Narcolepsy: A Historical Review

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Citation

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Abstract

Narcolepsy is a disorder characterised by diurnal somnolence and episodes of short duration sleep. Cataplexy is frequently associated as are the symptoms of sleep paralysis, hypnagogic hallucinations and disordered night-time sleep. The condition has been recognised since the 19th century with many prominent late 19th and earl 20th century neurologists contributing to our knowledge of the condition. Recent research from sleep laboratories as well as laboratory research on hypocretins (oroxins) has led to a greater understanding of this debilitating condition.

HISTORY

Narcolepsy is the English form of the French word narcolepsie, and was first used in 1880 by the French physician Jean-Baptiste-Edouard Gélineau (1828-1906) [1]. The origin is from the Greek, narke (numbness, stupor) and lepsis (attack, to seize). In two landmark papers published in Paris in 1880 Gélineau described this condition in a wine merchant who had been afflicted through his adult life with somnolence and short sleep attacks. He proposed that it was a neurosis or functional condition. Gélineau's definition was somewhat open ended, as he did not distinguish it from other forms of somnolence and some investigators spoke of ‘Narcolepsies'. The term cataplexy, from the Greek kataplexis (fixation of the eyes), was first used by Löwenfeld in 1902 in his paper describing sufferers with episodes of muscle weakness triggered by emotions [2].

Gélineau was born in 1828 at Blaye, Gironde, close to the Bordeaux region. He studied medicine at the Rochefort navy medical school and in 1849 became a physician at the navy hospital in Rochefort, a 17th century military base on the Atlantic coast. He introduced a treatment for epilepsy, which became known as Dr Gélineau's tablets containing bromide and arsenic. The bromide no doubt had some efficacy and his treatment became popular and successful. He relocated his practice to Paris in 1878 where he established a private neurological clinic. His first patient with narcolepsy was a wine cask maker reported in the Journal, La Gazette des Hôpitaux de Paris. The attacks began at age 36 and lasted between one and five minutes and occurred up to 200 times per day. His paper speculated on the nature of narcolepsy which he thought was a form of normal sleep and distinct from epilepsy. Although Gélineau had achieved some success with his epilepsy treatment, he was relatively unknown in Paris and an outsider to Charcot's circle of Parisian colleagues. Despite this handicap, the term narcolepsy was used by Charcot and became generally accepted.

Early descriptions of narcolepsy were in case reports from the German physicians Westphal (1877) and Fisher (1878) [3, 4]. Both authors noted the association between sleep episodes and attacks of muscle weakness triggered by emotion. Both also observed a hereditary factor; the mother of Westphal's patient and a sister of Fisher's patient had features of the same condition. Thomas Willis (1621-1675) described patients ‘with a sleepy disposition who suddenly fall fast asleep' which may represent the earliest account of narcolepsy [5].

William Gowers in his writings attempted to restrict the term narcolepsy to short duration sleep attacks on a background of normal wakefulness. He sought to distinguish the condition from other neurological or degenerative conditions associated with somnolence [6]. Kinnier Wilson coined the term ‘sleep paralysis' in 1928 [7]. His patient suffered from narcolepsy and cataplexy and exhibited attacks of ‘tonelessness precipitated by a terrifying dream.’ Reports by Adie (1926), Wilson (1928) and Daniels (1934) helped to identify the characteristic features of the condition whilst in 1957 [8]. Yoss and Daly at the Mayo Clinic defined the classic tetrad of excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations [9]. Many patients however do not have all symptoms and only 20-25% have all four. A proposed fifth symptom of disturbed nocturnal sleep occurs in 50% of patients.

Various causes or lesions were proposed for narcolepsy. Late 19th and early 20th century reports suggested seizure disorders or degenerative condition whilst Kinnier Wilson suggested tumours situated in relation to the 3rd ventricle [7]. Von Economo is credited with recognising the posterior hypothalamus as a crucial region governing wakefulness.

Vogel in 1960 first recorded REM sleep at the onset of an attack in a patient with narcolepsy [10]. Further investigations by Nathaniel Kleitman at University of Chicago and William Dement at Stanford University established the classical hypothesis of dissociated REM sleep in narcolepsy [11]. The work led to the development of the multiple sleep latency test (MSLT) for the diagnosis of narcolepsy.

Since the 1960's there has been a dramatic increase in research in narcolepsy and sleep medicine associated with expansion of sleep centres in many countries. Canine narcolepsy was identified in the 1970's in various breeds of dogs including Dobermans, Beagles and Labradors. In Labradors, the condition was found to be transmitted by a single autosomal recessive gene [12]. In the 1980's, investigators established a link with the HLA-DQB1*0602 gene on chromosome 6 in up to 90% of affected human subjects with narcolepsy and cataplexy [13]. These findings are evident across race and ethnicity. As many HLA associated disorders are also autoimmune in nature, it raises the possibility that narcolepsy may be an autoimmune disorder.

