# Cataplexy

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## ABSTRACT

Remarkably and almost invariably, the clinical phenomenon of cataplexy results from the loss of around 40 000 hypocretin-containing neurones in the lateral hypothalamus in the context of narcolepsy type 1. Cataplexy reflects the dysregulation of rapid-eye-movement (REM) sleep, such that REM-sleep atonia intrudes inappropriately into wakefulness as brief episodes of either focal or total paralysis of voluntary muscle. The semiology of cataplexy differs between adults and children. A defining and enigmatic aspect is that certain emotional stimuli usually trigger the episodes. Cataplexy can be the most disabling symptom of the narcolepsy syndrome, severely limiting normal activities of daily living. Antidepressant drug therapy at relatively low doses is the traditional treatment; these most likely work through inhibiting REM sleep, predominantly by increasing brain monoamine concentrations. Sodium oxybate is probably the most effective drug for severe cataplexy, taken before overnight sleep and once through the night; its precise mechanism of action remains obscure. Pitolisant is a new agent for treating the excessive daytime sleepiness of narcolepsy that also helps cataplexy control by increasing histamine concentrations in the hypothalamus. Further understanding of the neurobiology of cataplexy and how it relates to hypocretin deficiency should improve our understanding of the brain's emotional processing and provide insights into REM sleep and its control.

## INTRODUCTION

Cataplexy reflects intermittent brief intrusions of voluntary muscle paralysis, normally associated with rapid eye movement (REM) sleep, typically when an awake subject experiences or expects a positive emotion. It is a fascinating clinical phenomenon but also important to recognise for several reasons. First, its presence is virtually diagnostic for narcolepsy type 1 as defined by the most recent classification guidelines[1] and correlates very strongly with a profound deficiency of the neuropeptide hypocretin, also called orexin.[2] Indeed, it remains an astonishing neuroscientific fact that the presence of cataplexy reliably predicts the specific loss of around 40 000 neurones in the lateral hypothalamus, most likely from a monophasic autoimmune insult usually in early adolescence. Second, for a significant minority of people with narcolepsy, it is the most disabling aspect of their syndrome, especially when repeatedly recurring on a daily basis. Not uncommonly, such patients become reclusive, avoiding social contact through fear of unpredictable collapses and injury. Third, the study of cataplexy has furthered our understanding of REM sleep and the neurobiology underlying the associated profound voluntary muscle atonia, a key defining aspect of this enigmatic sleep state.

This review focuses on the clinical features of cataplexy, emphasising the diversity and wide spectrum of severity in people with narcolepsy. There is clearly a differential diagnosis when a subject collapses while being emotional. The review briefly covers our current knowledge of the underlying neurobiology and neural circuitry that generates cataplexy and finally discusses drug treatment options, despite the relative paucity of controlled evidence.

## HISTORY

The term 'cataplexy'—from the Greek 'kata' (down) and 'plak' (strike)—first appeared in the German physiology literature around 1880 to describe the phenomenon of tonic immobility ('playing possum'), that is, an animal feigning death when under threat. It should not be confused with 'catatonia' or 'catalepsy', which most often occur with severe neuropsychiatric disturbance, and refer to states of immobile rigidity as opposed to the profound atonia of full-blown cataplexy.

Also in 1880, the Parisian neuropsychiatrist Jean-Baptiste Gélineau published his landmark monograph, for the first time describing several clinical cases of narcolepsy. He is credited with coining the term



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narcolepsy ('to be seized by somnolence') and with great prescience speculated that the syndrome could have primary and secondary forms. We should not be too surprised, given where and when he lived, that neurosyphilis was the most common secondary cause. Although he did not use the actual term 'cataplexy' (preferring 'astasia') his elegant case histories remain iconic descriptions of the full narcoleptic syndrome. Most striking is the case of the wine merchant who would collapse repeatedly throughout the day with retained consciousness when confronted by 'grotesque figures in the street' or when dealt a particularly good hand of cards.

