Sleepless and Sleepy

50 Challenging Sleep Medicine Cases

Alcibiades J. Rodriguez
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Editor
Alcibiades J. Rodriguez, MD, FAASM
Medical Director, NYU Langone Comprehensive
Epilepsy Center-Sleep Center
Director, Neurology Sleep Medicine
Associate Professor of Neurology
NYU Grossman School of Medicine
New York, NY, USA

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To my mother Flora and father Alcibiades, whose teachings of hard work, discipline, and love made me a better person and professional.

Foreword

Teaching the art and science of medicine is a difficult and fundamental task with the goal of sharing clinical experience with students. This transmission of knowledge can be done in different forms, from conventional lectures to focused seminars, activities that need to be complemented with individual work with good teaching material.

An excellent way to promote this learning process is also sharing selected clinical cases with students in the form they were experienced by their doctors in real life. This usually starts with the patient complaints and relevant clinical questions, follows with the physical examination and the differential diagnoses, continues with the ancillary tests results and ends with a final interpretation of all the findings with a diagnosis and management plan. To reflect all this process in a case presentation requires excellent teaching material shown in an appropriate way by experienced authors.

I think this has been achieved in this book, which contains 50 sleep medicine teaching cases written by their physicians as they were experienced in their practice. They refer to adult and pediatric patients with common and unusual sleep medicine problems that clinicians have seen in their professional activity and were selected by their specific learning value. Authors are experienced sleep medicine clinicians from all over the world, coordinated by the editor of this book, Dr (Prof) Alcibiades Rodriguez. Dr(Prof) Alcibiades Rodriguez—a former Mayo Clinic Fellow in Sleep Medicine and currently *Director, Neurology Sleep Medicine, and Associate Professor of Neurology at New York University School of Medicine*—has assembled the book by selecting the contributors and topics, editing the chapters, and organizing the final version of this book. His ample clinical experience in sleep disorders has allowed him to give the book the flavor of real daytime sleep clinics.

It has been my pleasure to know Prof Alcibiades Rodriguez for the last 10 years, as we both are teachers in a yearly seminar in Sleep Medicine organized in the Monastery of Les Avellanes, in Lleida, Spain. I have had the opportunity to enjoy his teaching abilities both in lecturing and particularly interviewing sleep medicine patients, an activity which has allowed many students to learn how to face a patient with sleep disorder.

I think the book may be an important aid for students, fellows, and doctors interested in sleep medicine and hope readers will find attractive the combination of solid scientific evidence with entertaining real-life experiences as is presented here.

Dr. Joan Santamaria
Emeritus Consultant and Researcher
Hospital Clínic of Barcelona
Barcelona, Catalonia, Spain

Preface

It was some years ago during my clinical rotation at the National Hospital for Neurology and Neurosurgery at Queen's Square, London, UK, that I decided to pursue an epilepsy, and later by extension, a sleep medicine career. The Grand Rounds performed there impressed me. During these rounds, actual patients were interviewed and examined in front of students, registrars (fellows), and seasoned neurologists. This experience had a long-lasting impact on me.

It was then that I discovered the book *Fifty cases from the National Hospital*, which was based on these Grand Rounds. I became fascinated with the diversity and complexity of the cases presented at this venerable institution. I read that book several times, case by case, to study for my certification and re-certifications boards and later, to review my general neurology knowledge. Later, during my neurology training at Tufts University in Boston, MA, we also presented difficult and demanding cases to senior physicians, which as trainees we encountered in our clinical rotations.

I have also been privileged to participate in the annual seminars in Sleep Medicine, organized by the Spain Neurological Society and the sleep-wake working group in Lleida, Cataluña, Spain. During these sessions, we witness sleep tests, in actual patients, being conducted at the Hospital Clínic of Barcelona and have the opportunity to interview them remotely. The last day, patients are brought in from the community and different specialists take turns to interview, examine, and, later, discuss the cases with the trainees.

Now, I find myself face to face with my past, paying tribute to all those influential experiences with a collection of cases of my own sleep medicine profession. This long-waited project aims to show the heterogeneous, unique, and challenging cases that we encounter in sleep medicine every day.

There are cases from different parts of the world, adults and pediatrics, some pulmonary, some more neurological/psychiatric, and some more surgically oriented, but sharing the same sleep medicine language. It will be useful to residents, sleep medicine fellows, and full-time sleep and non-sleep professionals to sit and read one or two cases at a time, especially to the young professionals starting their journey within this wonderful specialty. Some cases are classic, some are not, some combine other specialties, and some are just related to sleep in different ways.

Some have a definite answer and some only time will tell their true nature. Let me introduce to you these 50 cases, hoping you enjoy the experience, just as much as I did reading, editing, and learning from them.

New York, NY
March 2022

Alcibiades J. Rodriguez

Acknowledgments

This book has been possible due to the contribution of many. Throughout my career, I have met people from all over the world, students, residents, fellows, colleagues, and teachers, some of them have become friends. Thank you all the contributors for your incredible help, for the outstanding and amazing cases that appear in this book, and for tolerating my multiple requests, questions, and demands.

To my dear colleagues at NYU Langone Medical Center, who helped with their expertise to review cases, videos, and illustrations for clarity, I would like to express my deepest gratitude.

I want to thank all the staff at the NYU Langone Comprehensive Epilepsy Center-Sleep Center, my home away from home. To my secretaries, who protected my time to work on this project; nighttime technicians, who take care of patients; and especially to my daytime technicians for their effort in obtaining the correct figures and video editing for several cases. It has been many years growing together. Finally, to the patients themselves for teaching all of us something new every single day. In my life, I have learned from them all.

Dear Sir or Madam, will you read my book?
It took me years to write, will you take a look?
Paperback writer
John Lennon/Paul McCartney, 1966

Contents

Contributors

Akinbolaji Akingbola, MD, MS Department of Pulmonary, Allergy, Critical Care and Sleep Medicine, University of Minnesota Medical School, Minneapolis, MN, USA

R. Nisha Aurora, MD, MHS Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Daniel A. Barone, MD Department of Neurology, New York-Presbyterian, Weill Cornell Medicine, New York, NY, USA

Zuzana Belisova, MD Department of Neurology, NYU Langone Medical Center, New York, NY, USA

Alok Bhatt, MBBS Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, NYU Grossman School of Medicine, New York, NY, USA

David J. Bond, MD, PhD Department of Psychiatry and Behavioral Sciences, University of Minnesota Medical School, Minneapolis, MN, USA

Ashura Williams Buckley, MD National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

Boris Chernobilsky, MD Otolaryngology—Head and Neck Surgery and Internal Medicine, NYU Langone Health, New York, NY, USA

Nishay Chitkara, MD Internal Medicine/Pulmonary, Critical Care and Sleep Medicine, NYU Langone Health and Bellevue Hospital, New York, NY, USA

Juan Enrique Bender del Busto, MD Department of Neurology, International Center for Neurological Restoration, La Habana, Cuba

Lourdes M. DelRosso, MD, MEd Department of Pediatrics, University of Washington, Seattle, WA, USA

Alex Desautels, MD, PhD Department of Neurosciences, Université de Montréal, Center for Advanced Research in Sleep Medicine, Hôspital du Sacré-Coeur, Montreal, QC, Canada

Hernando Pérez Díaz, MD Sleep and Epilepsy Program, Centro de Neurología Avanzada, Seville, Spain

Raffaele Ferri, MD Sleep Research Centre, Oasi Research Institute—IRCCS, Troina, Italy

Carles Gaig, MD, PhD Department of Neurology, Hospital Clinic Barcelona, Barcelona, Spain

Diego Garcia-Borreguero, MD, PhD Sleep Research Institute, Madrid, Spain

Celia Garcia-Malo, MD, PhD Sleep Research Institute, Madrid, Spain

Steve A. Gibbs, MD, MSc Department of Neurosciences, Université de Montréal, Center for Advanced Research in Sleep Medicine, Hôspital du Sacré-Coeur, Montreal, QC, Canada

Madeleine Grigg-Damberger, MD Department of Neurology, University of New Mexico Medical Center, Albuquerque, NM, USA

Thomas Gustafson, MD Department of Sleep Medicine, M Health Fairview, Minneapolis, MN, USA

Scott Hirsch, MD NYU Langone Medical Center, Rye Brook, NY, USA

Xinyi Hong, BS National Institutes of Health, Bethesda, MD, USA

Alex Iranzo, MD, PhD Department of Neurology, Hospital Clinic Barcelona, Barcelona, Spain

Ioanna Kouri, MD Department of Pediatrics, Mitera, Athens, Greece

Ewa I. Koziorynska, MD Department of Neurology, Columbia University Irving Medical Center, New York, NY, USA

Marta Maczaj, MD Sleep Disorders Center, St. Charles Hospital and Rehabilitation Center, Port Jefferson, NY, USA

Mandana Mahmoudi, MD, MPH, PhD Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, NYU Grossman School of Medicine, New York, NY, USA

Saif Mashaqi, MD Pulmonary, Allergy, Critical Care, and Sleep Medicine, Banner University Medical Center, University of Arizona College of Medicine, Tucson, AZ, USA

Carolina Miranda-Castillo, MD Sleep Research Institute, Madrid, Spain

Amaia Muñoz-Lopetegi, MD Department of Neurology, Hospital Clinic Barcelona, Barcelona, Spain

Susan Muraida, MD Internal Medicine, University of New Mexico Hospital, Albuquerque, NM, USA

Siddhartha S. Nadkarni, MD Neurology and Psychiatry, NYU, New York, NY, USA

Justa Elizabeth González Naranjo, MD Clinical Neurophysiology, International Center for Neurological Restoration, La Habana, Cuba

Milan Nigam, MD Department of Neurosciences, Université de Montréal, Center for Advanced Research in Sleep Medicine, Hôpital du Sacré-Coeur, Montreal, QC, Canada

John G. Park, MD Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

Snigdha Pusalavidyasagar, MD Division of Pulmonary, Allergy, Critical Care and Sleep, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN, USA

Taaha Rafi, MD Sleep Medicine, Banner University Medical Center, Tucson, AZ, USA

Alcibiades J. Rodriguez, MD Department of Neurology, NYU Langone Comprehensive Epilepsy Center-Sleep Center, New York, NY, USA

Sofia Romero-Peralta, MD Department of Neurology, Sleep Research Institute, Madrid, Spain

Sleep Unit, Pneumology Department, University Hospital of Guadalajara, Guadalajara, Spain

Marta Ros, MD Department of Neurology, Parc Taulí Hospital Universitari, Sabadell (Barcelona), Spain

Montserrat Pujol Sabate, MD, PhD Neurology Service and Multidisciplinary Sleep Unit, Hospital Universitari Santa Maria, Lleida, Spain

Gemma Sansa, MD, PhD Department of Neurology, Parc Taulí Hospital Universitari, Sabadell (Barcelona), Spain

Joan Santamaria, MD, PhD Neurology Service, Hospital Clínic of Barcelona, Barcelona, Catalonia, Spain

Morris H. Scantlebury, MD Department of Pediatrics, Alberta Children's Hospital, Calgary, AB, Canada

Matthew T. Scharf, MD, PhD Department of Medicine and Neurology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Carlos H. Schenck, MD Department of Psychiatry and Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center and University of Minnesota Medical School, Minneapolis, MN, USA

Rebecca Q. Scott, PhD Department of Neurology, NYU Langone Comprehensive Epilepsy Center-Sleep Center, New York, NY, USA

Rasik Shah, MD Department of Pediatrics, NYU Grossman School of Medicine, Hassenfeld Children's Hospital, New York, NY, USA

Patrick Sorenson, MA Sleep and Neurodevelopment Service, National Institute of Mental Health, Bethesda, MD, USA

Jordan C. Stern, MD Otolaryngology/Sleep Medicine, BlueSleep, New York, NY, USA

Nida F. Tascilar, MD Department of Neurology and Electroneurophysiology and Sleep Laboratory, Camlica Medipol University Hospital and Istanbul Medipol University Medical School, Istanbul, Turkey

Juan Jesús Rodríguez Uranga, MD Epilepsy Program, Centro de Neurología Avanzada, Seville, Spain

Andrew J. Westwood, MD Department of Neurology, Maidstone and Tunbridge Wells NHS Trust, Kent, UK

Case 1. The Borderlands of Sleep-Wake Movements and Epilepsy

1

Hernando Pérez Díaz and Juan Jesús Rodríguez Uranga

History

A 53-year-old woman was referred for a second medical opinion in 2020 by a colleague. She had originally presented in 2016 with several episodes of complex abnormal movements occurring during sleep and, upon awakening from sleep, but without loss of consciousness. Previously, this had been diagnosed as a drug-refractory epilepsy.

My colleague ordered video-EEG monitoring (see report), which registered a total of 23 paroxysmal episodes of complex motor semiology that occurred both during sleep, upon awakenings and the wake period in the daytime. There was no associated change in the electroencephalogram (EEG) activity and no interictal epileptiform discharges.

The patient reports that she can have up to 6 episodes per night, lasting between 5 and 15 s each time and that they can occur at any time of the night [according to a 2020 video-EEG-polysomnography (PSG), she underestimated the frequency and duration of episodes (see report)]. During the episodes, the patient can speak "with difficulty".

These episodes started around age 2. Until approximately age 50, they occurred mainly during sleep with rare events during wakefulness. After age 50, they could happen during the day, but only after awakening from a nap. There are no triggers for these events.

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H. P. Díaz (✉)
Sleep and Epilepsy Program, Centro de Neurología Avanzada, Seville, Spain

J. J. R. Uranga
Epilepsy Program, Centro de Neurología Avanzada, Seville, Spain

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She does snore and frequently has problems with falling and staying asleep. During the day, the patient feels extremely tired and has complaints of neck, arm and knee pain.

For these events, the patient has previously trialed (alone or in combination) carbamazepine, levetiracetam, valproic acid, diazepam, amitriptyline, clobazam, oxcarbazepine (worsened symptoms), quetiapine, perampanel and mirtazapine—all with no response to treatment. She does note that she sleeps a bit better with 100 mg of trazodone nightly, but the episodes persist.

The patient started to walk at around age 2, but there were no other developmental issues. There is no family history of movement disorders or epilepsy.

Examination

Normal general and neurological examination.

Investigations

3-Tesla brain magnetic resonance imaging (MRI): normal.

Video-EEG monitoring 2016:

EEG background activity within normal range.

Interictal EEG: no interictal epileptiform abnormalities.

A total of 23 episodes are recorded, both during the wake period and during the night on waking up, with a complex motor semiology with no change in consciousness, which has no effect on EEG activity.

Video EEG-polysomnography (2020): There were 12 events consisting of choreoathetosis and ballistic movements with no loss of consciousness, lasting an average of 30 s and occurring during NREM sleep stages. Due to these clinical manifestations, the episodes were very suggestive of paroxysmal hypnogenic dyskinesia. There was no sleep disordered breathing or periodic limb movement of sleep observed. REM sleep stage had normal muscle atonia. Description of one of these events (see Video 1.1): the patient started with right hand flickering movement, then both legs extended, followed by flexion of legs, turning her body to the right side, truncal extension, arm stretching and semi-purposeful movement of hands reaching out to her body as if she is picking on her clothes. It subsided in 50 s and she had only occasional feet flexion.

Home video (not included) showed similar movements and extension of trunk, flexion of legs, arms folded around her chest in a brief period without opening eyes. She woke up after one episode.

Genetic study: mutation c.640G.C (p.Ala214Pro) in gene PRRT2.

Diagnosis

PAROXYSMAL HYPNOGENIC DYSKINESIA

Discussion

Paroxysmal dyskinesias are defined as a heterogeneous group of syndromes characterized by recurring episodes of sudden onset involuntary movements of an intermittent or episodic nature without associated loss of consciousness. Abnormal movements are primarily dystonia and/or chorea, and to a lesser extent ballismus or athetosis, but do not include tremor or myoclonus.

The following movement disorders differ based on their triggers and duration: paroxysmal kinesigenic dyskinesia (PKD), paroxysmal nonkinesigenic dyskinesia (PNKD), paroxysmal exertion-induced dyskinesia (PED), and paroxysmal hypnogenic dyskinesia (PHD) [1].

PHD is a disease that is likely underdiagnosed and often confused with sleep-related hypermotor epilepsy. In our experience, it is not rare for some of the patients treated for this disease in our unit to be referred with the diagnosis of refractory epilepsy on various anti-seizure medications (ASMs) with no improvement, although the literature indicates responses to ASMs due to the still confusing distinction and overlap that exists between both disorders. This disorder normally starts during adolescence (range 2–47 years of age) and shows no sex predominance. The trigger for PHD is non-REM sleep. The literature indicates average episode durations of 30–45 s and average frequencies of between 5 episodes per year to up to 5 episodes per night; however, in our experience, episodes can last as long as 2–5 min and the patient may suffer frequencies in excess of 20 episodes per night [1].

In its primary form, PHD is a channelopathy and is associated with two genes:

– **PRRT2** -c.649dupC- for which over 70 mutations have been identified (95% nonsense or frameshift) and which is mainly associated with PKD, but also with the other 3 forms of paroxysmal dyskinesia as its transmission is autosomal dominant. Syndromic signs and symptoms usually start before the age of 18 years. It is also associated with infantile convulsions and choreoathetosis, benign familial infantile seizures, migraines, familial hemiplegic migraine, episodic ataxia, childhood absence epilepsy, febrile seizures, and benign paroxysmal torticollis. In homozygosity, it can lead to intellectual disability (to a greater or lesser degree), persistence of the paroxysmal episodes and prolonged ataxia episodes [2].

  The PRRT2 protein is ubiquitously located in the neocortex, hippocampus, basal ganglia and cerebellum, which anatomically correlate with the range of clinical symptoms. PRRT2 interacts with the synaptosomal-associated protein 25 (SNAP25) in glutamatergic synapses. SNAP25 is a presynaptic membrane protein that allows for fusion of synaptic vesicles and calcium-mediated neuronal exocytosis in order to modulate glutamate release. In *PRRT2* mutations, the PRRT2 protein changes its usual location from the membrane to the cytoplasm,

interacts with SNAP25, alters the properties of the calcium voltage-dependent channel Cav2.1, and therefore enhances intracellular glutamate levels leading to neuronal hyperexcitability. Otherwise, PRRT2 expression increases during the development and is correlated to neuronal migration and synaptic density. This explains why biallelic *PPRT2* mutations can result in neurodevelopmental disorders [1, 2].

– **ADCY5** is fundamentally associated with PHD, and to a lesser extent PKD and PNKD, which are also autosomal dominant. It has been associated with alternating hemiplegia of childhood, axial hypotonia, nonparoxysmal dystonia and chorea.

  ADCY5 gene encodes for adenylate cyclase 5, which is strongly expressed in the striatum and converts adenosine triphosphate to 3′,5′-cyclic adenosine monophosphate and pyrophosphate. ADCY5 integrates signals from adenosine A2A, D1 and D2 dopamine receptors, among others. *ADCY5* mutation carriers display a broad phenotypic spectrum with a genotype–phenotype correlation. The most common mutation, p.Arg418Trp, presents with a more severe phenotype than that of p.Arg418Gln and p.Ala726Thr. These mutations likely increase adenylate cyclase activity, thereby distinctly affecting signal transduction in the striatum [1].

  ADCY5 patients typically show onset of signs during childhood with a mixture of persistent hyperkinetic movements (chorea, dystonia or myoclonus) characterized by: axial hypotonia, orofacial jerks (not true myokymia), sleep-related paroxysmal dyskinesia and painful paroxysmal dyskinesia. They have marked fluctuations in frequency and severity of movements without seizures, ataxia or marked cognitive impairment. They have normal brain MRI scans and stable or very slow progression of symptoms. Attacks of paroxysmal dyskinesia last for minutes with discrete onset and offset, waxing and waning over the course of weeks to months. This pattern makes it difficult to distinguish triggers or response to medications. In fact, the combination of multiple paroxysmal dyskinesia subtypes (e.g., PKD, PNKD and PHD) or paroxysmal dyskinesia that do not fit clearly into previous defined paroxysmal dyskinesia categories are clues to suspect *ADCY5* mutations [1].

Patients with PHD are usually referred as refractory epilepsy and there are patients with an overlap between epileptic seizures and PHD episodes, so it is difficult to know where the limits are. However, in PHD the movements—dystonia, chorea, ballismus and/or athetosis—seem to have a subcortical origin, are intrinsically anarchic and non-stereotyped, the consciousness is maintained, and the duration of the episodes is longer than in the epileptic seizures. The differential diagnosis of paroxysmal events during sleep must include PHD, which may help for faster work up, diagnosis and therapeutic intervention.

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Case 2. Sometimes Lightheadedness a Harbinger

2

Susan Muraida and Madeleine Grigg-Damberger

History

Determined to join her school pep squad practicing long and hard, a 13-year-old girl began complaining of episodes of awakening feeling nervous and lightheaded, especially when awakened by her new loud alarm clock. One night resting in bed, she ran from the room complaining of chest pain and shortness of breath. She saw her pediatrician who examined her and said it was "just stress." One week later, awakened by her alarm clock, she had a generalized convulsion followed by a cardiac arrest. Parents performed cardiopulmonary resuscitation. She took no medications, had no significant past medical history, and used no recreational drugs.

S. Muraida (✉)
Internal Medicine, University of New Mexico Hospital, Albuquerque, NM, USA
e-mail: smuraida@salud.unm.edu

M. Grigg-Damberger
Department of Neurology, University of New Mexico Medical Center, Albuquerque, NM, USA
e-mail: mgriggd@salud.unm.edu

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Examination

Paramedics arrived and patient was successfully resuscitated.

Exam following successful cardiac conversion showed: blood pressure 102/60 mmHg, pulse rate 65 beats per minute, respiratory rate 16, pulse oximetry 96%, body mass index (BMI) 17 kg/m^2. Patient appeared well-nourished. Cardiac, pulmonary, and neurological exams were normal.

Investigations

Point-of-care glucose was 85. Complete metabolic panel showed normal potassium, magnesium, and calcium. Post-conversion she was found to have an abnormal EKG showing alternating T waves. A 12-lead electrocardiogram (EKG) was performed at the hospital and found to be abnormal (shown in Fig. 2.1).

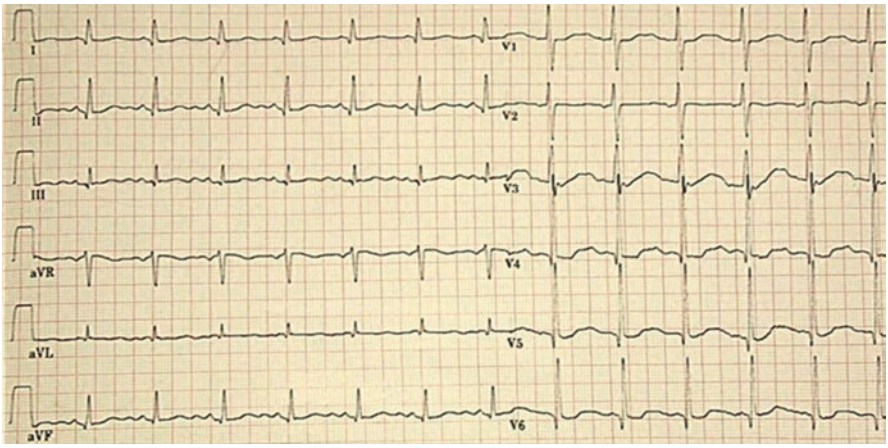


Fig. 2.1 EKG shows a prolonged QT interval of 544 ms (QTc interval corrected for the heart rate 647 ms). Notched T waves noted in leads II, III, aVF, and V1–V6

Differential Diagnosis

Brugada syndrome, cardiac syncope; convulsive syncope; hypertrophy cardiomyopathy, long QT syndrome.

Discussion and Management

Syncope, seizure, cardiac arrest or death awakened by an alarm clock warrants consideration of congenital long QT syndrome (LQTS) type 2. The EKG showed prolonged QTc interval of 647 ms and notched T waves. Genetic testing showed she had a loss of function mutation in the hERG (KCNH2) cardiac potassium channel gene (LQTS type 2).

Congenital LQTS (c-LQTS) is a disorder of ventricular myocardial repolarization characterized by a prolonged QT interval on the EKG which can lead to torsades de pointes (TdP), sudden cardiac arrest, and sudden cardiac death [1, 2]. LQTS can be congenital or acquired. Congenital LQTS (c-LQTS) has a prevalence of 1 in 2000 live births.

Mutations in three cardiac ion channel genes account for 80% of c-LQTS cases: KCNQ1 (LQT1); KCNH2 (LQT2); and SCN5A (LQT3). The congenital form typically presents in the first two decades. The initial symptom (most often between ages 8 and 10 years) is syncope in 69%; cardiac death in 10–13%. c-LQTS cause 3000–4000 sudden deaths children and young adults each year in the United States.

Patients during LQTS cardiac events often report palpitations, lightheadedness, dizziness, near-syncope and/or syncope. TdP can be a transient short self-limited arrhythmia but when longer and/or evolving to ventricular fibrillation can lead to cardiac arrest and cardiac death. When cardiac output decreases significantly during non-sustained episodes of TdP it leads to cerebral hypoperfusion sufficient to cause syncope and/or seizures.

LQTS cardiac events are often triggered by specific triggers which vary with the specific LQTS genotype (summarized in Fig. 2.2). Patients with LQT2 (our patient) typically have LQT cardiac events triggered by sleep, rest or auditory stimuli (such as an alarm clock, telephone ringing, thunderbolt, or baby crying). In one case series of 670 patients with c-LQTS, a lethal event in 110 was provoked by a specific trigger. In LQT1 patients, 90% events occurred during a particularly emotional event or exercise (especially while swimming). LQT events occurred during sleep or rest in 80% with LQT3, 63% in LQT2. Eighty percent of events in LQT3 occurred at sleep/rest; arousal 80% LQT3, 63% LQT2. Night rest lengthens PR and QT intervals, and prolongs QRS.

TdP is the classic cardiac arrhythmia associated with LQTS in which peaks of the QRS complexes twist around an isoelectric line of the EKG tracing. TdP episodes are usually brief and end spontaneously. However, patients may experience multiple episodes of the arrhythmia, and episodes can recur in rapid succession and may induce syncope or progress to ventricular fibrillation. A markedly prolonged

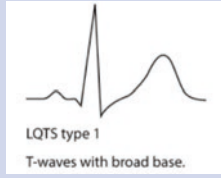
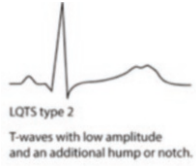
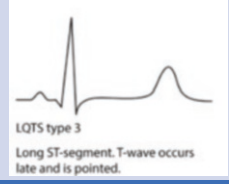
LQTS Type, Genotype, Gene Mutation and Effect	Triggers for Sudden Death	T-wave morphology
LQT1 Loss of function in **KCNQ1** cardiac **potassium** channel gene 40% of all mutations	• 75% **exercise (especially swimming)**; • 15% emotional stress; • Adolescent boys more events girls; • Testosterone shortens QT interval; • Estrogen may affect potassium channel function → longer QTc.	
LQT2 Loss of function in **hERG (KCNH2)** cardiac **potassiu**m channel gene 40% of all mutations	• 63% sleep or rest; • 37% sudden loud noises, acute arousals, or emotions;	
LQT3 Gain of function in cardiac sodium channel gene **SCN5A** 10% of all mutations	• 80% sleep, rest, night; • 15% exercise; 5% emotions; • Cardiac events more lethal, tend to have marked resting bradycardia and arrhythmias bradycardia related.	

Fig. 2.2 Most common congenital long QT syndrome phenotypes

QT interval precedes the onset of TdP; the ventricular rate 160–250 beats/min, irregular R-R intervals, and cycling of the QRS axis 180° every 5–20 beats. Bradycardia is usually associated with TdP in acquired LQTS, whereas catecholamine surges trigger TdP in c-LQTS.

Acquired LQTS is far more common than c-LQTS, and is most often triggered by QT-interval prolonging drugs or electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia, starvation, liquid protein diets, and anorexia nervosa) or cocaine. Twenty percent of patients with symptomatic acquired LQTS have subclinical LQTS mutations.

The importance of a good history to identify LQTS before it is lethal cannot be understated. Clinicians should explore situational factors that trigger syncopal symptoms, obtain a thorough history of medications, substance use and family history of unexplained sudden death <40 years old. Consider performing serial EKGs to evaluate for prolonged QTc interval ≥500 ms, and chemistry panels to evaluate for electrolyte disturbances.

Empower patients with LQTS and their families to immediately report warning signs or symptoms. They need to be advised to avoid potential triggers such as strenous exercise, stressful situations, alarm clocks, abrupt awakenings, electrolyte disturbances and QT-prolonging medication (www.crediblemeds.org). Most are first treated with beta-blockers (preferably propranolol or nadolol for LQT1 and LQT2, sodium-channel blockers LQT3). An implantable cardioverter defibrillator (ICD) is inserted for patients who had a prior cardiac arrest, refractory symptoms, or family history of sudden cardiac death. Our patient was treated with propranolol and an ICD.

Final Diagnosis

Congenital Long QT syndrome type 2 with a cardiac arrest and convulsion triggered by awakening to an alarm clock.

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Case 3. Testosterone and Gender: Not What You Think

3

Jordan C. Stern

History

A 35-year-old transgender man (assigned female at birth) presents for evaluation of new onset snoring. The symptoms began 1 year ago, and now have worsened to the point that the bed partner is unable to sleep in the same room. No significant breathing pauses, gagging or gasping were reported. The patient is an attorney and has noted greater difficulty concentrating on his work, especially in the afternoon. Current medications include 100 mg testosterone topical gel for masculinizing hormone therapy. There is no previous history of sleep disorder as a child or in adolescence. Past medical history is otherwise negative, and there was no reported family history of sleep apnea.

Examination

The patient is a well-developed male in no acute distress, although short in stature: height 5 ft 3 in., and 130 lb, body mass index (BMI) of 23 kg/m^2. Examination of the head and neck revealed normal ear and nose examination. Anterior rhinoscopy revealed slight deviation of the septum to the right, normal inferior turbinates, and no evidence of nasal polyps in the anterior nasal cavity. Examination of the oral cavity and pharynx revealed Mallampati class II and tonsils size 2. There was mild edema along the free edge of the uvula. Examination of the neck was significant for a circumference of 16 in.; no significant adenopathy, salivary glands were normal on palpation, as was the thyroid gland. Epworth Sleepiness Scale (ESS) of 10/24.

J. C. Stern (✉)
Otolaryngology/Sleep Medicine, BlueSleep, New York, NY, USA
e-mail: jstern@bluesleep.com; https://www.BlueSleep.com

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_3

Investigations

Fiberoptic nasopharyngolaryngoscopy (NPL) was performed and was significant for mild narrowing at the level of the base of tongue, which resolved upon mandibular protrusion. There was further narrowing of the airway upon Mueller maneuver (inspiration against a closed glottis). Moderate obstructive sleep apnea with an apnea-hypopnea index (AHI) of 23/h (Fig. 3.1).

Device			**ApneaLink Air**	Type:	**III**
Recording	Start: **10:37pm**		End: **5:30am**	Duration - hr:	**6:53**
Flow Evaluation	Start: **10:47pm**		End: **5:28am**	Duration - hr:	**5:48**
Oxygen saturation evaluation	Start: **10:47pm**		End: **5:30am**	Duration - hr:	**6:32**

Statistics

Events index	AHI: **23.3**	AI: **5.2**	HI: **18.1**
Events totals		Apneas: **30**	Hypopneas: **105**
Apnea Index Obstructive: **2.4**	Central: **0.3**	Mixed: **0.0**	Unclassified: **2.4**
Cheyne-Stokes respiration		Time - hr: **0.00**	Percentage: **0**
Oxygen desaturation		ODI: **28.9**	Total: **189**
Oxygen saturation %	Baseline: **95**	Avg: **94**	Lowest: **80**
Oxygen saturation - eval time %	<=90%sat: **9**	<=85%sat: **0**	<=80%sat: **0**
		<=88%sat: **5**	<=88%Time - hr: **0:18**
Breaths	Total:**4045**	Aug/min: 11.6	Snores: **2353**
Pulse - bpm	Min: **50**	Aug: **65**	Max: **96**

Fig. 3.1 Patient's Home Sleep Apnea Test consistent with moderate obstructive sleep apnea AHI 23.3/h. (ApneaLink Air Resmed, San Diego CA)

Diagnosis

Obstructive Sleep Apnea (OSA).

Discussion and Management

This young otherwise healthy transgender male patient did not present with comorbidities usually associated with OSA such as obesity, diabetes, and hypertension; and without any obvious history or risk factors for obstructive sleep apnea including excessive daytime sleepiness. Findings on NPL revealed some mild narrowing of the upper airway at the level of the base of tongue, but otherwise Mallampati and tonsil size were not major risk factors in this case. Given the new onset of snoring, rapidly worsening since the beginning of the testosterone replacement therapy, an HST was ordered because of the suspicion of OSA developing as a result of the masculinizing hormonal therapy. Moderate sleep apnea was diagnosed on HST and the patient underwent digital 3D scanning of upper and lower jaws, and a bite registration for production of a mandibular advancement device (MAD) as primary treatment (Fig. 3.2). After delivery of the MAD, the patient self-titrated for 4 weeks, and a post titration visit revealed resolution of snoring, improvement of ESS from 10 to 7/24, and reduction of AHI from 23/h to 6/h using the MAD.

This case illustrates the potential risk of sleep apnea in the transgender male undergoing masculinizing hormone therapy. The current prevalence of gender dysphoria in the U.S. is in the range of 0.7% of adults 18–24 years old and 0.5% of adults 65 and older. A recent study has found that the ratio of female to male transgender individuals has increased steadily since 1990 and now equals that of male to female individuals [1].

Many aspects of sleep are affected by androgens and estrogens, including the risk for sleep apnea. It is well established that OSA occurs more frequently in men, and that the prevalence of OSA in postmenopausal women is 3.5 times that of

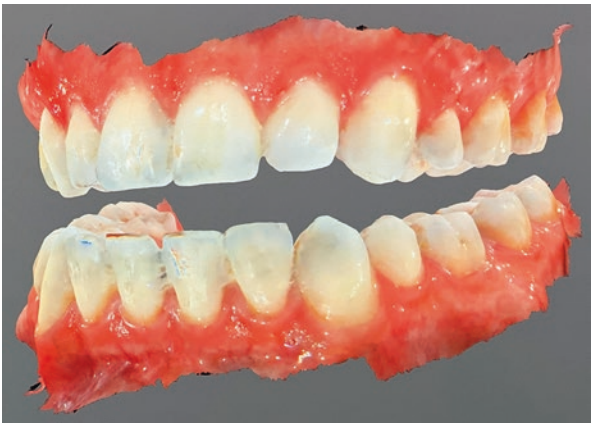

Fig. 3.2 3D Digital impressions for Mandibular Advancement Device (MAD). Associated video (https://vimeo.com/673313532) shows patient's normal bite, 50% protrusion bite, and maximum protrusion bite

premenopausal women. However, the impact of administration of testosterone and estrogens on the development of sleep apnea remains controversial. Many studies have evaluated the role of estrogen and testosterone in both men and women, but no studies have evaluated the role of testosterone treatment in transgender men [2].

While hormone therapy is unlikely to change the bony and cartilaginous structures supporting the airway (trachea, cricoid, thyroid cartilage, and hyoid bone), hormonal treatments can change the deposition of fat in the upper airway. There are known gender differences in fat deposition in the pharynx and tongue which can increase the risk of sleep apnea by narrowing the upper airway. One of the suspected causes of the increased incidence of OSA in postmenopausal women, is an android fat deposition pattern (upper body and trunk) that occurs during menopause. In our patient's case, the female born airway which is smaller in dimension than the male airway, may have further narrowed once exposed to the testosterone therapy. Both intrinsic and extrinsic volume changes can narrow the airway and increase the likelihood of developing OSA, or worsening OSA, even with no significant change in BMI. It has been shown that males have a larger cross-sectional upper airway than females. Clearly the size of the airway (larger in men than women) is not the explanation for increased OSA in men, but rather the longer length of the airway and the larger soft palate and tongue.

Testosterone, both endogenous and exogenous, is also thought to contribute to an increased OSA risk in women with polycystic ovary syndrome (low estrogen levels and high testosterone levels). While controversial, it appears that low testosterone levels in cisgender men may be associated with a higher risk of OSA, and testosterone replacement may worsen sleep apnea in cisgender and transgender men.

In this case, given the absence of obesity, enlarged neck size, excessive daytime sleepiness, or associated medical conditions such as hypertension or diabetes, the risk of sleep apnea would be considered relatively low. However, a neck size of 16″ in a cisgender female is a significant risk factor. The patient did not know his neck size before receiving his masculinizing hormonal treatment but did notice a significant change in upper body muscle mass after the onset of treatment. Testosterone replacement therapy has many other physiological effects which can increase the risk of sleep apnea, and patients should be specifically questioned about its past or current use—especially transgender men.

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Case 4. "Despite of CPAP Therapy, My Husband Still Has a Disturbed Nocturnal Sleep"

4

Amaia Muñoz-Lopetegi and Carles Gaig

History

A 53-year-old male with a previous diagnosis of obstructive sleep apnea syndrome (OSAS) and no other relevant medical history, was referred due to persistent excessive daytime sleepiness and non-restorative nocturnal sleep associated with frequent abnormal movements and behaviors despite of CPAP therapy. These sleep problems have been noted since the last 2 years. Patient's wife reported that while asleep he developed an intense heavy "*snoring*" with respiratory pauses and frequently talked (usually incomprehensibly), groaned, moved and sometimes gesticulated as acting out of his dreams (e.g. like discussing, manipulating something or working). The patient was unaware of all these problems (dream mentation was absent) and complained mainly of non-restorative sleep and intense daytime sleepiness. A respiratory polygraphy was performed in another center and frequent obstructive apneas were recorded (apnea hypopnea index—AHI—33/h). CPAP at 9 cmH_2O eliminated apneas and the "snoring", but daytime somnolence was only partially improved, and movements and behaviors during sleep persisted. During this time, the patient also presented a continuous inner-feeling of restlessness resembling akathisia (without nocturnal worsening). In addition, he complained of mild swallowing difficulties with occasional choking, mild unsteadiness with infrequent falls and mild attention and memory problems.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/978-3-031-18374-4_4.

A. Muñoz-Lopetegi · C. Gaig (✉)
Neurology, Hospital Clinic Barcelona, Barcelona, Spain
e-mail: ammunoz@clinic.cat; cgaig@clinic.cat

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_4

Examination

Neurological examination revealed mild bilateral horizontal gaze limitation. Mild distal upper and lower limb choreic movements were noticed and gait was normal except for mild instability while turning. Cognition and the remaining neurological and physical examination was normal.

Investigations/Studies

A nocturnal video-polysomnography (vPSG) revealed a sleep efficiency 72% (with the patient wearing his CPAP), no obstructive sleep apneas nor other sleep breathing abnormalities, but recorded prolonged periods of sleep with abnormal architecture and motor activation with frequent limb and body movements and purposeful-looking gestures (e.g. talking, eating, manipulating imaginary wires or tools; see Video 4.1). The electroencephalogram (EEG) during these periods was characterized by a diffuse theta activity, sometimes with sparse sleep spindles or K complexes (Fig. 4.1a, b). These periods of disorganized sleep occurred mostly at onset of nocturnal sleep and re-entering of sleep after awakenings and alternated with episodes of normal N2 and N3 sleep with frequent sleep spindles, K complexes and delta activity, without abnormal movements or behaviors (Fig. 4.2a). REM sleep was characterized by a loss of its normal atonia with frequent limb and body jerks typical of REM sleep behavior disorder (RBD) (vocalizations or behaviors in REM sleep, however, were very rare) (Fig. 4.2b).

Blood analysis and brain magnetic resonance imaging (MRI) were normal. Cerebrospinal fluid (CSF) showed no cells and normal protein levels but antibodies against IgLON5 were detected. Other neuronal antibodies (including those directed against CASPR2) were negative. Mutations in the prion protein gene were absent. A new vPSG without CPAP showed persistence of the NREM and REM sleep abnormalities and disclosed stridor (accounting for the intense heavy "*snoring*" reported by the patient's wife) and frequent obstructive sleep apneas (AHI: 37/h), especially prominent during periods of normal NREM sleep. Laryngoscopy during wakefulness showed mild bilateral vocal cord paresis.

