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Narcolepsy Type 1 and Idiopathic Generalized Epilepsy: Diagnostic and Therapeutic Challenges in Dual Cases

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Study Objectives: The aim of this study is to describe the possible co-occurrence of narcolepsy type 1 and generalized epilepsy, focusing on diagnostic challenge and safety of dual treatments.

Methods and Results: Four patients with comorbidity for narcolepsy type 1 and idiopathic generalized epilepsy are reported: in three cases the onset of epilepsy preceded narcolepsy type 1 appearance, whereas in one case epileptic spells onset was subsequent. Patients presented with absences, myoclonic and tonic-clonic seizure type: in the patient with tonic-clonic seizures the dual pathology was easily recognized, in the other cases the first diagnosis caused the comorbid disease to be overlooked, independent of the time-course sequence. All four patients underwent neurological examination, video-electroencephalogram during which ictal and interictal epileptic discharges were recorded, and sleep polysomnographic studies. Repeated sleep onset rapid eye movement periods (SOREMPs) were documented with the multiple sleep latency test (MLST) in all the four cases. All patients had unremarkable brain magnetic resonance imaging studies and cerebrospinal hypocretin-1 was assessed in two patients, revealing undetectable levels. The association of antiepileptic drugs and substances currently used to treat narcolepsy type 1, including sodium oxybate, was effective in improving seizures, sleep disturbance, and cataplexy.

Conclusions: Narcolepsy type 1 may occur in association with idiopathic generalized epilepsy, leading to remarkable diagnostic and therapeutic challenges. Electrophysiological studies as well as a comprehensive somnologic interview can help confirm the diagnosis in patients with ambiguous neurological history. Sodium oxybate in combination with antiepileptic drugs is safe and effective in treating cataplexy and excessive daytime sleepiness.

Keywords: epilepsy, narcolepsy type 1, sodium oxybate, video-EEG

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Narcolepsy type 1 (NT1) is a rare hypersomnolence of central origin, presumably related to an autoimmune attack leading to loss of hypothalamic hypocretinergic cells, witnessed by low undetectable cerebrospinal fluid (CSF) hypocretin 1 (hcrt-1).[1] Cataplexy, which is defined as sudden decrease or loss of muscle tone triggered by strong emotions, mostly positive (i.e., laughing), with retained consciousness, is a highly specific and therefore diagnostic symptom of NT1. Cataplectic attacks are usually bilateral and symmetric, and often mainly involve facial muscles (the cataplectic facies), or the entire voluntary musculature, causing motor arrest, body collapse, and falls to the ground. The episode duration is short, lasting usually a few seconds and generally less than 1 min.[2–4] Cataplexy attacks may cluster, a condition known as cataplectic status, affecting mainly children close to disease onset[4,5] or patients with NT1 after abrupt antidepressant withdrawal.[6–8]

The clinical diagnosis of cataplexy is often challenging, and sometimes patients with NT1 receive an incorrect diagnosis of epilepsy.[4,9,10] Cataplexy can sometimes be misdiagnosed as epileptic drop attacks or atonic seizures,[11] resulting in a delay in diagnosis and often in the prescription of inappropriate investigations and treatments.[12]

