- hypocretin deficiency syndrome, narcolepsy with cataplexy. A and B must be met:

A. daily periods of irrepressible need to sleep or daytime lapses into sleep for 3 months or more.

B. Presence of 1 or both of the following:

1. Cataplexy and a mean sleep latency of 8 minutes or less and 2 sleep-onset REM periods or more (SOREMPs) on MSLT, a SOREMP on PSG may replace 1 of the SOREMPs on MSLT.
2. CSF hypocretin-1 is either 110 pg/ml or less, or < 1/3 of mean normal values.

DIAGNOSIS

Criteria of Type 2: A-E must be met:

A. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring 3 months or more.
B. A mean sleep latency of 8 minutes or less, and 2 sleep-onset REM periods or more (SOREMPs) on MSLT, a SOREMP on PSG may replace 1 of the SOREMPs on MSLT.
C. Absent of cataplexy.
D. Either CSF hypocretin-1 not measured, or measured but is either >110 pg/ml or >1/3 of mean normal values.
E. The hypersomnolence and/or MSLT findings are not better explained by other causes.

DIFFERENTIAL DIAGNOSIS

- Periodic limb movement disorder
- Sleep apnea
- Idiopathic hypersomnia
- Delayed sleep phase syndrome (DSPS)
- Kleine-Levin syndrome

TREATMENTS

Lifestyle Changes

Sleep regulations and Behavioral modification-

- Regular bedtime hours
- Scheduled daily naps
- Regular exercise
- Avoid caffeine, smoking, alcohol
- Avoid heavy meals before bedtime
- Avoid sleep deprivation or long naps
- Relax before bed

TREATMENTS

Medications

Stimulants- to treat sleepiness. Modafinil (Provigil) is the first line. Methyphenidate (Ritalin), amphetamines if modafinil is ineffective. Solriamfetol (Sunosi) help stay awake for longer periods. Others are manzindol, selegiline, and pemoline.

CNS depressant- Sodium oxybate (Xyrem) treat cataplexy, decreases sleepiness by promoting stage 3 sleep and suppresses REMs.

TREATMENTS

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H3 receptors antagonist/inverse agoinst- Pitolisant (Wakix) to help stay awake for longer periods.

Antidepressants- to treat cataplexy, sleep paralysis and/or hypnagogic hallucinations, problems with REM sleep, especially SSRI, which suppress REM sleep, includes fluoxetine (Prozac, Serafem), sertraline (Zoloft), atomoxetine (Strattera) and venlafaxine (Effexor). TCAs such as imipramine, desimipramine, protriptyline, and clomipramine.

TREATMENTS

Other therapies: Immunotherapy with steroids, intravenous immunoglobulins, plasmapheresis and alemtuzumab prevent neuronal death.

Other new medications : Solriamfetol (JZP-110), a selective DNRI, is a new drug that approved in Jan/2020. Recently, FDA accepts filing for investigational new drug application for JZP-258.

TREATMENTS

Future treatments :

- Administration of hypocretin peptides, Orexin-based drugs, by IV, intranasal, intracisternal, intracerebroventricular, and intraperitoneal.

- Hypocretin (ORX) neuronal transplantation .

- Transforming hypocretin stem cells into hypothalamic neurons, and hypocretin gene.

- Replacement with hypocretin receptor agonists.

SOURCES

NIH: Narcolepsy Fact Sheet. (2020, March, 16). Retrieved from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Narcolepsy-Fact-_Sheet

Penn State Hershey, Milton S. Hershey Medical Center: Narcolepsy. (2018, January 1). Retrieved from http://pennstatehershey.adam.co/content.aspx?productid=116&pid=10&gid=000098

NORD: Rare Disease Database Narcolepsy. (2017). Retrieved from https://rarediseases.org/rare- diseases/narcolepsy/

NHS: Causes Narcolepsy. (2019, May, 13). Retrieved from https://www.nhs.uk/conditions/narcolepsy/causes/

SOURCES

5. National Library of Medicine: The ICSD-3 and DSM-5 guidelines for diagnosing narcolepsy: clinical relevance and practicality. (2016, July 20). Retrieved from https://pubmed.ncbi.nlm.nih.gov/27359185/

6. MAYO CLINIC: Patient Care & Health Information>Diseases & Conditions: Narcolepsy. (2019, January, 12). Retrieved from https://www.mayoclinic.org/diseases-conditions/narcolepsy/symptoms-causes/syc-20375497

7. Narcolepsy Link: Diagnostic Criteria. (2018, December, 6). Retrieved from https://www.narcolepsylink.com/diagnose/diagnostic-criteria/

8. OXFORD: Neuro-Oncology. (2017, May, 3) Retrieved from https://academic.oup.com/neuro-oncology/article/19/suppl_3/iii4/3743815

Thank You