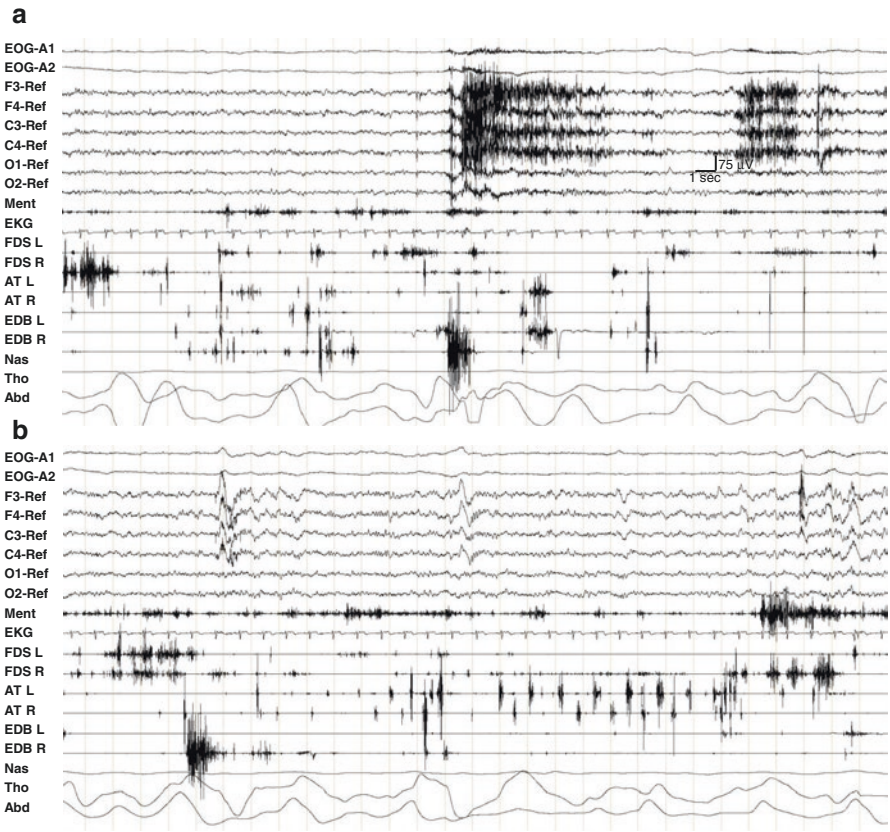

Fig. 4.1 VPSG showing 30 s epoch of undifferentiated NREM sleep with diffuse theta activity (**a**) and poorly-structured N2 sleep with K complexes and sleep spindles (**b**). Note the motor-muscular activation, which is associated with vocalizations, movements, and behaviors. EMG: electromyogram; EOG: electrooculogram; Ment: electromyography of mentalis muscle; EKG: electrocardiogram; FDS: flexor digitorum superficialis muscle left (L) and right (R); EDB: extensor digitorum brevis muscle left (L) and right (R); AT: anterior tibialis left (L) and right (R); NAS: nasal air flow; THO: thoracic respiratory movement; ABD: abdominal respiratory movement. Note the calibration mark for time/EEG voltage. EEG electrodes were referenced to both ears

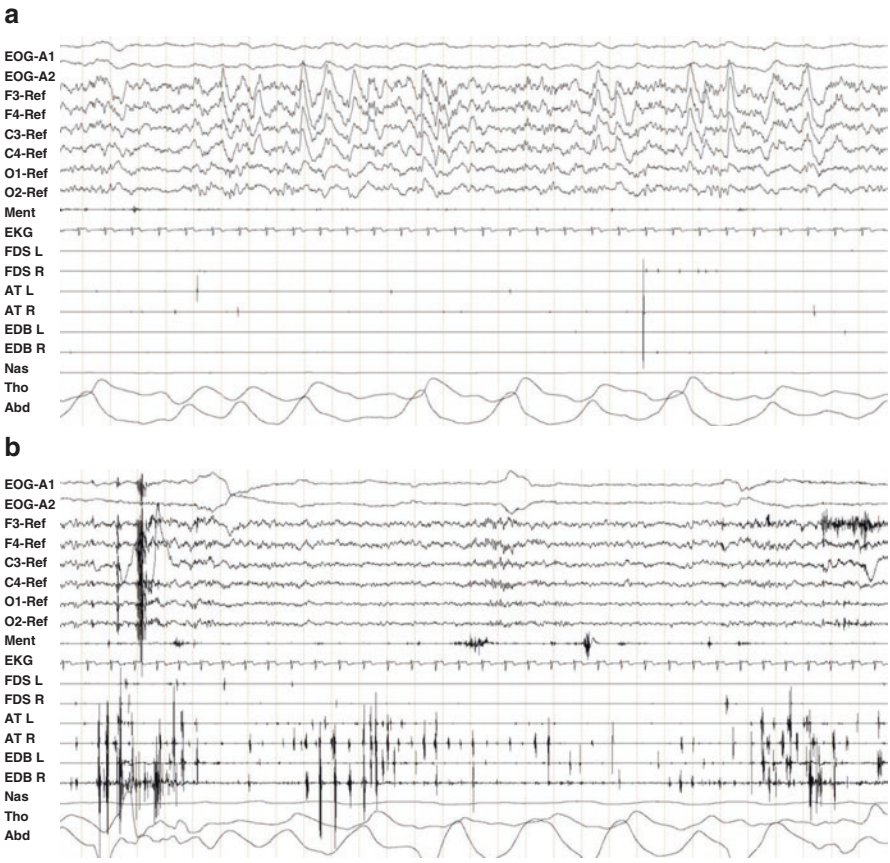

Fig. 4.2 VPSG showing 30 s epoch of normal N3 sleep without motor activation (**a**) and REM sleep with excessive muscular activity, which is associated with limb and body jerks (**b**). EMG: electromyogram; EOG: electrooculogram; Ment: electromyography of mentalis muscle; EKG: electrocardiogram; FDS: flexor digitorum superficialis muscle left (L) and right (R); EDB: extensor digitorum brevis muscle left (L) and right (R); AT: anterior tibialis left (L) and right (R); NAS: nasal air flow; THO: thoracic respiratory movement; ABD: abdominal respiratory movement. Note the calibration mark for time/EEG voltage. EEG electrodes were referenced to both ears

Differential Diagnosis

The sleep disorder of our patient is characterized by (1) a parasomnia of the onset of NREM sleep with undifferentiated NREM sleep and poorly-structured N2 NREM sleep (with sparse sleep spindles and K complexes) with limb movements and purposeful-looking behaviors; (2) RBD with frequent jerks and (3) Stridor with obstructive sleep apneas, particularly severe during periods of normal NREM sleep. This sleep disorder is the typical of anti-IgLON5 disease and should be differentiated from status dissociatus and agrypnia excitata, idiopathic RBD, conventional

NREM parasomnias (or disorders of arousal), and overlap parasomnia (the rare association of RBD with confusional arousals) [1].

Status dissociatus can be observed in neurodegenerative diseases (e.g. multiple system atrophy, dementia with Lewy bodies), brainstem lesions, narcolepsy or in patients treated with multiple psychoactive drugs. Agrypnia excitata is an extreme form of status dissociatus occurring in Morvan syndrome (an autoimmune encephalitis associated with CASPR2 antibodies), fatal familial insomnia (a genetic prion disease), or alcohol withdrawal syndrome. In these conditions, the sleep-wake pattern is lost. Distinguishing sleep from wakefulness can be very difficult as patients are displaying frequent vocalizations and movements, while posterior alpha rhythm of wakefulness is lost, sleep spindles, K complexes and high-voltage delta activity typical of NREM sleep are absent, and REM sleep is identified. In contrast, in anti-IgLON5 disease the sleep-wake rhythm is preserved, wakefulness can be clearly differentiated from sleep (the alpha rhythm is preserved), REM sleep can be identified, and there were periods of normal N2 and N3 sleep. In anti-IgLON5 disease, most sleep behaviors occur during undifferentiated NREM sleep or poorly-structured N2 sleep, and not in REM sleep as occurs in idiopathic RBD, nor in arousals from NREM sleep typical of disorders of arousal. Since patients with severe obstructive sleep apneas can present complex behaviors in post-apneic arousals, anti-IgLON5 disease can be also misdiagnosed with isolated OSAS, as occurred in our patient [1].

Discussion and Management

Anti-IgLON5 disease is a rare neurological disorder characterized by a distinctive sleep disorder associated with other neurological symptoms, mainly gait difficulties with instability, chorea and orofacial dyskinesias and symptoms of brainstem dysfunction including dysarthria, dysphagia, vocal cord palsy and oculomotor abnormalities. Antibodies against IgLON5, a neural cell adhesion molecule of unknown function, are the diagnostic hallmark of the disease. Neuropathological examination in most patients shows neuronal loss with abnormal tau deposits in the hypothalamus and tegmentum of the brainstem. The disease is associated with specific HLA alleles (the DRB1*1001 and DQB1*0501). The physiopathology of the disease seems to include an interplay between neurodegeneration and autoimmunity. Response to immunotherapies (e.g. high dose intravenous steroids, immunoglobins, plasmapheresis or rituximab) is still unclear but worth to try as some patients can benefit. In addition, a substantial proportion of patient present a sudden death during sleep, and CPAP could be useful to prevent this fatal complication [2].

The sleep disorder in anti-IgLON5 disease (present in more than 80% of the patients) is so unique that led to the discovery of the disease. However, if other neurological problems are prominent and severe, they can be the symptom leading to medical consultation and overshadow the sleep disorder. Identification of this sleep disorder is important to suspect the condition and lead to test for anti-IgLON5 antibodies.

Final Diagnosis

Anti-IgLON5 disease.

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Case 5. Multiple Causes for Sleepiness

5

Joan Santamaria

History

A 39-year-old male was referred for a second opinion of a 10-year history of excessive daytime sleepiness that had worsened the last 3 years. He had chronic difficulties in breathing through the nose and habitually snored and breathed with the mouth open awake and asleep. He reported a mild urge to move the legs during a few nights each month which did not cause sleep-onset or maintenance difficulties. Cataplexy or sleep paralysis were absent. As a child he had presented occasional somniloquia. During weekdays he slept 6 h/day and 8 hr/day or more in weekends or holidays, but referred that sleep extension did not modify daytime sleepiness. He experienced anxious and frustrating dreams that appeared with ever increasing frequency in recent times, with similar content, where, for instance, a big bear entered his house following him while he tried to escape through the house by moving to a different room, which had smaller doors, but the bear, surprisingly passed through each of them, even though they became every time smaller and smaller until he woke up anxious, with a feeling of having slept a lot. There were no other types of dreams. If he could nap during the day for 30–60 min his sleepiness improved. An ambulatory respiratory polygraphy was performed at 36 years in another center showing frequent obstructive apnea/hypopnea [apnea-hypopnea index (AHI) 40/h] and, with a diagnosis of obstructive sleep apnea/hyponea syndrome (OSAH), he was started on nasal continuous positive airway pressure (CPAP) during a few weeks, with suboptimal tolerance and no change in sleepiness. At 38 years he was newly evaluated in another sleep center, where a full nocturnal polysomnography (PSG) showed frequent periodic leg movements during sleep (PLMS) but no significant sleep disordered breathing (AHI of 4/h). He was treated with pramipexole 0.18 mg at bedtime

J. Santamaria (✉)
Neurology Service, Hospital Clínic of Barcelona, Barcelona, Catalonia, Spain
e-mail: jsantama@clinic.cat

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_5

without improvement in sleepiness, and then 0.36 mg, which did not tolerate due to decrease in alertness and diffuse discomfort, reducing again to 0.18 mg each night. A surgeon recommended a maxillomandibular advancement surgery but the patient decided to wait and ask for another evaluation.

Examination

General and neurological examination were normal except for moderate retrognatia. His weight was 72 kg, his height 1.74 m, although he referred an increase in 3–4 kg the previous years. The Epworth Sleepiness Scale (ESS) score was 22.

Investigations/Studies

A 10-day actigraphy followed by full polysomnography and a Multiple Sleep Latency Test (MLST) were performed 1 month after withdrawing pramipexole. Actigraphy (Fig. 5.1) showed a ≥2 h longer duration of sleep/relaxed time in weekends than in weekdays, suggesting sleep deprivation.

Nocturnal PSG showed a total sleep time of 442 min, with a REM sleep latency of 101 min, an AHI of 22/h, without significant oxyhemoglobin desaturations and multiple arousals related with hypopneas with a low PLMS index (8/h). The mean sleep latency in the next day MSLT was of 5 min with no sleep onset REM periods. In a second study performed for CPAP titration with an oronasal mask the AHI decreased significantly (14/h) at 10–12 cm of H_2O and sleep fragmentation decreased, although the patient presented frequent PLMS (index of 42/h) which were not associated to arousals (Fig. 5.2).

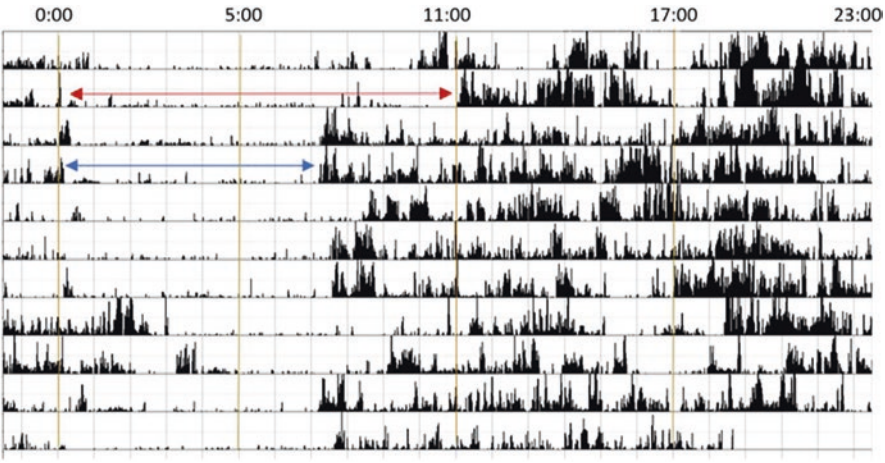

Fig. 5.1 Actigraphy shows late onset of sleep (24:00–1:00) and a >2 h difference between sleep/relaxed time on weekdays (blue arrow) as compared to weekends (red arrow)

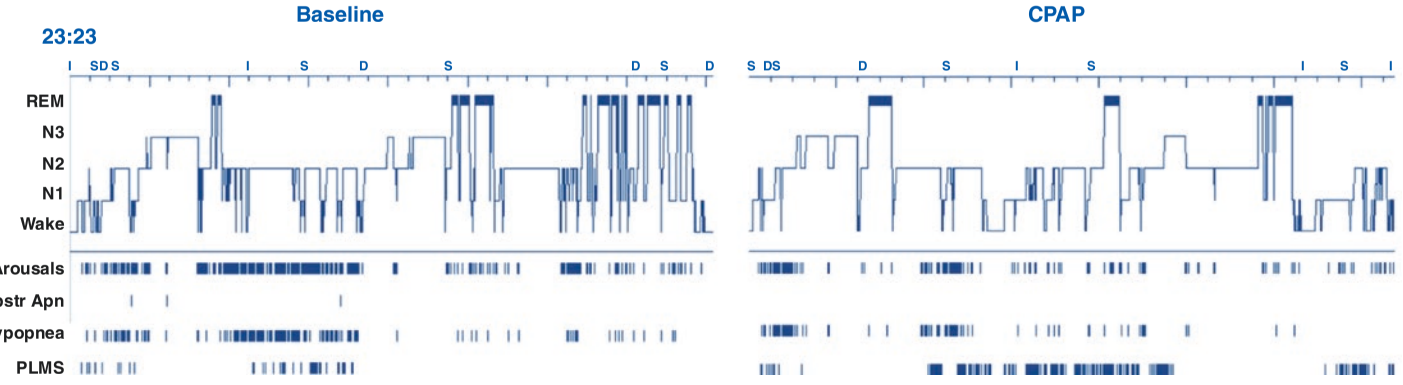

Fig. 5.2 Polysomnography at baseline (left half-side) showed frequent hypopneas (AHI 27/h) with associated arousals fragmenting sleep. A CPAP titration study with oronasal mask showed that at 10–12 cm of H_2O (right half-side) hyponeas largely decreased although with remaining PLMS, not associated to arousals

The patient was placed on CPAP and given his previous history of poor tolerance he was closely followed by a specialized nurse, obtaining good compliances, with disappearance of bad dreams [1], although with incomplete resolution of sleepiness. An extension of daily sleep time was highly recommended and the patient managed to accomplish a 1–2 h extra sleep each night, with clear improvement of sleepiness (ESS score of 8) which only reappeared when the patient reduced his sleep time.

Differential Diagnosis

This patient had three objective causes that have been associated with excessive daytime sleepiness: obstructive sleep apnea/hypopnea (an AHI of 27–40/h repeatedly encountered), frequent periodic leg movements of sleep (index of 42/h) and sleep deprivation.

Discussion and Management

Sleepiness has no special features allowing to determine its specific cause making it difficult to decide, when several possible causes of sleepiness are present, which is the most likely responsible. A step by step approach is necessary. The patient was initially treated with CPAP, but due to poor tolerance, the treatment was withdrawn, wrongly assuming that another cause could be responsible. Due to the apparent resolution of OSAH in the PSG study 2 years later, the presence of frequent PLMS was considered then the cause of the problem, but treatment with dopaminergic agents, which are powerful agents to decrease PLMS, did not modify sleepiness. In the final evaluation, however, the presence of anxious, frustrating dreams, which are often reported by patients with severe OSAH, together with clear and frequent hypopneas in the PSG in a patient with retrognatia suggested that the most likely cause was OSAH, prompting a new trial with CPAP with close nurse supervision in order to obtain good compliances. Despite good compliance, however, sleepiness did not fully resolve until sleep extension was accomplished by the patient, in combination with good CPAP use.

Final Diagnosis or Most Likely Diagnosis

Excessive daytime sleepiness caused by OSAH and sleep deprivation.

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Case 6. COVID-19, Breathing and Insomnia: There Is More Than One Story

6

Justa Elizabeth González Naranjo
and Juan Enrique Bender del Busto

History

A 54-year-old healthy woman with no previous medical history presented to the sleep clinic with new onset severe difficulties in maintaining sleep during and after hospitalization for coronavirus disease 19 (COVID-19). She was hospitalized for 25 days in a serious condition due to COVID-19 bronchopneumonia with moderate hypoxemia, which did not require intubation. One month after her discharge, she continued to have persistent insomnia symptoms despite healthy sleep habits. She reported additional problems with fatigue, daytime sleepiness, difficulties concentrating, moderate snoring with respiratory pauses and waking up with a feeling of suffocation, and dry mouth. None of these manifestations were present prior to her COVID-19 hospitalization.

Physical Examination

Physical examination revealed a body mass index (BMI) of 27.33 kg/m^2 and a neck circumference of 33 cm.

An evaluation of the upper respiratory tract was carried out by an otorhinolaryngology specialist, who described marked edema of the structures of the upper

J. E. G. Naranjo (✉)
Clinical Neurophysiology, International Center for Neurological Restoration, La Habana, Cuba
e-mail: egonzalez@neuro.ciren.cu

J. E. B. del Busto
Neurology, International Center for Neurological Restoration, La Habana, Cuba
e-mail: jebender@neuro.ciren.cu; jebender@infomed.sld.cu; cineuro@neuro.ciren.cu

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Table 6.1 Investigations performed before and at 1 month after treatment

Investigations	Before treatment	1 month after treatment
AHI (events/h)	19.21	4
Oxygen desaturation index (events/h)	14.33	0
Sleep efficiency (%)	47.87%	92%
ISI	26	7
PSQI	20	5
STOP BANG questionnaire	5	2
ESS	13	0

AHI Apnea-Hypopnea Index, *ISI* Insomnia Severity Index, *PSQI* Pittsburgh Sleep Quality Index, *ESS* Epworth Sleepiness Scale

respiratory tract with the descent of the soft palate and uvula contacting the base of the tongue, making it difficult to visualize the posterior wall of the pharynx.

At the time of examination, the insomnia severity index (ISI) was 26, the Pittsburgh Sleep Quality Index (PSQI) was 20, the STOP-BANG questionnaire was 5, and the Epworth Sleepiness Scale (ESS) was 13/24 (see Table 6.1).

Investigations

Polysomnography (PSG)

Total sleep time was 180 min and only 1 REM-NREM sleep cycle was observed with 11.43% N1, 30.09% N2, 4.07% N3 and 3.02% REM sleep stages. Sleep quality was poor, as evidenced by the elevated arousal index (28/h), elevated wake time (51.37%) and very low sleep efficiency (47.87%). The majority of the sleep fragmentation resulted from moderate obstructive sleep apnea (OSA), characterized by an apnea hypopnea index (AHI) of 19.21/h and an oxygen desaturation index (ODI) of 14.33/h (see Fig. 6.1). Obstructive hypopneas occurred primarily during NREM sleep. During the 11 min of REM sleep, apnea events were more frequent, of longer duration and were accompanied by greater oxyhemoglobin desaturations, with a nadir of 74%.

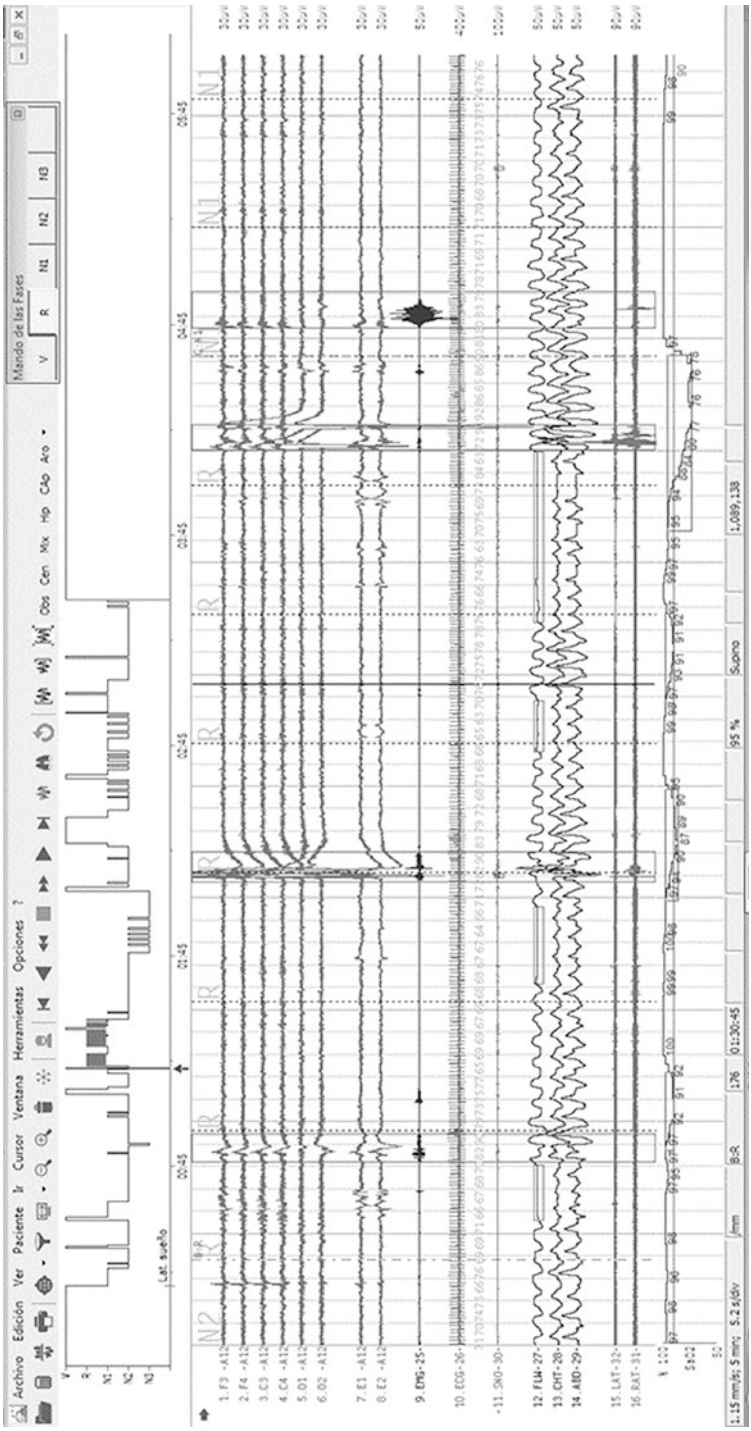

Fig. 6.1 Five minute EPOCH segment, showing periods of obstructive apneas with desaturations during REM sleep. EEG (F3, F4, C3, C4, O1, O2), EOG (E1, E2), EMG, ECG, SNO, FLW, CHT, ABD, SaO2

Diagnosis

Obstructive sleep apnea hypopnea syndrome, post COVID-19.

Discussion

Treatment was started with an auto positive airway pressure (APAP) device, maintenance of optimal sleep habits and prednisolone 20 mg per day, at the recommendation of her otolaryngologist to address the inflammation of the structures of the upper respiratory tract.

Treatment responses were evaluated at 1 week and 1 month post-treatment. The upper respiratory track edema showed improvement at 1 week with complete resolution at 1 month. A second PSG without PAP at 1 month revealed AHI values within normal limits, normal oxyhemoglobin saturation and significant improved sleep quality, with a sleep efficiency of 92% (see Fig. 6.2). The applied surveys also showed significant improvement (Table 6.1).

The moderate obstructive sleep apnea (OSA), with more pronounced events during REM sleep, accounts for the insomnia symptoms described by this patient. Excessive daytime sleepiness is a typical manifestations of OSA; however, insomnia symptoms also have been reported in patients with mild, moderate and severe OSA. In most of these cases, there is a marked improvement in insomnia symptoms with the use of PAP therapy, emphasizing the importance of performing PSG in selected patients with insomnia who may also have OSA symptomatology.

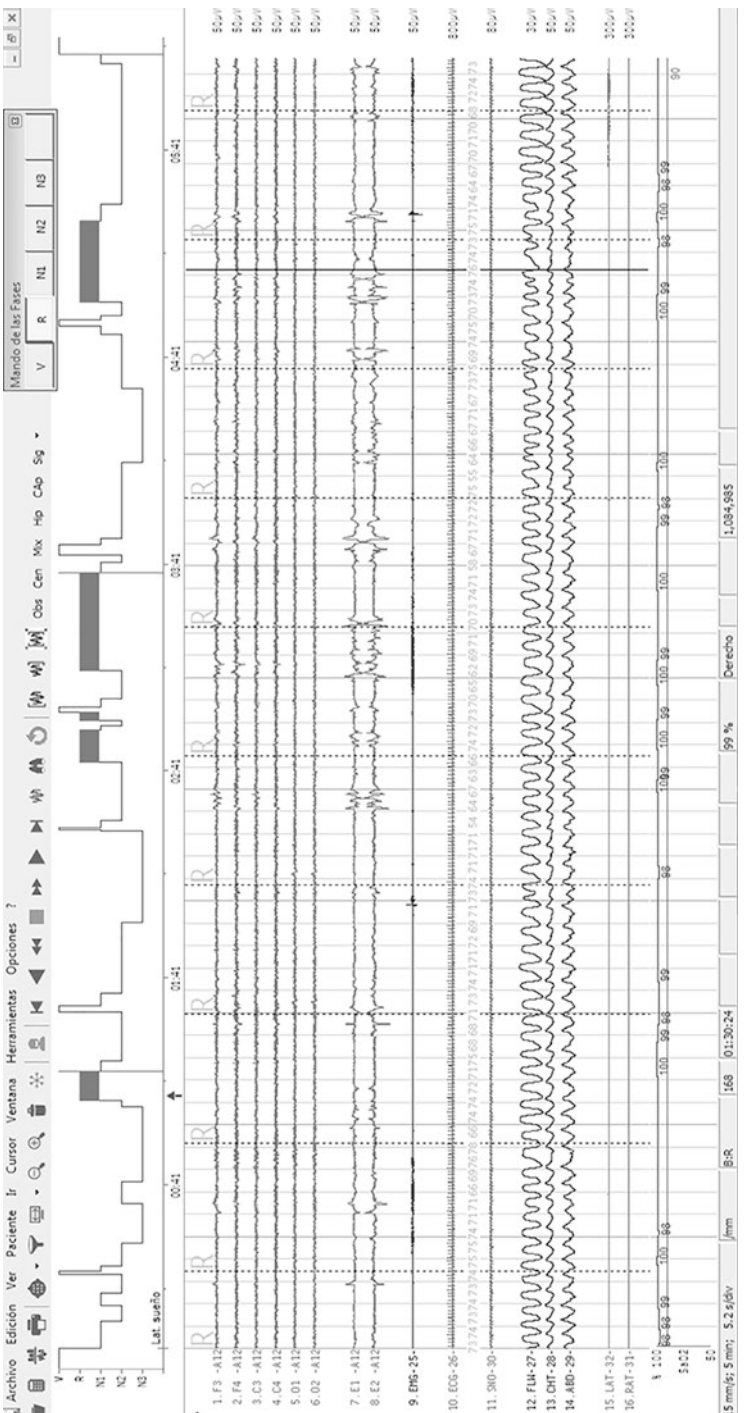

Fig. 6.2 After treatment 5-min EPOCH segment, showing the absence of periods of obstructive apneas during REM sleep, as well as the absence of desaturations. EEG (F3, F4, C3, C4, O1, O2), EOG (E1, E2), EMG, ECG, SNO, FLW, CHT, ABD, SaO2

The absence of a relevant clinical descriptor consistent with OSA prior to hospitalization suggests the presence of acute OSA onset directly related to COVID-19 infection and associated to inflammation of the upper airway. In this sense, the reported inflammation of the uvula and soft palate is striking [1]. There is growing evidence of post-COVID-19 syndrome, suggesting that many patients with COVID-19 do not fully recover and present a wide variety of symptoms for weeks to months after infection with neurological, cognitive and/or psychiatric manifestations. In relation to sleep disturbances, most studies have carried out surveys in their evaluations, observing a high prevalence of insomnia symptoms with a consequent effect on the quality of life of these patients. Some case reports with PSG have exposed the presence of OSA with subsequent improvement after PAP treatment [2].

This case illustrates that beyond the pulmonary and other systemic manifestations of COVID-19, we need to take into account local inflammation of the upper airway. Furthermore, insomnia had been reported to be highly prevalent in post COVID-19 patients. We strongly recommend that OSA be considered as a part of the sleep disturbances that can affect these patients.

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Case 7. Waking Up the Household

7

Steve A. Gibbs and Alex Desautels

History

A 21-year-old female was referred for recurrent sleep-related episodes of unknown etiology. Personal medical history was unremarkable, including normal birth and development. The father had a history of childhood sleepwalking.

At the age of 12, the patient began experiencing sudden nocturnal awakenings lasting 5 s and consisting of loud moaning with abrupt eye opening and truncal flexion. These episodes initially occurred two to three times per night with an early morning predominance, progressing over the years to a frequency of up to ten episodes per night, sometimes occurring in clusters and greatly decreasing subjective sleep quality. These were hypothesized to be nightmares or NREM parasomnias (e.g. night terrors). The patient was referred to a child psychiatrist. No psychiatric disorder was identified.

In adulthood, the episodes increased in frequency, duration and complexity. The patient developed sleep-onset insomnia, often sleeping in an armchair for fear of these recurrent episodes. She also experienced daytime fatigue due to non-restorative sleep which resulted in poor school performance. During the nocturnal awakenings, she described an undefined diffuse sensation in the chest and arms followed by truncal flexion and sitting in bed "like a robot", unable to speak but aware of her surroundings. These episodes could also occur during daytime naps.

S. A. Gibbs (✉) · A. Desautels
Department of Neurosciences, Université de Montréal, Center for Advanced Research in Sleep Medicine, Hôspital du Sacré-Coeur, Montreal, QC, Canada
e-mail: steve.gibbs@umontreal.ca; alex.desautels@umontreal.ca

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Examination

Right-handed female with a body mass index (BMI) of 20 kg/m^2 and a neck circumference of 31 cm. The neurological assessment was normal including language and memory. Epworth Sleepiness Scale score was 13/20.

Investigations

Overnight polysomnography (PSG) with a complete electroencephalogram (EEG) montage was performed. PSG revealed fragmented sleep with frequent sudden and brief unprovoked arousals with truncal flexion or pelvic thrusting (paroxysmal arousals). Three stereotyped major episodes were recorded and consisted of rhythmic guttural moaning, left head deviation, gripping the mattress with both hands, followed by pelvic thrusting and subtle pedaling movements of both legs lasting 20–30 s. The family confirmed that these episodes were consistent with those observed at home, captured with personal video recording devices. All major episodes occurred in NREM stage 2. During the episodes, no abnormal rhythmic activity was seen on the EEG. No interictal epileptiform discharge were visualized during wake or sleep. A brain magnetic resonance imaging (MRI) was normal.

Differential Diagnosis

The differential diagnosis of complex sleep-related behaviors can be quite extensive but largely depends on age of onset and the signs and symptoms associated with the particular disorder. In an adult patient, differential diagnosis classically includes sleep-related hypermotor epilepsy (SHE), NREM parasomnias or REM-sleep behavior disorder (RBD). Here, sleep-related movement disorders, such as periodic limb movement disorder (PLMD) or sleep-related rhythmic movement disorder (SRMD) could also be considered although the patient's description and the complexity of movements render both diagnosis unlikely.

Discussion and Management

The patient's clinical history and the PSG-recorded events are compatible with a diagnosis of video-documented SHE. Table 7.1 reviews key clinical features of SHE in comparison to both NREM parasomnia and RBD. The abrupt onset and offset, the stereotypic nature, the high frequency and clustering of events, NREM stage 2 and daytime nap occurrence strongly support the diagnosis of SHE. Documentation of clear-cut epileptic seizure discharges or interictal epileptiform abnormalities on the EEG-PSG would have confirmed the diagnosis but is not mandatory since EEG abnormalities are often absent or obscured by muscular artifacts in SHE. PSG with a full EEG montage is nonetheless required to increase the diagnostic and localization

Table 7.1 Key clinical features of sleep-related hypermotor epilepsy, NREM parasomnia and REM-sleep behavior disorder

	SHE	NREM parasomnia	RBD
Age of onset	Any (usually before 20)	3–8 years	After 50 years
Family history of parasomnias	Possible	Very high	Rare
Time of occurrence during the night	Any time (and during daytime naps)	Usually first third	Usually last third
Sleep stage	Usually NREM stage 2	Usually NREM stage 3	REM sleep
Frequency of events	Almost every night	Variable	Weekly
Event clusters	Often	Rare	Rare
Duration	Seconds-3 min	1–20 min	1–10 min
Natural history	Usually increases in frequency, rare remission	Tend to decrease with age	Chronic, severity may fluctuate
Stereotypic motor pattern	Yes	No	No
Triggering factors	Rare	Sleep deprivation, sleep fragmentation, stress, fever	Alcohol withdrawal, antidepressants
Consciousness after the event	Usually preserved	Usually impaired	Preserved
Recall of the event on awakening	Variable	Variable	Vivid dream recall

REM rapid eye movement, *RBD* REM-sleep behavior disorder, *SHE* sleep-related hypermotor epilepsy

sensitivity of the EEG in suspected sleep-related epilepsies [1]. It is worth mentioning that because NREM parasomnias are frequent in childhood (5–12%) and because sleep fragmentation is a priming factor for both NREM parasomnias and SHE, these conditions might co-exist in a single individual. The occurrence of a major event outside of NREM stage 3 is nonetheless significantly indicative of SHE.

SHE, formerly known as nocturnal frontal lobe epilepsy (NFLE), is a rare form of focal epilepsy that affect both sexes, and involve sleep-related seizures with various complex motor manifestations occurring during NREM sleep. The condition was recently renamed SHE because seizures are not nocturnal per se but are sleep-related. Moreover, although the seizure onset zone is frequently in the frontal lobe, one third of patients will have an extra-frontal onset [2]. Etiology is often unknown but can include structural cortical anomalies, such as focal cortical dysplasia, and genetic causes including CHRNA4, KCNT1 or DEPDC5 mutations. Therefore, gene screening and MRI brain imaging is warranted. In this present case, both tests were performed and were non-diagnostic.

Seizure semiology is characterized by complex and highly stereotyped hypermotor features such as kicking, pedaling and/or body rocking. Symmetric or asymmetric tonic or dystonic features can also be observed due to specific brain networks of the frontal lobe. Rarely, patients can leave their bed and walk around the room in a non-purposeful manner during the seizure (ictal deambulation). Capturing multiple episodes, either in the sleep laboratory or using home video recording devices, is

often diagnostic due to the stereotypic nature of seizures. Shorter seizures, termed paroxysmal arousals, represent seizures fragment. They are more frequent and are characterized by sudden arousals with brief dystonic postures, vocalization and/or emotional features such as fear.

Sleep co-morbidities are frequent in patients with epilepsy in general and should be sought out. Sleep-related breathing disorders, NREM parasomnia, insomnia and restless leg syndrome being the most common. A bi-directional influence is often observed between these disorders, where one uncontrolled condition will worsen the other.

In our patient, a nighttime treatment of carbamazepine was instituted. Progressive increase in carbamazepine dosage and adding levetiracetam lead to a satisfactory reduction of seizure frequency. This significantly improved sleep quality and reduced daytime sleepiness. Unfortunately, seizure gradually reappeared during the following 3 years despite modifications in anticonvulsant drug therapy. The patient was therefore diagnosed with drug-resistant SHE and referred to the epilepsy surgery clinic to undergo a multi-modal pre-surgical investigation. A small bottom of sulcus cortical dysplasia was identified in the left anterior cingular region using intracranial stereo-EEG implantation. The patient is now awaiting epilepsy surgery, a proven and effective treatment in selected cases.

Final Diagnosis

Sleep-related hypermotor epilepsy (SHE).

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Case 8. "Explosion in My Head is Waking Me Up"

8

Zuzana Belisova

History

An 18-year-old right-handed female presented with complaints of episodes that she described as "explosion like sensation in her head", occurring usually while falling asleep. She further described it as an extremely loud noise inside her head that wakes her up. It is sudden and only lasts seconds; but it is frightening, and she subsequently has difficulties falling back to sleep. She had no pain with this sensation and it entirely resolves once she is awake. There are no other associated symptoms. It occurs exclusively while asleep; at various frequencies, up to twice per week for the last 3 months. She stated she was under a lot of stress as she was in the last year of high school and applying for colleges. Due to her school demands, she was often sleep deprived. She estimated her total sleep time to be 6–7 h/night. She reported occasional sleep paralysis, but denied any snoring, bruxism, sleepwalking, sleep talking or symptoms suggestive of restless leg syndrome or periodic leg movement disorder. She had no difficulties initiating sleep. Her past medical history was significant for migraine with aura for which she was on amitriptyline 25 mg daily and sumatriptan 100 mg on as needed basis. The patient had no other medical problems.

Examination

Vital signs were within normal limits. Body mass index (BMI) was 22.46 kg/m^2. Mallampati score of 1. General physical as well as neurological examination was unremarkable.

Z. Belisova (✉)
Neurology, NYU Langone Medical Center, New York, NY, USA
e-mail: Zuzana.Belisova@va.gov

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_8

Investigations

Prior to her sleep consultation, the patient already completed magnetic resonance imaging of the brain, which was normal. A 72-h electroencephalogram was also normal. In-laboratory polysomnography was unremarkable. The patient did not experience the sensation the night of the study.

Diagnosis

Exploding head syndrome (EHS)

Discussion

Exploding head syndrome is a rare sensory parasomnia of unknown etiology, also known as "episodic cranial sensory shocks", during which patients experience sudden, brief perception of a very loud noise that is often described as a bomb like explosion or gunshot sound originating within the head [1]. Occasionally, simultaneous visual phenomenon described as instant flash of light is also reported. These sensations are typically occurring at sleep onset or during sleep transitions. They lead to abrupt arousal and disappear entirely when awake. Although there is no pain associated with these episodes, they can be quite terrifying. Patients may experience palpitations and, as in our patient, difficulties returning to sleep. Some consider EHS to be a sensory variant of hypnic jerk. On polysomnography EHS episodes usually originate from drowsiness, but it can occur during any sleep stage, including rapid eye movement sleep [2]. It can start at any age. As in our case, it can be triggered by sleep deprivation and stress. Abrupt withdrawal from benzodiazepines and selective serotonin reuptake inhibitors seems to also be a possible trigger. Diagnosis is made by the accurate history and testing is usually not required. Differential diagnosis includes seizures as well as primary and secondary headache disorders, since patient localize their symptoms inside the head. However, in headaches disorders, headache persists upon awakening. Our patient suffered from migraine with aura, but the new symptoms she described were very distinct from her typical migraines and not followed by headache. A migraine aura without a headache is also unlikely given the attacks were very brief, lasting only seconds. The management typically consist of reassurance and education about the benign nature of this condition as patient are often concerned about having brain tumor or hemorrhage. Pharmacological treatment is rarely needed. Per anecdotal reports clonazepam, nifedipine, topiramate, and clomipramine were found to be effective. It is unclear if behavioral intervention or relaxation techniques can be can helpful to prevent the attacks.

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Case 9. A Case of Opposites?

9

Rebecca Q. Scott

History

The patient is a 41-year-old female attorney who has always been a light sleeper, especially since the birth of her first child at the age of 32, but experienced no significant compromise in overall functioning, taking over-the-counter (OTC) sleep aids on rare occasion. She presented to the sleep center because of a 3–4 year history of progressively worsening difficulties falling and staying asleep, characterized by brief and/or sustained awakenings, and daytime tiredness and sleepiness that were starting to interfere with her work performance and quality of life. She attributed her symptoms to increased work stress and having 2 young children who sometimes required nighttime attention. Independently, she tried different preparations of diphenhydramine, doxylamine, melatonin, γ-aminobutyric acid (GABA), valerian root and magnesium, which were either ineffective or left her feeling sedated. When her insomnia symptoms persisted even after her work stress resolved and her children were sleeping through the night, she consulted with her primary care physician (PCP), which cleared her medically. She had trials on zolpidem 5–10 mg, zolpidem CR 6.25 mg, eszopiclone 3 mg, trazodone 50 mg, suvorexant, zaleplon 10 mg (upon waking in the night) and clonazepam 0.25–0.5 mg, which were either ineffective, lost effectiveness after a few weeks or resulted in side effects (next day sedation; complex sleep related behaviors with zolpidem). She was then referred to the sleep center.

Sleep-related symptoms Rare snoring reported by her husband; she endorsed occasional restlessness during sustained awakenings and infrequent episodes of sleep paralysis while in college and law school; there was no history suggestive of restless

R. Q. Scott (✉)
Department of Neurology, NYU Langone Comprehensive Epilepsy Center-Sleep Center, NYU Langone, New York, NY, USA
e-mail: rebecca.scott@nyulangone.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_9

legs syndrome (RLS), a non-REM or REM sleep parasomnia (except for the above mentioned episodes of sleep paralysis), cataplexy or hypnagogic or hypnopompic hallucinations

Medical/Surgical/Psychiatric History Self-described "type A" personality; "worrier" with tendency toward anxiety; otherwise unremarkable

Medications Multivitamins

Social History Born and raised in New York City; partner in a law firm; married with 2 sons (ages 8 and 6); drinks 2–3 cups of coffee qAM; 1–2 glasses of wine 1–2×/week; exercises 3–4×/week; non-smoker; no drug history

Examination

- Body mass index (BMI): 21.3 kg/m^2
- Neck circumference: 13 in.
- Vitals: RR: 16, HR: 68 bpm, BP: 110/70

General physical neurological and mental status examination: cooperative, alert and oriented in person, place, time and situation; mood was euthymic; affect was of full range and congruent with mood; thought process was logical, linear and goal directed

Investigations/Studies

Blood Work complete blood count, comprehensive metabolic panel, thyroid function tests and iron panel were all within normal limits.

Sleep Diary

Differential Diagnosis

- Circadian Rhythm Disorder, irregular sleep/wake type
- Psychophysiological Insomnia
- Insomnia due to anxiety
- Periodic Limb Movements in Sleep

Discussion and Management

Her sleep diaries are notable for variable sleep/wake times and excessive amounts of time in bed, common initial coping strategies amongst insomnia patients who believe a longer time in bed will increase sleep and relieve exhaustion. She was also napping daily during her commute to and from work and while reading to her children before bedtime (see Fig. 9.1a).

Initial interventions focused on behavior modifications to address sleep-incompatible behaviors, stabilize her sleep schedule and reduce her time in bed [1]. Following an explanation of the rationale for suggested behavior modifications, the initial agreed upon treatment plan included: limiting naps, avoiding melatonin inhibiting screens the hour before bed and during the night, reading a paper book if she awakened in the night and had trouble returning to sleep, maintaining a consistent sleep schedule, limiting time in bed to 7.5 h/night and getting 10–15 min of direct sunlight exposure within the first 2 h of waking up. She was also prescribed zaleplon 10 mg to use up to 2 times a week if needed to return to sleep.