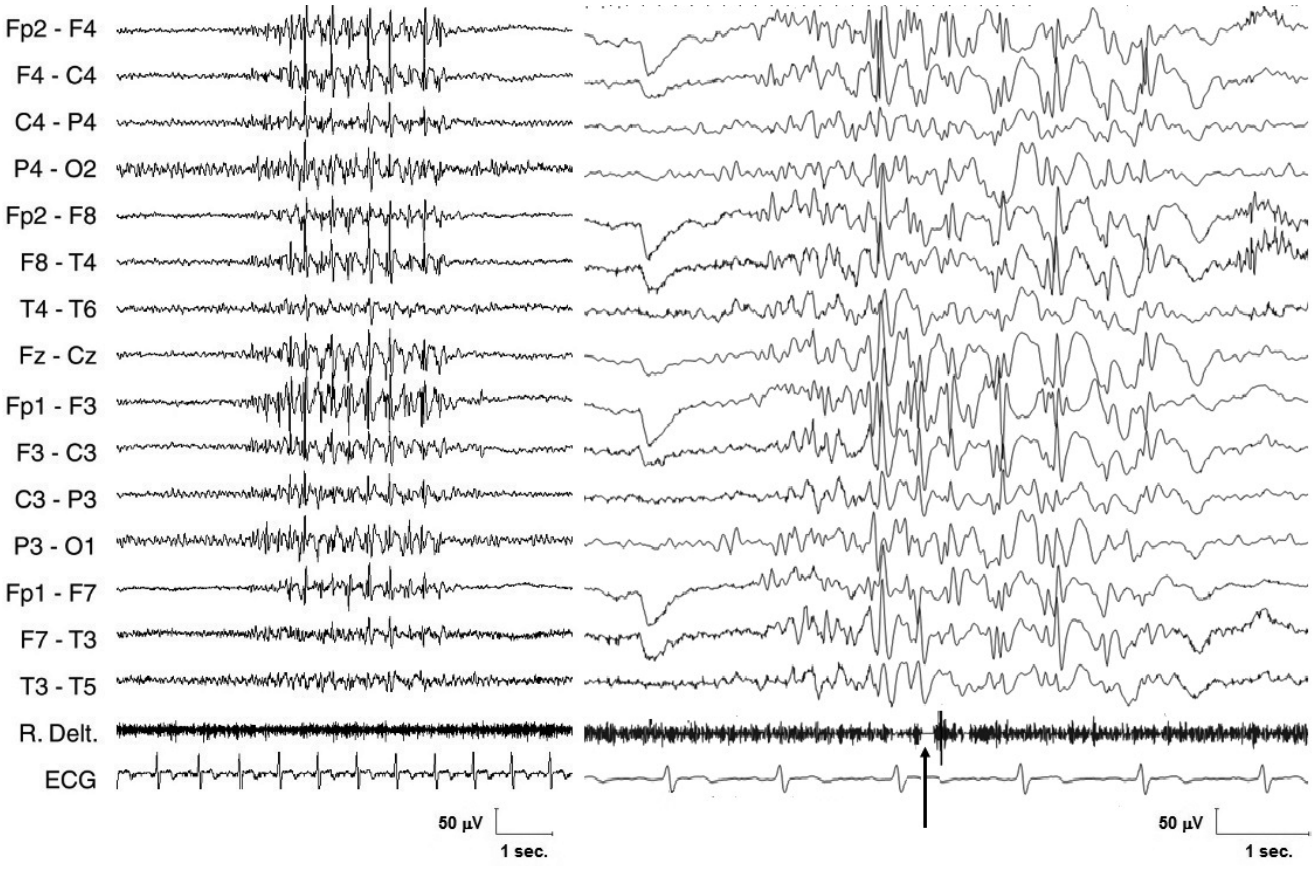
Although dual cases of NT1 and epilepsy have been reported,[13–15] no specific type of seizure/epileptic syndrome has been associated with them: one reported case suffered from Rasmussen syndrome,[13] and two had myoclonic seizures.[14,15]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Misdiagnosis of NT1 as generalized epilepsy is not rare, especially in children and young adults close to disease onset. The prevalence of dual cases of NT1 and generalized epilepsy is unknown; although probably rare they represent diagnostic and therapeutic challenges.

Study Impact: A comprehensive neurologic and hypnologic interviews as well as electrophysiological studies (namely, EEG, nocturnal polysomnography, MSLT, videopolygraphy) are mandatory for the differential diagnosis and to disclose dual cases. Sodium oxybate in combination with antiepileptic drugs is safe and effective in treating cataplexy and excessive daytime sleepiness in comorbid NT1 and generalized epilepsy.

Figure 1—Case 1.