## CLINICAL FEATURES

Cataplexy is nearly always part of the narcoleptic syndrome. It is therefore associated with significant daytime somnolence along with other REM sleep-related phenomena, such as vivid dream-like hallucinations or sleep paralysis. Very rarely, cataplexy and less specific stimulus-induced drop attacks may be a component of disparate rare genetic syndromes, including Niemann–Pick disease type C,[3] Norrie disease[4] and Coffin–Lowry syndrome.[5] Clearly, the cardinal manifestations of these disorders dominate the clinical picture and there is conflicting evidence whether the associated episodes of collapse reflect true cataplexy with associated hypocretin deficiency. Of great interest, however, typical cataplexy also occurs in autosomal dominant cerebellar ataxia, deafness and narcolepsy (ADCA-DN), another extremely rare genetic disorder in which there is a point mutation of DNA methyl transferase.[6] Affected subjects usually have many other clinical features that superficially resemble a mitochondrial cytopathy, with ataxia, impaired cognition, peripheral neuropathy and myoclonus. Further clarification of the pathophysiology of the associated hypocretin deficiency in these rare subjects will probably provide insights into the neurobiological mechanisms that underlie idiopathic narcolepsy type 1.

Very rarely, severe cataplexy can be the initial presenting symptom of narcolepsy type 1 and occur in relative isolation without overt excessive sleepiness or other REM sleep-related symptoms (see the Case Section, (figure 1 and online supplementary video 1).

It is very uncommon for neurologists to witness cataplexy in a clinical situation although, increasingly, patients provide diagnostically helpful video material. In typical episodes, a subject reports a stuttering onset of weakness that spreads over a few seconds to complete paralysis of voluntary musculature if the attack is full-blown. Subjects use phrases such as 'jelly attacks', 'zombie episodes' or 'cabbaging', as opposed to terms describing frank weakness. Initially, symptoms are usually in the neck or facial muscles, causing slurred speech and an associated jerky irregular tremor of the head with prominent facial twitching,

**Figure 1** A 32 year-old woman with severe cataplexy. Still from accompanying online supplementary video 1.

sometimes leading to an erroneous suspicion of an epileptic seizure. The weakness may then spread cephalo–caudally over a few seconds with subsequent sagging of the knees and collapse to the ground. The mouth may hang open and the eyes are shut. Episodes tend to last for 10 s or less but recovery may be incomplete and a subject's weakness may appear to wax and wane for several minutes. Importantly, consciousness and sensory perceptions are entirely preserved during episodes although, if they are prolonged, many report intrusions of dream-like experiences or a general sense of detachment.

Minor or partial attacks are common and can be difficult to recognise even for close family members. Slight drooping of the head, slurred speech or dropping an item from the hand, for example, may be the only observable manifestation of a cataplectic event. Very occasionally, there is unilateral weakness of a limb, potentially mimicking a transient ischaemic attack.

Perhaps, the most intriguing aspect of cataplexy is its link to emotional stimuli, either internal or external. With emotional stimuli, it is often the anticipation of a rewarding event such as the punch line of a joke that triggers an event. The most effective precipitants are positive emotions, such as humour or a pleasant surprise, although frustration and even mild anger can also provoke events. However, significant negative emotions in times of potential danger rarely provoke episodes, perhaps due to concomitant sympathetic activation or increased adrenaline concentrations. This may also explain why intense emotions during 'road rage', for example, do not generally provoke cataplexy. Indeed, events generally occur in a relaxed environment with friends or family. Increased drowsiness, clearly very common in narcolepsy, amplifies the likelihood of attacks.

People with severe cataplexy tend to avoid situations or environments that risk provoking episodes though clearly they cannot avoid unexpected provoking stimuli. The weakness evolves relatively slowly and so the patient can usually adopt a safe position; thus, injuries are rare unless episodes occur on a flight of stairs, for example. It can be very difficult to judge whether someone with ongoing cataplexy is safe to drive but road traffic crashes due to cataplexy appear exceptionally rare.

Sleepy children with narcolepsy and cataplexy often have different symptoms to adults. For example, children may display irritability, inattentiveness or hyperactivity rather than frank somnolence. Similarly, cataplexy in childhood has some characteristic features.[7] In particular, limb and trunk muscles are less involved than facial muscles. Children often appear to grimace repeatedly, as if fighting facial muscle atonia, and show other seemingly positive motor phenomena including tongue protrusion. A characteristic 'cataplectic facies' has ptosis and a slackened jaw along with slurred speech. Childhood episodes are often partial but prolonged and sometimes there are no obvious emotional precipitants, although many patients report that playing video games is a reliable trigger.