After initial difficulties reducing naps and limiting her time in bed to 7.5 h, she made significant progress and her insomnia resolved. Due to persistent daytime

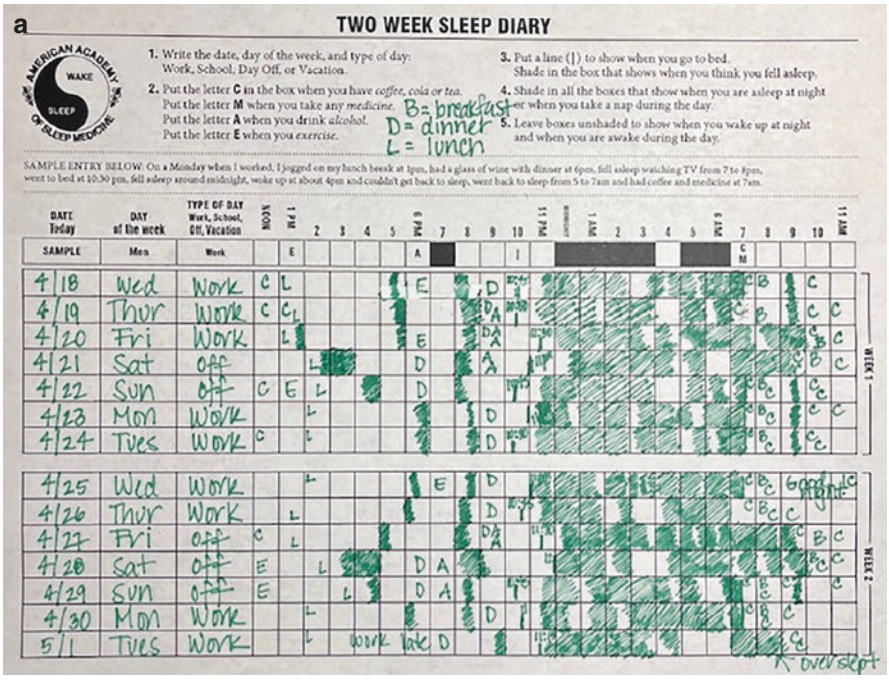

Fig. 9.1 (**a**) Before behavioral treatment. (**b**) After behavioral treatment. B = breakfast; C = caffeine; L = lunch; E = exercise; D = dinner; A = alcohol; I = in to bed; Shaded Area = estimated sleep

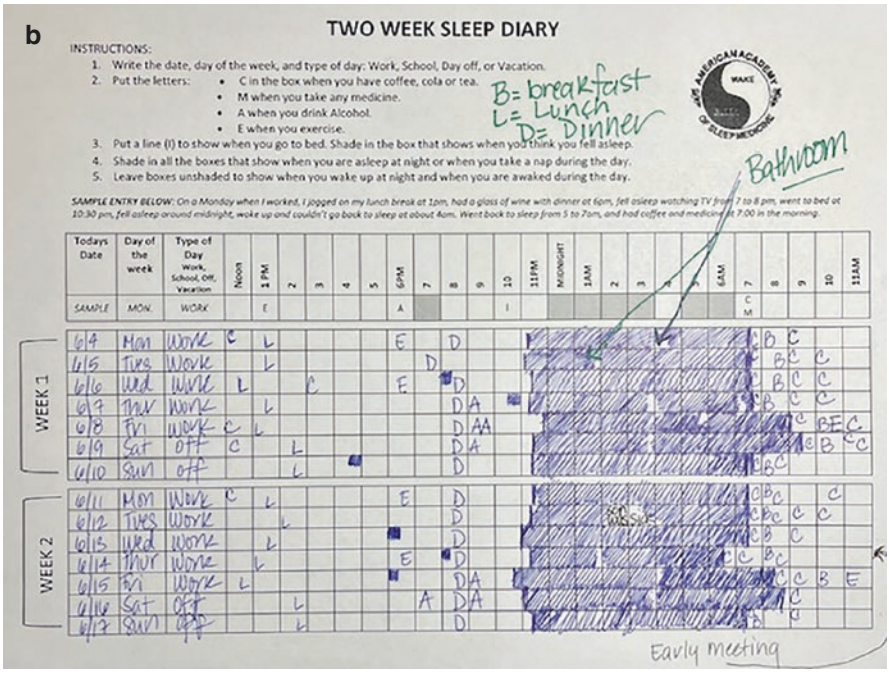

Fig. 9.1 (continued)

sleepiness and tiredness despite improved sleep quality, we increased her time in bed to 8 h/night; however, she reported ongoing difficulties with focus and could occasionally doze when sedentary for sustained periods. Given her history of snoring, home sleep testing was recommended to rule out sleep apnea as a contributing factor to her daytime symptoms. When apnea was ruled out, her PCP recommended trials on antidepressant medications in case an underlying mood disorder could explain her symptoms. Although she did not feel particularly depressed, she agreed to this approach because of increased anxiety and distress about the impact of her symptoms on her quality of life. She tried and failed (due to side effects or lack of benefit) four trials of antidepressants.

When she returned in follow up, she reported continued resolution of the insomnia but felt "overwhelmed" and discouraged by her exhaustion and inability to "keep up" with family and work responsibilities. She started weekly therapy as a result.

Given her clinical presentation and progress, the historical belief that her daytime symptoms, which she described as "tiredness, sheer exhaustion, feeling drained, hitting a wall and overwhelmed" were secondary to insomnia was discarded. Further probing revealed that in addition to the exhaustion, she also

experiences frank sleepiness, finding it hard to stay awake when sedentary for extended periods. To compensate, she requested a standing desk at work, avoided sitting during her commute and engaged in other coping strategies such as chewing gum during meetings.

Although tiredness is common with insomnia, given that daytime sleepiness is far less common [2], we recommended an in-lab polysomnography (PSG) followed by a multiple sleep latency test (MSLT). Surprisingly, those study results revealed pathological sleepiness consistent with central nervous system hypersomnia. The diagnosis surprised her given her history of insomnia; however, she agreed to a trial on modafinil and achieved significant and satisfactory benefit with 100 mg qAM and an additional 50 mg in the early afternoon as needed. At her 1 month follow up she reported that treatment was "life changing" and feeling "as if a veil I didn't know existed was lifted." Her sleep related symptoms continued to be well-managed 3 years later.

Investigations/Studies (Following Resolution of Insomnia)

Home sleep test (HST) Negative for obstructive sleep apnea (OSA) with a total apnea/hypopnea index (AHI) of 0.6/h, supine AHI 1.6/h; minimal oxygen saturation of 92%.

PSG/MSLT She was not taking any medication. Her 2-week sleep diaries prior to testing revealed a consistent sleep/wake schedule with an average nightly sleep time of ~8 h (see Fig. 9.1b). The PSG demonstrated well-consolidated sleep with no abnormalities; all sleep stages were achieved; sleep architecture was normal. The MSLT revealed pathological sleepiness with a mean sleep latency of 3.5 min; there was no slow wave or REM sleep (see Table 9.1).

Table 9.1 Polysomnogram (PSG) and Multiple sleep latency (MSLT) data

		MSLT results		
PSG results		Nap time	Sleep onset latency	Sleep stage
Total sleep time	493 min	7:45 am	2 min	I, II
Sleep Efficiency	96.9%	9:45 am	3 min	I, II
Sleep onset latency	2 min	11:45 pm	3 min	I, II
REM onset latency	75 min	1:45 pm	4.5 min	I, II
Stage I sleep	4%	3:45 pm	5 min	I, II
Stage III sleep	20.7%			
REM sleep	25.1%		Mean sleep latency: 3.5 min	
Arousal Index	7.4/h			

Final Diagnosis

Psychophysiological Insomnia

Central Nervous System Hypersomnia

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Case 10. Mom Knows Best: No So Transient

10

Rasik Shah

History

The patient was a baby boy born by 32-years-old mother Gravida 2 Para 0 at full term by normal spontaneous vaginal delivery with birth weight of 3390 g with Apgar 7 at 1 min and 8 at 5 min. He had weak cry and hypotonia at birth. Mom was a known case of autoimmune myasthenia gravis (MG) with antibodies against acetylcholine receptor (AChR). She had recent exacerbation of her MG requiring treatment with Intravenous Immunoglobulin only. No systemic steroids were given. She was on pyridostigmine 30 mg three times a day and thyroxine during labor. Due to hypotonia and ptosis noted at birth with a maternal history of MG, he was diagnosed with transient neonatal myasthenia gravis (TNMG). Because of severity of clinical symptoms, his blood was tested for antibodies against AChR which confirmed the diagnosis. He was treated with neostigmine and pyridostigmine which he did not tolerate, developing bradycardia. He required respiratory support in the form of nasal continuous positive airway pressure (CPAP) and oxygen by nasal cannula during the neonatal period and required nasogastric feeding. He was sent home on modified breast and bottle feeding after prolonged stay for 35 days. No polysomnogram (PSG) was done during his stay in neonatal intensive care (NICU). Mom monitored his pulse oxygen and noted frequent desaturation during sleep and hence referred to the sleep specialist.

R. Shah (✉)
Department of Pediatrics, NYU Grossman School of Medicine, Hassenfeld Children's Hospital, New York, NY, USA
e-mail: rasik.shah@nyulangone.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_10

Examination

At first exam at age of 3 months, mom came with few videos recording of episodes in sleep which showed fast eye movements consistent with REM stage of sleep, snoring and desaturation in the upper 80s, thus confirming clinical impression of significant obstructive sleep apnea (OSA) during REM sleep. He was getting tired during feeding and hence getting small amount (60 mL instead of 120 mL) of frequent feedings (every 2 h instead of 4 h) including in sleep. He choked when he tried to take more volume. Hence, mom was strict with feeding volume and precaution. During office visit, he got tired with 5–6 sucks and started retraction and portable carbon dioxide (CO_2) monitoring went up from 30 to 38. He recovered quickly on stopping feeding. He did not have head control (expected by 2 months) and had drooping of eye lids. At 6.5 months, there was no drooping of eyelids, improved head control and he tried to seat with support. Also, choking was less frequent than before. His pulse oxygen was normal when he slept in prone position. But in supine position, it decreased to 91–94%. His other mental developmental milestones were good. He was gaining weight at a normal pace.

Investigations

Swallow study done at age of 7 days
Findings:

- First swallow: Thin liquid by level 1 nipple, recumbent position. Severe oral delay and mild swallow trigger delay.
- Second swallow: Thin liquid by level 1 nipple, upright position. Moderate oral delay and mild swallow trigger delay. Nasopharyngeal regurgitation.
- Third swallow: Thin liquid by level 2 nipple, upright position. Moderate oral delay and mild swallow trigger delay. Nasopharyngeal regurgitation.

Impression:

1. No aspiration observed.
2. Moderate to severe oral delay and mild swallow trigger delay as described.
3. Nasopharyngeal regurgitation.

Lab results for AChR antibodies are shown in Table 10.1.

ECHO: done at age of 10 weeks: normal.

PSGs done at age of 4 and 7.5 months are shown in Table 10.2.

Table 10.1 Acetylcholine receptor antibodies over time

Name of test	Test date 03/2021	Test date 01/2022	Interpretation Negative	Interpretation Indeterminate	Interpretation Positive
ACh receptor Blocking Ab	74%	0%	0–26%	27–41%	≥42%
ACh receptor Binding Ab	24.9 nmol/L	0.04 nmol/L	0.0–0.4 nmol/L		≥0.5 nmol/L
ACh Modulating Ab	89%	1%	0–45		≥46%
Muscle Specific Tyrosine Kinase		0	0–0.3 nmol/L		≥0.04 nmol/L

Ach = acetylcholine; Ab = antibodies

Table 10.2 Polysomnography data over time

Polysomnogram	4 months	7.5 months
AHI-total	15.9	4.6
AHI: REM sleep	20 (all supine)	9.2 (supine 10.1/h)
AHI: Non-REM sleep	12.2	2.5
Pulse oxygen: 92–96%	1.2%	0.9%
Pulse oxygen: <92%	0.5%	0.1%
REM sleep %	47.7%	31.3%
PLMS	6.8%	0
CO_2 > 50 mmHg	0%	0%

AHI = apnea-hypopnea index; PLMS = periodic limb movements of sleep; CO_2 = carbon dioxide

Diagnosis

Transient neonatal myasthenia gravis with OSA, improving with time.

Discussion

Transient neonatal myasthenia gravis (TNMG) is a neuromuscular junction disorder secondary to trans-placental transfer of maternal IgG antibodies again AChR [1]. Normally, such antibodies get degraded and disappear from the body fast, around 4 months [1]. Most important issue for TNMG is risk for aspiration/choking during feeding. Hence extreme precaution is required during feeding. As managed in this case, small frequent feeding is advised [2]. In some cases, the infant may need gastric tube feeding. Other major issue is difficulty in breathing/respiratory distress. Normally, it is managed by supportive care like nasal CPAP or supplemental oxygen as needed [2]. Medications like neostigmine and pyridostigmine are

reserved for the severe cases such as this one in order to help in feeding and breathing [2]. The medications are known to produce significant side effects, more severe being cardiac side effects such as bradycardia and cardiac arrhythmias [2]. Hence, usually conservative approach is done especially if the child cannot tolerate the pharmacological treatment. As hypotonia is primary problem, it gets worst in REM sleep due to its associated muscle atonia. The obstruction of airway is caused by tongue falling backward, blocking the oropharynx along with atonia of upper airway muscles. Often, caregiver learns and tries to keep babies in prone or side position during sleep. This position prevents obstruction of upper airway. The recovery period depends on the original titer of those three antibodies [1] as shown in Table 10.1. This condition affects skeletal muscles only [2] and the brain function is not affected. Thus, such patients' response to desaturation is appropriate and fast, making frank apnea rare. Also, for the same reason, the severity of desaturation is not bad as shown in the Table 10.2. Always, question arises if to treat such patients with PAP therapy or not. As most of infants fight with PAP therapies and cry, thus exhaust their muscles, often conservative approach is the best approach. It avoids midfacial hypoplasia secondary to compression of bridge of nose from use of PAP therapy. Prone and side position is an alternative approach worth considering especially if family is reliable. Caregivers prefer this approach though most physicians are not in favor of prone positioning due to risk for sudden infant death syndrome (SIDS)/apparent life threatening episode (ALTE)/brief resolved unexplained episode (BRUE). In such situation, family should be provided with pulse oximetry to monitor the condition. It must be used during all sleep time including naps.

Family must be provided with list of medications to be avoided, for example, aminoglycosides, macrolides (like azithromycin), fluoroquinolones, beta blockers, procainamide, quinidine, neuromuscular blocking agents and magnesium [2].

It is also important to inform the mom that her subsequent babies are at higher risk of developing TNMG [1].

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Case 11. Two Faces of the Medallion

11

Nida F. Tascilar and Carlos H. Schenck

History

A 76-year-old retired, highly-educated industrialist man with coronary heart disease, diabetes mellitus type 2, silent cerebral ischemia and depression was accepted to our out-patient sleep center with his family in February 2019 with the complaint of abnormal nocturnal behaviors. The family informed that the patient was shouting loudly, behaving as if quarreling with someone, while he was sleeping within that fortnight. The patient reported that he was having dreams involving drowning in the sea, fighting for his life, along with trying to escape from a flood. They told that he might have fallen out of bed in one of these episodes, due to finding him on the floor near his bed. Six months before, a neurologist prescribed an acetylcholinesterase inhibitor (AEI), rivastigmine patch 10 cm^2 for his forgetfulness and irritability, which he refused to use until recently. At presentation, he could still do shopping with the help of a list, and play cards/backgammon with his cronies. Two months before our encounter, his family observed that he had had some behavior changes, such as becoming more affectionate, more generous and extravagant. Due to this behavior change, he had been persuaded to use rivastigmine transdermal patch 10 cm^2 regularly. He had been using it for the past 3–4 weeks before presentation.

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N. F. Tascilar (✉)
Department of Neurology and Electroneurophysiology and Sleep Laboratory, Camlica Medipol University Hospital and Istanbul Medipol University Medical School, Istanbul, Turkey

C. H. Schenck
Department of Psychiatry and Minnesota Regional Sleep Disorders Center, Hennepin County Medical Center and University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: schen010@umn.edu

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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He had been on escitalopram 10 mg/day since 2016. Other than snoring and leg movements during sleep, he had no other sleep complaints nor daytime sleepiness. Additionally, he did not have any visual or auditory hallucinations nor delusions. There was no past history of parasomnia.

Examination

Other than absence of Achilles reflexes, neurological examination (including extrapyramidal system) was normal. Mini-mental state examination was 24 out of 30: the only decline was in orientation (6/10) and recognition (1/3). Body mass index (BMI) was 23 kg/m^2, neck circumference was 39 cm and Friedman tongue position was IIa.

Investigations/Studies

LDL-cholesterol—143 mg/dL—, fasting blood glucose, kidney, hepatic and thyroid function tests, electrolytes, vitamin B12, folic acid, ferritin and complete blood count were within normal limits. Cranial magnetic resonance imaging (MRI) showed minimal cerebellar atrophy with non-specific T2A hyperintense lesions. A full-night polysomnography with 24 channel EEG was performed while the patient was on rivastigmine. It was concordant with obstructive sleep apnea (OSA) and periodic limb movements of sleep (PLMS) (Table 11.1). He had 8 REM sleep periods with a duration ranging from 1 to 17 min (Fig. 11.1a). In 5 of them, he had REM sleep behavior disorder (RBD) episodes ranging in duration from 20 to 105 s. RBD episodes consisted of meaningless shouting, whispering and gesticulating movements (as if he was pushing something, trying to put something to his mouth, trying to catch or take something with his fingers) (see Video 11.1). REM sleep without atonia (RSWA) was observed throughout REM sleep (Fig. 11.1b, c). There was also an extraordinarily high PLM index of 151/h.

Table 11.1 A full-night polysomnography with 24 channel EEG parameters of the patient

Parameters	Results
Time in bed	390.6 min
Total sleep time	280 min
Sleep period time	340.9 min
NREM Sleep latency	0 min
REM sleep latency	14 min
Sleep continuity index (%)	82.4
Sleep efficiency index (%)	71.9
N1 (%)	60.9
N2 (%)	26.4
N3 (%)	0
R (%)	12.7
Apnea hypopnea index	51.7/h
Respiratory disturbance index	52.1/h
Minimum oxygen saturation	83%
Average oxygen saturation	94%
Total arousal index	37.8/h
Respiratory arousal index	8.6/h
Leg movement arousal index	25.3/h
Spontaneous arousal index	3.9/h
Number of periodic limb movements	706
Periodic limb movement of sleep index	151.3/h
Epileptic activity in EEG	None

The results of the detailed neuropsychological tests which were applied in neuropsychology laboratory showed impairment primarily in memory function along with partial impairment in executive and with no impairment in visual-spatial functions. In the "forgetfulness and behavioral disorders clinic", he was diagnosed as probable Alzheimer's disease (AD) dementia according to 2011 guidelines for AD. Clinical dementia rating scale was at Stage 1. Scores of geriatric depression scale and neuropsychiatric inventory were concordant with a definite depression.

Dopamine transporter (DAT) single-photon emission computerized tomography (SPECT) and metaiodobenzylguanidine (MIBG) scans were not ordered because they were not available in most hospitals and lack of insurance coverage for these expensive tests.

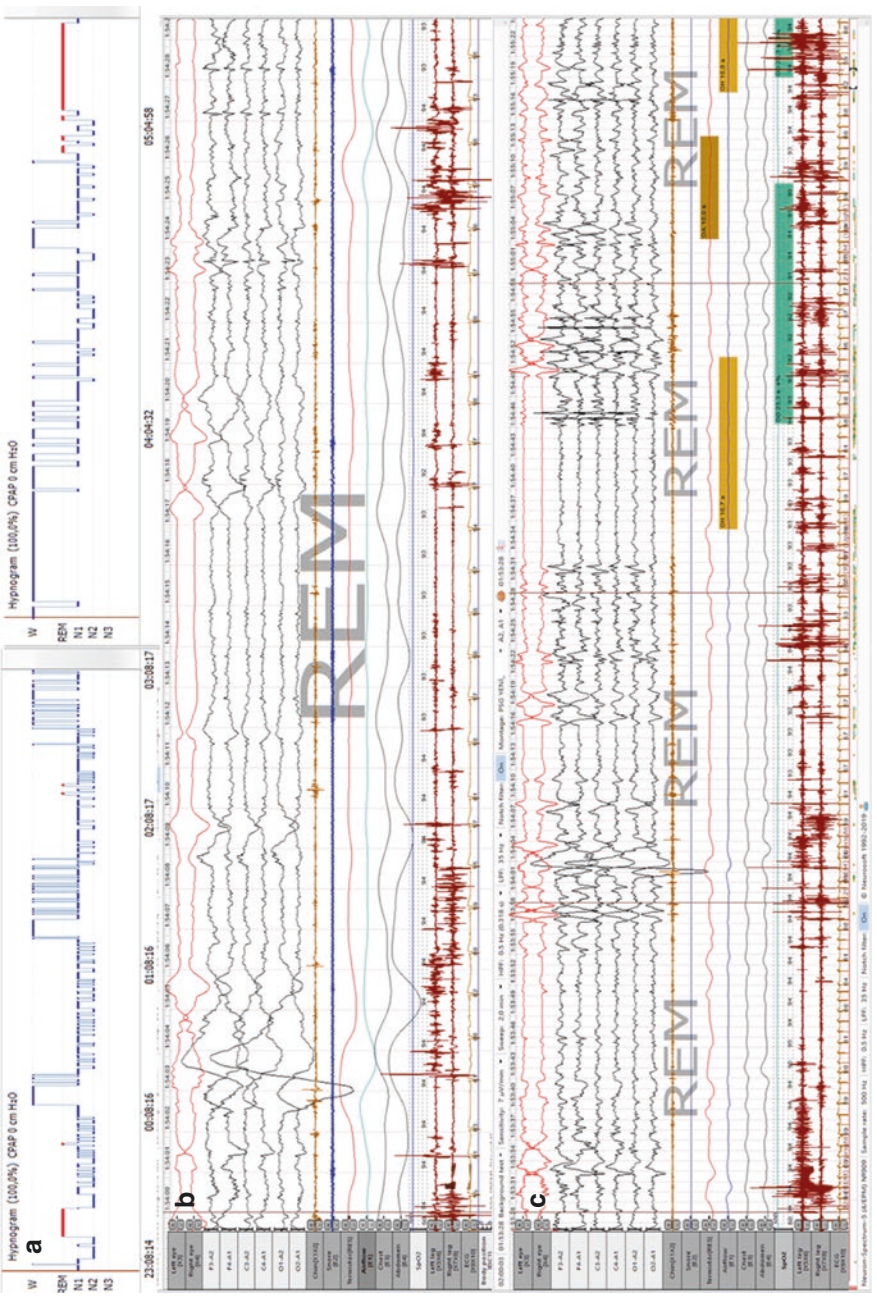

Fig. 11.1 Hypnogram and epochs of REM sleep. (**a**) Hypnogram of the patient showing the distribution of sleep stages; (**b**) 30-s epoch of REM sleep, presenting REM without atonia in nocturnal PSG; (**c**) 2-min epochs of REM sleep, presenting dense REMs and REM without atonia

Differential Diagnosis

Secondary RBD in association with dementia (AD/DLB) or drug use (AEI)

Discussion and Management

RBD is one of the most frequent chronic parasomnias among elderly individuals with neurodegenerative disorders, especially in α-synucleinopathies, but it is also present in some cases of non–synuclein-mediated neurologic disorders. Therefore, the presence of RBD or RSWA in a patient with dementia favors the diagnosis of dementia of Lewy bodies (DLB), but does not completely rule out the diagnosis of AD or progressive supranuclear palsy (PSP). They have been sporadically reported in long-term AD. However, in postmortem studies of the brains of those with AD with RBD and/or RSWA, lesions of AD (Aβ amyloid) and Lewy bodies frequently coexist. It has been suggested that the presence of RBD and RSWA in neurodegenerative disorders may be related more to the localization of the degeneration than to a specific type of neuronal degeneration [1].

Thus, we cannot exclude completely that this case with probable early stage AD showing RBD and RSWA may also show Lewy bodies at autopsy.

Furthermore, in our patient RBD emerged acutely. RBD triggered in this manner could occur as an incidental phenomenon within the context of other subacute or acute-onset disorders, such as medications, drug/alcohol withdrawal, focal insults at brain stem level, etc. Although AEIs, being suggested to have a facilitator effect on the pedunculopontine nucleus, are one of the drugs of choice in the treatment of patients with RBD with and without parkinsonism, they were also reported to cause acute RBD in two patients with AD [2]. This could be due to the facilitator effect of these drugs on brainstem reticular neurons (such as shortening of REM sleep latency, which was also shown in our patient) or the brain substrate in AD.

Because of the close temporal relationship between the onset of the regular AEI usage and the onset of RBD, rivastigmine was suspected to be the cause of acute RBD with this patient.

He was treated with a rivastigmine transdermal patch 15 cm^2; melatonin 3 mg; escitalopram 10 mg/day; and risperidone 1 mg/day. Nasal continuous positive airway pressure (CPAP) with a 12 cm of water pressure was initiated for his OSA. Although RBD was minimally improved with melatonin, clonazepam was not an option because of OSA.

To this date, he continues with regular follow-up visits, and has not exhibited parkinsonism, visual hallucinations, or fluctuating cognition. So in conclusion, the RBD in this patient could be due to AEI usage and/or could be a feature of evolving DLB which could become manifest during long-term follow-up, which could include combined use of DAT SPECT and MIBG scans, myocardial scintigraphy, or upon postmortem analysis.

Final Diagnosis or Most Likely Diagnosis

REM sleep behavior disorder due to acetylcholinesterase inhibitor use.

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Case 12. Watchful Waiting

12

Matthew T. Scharf and R. Nisha Aurora

History

A 62-year-old man presents with several years of snoring and, more recently, progressive daytime sleepiness over months. He reports that he has multiple awakenings throughout the night, some of which he recalls being associated with choking/gasping during sleep. He reports a need to urinate 1–2 times/night. There are also reports of witnessed breathing pauses noted by his bedpartner. He feels unrefreshed upon awakening and fatigued throughout the day. He rarely wakes up with a headache. He does wake up with a dry mouth frequently. His Epworth Sleepiness Scale score is 12/24. His sleep schedule is similar on workdays and days off. He has a lights out time of 10:00–10:30 PM, a short sleep latency of a "few minutes", and a final rise time of 6:00 AM. The patient takes a daily nap in his recliner chair for about 15–20 min every afternoon or evening.

His prior medical and surgical histories are notable for gastroesophageal reflux disease (GERD) confirmed on esophagogastroduodenoscopy (EGD), hypertension, hyperlipidemia, chronic rhino sinusitis, and left knee replacement. Family history is notable for coronary artery disease, with both his father and older brother having

M. T. Scharf
Department of Neurology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
e-mail: matthew.scharf@rwjms.rutgers.edu

R. N. Aurora (✉)
Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
e-mail: ra768@rwjms.rutgers.edu

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suffered myocardial infarctions. He is a nonsmoker. Alcohol consumption is less than one drink per week. He has two caffeinated beverages in the morning.

His medications include omeprazole, amlodipine, losartan, atorvastatin, fluticasone nasal spray.

Examination

On physical exam, his blood pressure is elevated at 151/100 mmHg, pulse = 96 beats/min, afebrile, oxyhemoglobin saturation on room air = 96%; height = 72 in., weight = 264 lb; body mass index (BMI) = 35.9 kg/m^2. His modified Mallampati score is 3; cardiac, pulmonary, extremity, and neurological exam are all normal.

Investigations

Due to a high suspicion of sleep-disordered breathing, i.e. obstructive sleep apnea (OSA), he is scheduled for an in-laboratory split-night study. The baseline/diagnostic portion of the study demonstrates severe OSA with an apnea-hypopnea index (AHI = 64.6/h) using the American Academy of Sleep Medicine (AASM) criteria of hypopnea scoring (i.e., 3% desaturation or arousal). The oxygen saturation nadir was 78%, and for ~41 min of the 143 min sleep time during the diagnostic portion the oxygen saturation was <90%. Positive airway pressure (PAP) therapy was initiated at a pressure of 4 cm H_2O. Central respiratory events emerged and persisted for the remainder of the titration portion of the study—pressure range of 4–10 cm H_2O. The AHI on PAP therapy ranged from 18.1 to 98.9/h—all central apneic events. Figure 12.1 is a sample of the findings from the baseline portion of the study (Panel A) and after initiation of PAP treatment (Panel B). The differential diagnoses included concurrent OSA and central sleep apnea (CSA), secondary to another CSA disorder such as congestive heart failure or a medication or substance. However, in the setting of concurrent OSA and CSA, the central AHI is ≥5 events/h during the diagnostic polysomnogram (PSG). Given that there were no central respiratory events during the diagnostic PSG, *a diagnosis of treatment emergent central sleep apnea (TECSA) was made*. The patient was prescribed auto titrating PAP therapy, as he was not able to return for a full titration PAP.

At the patient's follow up visit ~4 months later, he reports that he is no longer snoring, that his sleep is less fragmented, and that he wakes up refreshed. The patient's PAP adherence reports demonstrate an average adherence of 6 h and 38 min/night. PAP therapy was used every night and adherence of ≥4 h/night was seen 93% of the time. His 95th percentile pressure was 9.8 cm H_2O. His leak was 4.2 L/min, suggesting a good seal with the mask interface. His overall AHI was 6.5/h (decreased from 64.6/h). His central apnea index (CAI) decreased to 4.1 events/h, and his obstructive respiratory event index 1.4/h, suggesting that his OSA was treated and TECSA had resolved.

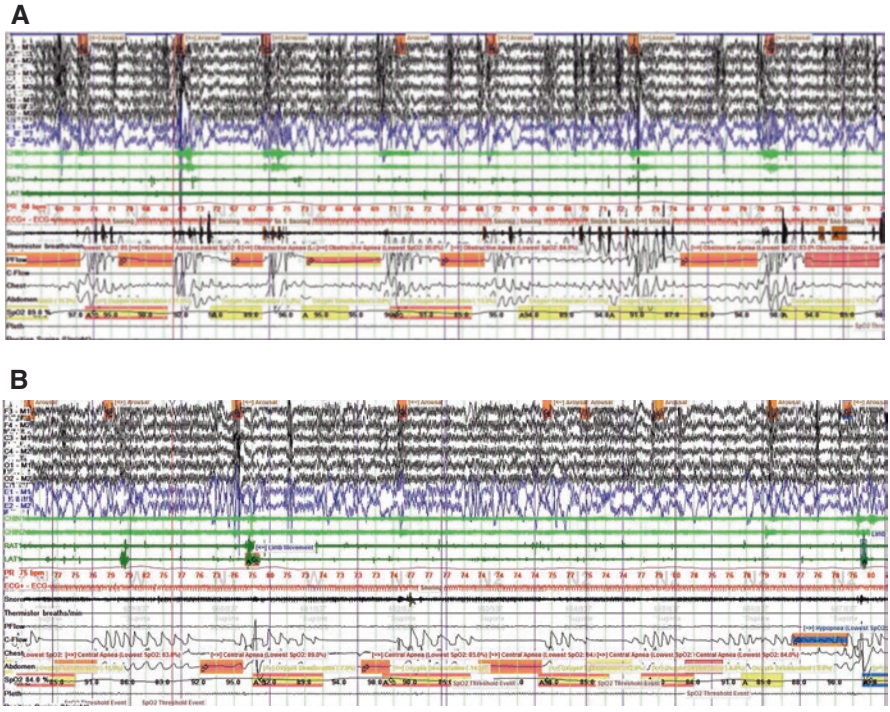

Fig. 12.1 (**A**, **B**) Split-night in-laboratory study

Final Diagnosis

Obstructive sleep apnea with treatment emergent central sleep apnea

Discussion

TECSA is defined by the following criteria according to the International Classification of Sleep Disorders—Third Edition [1]: (1) the presence of predominantly OSA on diagnostic PSG; (2) resolution of obstructive events with PAP therapy without a backup rate; (3) the emergence or persistence of central respiratory events on PAP therapy with a central AHI ≥5/h and central events are ≥50% of the total apneas and hypopneas; and (4) the CSA is not better explained by another CSA disorder. While, the overall prevalence of TECSA is estimated to be between 5% and 20%, there is uncertainty regarding the true prevalence given that central and obstructive hypopneas are not differentiated on most sleep studies. Demographic factors associated with TECSA include male sex, older age, lower body mass index,

congestive heart failure, coronary artery disease, and opioid use. Moreover, baseline PSG and PAP titration factors can also be associated with TECSA. For example, more severe OSA, a high baseline CAI or mixed apnea index, high arousal index, a split-night study, aggressive PAP titration, high residual AHI, and lower totals sleep time and/or sleep efficiency are reported to be associated with TECSA. The most common treatment of TECSA is watchful waiting. Between 54% and 86% of TECSA cases resolve within 2–3 months of PAP use [2]. This approach requires close monitoring of symptoms, encouraging PAP adherence, and optimizing treatment of comorbid conditions associated with CSA (e.g., heart failure, opioid use). For those with persistent symptoms or an AHI ≥15/h on follow-up, alternate therapies such as bi-level pap therapy in spontaneous timed mode (BPAP-ST) or adaptive servo-ventilation (ASV) can be considered.

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Case 13. Measure Twice, Cut Once … or Not at All …

13

Boris Chernobilsky

History

A 63-years-old male who presented with profound sleepiness that has been worsening over the past several years. The patient had fallen asleep driving and had to hire a driver. His profound sleepiness has also impacted his work as a trial attorney and affects all aspects of his life. The patient has an extensive medical and surgical history. At age 48, he was diagnosed with tonsillar carcinoma and underwent tonsillectomy and chemotherapy and radiation. At age 61, he was involved in a motor vehicle accident and required a fusion of C4-C6. This needed to be revised 8 months later and had further fusion at C2 to L3 level. These two major factors led the patient to developing aspiration pneumonia, bronchiectasis, hoarseness, dysphagia and chronic musculoskeletal and neurologic pain. He has been taking multiple medications, including buprenorphine patch, oxycodone and pregabalin. The patient presented to his pulmonologist and was diagnosed with severe obstructive sleep apnea (OSA) and prescribed Bi-level positive airway pressure (Bi-level PAP). The patient could not tolerate his titrated settings of 15/10 cm H_2O with 4 L/min oxygen via full face mask. Lower settings did not relieve his obstructions or somnolence. He presented for surgical consultation inquiring about hypoglossal nerve stimulation (HNS) implant.

Examination

The patient is a well-developed, well-nourished male appearing in discomfort from his head positioning. His vital signs were stable and his body mass index (BMI) was 22.5 kg/m^2. His voice was hoarse without dysarthria. Mild nasal septal deviation

B. Chernobilsky (✉)
Otolaryngology - Head and Neck Surgery, NYU Langone Health, New York, NY, USA

Internal Medicine, NYU Langone Health, New York, NY, USA
e-mail: boris.chernobilsky@nyulangone.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_13

was noted with mild flow restriction on the right. Oral cavity exam revealed dry mucosa, scarring in bilateral tonsillar fossae, tonsil grade 0, Friedman tongue position 2. There was left tongue atrophy and weakness/paresis. Neck exam is significant for severe atrophy of almost all anterior cervical musculature including sternocleidomastoid, sterno- and thyrohyoid muscles. Well healed anterior cervical fusion and posterior C2-L3 scars. Patient had severely decreased cervical range of motion. Skin showed typical post-radiation thickening and bronzing.

Diagnostic Studies

Polysomnogram (PSG):

Apnea/hypopnea index (AHI) 45.2/h
Oxygen desaturation index ODI) 47.6/h
O_2 < 88% 64% (274 min) <80% 22.3% (22.3 min) <70% 9.1% (38.9 min)
100% of sleep was supine. Most severe desaturations during REM sleep stage.

Flexible Nasolaryngoscopic Exam:

Radiation changes to torus tubarii and posterior nasopharyngeal wall.
Thick mucus between palate and posterior nasopharyngeal wall.
Mild radiation change to tip of epiglottis. No vocal fold excursion with respiration. ~3 mm opening.
Right fold severely paretic, left is fixed.

Differential Diagnosis

Hypersomnolence from medication
Severe obstructive sleep apnea complicated by

1. Bilateral vocal fold paralysis
2. Muscle tone loss secondary to muscle atrophy from spinal fusion
3. Muscle tone loss from post-radiation neuropathy
4. Tongue weakness due to left hypoglossal nerve injury
5. Supine REM
6. Hypoxemia from asthma and chronic aspiration pneumonia and bronchiectasis

Bi-level PAP intolerance due to high pressure, full face mask requirement.

Discussion and Management

The patient had an extremely complicated medical and surgical history. The patient requested HNS but concern about potential injury to the right hypoglossal nerve in the setting of left sided weakness, daytime sedation from medicines as well as the

poor glottal opening due to radiation and spinal fusion were of great concern. Tracheostomy was discussed with the patient as a simpler and more effective solution given the significant issues complicating this patient's OSA. In order to better understand this patient's pathophysiology and candidacy for HNS, the patient was taken to the operating room for a drug induced sleep endoscopy (DISE) which showed the vellum had complete anteroposterior collapse, the oropharynx had none, the tongue showed profound complete anteroposterior collapse and the epiglottis with partial anteroposterior collapse secondary to the tongue. Laryngeal opening with relaxation due to sleep was slightly greater than on awake flexible exam. Most notable was the extreme jaw laxity and near complete mouth opening during sleep. There was significant improvement at all levels with mouth closure and near resolution of obstruction but not desaturation with minor jaw advancement.

Based on the findings of the sleep endoscopy, recommendations were made for a chin strap, Dreamwear® nasal mask (Philips) and changing the patient to an auto positive airway pressure setting (APAP). The patient was able to tolerate the therapy, AHI normalizing to 4/h on average with resolution of his daytime somnolence and able to sit through dinner without falling asleep. He felt safe enough to start driving on his own as well. Surgical planning was obviously postponed.

DISE is a powerful technique that helps to elucidate the site and character of a patient's obstructive sleep apnea and an invaluable tool not just in surgical planning but in management of PAP and mandibular advancement devices. The patient's most significant issue turned out to be muscle tone given the tongue weakness, post-radiation neuropathy and muscle atrophy. Bi-level PAP pressures and need for tightening of a full face mask to overcome the completely obstructed tongue and weight of the mandible were simply too much for this patient to tolerate. DISE allowed for an elegant non-surgical solution in this case. Multiple studies have shown significant changes in surgical decision making following DISE, with one systematic review finding an aggregate rate of 50% compared to treatment decision based just on awake examination. DISE should be strongly considered in all complicated, non-CPAP complaint OSA patients, even potentially poor surgical candidates, to help guide medical and surgical decision making [1, 2].

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Case 14. Snoring Vividly

14

Andrew J. Westwood

History

A 54-year-old man presents to the outpatient sleep clinic after injuring his wife on several occasions during his sleep. He has frequent nightmares and recalls disturbing dreams of being held down under water. He wakes up with his arms flailing and gasping for air. On several occasions he has struck his wife and these events occur often at the weekends in the early morning hours. In the last year he has gained 20 lb and began to snore loudly. His sleep pattern has remained consistent and he continues to obtain an estimated 7 h of sleep per night though recently he feels unrefreshed in the mornings. He yawns during the daytime but does not fall asleep. His father was diagnosed with Parkinson's disease at the age of 92. He takes amlodipine for hypertension and a daily multivitamin. He does not smoke. He drinks a bottle of wine on Saturday nights and is abstinent during the rest of the week.

Examination

Cranial nerve examination was normal with full visual fields, intact extraocular movements and sharp optic discs. Face was symmetric and tongue protruded in the midline. There were no craniofacial abnormalities and a class III airway on the modified Mallampati scale was observed. Tone, strength and reflexes were normal. Gait was normal and sensation was intact.

A. J. Westwood (✉)
Department of Neurology, Maidstone and Tunbridge Wells NHS Trust, Kent, UK
e-mail: andrew.westwood1@nhs.net

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_14

Investigations

Complete blood count, basic metabolic panel, thyroid stimulating hormone, ferritin and liver function tests were normal. A home sleep apnea test revealed a respiratory event index of 4/h. In-lab polysomnography revealed an apnea hypopnea index (AHI) of 8/h with a REM-AHI of 40/h. Phasic bursts of muscle activity were preceded by apneic events throughout REM.

Differential Diagnosis

Dream enactment behaviour (DEB) can occur from a broad range of causes [1]. It oftentimes comes to the attention of the clinician due to injuries sustained either to the individual or to their bedpartner. Adults with NREM parasomnias may recall some vague dreams or partial recall of behaviours; other conditions such as dissociative disorder, parasomnia overlap disorder and trauma associated sleep disorder also need to be considered. Dream enactment behaviour is also a defining feature of REM behaviour disorder (RBD). Secondary causes of RBD need to be considered such as periodic limb movements or sleep-related breathing disorder that can fragment REM sleep. Idiopathic RBD has been associated with α-synucleopathies such as Parkinson's disease—sometimes as a precursor or as a concomitant feature of the disease and therefore examining the individual for evidence of Parkinsonism is important.

Discussion and Management

A polysomnogram can be helpful to confirm from which sleep stage the behaviours arise or if there is an underlying provoking factor such as medications, limb movements or obstructive sleep apnea. In a history of new onset snoring and weight gain a home sleep apnea test may be a quick and accessible screen to evaluate for sleep related breathing disorder. Many of these devices use simple algorithms for approximate sleep staging or may not provide any sleep architecture information. It is important therefore to ensure that not only the overall AHI is reviewed but the pattern of respiratory events through the night as they may appear more frequently in clusters—either due to an alteration in body position/body:head position or due to shift in sleep stage. If diagnostically this is equivocal or negative then in-lab polysomnography should be obtained.

Obstructive sleep apnea is often worse in REM sleep due to paralysis of the body and reliance upon the diaphragm for ventilation. Alcohol can exacerbate sleep related breathing disorders as well as acutely reduce REM sleep and cause subsequent REM rebound on cessation of alcohol. Fragmentation of REM sleep can trigger reports of nightmares, dreams of choking and drowning, and in some individuals provoke arousal responses sufficient to cause movements. In this individual with recent weight gain and snoring it is important to consider secondary causes of DEB. The

degree of obstructive sleep apnea may be negligible or mild based on the overall AHI. However with details from the in-lab polysomnogram the degree of sleep disordered breathing in REM specifically was severe and associated with myogenic activity. In this individual, treatment with positive airway pressure resolved both the snoring and the DEB allowing the individual to achieve restorative sleep. Another cause of secondary DEB is medication such as selective serotonin reuptake inhibitors [2]. There is some evidence that these are catalysts for the presentation of RBD: when they are removed the behaviours may resolve however the individual may present years later with DEB, at that time without a secondary cause. Clinicians should therefore be mindful that sleep-disordered breathing in these individuals may also be a precipitant in a similar way and should be monitored longitudinally.

Final Diagnosis

Dream enactment behaviour secondary to obstructive sleep apnea

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Case 15. Central Sleep Apnea and Worsening Headaches

15

John G. Park

History

A 25-year-old female without any known medical comorbidities presents with a 10-year history of non-restorative sleep, mild daytime sleepiness with Epworth Sleepiness Scale of 10/24, and concerns of witnessed pauses in her breathing during her sleep. She denies any diplopia, blurred vision, or dysphagia. She reports occasions of non-bothersome exertional and cough-related headaches, which seem to be getting progressively worse.

Physical Examination

Her body mass index (BMI) is 30.5 kg/m^2, neck circumference 35 cm, with Friedman palate position 4. Her neurologic exam was notable only for mild end-gaze nystagmus with some weakness of her lower extremities and hyperreflexia. Her cardiac and pulmonary examinations were normal.