On the left: the polygraphic recording, including electroencephalogram (EEG,10–20 system), surface electromyogram of right deltoid muscle, and electrocardiogram, discloses a generalized, synchronous, 3–4 Hz EEG spike- and polyspike-waves discharge. On the right, a similar discharge is associated with transient muscle atonia (black arrow), which clinically corresponds to a negative myoclonus of the upper limbs.

Confounding reflex epilepsy also has to be considered during the differential diagnosis process.[10] This heterogeneous case collection does not suggest a common pathophysiology, but a chance association seems plausible, although speculation about a common origin of NT1 and epilepsy could be inferred. It is a matter of fact that comorbid cases do represent diagnostic and therapeutic challenges.

We report four patients who shared the coexistence of NT1 and idiopathic generalized epilepsy and their different clinical course.

CASE 1

A 30-y-old man who is a professional biker, with an unremarkable family history, presented at the age of 22 y with viral myocarditis. Concurrently, excessive daytime sleepiness with sudden and refreshing sleep attacks (one or two per day) of short duration (10–15 min) occurred in monotonous situations. The patient retired from professional sport and at 24-y-old he presented with very brief (sec) episodes of knees weakness, speech arrest, tongue protrusion, dopey look, and even generalized body collapse with falls to the ground, elicited by strong positive emotions (i.e., laughter). His electroencephalographic (EEG) recording displayed bursts of generalized spike and waves lasting few sec; brain magnetic resonance imaging (MRI) was normal. Sleepiness and the presence of triggered spells were overlooked and a diagnosis of generalized idiopathic epilepsy was made. Valproic acid and lamotrigine were titrated respectively up to 1,000 mg/day and 300 mg/day. Due to the lack of improvement of spells, to the worsening of daytime sleepiness and to a progressive and relevant weight gain, the patient spontaneously stopped taking the antiepileptic drugs (AEDs). At the time of our observation at the Center for Narcolepsy, Bologna University, the patient was overweight (BMI 28.3 kg/m^2), and had remarkable daytime sleepiness (scoring 13 on Epworth Sleepiness Scale [ESS]). His neurologic examination disclosed a frequent negative myoclonus (only sometimes perceived by the patient) affecting the upper limbs. Videopolygraphy documented the presence of generalized, synchronous 3–4 Hz EEG spike-waves and polyspike-waves discharges lasting 2–10 sec, spontaneous and triggered by hyperpnea and intermittent photic stimulation. These EEG epileptic activities were coincident with negative myoclonic jerks of the upper limbs (**Figure 1**; **Video 1**, segment 2) without consciousness impairment. A 48-h video-polysomnographic monitoring documented nocturnal sleep fragmentation and repeated daytime naps with reduced rapid eye movement (REM) sleep latency. The multiple sleep latency