## MIMICS OF CATAPLEXY

The clinical assessment of any significantly sleepy subject should ideally include a screen for cataplexy (table 1). However, clinicians must interpret positive features carefully given the widely held perception that it is normal to go 'weak at the knees' during significant emotion, including laughter. Interestingly, this idiom translates across virtually all languages and probably reflects a subclinical physiological phenomenon. Around one-third of normal subjects report mild leg weakness when laughing heartily. In a Dutch study, normal subjects induced to laugh in a laboratory setting had a diminished knee H-reflex .[8] Cataplexy may therefore reflect the exaggeration of a normal physiological tendency to become briefly atonic under certain emotional circumstances.

The term 'pseudocataplexy' has been used to describe psychogenic episodes of sudden collapse under emotional and usually stressful situations.[9] These can be difficult to diagnose if not witnessed and can occur alongside true narcolepsy with cataplexy. Such attacks typically start abruptly as a true 'drop attack' and are relatively brief and with or without loss of awareness. There is usually no report of the minor positive motor phenomena often seen in cataplexy, such as facial muscle twitching or head bobbing. The episodes can be disabling and tend to occur in public, unlike cataplexy. As in other functional neurological disorders with motor symptoms, there is a strong correlation with mood disorder.

Laughter-induced or gelastic syncope is rare but well described, in which brief loss of awareness occurs in

**Table 1** The differential diagnosis of cataplexy

| Potential cataplexy mimic | Nature of episodes | Comments |
|---|---|---|
| Normal weakness when laughing | Mild sagging of the knees when laughing heartily or experiencing a severe negative emotion | Many people probably have mild peripheral atonia when laughing as a normal physiological response |
| Pseudocataplexy | Sudden collapses or 'drop attacks' to the ground when emotional, usually in the context of stress | There is no progression of weakness over several seconds as commonly occurs in cataplexy. There are no positive motor phenomena such as head bobbing or facial jerks. Episodes that are triggered only by negative emotions should raise diagnostic doubt that attacks are truly cataplectic |
| Laughter-induced (gelastic) syncope | Hearty laughter produces brief collapse with pallor and loss of awareness | Attacks are relatively rare and not triggered by other stimuli (positive or negative). No other features of narcolepsy. Brief loss of awareness is usually recognised and reported |
| Gelastic seizures | Stereotypical episodes of laughter, usually without mirth, as manifestation of a focal seizure, occasionally with collapse | There is often accompanying brief loss of awareness or speech arrest and an associated lesion on cerebral imaging |
| Hyperekplexia | Increased startle and associated stiffness with sudden(acoustic) stimuli | The increased tone and posturing do not resemble the atonia of cataplexy and nor do the typical triggers |