Investigations

Polysomnogram (PSG):

The study was performed at sea level. Sleep efficiency was 81.2%, with relatively normal sleep architecture. Apnea-hypopnea index (AHI) was 155/h, of which 142/h were central apneic events. Mean oxygen saturation of 94%, but nadir of 86%.

Minimal snoring was noted. The pattern was not suggestive of Cheyne-Stokes respiration. There was no evidence of hypoventilation.

Imaging:

J. G. Park (✉)
Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA
e-mail: park.john@mayo.edu

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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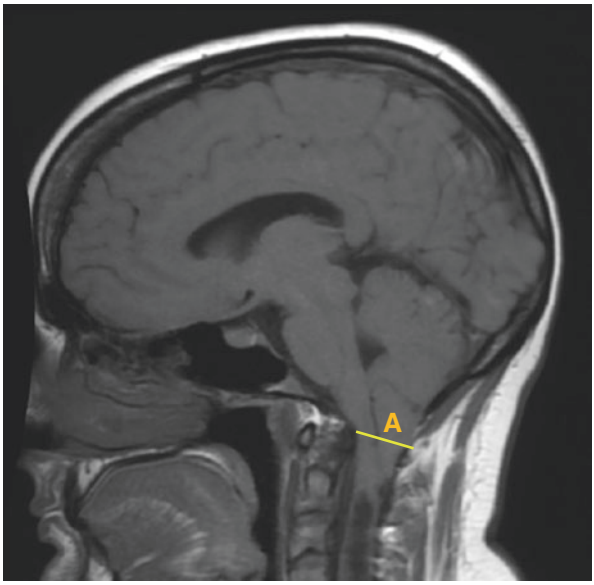

Fig. 15.1 Sagittal brain magnetic resonance imaging (MRI) showing the cerebellar tonsil (A) extending beyond the foramen magnum (dashed line)

Differential Diagnosis

Central sleep apnea (CSA) may be due to high altitude, medications or substances, Cheyne-Stokes breathing, or medical disorders. Another possibility is treatment-emergent CSA (ICSD-3).

Another way to consider differential diagnosis is based on the presence or absence of hypercapnia. If there is associated hypercapnia with CSA, the differential includes congenital central hypoventilation syndrome, primary chronic alveolar hypoventilation syndrome, neurodegenerative disorder, and muscular or peripheral nerve system disorder. In comparison, non-hypercapnic CSA differential includes heart failure (Cheyne-Stokes breathing), high altitude, primary (idiopathic) CSA, or associated with medical conditions: CNS-associated disorders such as Chiari malformation, stroke, brainstem neoplasm, multisystem atrophy, or associated with end-stage renal disease, among others.

Discussion and Management

A magnetic resonance imaging (MRI) of the brain was obtained based on the history of progressively worsening headaches, especially with exertion, and the PSG findings. This revealed an elongated cerebellar tonsil, herniating below the foramen magnum (see Fig. 15.1). This is an example of Chiari I malformation. Of the four subtypes of Chiari malformations, Chiari 1 is the most common [1]. These patients usually present in adolescence or early adulthood. While neurologic examination

may be normal, they often present with symptoms that include headaches (typically exacerbated by physical activity, coughing, laughing, or sneezing), sneeze syncope, nystagmus (typically downbeat), truncal ataxia, hoarseness, vocal cord paralysis, dysarthria, recurrent aspiration, and both obstructive and central sleep apnea, often resulting in hypersomnia. Cognitively, they may have lower intelligence quotient scores and behavioral difficulties. Brain MRI is the best imaging test to confirm the diagnosis. Depending on the severity of their symptoms, they can be managed conservatively with follow-up imaging or decompressive surgery. The benefit of decompressive surgery (e.g., posterior fossa decompression) on sleep-related breathing disorder (SRBD) is clouded by the lack of any rigorous studies [2]. Many case reports suggest partial improvement of their SRBD with some residual SRBD after surgery. Some suggest, however, that further improvement in SRBD may occur with time.

Final Diagnosis

Severe CSA due to Chiari I malformation

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Case 16. "I Am Scared I Will Die from Sleeplessness"

16

Mandana Mahmoudi and Alok Bhatt

History

A 36-year-old woman presented with a complaint of insomnia, reported as a complete inability to sleep. Six years prior to presentation, she began to experience skin symptoms of redness and a burning sensation most prominently felt over the head, neck, and chest. Difficulty sleeping developed alongside these symptoms, but was initially controlled with the use of mirtazapine. However, a year prior to presentation, her sleep worsened somewhat abruptly. This included a reported 6 day period without sleep resulting in an emergency room (ER) visit where she was prescribed clonazepam three times daily along with quetiapine at bedtime. This regiment helped break her cycle of insomnia, according to the patient. She reported this experience as having been very traumatic and expressed that she was fearful that she could die from sleeplessness. She reported that light and temperature changes made her skin condition worse, and she also had heightened tactile sensitivity making it uncomfortable to sleep.

Examination

The patient was of normal habitus with a body mass index (BMI) of 18.5 kg/m^2, and appeared well. Skin examination showed erythema especially involving the face and scalp, with scaling. Mild dermographia was also noted.

M. Mahmoudi (✉) · A. Bhatt
Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, NYU Grossman School of Medicine, New York, NY, USA
e-mail: mandana.mahmoudi@nyulangone.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_16

Investigations

Complete blood count examination showed leucopenia (WBC $2.8 \times 10^3/\mu L$) related to the use of immunosuppressive medication. Electrolytes, urea, nitrogen, and coagulation parameters were normal. Liver function tests showed mild elevation of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) at 48 IU/L and 101 IU/L respectively). Erythrocyte sedimentation rate, creatine kinase, autoimmune panels were normal. 25-hydroxy vitamin D was low (16 ng/mL).

Diagnosis

Circadian misalignment due to lack of light and dark cues, psychophysiologic insomnia related to dermatologic disease.

Discussion

Dermatologic conditions are underrecognized as an association to sleep disorders. This patient's complex dermatologic disease has led to lifestyle modification in the form of light avoidance. However, there is also a significant somatic effect from her disease, which causes her to experience pain resulting in difficulty lying still to sleep. Third, the additional psychologic toll of dealing with a chronic dermatologic condition and the effects of its medical management have led to the development of severe insomnia.

Inadequate diurnal light exposure disrupts the circadian suppression and subsequent release of melatonin, which can result in circadian phase delay, or even misalignment and a non 24 h sleep wake disorder (N24SWD) [1]. Disease related hyperesthesia, including allodynia, may cause discomfort that affects sleep. Medications like mycophenolate mofetil and hydroxychloroquine, used for the management of chronic autoimmune disorders (including in this patient), are well known to cause insomnia as a potential adverse effect. These factors can have a significant psychologic effect on patients. Patients should ensure circadian light exposure and routine physical activity within the limitations of their disease. Melatonin receptor agonists like tasimelteon can be used in the treatment of N24SWD, by timing their dosage to align with dim light melatonin onset (DLMO). Sedative hypnotics or other sleep promoting agents may be useful in an adjunctive role.

Reference

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Case 17. Difficulty Breathing, Difficulty Functioning

17

Daniel A. Barone

History

This is a 36-year-old man with a history of severe fatigue who initially presented from his epilepsy specialist for an evaluation. In December 2019, he first started noticing symptoms, which comprised of pain in his legs for almost a week after he played basketball. Around this time, he went on a vacation which entailed excessive walking, and noticed weakness and pain in his legs again. This led him to the emergency department (ED) presentation to rule out DVT and ultimately brought to the forefront the previously asymptomatic Pompe's disease that he was diagnosed with earlier in life.

Due to his fatigue and the lack of snoring or other signs of OSA, he was scheduled to undergo a polysomnogram (PSG) and multiple sleep latency test (MSLT). The PSG demonstrated 359 min of sleep with 87% sleep efficiency. Apnea-hypopnea index (AHI) was 1/h, respiratory effort related arousals (RERA) index 1/h, with lowest oxygen saturation of 92%. His electrocardiogram (EKG) was unremarkable. Periodic limb movements of sleep (PLMS) were noted 22/h, with arousal index 1/h. Multiple sleep latency test (MSLT) performed the next day showed borderline hypersomnia with a mean sleep latency of 8.8 min, without sleep onset REM periods (SOREMPs); thus was diagnosed as having idiopathic hypersomnia.

He was placed on modafinil at that time and responded well. By March 2020 (several months later), he started receiving enzyme replacement therapy with lumizyme infusions; after 5 months he felt that his symptoms were stable. Upon presentation, he was still not snoring but wife had noted that was "struggling to breathe" at night, and his fatigue was increased despite modafinil 200 mg daily.

D. A. Barone (✉)
Neurology, New York-Presbyterian, Weill Cornell Medicine, New York, NY, USA
e-mail: dab9129@med.cornell.edu

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_17

Examination

This is a thin-appearing, 36-year-old man without distress. Body mass index (BMI) 20.5 kg/m^2, but no further examination was possible as this was done via video visit. However, no gross pulmonary or neurologic abnormalities were noted.

Investigations/Studies

A repeat PSG was performed based on the new breathing complaints. The PSG demonstrated total sleep time of 452 min with sleep efficiency 86%. The AHI was 1/h. Average SaO_2 during wakefulness was 97%. End-tidal CO_2 ($EtCO_2$) was below 50 mmHg throughout the night but the highest reading was 49 mmHg. The lowest SaO_2 was 94%. His EKG was unremarkable. PLMS were noted 15/h, with arousal index of 1/h.

Differential Diagnosis

There were several possibilities noted in this case. One being hypersomnia or fatigue due to Pompe's disease itself. Another was fatigue on account of his impending hypoventilation. Yet another possibility was fatigue due to his anti-seizure medications. Finally, although remote, was the possible sleep disruption caused by borderline abnormal PLMS (although his arousal index was quite low).

Discussion and Management

Pompe disease is a rare autosomal recessive glycogen storage disease that results in accumulation of glycogen in muscle cells resulting in muscular weakness. It is characterized by progressive proximal myopathy, accompanied by respiratory muscle weakness, which may lead to ventilatory failure and, if left untreated, death [1]. Initially, symptoms of sleep disordered breathing (SDB) occur before overt signs of respiratory failure; weakness of the diaphragm leads to nocturnal hypoventilation, which can result in sleep disruption. This impairment in sleep quality can be associated with hypersomnia and worse health-related quality of life. The mainstay of treatment for SDB and respiratory failure in Pompe disease is non-invasive ventilation (NIV), which aims to ensure adequate ventilation, particularly during sleep, and prevent acute hypercapnic respiratory failure. Disease-modifying enzyme replacement therapy (ERT) delays progression of locomotor dysfunction and prolongs life, its effect on respiratory function and SDB remains unclear.

Final Diagnosis or Most Likely Diagnosis

Given his impending hypoventilation, we chose to attempt NIV with average volume-assured pressure support (AVAPS). It allows for the delivery of a fixed tidal volume along with pressure support ventilation. His AVAPS titration study demonstrated a marked improvement in snoring and highest $EtCO_2$ was 43 mmHg. He was placed on this at home and uses frequently. The days following full-night usage are much more productive for him, and the modafinil 200 mg, which had previously become less effective, has resumed its positive impact on his excessive daytime sleepiness/fatigue. He remains stable on this combination as well as regular ERT. Thus, his residual symptoms were due at least partially to worsening Pompe disease-related hypoventilation, which upon being addressed stabilized his quality of life.

Reference

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Case 18. "MAD That Stops Breathing"

18

Saif Mashaqi and Taaha Rafi

History

This is a 67-year-old male with a past medical history of coronary artery disease, aortic stenosis, and high-degree atrioventricular (AV) block (status post pacemaker placement) who presented with complaints of excessive daytime sleepiness, vivid dreams, thrashing and kicking at night. His wife witnessed loud snoring but did not witness any apnea, gasping, or snorting. He denied any headaches in the morning. Sometimes, he woke up with dry mouth. His routine bedtime is around 9 PM and wake up time is 5 AM. He denied any difficulties falling asleep and mentioned two awakenings during the night. He takes two naps during the day (each for about 45–60 min). He endorsed symptoms of legs restlessness and urge to move them, which was worse at night, relieved by walking and exacerbated by rest.

Examination

The patient is awake, alert, oriented to person, place and time. He is not in distress, does not look sleepy or fatigued. Vital signs: HR 57, BP 154/90, SPO_2 99%, RR 8, body mass index (BMI) 27.1 kg/m^2. Examination of the head and neck did not reveal any nasal septal deviation, enlarged turbinate, or obstructed nasal flow. Mallampati score was II/IV. Tonsils were not enlarged (grade I). No retrognathia. No collapse of the ala nasi. No tenderness over the temporomandibular joint. Neck circumference is 15 in. (38.1 cm). The rest of the physical examination was within normal limits.

S. Mashaqi
Pulmonary, Allergy, Critical Care, and Sleep Medicine, Banner University Medical Center, University of Arizona College of Medicine, Tucson, AZ, USA
e-mail: saifmashaqi@email.arizona.edu

T. Rafi (✉)
Sleep Medicine, Banner University Medical Center, Tucson, AZ, USA

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_18

Investigations/Studies

A diagnostic polysomnogram (PSG) was completed which showed mild obstructive sleep apnea (OSA) showing an apnea-hypopnea index—AHI 13.9/h. The study also showed excessive transient muscle activity during REM, and periodic limb movements of sleep (PLMS) index of 30.9/h.

Due to the patient's frequent travel to remote areas of the world, positive airway pressure (PAP) treatment was very inconvenient for him and he chose to pursue mandibular advancement device (MAD) therapy for the treatment of his mild OSA. Accordingly, he was referred to the department of sleep dentistry and was fitted with a MAD. Home sleep apnea testing (HSAT) was completed after the patient was fitted with the oral appliance. This study showed a respiratory event index (REI) of 16.4/h, mainly obstructive in nature. Clinically, the patient noticed improvement in his symptoms but due to his elevated REI he was referred to sleep dentistry for further advancement of the MAD. The device was advanced twice (over an 18-month period) followed by a full night PSG to evaluate the effectiveness of the MAD advancement. Clinically, he endorsed worsening of excessive daytime sleepiness and recurrent awakening although there was a minimal improvement in vivid dreams, thrashing and kicking at night. During the first 2 h of sleep the overall AHI was 88.9/h. There was a predominance of central sleep apnea with Cheyne-Stokes breathing (CSB) pattern, and the central AHI was 55/h. The study was then converted to a split-night polysomnogram, and the patient was treated with PAP therapy. At the conclusion of the study, the PAP mode in use was Bi-level PAP-ST (Table 18.1).

Table 18.1 Summary of sleep studies before and after MAD use

	Study 1 without MAD—baseline	**Study 2** with MAD	**Study 3** with maximum advancement of MAD
	(PSG)	(HSAT)	(PSG)
AHI (events/h)	14	16.4	89
OAI (events/h)	1.2	1.6	3.3
HI (events/h)	10	14.2	24
CAI (events/h)	2.3	0.6	55
m SpO_2 (%)	88	92	94
T-90 (%)	3.1	1	8

AHI = apnea-hypopnea index; OAI = obstructive-apnea index; HI = hypopnea index; CAI = central-apnea index; m SpO_2 = mean SpO_2; T-90 = % total sleep time with $SpO_2 < 90\%$; PSG = polysomnography; MAD = mandibular advancement device; HSAT = home sleep apnea test

Differential Diagnosis

Central sleep apnea secondary to MAD use.
Central sleep apnea with CSB
Central sleep apnea secondary to opioid use
Central sleep apnea secondary to medical condition
Idiopathic central sleep apnea

Discussion and Management

Our patient presented with a mild degree of obstructive sleep apnea, which was complicated by a severe degree of central sleep apnea with the use of MAD that was advanced twice. Clinically, the patient endorsed improvement in symptoms (witnessed snoring, apnea, excessive daytime sleepiness, recurrent awakening, vivid dreams, thrashing and kicking at night), especially in the early phase of treatment with the initial advancement of MAD. This was followed by worsening of these symptoms later with the maximal advancement of MAD.

The patient has history of aortic stenosis, and he underwent transcatheter aortic valve replacement. However, his ejection fraction on several echocardiograms was within normal limits making the diagnosis of central sleep apnea with Cheyne Stokes breathing secondary to heart failure with reduced ejection fraction (HFrEF) not possible. The patient does not have a history of stroke, neurological disorders, or end stage renal disease making the diagnosis of central sleep apnea secondary to medical condition less likely. He does not take opioids or narcotics for pain control. Since severe central sleep apnea developed in the context of using MAD (that was advanced twice) in association with worsening in symptoms, this makes this entity the most likely diagnosis. Treatment-emergent central sleep apnea associated with the use of MAD is not common and poorly understood. It was described in the literature of sleep medicine as early as 2006. Avidan et al. reported a case of mild OSA who elected to be treated with MAD. Although this helped with snoring, it did not help with excessive daytime sleepiness and follow up PSG showed new onset central sleep apnea (moderate), in addition to mild worsening in obstruction events [1]. This thought to be related to MAD. More recently, another case report was published by Mohan et al., presenting a patient with a moderate degree of OSA who was treated with MAD and developed new onset central sleep apnea with MAD (mild), which resolved after 1 year of acclimation [2]. Whether the pathophysiology of these central events is similar to complex sleep apnea (i.e., PAP treatment emergent central sleep apnea) is not fully understood.

Final Diagnosis or Most Likely Diagnosis

Central sleep apnea secondary to mandibular advancement device use.

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Case 19. Two for One Isn't Always Better: When Is a Dual Diagnosis Problematic?

19

Xinyi Hong, Patrick Sorenson, and Ashura Williams Buckley

History

A 13-year-old boy of African American descent was admitted to National Institute of Health (NIH) Clinical Center with a 6-year history of refractory excessive daytime sleepiness (EDS) resulting in near incapacitation. At the age of 8 years, the patient presented with precocious puberty, including a rapid increase in linear growth and weight, progressive somnolence, ataxia, acanthosis nigricans, confusion and aggression. Narcolepsy type 1 (NT1) was confirmed by polysomnography (PSG)/multiple sleep latency test (MSLT) at age 9. Multiple failed trials of stimulants for EDS and escalating behavioral issues had led to multiple psychiatric admissions and diagnoses of attention deficit hyperactive disorder (ADHD), oppositional defiant disorder (ODD), and at age 11, a diagnosis of childhood-onset schizophrenia (COS) following paranoid ideation around food and responding to internal stimuli. Upon admission, he was also suffering from chronic constipation, vitamin D deficiency, hyperlipidemia, type 2 diabetes, enuresis, and tachycardia. His fraternal twin had also been diagnosed with ADHD and had had a similar trajectory of rapid weight gain and aggression. His mother's twin sister has been diagnosed with schizophrenia and bipolar disorder at separate evaluations.

X. Hong (✉)
National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

Sleep and Neurodevelopment Service, National Institute of Mental Health, Bethesda, MD, USA
e-mail: xinyi.hong@nih.gov

P. Sorenson · A. W. Buckley
Sleep and Neurodevelopment Service, National Institute of Mental Health, Bethesda, MD, USA
e-mail: sorensonpg@nih.gov; shu.buckley@nih.gov

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_19

During an 8-month psychiatric hospitalization shortly before admission, the patient suffered a tonic-clonic seizure concurrent with the initiation of a trial of a mixed-salt oxybate oral solution, which was subsequently discontinued. The new onset seizure, encephalopathic features, and psychiatric symptoms led to further evaluation for autoimmune encephalitis (AE). On admission to NIH his medications included clozapine at 300 g/day, lithium at 900 mg/bid and 20 mg methylphenidate daily. A trial of intravenous immunoglobulin (IVIg) therapy was initiated. Afterwards, the patient was noted by the psychiatric care team to become more conversant, demonstrate greater ability to engage in daily activities, with improvements in wakefulness, concentration, attention, memory, and fine and gross motor movements.

Examination

The patient was 6′1″ with a body mass index (BMI) of 33 kg/m^2. He was observed to be most alert around breakfast time, but nonetheless fell asleep immediately when he was required to lay down for his intravenous line to be flushed. He was noted to lose balance easily and required assistance with ambulation. He experienced incontinence, enuresis and excessive drooling and seemed to lack understanding of his own physical and cognitive limitations. In conversation, he responded with monosyllabic agreements, with eyes closed and voice without inflection. By early afternoon each day he was very sleepy and difficult to arouse. He struggled heavily to sustain eye opening and follow commands. His pupils were round and reactive to light. His oropharynx was clear and pink with no evidence of tonsillar tissue. He was diffusely hyporeflexic and tachycardic into the 120 s at rest.

Investigations/Studies

A sleep study was performed at the NIH while patient was on polypharmacy (clozapine and lithium) to investigate for sleep disordered breathing (SDB) given cardiac findings. REM onset occurred at 11 min with fragmented REM throughout the night, with otherwise normal ultradian rhythm (see Fig. 19.1). Sleep spindles appeared to be scanty or absent. Please see Fig. 19.2 for additional data regarding sleep architecture and arousal summary. No evidence was found for sleep-disordered breathing and nocturnal electrocardiogram (EKG) demonstrated wide-complex tachycardia. Follow-up cardiology exam found evidence of left ventricular hypertrophy (LVH). Magnetic resonance imaging (MRI) showed normal brain parenchyma. Endocrine consult determined bone age of 18 years and 6 months. Cerebrospinal fluid (CSF) exam revealed orexin (<50 pg/mL). Behavioral tests demonstrated low scores on the Weschler Intelligence Scale for children (full scale IQ of 68, 2nd percentile), the Peabody Picture Vocabulary Test (score of 86, 18th percentile), and below average reading (score of 89, 23rd percentile), spelling (score of 82, 12th percentile), and math skills (score of 61, 0.5th percentile) as demonstrated on the Wide Range Achievement Test.

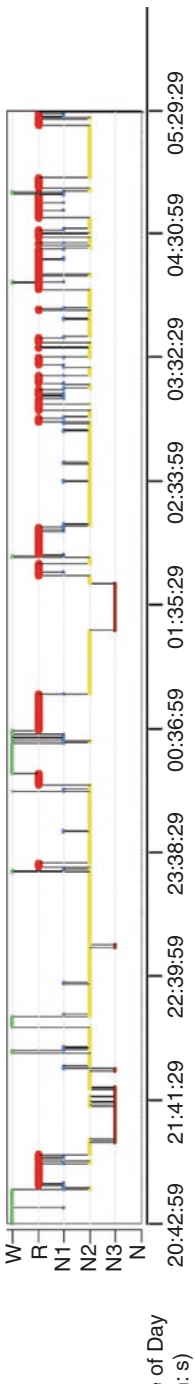
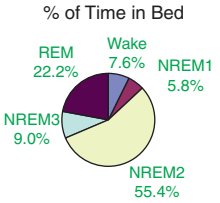


Fig. 19.1 Hypnogram generated from patient's polysomnogram conducted at the NIH showing early REM onset and fragmented REM periods throughout the night

Sleep Architecture

Stages	Time (mins)	% Sleep Time
WAKE	44.5	
Stage N1	33.5	6.2%
Stage N2	322.5	60.0%
Stage N3	52.5	9.8%
REM	129.0	24.0%



Arousal Summary

	NREM	REM	Sleep	Index
Respiratory Arousals	1	-	1	0.1
PLM Arousals	-	-	-	-
Isolated Limb Movement Arousals	2	-	2	0.2
Spontaneous Arousals	38	13	51	5.7
Total	42	13	55	6.1

Fig. 19.2 Tables summarizing data from PSG, including sleep architecture and arousals

Differential Diagnosis

The patient had been to numerous providers and centers throughout the course of his illness with inconsistent medical care. It is unclear if the diagnosis of COS is warranted or if his symptoms could be better explained by poorly controlled narcolepsy combined with periods of confusion caused by sleep state instability. Given the history of seizure (potentially provoked by initiation of the mixed-salt oxybate oral solution) in the setting of nystagmus, ataxia, and titubation, secondary narcolepsy owing to an antibody mediated autoimmune encephalitis is a possibility, although all investigations of antibody panels were negative. Consistently normal brain MRIs at ages 7, 11, and 13 ruled out pituitary or other central nervous system (CNS) lesion. Hereditary disorders related to narcolepsy with cataplexy such as Niemann Pick Type C can present with psychiatric manifestations, but severe orexin deficiency, as presented here, has not been documented in this progressive disease. The child continues evaluation with genetics and cardiology for unexplained LVH.

Discussion and Management

The primary psychiatric team recommended continuation of IVIg transfusions which had provided symptomatic improvement, but it should be noted that the benefit of this course of treatment for narcolepsy with cataplexy has not been established. A trial of orexin agonist could also be beneficial in this child with refractory EDS, but these treatments have not been made commercially available to children at the time of publication. A request for compassionate use was denied. Incontinence and excessive salivation are known side effects of clozapine and given the uncertainty of the nature of the aggression and altered mentation,

clozapine taper while optimizing medications for EDS in a controlled setting, including potentially a repeat challenge of mixed-salt oxybate oral solution, was the final recommendation.

Narcolepsy patients have a higher risk for depression and other psychiatric disorders than the general population. The relationship between NT1 and psychosis is not well understood and is thought to be rare and has been estimated at 1–18 cases in two million [1]. However, recent attention to developmental associations between the diagnoses suggests that it may be more prevalent than previously thought, particularly when NT1 has a prepubertal onset and there is an early dramatic change in BMI [2] potentially signifying widespread influence of orexinergic loss on other hypothalamic functions. For example, a study from 2014 of 102 children with NT1 in Taiwan revealed that *9.8%* of them went on to develop schizophrenia [2]. In addition, in this patient's case, the relationship of psychotic symptom onset to medication introduction/withdrawal is unclear. There is currently no standard treatment model for patients with psychosis and narcolepsy.

Final Diagnosis

- Narcolepsy type 1; psychotic variant
- Cardiomyopathy
- Diabetes type 2

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Case 20. The Mysterious Mustache

20

Marta Maczaj

History

An 84-year-old man with no prior history of psychiatric or psychotic illness, presented with visual hallucinations of 2 weeks duration. The hallucinations started abruptly and consisted of him seeing mustaches on female television reporters' faces and on the face of his female secretary. He initially thought that the mustaches were real, but upon checking with his wife, ascertained that she did not see them. He did not experience any auditory hallucinations, did not have any ideas of reference with respect to the television and had no other psychiatric symptoms. He felt well, denied any symptoms of anxiety and depression and was able to carry out fully his duties as a lawyer. He had a medical history of obstructive sleep apnea (OSA), which was well controlled with CPAP therapy and of periodic limb movement disorder for which he was taking gabapentin 400 mg for a few months before it was increased to 500 mg a month ago.

Examination

Well developed, well-nourished elderly man who was alert and oriented to person, place and time. He was not in any distress. His affect was full range and appropriate and his mood was euthymic. Mental status examination did not reveal any evidence of paranoia or other psychotic symptoms other than the reported visual hallucinations of mustaches on his secretary and television reporters. His pupils were equal and reactive and his visual fields were intact. Cranial nerves were intact. Motor

M. Maczaj (✉)
Sleep Disorders Center, St. Charles Hospital and Rehabilitation Center, Port Jefferson, NY, USA
e-mail: marta.maczaj@chsli.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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function and reflexes were within normal limits. Balance and gait were within normal limits. There was no evidence of head injury.

Investigations/Studies

He was referred to a neuro-ophthalmologist and his ophthalmological evaluation - which included visual acuity testing, glaucoma testing, evaluation for macular degeneration, and full visual field evaluation – found no abnormalities. A brain magnetic resonance imaging (MRI) found no pathology other than expected age related changes. Complete blood count, comprehensive metabolic panel, thyroid function tests and iron studies were normal.

Differential Diagnosis

The new onset very specific visual hallucinations were of unclear etiology but did not appear to be psychiatric in nature due to the overall excellent psychological status of this man. He did not appear physically ill and his blood work did not reveal an infection. He was not taking any prescription or over-the-counter anticholinergic medications with a known association of visual hallucinations in the elderly.

Discussion and Management

An acute neurological and/or ophthalmological process causing the hallucinations had to be investigated and ruled out. In addition, a toxic metabolic state had to be considered. The recent increase in gabapentin was a suspect since the onset of the visual hallucinations occurred within a few weeks of the dose increase to 500 mg po qhs. The patient was advised to discontinue the gabapentin and within 2 days of stopping it, the visual hallucinations disappeared. The gabapentin was restarted at a lower dose (400 mg po qhs) 2 weeks later and the mustache visual hallucinations returned. The patient was then advised to discontinue and not restart gabapentin. The visual hallucinations again disappeared. Gabapentin has been used to treat visual hallucinations; however, in this particular case it appeared to do just that, even though this phenomenon is not listed as a side effect. It is unclear how gabapentin caused the hallucinations since it appears to inhibit the release in the presynaptic area of excitatory neurotransmitters and not increase their levels [1, 2].

Most Likely Diagnosis

Medication induced (gabapentin) visual hallucinations.

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Case 21. Is There a Link Between Insomnia and Diet?

21

Celia Garcia-Malo and Diego Garcia-Borreguero

History

A 46-year-old woman, who followed a vegetarian diet, reported that she had suffered from insomnia since she was 16. She had been diagnosed with depression and anxiety in the past and had tried a multitude of different drugs (i.e., sertraline, amitriptyline, mirtazapine, trazodone, quetiapine, clonazepam, zolpidem, desvenlafaxine, venlafaxine, and olanzapine) often with either poor results or bad tolerance. She also reported that she had been treated with several different benzodiazepines, again, with poor results. In addition, she had hypothyroidism for which she had received treatment with levothyroxine.

Her sleep schedule was regular. She went to bed at 10:30 PM and usually fell asleep after 1–3 h. Once asleep she had uncountable interruptions and would wake at 7:30 AM feeling like her sleep had been non-refreshing. She practiced regular physical exercise, including yoga and also practiced meditation. She denied snoring or restless legs syndrome symptoms. At the time of consultation, her treatment consisted of levothyroxine 75 mcg and escitalopram 10 mg at breakfast, and lormetazepam 1.5 mg, lorazepam 1 mg, melatonin and gabapentin 100 mg before bedtime.

Examination

Her physical examination was normal.

C. Garcia-Malo (✉) · D. Garcia-Borreguero
Sleep Research Institute, Madrid, Spain
e-mail: dgb@iis.es

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_21

Investigation

Due to the lack of response and non-refreshing sleep, we decided to perform a polysomnography. The result showed reduced sleep efficiency (79.4%), increased wakefulness after sleep onset (57.2 min), and an arousal index of 11.7/h. Furthermore, the sleep architecture showed 11.3% of N1, 61.6% of N2, an absence of N3, and 27.1% of rapid eye movement (REM) sleep. The apnea-hypopnea index was 0/h. However, the periodic limb movement index (PLMI) was 53.9/h (see Fig. 21.1).

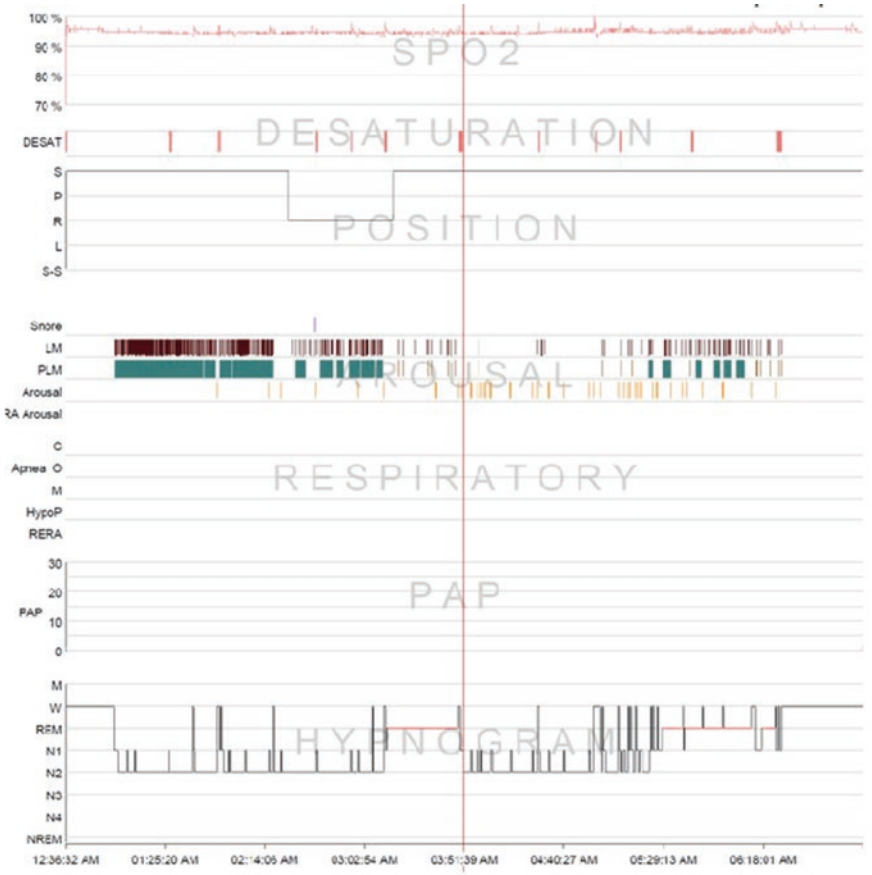

Fig. 21.1 Image of the hypnogram of our patient. Note the absence of slow-wave sleep (N3) and the presence of abundant periodic limb movements (PLMS)

Diagnosis

As she had a PLMI above normal (15/h) and her main complaint was insomnia, we diagnosed her with periodic limb movement disorder (PLMD).

Management

A complete blood analysis, assessing serum iron status was performed, showing serum ferritin of 6 mg/dl with transferrin saturation (TSAT) of 19%. Substantia nigra iron stores were evaluated using transcranial sonography, and showed hypoechogenicity (decreased iron stores), with a substantia nigra echogenicity index (SNEI) of 0.18 (see Fig. 21.2). According to these results, iron replacement therapy was recommended. She reported having been treated with oral iron in the past with bad gastrointestinal tolerance, leading to poor compliance. Because she met the criteria for receiving IV iron, she received 1000 mg of IV ferric carboxymaltose, with no side effects.

Regarding symptomatic treatments, lorazepam and lormetazepam were interrupted and replaced by clonazepam at a progressively decreasing dosage. Gabapentin was progressively increased to 1200 mg/day, resulting in a significant improvement in sleep quality.

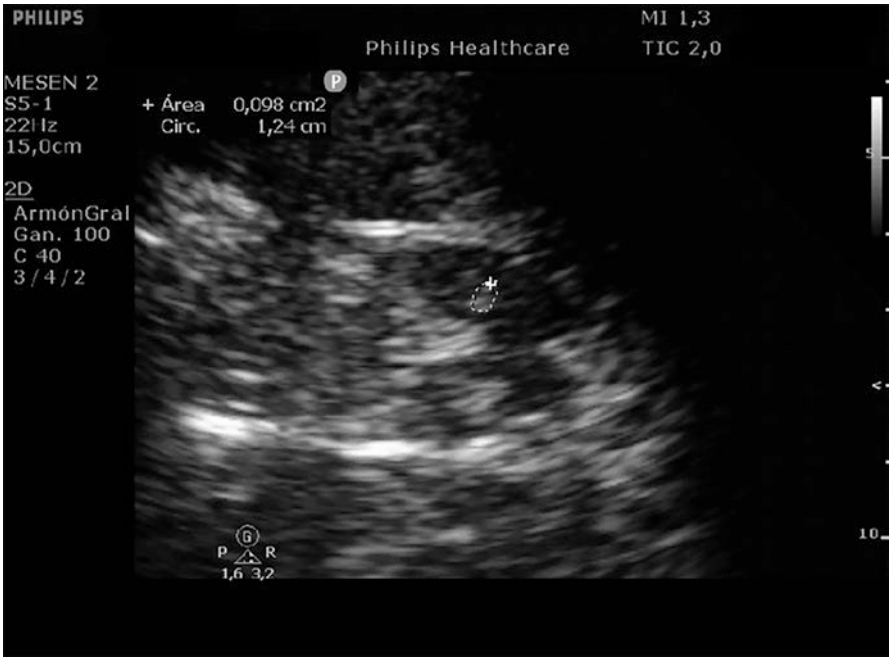

Fig. 21.2 Image showing transcranial sonography of our patient. The mesencephalon shade is visible and, inside it, a more echogenic and manually delimited area, that corresponds with the substantia nigra

At 3 months follow-up, another blood test was undertaken, with a serum ferritin of 152 mg/dl and a TSAT of 42%. Her SNEI was 0.20 cm^2. Since she reported progressive improvement of her sleep quality, gabapentin was reduced to 600 mg/day over the following months.

Discussion

This case shows how chronic insomnia should be carefully evaluated. It is important to note that the patient had previously been treated with a myriad of drugs from different therapeutical groups, invariably with poor clinical results. This adds weight to the relevance of performing a polysomnography; despite the patient's denial of symptoms, she was finally diagnosed during a clinical interview with a physical condition that caused insomnia and poor sleep quality.

Clinicians need to be aware that several drugs with hypnotic effects—antipsychotics, antihistamines and almost every antidepressant—may worsen PLMD because they can ultimately reduce dopaminergic transmission. Also, attention should be paid to the fact that the patient is a woman with a vegetarian diet, both risk factors for iron deficiency. Iron deficiency has been related to both PLMD and restless legs syndrome. Regarding PLMD, iron replacement therapy should always be considered in the first instance [1]. International guidelines define safe cut-offs for indicating this therapy [2]. Brain iron deposits can be assessed using transcranial sonography and PLMD usually shows hypoechogenicity. In this case, the preference of IV iron over the oral preparation was based in the previous failure whenever the latter had been used. When IV iron is administered, it usually takes a few months to see an effect, therefore, in the meantime, symptomatic treatment should be titrated to improve sleep. In this case, the gabapentin dose was increased for this purpose.

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Case 22. Not Your Typical Sleepy Adolescent

22

Ioanna Kouri

History

A 12-year-old boy presented with recurrent "sleep attacks" over the previous three years, consisting of five episodes of hypersomnia during which he would sleep for 18 to 20 h. The patient was difficult to arouse during the episodes and irritable with inappropriate behavior, language, and voracious appetite. He appears a well-behaved 12-year old in between episodes with good academic performance at school. The patient had not taken any sedating medications prior to the episodes and denies substance abuse. He did not report symptoms concerning for sleep-disordered breathing, narcolepsy, or restless legs syndrome. A psychiatrist determined that he did not fulfill the criteria for a psychiatric disorder.

Examination (Between Attacks)

Body mass index (BMI) 25.4 kg/m^2. The patient was in no acute distress. Mallampati II oropharynx. Tonsils graded 2+. Neurological exam: within normal limits.

Investigations

Polysomnogram (PSG) was performed between episodes. Sleep Latency: 5 min. Sleep efficiency: 95%. Total Sleep Time: 482 min. N1: 20%, N2: 50%, N3:20%, REM: 10%. AHI: 0.8/hr. Sat O2 < 90%: 0 min. Low Sat O2: 95%. (see Table 22.1).

I. Kouri (✉)
Department of Pediatrics, Mitera, Athens, Greece

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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Table 22.1 PSG comparison between episodes and during an episodes

	PSG between episodes	PSG during an episode
Sleep latency (min)	5	10
SE (%)	95	75
TST (min)	482	680
N1 (%)	20	30
N2 (%)	50	50
N3 (%)	20	10
REM (%)	10	10
AHI (events/h)	0.8	0.4
TST <90% sat/ Low O2 sat	0%/95%	0%/95%
PLMI (events/h)	0	0

PSG polysmonogram, *SE* sleep efficiency, *TST* total sleep time: apnea-hypopnea index (AHI), *PLMI* periodic limb movement index

Table 22.2 MSLT performed after PSG during an episode

Nap	Sleep latency (minutes)	REM latency
1	11.1	–
2	12.2	–
3	11.5	–
4	10	–
5	12.1	–
Mean sleep latency	**11.3**	–

PSG polysomnogram, *MSLT* multiple sleep latency test

PSG during an episode: Sleep Latency: 10 min. Sleep efficiency: 75%. Total Sleep Time: 680 min. N1: 30%, N2: 50%, N3:10%, REM: 10%. Multiple sleep latency test (MSLT): No sleep onset REM periods (SOREMPs). (see Tables 22.1 and 22.2).

Routine electroencephalogram (EEG) did not show epileptiform discharges. Magnetic resonance imaging (MRI) of the brain was normal.

During an episode: complete blood count, basic metabolic panel and thyroid function tests were within normal limits. Urine drug screen was negative.

Differential Diagnosis

Kleine-Levin syndrome (KLS). The age of onset, relapsing, and remitting character of episodes suggest KLS. Obstructive sleep apnea (OSA) should be considered because the patient is obese. However, the lack of sleep-disordered breathing symptoms does not support this diagnosis. Narcolepsy is unlikely in the absence of characteristic symptoms.

Bipolar disorder/depression is a consideration; however, evaluation revealed no psychiatric illness. Substance abuse should be a differential diagnosis in every adolescent with recurrent hypersomnia. However, the urine drug screen was negative.

Final Diagnosis

Kleine-Levin syndrome.

Discussion

The patient was given methylphenidate at a dose of 5 mg three times a day and recovered after a further 48 h. He was prescribed lithium to prevent recurrences and decrease the severity of the episodes.

Kleine-Levin syndrome (KLS) [1] is a disorder of relapsing-remitting episodes of severe hypersomnolence and cognitive, psychiatric, and behavioral disturbances. It is a rare syndrome affecting an estimated 1 to 5 per million individuals. KLS occurs mainly in male adolescents. Cases are primarily sporadic. The episodic nature of its symptoms characterizes KLS. The classic triad of symptoms is hypersomnia, hyperphagia, and hypersexuality.

Recurrent hypersomnia is a cardinal symptom of KLS. Sleepiness is profound. Patients become abruptly or gradually sleepy over 1–7 days. Patients may sleep for 16–20 h during an episode. Their sleep is calm or agitated with dream enactment behavior, and hypnagogic hallucinations with insomnia reported briefly at the end of an episode.

In addition to hypersomnia, four other symptoms are often present in KLS. Firstly, cognitive disturbances are reported in all patients. Patients have anterograde amnesia, are exhausted, and are slow in reading and speaking. They report a dream-like, altered perception of the environment (derealization) and changes in vision, taste, hearing, smell, and tactile sensation. The second symptom is compulsive hyperphagia. Excessive caloric intake (66% of cases) during episodes may result in obesity. The third symptom is improper sexual behavior (53% of cases), including increased sexual drive, unwanted sexual advances, masturbation, and exhibitionism. The fourth symptom is mood disturbances with irritability, depression (53% of cases), anxiety, and suicidality.

The duration of the episodes ranges from 2 days to several weeks, with a median duration of 10 days. In between episodes, patients are normal.

While first described over 200 years ago, the etiology of KLS is unknown. The high prevalence in Ashkenazi Jews could stand for founder effect. The higher frequency in HLA DQB1*02 reported in a retrospective series was not replicated in a larger prospective series. A precipitating factor like flu-like illness, fever, head trauma, alcohol consumption, travel, or anesthesia signals the onset of symptoms, inviting infectious or autoimmune underlying causative speculations. Researchers hypothesize a functional abnormality at the level of the diencephalon, as supported by hypometabolism in functional brain imaging studies and neuropathology reports.