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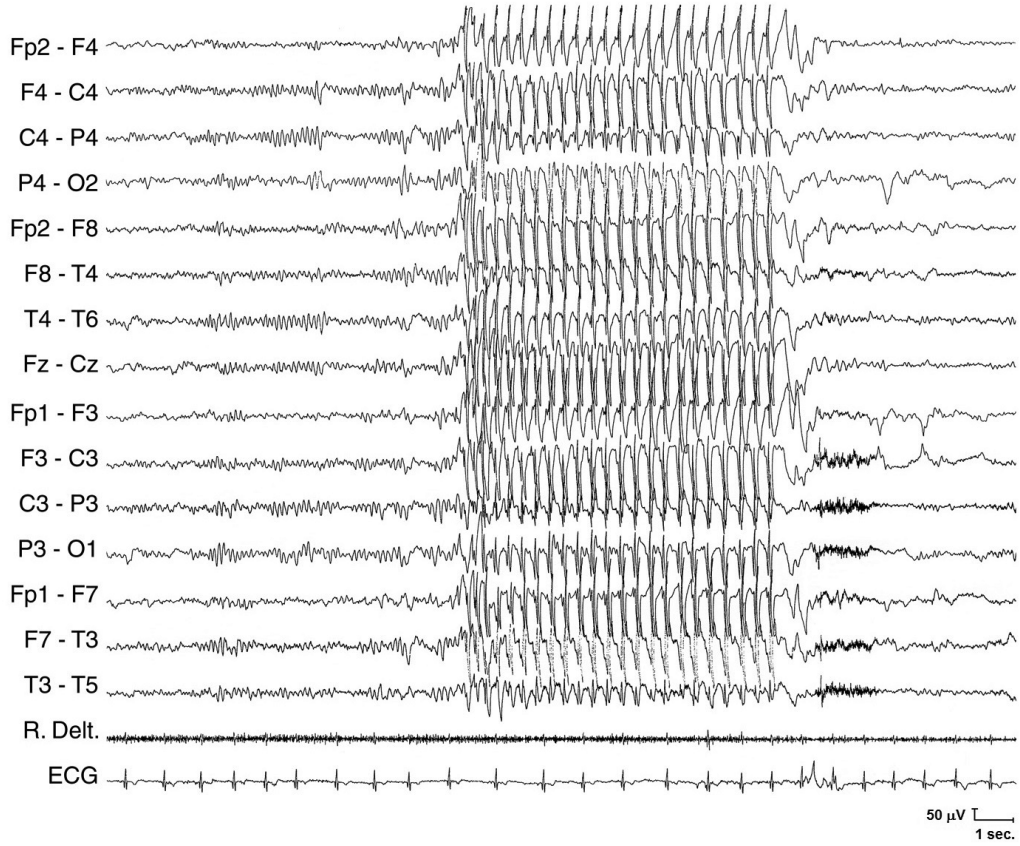
Figure 2—Case 2.



The polygraphic recording (electroencephalogram [EEG], surface electromyogram of right deltoid muscle, and electrocardiogram) shows 3 Hz generalized, synchronous, EEG spike-and-wave discharge, lasting 8 sec, that is clinically associated with absence seizure.

test (MSLT) confirmed a pathological sleepiness (mean sleep latency of 1 min, 30 sec) with three sleep onset rapid eye movement periods (SOREMPs) out of five nap opportunities. During the standardized videopolygraphy for the recording of cataplexy events,[2,4] the patient presented with drooping eyelids and tongue protrusion, more explicit while laughing watching funny videos (**Video 1**, segment 1), but not enhancement of negative myoclonus nor epileptic EEG bursts. Hcrt-1 was undetectable, confirming the diagnosis of NT1. The patient also carried the human leucocyte antigen (HLA) DQB1*06:02 allele. Modafinil was started at up to 300 mg/day without any improvement of sleepiness. Then the patient was switched to sodium oxybate up to 9 g/night with remarkable improvement of hypersomnolence and cataplexy. At 1-y follow-up negative myoclonus and epileptic EEG activity remained unchanged, but the patient refused AEDs.