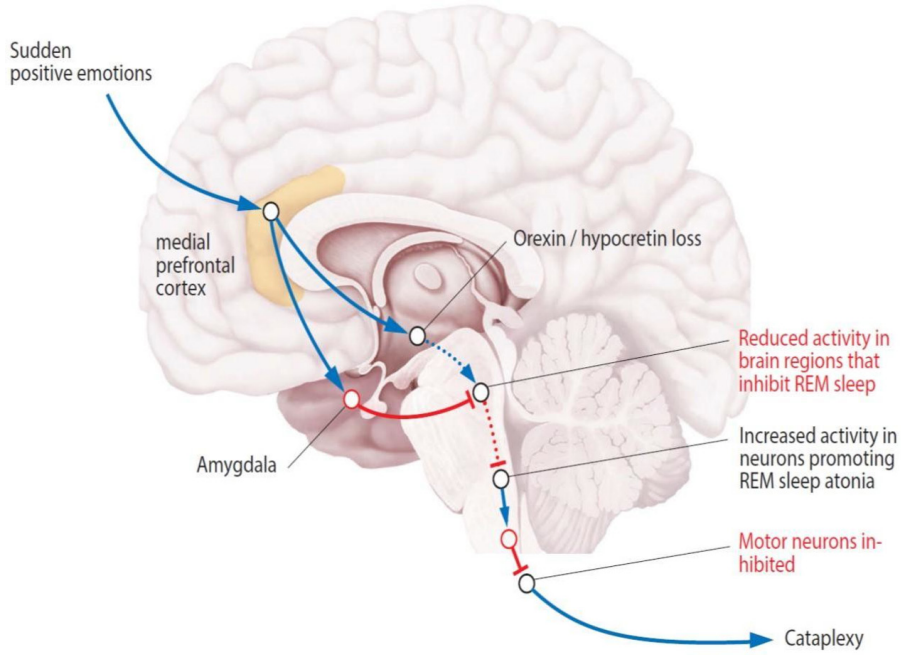


**Figure 2** Blue lines indicate activation of a neural pathway; red lines indicate an inhibitory pathway. Dotted lines reflect lack of normal neural activity resulting from hypocretin deficiency in narcolepsy. Based largely on functional imaging studies in controls and subjects with narcolepsy, there is a proposed circuitry explaining cataplexy. Sudden positive emotions such as humour are processed in the medial prefrontal cortex with subsequent activation of pathways to amygdala and the hypocretin-containing neurones within the lateral hypothalamus. With no hypocretin neurones, there is an imbalance such that a 'REM-off' centre in the dorsal pons is inhibited. This, in turn, disinhibits the REM-atonia nucleus just beneath the locus coeruleus, the normal centre for producing muscle paralysis during REM sleep. A descending pathway that includes glycinergic neurones then actively inhibits motor neurones. This model is likely to be oversimplified given that the mesolimbic dopamine ('reward') pathway is almost certainly also involved either at the level of the ventral tegmental area or ventral striatum. REM, rapid eye movement.

the context of hearty or unrestrained laughter.[10] It may occur in people with no obvious neurological or vascular pathology although sometimes accompanies other 'situational' syncopes. The mechanisms are probably similar to cough syncope, in which intrathoracic pressure rises through a Valsalva mechanism, leading to reduced cerebral perfusion. Dampened sympathetic activation may be a risk factor, explaining why some cases also have impaired autonomic reflexes, for example from diabetic neuropathy.[11] Episodes are usually easily distinguished from true cataplexy by the brief loss of awareness during attacks, associated pallor and the lack of alternative precipitants such as pleasant surprise.

Gelastic seizures are a form of focal epilepsy where laughter itself, typically without mirth, is the initial seizure manifestation or even its sole feature.[12] There is often brief loss of awareness, reduced accessibility or subsequent speech arrest and some people may collapse with apparent atonia. It can usually be clearly distinguished from cataplexy by a detailed history, including the stereotyped nature of the events and by its usual context of associated structural cerebral pathology in various brain regions.[13] Given the hypothalamic neurochemical deficit underlying narcolepsy, there has been speculation that cataplexy and gelastic seizures—when caused by hypothalamic hamartomas, their most common associated pathology—might have a shared mechanism . However, this seems unlikely given their significantly different semiology.

Startle syndromes such as hyperekplexia may lead to falls when a subject is exposed to sudden intense acoustic or tactile stimulation. However, the nature of the collapse is very different to cataplexy given the associated hypertonia and forced eye closure. Moreover, most cases start in infancy and have a genetic basis with mutations affecting glycine transmission or its receptor.[14] It is intriguing to note that the final common pathway of REM sleep paralysis—the intrusion of which forms the basis of cataplexy—involves activation of glycinergic neurones in the medulla that, in turn, directly inhibit alpha motor neurones.[15]

## NEUROBIOLOGY

Although our understanding of the neurochemistry and (psycho)biology of cataplexy remains far from complete, animal studies and human functional imaging techniques have provided information to guide treatment. The canine model of narcolepsy, particularly the familial autosomal dominant form affecting Doberman dogs, has furthered our understanding of narcolepsy in general and of cataplexy in particular.[16] The dog model is relatively easy to study given that canine cataplexy is reliable elicited by play or by presenting food

to a hungry animal. Several studies monitoring cataplexy have used either systemic or local cerebral perfusions of pharmacological compounds that activate cholinergic, adrenergic and dopaminergic systems.[17] The data strongly suggest that cholinergic activation in the pontine reticular formation or basal forebrain will stimulate cataplexy whereas general monoaminergic activation will suppress episodes. Early on, it was clear that an intracerebral neurochemical milieu that suppressed REM sleep would also inhibit cataplexy. This is not surprising given that the intrusion of muscle atonia (an manifestation of REM sleep) probably explains the physical expression of cataplexy.

