Narcolepsy: origins and insertions

My first encounter with narcolepsy was memorable. As a visiting medical student in Aarhus, Denmark, I was astonished to see a fellow student suddenly fall asleep standing upright in a doorway when awaiting the arrival of a minibus to take us to the hospital. He quickly regained his senses and told us of his affliction. This was clearly different from the physiological post–prandial or ethanolic dozing of middle–aged and elderly people, and from Dickens' account of Joe, the fat boy in The Pickwick Papers:

> *On the box sat a fat and red-faced boy, in a state of somnolency… the fat boy waddled to the same perch, and fell fast asleep instantly. "Damn that boy, he's gone to sleep again. … Sleep!" said the old gentleman, "he's always asleep. Goes on errands fast asleep, and snores as he waits at table. How very odd!" said Mr. Pickwick.*

The obesity, daytime sleepiness, snoring, and possible sleep apnoea are now labelled the "obesity hypoventilation syndrome" or "Pickwickian syndrome."

Narcolepsy derives from the Greek ναρκωστς (narkē, numbness or stupor, and lepsis, seizure); cataplexy is from the Greek καταπληκτικός being stricken down. It is often called Gélineau's syndrome, after the French physician and naval surgeon Jean Baptiste Edouard Gélineau (1828–1906) who in 1880 described both cataplexy and narcolepsy triggered by sudden emotions. He said: "Therefore, I feel justified in designating narcolepsy as a specific neurosis, little known until now," in a 38-year-old man with frequent narcoleptic sleep attacks, up to two hundred daily:

> *When laughing out loud or when anticipating a good business deal in his profession, he would feel weakness in his legs, which would buckle under him. Later, when playing cards, if he was dealt a good hand he would freeze, unable to move his arms. His head would nod forward and he would fall asleep. He would wake up a minute later [1,9].*

Gélineau briefly described cataplexy as "astasia", the sudden muscle weakness initiated by surprise, laughter or unexpected emotions. He reported sleep paralysis but not hypnagogic/hypnopompic hallucinations. Years later he was awarded the Chevalier de la Légion d' Honneur, and in his retirement was a prize–winning wine producer.

An earlier probable portrayal is that of Thomas Willis who noted that it was not just an embarrassing somnolence but a humoral disease in which the body produced its own narcotic substances [2]. He described patients with:

> *A sleepy disposition—they eat and drink well, go abroad, take care well enough of their domestick affairs, yet whilst talking or walking, or eating, yea their mouthes being full of meat, they shall nod, and unless roused by others, fall fast asleep [3].*

Gowers stressed the importance of separating narcolepsy (NT1)* from other neurological disorders associated with somnolence. WJ Adie at Queen Square described six of his patients with cataplexy and fifteen from the literature:

> *THE disease I am about to describe is characterized by the occurrence of attacks of irresistible sleep without apparent cause, and curious attacks on emotion in which the muscles relax suddenly, so that the victim sinks to the ground fully conscious but unable to move. As a rule the attacks occur independently ; occasionally an attack on emotion ends in sleep [4].*

Kinnier Wilson added more examples in a masterly review and coined the term "sleep paralysis [5]." Daniels [6], Yoss and Daly [7] drew attention to the concurrence of narcolepsy, cataplexy sleep paralysis, and hypnagogic hallucinations, although the complete tetrad is observed in only about twenty per cent of narcolepsy cases.

Episodes of both narcolepsy and cataplexy last for about two minutes with widely varying frequency, accompanied by excessive daytime sleepiness. Sleep paralysis and hypnagogic hallucinations can occur in normal subjects during the twilight states as well as in narcolepsy. In sleep paralysis, the terrified patient lies wide awake unable to move for seconds or a few minutes. Hypnagogic (on falling sleep) and hypnopompic (on awakening) hallucinations may be isolated or accompany sleep paralysis. Patients describe frightening hallucinations of kaleidoscopic shapes, animals or people, sometimes as a terrifying incubus squashing the chest.

Westphal, narcolepsy and cataplexy

Carl Friedrich Otto Westphal (1833-90) provided an earlier but often overlooked account and described both narcolepsy—"peculiar attacks associated with falling asleep"—and cataplexy. In July 1876 three years before Gélineau's paper he presented two patients, a bookbinder and a cooper to the Berlin Medical and Psychological Society, published in 1877 [8].