CASE 2

This 19-y-old boy has been followed up at the Center for Narcolepsy, University of Bologna, since he was 8 y old for a severe form of NT1 with acute onset, characterized by severe daytime sleepiness, spontaneous and triggered cataplexy (from repetitive head drops to body collapse and persistent cataplectic facies) (**Video 2**, segment 1), hypnagogic hallucinations, sleep paralysis, automatic behaviors, nightmares, and a dramatic disruption of nocturnal sleep. Nighttime polysomnography confirmed an altered sleep structure with SOREMP and reduced sleep efficiency, and the MSLT disclosed a mean sleep latency of 2 min, 36 sec with five SOREMPs out of five nap opportunities. Brain MRI and EEG were normal, he carried the HLA DQB1*06:02 allele, and cerebrospinal fluid (CSF) hrct-1 was undetectable. For the concurrent finding of precocious puberty a treatment with triptorelin, a gonadotrophin-releasing hormone-release agonist, was started. Because modafinil up to 200 mg and venlafaxine were poorly effective on sleepiness and cataplexy, sodium oxybate up to 7.5 g/night was started, resulting in immediate benefit. However, multiple scheduled short naps at school and during afternoon home working were needed in order to avoid unwanted sleep attacks and automatic behaviors. At 13-y-old the patient experienced daily episodes of abrupt interruption of ongoing activities, speech arrest, and blank stare, lasting a few seconds. These episodes were firstly interpreted as due to sleepiness; however, a video-EEG recording performed at 14-y-old revealed 3 Hz generalized spike-and-wave discharges, lasting from 3 to 10 sec (**Figure 2**; **Video 2**, segments 2 and 3) associated with absence seizures, allowing the diagnosis of comorbid juvenile absence epilepsy. To rule out possible side effects of sodium oxybate, this was withdrawn for 6 mo with a remarkable worsening of NT1 symptoms but no effect on absence seizures. Valproate up to 600 mg/day was well tolerated and immediately stopped seizures and EEG abnormalities. The

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Table 1—Characteristics of narcolepsy type 1 and idiopathic generalized epilepsy.

	Narcolepsy Type 1	Idiopathic Generalized Epilepsy
Onset	Childhood, 30–40 y	Childhood or adolescence, rarely adult
Pathogenesis	Autoimmune (probable)	Genetic (unknown)
Predisposing factors	HLA DQ B1*06:02, HLA DR2/DQ B1*15:01	Familiar history
Precipitating factors	H1N1 flu vaccine, Streptococcal pharyngitis	
Cardinal symptom	Excessive daytime sleepiness with sleep attacks, cataplexy	Seizures (absence, myoclonic, tonic-clonic, atonic, tonic, clonic)
Associated symptoms	Disruption of nocturnal sleep, hypnagogic hallucination, sleep paralysis	
Associated clinical features	Obesity, precocious puberty	
Neurophysiologic findings	SOREMPs, MSLT sleep latency < 8 minutes, hypersynchronous paroxysmal theta activity	Generalized, bilateral, synchronous, symmetrical, EEG discharges (spikes, polyspikes or spike/polyspike-wave), ictal and interictal
Biomarkers	CSF hypocretin-1 < 110 pg/mL	None
Brain imaging	Normal	Normal

CSF, cerebrospinal fluid; EEG, electroencephalogram; MSLT, multiple sleep latency test; SOREMPs, sleep onset rapid eye movement periods.

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resumption of sodium oxybate therapy up to 8 g/night in association with valproate did not worsen seizures nor interictal EEG discharges. A 4-y follow-up confirmed the disappearance of seizures. The gradual washout of valproate when the patient was 19-y-old did not cause any reappearance of seizures.

CASE 3

A 32-y-old man was followed up at the Hephata Klinik in Schwalmstadt, Germany. He had an unremarkable medical history but for bruxism and sleep-talking. At 16 y old he presented with the first tonic-clonic seizures during wakefulness; his EEG recordings showed bursts of generalized slow waves. He received a diagnosis of generalized idiopathic epilepsy. Valproate was started and suppressed seizures until age 19 y, when the patient decided to stop treatment. At age 21 y tonic-clonic seizures reappeared and the patient underwent treatment with lamotrigine, which was not effective, and levetiracetam and gabapentin were added. Due to increased sleepiness, at age 25 y the patient switched to topiramate monotherapy, which controlled seizures but caused depression. Topiramate was tapered and replaced by a valproate and lamotrigine combination that helped the patient remain seizure free.