Based on the canine narcolepsy neurochemical studies as well as postmortem data, it was initially proposed that the pathophysiology of narcolepsy/cataplexy arose from a cholinergic/monoaminergic imbalance. It was, therefore, a truly landmark study that first identified the hypocretin receptor mutation in the affected Dobermans.[18] Following this breakthrough in understanding familial canine narcolepsy, it was quickly realised that deficiency of the hypocretin neuropeptide itself due to pathology in the hypothalamus could cause human narcolepsy. In simple terms, one of the main functions of the hypocretin system is to regulate or stabilise the waking state and actively suppress both non-REM and REM sleep states.[19] In its absence, the brain cannot easily remain 'purely' awake or, indeed, asleep for more than an hour or two. The resulting instability causes the brain to flip from one state to another, occasionally partially, across the full 24 hours cycle. Regulation of REM sleep and its components is particularly chaotic or unstable, explaining the nature of cataplexy, sleep paralysis and hallucinatory (REM sleep) intrusions at sleep/wake boundaries.

The final common neural pathway that generates the paralysis in both REM sleep and cataplexy is fairly well established. A small nucleus distal to the locus coeruleus near the floor of the fourth ventricle is the likely centre for REM sleep atonia.[20] Largely, glutaminergic activity in these neurones stimulates descending pathways that involve glycine with eventual active inhibition of alpha motor neurones in the spinal cord. This produces temporary paralysis of voluntary muscles and loss of deep tendon reflexes. Pathology in this small area of the brain probably explains REM sleep behaviour disorder, in which there is often aggressive dream enactment in the absence of REM sleep atonia.[21] Of interest, and perhaps paradoxically, along with most of the parasomnias, REM sleep behaviour disorder is extremely common in narcolepsy although the dreams tend not to be particularly aggressive or troublesome. This contrasts to the situation in early Parkinson's disease where REM sleep behaviour disorder not infrequently leads to physical injury.

Although it is relatively easy to conceptualise cataplexy as reflecting 'instability' and inappropriate intrusions of REM sleep paralysis due to hypocretin deficiency, the fascinating link to emotional triggers remains largely unexplained. The hypocretin system has strong reciprocal links with limbic areas such as the dopaminergic ventral tegmental area and the amygdala, areas intimately involved in reward and emotional processing.[22] Hypocretin deficiency most likely 'releases' inappropriate activation of the REM sleep paralysis pathway when the brain is experiencing a specific emotion, although the circuitry involved is still speculative. Two functional imaging studies have shown markedly reduced hypothalamic metabolism during episodes of cataplexy.[23 24] There also appears to be increased activation of the amygdala during humour processing in narcoleptic subjects. At least one study has shown reduced responsivity in the ventral striatum, the brain's traditional dopaminergic 'reward centre'. figure 2 shows one possible model by which cataplexy is generated, based on functional imaging data from controls and our knowledge of the hypocretin system.

Detailed structural imaging, including diffusion tensor imaging, has shown several subtle differences between people with narcolepsy and controls.[25] The data have been difficult to interpret, partly due to the recent demonstration that even relatively mild sleep deprivation is associated with changes in white matter tract integrity.[26] The specificity of reported diffusion-tensor imaging changes is, therefore, uncertain, given that most people with narcolepsy are effectively sleep-deprived at any given time.

## TREATMENT

About half of patients with type 1 narcolepsy have cataplexy sufficiently severe or intrusive enough to warrant attempts at specific therapy. However, any improvement in general alertness with wake-promoting therapy often also seems to help cataplexy symptoms, even though the data from trials of drugs such as modafinil are largely negative in this respect. Indeed, there are few data from controlled randomised treatment trials of cataplexy.