Hypocretins (oroxins) were identified in the 1990's. These small peptides were found to be involved in canine narcolepsy, which show hypocretin-2 gene deletions as the disease mechanism. Subsequently a knockout mouse for the preprohypocretin gene has been shown to exhibit sleep abnormalities resembling narcolepsy. In human studies, several lines of research have implicated hypocretins in the condition. Low levels of hypocretin-1 are found in CSF of narcolepsy patients and loss of over 80% of hypocretin-producing neurons in dorsolateral hypothalamus has been reported in autopsy studies [14]. These findings have led to a proposed disease mechanism that hypocretin producing cells in the hypothalamus may be affected by an autoimmune process in HLA-associated narcolepsy.

CURRENT PERSPECTIVES

The prevalence of narcolepsy is approximately 1 per 200 of the general population [15]. It is estimated that there are up to 3 million sufferers worldwide and its frequency is similar to Parkinson's disease and multiple sclerosis. Many cases remain undiagnosed which may relate to variation in severity of the condition with many incomplete or atypical forms. It may be misdiagnosed as other sleep disorders, epilepsy or side effects of medication.

Narcolepsy occurs in all ethnic groups and has equal incidence in males and females. The age of onset varies widely but the peak age of first symptoms is in adolescence or early adult life. Up to 12% report a positive family history. Many studies have shown a delay in diagnosis, which may be up to 15 years from first symptoms. Such delays add to the burden of disease in social, educational and occupational fields. Whilst cognitive impairment may occur, poor school performance usually reflects excessive daytime sleepiness.

The diagnosis of narcolepsy is straightforward when the characteristic features are all present. A history of diurnal somnolence associated with cataplexy is sufficient for a clinical diagnosis. Cataplexy may be absent and only a minority have all of the classic tetrad of features. The main characteristic of short duration sleep disorder is often apparent in the evenings. These brief episodes are often irresistible and may occur several times per day often at inappropriate times. As well, suffers frequently report disordered night-time sleep with frequent awakenings and up to 40 percent report night-time automatisms or frequent nightmares. The symptom of cataplexy consists of a sudden loss of muscle tone, which may vary from mild episodes of weakness at the knees or limpness of arms, neck or trunk muscles to complete collapse. Triggers are usually an emotional reaction to laughter, startle or fear. There is no loss of consciousness and the duration is usually a few seconds but may extend to a few minutes. Sleep paralysis is the short duration inability to activate voluntary muscles whilst waking from sleep. It typically lasts from seconds to minutes and may occasionally be reported whilst falling asleep. Hypnagogic (at sleep onset) and hypnapompic (on awakening from sleep) hallucinations are usually vivid visual or auditory phenomena, which may be quite frightening. The feature of cataplexy is closely associated with narcolepsy but the other features may all occur in isolation.

Investigations in a diagnostic sleep centre are frequently required to secure the diagnosis. The two tests employed are the polysomnogram and multiple sleep latency test (MSLT) [16]. The polysomnogram involves the continuous recording of EEG and muscle activity during sleep. Patients with narcolepsy fall asleep quickly with early onset REM sleep. A

sleep disorder with frequent awakenings is often detected. The sleep study can assist in confirming the diagnosis and excluding other causes for somnolence such as sleep apnoea. A multiple sleep latency test measures a subject's ability to fall asleep at five, two-hour intervals during normal awake times. With EEG recording, observations are noted on the time to reach the stages of sleep (sleep latency). Falling asleep with immediate onset of REM sleep on at least 2 occasions constitutes a positive test. HLA typing is not routine in diagnostic testing but can identify carriers of the at-risk genotype of HLA.DQB1*0602. This HLA type is found in 20-25% of the normal population which limits its diagnostic value [$_{17}$].

Gélineau administered various treatments for narcolepsy including bromides, strychnine and amyl nitrate. Some benefit was associated with the use of caffeine, which was also endorsed by Gowers who suggested stimulant drugs including ephedrine. Amphetamine and methylphenidate (Ritalin) were first used for narcolepsy in the 1950's whilst more recently cerebral stimulants, modafinil and pemoline, have been advocated [$_{18}$]. The treatment of narcolepsy involves allowing adequate time for regular night-time sleep. Frequent naps through the day may also assist with somnolence. Modafinil is well tolerated and is effective in up to 75% of patients and has become the drug of first choice. The mechanism of action of Modafinil is unknown although laboratory studies have shown an increase in monoamines in the hypothalamus. Adverse reactions are uncommon though there are rare reports of severe cutaneous reactions including Stevens-Johnson syndrome. Ritalin is used for subjects who have limited response to Modafinil. The treatment of cataplexy and other non-REM sleep abnormalities is with tricyclic antidepressants but the responses are often limited. Venlafaxine is a newer antidepressant which blocks serotonin and noradreanaline uptake and has shown efficacy in cataplexy. The identification of hypocretin deficiency in human narcolepsy raises the possibility that hypocretin analogues or receptor agonists may provide novel therapeutic interventions in this condition.

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