At age 17 y the patient also presented with excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. Cataplexy and hypersomnolence severity forced the patient to retire from school, and NT1 comorbid to idiopathic generalized epilepsy was diagnosed at age 19 y (the MSLT documented pathological mean sleep latency of 2 min with three SOREMPs out of four nap opportunities). The patient carried the human leucocyte antigen (HLA) DR15, DQ6 allele. CSF hcrt-1 was not performed. Only sleepiness required medications, cataplexy was controlled by coping with emotions. Wake-promoting agents and stimulants (the patient started with modafinil, then methylphenidate, and finally lisdexamphetamine) displayed only partial efficacy on hypersomnolence. At age 22 y the patient started to experience severely fragmented sleep, sodium oxybate was increased to 8 g/night and improved narcoleptic symptoms, but did not modify the course nor presentation of his epilepsy.

CASE 4

This 25-y-old man was followed up at the Hephata Klinik in Schwalmstadt, Germany. He suffered from juvenile myoclonic epilepsy since age 12 y. His EEG displayed generalized discharges of spike and wave activity particularly elicited by photostimulation at 5–15 Hz. At age 16 y he started to experience daytime sleepiness during monotonous situations, sleep paralysis (two episodes per week), acoustic hallucinations, and fragmented night sleep with a tendency to deteriorate in time. At age 19 y cataplexy appeared accompanied by a feeling of heaviness in the arms, face, and rarely the complete body for several seconds without any falls. The patient had a diagnosis of narcolepsy at the age of 18 y, better defined as NT1 when cataplexy appeared. At this time the MSLT disclosed pathological sleepiness (mean sleep latency 4 min, 10 sec) and four SOREMPs out of five nap opportunities. The patient carried HLA DRB1*11:15; DQB1*03:06. He did not benefit from modafinil, whereas his symptoms improved with sodium oxybate up to 5 g/night, which he began taken at age 19 y. His epilepsy was treated with valproic acid 450 mg/day. Myoclonic discharges appeared about twice per month in the morning.

DISCUSSION

Misdiagnosing NT1 as generalized epilepsy is not rare in clinical practice, especially in children with recent onset of

disease.[4,16,17] Particularly, the differential diagnosis between cataplectic phenomena and generalized seizures (i.e., atonic or absence seizures) may be complicated in relation to common phenotypic features. Some peculiar and distinctive clinical characteristics can help to distinguish one from the other (**Table 1**). Cataplexy is characterized by retained consciousness (the patient recalls what happened) and it is often triggered by strong emotions such as laughter, rarely fear or anger. Seizures are mainly unpredictable, not triggered by endogenous or exogenous stimuli, except reflex epilepsies, and are often associated with impaired consciousness.

However, the coexistence of the two conditions is possible as demonstrated by isolated case reports, including ours. The prevalence of dual cases was set at 0.91% in Bologna (four patients of 440) and at 1.51% (six patients of 396) in Marburg NT1 case series, respectively. Although these dual cases are rare, distinguishing red flags identifying generalized epilepsy or NT1 may have important value in clinical practice in order to avoid misdiagnosis. Case 1 pinpoints how excessive daytime sleepiness is often trivialized: this patient had a clear complaint of NT1 symptoms, but the EEG abnormalities steered the diagnosis and treatment toward epilepsy. Case 2, conversely, underlines how the onset absence seizures in a patient with NT1 can be overlooked. In this latter case speech arrest and blank stare due to nonconvulsive generalized epileptic spells had been referred to cataplexy/sleepiness/automatic behavior, but the red flag toward the correct diagnosis would have been the change in semiology of paroxysmal events. Case 3 displays a much easier and successful diagnosis when tonic-clonic seizures appeared. In case 4, finally, NT1 was recognized when excessive daytime sleepiness, hallucinations, and sleep paralysis appeared. Although associated with a constellation of symptoms and signs, an accurate electroclinical study (namely video-EEG or videopolygraphy)[18] represents the gold standard for an accurate differential diagnosis. Clearly distinguishing neurophysiological features (namely spike and waves generalized EEG abnormalities) represent the fingerprint of idiopathic generalized epilepsy, although EEG frontal hypersynchronous paroxysmal theta bursts have been associated with cataplexy in some cases.[19] Therefore, we suggest that electroencephalographic recording in patients with narcolepsy and atypical cataplexy be performed in order to exclude epileptic discharges. Similarly, a somnologic interview may be useful to investigate sleep disturbances in patients with epilepsy; when excessive daytime sleepiness or cataplectic attacks are suspected a complete sleep study (nocturnal polysomnography and MSLT) should be performed. A further step is to carry out a video-EEG study, and also administer emotional stimuli (i.e., funny videos) in order to elicit cataplexy.[2,4,20]