The diagnosis relies on clinical criteria. However, because of the rarity of the disease and the possibility of organic and psychiatric conditions, laboratory investigations are obtained, including complete blood count, electrolytes, liver function

tests, autoimmune and microbiological investigations, which are normal. Routine EEG obtained during the attacks may show generalized slowing of background activity or maybe normal in about 30% of patients. Brain MRI is normal.

Prolonged PSG may show increased total sleep time, poor sleep efficiency and a significant reduction in slow-wave sleep at symptom onset with progressive return to normal in the second half, while REM sleep was normal in the first half and decreased during the second half of the symptomatic period. Multiple sleep latency test (MSLT) can reveal abnormal sleep latency and sleep-onset REM periods during symptomatic periods. However, MSLT findings do not correlate with symptom onset. During asymptomatic periods PSG and MSLT are both normal.

Complications are mainly social and occupational. Life-threatening consequences include choking during episodes of voracious eating, suicide, and car accidents.

Patients should rest at home under supervision and not drive or operate heavy machinery during an episode [2]. Caregivers should monitor eating behavior, identify symptoms of depression and seek medical attention if signs of suicidality occur. Between episodes, patients should avoid identified triggers and maintain sleep hygiene and regular sleep-wake patterns.

A Cochrane review of 257 drug trials deferred from making pharmacological recommendations. One prospective open-label controlled study showed promise for lithium in decreasing the frequency, severity, and duration of episodes. Stimulant medications and amantadine, valproic acid and carbamazepine are not consistently successful in preventing or treating recurrences. KLS often has a benign course. Episodes tend to recur less frequently and are less severe. KLS typically self resolves by the 4rth decade of life, with a median duration of 13.6 years, except in adult-onset cases, when the course may be more prolonged.

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Case 23. Sleep Trauma

23

Scott Hirsch

History

A 50-year-old woman presented with sadness, anxiety, insomnia, and excessive daytime sleepiness that hampered her capacity to function at work and home. A review of symptoms also revealed complaints of frequent headache, word finding difficulty, and short term memory deficits. She described extensive childhood trauma, growing up with a mother who was emotionally and physically abusive. Her father abandoned the family when she was twelve years old, after which she experienced persistent anxiety and episodic depression, as well as a pattern of binging food. She blamed herself for what happened and felt isolated. As an adult, she experienced recurring flashbacks and vivid nightmares of her childhood trauma. She avoided contact with her family and described anticipatory anxiety in the hours prior to bedtime fearing what would happen during sleep. Her husband noted she moved frequently when sleeping and would wake him in the middle of the night with her yelling and kicking. There was no report of snoring. Her medications included included bupropion, metformin, liraglutide, phentermine, spironolactone, estradiol, and propranolol.

Examination

The patient was tearful and dysphoric, though speech and cognition was normal. She was somatically preoccupied and provided evocative detail about her early childhood experiences accompanied by intense emotional expression. The Beck Depression Inventory score was 27 and the Beck Anxiety Inventory score was 18. She appeared to be in some discomfort, though was well-appearing. She was mildly

S. Hirsch (✉)
NYU Langone Medical Center, Rye Brook, NY, USA

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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overweight with a body mass index (BMI) of 28 kg/m^2; the objective physical examination was significant for normal blood pressure without orthostasis and a normal heart rate. The neurological physical examination was unremarkable.

Investigations

Routine laboratory investigations were unrevealing. Brain magnetic resonance imaging (MRI) was normal. Routine electroencephalogram (EEG) was normal in the awake and drowsy states. Neuropsychological testing revealed superior general intellectual ability, no processing or memory deficits, and normal executive functioning, processing speed, visuospatial skills, and fine motor dexterity. A polysomnogram (PSG) showed increased muscle tone during REM sleep with vocalizations, sleep talking, and pedaling consistent with REM Sleep Behavior Disorder (RBD). There was evidence of a mild degree of positional sleep disordered breathing consistent with Obstructive Sleep Apnea (OSA). The total Apnea-Hypopnea Index was 12.8/hr. The minimal oxygen saturation was 82%.

Discussion

At age 50, the patient complains of a combination of psychological, cognitive, neurological, and pain symptoms. She exhibits longstanding psychological distress in the setting exposure to childhood trauma, a major stressor. Over many years, she experienced intrusion symptoms, avoidance of trauma-related stimuli, negative alterations in cognition, and alternations in arousal. These findings are consistent with a diagnosis of post-traumatic stress disorder (PTSD). Her pattern of recurrent binge eating suggested a diagnosis of binge eating disorder (BED).

However, these diagnoses do not fully account for the patient's cognitive and neurological symptoms. Her PSG showed OSA and also revealed evidence for RBD. While some patients with severe OSA are described as having pseudo-RBD, this patient has relatively mild OSA [1]. Some patients on antidepressant medications have exhibited REM sleep without atonia, though this is less commonly seen with the bupropion she was on at the time of the PSG. As such, co-morbid RBD is likely in this patient.

It is likely that the patient's underlying PTSD and BED have contributed to the development of OSA as she has aged. In addition, there is some suggestion in the literature that RBD is more common in patients with PTSD [2]. The combination of OSA and RBD has diminished the amount of nightly restorative sleep, in turn, resulting in chronic headache and excessive daytime sleepiness. Headache and sleepiness both contribute to her perception of worsened cognitive functioning and may also intensify her underlying psychological issues.

Of note, while the development of anticipatory anxiety in the evening may be related to the nightmares of chronic PTSD, the presence of confirmed OSA and RBD precludes a diagnosis of insomnia disorder.

Presently, the patient is treated with continuous positive airway pressure (CPAP) for OSA, clonazepam for RBD and evening anticipatory anxiety, prazosin for nightmares, and a combination of fluoxetine and bupropion for PTSD. She attends a weight management program in addition to psychotherapy.

Diagnoses

REM Sleep Behavior Disorder and Obstructive Sleep Apnea in a patient with Post-Traumatic Stress Disorder and Binge Eating Disorder.

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Case 24. Getting to the Heart of the Matter

24

Nishay Chitkara

History

A 28-year-old woman with a history of anxiety and depression, back pain, and Marfan's syndrome, presented for evaluation of a longstanding history of excessive daytime sleepiness. She would feel sleepy while driving long distances, and would have to pull over to the roadside. She would feel sleepy at work, and would take naps during lunch or while on a break. She would also fall asleep while reading. Her sleep schedule was consistent, with an 11 PM bedtime (and a sleep latency of about 15 min) and a 7:15 AM wake time. She reported frequent nocturnal awakenings, sometimes to use the bathroom and sometimes for a snack, but no snoring, witnessed apneas, or episodes of choking/gasping awake. When she started taking clonazepam for anxiety, her sleep was more consolidated and she would be able to sleep through the night. She would take daytime naps twice weekly, for about 30–40 min each time. Her naps were more refreshing when they were longer. She denied episodes of cataplexy or sleep paralysis. She had frequent nightmares before starting clonazepam. While on clonazepam, her nightmares became fewer, and were varied, surreal and somewhat abstract, not about specific things. A home sleep study demonstrated no evidence of sleep disordered breathing. A multiple sleep latency test was recommended, but she was not able to schedule it. She was prescribed dextroamphetamine/amphetamine for her hypersomnia, and with its use, she reported improved concentration and daytime vigilance. She later tried methylphenidate, with similar benefit.

She has no family history of sleep disordered breathing, narcolepsy, or hypersomnia. Her father has an unspecified heart condition.

N. Chitkara (✉)
Internal Medicine/Pulmonary, Critical Care and Sleep Medicine, NYU Langone Health and Bellevue Hospital, New York, NY, USA
e-mail: nishay.chitkara@nyulangone.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_24

Examination

The patient was of tall stature, with long limbs typical of Marfan's syndrome. She is able to wrap her arms around her head in a hypermobile form. Her oropharyngeal exam was significant for a high arched palate, a crowded posterior pharynx with a Mallampati grade 4, and a low hanging soft palate. She had normal muscle tone and strength. Her cardiac exam was normal, with a regular rate and rhythm, nondisplaced apical impulse, and no murmurs rubs or gallops.

Investigations

A diagnostic in-lab sleep study was performed to re-evaluate for possible sleep disordered breathing (see Fig. 24.1). It demonstrated evidence of moderate obstructive sleep apnea (OSA) with an apnea-hypopnea index (AHI) of 18.0/h and a minimum oxygen saturation of 85%. OSA was worse in REM sleep with a REM AHI of 46.1/h, and during supine sleep, with an AHI of 47.4/h. The REM/supine AHI was 61.3/h. Mild to moderate snoring was observed.

A multiple sleep latency test was performed following the diagnostic sleep study. It showed a mean sleep latency of 4.5 min, and 0 sleep-onset REM periods. The MSLT findings were consistent with excessive daytime sleepiness.

A 2-D transthoracic echocardiogram demonstrated normal left ventricular (LV) function, with normal wall motion, and an LV ejection fraction of 60%. All four

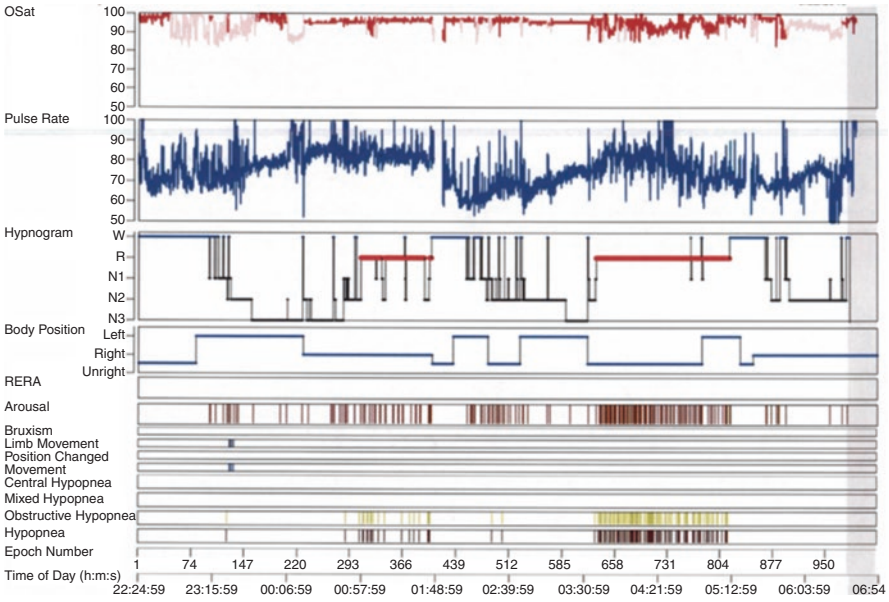

Fig. 24.1 Hypnogram showing obstructive sleep apnea worse during stage REM sleep, in a patient with Marfan's syndrome

chambers were normal in size and function. There was no significant valvular disease. The aortic root was normal in size (3.2 cm). The ascending aorta was normal in size, with a diameter of 2.7 cm. The aortic arch was normal in size, with a diameter of 2.2 cm.

Diagnosis

Severe Obstructive Sleep Apnea (OSA) in a patient with Marfan's Syndrome.

Discussion

Marfan's syndrome is an autosomal dominant connective tissue disorder, with most patients harboring mutations in the FBN1 gene on chromosome 15q21 (encoding the glycoprotein fibrillin-1, the main component of microfibrils in the extracellular matrix). Clinical manifestations include cardiac disease (mitral valve prolapse, aortic root disease), skeletal findings (arachnodactyly, pectus deformity, hindfoot valgus, abnormal upper segment/lower segment ratio and arm span/height, scoliosis, kyphosis), ocular abnormalities (ectopia lentis), and pulmonary disease (emphysematous changes with upper lobe bullae and a propensity to pneumothorax).

The main cause of premature death is aortic root dilatation, leading to aortic regurgitation and subsequent aortic dissection. Aortic aneurysmal dilatation begins during childhood and progresses at an unpredictable rate. A prime goal of monitoring patients with Marfan's syndrome is control of aortic disease.

Obstructive sleep apnea is strongly associated with Marfan's syndrome. A high prevalence of OSA exists among patients with Marfan's syndrome. Upper airway obstruction occurs due to craniofacial abnormalities and a lax upper airway, resulting from the underlying connective tissue defect of this disorder. Patients have an increased propensity to upper airway obstruction and collapse during sleep. Untreated OSA accelerates progression of aortic dissection and rupture, due to the transmural forces resulting from attempts to open the obstructed upper airway. Obstructive apneas lead to the production of large negative intrathoracic pressure swings, which increase the transaortic pressure and may therefore accelerate aortic dilatation, via shear stresses on blood vessel walls [1]. Effective treatment of OSA could postpone aortic dilatation in patients with Marfan's syndrome.

In this young patient, OSA was identified early, and she was found to have no aortic disease. She was initiated on auto-titrating positive airway pressure (APAP) treatment. An ophthalmology exam was normal. With adherence to APAP treatment, her risk for development of aortic disease will likely be significantly reduced.

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Case 25. Movements Come in Different Ways

25

Montserrat Pujol Sabate

History

A 76-year-old man presented with a five-year history of abnormal sleep behaviors. The patient's bed partner reported episodes of kicking and arm knocking, talking and singing. He never fell out of bed or assaulted the spouse. These behaviors and vocalizations occurred every night and appeared intermittently during the entire sleep period. The patient did not remember any dreams nor was aware of the sleep behaviors. His only complaint was insomnia, frequent awakenings at night, early awakening and non-restorative sleep without excessive daytime sleepiness. He referred snoring but without cessation of breathing and did not complain of restless legs syndrome, and had no cognitive complaints.

In a first sleep study, the patient was diagnosed with obstructive sleep apnea syndrome (OSAS) with apnea-hypopnea index (AHI) of 64/h. Nasal continuous positive airway pressure (CPAP) at 10 cm of H2O was recommended after titration. CPAP was partially tolerated without any significant response for several months, for which he was referred for a second evaluation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/978-3-031-18374-4_25.

M. P. Sabate (✉)
Neurology Service and Multidisciplinary Sleep Unit, Hospital Universitari Santa Maria, Lleida, Spain
e-mail: mpujol@gss.cat

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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Physical Examination

Neurological examination was normal. Body Mass Index (BMI): 24 kg/m^2. Mallampati: 1.

Investigations

- Video-polysomnography (vPSG) recorded a total sleep time of 201 min with a sleep efficiency of 42%, in part due to a long wake period after sleep onset (209 min). Sleep architecture showed a high arousal index (136/h), normal N2, lack of N3 sleep and a low percentage of REM sleep (4.5%). The AHI was 5/h, but the periodic limb movements of sleep (PLMS) index was very high (70/h), all movements associated with arousal. The video showed vigorous and prominent movements involving mostly the right leg, but also the arm and appearing in NREM sleep during the arousals that immediately followed PLMS (see Video 25.1). The frequency and intensity of PLMS in REM sleep was less severe than in NREM sleep, but with the same stereotyped motor pattern. REM sleep showed normal muscle atonia and no behavioral motor manifestation other than PLMS.
- Blood tests showed low iron: 53.0 µg/dl (59.0–158.0); and ferritin levels 21.4 ng/mL (30.0–400.0). Normal blood count.

He was started with oral iron supplements but due to the lack of improvement a work up for iron deficiency anemia was initiated. A colonoscopy was performed showing a moderately differentiated adenocarcinoma of the colon (pT1 Haggitt level 3), 19 mm in maximum diameter, infiltrating the submucosa of the stalk that was resected.

Differential Diagnosis

REM sleep behavior disorder.
Obstructive sleep apnea with leg movements arousals.
Periodic limb movements during sleep.

Discussion and Management

The patient had abnormal sleep behaviors mimicking REM sleep behavior disorder (RBD). A polysomnography (without video) ruled out REM without atonia and detected: repeated episodes of decrease in the amplitude of the airflow signal (greater than 30%) lasting each more than 10 seconds, apparently followed by an arousal, associated with leg movements but without oxygen desaturation. Such episodes were interpreted as hypopneas and OSAS mimicking RBD was diagnosed [1], despite the

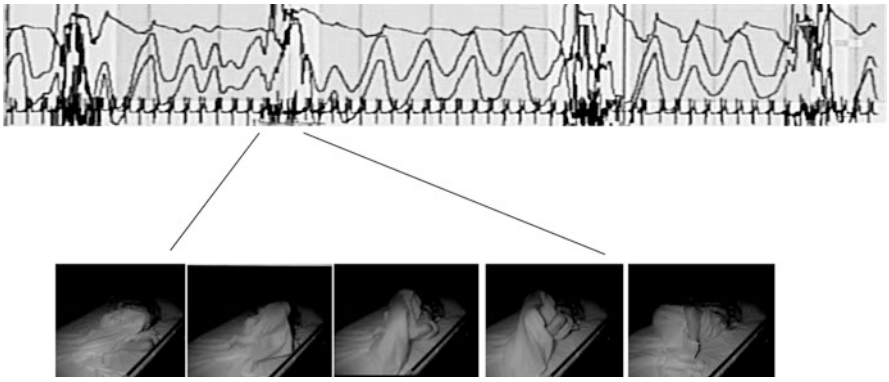

Fig. 25.1 A 1-min sample of respiratory channels monitoring shows: 3 hypopnea episodes ending with a large increase in the amplitude of the respiratory signals and a movement artifact involving also EKG channel, although not showing O_2 saturation changes. Synchronized video recording shows that each "end-of-apnea" episode is, in fact, a large leg and trunk movement that the patient performed periodically through the study

lack of severe oxyhemoglobin desaturations Treatment with CPAP was mildly tolerated but did not resolve the abnormal sleep behaviors.

A second polysomnogram, this time with synchronized audiovisual recording, demonstrated severe PLMS inducing arousals and associated with hyperventilation followed by relative breathing amplitude decrease with sleep resumption (Fig. 25.1).

The PLMS were frequent, highly stereotyped, intermittent and occurring through the entire night, mainly in NREM sleep, involving the 4 limbs, mainly the right ones, and the trunk. Vigorous PLMS were associated with arousals that contained abnormal motor behaviors and resulted with sleep fragmentation, leading to insomnia, non- restorative sleep, and hypersomnia.

The vigorous PLMS in upper and lower limbs, together with the motor behaviors and vocalizations, were misinterpreted during the clinical interview as suggestive of RBD [2].

The study of the low ferritin levels in blood allowed an early diagnosis of a colon adenocarcinoma.

We prescribed dopaminergic agents (ropinirole 1 mg/night), that reduced the number of PLMS, restored sleep continuity and improved all symptoms. The patient also received oral iron supplements. The clinical improvement has been maintained for the last ten years.

It is necessary to emphasize the usefulness of vPSG, as it was the instrument able to distinguish RBD from its mimics.

Final Diagnosis

Severe periodic limb movement disorder mimicking OSA and RBD.

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Case 26. Sometimes Sleep Hygiene Is Not Just Sleep Hygiene

26

Rebecca Q. Scott

History

Twenty-nine year old male presented with life-long intermittent difficulties falling and staying asleep. He developed more significant insomnia after graduating from college, moving to New York City and starting his first fulltime job in finance. He worked 11–12 h/day and interacted with a team in India, requiring that he occasionally take calls at 4–5 AM. He experimented with over-the-counter (OTCs) medications, alcohol and then with prescription sleeping aids (through his PCP) at the age of 25. Although initially helpful, they eventually "stopped working" and he continued to struggle with poor quality sleep, fatigue, irritability, low motivation, decreased productivity and difficulties with focus/concentration. After receiving an unfavorable work performance review at age 27 he established care with a psychiatrist and tried numerous medications and combinations, which resulted in side effects or became less effective, requiring escalating doses.

He presented to the sleep center after being suspended from work for sending an incoherent email with sensitive client information to his executive director, 3 colleagues and 2 friends unaffiliated with the bank. He recalled working on the project the night prior and canceled dinner with the 2 friends because of work but had no recollection of sending the email and was "in shock" and "mortified" when his executive director presented it to him. Approximately 1 h before the email was sent, he took zolpidem 10 mg, his common practice (see Fig. 26.1), as he felt it took ~1.5–2 h to "kick in."

During his initial assessment he reported feeling "trapped" by his insomnia and "regretted the day" he started sleeping medication. He often tried to sleep without

R. Q. Scott (✉)
NYU Langone Comprehensive Epilepsy Center-Sleep Center, Department of Neurology, NYU Langone, New York, NY, USA
e-mail: Rebecca.scott@nyulangone.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_26

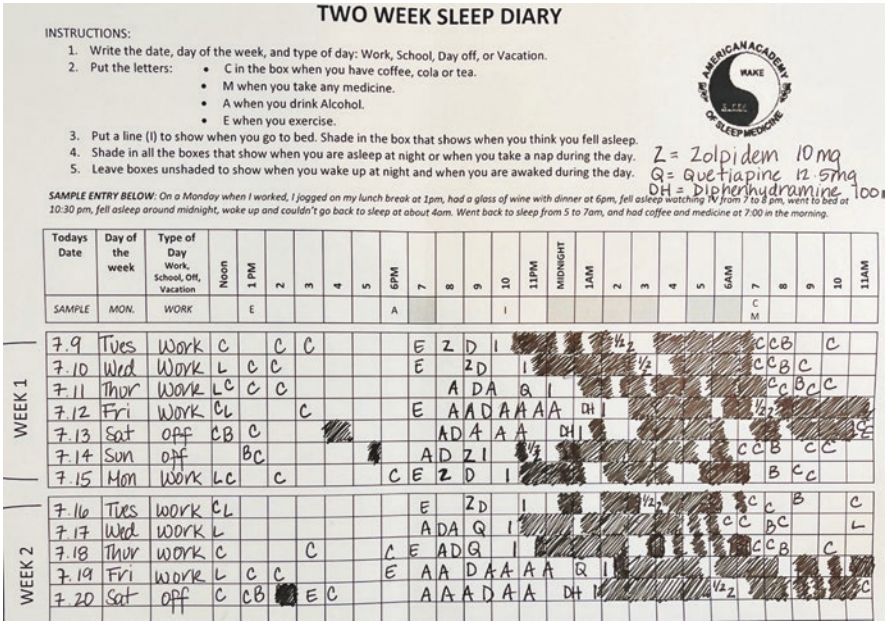

Fig. 26.1 Sleep diary before behavioral treatment: . Key: B = breakfast; C = caffeine; L = lunch; E = exercise; D = dinner; A = alcohol; Z = zolpidem 10 mg; Q = quetiapine 12.5 mg; DH = diphenhydramine 100 mg; I = in to bed; Shaded Area = estimated sleep

medication but invariably went back on after 1 or 2 nights because of severe insomnia. He tried "all sleep hygiene approaches," yoga, meditation and hypnosis, all without significant benefit. He rotated between different medications for fear of becoming "addicted." He was also distressed that he was "barely getting REM sleep" as per his sleep tracker.

Previously tried prescription medications: Trazodone, zolpidem SL, zolpidem CR, eszopiclone, zaleplon, gabapentin, quetiapine, suvorexant, clonazepam, alprazolam, temazepam, amitriptyline, ramelteon, mirtazapine, propranolol, dextroamphetamine-amphetamine.

Sleep-related symptoms: Sporadic snort arousals with alcohol; occasional complex sleep behaviors with zolpidem or eszopiclone.

Medical/Surgical/Psychiatric History: Hypercholesterolemia, reflux, anxiety; no surgical history.

Medications: Simvastatin 10 mg, omeprazole 10 mg, CoQ10, rogaine, propecia; rotates between 1) zolpidem 10 mg hs and 5–10 mg upon waking in the night, 2) quetiapine 12.5 mg hs or 3) diphenhydramine 100 mg hs and 25 mg prn upon waking in the night.

Social History: single; no children; 3–7 cups of coffee/day (2 qAM, 1–2 before lunch,1–3 late afternoon prn); 1–2 glasses of wine or shots of liquor 1–2 nights during the workweek and 4–6 drinks/night on weekends; exercises 3–5x/week, non-smoker.

Examination

- Body mass Index (BMI): 21.81 kg/m^2 Vitals: RR: 18, HR: 62 bpm, BP: 120/74
- Physical, neurological and mental status exam were all unremarkable

Investigations/Studies

Blood Work Complete blood count, electrolytes and other laboratory studies, including thyroid panel obtained 1 month prior to initial visit were normal.

Differential Diagnosis

Circadian Rhythm Disorder, irregular sleep/wake type
Psychophysiological Insomnia
Insomnia due to mental disorder

Discussion and Management

This case reveals behavior patterns and belief systems common amongst patients with chronic insomnia: sub-optimal sleep habits, variable sleep schedule, haphazard medication use and at doses higher than prescribed, excessive time in bed, sleep incompatible behaviors when awake in the night, ruminating in bed and worry about potential consequences of sleep loss.

The following discussion highlights some challenges of working with insomnia patients in the clinical setting and offers management strategies to enhance patient participation in treatment and ultimately achieve symptom resolution.

Explore Patient's Understanding/Beliefs About Their Symptoms, Precipitating Factors, Triggers, Management/Treatment Strategies and Outcomes

Patients presenting to the sleep center have often consulted with other specialists, tried a variety of supplements and prescription sleep aids and have some understanding, though often superficial and incomplete, of "sleep hygiene" and behavioral strategies, most of which have led to disappointment, frustration and a sense of having "tried everything but nothing works".

This was the experience of this patient; however, further probing into his medication history and responses to "sleep hygiene" was revealing. He believed that medications did not work for him though he often started a new medication after abruptly stopping another, unaware that this practice could trigger a rebound insomnia, his typical experience. Not only did each medication "failure" exacerbate his sleep

related anxiety and strengthen his belief that his situation was "hopeless," but it also discounted some potentially helpful medications.

Additionally, his sleep hygiene experience was limited to stopping caffeine and alcohol "for a few days", "trying meditation and yoga" but not consistently, dimming the lights in the evening and scrolling through social media/watching videos on his phone before bed instead of reading work documents or watching a TV show.

Understanding a patient's experience with and attitude toward behavioral strategies before proposing a treatment plan is often a key determent to treatment success.

Sleep Psychoeducation

Table 26.1 reveals some of the faulty beliefs, misconceptions and unrealistic expectations held by the patient and by many insomnia sufferers about sleep, insomnia and treatment [1].

Psychoeducation regarding sleep need, sleep architecture, normal sleep stage percentages, sleep changes with age, circadian rhythms, sleep regulation, the 3-P model of insomnia as it pertains to their history and medication uses and misuses plays an important role in addressing these faulty beliefs and in laying the foundation for cognitive and behavioral treatments. The benefits are far-reaching and serve to dispel several preconceived notions that typically perpetuate insomnia.

Had our patient had a better understanding of medication uses/misuses, he may not have had the complex sleep behaviors that resulted in his suspension from work. He believed he was taking the medication "at bedtime" as his psychiatrist (who was unaware of his variable sleep schedule and poor sleep habits) prescribed. He incorrectly assumed that "at bedtime" meant when he wanted/hoped to fall asleep rather than closer to the time that he was actually falling asleep, which for medications like zolpidem and eszopiclone, can increase the risk for complex sleep behaviors [2]. Furthermore, our patient incorrectly assumed he should take his medication earlier

Table 26.1 Faulty beliefs/expectations

• He should be able to sleep 8 h a night
• Sleep through without waking
• Fall asleep quickly and sleep well without consideration of medication time, pre-sleep behaviors or time in bed
• Rotating between different sleep aids every night would prevent dependence
• He was "addicted" to sleeping pills
• He was not getting REM sleep, which for him meant restorative sleep
• "Shutting off" the brain is needed to sleep well
• Reading/watching a show on a cell phone/tablet will not interfere with sleep as long as the material is not stressful
• Lying in bed and "trying" to sleep is useful
• The less he sleeps, the more time he needs to spend in bed
• Sleep tracking devices are accurate
• He should sleep well if he "tired myself out" with exercise

because "it was taking longer to kick in," not realizing this practice actually decreases the medication's effectiveness. He also did not understand that his heavy pre-bedtime meals could affect his medication's absorption rate.

Setting the Stage for Behavior Change

As some treatment strategies for insomnia, such as sleep restriction, are counterintuitive and can result in initial discomfort, it is not surprising that patients give up prematurely, especially if they do not understand the theory behind the strategies. With better insight into behaviors and thought patterns that have impacted their symptoms, patients generally become more receptive to cognitive and behavioral treatment strategies. An explanation of the treatment's rationale and the flexibility to progress at their pace can move a patient from reluctance to participation. For example, the standard sleep restriction guidelines would prescribe a 6 h time in bed for our patient which he found too anxiety provoking. He was most comfortable starting with 8 h, which was likely still more time in bed than he needed; however, it was less than his current time and gave him the confidence to initiate meaningful treatment steps, thereby increasing the likelihood that he would follow through with future recommendations.

Treatment Plan and Response

Despite initial skepticism, he fully participated in the following planning:

- Hour before bed: Watch TV; no phone/tablet/laptop (with permission to watch TV before bed, he felt more capable of staying off other electronics)
- 15 min before bed: zolpidem 10 mg nightly; will taper once sleep improves
- Bedtime: 11:30 pm or later
- Waketime: 7:30 am or earlier
- Read paper book in or out of bed if trouble falling or returning to sleep (to eliminate rumination/"trying" to sleep)

Outcomes

The patient was seen in follow up every 2–3 weeks, at which time sleep diaries were reviewed and the treatment plan was modified depending on his progress. Despite initial difficulties, after 5 months he reported resolution of his insomnia (see Fig. 26.2), had a consistent sleep schedule, was taking zolpidem 5 mg ~1–2x/week, felt rested and reported no episodes of complex sleep behaviors. He felt more "relaxed" about sleep and confident in his ability to handle any future bouts of insomnia. His work performance improved and he received a promotion that following year.

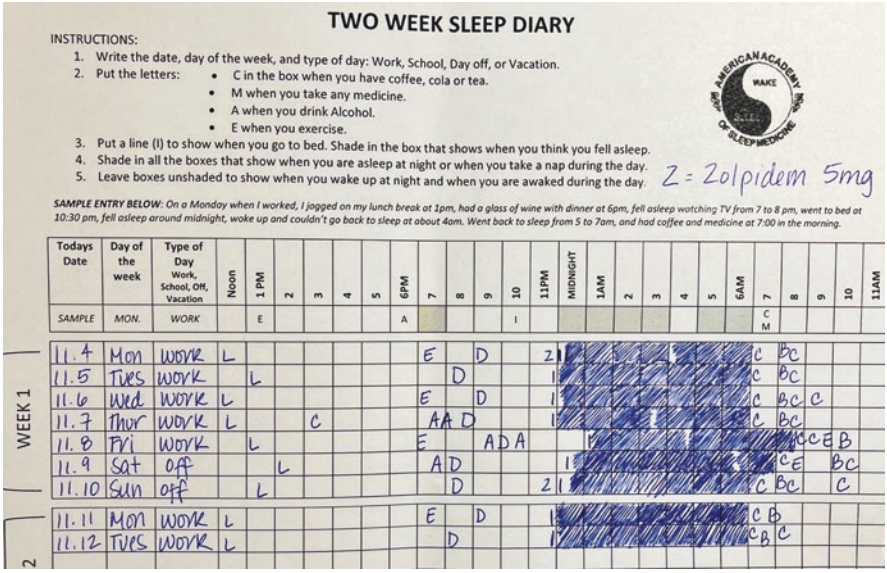

Fig. 26.2 Sleep diary following behavioral treatment. Key: B = breakfast; C = caffeine; L = lunch; E = exercise; D = dinner; A = alcohol; Z = zolpidem 5 mg; I = in to bed; Shaded Area = estimated sleep

Final Diagnosis

Psychophysiological Insomnia
Inadequate sleep hygiene

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Case 27. Storage Wars

27

Thomas Gustafson and Snigdha Pusalavidyasagar

History

A 61-year-old female with a history of obstructive sleep apnea (OSA) with chronic hypoxemia and hypercapnic respiratory failure, and late-onset Pompe disease (LOPD) presented to a sleep clinic to establish continuity of care for previously diagnosed sleep related breathing disorder (SRBD). Patient was being treated with a Bi-level positive airway pressure (Bi-level PAP) device with inspiratory positive airway pressure (IPAP):18 cmH_2O, expiratory positive airway pressure (EPAP): 6 cmH_2O with backup rate (BUR) of 15 bpm for the management of SRBD and supplemental O_2. Patient was not in any apparent distress. Respiratory exam sitting upright was normal.

Examination

Diagnosis of LOPD The diagnosis of LOPD was made after her hospitalization for acute hypoxic/hypercapnic respiratory failure five years ago. Symptoms preceding the hospitalization included progressive difficulty maintaining sleep, bilateral leg weakness, orthopnea, morning headaches, and excessive daytime sleepiness (EDS)**.** At the emergency room, arterial blood gas analysis (ABG) performed while on oxygen (O_2) 2 liters per minute (LPM) showed respiratory acidosis with pH 7.25,

T. Gustafson
Department of Sleep Medicine, M Health Fairview, Minneapolis, MN, USA
e-mail: tgustaf2@faivview.org

S. Pusalavidyasagar (✉)
Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep, University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: pusal001@umn.edu

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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pCO_2 97, pO_2 105, HCO3 41. She was intubated, and transferred to the intensive care unit (ICU). She was subsequently extubated and maintained on nocturnal non-invasive ventilation (NIV) with Bilevel PAP (timed mode) with continuous supplemental O_2 at 2 LPM. Neurology, rheumatology and pulmonary services were consulted prior to discharge.

Investigations/Studies

During hospitalization Echocardiogram showed left ventricular ejection fraction of 55–60%, without pulmonary hypertension. Muscle biopsy was positive for Pompe disease, glycogen storage disease Type II via gene sequencing.

Sleep studies obtained after the diagnosis of LOPD prior to sleep clinic visit Patient underwent a diagnostic polysomnogram (PSG) #1 following the hospital discharge in 2006, which showed mild REM predominant OSA with hypoxemia and hypoventilation: apnea hypopnea index (AHI) of 13.3/h, REM respiratory disturbance index (RDI) of 40/h and lowest O_2 sat of 82%. Due to hypoxemia, supplemental O_2 at 1 lpm was started at the beginning of the study, which may have underestimated the overall severity of the OSA. Transcutaneous pCO_2 ($TcPCO_2$) ranged from 68–83 mmHg. ABG pre and post PSG showed pCO_2 of 63 and 86 mmHg respectively. A subsequent titration study, PSG #2, showed adequate control of SRBD with Bilevel PAP at IPAP: 20 cmH_2O and EPAP:10 cmH_2O with O_2 at 2 lpm.

After the sleep clinic visit, titration study, PSG #3, was obtained. Optimum titration was achieved using Bilevel PAP at IPAP:18 cmH_2O, EPAP: 6 cmH_2O and BUR of 10 bpm. $TcPCO_2$ was stable in the mid-50's. ABG pre study: pH 7.4, pCO_2 51, $pO_2$79, HCO_3 31.

Patient presented for a follow up visit a few years later due to progressive decline in lung function (Table 27.1) despite treatment with recombinant alpha glucosidase (lumizyme). Pulmonary function tests (PFTs) showed decreased maximum inspiratory pressure (MIP) at −36 cmH_2O from previous MIP of −45 cmH_2O. A repeat titration sleep study, PSG #4, was obtained using a volume assured pressure support (VAPS) device. Due to the progressive nature of the disease and high likelihood of eventual need for on-demand ventilation, treatment was initiated using NIV in VAPS mode based on the PSG results with target alveolar rate 4.1 L/min, target

Table 27.1 Pulmonary function tests

Date	FVC (%)	FEV1 (%)	FEF 25–75 (%)
2011	30	31	32%
2013 (post lumizyme)	37	42	71
2015 (sitting)	46	45	42
2015 (supine)	20	23	27
2016	36	38	45
2021	33	36	48%

FVC Forced vital capacity, *FEV* forced expiratory volume, *FEF* forced expiratory flow

breath rate 15 bpm, EPAP: 8 cmH_2O, min PS: 4 cmH_2O, max PS: 20 cmH_2O, TiMax: 2, TiMin: 1, rise time: 600 ms, trigger medium, cycle medium on room air.

Management

To summarize, the patient is being managed with lumizyme infusions, to slow the disease progress and the respiratory failure is managed with nocturnal NIV with VAPS along with nocturnal supplemental O_2.

Discussion

Pompe disease is a glycogen storage disease that is autosomal recessive that can present during infancy, infantile-onset Pompe disease (IOPD) or any time after infancy to adulthood, late-onset Pompe disease (LOPD) [1]. It is caused by the deficiency of the lysosomal enzyme acid-alpha glucosidase (GAA) that leads to glycogen build up in the smooth, skeletal muscles with subsequent progressive muscle weakness. Dried blood spot-based GAA activity assay is commonly used for screening followed by GAA activity testing in fibroblasts or genetic testing for GAA mutations to confirm the diagnosis. Muscle biopsies are less commonly used for the diagnosis. IOPD patients have absent GAA and majority of the patients present with cardiomyopathy and high mortality and usually do not survive beyond 18 months. In contrast, the LOPD patients have reduced GAA, with respiratory involvement in more than 50% patients and comparatively less cardiovascular involvement.

LOPD is a progressive condition, with an estimated prevalence of 3.9 per million, and can occur in both men and women. Patients report shortness of breath, frequent respiratory infections, snoring, daytime headaches and EDS. Diaphragmatic involvement can impact nocturnal ventilation, predominantly during REM sleep resulting in sleep disruption, poor sleep quality and EDS. Respiratory failure is the most common cause of mortality in these patients. Fatigue severity scores have been shown to be higher in patients who report sleep disturbance and those who need NIV.

PFTs including MIP and maximal expiratory pressure (MEP) are useful in assessing the disease progression including predicting the need for nocturnal or 24-h ventilation. Spirometry shows restrictive lung disease. Spirometry measurements with forced vital capacity (FVC) in both sitting and supine positions are helpful to assess diaphragmatic weakness, since FVC reduces from sitting to supine by more than 25% in those with diaphragmatic weakness. MIP and MEP are progressively reduced in LOPD patients, with an estimated decline of 3–4% per year.

Enzyme replacement therapy with recombinant alpha glucosidase is used in these patients, to attenuate the disease progression. However, there is paucity of data regarding its impact on SRBD. NIV is the main treatment for SRBD and respiratory failure in LOPD patients. Long-term invasive ventilation via tracheostomy is needed for some patients whose ventilation does not improve with NIV or if NIV is contra-indicated.

Final Diagnosis

Obstructive sleep apnea and chronic hypoxemia and hypoventilation in adult onset Pompe disease (glycogen storage disease Type II).

Reference

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Case 28. Sleeping Up an Appetite

28

Milan Nigam and Steve A. Gibbs

History

A 45-year-old male patient with was referred for abnormal nighttime eating behaviours. His medical history included type 2 diabetes and childhood sleep terrors. His father had a history of occasional sleepwalking.

The patient reported a four-year history of sleep initiation and maintenance insomnia. During bouts of nighttime wakefulness, he was unable to fall back asleep unless he snacked first. He was fully alert during these episodes, occurring multiple times per night, wherein he would generally eat unhealthy foods. This resulted in poor daytime appetite.

Six months prior to his referral, a trial of quetiapine 50 mg had been prescribed off-label for insomnia. Although the patient reported a shortened sleep latency, nighttime awakenings persisted and a new type of abnormal eating behaviour emerged. Whereas he would previously snack during full arousals from sleep, he now suspected that he was eating while he was still asleep. He found evidence that he had prepared and eaten foods during the night, with no recollection of the events. On one occasion, he realized he had emptied an entire carton of eggs, which had been cooked in a skillet and half eaten. On another morning, he awoke in bed with a bag of uncooked, partially eaten rice.

The patient reported a gain of 40 pounds and worsened glycemic control. He was concerned about possible injuries associated with preparing food while asleep.

M. Nigam · S. A. Gibbs (✉)
Department of Neurosciences, Université de Montréal, Center for Advanced Research in Sleep Medicine, Hôspital du Sacré-Coeur, Montreal, QC, Canada
e-mail: steve.gibbs@umontreal.ca

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Examination

Examination revealed an elevated body mass index (BMI) of 35 kg/m^2, and a neck circumference of 44 cm. Examination of the oral cavity revealed a Mallampati score of 2 without macroglossia or retrognathia. Neurological examination was unremarkable except for mildly reduced pinprick sensation in his feet.

Investigations

Overnight polysomnography with a seizure electroencephalogram (EEG) montage was performed. The patient was asked to bring snack foods with him to leave at his bedside. The study revealed several sudden, unprovoked mild arousals from N3 sleep associated with an EEG pattern of persistent anterior slow waves, with alpha rhythm in the posterior regions (Fig. 28.1). During one such arousal, the patient opened his eyes, sat up, reached for a bag of chips and ate them over ten minutes before lying back down to sleep. The patient had no recall of this episode the following morning. Furthermore, the periodic limb movement index was elevated at 27/h and no significant sleep-disordered breathing was noted.

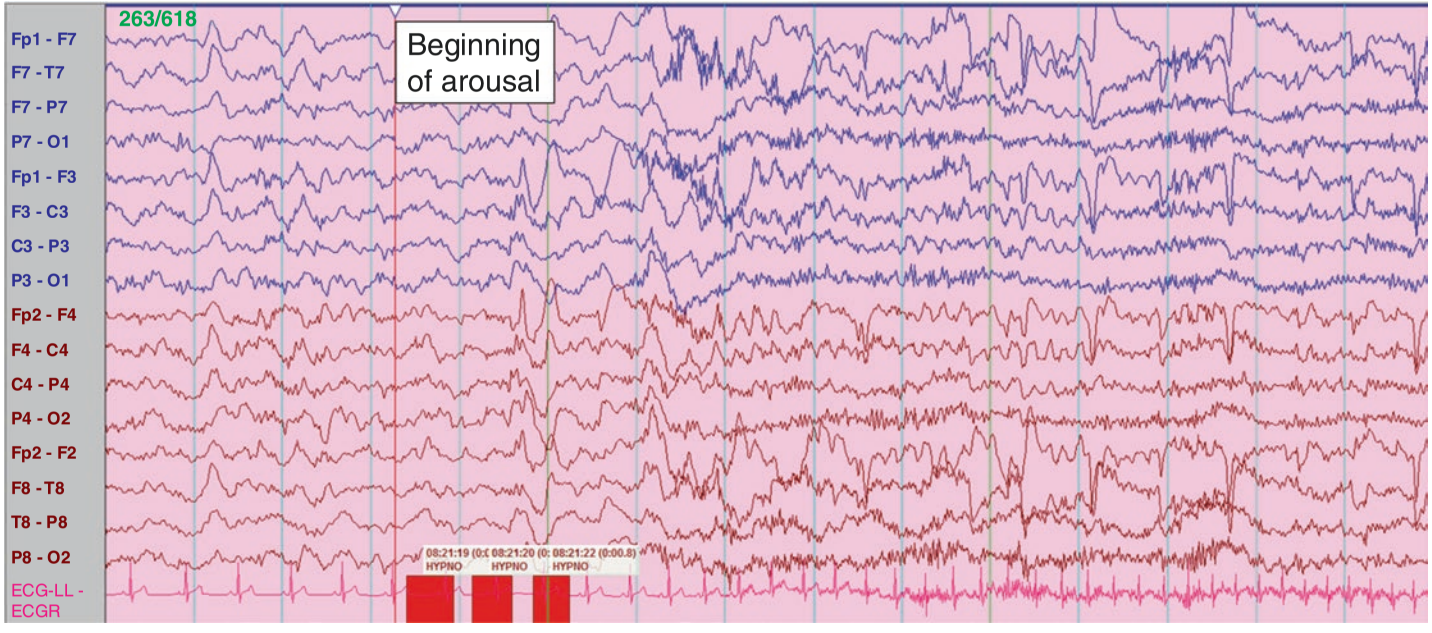

Fig. 28.1 16 channel EEG showing the typical appearance NREM parasomnias. Slow wave activity carries over from stage N3 sleep in the anterior regions, while alpha range rhythms appear in the posterior regions during an arousal from N3 sleep

Differential Diagnosis

The differential diagnosis of abnormal nocturnal food consumption includes sleep-related eating disorder (SRED), night eating syndrome (NES), binge eating disorder (BED) and bulimia nervosa (BN) Table 28.1 summarizes the main differences between these entities.