Schenck and colleagues drew attention to English translations of Westphal's report: He described narcolepsy associated with cataplexy:

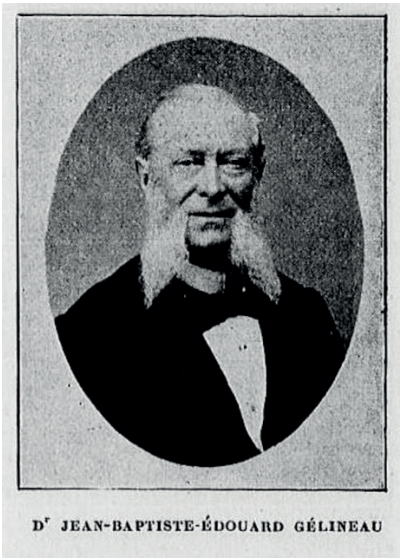

Figure 1. Jean Baptiste Edouard Gélineau

> *At times…these attacks [of cataplexy] do cause the patient to fall asleep. The falling asleep appears, as it were, to be an extension or increase of the attack…while "strolling around quietly and aimlessly.*

In the sleep attacks:

> *His upper eyelids lowered gradually like those of a person falling asleep (during which the eyes roll upward). Then they opened again once or twice, seemingly with great effort, until they finally shut completely, whereupon the patient stopped speaking after murmuring something incomprehensible. His head sank down to his chest, and his brow seemed forcefully knit… he hears and understands what is said to him during the attack [9].*

He emphasised that he did not lose consciousness. He was also the first to describe familial cataplexy: the mother of his 36-year old patient also suffered from recurrent episodes of cataplexy.

Westphal made many important neurological contributions and is remembered eponymously for the Edinger Westphal nucleus and for introducing tendon reflex examination into routine clinical practice. He trained Arnold Pick, Hermann Oppenheim and Carl Wernicke.

Löwenfeld in 1902 recognised narcolepsy with cataplexy as a "disease sui generis, and gave cataplexy its name [10]. Von Economo in 1930 with prescience proposed "narcolepsy has its primary cause in an yet unknown disease of that region"— the posterior hypothalamus.

> *"On the box sat a fat and red-faced boy, in a state of somnolency… the fat boy waddled to the same perch, and fell fast asleep instantly. "Damn that boy, he's gone to sleep again. … Sleep!" said the old gentleman, "he's always asleep. Goes on errands fast asleep, and snores as he waits at table. How very odd!" said Mr. Pickwick.*

Narcolepsy has a prevalence of about 25–50 per 100,000. The onset is usually in the second or third decade, succeeded by lifelong attacks of falling asleep during the day, often with disturbed sleep at night. It is usually clinically distinguishable from obesity hypoventilation sleep apnoea and other causes of hypersomnolence. Polysomnography and a mean latency sleep test (MLST) are common aids to diagnosis [11].

Recent advances

In 1963 narcolepsy was related to sleep onset rapid eye movements (REM) [12]. Normal sleep is accompanied by dreaming and loss of muscle tone; in narcoleptics these features occur when the subject is awake, resulting in attacks of daytime sleep often accompanied by cataplexy, nocturnal hypnagogic hallucinations, and sleep paralysis which are pathological manifestation of REM sleep.

Although human narcolepsy is not a simple genetic disorder [13], first-degree relatives of a narcoleptic patient, have a risk estimated at 1–2 per cent, some 10 to 40 times higher than in the general population. The concordance rate in monozygotic twins is approximately 20–30 per cent.

Most narcoleptics carry a HLA-DR or DQ haplotype. The DQB1 alleles are haplotypes associated with narcolepsy, suggesting an autoimmune basis; but this is unproven [14]. HLA gene variations may increase susceptibility to a putative immune attack on hypocretin cells. However, 30 per cent of families have no association with HLA DQB1∗0602, which suggests other environmental or immune factors. Emmanuel Mignot and others have shown that neurons that secrete hypocretin (orexin) are depleted in the brain and cerebrospinal fluid in the narcoleptic syndrome [15]. Two hypocretin neuropeptides are produced in the lateral hypothalamus and act on specific receptors, which modulate sleep, arousal, feeding, anxiety and cognition. Narcolepsy patients also show loss of hypothalamic corticotrophin-releasing hormone producing neurons, which suggests mechanisms other than a cell-specific autoimmune attack.

Modafinil and low sodium oxybates are the mainstays of treatment. The current development of orexin receptor agonists promises the possibility of better symptomatic control.

**Narcolepsy type 2 (NT2) is a poorly understood variant without cataplexy and with normal orexin levels.*

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Conflict of Interest Statement: None declared
Provenance and peer review: Submitted and reviewed internally.

Date First Submitted: 31/8/2023 ***Acceptance Date:*** 4/9/2023 ***Published Online:*** 19/12/2023

To cite: Pearce JMS. "Narcolepsy: origins and insertions." Adv Clin Neurosci Rehabil 2023;
https://doi.org/10.47795/UZPI8935

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