Although previous reports[14] suggested the possibility of a common autoimmune pathogenesis, in our opinion, the wide variability observed both in time evolution (NT1 may precede or follow the onset of epilepsy by many years) and in seizure type together with the high prevalence of generalized epilepsy does not suggest a common origin but rather a by-chance association. However, a relationship between hypocretin and epilepsy is still scientifically debated, and an antiepileptic role of the hypocretin system has been suggested in experimental settings,[21] suggesting that anatomical and functional alterations of the hypocretinergic network may lead to an increased susceptibility to seizures in NT1.

Myoclonic epilepsy and absence seizure epilepsy were definitely diagnosed in cases 1, 4, and 2; valproate treatment was effective in cases 2 and 4, and no side effects were reported. Similarly, the sodium oxybate treatment was safe and effective in improving daytime sleepiness and cataplexy. Under sodium oxybate, indeed, seizures did not worsen and the EEG did not show any increase in epileptic activity in our cases. This observation confirms in a clinical setting that sodium oxybate is not aggravating epilepsy, although in contrast with previous reports in which its administration has been suggested to induce seizures.[22,23]

Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB), a short-chain fatty acid that occurs naturally in mammalian brain. GHB induces absence-like seizure in several animal models (rats, mice, cats, and monkeys),[24] via a not-yet-explained pathological mechanism. A plausible hypothesis suggests that GHB brain excess induces the release of gamma-aminobutyric acid (GABA) and glutamate in the cortex and thalamus resulting in an altered inhibitory/excitatory control of corticothalamic pathways.[25] Other authors postulated that a portion of exogenous GHB may be converted into GABA,[26] leading to burst firing and oscillatory behavior in thalamic neurons, by $GABA_B$ receptor-mediated mechanisms.[27]

Importantly, while treating dual cases of NT1 and epilepsy the bimodal modulation of GHB brain concentration induced by valproate has to be taken into account and sodium oxybate tapered accordingly.

NT1 can rarely occur in association with generalized epilepsy, leading to remarkable diagnostic and therapeutic challenges. Although NT1 and idiopathic generalized epilepsy seem to coexist by chance, and further investigations in larger samples are warranted, dual cases maybe underdiagnosed or misdiagnosed.

VIDEO DESCRIPTIONS

Video 1 is a recording from Case 1. Segment 1 shows cataplexy. The patient is watching a funny video and while laughing, he presents with abrupt arrest of facial expression, tongue protrusion, partial droop of eyelids (cataplectic facies), and swinging of trunk and head. Segment 2 shows that during the Mingazzini maneuver the discharge is associated with a negative myoclonic jerk of the upper limbs.

Video 2 is a recording from Case 2. Segment 1 shows a generalized cataplectic attack with body collapse and fall to the ground triggered by laughter (the patient is watching a funny video). Segments 2 and 3 show generalized 3 Hz spike-waves discharge associated with loss of contact (the patient fails to respond), staring, and apnea, symptoms typical of absence seizures.

ABBREVIATIONS

AEDs, antiepileptic drugs
BMI, body mass index
CSF, cerebrospinal fluid
EEG, electroencephalography

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ESS, Epworth sleepiness scale
GABA, gamma-aminobutyric acid
GHB, gamma hydroxybutyrate
Hcrt-1, hypocretin 1
HLA, human leucocyte antigen
MRI, magnetic resonance imaging
MSLT, multiple sleep latency test
NT1, narcolepsy type 1
REM, rapid eye movement
SOREMP, sleep onset rapid eye movement period

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