Table 28.1 Key differences between sleep related eating disorder, night eating syndrome, binge eating disorder and bulimia nervosa

	Sleep related eating disorder	Night eating syndrome	Binge eating disorder/bulimia nervosa
Timing of inappropriate food intake	Nighttime	Nighttime	At any time
Level of arousal	Partially or completely impaired	Alert	Alert
Recall of episodes	Absent or partial recollections	Yes	Yes
Consumption of unusual foods or inedible substances	Common	Rare	Rare
Volume of food intake	Often large quantities	Variable, often multiple smaller snacks	Large quantities
Purging behaviours	No	No	Yes, in bulimia nervosa
Polysomnographic findings	Slow-wave arousals, spontaneous awakenings in N3 sleep	Non-specific, impaired sleep maintenance.	Normal
Associated conditions	Sleepwalking, restless leg syndrome, eating disorders, mood disorders	Eating disorders, mood disorders	Mood disorders
Associated medications	Benzodiazepine receptor agonists, antipsychotics	–	–
Treatment	Topiramate, clonazepam	Sertraline	Psychotherapy, fluoxetine

Discussion and Management

This patient's previous history of sleep disruption with consumption of excessive food intake during full arousals during typical sleep hours with resultant daytime anorexia is fully consistent with night eating syndrome (NES). The absence of episodes of uncontrollable eating during the daytime and the absence of compensatory purging behaviours rule out both binge eating disorder (BED) and bulimia nervosa (BN). NES may occur in isolation, or it may be associated with psychiatric comorbidities, including eating disorders. It is thought to result from disordered circadian appetite regulation. The selective serotonin re-uptake inhibitor (SSRI) antidepressant sertraline has been shown to be efficacious in reducing nocturnal eating in most subjects [1].

Upon introduction of quetiapine for insomnia, the patient began preparing and consuming foods during partial arousals from NREM sleep, consistent with sleep-related eating disorder (SRED). The impaired awareness and amnesia of the episodes distinguish SRED from NES. SRED is classified as a NREM parasomnia which shares many common clinical and polysomnographic features with somnambulism and may occur in the context of a broader repertoire of NREM parasomnias (including sleep terrors and confusional arousals). It has also been associated with restless-leg syndrome and periodic limb movement disorder, possibly suggesting dopamine dysregulation as a shared pathophysiological feature. Because SRED frequently co-occurs with NES, some authors suggest that these two entities may lie on a continuum [2].

Underlying sleep conditions (sleep apnea, periodic limb movements of sleep) and sedative medications, including antipsychotics and benzodiazepine receptor agonists have the potential to precipitate NREM parasomnias by impairing full cortical arousals from NREM sleep. This leads to sleep-wake state dissociation resulting in an abnormal behaviour with impaired consciousness. The previous history of sleep terrors in childhood and positive family history demonstrate a genetic predisposition to NREM parasomnias, which were primed by the addition of a quetiapine. In addition to lacking evidence for the treatment of insomnia, atypical antipsychotics are well known to worsen metabolic syndrome, making them a particularly poor choice in this diabetic patient.

The first step in the management of this patient involved the discontinuation of quetiapine, which had served as a primer for his SRED. The episodes of SRED quickly remitted and the patient reverted to his previous phenotype of isolated NES, which remained problematic. At this point, sertraline was introduced and titrated to a dose of 100 mg daily and the patient was referred for dietary counselling. At follow-up 3 months later, the patient reported a dramatic reduction in his nighttime snacking and had lost 10 pounds.

Final Diagnosis

Sleep related eating disorder precipitated by quetiapine in a patient with a history of night eating syndrome.

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Case 29. Not All Sleep Studies Are the Same, Timing and Teaming Are Essential

29

Rasik Shah

History

The patient is a baby boy born by mother 37 years, Gravida 2, Para 1, at 35 weeks gestation by repeat caesarian section. Pregnancy was complicated by preeclampsia and intrauterine growth restriction (IUGR). Apgar score was 9 at 1, 5, and 10 min. Birth weight was 1902 g. After delivery, he was diagnosed with Pierre Robin sequence (PRS) with cleft palate and nevus flavus without any features of various syndromes. His airway obstruction was severe clinically as noted on neonatal intensive care unit (NICU) monitor, consistent with clinical diagnosis of obstructive sleep apnea (OSA). It did not respond to nonsurgical management like prone position. Computed tomography (CT) of airway was done to evaluate his mandibles and airway to plan for the surgery. It showed that occlusal plane was offset by seven millimeters (Fig. 29.1). At age of 23 days, his airway evaluation confirmed the obstruction of upper airway and glossoptosis. Hence sleep study was not considered necessary. At age of 30 days of life, he underwent mandibular distraction osteogenesis (MDO). He underwent 15–16 mm distraction without any complication, judged to be adequate clinically during monitoring in NICU in postoperative period. The distraction device was removed at age of 5 months together with endoscopy. His oral feeding remained poor, leading to poor weight gain. Hence, he underwent placement of gastric (G) tube at age of six months. At that time, sleep endoscopy was done and the airway was considered adequate from breathing stand point. But parents felt that he continued to have issues with breathing in sleep. Hence, he underwent first polysomnogram (PSG) at age of 7.5 months and was diagnosed with severe OSA (no central apneas). He did not cooperate for emergency positive

R. Shah (✉)
Department of Pediatrics, NYU Grossman School of Medicine, Hassenfeld Children's Hospital, New York, NY, USA
e-mail: rasik.shah@nyulangone.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_29

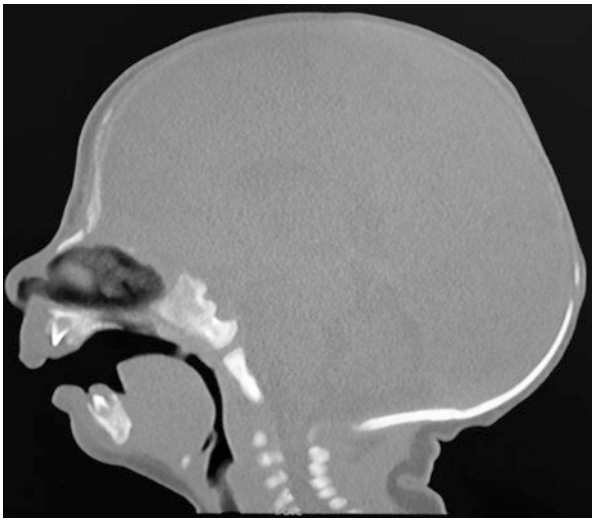

Fig. 29.1 CT scan of the oropharynx showing cleft palate and hypoplastic mandible and glossoptosis

airway pressure (PAP) therapy for his severe OSA. He was referred to sleep specialist at age of 8 months for help in management of PAP therapy. He underwent repair of cleft palate at age of 11 months. But, the repair of cleft palate did not resolve his symptoms of OSA.

Examination

At 8 months: Loud snoring, choking in supine position; prefer to sleep on side and restless sleep. Examination was significant for retro micrognathia, U-shaped cleft soft and part of hard palate, high arch hard palate and widely open mouth.

At 9 months: No change in symptoms. Family was unable to desensitize him and hence unable to use PAP therapy at night.

At 11 months: Healed cleft palate, very high arch palate, significant retrognathia and micrognathia, widely open mouth, no choking on feeding. Loud snoring in supine position once went to sleep.

At 14 months: persistent of symptoms of OSA.

Investigations

CT scan (age of 16 days): It showed micrognathia and retrognathia. The occlusal plane is offset by an approximate 7 mm. Mandibular condyles are small.

Bronchoscopy (age of 23 days): Severe upper airway obstruction from pharyngeal collapse, glossoptosis and facial deformity.

Sleep laryngoscopy (age of 23 days): There is large palate cleft; its edges are very mobile and prolapsed in the nasopharynx during inspiration creating certain degree of upper airway obstruction. There is significant pharyngeal collapse. Base of the tongue presses on epiglottis, obstructing the airway completely and creating inspiratory noise.

Bronchoscopy (Age 7 months): Severe upper airway obstruction and pharyngeal cleft. No glossoptosis.

Sleep laryngoscopy (Age 7 months, after MDO surgery): There is severe obstruction of pharyngeal airway at the level of the cleft with complete collapse during inspiration. There is partial collapse of pharynx during inspiration in the lower pharynx as well. The base of the tongue is not pressing on epiglottis at all.

PSG (age of 7.5 months): Apnea-hypopnea index (AHI): 14.4/h, only non-supine sleep recorded. Rapid Eye Movement (REM) AHI: 27.5/h, Non-REM AHI: 12.2/h. Periodic leg movement of sleep (PLMS) index of 0.7/h. Pulse oximetry <90% for 1.5% of the time, lowest oxygen saturation of 79%, moderate snoring, carbon dioxide (CO_2): within normal limits. REM sleep: 14.6%. He did not cooperate for emergency PAP titration.

Genetic testing: Whole genome chromosomal microarray did not identify any copy number changes of known clinical significance.

Diagnosis

Pierre Robin sequence S/P Mandibular Distraction Osteogenesis and repair of cleft palate with persistent of severe OSA.

Discussion

OSA in neonates/infants with PRS is primarily due to severe mandibular hypoplasia [1, 2]. In the past, severe cases were managed by tracheostomy to bypass the obstruction of the upper airway [1]. It is now managed with MDO, a major advance in the management [1, 2]. PSG should be done before surgery to quantify the severity of OSA [1, 2]. There is significant difference between monitoring of the neonate in NICU vs. actual PSG (Table 29.1). NICU monitoring for OSA must not replace a PSG.

It is equally important to have a repeat PSG to decide the degree of improvement in OSA before concluding MDO [2]. This case highlights the disparity in CT findings and the effect of sleep on breathing (via PSG) as CT gives anatomical finding while sleep study gives physiological data in real time, which quantify effect of position and sleep stages. This case also highlights inadequacy of sleep laryngoscopy for diagnosis of OSA and difference between clinically improved vs. well controlled OSA [2]. There are no guidelines about the opening of screw during the MDO. Recent suggestion is to continue to open screw to achieve 2–3 mm overjet of

Table 29.1 Comparison between PSG and NICU/PICU monitoring

Criteria	PSG	NICU/PICU monitoring
Hypopnea	Airflow <30% from baseline with microarousal or desaturation	Not known
Desaturation	Decrease 3% from baseline	<90%
Micro-arousal	scored	unknown
Differentiation between Central and Obstructive events	Possible	Not possible
Quantification of Sleep Apnea/ Hypopnea	Available	Not possible
Effect of position	Scored	Unknown
Effect of sleep stage	Scored	Unknown
CO2 measurement	Done	May be
Video recording	Always	No
Alarm	None	On Sound of alarm can affect sleep

PSG = polysomnogram, *NICU* = neonatal intensive care unit, *PICU* = pediatric intensive care unit

mandible [2]. An ideal way is to repeat PSG and confirm resolution or marked improvement of OSA [2]. An acceptable AHI is <5/h with minimal oxygen saturation no lower than 90% could represent an initial goal. Once the child passes the window of distraction or after first distraction surgery, it is very difficult to manage OSA in infant. Most infants don't tolerate interface and its prolonged use can lead to secondary mid-face hypoplasia [1]. Prone/side position is preferred by family (with the consideration that prone position could be risky due the risk of sudden infant death syndrome among some conditions). The oxygen therapy does not remove the obstruction, just prevent desaturation.

Conclusion

This case highlights the important of PSG in management of airway obstruction and OSA in severe cases of neonate and infant with PRS both before and during MDO to get optimal outcome [2].

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Case 30. Cyclical Insomnia and Hypersomnia

30

Alok Bhatt and Mandana Mahmoudi

History

A 60-year-old man presented with a complaint of worsening insomnia accompanied by excessive daytime sleepiness over the last 3 years. He had a history of chronic insomnia and severe obstructive sleep apnea [apnea-hypopnea index (AHI) 73/h], and used a continuous positive airway pressure (CPAP) device nightly. He reported that his problem was "cyclical"—he could usually sleep 9–11 h a night, would occasionally sleep 16–19 h, but sleep never felt restorative. He had no set bedtime, and would try to wake up at 10 A.M. with ~50% success. As a result, he was missing work appointments and could no longer work.

Examination

The patient was overweight (BMI 26 kg/m^2), with a crowded oropharynx and a bulky tongue. Brief neurologic exam did not show neurologic deficits.

A. Bhatt · M. Mahmoudi (✉)
Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, NYU Grossman School of Medicine, New York, NY, USA
e-mail: mandana.mahmoudi@nyulangone.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_30

Investigations

Complete blood counts showed normocytic anemia. Electrolytes, urea, nitrogen, and coagulation parameters were normal. Polysomnography on CPAP showed a reduced sleep efficiency of 54% with a total sleep time of 247 min. Sleep latency was 25 min. The arousal index was 32.6/h, not related to periodic limb movements (PLMs) or apnea/hypopnea. The AHI was 0/h, and the PLM-index was 40.5/h. No supine sleep was recorded. The patient also underwent salivary melatonin assessment on two separate occasions as seen in the figure below (Fig. 30.1). Testing showed no discernible cyclical or diurnal pattern of melatonin release. Actigraphy was performed, which confirmed a free running sleep cycle; along with periods of insomnia followed by increased sleep time (Fig. 30.2).

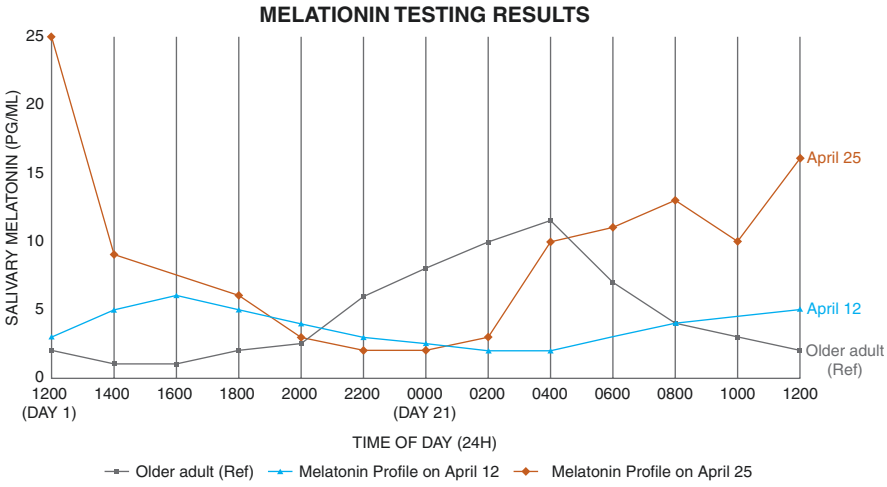

Fig. 30.1 Salivary melatonin profile of the patient on 2 separate days, showing non-cyclical melatonin release

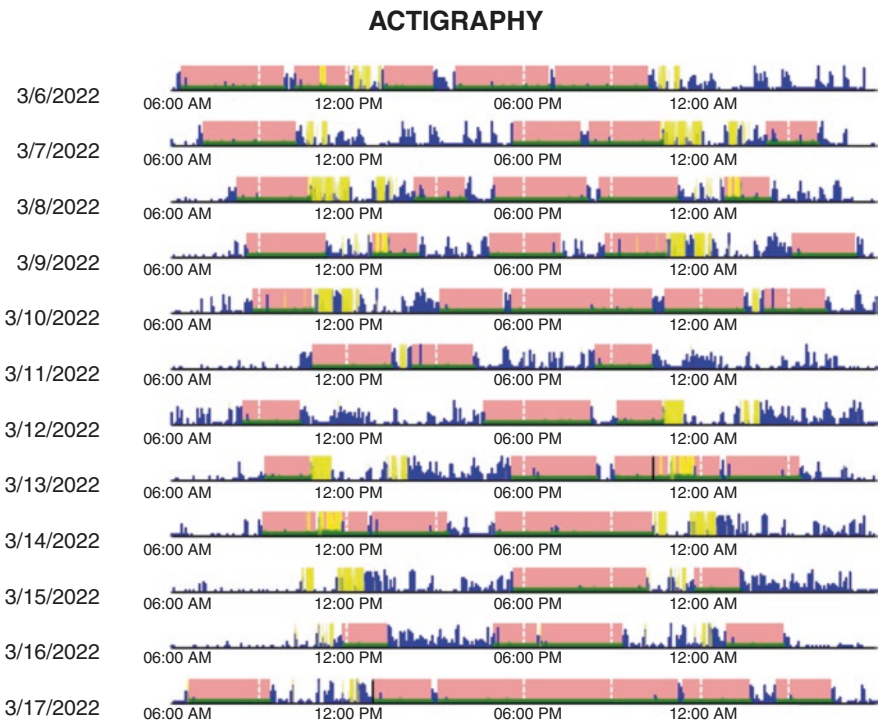

Fig. 30.2 Actigraphy results showing a free running sleep cycle. Areas highlighted in pink represent sleep, and blue annotations represent wrist activity

Diagnosis

Non 24 h sleep wake disorder due to non-cyclical melatonin release.

Discussion

This patient has a complex combination of sleep disorders, including longstanding severe obstructive sleep apnea associated with chronic insomnia, with more recent development of a circadian rhythm disorder. The lack of a consistent sleep or wake time, along with variable periods of sleep indicates an inability to regulate a near 24 h sleep wake cycle. Non 24 h sleep wake disorders (N24SWD) are well described in individuals without diurnal light exposure, e.g. blind persons, who lack photic input to their circadian pacemaker. However, this disorder may be seen in

individuals without visual impairment for various reasons. Entrainment of the 24 h cycle involves multiple factors, including exposure to both light and social cues at key times of day, periodic melatonin release during dim light hours at dusk, and coupling between sleep cycles and the circadian pacemaker.

Identifying circadian rhythm disorders can be assisted by the use of sleep diaries or sleep actigraphy, which often identifies a phase change, or a "free running" sleep cycle. Dim light melatonin onset (DLMO) testing allows for accurate assessment of the circadian pacemaker. Under settings of dim light (<10 lx), hourly salivary or urinary sampling can be used to determine the profile of melatonin release. Dim light exposure is usually started 1–2 h prior to the expected earliest melatonin release onset. This can also be coupled with timed light exposure to assess the photic sensitivity or communication of signals to the pineal gland. This patient's melatonin release did not follow any set pattern, indicating that their internal circadian rhythm was totally disrupted. Pharmacologic treatment options for N24SWD in this case include timed use of melatonin or melatonin receptor agonists to coincide with DLMO, along with bright light exposure after wake [1]. Concurrent assessment and management of environmental and social factors is critical.

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Case 31. Restless Pelvis

31

Daniel A. Barone

History

This is a 52-year-old man with a history of restless legs syndrome (RLS) for the past few years. In the last 2 years, noted "PLMD" (as he referred to them) resulted in him only sleeping for 1 h at a time. He was treated initially with gabapentin which helped the RLS. However, upon follow-up, he endorsed what sounded like an extension of his RLS; pelvic floor spasms occurring in the transition to sleep would prevent him from falling asleep, while, at the same time, his original RLS was stable. We increased the gabapentin up to 600 mg and had added melatonin up to 10 mg, which did not help the pelvic floor symptoms. Additionally, he developed further twitching sensations in his left hand and face.

Examination

Healthy man in no acute distress. Body mass index (BMI) was 24.8 kg/m^2, but no further examination was possible as this was done via video visit. However, no gross neurologic abnormalities were noted, there were no tremors in particular.

Investigations/Studies

Polysomnogram (PSG) testing revealed a total sleep time of 285 min and reduced sleep efficiency at 60%. Sleep latency was 17 min; REM latency was 201 min. The percentage of N1 sleep stage was elevated at 13%. The apnea-hypopnea index

D. A. Barone (✉)
Clinical Neurology, Department of Neurology, New York-Presbyterian, Weill Cornell Medicine, New York, NY, USA
e-mail: dab9129@med.cornell.edu

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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(AHI) was 1/h. The lowest SaO_2 was 92%. Snoring was not noted. There were Periodic Limb Movements of Sleep (PLMS) with an index of 22/h. PLM-arousal index was <1/h. Ferritin level was 100 ng/mL Magnetic resonance imaging (MRI) of the brain was unremarkable.

Differential Diagnosis

This was initially thought to be a form of RLS as this condition could present itself in the hands, arms and trunk. The other possibility was rhythmic movement disorder or another movement disorder of unclear etiology. He was referred to a movement disorder specialist following the prior workup.

Discussion and Management

This case has similar features to rhythmic movement disorder, which has an overlap with RLS [1]. The medical literature is parse, but there is one case report of a PSG evidence of a patient with a 4-year history of an unpleasant restless sensation originating in his lower abdomen with stereotyped, repetitive, rhythmic pelvic body movements resembling coital behavior at the wake–sleep transition. The authors noted the spectrum of rhythmic sleep-related movement disorders, of which our patient in question may have been suffering from. Our patient was placed on ropinirole 2 mg time release and symptoms decreased dramatically; as of this writing he is sleeping through the night. He tapered down melatonin and is no longer on gabapentin.

Final Diagnosis or Most Likely Diagnosis

This is likely RLS perhaps with comorbid rhythmic movement disorder. Both have been shown to respond to dopamine agonists (DA) of which ropinirole is one. The conundrum about this case is that the patient described what sounded like augmentation, which can be seen following chronic use of DA; but given the fact that he was initially not on a DA, the likelihood is that this presentation was actually rhythmic movement disorder in conjunction with RLS.

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Case 32. A Young Child with Sleep Onset Insomnia and "Weird" Feelings on His Legs

32

Lourdes M. DelRosso and Raffaele Ferri

History

A 6-year-old boy is referred to sleep clinic for complaints of "insomnia". The parent states that his is a normally developing child with no other medical history. He was born full term, without complications. The parent states that sleep was never an issue until about 9 months ago. The parent first noticed restlessness at bedtime which worsened with time. A couple of months ago the child reported leg pains at bedtime that were diagnosed by his pediatrician as "growing pains." The parent reports a consistent bedtime of 8 P.M. The bedtime routine includes brushing teeth, changing into pajamas, and turning lights off. The parent leaves the room but hears the child moving and fidgeting for at least 1–2 h before he finally falls asleep at around 10 PM. When asked directly about what happens in those 2 h prior to sleep, the child responds, "my legs feel weird." He is not able to tell whether symptoms improve with movement. The parent does not notice snoring, sleepwalking, enuresis, or any other abnormal behaviors at night. Some nights the parent hears him kicking in the middle of the night but when the parent goes to check on the child, finds the child sleeping and with bedcovers on the floor. He wakes up at 6:30 A.M. to go to school. During the day the child is tired but does not fall asleep in class and does not take naps. The teachers describe him as a child that "can't sit still for prolonged periods of time" but does not leave his chair and does not usually run around or interrupt in class. On occasions he appears to be easily distractible but for the most part he is organized, listens when spoke to, and follows instructions. His grades are below average but not failing. He does not report symptoms of

L. M. DelRosso (✉)
Department of Pediatrics, University of Washington, Seattle, WA, USA

R. Ferri
Sleep Research Centre, Oasi Research Institute—IRCCS, Troina, Italy
e-mail: rferri@oasi.en.it

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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depression or anxiety. Past family history of sleep disorders is significant for obstructive sleep apnea in his paternal grandmother. Upon further questioning about sleep related movement disorders the mother remembers feeling the "urge" to move her legs during pregnancy, but was never diagnosed.

Examination

The vital signs are within normal. Body mass index is within the 45th percentile per age. The child is cooperative and appears in no distress. He does not show adenoidal facies, his palate is normally positioned. Mallampati score is I. Tonsils are 1+ bilaterally. He does not have retrognathia or micrognathia. He has normal tone and strength. There are no skin lesions. The remainder of the exam is normal.

Investigation/Studies

Polysomnography (PSG) was ordered and showed a sleep latency of 52 min (normal <30 min). Sleep efficiency of 80% (normal >85%). Arousal index 10/h. (normal). The obstructive apnea hypopnea index is 0.3 (normal <1). There were no significant desaturations and no hypoventilation. The central apnea index was normal. The periodic limb movement index (PLMI) is elevated to 17/h. (normal PLMI <5/h) (Fig. 32.1).

Laboratory tests included Ferritin level of 12 ng/mL.

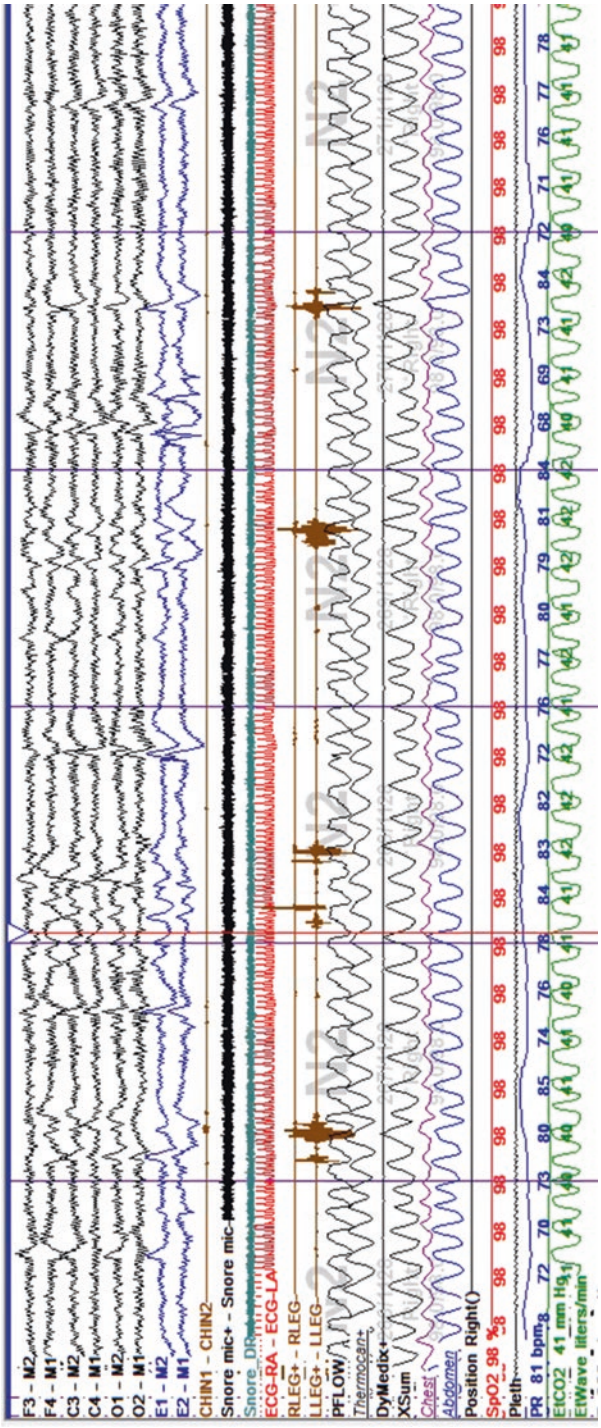

Fig. 32.1 Polysomnographic fragment showing a sequence of four periodic limb movements of sleep in lead LLEG and RLEG

Differential Diagnosis

Sleep onset difficulty and restlessness in children can have a wide differential diagnosis. First inadequate sleep hygiene can contribute to delayed sleep. It is important to further assess use of electronics after the parents leave the room, need to inquiry if the child has access to phone, video games, television, etc. Insomnia in children can be behavioral and consist of limit setting or sleep association insomnia. This does not appear to be the case in our patient since the child stays in his room without requiring parental intervention or having any requests from the parents. Psychiatric disorders including anxiety can contribute to sleep onset insomnia and nocturnal awakenings. Sleep disruption secondary to medical disorders (eczema, asthma, and others) has demonstrated restlessness and inability to sleep due to itching, coughing or another disrupting symptom. Medications or caffeine use close to bedtime can adversely affect sleep. Growing pains, mentioned in the history are often diagnosed in children without a detailed history, in fact restless legs syndrome (RLS) is often misdiagnosed as growing pains. The key in RLS is the improvement of symptoms with movement which is not always seen in growing pains. But there are many overlapping characteristics. Finally, RLS has shown to present with sleep onset insomnia in children. The fidgety, restlessness, leg kicks, (PLMI >5) and family history of RLS in mother are factors that support the diagnosis of RLS. In children the diagnosis of RLS is made with the child expressing in his/her own words the symptoms. Many children, particularly younger children cannot elicit all four criteria, and supportive findings (PSG and family history) are important clues to the diagnosis.

Discussion and Management

Restless legs syndrome affects approximately 2% of children. The main presenting symptom can be insomnia. In fact sleep disturbances can often precede the diagnosis of RLS by many years. The diagnosis of RLS in children must include the description of the symptoms in the child's own words, but unfortunately in young children we do not always elicit all four criteria [1]. In fact Picchietti, et al. described that younger children with RLS did not fit all diagnostic criteria, which contributed to the delay in diagnosis and treatment. Other important symptoms besides the "urge to move the legs" include worsening of symptoms in the evening or during prolong periods of rest, and improvement of symptoms with movement. Although polysomnography is not indicated for the diagnosis of RLS, the presence of PLMS can be supportive of the diagnosis of RLS as 70% of children and 80% of adults with RLS have PLMS on PSG. Figure 32.1 shows a series of 4 PLMS during polysomnography that in total yielded an elevated PLMS index.

The treatment of RLS in children is iron supplementation when ferritin levels are below 50 ng/mL. Oral iron supplementation usually ferrous sulfate 3 mg/kg/day for 3 months is the initial recommended treatment. Due to poor absorption and challenges with adherence secondary to side effects to oral iron, intravenous iron supplementation has recently emerged as a promising therapeutic option for children with RLS [2].

Final Diagnosis

Restless legs syndrome with Periodic limb movements of sleep.

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Case 33. Hallucinations May Be the Clue

33

Alex Iranzo

History

In 2006, a 68-year-old right-handed woman was self-referred to our sleep center because of snoring. She was a widow for 20 years. Detailed clinical history revealed a 3-year-history of nightmares and dream-enacting behaviors witnessed by her daughter when they slept together while they were on vacation. Observed behaviors consisted in kicking the wall and shouting sentences such as *get out of here dirty robber! leave me alone!* and *retreat!* She was completely unaware of these behaviors. As she broke her leg kicking the wall during her sleep, she placed cushions and a rail on the bed so as not to hurt herself or fall out of bed. She recalled recurrent nightmares where she was threatened by burglars who broke into her house to steal and hit her. She never sought medical advice for these vigorous sleep behaviors and nightmares because she thought that they were a normal phenomenon. Her past medical history included constipation and hyposmia. The patient had no overt cognitive or motor complaints and she was not taking medications.

Examination

Physical and neurological examinations were unremarkable. Pyramidalism, parkinsonism and cerebellar syndrome were ruled out. Unified Parkinson's disease rating scale (UPDRS-III) motor examination score was 0, as bradykinesia, rigidity, tremor, and gait abnormalities were absent.

A. Iranzo (✉)
Sleep Disorders Center, Neurology Service, Hospital Clinic de Barcelona, Barcelona, Spain
e-mail: airanzo@clinic.cat

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Investigations and Follow-Up

At referral, polysomnography (PSG) was performed including synchronized audiovisual recording plus surface electromyographic (EMG) evaluation of the chin (mentalis), and the lower (anterior tibialis) and upper (flexor digitorum superficialis) limbs. PSG excluded obstructive apneas and periodic leg movements during sleep. Snoring was detected only in the supine position. Excessive EMG activity was detected in the mentalis and in the four limbs during REM sleep (accounting for 47% of the total REM sleep time) that was associated with prominent body jerks, raising the hands, laughing, and moaning. Brain magnetic resonance imaging (MRI) and a comprehensive neuropsychological battery of tests were normal. Folstein mini mental state exam (MMSE) score was 28/30. With all this information, the diagnosis of idiopathic REM sleep behavior disorder (IRBD) was made.

During a 10-year period, between 2006 and 2015, the patient did not experience remarkable changes in her neurological and sleep conditions. She refused to take medications (e.g., clonazepam, melatonin) to improve her RBD symptomatology. She also declined to undergo ancillary tests such as dopamine transporter-single photon emission computed tomography (DAT-SPECT) scan and a smell test to estimate her risk to be diagnosed with a neurodegenerative disease. She declined to participate in investigations done in our institution (organ biopsies, lumbar puncture, and nasal swab) searching for synuclein in some peripheral organs, the olfactory mucosa, and the cerebrospinal fluid.

In 2016, at the age of 78, she first reported abnormal experiences when she went to bed and turned off the lights but also in the middle of the night. These experiences consisted of the "vision" of a man (an unknown person or his dead husband) standing in front of her or sitting at her bed looking at her with a menacing face. Other times the man would show her his penis and attempt to have sex with her in a gentle manner. The patient was very afraid of these people and would talk to them and ask them to leave. The people would reply that they would not go away. At other times, shadows would appear coming in and out of the walls. When the patient turned on the lights, the people and the shadows vanished, but she needed to get out of bed and checked all over the house to see that they were gone. The patient was convinced that these experiences were dreams because she reported to be asleep when they appeared. Although these experiences occurred every night and they frightened her, she preferred not to take medications, thinking that she would get used to them.

During a 3-year period of "visions", between 2016 and 2019, she did not report cognitive problems and motor examination was normal with a UPDRS-III score of 1. In 2016, brain MRI was normal, and the comprehensive neuropsychological battery testing showed mild abnormalities in the Trail-Making Tests A and B, while memory and visuospatial functions were normal and the MMSE score was 27/30.

In November 2019 she reported a 3-month history of memory problems and impairment of the activities of daily living. Neuropsychological testing showed marked

abnormalities in the executive, memory, and visuospatial domains and a MMSE score of 23/30. Motor examination excluded parkinsonism. Video-PSG showed: (1) theta activity of 6–7 Hz during wakefulness with the eyes closed, (2) an abnormal sleep architecture characterized by absence of K complexes and sleep spindles during no-REM sleep plus RBD, and (3) two episodes arising from REM sleep where the patient opened her eyes, seemed confused, gesticulated as she was trying to grab someone or something, and shouted "I'm going to hit you with a heavy stick". The morning after this study the patient reported that she had "seen" the sleep technician entering in the room and trying to hurt her with some scissors.

Differential Diagnosis

The patient was unaware of displaying abnormal complex behaviors and reported sleeping well, a situation not uncommon with IRBD. Besides, she was not aware that dream-enacting behaviors may be a pathological phenomenon, particularly in people older than 60 years. In fact, most people with idiopathic RBD do not seek medical advice.

At referral, her RBD symptomatology included a 3-year history of frightening dreams where she was threatened by burglars who broke into her house to steal and hit her. After several years of follow-up, she experienced new fearful experiences where she "visioned" people and shadows who threaten her in her bedroom. She could communicate with them, and she was able to make them disappear as she turned on the light. However, the experiences were so real that she needed to check all over the house to see that they had disappeared. She reported that these "visons" corresponded to nightmares like those that she had experienced in the past. However, PSG showed that these events occurred when she had the eyes open and occurred during wakefulness arising from REM sleep. Thus, we concluded that they were no dreams but complex nocturnal visual hallucinations. Interestingly, these complex visual hallucinations occurred almost nightly during approximately 3 years where the patient did not report cognitive problems and neuropsychological testing was normal. However, follow-up showed the appearance of dementia as she developed cognitive problems, and neuropsychological testing plus the activities of daily living were impaired. The patient was finally diagnosed with dementia with Lewy bodies [1] because she had dementia, RBD and hallucinations.

This case illustrates that (1) nightmares are sometimes difficult to differentiate from complex nocturnal visual hallucinations, and that (2) hallucinations may precede cognitive impairment during several years. Nightmares are disturbing well-remembered dreams where the patient is oriented and alert on awakening realizing that he had an unreal dream. In contrast, complex nocturnal visual hallucinations occur following a sudden awakening or during the transition from wakefulness to sleep. They are vivid, detailed, relatively stereotyped, static, or mobile, and may include colorful images of people, animals, and elaborated scenes resembling a dream. They can last a few seconds or several hours. They usually disappear if the

eyes are opened or if the lights of the room are switched on. Insight regarding the hallucinations is reduced and subjects may believe they are true and leave the bed to investigate if the images were real or not [2]. The anatomical substrate of the complex nocturnal visual hallucinations shares a final common pathway where the occipital visual cortex generates false images from reduced sensory inputs. Input deficit may arise from the occipital cortex itself (e.g., in dementia with Lewy bodies) or its afferents from the thalamus (e.g., peduncular hallucinosis), the brainstem (e.g., Parkinson disease) and the retina (e.g., Charles Bonnet syndrome).

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Case 34. Hard to Diagnose, Hard to Treat

34

Akinbolaji Akingbola, David J. Bond,
and Snigdha Pusalavidyasagar

History

The patient was a 44-year-old man with bipolar disorder (BD) type 2 and generalized anxiety disorder. He was prescribed desvenlafaxine, cariprazine, and electroconvulsive therapy (ECT) every 5 weeks. He presented to the sleep clinic complaining of excessive daytime sleepiness (EDS) for 6–12 months. He worked at a local news station and kept non-conventional work hours, including 5 AM to 1 PM or 12:30 PM to 8:30 PM shifts. When he worked the 5 AM to 1 PM shift, he typically went to bed at 9 PM and woke at 4 AM. When he worked the 12:30 PM to 8:30 PM shift, he typically went to bed at 10 PM and woke at 7:30 AM. He denied difficulty falling asleep, and reported 0–3 nocturnal awakenings per night, with no difficulty resuming sleep. He reported frequent daytime napping. Naps lasted 30 min to 1.5–2.5 h. His daytime sleepiness was so significant that he began sleeping in his car on work breaks. He had an Epworth Sleepiness Scale score of 19, consistent with EDS and an Insomnia Severity Scale (ISS) of 19, consistent with moderate insomnia. He reported snoring and morning headaches once per week, but denied snort arousals or gasping, choking, witnessed apneas, or dry mouth. He reported occasional

A. Akingbola
Department of Pulmonary, Allergy, Critical Care and Sleep Medicine, University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: aaking@umn.edu

D. J. Bond
Department of Psychiatry and Behavioral Sciences, University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: djbond@umn.edu

S. Pusalavidyasagar (✉)
Division of Pulmonary, Allergy, Critical Care and Sleep, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: pusal001@umn.edu

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_34

hypnopompic sleep paralysis, but denied cataplexy or hallucinations. He denied sleep walking, sleep eating, vivid dreams, nightmares, confusional arousals, night terrors or dream enactment behavior.

Examination

The patient appeared awake, alert, and in no acute distress. He was 5′10″ tall, weighed 206 pounds, with a body mass index (BMI) of 29.8 kg/m^2. Neck circumference was 41 cm. His mood appeared euthymic, and his affect was congruent.

Investigations/Studies

Two weeks of actigraphy with concomitant sleep logs, diagnostic polysomnogram (PSG), and multiple sleep latency test (MSLT) were obtained. After consultation with his psychiatrist, his desvenlafaxine and cariprazine were held for 2 weeks prior to the sleep tests. Actigraphy demonstrated variability in the sleep pattern that was consistent with his described sleep pattern dictated by his work schedule (see Fig. 34.1). During the majority of the recordings the patient's total sleep time was 8 h except for three nights when he had a reduced sleep time of 7 h. Prior to the PSG, he consistently obtained 8 h of sleep. His PSG demonstrated reduced sleep latency of 8.2 min and prolonged REM latency of 257 min. Despite an increased arousal index of 28/h (mostly spontaneous), his sleep efficiency was normal and all sleep stages were observed. There was no evidence of sleep-related breathing disorder [(apnea-hypopnea index (AHI):1.7/h] or limb movements or abnormal sleep related behaviors. Urine toxicology was negative. MSLT obtained the morning following the PSG consisted of 4 nap sessions. The mean sleep latency for the naps was 3.9 min. There were 3 sleep onset REM periods during naps 2–4. The findings of this MSLT fulfilled the American Academy of Sleep Medicine (AASM) criteria for narcolepsy without cataplexy.

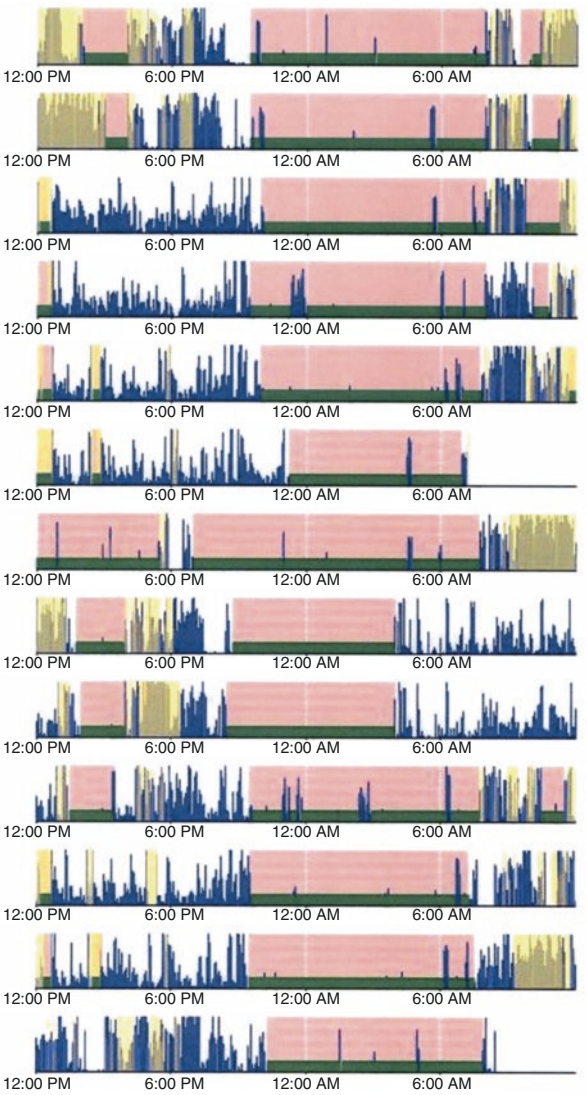

Fig. 34.1 Actigraphy data for the 2 week period. Areas in pink indicate the sleep periods, yellow indicates light exposure, blue indicated muscle activity

Differential Diagnosis

In addition to narcolepsy, the differential diagnosis includes idiopathic hypersomnia, hypersomnia due to psychiatric disorder, hypersomnia due to medication, insufficient sleep syndrome, irregular sleep-wake rhythm disorder, shift work sleep disorder, and long sleeper.