In clinical practice, the most commonly used drugs are venlafaxine (doses 75–225 mg daily) or clomipramine (25–100 mg daily) with possible preference for clomipramine if the patient wishes to have some sedative effect. Both drugs create a neurochemical milieu that tends to suppress all components of REM sleep, largely by increasing brainstem monoaminergic levels. Other antidepressants such as fluoxetine or other specific serotonin-reuptake inhibitors can also suppress cataplexy in some people, presumably also by REM sleep suppression. Any positive effect occurs fairly soon after starting treatment, in contrast to the expected delay when using such agents for depression. Once established on treatment, patients are encouraged to adhere strictly to the medication, as suddenly stopping it commonly leads to severe rebound cataplexy.[27] From animal studies, cataplexy

can be exaggerated by agents such as prazosin that enhance or promote REM sleep,[28] implying that such drugs should be avoided in narcolepsy.

Sodium oxybate has been used effectively to treat narcolepsy for over 15 years. It is a controversial agent partly because of its abuse potential as a 'date rape' drug but also due to its expense. It is short acting and generally given as an oral solution before bed, with a second dose required at around 03:00 hours. The early pivotal trial data showed clear effects on reducing cataplexy, with optimal control occurring after several weeks of treatment. At full dose (4.5 g twice nightly), it abolished up to 90% of episodes.[29] The mechanism remains speculative given that its main effect is to enhance or consolidate deep slow wave nocturnal sleep by GABA-ergic activation. Helping to normalise sleep architecture overall may allow REM sleep to occur in a more normal setting and inhibit subsequent daytime intrusion of some of its elements, namely paralysis during cataplexy. Anecdotally, several other agents that potentially enhance deep non-REM or slow wave sleep also improve cataplexy. Examples include baclofen and pregabalin taken as a single dose before bed.

Pitolisant is a new drug with a specific action that increases hypothalamic levels of histamine by antagonising histamine (H3) auto-receptors in the tuberomammillary nucleus, the origin of wake-promoting histaminergic neurones.[30] Recent placebo-controlled studies have confirmed a modest positive effect on cataplexy symptoms with improved wakefulness in people with narcolepsy.[31] The agent is taken once daily in a dose range 9–36 mg. It may become a useful addition to conventional treatments in narcolepsy and cataplexy, not least due to its excellent side effect profile.

There is great interest in specific drug treatment to restore the hypocretin deficit causing cataplexy, especially since various experimental techniques in animal models of the disease have been very encouraging. In particular, either intrathecal or intravenous delivery of hypocretin or an analogue can abolish cataplexy.[32] There are considerable logistical problems in developing a suitable oral compound for human administration although early animal model data look promising.[33]

## FURTHER READING

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## CASE

There is accompanying video material of a 32-year-old woman who presented with episodes of collapse when laughing. The clip shows a typical episode of full-blown cataplexy induced by amusement when a family member makes fun of a person's name. There is initial bobbing of the head followed by descending weakness over a few seconds. Consciousness is fully preserved and recovery takes around 10 s.

Although she was found to be totally deficient of CSF hypocretin at presentation, she initially reported no daytime drowsiness or disturbed nocturnal sleep other than very occasional sleep paralysis. Within 2 years, however, she could not avoid frequent daytime naps and reported numerous episodes of automatic behaviour, such as placing inappropriate objects in the refrigerator. She has done well on treatment, taking venlafaxine for cataplexy and a combination of modafinil with low-dose dexamphetamine for daytime sleepiness.

### Key points

- The presence of typical cataplexy is a very reliable marker for hypocretin deficiency in the context of narcolepsy type 1.
- Cataplexy varies greatly in its severity and frequency between subjects but episodes can occur daily and be disabling.
- Cataplexy has a defined semiology and may sometimes be mimicked or accompanied by functional drop attacks.
- Drug treatment of cataplexy is often appropriate and effective; antidepressant drugs such as venlafaxine and clomipramine are the usual first-line options, with strong evidence for the efficacy of sodium oxybate.
- Psychostimulants that increase levels of alertness almost certainly help cataplexy, although the only positive controlled evidence is for the new drug pitolisant.

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