Discussion and Management

The diagnosis and management of narcolepsy in patients with BD is challenging. It is important to consider multiple factors including sleep quantity, sleep quality, circadian disturbances, psychiatric diagnosis and medications, and comorbidities which may contribute to hypersomnia.

This patient presented several diagnostic challenges including his diagnosis of BD requiring two medications and ECT. While the effects of his medications on sleep architecture are well known, it is unclear how ECT impacts sleep architecture. We were able to control medications by safely holding them under his psychiatrist's supervision. Additionally, shift work disorder could be considered on the differential diagnosis due to the variability of sleep-wake schedule. However, per actigraphy it appears that he obtains adequate sleep despite his shifting schedule and the addition of naps are not helpful. In the setting of adequate sleep duration, it is possible that his hypersomnia is a result of his mental health condition, however, with the addition of ECT his mood has significantly improved and is euthymic. The MSLT findings are more consistent with narcolepsy than with idiopathic hypersomnia. It is plausible that the absence of cataplexy may be explained by the patient's long-standing serotonin norepinephrine re-uptake inhibitors use. Ultimately this presentation was deemed to be most consistent with narcolepsy without cataplexy, especially in light of adequate sleep duration and a normal sleep-wake cycle immediately preceding his PSG/MSLT.

With respect to management, the patient was advised to modify his work schedule to achieve a consistent sleep schedule, with scheduled daytime napping for 15–20 min, regular exercise, and optimized sleep hygiene. A trial of modafinil or armodafinil is an option for the management of narcolepsy. However, there is a concern for mood destabilization in BD patients, even in those treated with mood stabilizers. This class of stimulant medications are best trialed under a psychiatrist's supervision so the patient was referred back to psychiatry.

Sleep disturbance is a core feature of BD and can impact mental health prognosis. Insomnia, long sleep time, and hypersomnia have been reported in BD [1]. Sleep disturbance has been associated with recurrence of depression, mania, and hypomania, and can negatively impact quality of life. Hypersomnia is more common in BD compared to other psychiatric disorders. Hypersomnia in BD patients is commonly attributed to medications, sleep disorders such as obstructive sleep apnea, atypical depression, and other medical comorbidities. However, there have been a small number of reports of narcolepsy in BD. Meats et al. reported a case of narcolepsy in a BD patient who presented with cataplexy in association with mania. Douglass et al. reported six cases of narcolepsy, with prominent hypnagogic hallucinations by MSLT in patients with BD and psychotic features. Recent studies suggest that EDS in BD patients may be related to decreased cerebrospinal fluid histamine levels and differences in the human leukocyte antigen (HLA) DQB1*0602. Even though narcolepsy is relatively rare in this patient population, sleep evaluation was helpful in the management of our patient.

Reference

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Case 35. High Pressure Situation

35

Xinyi Hong, Patrick Sorenson, and Ashura Williams Buckley

History

A 13-year-old male child was admitted to the National Institutes of Health (NIH) Clinical Center in July 2021 with a history of relapsed anaplastic lymphoma kinase (ALK) negative anaplastic large cell lymphoma initially diagnosed in September 2017 at age 9. He had subsequently undergone six cycles of chemotherapy, which completed in January 2018. The patient was admitted to a pediatric intensive care unit in June 2020 due to eosinophilia and respiratory distress, requiring Bi-level positive airway pressure (PAP) support. A chest computed tomography (CT) showed diffuse parenchymal lung inflammation, increased lymphadenopathy, and the presence of new pulmonary nodules. A second cycle of chemotherapy was started in February 2021 due to relapse of lymphoma and was continued during his stay at the NIH. He was newly enrolled in a protocol for allogeneic hematopoietic cell transplantation.

The patient had no family history of cancer or autoimmune disorders. He had had a history of lower back pain since November 2020, and a magnetic resonance imaging (MRI) several months before admission showed multiple vertebral compression

X. Hong (✉)
National Institute of Mental Health, National Institutes of Health Clinical Center, Washington, DC, USA

Sleep and Neurodevelopment Service, National Institute of Mental Health, Bethesda, MD, USA
e-mail: xinyi.hong@nih.gov

P. Sorenson · A. W. Buckley
Sleep and Neurodevelopment Service, National Institute of Mental Health, Bethesda, MD, USA
e-mail: sorensonpg@nih.gov; shu.buckley@nih.gov

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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fractures requiring a back brace be worn during waking hours. In addition, the patient had been receiving high-dose prednisone treatment, and efforts to wean off steroids resulted in recurrence of respiratory distress and eosinophilia. He also had steroid-related hyperglycemia, for which he was started on daily subcutaneous insulin injections several weeks prior to admission. Other medications included; levalbuterol, cetirizine, magnesium, montelukast, omeprazole, pentamidine, spironolactone, triamcinolone, and valacyclovir. A diagnosis of obstructive sleep apnea (OSA) had been made about nine months prior to admission for which he used continuous positive airway pressure (CPAP) nightly. Comorbidities included enlarged pulmonary artery with pulmonary hypertension, chronic sinus tachycardia, glucose-6 phosphate dehydrogenase (G6PD) deficiency, atopic dermatitis, eczema, recurrent ear infections, and lower extremity edema.

Examination

Child was noted to be alert, quiet, and cooperative, answering questions appropriately for his age. He had moon facies and a distended abdomen with striae throughout and no rebound. Breath sounds indicated good air entry bilaterally. Cardiovascular exam indicated tachycardia, with no murmurs, gallops, or rubs. His skin was dry and scaly in places and was thin and fragile. He used a rolling walker to get up from sitting position and during ambulation to support his weight. Patient's left foot was swollen and edematous.

Investigations/Studies

A sleep medicine consult was obtained after the respiratory therapy team noted multiple desaturation nocturnal events into the 80's despite CPAP usage. Compliance data obtained from the durable medical equipment (DME) company showed near 100% compliance at 8 h/night, at 15 cm of water pressure (cwp), for the past 6 months. In-house polysomnogram evaluation demonstrated 207 total sleep-related respiratory events, resulting in a respiratory disturbance index (RDI) of 25/h with the patient's current mask and settings. A high mask leak was found via a CPAP algorithm download, and a new nasal mask was subsequently trialed. Pressure was lowered and exogenous oxygen added with titration to the low 90's. Final pressure of 8–10 cwp was determined to provide resolution of the patient's obstructions with the new properly fitting mask.

Differential Diagnosis

The persistent low readings on the finger probe on the floor, despite very high CPAP settings were concerning. Hypoxemic values could have been due to a faulty signal in this child with poor skin integrity, although there was no evidence of digital

clubbing, deep pigmentation, or the presence of methemoglobinemia, either due to hereditary or medication reasons, that might suggest a cause for persistent erroneous readings. Child did have history of chronic lung disease, including new pulmonary nodules and pulmonary hypertension and diffusion impairment due to lung fibrosis, V/Q mismatch potentially due to a pulmonary embolus or a right-to-left shunt due to an obstructed airway were each considered. Medications that decrease ventilatory drive such as opioids, as well as neuromuscular weakness in this child with compression fractures are also important parts of the differential.

Discussion and Management

This child had had OSA properly identified prior to admission, but the essential follow up and assessment of his CPAP treatment had not been evaluated for almost a year after it was prescribed. The mask had not been appropriate initially and was showing signs of wear and tear when evaluated by the sleep medicine team. In addition, subsequent steroid induced changes to facies had likely made the fit worse. The family had been completely compliant but had been unaware that they could reach out to the DME company to have the mask fit checked. The presence of the leak and subsequent change of mask and decrease of cwp allowed resolution of apneic events. Sleep disordered breathing (SDB) is an independent risk factor for the development of systemic hypertension and is associated with congestive heart failure, atrial fibrillation and all cause morbidity and mortality [1]. Identification is necessary, especially in vulnerable patients like the proband, but follow up care and patient/caregiver education is essential.

Final Diagnosis

Improper CPAP management due to incorrect mask fitting.

Reference

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Case 36. A Cerebral Change in Eating Behavior

36

Nishay Chitkara

History

A 27-year-old man with a history of a car accident complicated by a femur fracture and facial injury requiring multiple surgeries presented for evaluation of sleep disruption. He wakes up suddenly at night, with 'a burst.' He has something to eat and goes back to sleep without any trouble. He eats anything he can find. If there is juice in the fridge, he may drink as much as a full carton. He knows he is awake, but he cannot stop himself from eating at night. This nocturnal behavior has occurred regularly since his accident. Before the accident, he would have nocturnal eating behavior once every 3 months or so. He usually has eating behaviors during the first half of the night, between 1:30 AM and 3:00 AM. He had woken up with eating behaviors every night for 4 months. He had been remembering these episodes more and more, unlike in the past when he would often not remember them. He reported a history of parasomnias, with episodes of sleep walking before age 13.

The patient had a lot of stress during the time of his accident and in the subsequent recovery period. His accident occurred when he was an adolescent, in his late teenage years. His mother tells him that he became a different person during that 1–2 year period.

N. Chitkara (✉)
Internal Medicine/Pulmonary, Critical Care and Sleep Medicine,
NYU Langone Health and Bellevue Hospital, New York, NY, USA
e-mail: nishay.chitkara@nyulangone.org

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Examination

The patient was alert and oriented to person, place and time. He had a normal mood and affect. He was of average build, with a body mass index (BMI) of 27.2 kg/m^2. His oropharyngeal exam was notable for crowding of the posterior pharynx, with a Mallampati class 4 airway. His physical exam was otherwise unremarkable.

Investigations

A diagnostic nocturnal polysomnogram showed no evidence of sleep disordered breathing, with an apnea-hypopnea index (AHI) of 1.9/h. Stage N3 sleep was reduced (0.3% of total sleep time) and REM sleep was reduced (17.2% of total sleep time) during this study.

Diagnosis

Sleep related eating disorder/Nocturnal eating syndrome.

Discussion

Nocturnal eating syndrome (NES) was originally described in 1955. It is characterized by the triad of nocturnal hyperphagia, insomnia, and morning anorexia, along with the absence of daytime eating disorders. NES occurs during wakefulness, usually resulting in a complaint of sleep-onset insomnia due to hunger. Patients will consume high calorie foods, and usually have a prominent component of underlying psychiatric conditions such as depression and anxiety. NES is often associated with stressful life events and periods of weight gain [1].

Sleep related eating disorder (SRED) is characterized by recurrent episodes of involuntary eating and drinking occur during the main sleep period. These episodes are associated with the following: (1) consumption of peculiar forms or combinations of food or inedible or toxic substances, (2) insomnia related to sleep disruption from repeated episodes of eating, with a complaint of nonrestorative sleep, daytime fatigue, or somnolence, (3) sleep-related injury, (4) dangerous behaviors performed while in pursuit of food or while cooking food, (5) morning anorexia, (6) adverse health consequences from recurrent binge eating of high calorie foods. The disturbance is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder. SRED has a strong association with other sleep disorders. It features partial or complete amnesia for eating episodes. It is a variant of a NREM arousal parasomnia, with a high frequency of arousals from slow wave sleep (SWS) [1].

The patient had features of both nocturnal eating syndrome and sleep related eating disorder. He was predisposed to these conditions by his history of parasomnias,

and significantly due to his history of traumatic injury (including face/head) and the subsequent period of stress he experienced. His early history of eating during sleep was consistent with SRED, given the amnestic component of his eating behaviors. After his accident, his eating behavior was more consistent with NES, due to the awareness/wakefulness related to his nocturnal hyperphagia.

Management of NES and SRED can include the following: cognitive behavioral therapy, education about healthy eating, relaxation strategies, establishing social support, improving physical activity. Both of these sleep-related eating behaviors can also be treated by having a moderate calorie fat/protein snack 30 min before bedtime. Such a meal may satiate one through the early part of night and thereby prevent sleep eating, since less SWS occurs in the later part of night. Pharmacologic treatment can include selective serotonin re-uptake inhibitors (SSRIs), topiramate, melatonin and clonazepam.

The patient was unfortunately lost to follow up.

Reference

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Case 37. "I'm Not Schizophrenic!" Is It Catalepsy or Cataplexy?

37

Marta Maczaj

History

36-year-old woman brought to the emergency room by her husband due to 2 days duration of paranoid thinking and irrational fears that her children will be taken away from her. She informed the emergency room (ER) staff that she is suffering from an acute asthma exacerbation due to bronchitis for which she is taking an inhaler and was started on clarithromycin and steroids a few days ago. She also informed the ER staff that she has narcolepsy with cataplexy for which she is treated with sodium oxybate oral solution. She self-discontinued this medication prior to starting the steroids. She was also taking paroxetine for an anxiety disorder. Her pulmonary and medical status was deemed stable in the medical ER and she was transferred to the psychiatric ER for further evaluation of her paranoid thinking. She was held in the comprehensive psychiatric emergency program for 24 h and then admitted to the psychiatric unit of a local hospital. During her hospitalization, she was not placed on any new medications, her steroids were discontinued since her pulmonary status improved and she was maintained on paroxetine.

Within 3 days, her mental status cleared and she no longer had paranoid ideation or unfounded fears of her children being taken away from her. She had frequent episodes of muscle weakness when she was at the nurses' station, causing her to lean on the desk or slump to the floor, which was interpreted by the nursing staff and psychiatrist as "hysterical" and attention seeking behavior. According to the patient, these episodes of whole body muscle weakness were triggered by emotion—specifically anger when she felt ignored at the nursing station. Episodes were also triggered by laughter. Although the patient's psychosis had resolved (she was euthymic with

M. Maczaj (✉)
Sleep Disorders Center, St. Charles Hospital and Rehabilitation Center, Port Jefferson, NY, USA
e-mail: marta.maczaj@chsli.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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organized thought process), the psychiatrist did not want to discharge her due to suspicion that the patient had schizophrenia—paranoid type, in addition to a histrionic personality disorder due to the "hysterical" behavior at the nursing station.

Examination

On physical examination, patient was of short stature and overweight. She was alert and oriented to person, place and time. Cranial nerves were intact. Motor strength was 5/5 throughout. Gait and balance were within normal limits. Lungs were clear and without wheezing.

Investigations/Studies

During her ER visit and psychiatric hospitalization, laboratory evaluation including complete blood count, comprehensive metabolic panel, thyroid function tests and venereal disease research laboratory (VDRL) tests were within normal limits. She did not have any neurological imaging studies during her ER or psychiatric hospitalization. Patient provided her medical records with polysomnogram (PSG) and multiple sleep latency test (MSLT) done approximately 10 years prior, which was consistent with narcolepsy. Her MSLT revealed a mean sleep latency of 4.5 min and 2 SOREMS with adequate sleep time in her PSG.

Differential Diagnosis

The treating psychiatrist diagnosed the patient with schizophrenia-paranoid type based on the patient's presenting symptoms of paranoia and unfounded fears of her children being taken away from her in addition to her symptoms of wanting to sleep most of the day—which was interpreted as a negative symptom of schizophrenia. The paranoid ideation cleared spontaneously following the discontinuation of steroids without any need of antipsychotics, and the mental status was marked by organized thought process. Mood was euthymic and patient was goal directed. Schizophrenia was a misdiagnosis. The patient had steroid induced psychosis, which cleared when the steroid was discontinued. Her daytime sleepiness was not a negative symptom of schizophrenia but a classic symptom of her known narcolepsy. Finally, her "hysterical" episodes at the nursing station were not a symptom of histrionic personality disorder—they were cataplectic attacks. Cataplexy is one of the main symptoms of narcolepsy as opposed to catalepsy, also known as waxy flexibility, which can be seen in patients with schizophrenia. Catalepsy is a phenomenon during which a person maintains certain postures, sometimes awkward or unusual, for prolonged periods. This patient did not exhibit catalepsy. The patient had narcolepsy type 1 (with cataplexy) [1].

Discussion and Management

It is vitally important for psychiatrists and neurologists to know that sleep disorders, such as narcolepsy type 1 and 2, obstructive sleep apnea, and periodic limb movement disorder are often associated with fatigue, sleepiness, lethargy, depressed mood and poor memory and concentration, which cross-sectionally can easily be misattributed to psychiatric conditions like depression, attention deficit hyperactivity disorder and psychosis.

Final Diagnosis

Steroid induced psychosis in a patient with Narcolepsy type 1—(with Cataplexy).

Reference

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Case 38. A Sleepy Patient with "*Epileptic Seizures*" and Disturbed Night Sleep

38

Amaia Muñoz-Lopetegi and Carles Gaig

History

A 73-year-old woman was referred for non-restorative nocturnal sleep, excessive daytime sleepiness (EDS), and nightmares. She had a history of systemic hypertension and treatment-resistant epilepsy diagnosed 5 years before. She did not report difficulties falling asleep at night, but complained of fragmented sleep, with three to four awakenings each night, worsened in the last 4 years. She snored, with no witnessed apneas. She explained frequent unpleasant nightmares (e.g., death of a relative, accidents, various misfortunes). Her husband told her that sometimes in her sleep she talked, moaned, and laughed, as if acting in a dream; once she moved vigorously and hit him. During daytime she rapidly felt sleepy in relaxed situations and fell asleep in short car drives or table talks. She napped at least twice daily, for no more than 10 min, but dreamt and even talked during these naps, and typically awakened refreshed. Hypersomnolence was present since she was young; she remembered fighting to stay awake at work and had quitted driving. When asked about her epilepsy, seizures consisted of 15- to 30-s episodes in which the mouth opened, arms and legs gave out, and she suddenly dropped to the floor, never losing consciousness. Recovery was rapid and complete in few seconds. The attacks occurred once or twice weekly for the last 20 years or more. She had injured herself several times, and recently had been taken to the emergency room twice. These "*seizures*" were always triggered by an emotion like laughter, surprise, or unexpected good news. Electroencephalogram (EEG) and brain magnetic resonance imaging (MR) studies were normal and different antiepileptic drugs never modified the episodes. She was currently on levetiracetam, lamotrigine, and pregabalin. She had experienced sleep paralyses very occasionally but not sleep-related hallucinations.

A. Muñoz-Lopetegi (✉) · C. Gaig (✉)
Department of Neurology, Hospital Clinic Barcelona, Barcelona, Spain
e-mail: ammunoz@clinic.cat; cgaig@clinic.cat

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_38

Physical Examination

The examination was unremarkable except for overweight, with body mass index (BMI) of 29.4 kg/m^2.

Investigations/Studies

A routine 30-min EEG performed without sleep deprivation, showed normal background activity, no epileptiform activity nor seizures, but diverse episodes of short sleep, including stage REM (Fig. 38.1). On nocturnal video-polysomnography (vPSG) the patient slept 6 h 15 min (sleep efficiency of 73%). Sleep latency was 30 s and REM sleep latency 129 min. She had an apnea-hypopnea index (AHI) of 67/h and an arousal index of 58/h (Fig. 38.2). REM sleep had normal surface electromyography (EMG) atonia, without associated movements or abnormal behaviors, and no seizures nor epileptiform activity were recorded. The 5-nap multiple sleep latency test (MSLT) demonstrated severely reduce mean sleep latency (0 min and 24 s), with four sleep onset REM periods (SOREMPs), three of them occurring from direct transition from wakefulness or N1 stage to REM, without N2 sleep preceding REM sleep (Fig. 38.2), a finding also present in the routine EEG. The HLA typing was DQB1 *06:02 positive. Hypocretin-1 levels in cerebrospinal fluid (CSF) were undetectable ($\leq$10 pg/mL).

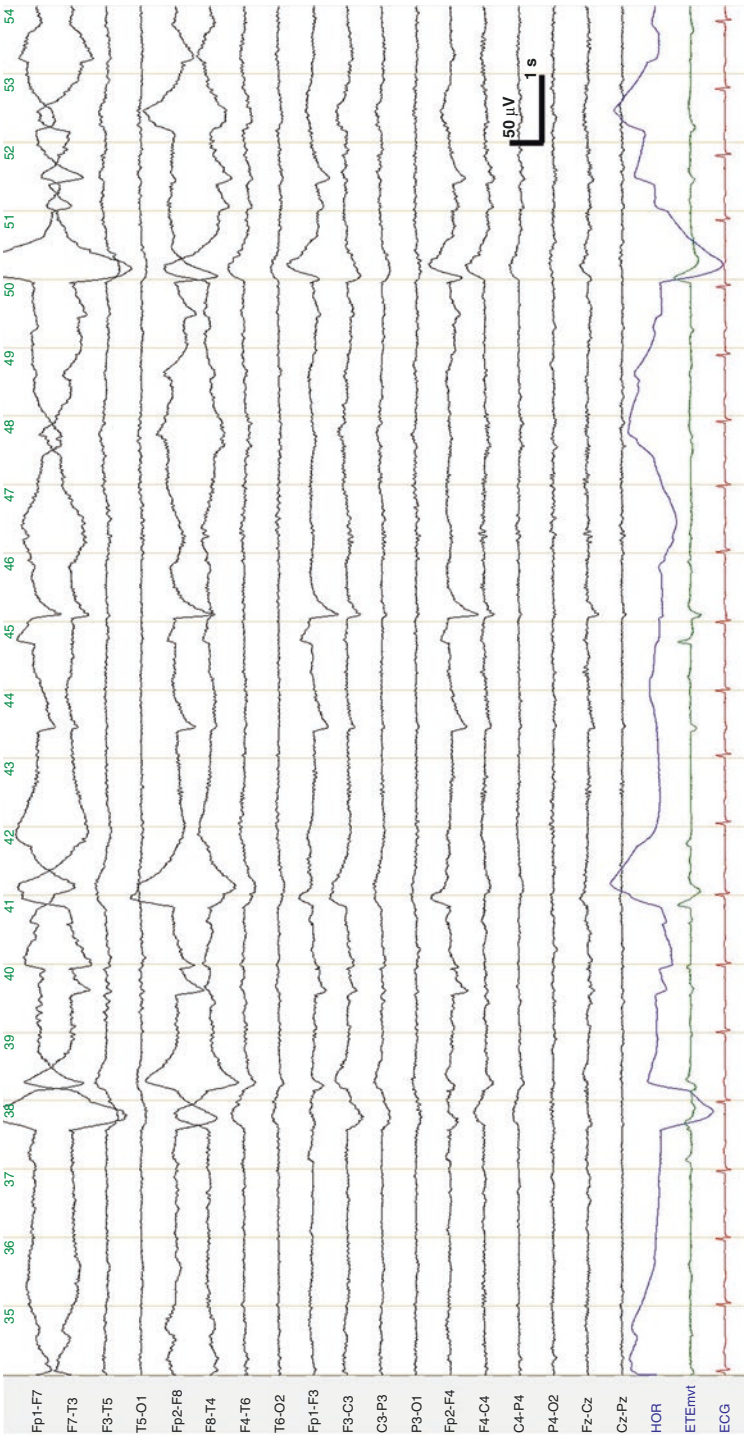

Fig. 38.1 REM sleep in routine EEG. The 30-min EEG showed rapid eye movements and low amplitude mixed frequency EEG activity typical of stage REM sleep. Bipolar montage with electrodes placed according to the International System 10/20. *HOR* horizontal eye movements (one eye referenced to the other eye), *EYEmvt* eye movement sensor placed on eyelid, *ECG* electrocardiogram

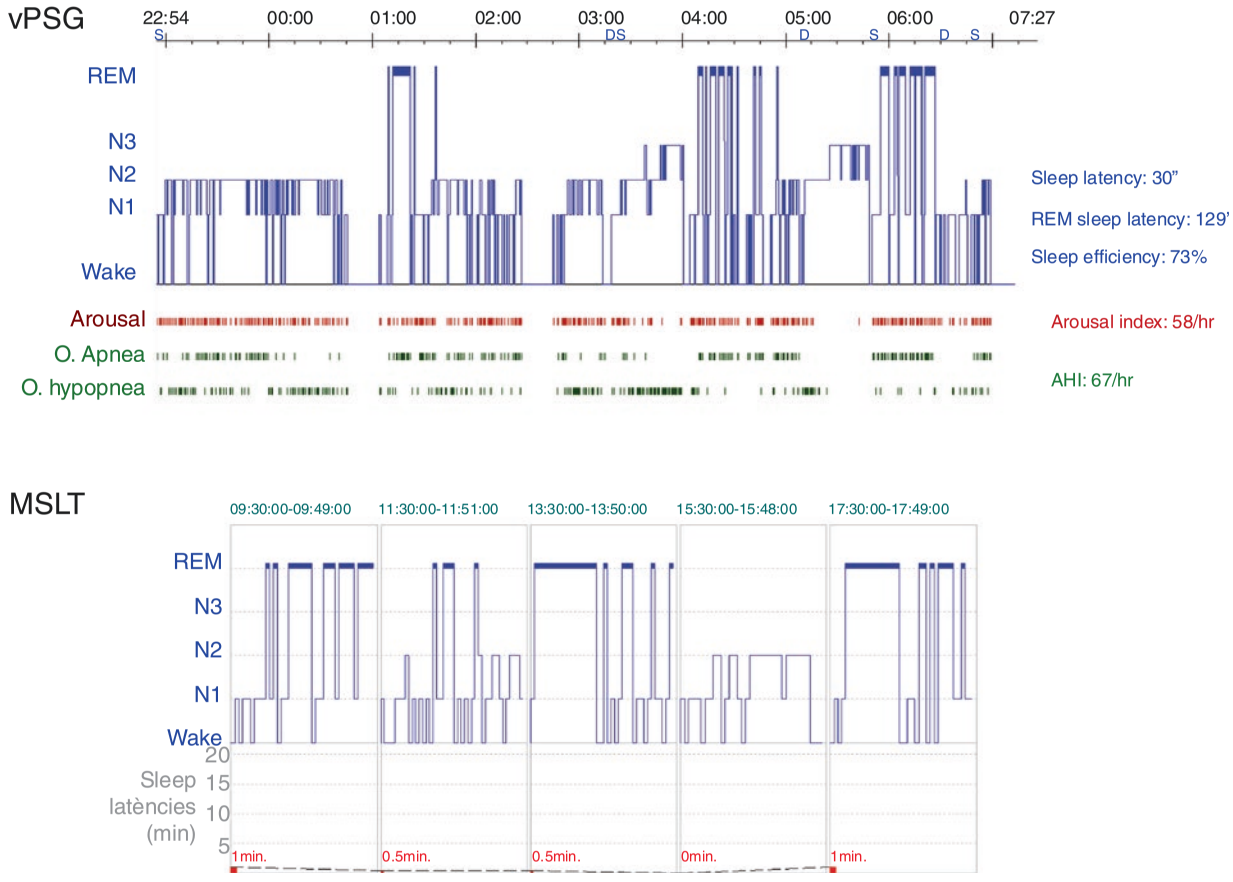

Fig. 38.2 Nocturnal video-polysomnography (vPSG) and multiple sleep latency test (MSLT). vPSG shows a short sleep onset latency without a sleep onset REM period (SOREMP) and a fragmented sleep with high index of obstructive apneas and hypopneas. MSLT shows a reduced average sleep onset latency (24 s) and four SOREMPs, three of them preceded by wake and N1 NREM, and only one with N2 NREM before entering REM sleep. *O* obstructive, *AHI* apnea-hypopnea index

Differential Diagnosis

This elder woman consulted for non-restorative nocturnal sleep with frequent awakenings and nightmares. However, she had a long-lasting history of EDS and a noteworthy previous diagnosis of epilepsy. When specifically asked about her seizures, they consisted of a sudden generalized loss of the muscle tone leading to falls. These paroxysmal episodes had been misdiagnosed as atonic seizures, but since they were triggered by emotions and associated with preserved awareness and rapid recovery, we considered cataplexy a more likely explanation [1]. These cataplectic attacks in addition to the sleep problems raised suspicion of a type 1 narcolepsy. There was a long-term history (since her youth) of intense, disabling somnolence, which was remarkably relieved by short naps, and occasional episodes of sleep paralysis and frequent movements and vocalizations during nighttime and daytime sleep. A routine EEG discarded epileptiform abnormalities but showed episodes of REM sleep (an unusual finding in the absence of sleep deprivation). Alternative or concomitant diagnoses, however, needed to be ruled out. After all, this woman complained of nocturnal sleep problems that worsened in the previous 4 years. Obstructive sleep apnea (OSA) is prevalent in women after menopause, especially if overweighted, and may explain sleep fragmentation and nightmares, and can also contribute to daytime sleepiness. Nocturnal vPSG confirmed a severe OSA in our patient, but the MSLT (with reduced mean sleep latency and four SOREMPS), the HLA typing, and specially the undetectable CSF hypocretin-1 levels, confirmed the type 1 narcolepsy [2].

Discussion and Management

Type 1 narcolepsy (or narcolepsy with cataplexy) is a rare, disabling neurological disorder presenting with a prominent sleep disorder. The diagnosis is often delayed (even for more than 10 years), but cataplexy is the key symptom to suspect and diagnose type 1 narcolepsy [1]. All patients complaining of EDS should be interrogated about this symptom, which is almost pathognomonic. Cataplexy can be misdiagnosed as other paroxysmal events, typically epilepsy or syncope. In this sense, in patients with sleep problems and a history of seizures or syncope, it is worth asking for the clinical features of the episodes and the details of these previous diagnoses. Our patient had been diagnosed with an adult-onset cryptogenic, drug resistant epilepsy with atonic seizures. Preserved consciousness and rapid and complete resolution of the attacks, and the fact that they were triggered by emotions, were findings atypical for atonic seizures and instead characteristic for cataplexy.

Once narcolepsy diagnosis was confirmed with an MSLT and CSF hypocretin-1, anticataplectic clomipramine was started (progressively titrated up to 50 mg/day) leading to complete disappearance of the episodes. EDS is a major symptom of type 1 narcolepsy and can be worsened by additional factors such as OSA (more prevalent in narcolepsy than in general population) [2] or sedative drugs, both present in our patient. For the severe OSA (AHI > 30/h), we prescribed a continuous positive

airway pressure (CPAP) device, which improved nocturnal sleep quality, including nightmares, and reduced EDS. She was taking three antiepileptic drugs, all with somnolence as a well-known, frequent adverse effect. The diagnosis of narcolepsy and exclusion of epilepsy allowed to safely withdraw them, and EDS further relieved. Still an additional improvement was observed with subsequent treatment with modafinil (up to 200 mg/day).

Final Diagnosis

Narcolepsy with cataplexy (or type 1 narcolepsy). Associated obstructive sleep apnea.

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Case 39. Behind the Sleepiness

39

Sofia Romero-Peralta and Diego Garcia-Borreguero

History

A 40-year-old woman with no cardiovascular risk factors and no familial history of hypersomnia was evaluated in our Sleep Medicine Center. She complained of excessive daytime sleepiness (EDS), snoring, lack of energy, and sleep attacks. She was first diagnosed in another center as having severe obstructive sleep apnea (OSA). She had an elevated apnea-hypopnea index (AHI 38.6/h) and had been treated with continuous positive airway pressure (CPAP) at a fixed pressure of 11 cmH_2O for 5 years. Despite CPAP treatment she still suffered from daytime sleepiness. Her nocturnal sleep schedule was from 00:00 to 08:20. She used CPAP for at least 7 h, five nights a week. During the day she complained of severe EDS (Epworth Sleepiness Scale score (ESS) was 18/24), morning headache, and memory loss. After 2 years of follow-up, she described episodes (2–3 per year) of transient symmetrical loss of muscle tone during positive emotions. She also reported episodes of sleep paralysis and hypnagogic/hypnopompic hallucinations.

Examination

On physical examination, vitals were within normal limits; height, weight, and body mass index (BMI) were 167 cm, 86 kg, and 30.84 kg/m^2, respectively. Inspection of the head and neck region did not reveal craniofacial abnormalities affecting the size

S. Romero-Peralta (✉)
Department of Neurology, Sleep Research Institute, Madrid, Spain

Sleep Unit, Pneumology Department, University Hospital of Guadalajara, Guadalajara, Spain

D. Garcia-Borreguero
Department of Neurology, Sleep Research Institute, Madrid, Spain
e-mail: dgb@iis.es

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of the upper airways. The oropharyngeal examination did not allow visualization of the tonsils or the uvula. The Mallampati score was IV. The neurological examination showed an absence of motor and sensory function deficits. Deep tendon reflexes were present and symmetrical. The results of coordination tests and gait tests were normal.

Investigations/Studies

Routine hematology, biochemistry, and thyroid function were normal. An actigraphy was performed for a week, which confirmed eight hours of sleep daily. Polysomnography (PSG) with CPAP followed by a multiple sleep latency test (*MSLT*) was performed. PSG with CPAP confirmed normal nocturnal cardiorespiratory parameters (AHI 4.2/h), the absence of periodic limb movements, and mild sleep fragmentation (Fig. 39.1). MSLT with CPAP showed a mean sleep latency of 5.8 min and two sleep-onset rapid eye movement periods (SOREMP). The patient also underwent a brain magnetic resonance imaging (MRI) that showed no

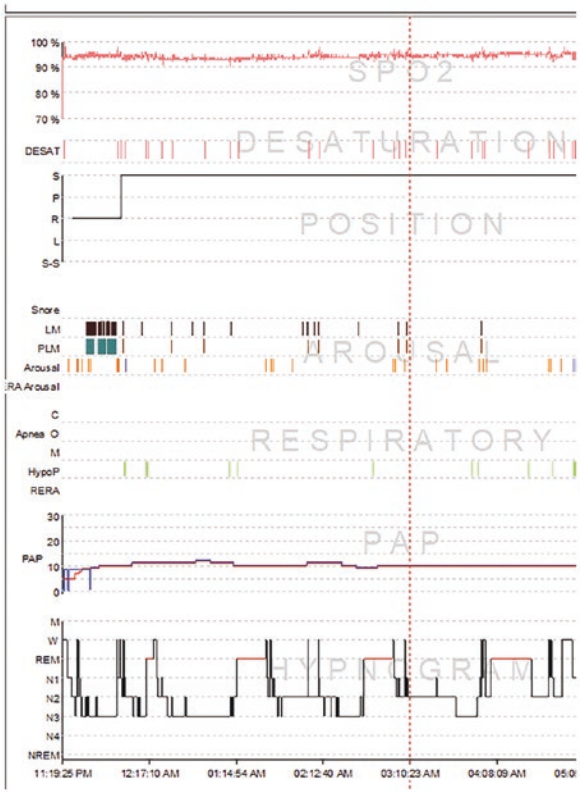

Fig. 39.1 Polysomnography with CPAP confirmed sleep latency was very brief, normal nocturnal cardiorespiratory parameters (AHI 4.2/h oxygen desaturation index (ODI) 4.1/h), the absence of periodic limb movements, and mild sleep fragmentation

abnormalities. She refused to undergo lumbar puncture sampling of cerebrospinal fluid (CSF) to investigate hypocretin levels. Determination of HLA DQB1 0602* was positive.

Differential Diagnosis

The symptoms that the patient described in this case report (EDS, nocturnal sleep disruption, fatigue, loss of energy, and weight gain) can be seen in several disorders. The first step when treating a patient with persistent sleepiness after CPAP is to review the clinical history to confirm the diagnosis of OSA and to verify CPAP pressure and compliance. The patient in this case had good compliance and adaptation to CPAP with no side effects. Manual CPAP titration was performed which confirmed that the CPAP pressure was able to correct the respiratory events. After checking CPAP treatment, it is mandatory to exclude associated conditions such as poor sleep hygiene, depression, narcolepsy, or idiopathic hypersomnia (Fig. 39.2) [1]. Actigraphy confirmed good sleep habits and the patient did not present symptoms of depression. The MSLT is the gold standard for the objective assessment of sleepiness. The basic parameters required for its interpretation are average sleep latency and the presence of rapid eye movement (REM) sleep in some of the naps allowed. The presence of REM sleep before 15 min of sleep is called sleep-onset REM periods (SOREMP). Sleep latency of 5–6 min is pathological, although the cut-off point for the diagnosis of hypersomnias of central origin has been set at 8 min. The MSLT of the patient showed a mean sleep latency of 5.8 min and two SOREMPs. With these results, the initial diagnosis of narcolepsy type 2 is established. After 2 years of follow-up, the patient reported two-cataplexy episodes, which permitted us to establish a diagnosis of narcolepsy type 1.

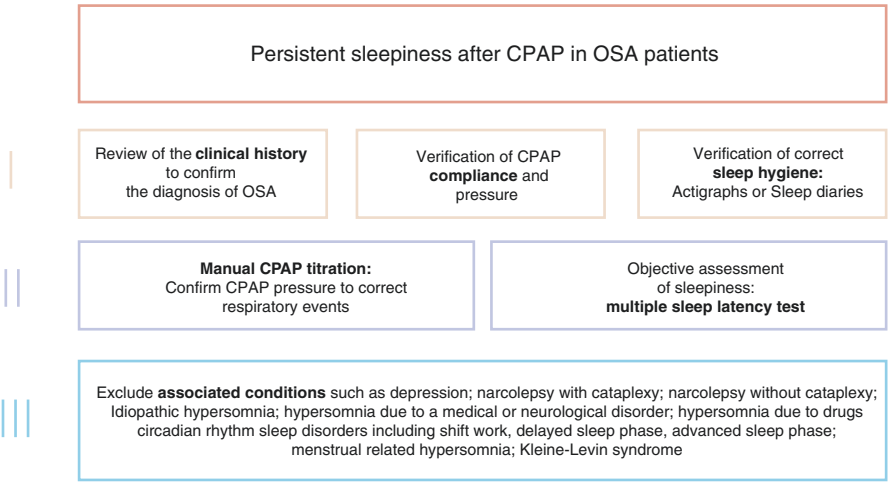

Fig. 39.2 Management of persistent sleepiness after CPAP treatment in patients with OSA

Final Diagnosis

Diagnosis of OSA to be effectively treated by CPAP and narcolepsy type 1 was confirmed.

Discussion and Management

OSA is a highly prevalent disorder. The estimated prevalence in the general adult population has been reported between 9% and 38%. OSA and narcolepsy can coexist in the same patient. Also, the incidence of overweight or obesity ranges from 25% to 74% in patients with narcolepsy type 1, obesity is one of the most important risk factors for the development of OSA. From a symptomatic point of view, both share EDS, which can often result in OSA delaying the diagnosis of narcolepsy. The patient described in this case report had several overlapping symptoms of OSA and narcolepsy: EDS, nocturnal sleep disruption, fatigue, and weight gain. When the sleepiness of a patient with OSA is not resolved with CPAP, it is necessary to consider that they may also suffer from narcolepsy [2]. Narcolepsy is a neurological disease of unknown origin, related to a disorder in the regulation of REM sleep and the sleep/wake cycle. In most cases of narcolepsy with cataplexy, there is a deficit of hypocretin in the CSF due to selective loss of hypocretin neurons in the hypothalamus. Although the cause of neuronal death is unknown, it has been suggested that there is an immunological basis given that the majority of patients with narcolepsy and cataplexy and 40% of cases without cataplexy present the specific haplotype HLA DQB1*0602, which is found in only 25% of the general population. The prevalence of the disease is one case in every 2000–5000 individuals, it affects both sexes equally and usually has an insidious onset in adolescence, with the first peak of presentation around 14 years and a second peak at 35 years. The first symptom is usually drowsiness, later, the other symptoms related to REM sleep dysfunction appear, such as cataplexy, hallucinations, episodes of sleep paralysis, and interrupted nighttime sleep. It is classified depending on whether or not it is accompanied by cataplexy: type 1 (with cataplexy), and type 2 (without cataplexy). Cataplexy is a pathognomonic symptom of the disease in type 1 narcolepsy, characterized by episodes of a sudden loss of muscle tone with preserved consciousness, whose trigger mechanism is usually an emotional stimulus. Symptomatic treatment with stimulant and anticataplectic drugs is usually efficacious. In the case of our patient, modafinil up to 100 mg bid added to venlafaxine 75 mg/day induced a significant improvement of sleepiness (ESS 5/24) and disappearance of suspected cataplexy.

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Case 40. All Stress No Rest

40

Andrew J. Westwood

History

A 32-year-old man disrupts his girlfriend's sleep by sitting up and shouting "no" in the middle of the night. These episodes also occur when she gets into the bed after he has fallen asleep. He vaguely recalls the episodes the following morning when questioned sometimes in association with a dream. It can occur a few times a month usually at the weekend. He has at times had behaviours where he can be found crouching by the end of the bed or stood at the bedroom window. His parents recall that he was found wandering the house a few times as a child but these stopped when he reached adolescence. The episodes have recently become more frequent after they moved house and he started a new job. He is not sleeping well during the week due to the pressure from the new job and at the weekend he feels exhausted and goes to bed early in an attempt to catch up on his sleep. He takes no medications or supplements and does not drink alcohol. He does report an occasional urge to move his legs at night. His father has obstructive sleep apnea and developed generalized tonic-clonic seizures after a motor vehicle accident.

Examination

Cranial nerve examination was normal with full visual fields, intact extraocular movements and sharp optic discs. Tone, strength and reflexes were normal. Gait was normal and sensation was intact. There were no craniofacial abnormalities and a class I airway on the modified Mallampatti scale was observed.

A. J. Westwood (✉)
Department of Neurology, Maidstone and Tunbridge Wells NHS Trust, Kent, UK
e-mail: andrew.westwood1@nhs.net

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Investigations

Complete blood count, basic metabolic panel, thyroid stimulating hormone and liver function tests were normal. His ferritin level was found to be 30 μg/L (normal range: 24–336).

Differential Diagnosis

Nocturnal behavioural episodes include parasomnias (NREM and REM), seizures and dissociative episodes. NREM parasomnias are behavioural episodes that include events that can be classified as confusional arousals, somnambulism, night terrors, sexsomnia and sleep-related eating disorder. REM parasomnias include REM behaviour disorder (RBD), recurrent sleep paralysis and nightmare disorder. These behaviours can be simple or complex and last on the order of minutes. Typically NREM parasomnias occur in the first third of the sleep and REM parasomnias in the last third of the night. Seizures are often stereotyped in character lasting seconds to a few minutes, may present in clusters and occur at any time of night (see Table 40.1). Episodes of dissociation can be simple or complex but occur during wakefulness, there may also reports of events through the daytime.

Table 40.1 Common variables to help distinguish between seizures, NREM parasomnias and REM behaviour disorder

Variables	Sleep related hypermotor epilepsy	Disorders of arousal	REM sleep behavior disorder
Age of onset	Any age, usually first or second decade	Childhood	Over 50 years
Sleep stage	N2, rarely N3	N3	REM
Timing in sleep	Anytime	First third	Last third
Duration of episodes	Seconds to minutes	Minutes	Seconds to minutes
Frequency	Multiple in same night and nightly	Not every night	Not every night
Phenotype	Stereotypical, hypermotor, dystonic posturing, sudden onset/offset	Variable complexity Not stereotypical or dystonic posturing, gradual onset/offset. May leave the bed	Not stereotypical, self-protective behavior, dream recall if awaken
Family history	Variable	Strong 60–90%	No
EEG	Epileptiform discharges (<10%) or normal	No epileptiform discharges, slow waves	Preserved tone in REM sleep
Eyes	Closed/open	Open	Closed
Triggers	Usually none	Stress, alcohol, sleep deprivation	Alcohol, medication

Discussion and Management

Non-REM parasomnias are disorders of arousal and include abnormal nocturnal behaviours, which can include somnambulism, somniloquy, confusional arousals and sleep terrors. They are typically seen in the first third of the night when slow wave sleep is most abundant. A childhood history of similar events supports the diagnosis and precipitating factors includes sleep fragmentation and prior sleep deprivation resulting in N3 rebound. Sleep fragmentation can arise from external factors such as noise or intrinsic disturbances such as periodic limb movements of sleep (PLMS) or sleep-related breathing disorders. In the history we see that he endorses symptoms consistent with restless legs syndrome, which may be accompanied by PLMS, and that his bed partner entering the bed can trigger an event. Typically in childhood, individuals are amnestic for the events but in adulthood there can be associated imagery recalled. This can result in being miscategorized as dream enactment behaviour and misdiagnosed as RBD [1].

Generally further testing after a thorough history has been obtained is not necessary, however if there is a cause for uncertainty then an in-lab polysomnogram could be considered to attempt to capture an event but also to evaluate for provoking factors: intrinsic sleep disorders such as obstructive sleep apnea. Protocols can be also be implemented to try to trigger an event, as oftentimes the unfamiliar environment of the laboratory results in a reduced amount of N3 sleep during a sleep study. Having an individual arrive in a sleep deprived state before introducing auditory stimuli at times of N3 sleep during the study may help provoke an episode.

The goal of management is reassurance and to ensure safety of the individual and those around them. In this individual iron supplementation may alleviate his restless legs symptoms that can be a provoking factor. The stress related to a new job and moving house has likely contributed to triggering these episodes. If there are ongoing psychosocial stressors then managing these to limit their impact on the individual's ability to obtain sufficient uninterrupted sleep is important. In children scheduled awakenings prior to the typical onset of events can be helpful particularly in night terrors. In some circumstances medications can be considered such as benzodiazepines or antidepressants.

Final Diagnosis

NREM parasomnia

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Case 41. Night Terrors Are Not Always What They Seem

41

Ewa I. Koziorynska

History

A 32-year-old man presented to the clinic after experiencing new onset of "night terrors". The first episode occurred 1 year previously. His girlfriend observed the patient screaming during sleep, accompanied by hyperactive behaviors such as jumping and kicking. During the episode, the patient was observed to have his eyes open with an expression of fear and panic on his face. The event lasted approximately 5 min. The patient had no recollection of the event, but admits to feeling slightly confused afterwards, with a persistent sensation of fear and panic accompanied by fast heartbeat. He denied any dream associated with the event. A few weeks prior to the event the patient was started on lysdexamfetamine due to attention deficit hyperactive disorder (ADHD), which he stopped immediately after the episode. Patient denied sleep deprivation prior to the event or any precipitating factors except the fact that event occurred when sleeping out of his habitual place. The behaviors occurred during the first half of the night, within 1.5 h of falling asleep.

The patient experienced his second event, with similar clinical presentation, several months later while staying in a hotel. The event occurred 1.5 h after falling asleep, with no precipitating factors observed, except that both events occurred when sleeping in a new place.

The patient reported a childhood history of sleepwalking that resolved by age 11. He also admitted to snoring. He has a history of ADHD. The patient has no prior history of antidepressant exposure. There is no history of seizures or risk factors for epilepsy such as febrile seizures, head trauma with loss of consciousness, brain

E. I. Koziorynska (✉)
Neurology, Columbia University Irving Medical Center, New York, NY, USA
e-mail: eik2109@cumc.columbia.edu

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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infections or family history of epilepsy. The patient denied smoking or illicit drug use and only reported occasional alcohol consumption. The relevant family history includes that his father and brother both have night terrors and obstructive sleep apnea (OSA), both using continuous positive airway pressure (CPAP) therapy with resulting decreased frequency of night terrors.

Examination

The patient was 6 ft. tall and weighed 180 lb., with a body mass index (BMI) 24.6 kg/m^2 and neck circumference 15 inches. Nasal septum was midline, oropharyngeal examination showed Mallampati 2 with no evidence of tonsillar hypertrophy. He had normal neurological and musculoskeletal examination.

Investigations/Studies

Home sleep apnea test: apnea-hypopnea index (AHI) 1/h, with a respiratory disturbance index (RDI) of 10/h. Magnetic resonance imaging (MRI) of the brain and routine electrocencephalogram (EEG) were normal.

Polysomnography (PSG) testing with prolonged video-EEG (vEEG):

Total seep time was 418 min, with 68.7% sleep efficiency. The patients sleep latency was 53.6 min. The REM latency was 54.5 min. The total AHI was 9.5/h. The periodic limb movements of sleep (PLMS) Index was 0/h. The mean oxygen saturation was 96.7%. There was normal muscle atonia during REM sleep stage.

The prolonged video-EEG showed bi-synchronous frontal (R > L) potentially epileptogenic abnormalities (see Figs. 41.1 and 41.2) and also Frontal Intermittent Rhythmic Delta Activity (FIRDA).

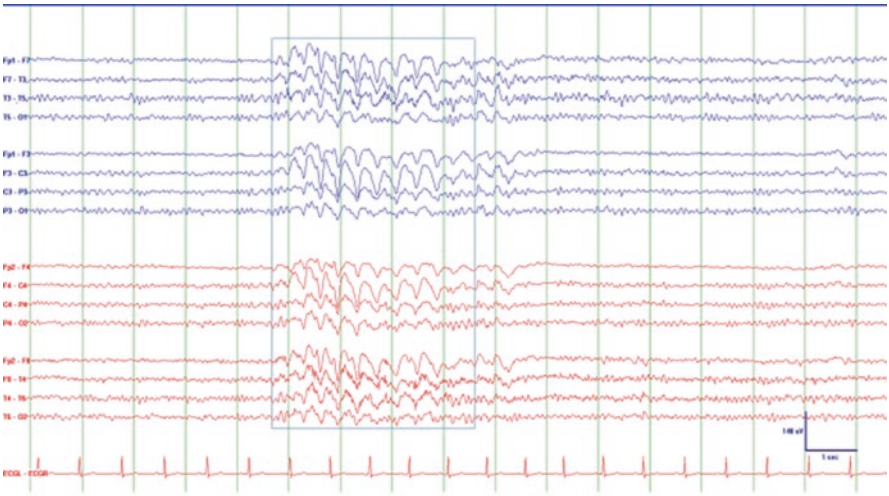

Fig. 41.1 Electroencephalogram, bipolar montage. EEG shows burst of mainly frontal epileptiform abnormalities (box). The international 10–20 system of electrode placement applied. Odd numbers, left; even numbers, right. Fp (frontopolar), F7 and F8 (anterior temporal), F3 and F4 (frontal), C3 and C4 (central), T3 and T4 (temporal), T5 and T6 (posterior temporal), P3 and P4 (parietal), O1 and O2 (occipital). ECGL-ECGR: Electrocardiogram. Sensitivity 7 μV/mm

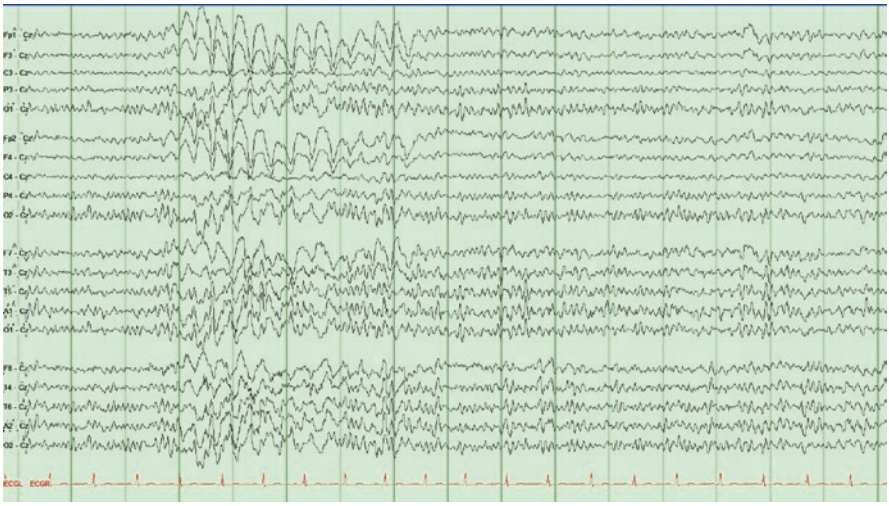

Fig. 41.2 Electroencephalogram, referential montage. EEG shows burst of mainly frontal epileptiform abnormalities (box). The international 10–20 system of electrode placement applied. Odd numbers, left; even numbers, right. Fp (frontopolar), F7 and F8 (anterior temporal), F3 and F4 (frontal), C3 and C4 (central), T3 and T4 (temporal), T5 and T6 (posterior temporal), P3 and P4 (parietal), O1 and O2 (occipital). ECGL-ECGR: Electrocardiogram. Sensitivity 7 μV/mm

Differential Diagnosis

The patient presented with new onset nocturnal episodes of paroxysmal motor behavior. The differential diagnosis of hyperactive nocturnal behavior includes NREM parasomnias (sleep terrors, confusional arousals and sleep walking), nocturnal seizures, rhythmic movement disorder, nocturnal panic attacks and REM behavior disorder (RBD).

NREM parasomnias such as sleep terrors, usually occur within the first half of the sleep period, as did patient's events, and are characterized by abrupt terror, alarming frightening scream and are accompanied by intense fear and signs of autonomic arousals. Patients with sleep terrors are usually unresponsive to external stimuli, and if awakened are confused and disoriented, which goes along with patient's clinical presentation. Sleep walking may occur in some cases. In contrast, patients with confusional arousals and sleep walking do not demonstrate autonomic changes such as tachycardia, tachypnea, mydriasis and diaphoresis during an episode [1].

Several types of epileptic syndromes predominantly manifest during sleep. Nocturnal frontal lobe epilepsy (NFLE), renamed sleep-related hypermotor epilepsy (SHE), considered in our patient (interictal potentially epileptogenic discharges: see Figs. 41.1 and 41.2), causes sleep disruption and may present as paroxysmal arousal with hyperactive movements, nocturnal paroxysmal dystonia or episodic nocturnal wandering. Seizures can look like simple arousal from sleep, at times confused as nightmare or night terror. More complex body movements like twisting, turning, pedaling, and vocalizations like screaming, moaning or crying may occur. Interictal EEG may show epileptiform activity in the frontal region, or may be normal. The seizure may last a few seconds to a few minutes, and are usually stereotyped. Frontal lobe seizures are most likely to occur during NREM sleep, especially stage N2 sleep; even during an episode epileptiform activity may not be apparent due to movement artifact.

Nocturnal panic attacks usually occur within the first half of the sleep period and can demonstrate autonomic changes. It usually occurs in individuals who have preexisting mood disorder, anxiety or panic attacks during wakefulness. Our patient has no prior history of mood disorders, but admits to ADHD. Even though ADHD and anxiety are separate conditions, about half of the adults with ADHD may also have anxiety disorder. However, patients can usually easily recognize the episode as a panic attack immediately after awakening.

Rhythmic movement disorder (RMD) is characterized by repetitive, stereotyped and rhythmic large muscle group body movements. Movements usually occur during drowsiness or sleep and are typically seen in infants and children, but may also occur in adults. In contrast to seizures this activity may be interrupted or stopped by environmental disturbance or being spoken to. Rhythmic movements have been reported in association with restless legs syndrome (RLS), narcolepsy, RBD, OSA and ADHD (last two being co-morbid conditions in our patient).

Idiopathic RBD usually affects older males. REM behaviors commonly occur during the later part of sleep. Episodes are often violent in nature, involving kicking

and punching in addition to vocalization. The behavior emerges from REM sleep with PSG recording demonstrating REM sleep without atonia (RSWA). The individual usually reports a dream that corresponds to the observed sleep behavior. The eyes remain closed during the episode.

Discussion and Management

It is known that the clinical similarities between NREM parasomnias and nocturnal epileptic seizures (frontal and temporal lobe seizures) may lead to misdiagnosis. Both may occur only out of sleep with inappropriate or absent responsiveness and complete amnesia for the episode. The patients may appear confused and disoriented for several minutes afterwards.

NREM disorders of arousals are more prevalent among children and adults younger than 35 years, with the prevalence rate 2.3–2.6% in adults. Disorders of arousals that begin in adulthood are often more disruptive and require more clinical attention. With frontal lobe epilepsy (FLE), over 85% of people are diagnosed before 20 years old, usually around the age of 9. Our patient used to sleepwalk in childhood but a new type of events started at age 32, which is not very typical for NREM parasomnias like night terrors nor FLE [2].

Stress, sleep deprivation, irregular sleep-wake rhythm and other coexisting sleep pathologies (OSA in our case) as well as use of medications/drugs that modify sleep architecture may provoke NREM parasomnias as well as seizures. Travel and sleeping in unfamiliar surrounding have been associated with the onset of some disorders of arousals such as sleep walking.

PSG studies demonstrate that disorders of arousal typically begin after an arousal from slow wave sleep, occasionally may emerge from stage N2 sleep, while frontal lobe seizures are most likely to occur from stage N2 sleep.

In our case there seem to be a familial pattern with patient's father and brother experiencing similar type of events. A genetic predisposition in disorders of arousals appear to play an important role. However, published research data is limited primarily to sleepwalking. There is known strong genetic predisposition reported in some nocturnal epilepsy types, such as SHE, with 70%–80% penetrance. It is usually a lifelong condition, with seizures controlled by medications. Most people are intellectually normal, but there may be associated mood disorders, behavioral problems or intellectual disability.

An admission for several days for EEG monitoring session may be useful should the events become more frequent. At times empiric treatment with anti-seizure medications may be considered, with events resolution favoring diagnosis of epilepsy.

Final Diagnosis

Possible frontal lobe epilepsy.

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Case 42. Asleep or Not Asleep, That Is the Question

42

Siddhartha S. Nadkarni

History

The patient is a 55-year-old right-handed woman who suffered a fall and marked concussion with head strike while walking down the street on the sidewalk. There was no loss of consciousness. After this injury she had several post-concussion symptoms including memory loss, executive dysfunction, difficulties with processing speed, and other cognitive and psychiatric symptoms. Two of her most prominent symptoms were loss of a sense of time passing and a belief that she was not sleeping at all. She stated she did not sleep during the day or night. She noted she would get into bed at 11 PM and then stay up all night ruminating and would not be able to fall asleep. She claimed to have had a polysomnogram (PSG) at an outside institution that recorded only three hours of sleep but that study was not available for review. She was convinced that she was not sleeping at all. Even if she lied down during the day, she would not sleep. She does not snore. She said she stares at the ceiling and the clock all night long. At the time of presentation she had tried mirtazapine, risperidone, venlafaxine, melatonin, and clonazepam without success in terms of insomnia. There is no history of restless legs syndrome or periodic leg movements of sleep. There is no history of dream enactment behavior, cataplexy, sleep paralysis, hypnopompic or hypnogogic hallucinations, or parasomnias. Her initial Epworth Sleepiness Scale was 0/24. She drank one cup of coffee a day and drank alcohol socially. There was no significant weight change recently around the time of the concussion. She had to stop working because of her symptoms and is currently disabled still.

Past medical history was significant for major depression and the current concussion/post-concussion symptoms. She had no past surgical history and was not taking any medications at the time of presentation.

S. S. Nadkarni (✉)
Neurology and Psychiatry, NYU, New York, NY, USA
e-mail: Siddhartha.nadkarni@nyumc.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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Examination

Vital Signs: 150/85, Pulse 72, Respiratory Rate 12, Weight 92.08 Kg, Body mass index (BMI) 35.97 kg/m^2.

The general exam was normal.

Neurological examination.

Mental Status:

Awake, alert, oriented. Normal language, praxis. Some distractibility. Memory intact. Well groomed, cooperative, forthright. Mood: "not good." Affect: dysphoric with full range, appropriate, congruent. Thought Content: no hallucinations, delusions, suicidal ideation, homicidal ideation. She was preoccupied with her injury and insomnia. Thought Process: sequential. Insight and Judgment are poor.

Cranial Nerves: 1–12 intact.

Motor: normal bulk and tone. 5/5 Strength throughout, no adventitious movements.

Sensory: pinprick, light touch, vibration, and cortical sensation intact.

Coordination: intact.

Gait: normal tandem gait.

Reflexes: 2+ throughout. No finger flexors. + palmomental reflex bilaterally. No other release signs.

Toes downgoing.

Investigations/Studies

1. Echocardiogram - normal
2. 24 h Video electroencephalogram (EEG) monitoring – normal with normal sleep architecture and sleep time
3. 72 h Video electroencephalogram (EEG) monitoring – normal with normal sleep architecture and sleep time
4. Auditory testing – normal
5. Magnetic resonance imaging (MRI) Brain – Ventricular dilatation and atrophy as well as bilateral hippocampal atrophy
6. PSG – No sleep related disordered breathing. Slept for 371 min. Some trouble staying asleep at the end of the night.
7. Multiple Sleep Latency Test – sleep latency of 14.2 min with no Sleep Onset REM episodes.

Differential Diagnosis

1. Sleep State Misperception Syndrome
2. Obstructive Sleep Apnea
3. Parasomnia
4. Restless Legs Syndrome

Discussion and Management

This patient suffered a concussion with protean post-concussion manifestations that have persisted. One of her primary complaints was total insomnia. Evidence from her video EEG's and sleep studies were presented to her, showing that she slept several hours in the night. Despite this evidence being presented to her, she continued to believe she was not sleeping at all. Multiple medications were trialed for sleep induction and maintenance with reported lack of efficacy. Eventually she stated she could sleep a few hours in the night, but her perception of sleeplessness persisted.

Sleep state misperception syndrome (also known as paradoxical insomnia) is a condition where subjective assessment of sleep duration is significantly less than objective measures identify. Multiple conditions are associated with sleep misperception including general insomnia, post-traumatic stress disorder (PTSD), mild traumatic brain injury (mTBI), depression and anxiety. One study of insomnia in the general population revealed that those with normal sleep duration by objective measures and subjective sleep misperception of shorter duration was associated with a Minnesota multiphasic personality inventory (MMPI) profile of high depression and anxiety scores and low ego strength on neuropsychological testing [1]. In this study, those with subjective lower duration of sleep out of proportion to decreased sleep time on objective measures was associated with a medical disorder.

In the case of mTBI, as was the situation in this case, one study with 37 patients showed a self-reported sleep duration of 342 ± 93.6 min and PSG-measured sleep duration was 382 ± 76.8 min [2]. In this study there was a unique correlation between self-reported sleep duration and the severity of insomnia. Sleep duration misperception was correlated with the number of alcoholic drinks the day prior to the PSG, but not to sociodemographic or psychological factors in this study (Fig. 42.1).

Sleep State Misperception Syndrome is a relatively common complaint in neurology and psychiatry clinics. In patients who report marked lack of sleeping, objective measures like PSG can be very helpful in assessing actual sleep times and can be used in psychoeducation of the patient. The mechanism of sleep misperception are unclear at this time, though it does seem particular comorbid conditions (depression, PTSD, Anxiety, mTBI, alcohol use, etc.) are more associated with this condition. There is not good evidence that pharmacologic interventions work in this condition, but sleep related cognitive behavioral therapy may be a promising avenue of treatment.

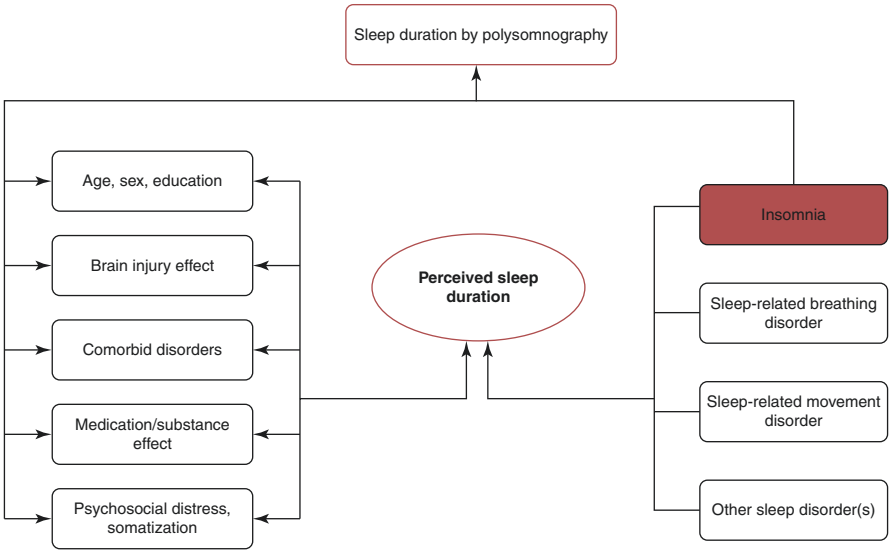

Fig. 42.1 Construct of factors influencing perception of sleep duration (Yang, *Brain Injury,* 2021)

Final Diagnosis

Sleep State Misperception Syndrome.

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Case 43. "Somebody Is Standing by My Bed When I Am Falling Asleep"…

43

Zuzana Belisova

History

A 23-year-old female with history of depression, attention-deficit hyperactivity disorder (ADHD), anxiety presented with chief complaint of excessive daytime sleepiness, which worsened 3 years ago after a bout of H1N1 influenza. She recalled having milder symptoms while in high school, when she was falling asleep during classes that she found boring. In college, the excessive sleepiness caused her to struggle academically, and she also avoided social situations due to embarrassment of falling asleep in inappropriate situations. Although she had troubles staying awake during the day, she would sometimes find it difficult to fall asleep at night and she woke up frequently through the night. Her symptoms were initially attributed to depression. She was started on prozac, which helped with anxiety, but she continued to have increased difficulty staying awake. She was also temporarily started on antipsychotics by her psychiatrist, when she complained that while falling asleep, she would often see an unfamiliar figure standing by her bed. It was discontinued when it did not eliminate hallucinations and worsened her sleepiness. She was eventually referred for a neurological evaluation when she started to experience brief episodes of sudden muscle weakness that varied in severity and most often consisted of flexion of the head, jaw/facial weakness, dropping things from her hands or knees buckling. Further questioning revealed that these episodes were triggered by laughter, excitement, surprise, or anger. The patient denied sleep paralysis. Her Epworth Sleepiness Scale was 19/24. The patient had no family history of any sleep disorders.

Z. Belisova (✉)
Neurology, NYU Langone Medical Center, New York, NY, USA
e-mail: Zuzana.Belisova@va.gov

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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Examination

Vital signs were normal. Body mass index (BMI) was 20.3 kg/m^2. Physical and neurological examination were both normal.

Investigations

In laboratory polysomnography followed by multiple sleep latency test (MSLT) was done. Sleep onset latency was 5.8 min, sleep efficiency was 92.6%, REM latency was 86.5 min, respiratory disturbance index was 0.0/h, minimum oxygen saturation 96.0%, and periodic limb movements of sleep associated with arousals was 5.1/h, total sleep time was 403.5 min. MSLT revealed mean sleep latency of 3.5 min and 3 sleep onset REM periods (SOREMPs). Magnetic resonance imaging (MRI) of the brain was normal.

Diagnosis

Narcolepsy type 1 (Narcolepsy with cataplexy).

Discussion

Narcolepsy is a chronic disabling neurological disorder characterized by disruption of sleep wake cycle in which elements of REM physiology intrude into wakefulness and elements of wakefulness intrude into sleep. It is still often unrecognized and initially misdiagnosed disorder as in the case above, although it is known to be the third most common cause of excessive daytime sleepiness (after sleep deprivation and obstructive sleep apnea). Its estimated prevalence is between 25 to 50 per 100,000 people. It typically starts in adolescence or early adulthood. It is caused by loss of neurons in hypothalamus producing hypocretin (also known as orexin) [1]. As in our case, onset may be heralded by a viral illness. It is a clinical syndrome consisting of classic tetrad of excessive daytime sleepiness, cataplexy, hypnogogic or hypnopompic hallucinations and sleep paralysis. It is important to recognize that only about one third of the patients will have all four symptoms. The most common and usually the first symptom is excessive daytime sleepiness. It is often exacerbated by sedentary activities. Children with excessive daytime sleepiness may become hyperactive as an attempt to overcome sleepiness. Patients fall asleep under inappropriate circumstances and in severe cases without preceding drowsiness (referred to as sleep attacks). Cataplexy is the only pathognomonic symptom of narcolepsy and occurs about 60–75% of patients. It represents an intrusion of REM sleep atonia into wakefulness, which the patient experiences as a sudden transient muscle weakness triggered by emotion such as laughter, surprise, or anger. It typically starts within 3–5 years of the onset of sleepiness. It lasts seconds to

minutes. The muscle weakness can be partial and most frequently begins in the face (ptosis, hypotonic face with jaw weakness) and in most severe cases it can be complete leading to bilateral weakness and causing the patient to fall. Respiratory and oculomotor muscles are spared. Consciousness is preserved. Many patients also experience hypnagogic or hypnopompic hallucinations (85% visual, less commonly auditory or tactile), which are sometimes, as in our case, mistaken for psychotic illness. They occur at transition between sleep and wakefulness. Sleep paralysis also occurs. It is a temporary muscle weakness leading to inability to move or speak while waking up or falling asleep. Patients also often experience disruption of nighttime sleep with frequent awakenings and poor sleep quality. Automatic behaviors can also occur when brief sleep episodes occur during a habitual activity (e.g., writing, talking, driving) and the patient automatically continues the activity during these episodes without awareness. The patients cannot recall their action and their performance is usually impaired. The differential diagnosis of narcolepsy includes other causes of excessive sleepiness such as insufficient sleep syndrome; chronic sleep deprivation; obstructive sleep apnea; idiopathic hypersomnia; medication, alcohol, and substance use; recurrent hypersomnia; circadian sleep disorders; and medical, neurologic, and psychiatric conditions. Therapy consists of pharmacologic therapy for sleep disruption and excessive sleepiness (stimulants such as amphetamines, methylphenidate, modafinil, armodafinil, pitolisant, solriamfetol) as well as prevention of cataplexy and other REM sleep phenomena (tricyclics antidepressants and selective serotonin re-uptake inhibitors). γ-Hydroxybutyrate or a hypnotic agent can be used to treat nocturnal sleep disturbance and consolidate nocturnal sleep. γ-Hydroxybutyrate (sodium oxybate), a gamma-aminobutyric acid (GABA) precursor, increases sleep continuity and decreases the frequency of cataplexy in persons with narcolepsy. Behavioral modification, education, and support are equally important. Therapy is commonly required for life.

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Case 44. Timing Is Everything

44

Matthew T. Scharf and R. Nisha Aurora

History

35-year-old man presents with an irregular sleep schedule. As a child, he was unable to go to sleep at his bedtime and his mother would often find him staying up late and reading under the blankets. When he enrolled in college, he was able to avoid morning classes and maintained a schedule where he would wake up around 11 AM on weekdays and later on weekends. During college, he began to note progressive lethargy, difficulty with concentration, intermittent dizzy spells, and diffuse pain. He was always sleepy. These symptoms were severe enough that he had to discontinue his college studies. After college, he would generally go to bed around 4–5 AM and would wake up around 1–2 PM. However, over time, he noted that "I physically couldn't fall asleep at a steady time anymore." He had been able to maintain a consistent bed time and wake time before this on a modified schedule, but after this period of time he was no longer able to maintain a steady bedtime and wake time at all.

His prior medical history is notable for alopecia totalis at age 6. The alopecia went into remission and returned at age 10 and has persisted since then. At age 12, he was diagnosed with Type I diabetes and found to have anti-glutamic acid decarboxylase 65 (anti-GAD65) antibodies. He was subsequently found to have thyroid disease with antithyroid peroxidase (anti-TPO) antibodies. He was diagnosed with fibromyalgia while in college.

M. T. Scharf
Department of Neurology, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
e-mail: matthew.scharf@rwjms.rutgers.edu

R. N. Aurora (✉)
Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
e-mail: ra768@rwjms.rutgers.edu

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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Examination

On physical examination, his body mass index (BMI) was 32.0 kg/m^2, BP = 138/81, RR = 16, Pulse = 105, SaO2 = 97%. He was awake, alert and interactive. His vision was grossly normal with corrective lenses.

Investigations

Cardiac, pulmonary and neurologic examination were normal. A lumbar puncture was normal except for a mildly elevated protein (78 mg/dL). Magnetic Resonance Imaging (MRI) of the brain and a routine electroencephalogram (EEG) were also normal.

Due to the persistence of his cognitive complaints and lethargy as well as the prior autoimmune diseases, the presumed diagnosis of an autoimmune encephalitis was considered. He was treated with multiple rounds of either plasmapheresis or intravenous immunoglobulin (IVIg) without improvement. During his college years, he had a polysomnogram and he was diagnosed with obstructive sleep apnea (OSA). He started positive airway pressure (PAP) therapy which improved his sleepiness partially but did not affect the timing of his sleep. Due to high pressure requirements, he had an uvuolopalatopharyngoplasty at around age 30. He remained on PAP therapy with lower pressures. PAP compliance data showed a fixed pressure Bi-level PAP of 15/10 cm of water, usage on 100% of days, with an average daily usage of 9 h and 8 min. Residual AHI = 1.8/h.

Since childhood, the patient noted a tendency to go to bed late and sleep late. These times became progressively later until a point at which there was no longer any consistent bed time and wake time. The hours at which he used PAP, a possible indicator of sleep time, is shown in Fig. 44.1. The differential diagnosis for an irregular sleep schedule is large. Psychophysiological insomnia can cause an irregular sleep schedule and maladaptive behaviors can exacerbate it. However, this patient did not present with difficulty falling or staying asleep when allowed to sleep on his preferred schedule. Patients with irregular work hours may also present with an irregular sleep schedule; this is known as shift work disorder. However, this patient did not have work or school obligations that interfered with his preferred sleep schedule. He likely had a delayed sleep phase since childhood, but patients with a delayed sleep phase generally report feeling well when allowed to maintain their preferred sleep schedule and can maintain consistent sleep hours. Patients with a hypersomnia, such as narcolepsy, may presents with sleepiness during the daytime and difficulty sleeping at night, but the sleep pattern does not tend to shift over time.

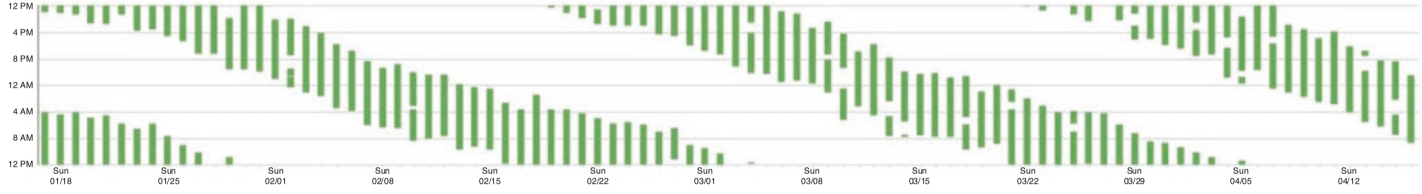

Fig. 44.1 Title: 90-day PAP Use Pattern. PAP was used daily, but the time of use shifted by approximately 45 min per day. Each green bar represents when the PAP was used. The y-axis shows time of day and the x-axis shows the date

Discussion and Management

For the presumed circadian rhythm disorder, he was given trials of melatonin before bedtime and bright light exposure after awakening. He was subsequently tried on 2 separate melatonin agonists, ramelteon and tasimelteon. His sleep schedule did not become regular with these treatments. Due to his persistent sleepiness, the diagnosis of idiopathic hypersomnia or narcolepsy without cataplexy was considered but his multiple sleep latency test showed a normal mean sleep latency of 12.4 min.

Most likely, this is a case of free-running/non-24 circadian rhythm. The central circadian clock in the suprachiasmatic nucleus of the hypothalamus contains an oscillator, or "clock," with an endogenous period of approximately 24 h. This circadian clock is synchronized with the external environment by entrainment with external stimuli, *zeitgeibers*. Light is the major stimulus, but other factors such as sleep/wake cycle, social factors and eating may also play a role. In the absence of entrainment with *zeitgeibers*, the endogenous timing of the clock proceeds uncoupled from the external environment. A free-running circadian rhythm is very common in blind patients with no light perception [1], presumably due to the inability of light to entrain the circadian clock. However, a free-running circadian rhythm has become an increasingly recognized, albeit rare, problem in sighted individuals. In one case series, the authors describe seven sighted patients who presented with a free-running circadian rhythm. Interestingly, similar to the patient discussed here, most of the patients in that series initially had a delayed sleep phase which appeared to progress to a free-running circadian rhythm [2]. The patient described here also had a number of autoimmune diseases which likely affected his central nervous system and it is possible that there was damage to the areas involved in transduction of the light signal to the suprachiasmatic nucleus.

Treatments for a free-running circadian rhythm include high-intensity light therapy, melatonin and melatonin receptor agonists. In the aforementioned case series, the patients were successfully entrained with melatonin and bright light therapy, but most discontinued therapy and reverted to a free-running circadian rhythm [2]. Unfortunately, this patient did not improve with bright light therapy, melatonin or melatonin receptor agonists. He appears to have a circadian period slightly longer than 24 h. He maintains a sleep schedule in accordance with his free-running circadian rhythm and shifts his sleep schedule by approximately ¾ an hour per day.

Final Diagnosis

Free running/non-24 circadian rhythm.

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Case 45. Lullaby and Goodnight Say Goodbye to These Spikes…

45

Morris H. Scantlebury

History

This patient is a 5-year-old right -handed girl who presented with episodes out of sleep characterized by an arousal, deviation of the eyes to the left, altered awareness, drooling, stiffening of her arms and legs followed by ictal emesis. Four months later she developed further episodes out of sleep characterized by an arousal, eye deviation upwards, she would attempt to vomit and at times this would be followed by generalized stiffening or shaking. These events could last between 20–30 min and occurred every other month. She had a normal development. There was a history of seizures in her father that stopped after age 6. Her sister also had a history of febrile seizures. She had difficulties with language and mathematics in school requiring individual program planning but excelled in drawing. There was no definitive history of cognitive regression. She was started on levetiracetam with good seizure control. There was also moderate improvement in her school performance with treatment as reported by her parents.

Examination

Her general and neurological examinations were normal.

M. H. Scantlebury (✉)
Pediatrics, Alberta Children's Hospital, Calgary, AB, Canada
e-mail: morris.scantlebury@albertahealthservices.ca

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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Investigations/Studies

Her initial electroencephalogram (EEG), done following her first seizure, showed multifocal epileptogenic discharges. The EEG done after the appearance of the nocturnal seizures showed right posterior hemispheric epileptogenic abnormalities.

Her magnetic resonance imaging (MRI) of the brain (Fig. 45.1a) showed volume loss of the right thalamus, thinning of the right fornix and mammillary body. There was also slight volume loss of the posterior right hippocampus without increased signal intensity or internal structure loss. There was also a thinned and irregular body and splenium of corpus callosum. These abnormalities were thought most likely related to remote prenatal or perinatal injury.

A positron emission tomography-computed tomography (PET/CT) (Fig. 45.1b) showed severely diminished activity noted within the right thalamus in comparison to the left and very subtly diminished activity within the right temporal lobe.

After 2 + years of seizure freedom a sleep deprived routine EEG was obtained to guide medication wean which showed frequent right frontal polar spikes maximal Fp2 that were activated and becoming almost continuous during hyperventilation and sleep. The awake background was normal, and sleep showed no vertex waves and very few sleep spindles. A subsequent EEG done 2 months later showed a shift of the discharges to become right posterior quadrant predominant but having a diffuse field involving the right central parietal and frontal regions that became almost continuous during sleep (Fig. 45.2). Neuropsychological testing showed significant weaknesses in domains of processing speed, attention, receptive language, and verbal memory. Her overall intelligence was normal.

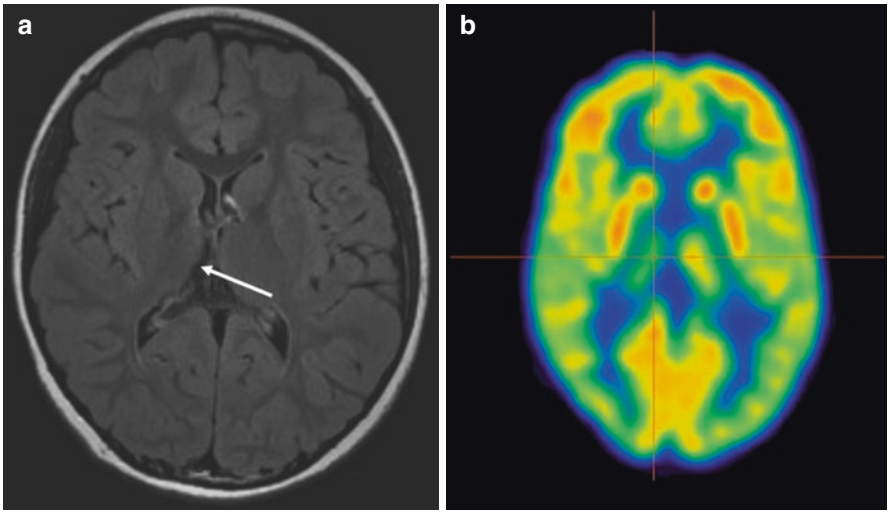

Fig. 45.1 (**a**) MRI brain: Axial Flair image showing volume loss of the right thalamus (arrow). (**b**) Axial PET CT image showing corresponding hypometabolism of the right thalamus (cross- hairs)

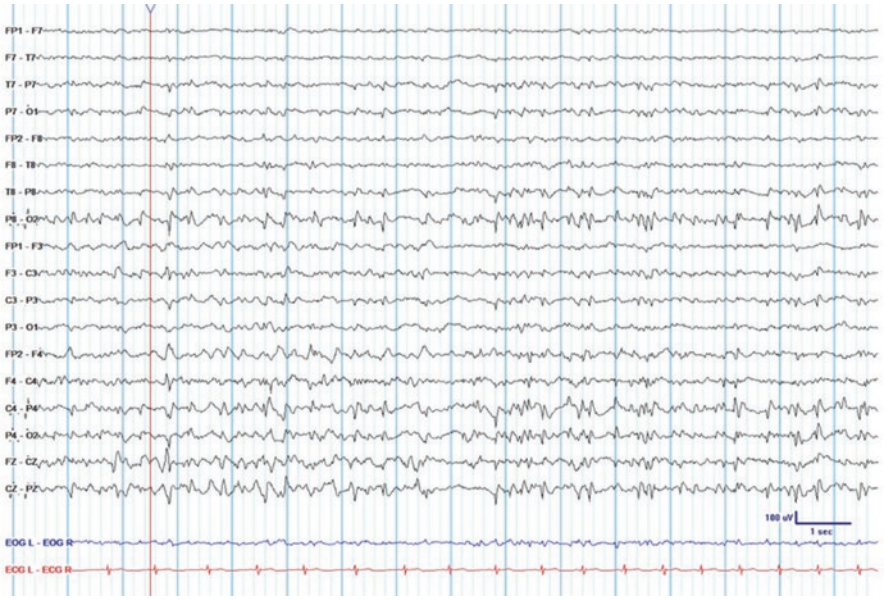

Fig. 45.2 EEG: Bipolar montage depicting right posterior hemispheric predominant CSWS

Differential Diagnosis

1. Epileptic encephalopathy with continuous spike wave during sleep
2. Landau Kleffner syndrome
3. Panayiotopoulos syndrome

Discussion and Management

This patient has a developmental epileptic encephalopathy. The unique feature of the developmental epileptic encephalopathies are that the frequent epileptic activity contributes (or highly suspected) to the progressive cognitive arrest or deterioration that is a prominent feature of these conditions.

Classified under the developmental epileptic encephalopathies are a group of age-related developmental disorders that include early infantile epileptic encephalopathy (EIEE), early myoclonic encephalopathy (EME), Infantile Spasms, Lennox Gastauat syndrome, Dravet Syndrome, Doose syndrome, the progressive myoclonic epilepsies, and Epileptic encephalopathy with continuous spike wave during slow wave sleep (CSWS).

The most likely diagnosis in this patient is epileptic encephalopathy with CSWS which is a rare syndrome that affects 0.5–0.6% of all epilepsies seen in tertiary pediatric centers.

As in our patient the seizures in CSWS start in childhood and tend to be focal with or without impaired awareness or focal to bilateral convulsive. Other seizure types such as absences, atonic seizures and focal motor seizures with negative myoclonus have also been described as the condition progresses.

The EEG in CSWS shows spike wave activity occupying greater than 80% of the sleep record which is diagnostic. However, a lower burden of spikes may lead to cognitive regression therefore a diagnostic cut-off of spikes wave activity occupying >50% of the sleep record has more recently been proposed. The spike-wave activity can be focal, multifocal or generalized depending on the etiology. Spike wave discharges may be recorded during wakefulness, but significant sleep activation is required to make the diagnosis. The spikes can shift locations as the patient matures and as the disease progresses as in our patient.

The etiology of CSWS is usually structural but can be genetic which would have a bearing on the type of seizures, pattern of spikes recorded on the EEG, responsiveness to treatment and outcome. The CSWS in our patient was likely due to the structural abnormalities but a family history of seizures was present which can be seen in up to 50% of patients with CSWS. Genetic testing was not done.

A temporal relationship between the onset of spikes and regression is key to the diagnosis. We were not able to strictly meet this requirement as her CSWS was diagnosed after 2 years seizure freedom without complaints of cognitive regression. Notwithstanding she had significant challenges in school requiring intervention. It is interesting to note that she was improving intellectually with the control of her seizures, which suggests the seizures themselves were impacting her cognitive function.

Our patient did not have Landau Kleffner syndrome as she did not have acquired auditory verbal agnosia and aphasia which is typical for this condition along with the CSWS. The observation of prolonged nocturnal seizures with prominent autonomic features (vomiting) and posterior hemispheric spikes on the EEG in our patient suggests Panayiotopoulos syndrome but the CSWS and structural brain abnormality would be atypical.

The pathogenesis of CSWS is poorly understood. Emerging evidence that patients with CSWS have thalamic injury or dysfunction [1] diagnosed with MRI and functional imaging, as in our patient, suggests a central role for thalamocortical network dysfunction in its pathogenesis. But why? During the awake state the ascending arousal systems exert a powerful cholinergic inhibition on the reverberatory thalamo-cortical system which becomes disinhibited as a person falls asleep leading to the development of sleep spindles. Studies in the thalamic slice preparation, and in behaving rats, indicate that blocking GABAergic inhibition in the thalamus can transform sleep spindles into rhythmic spiking activity. These results support that spike wave activity and sleep spindles share a commonality in networks that may in part explain the sleep activation of spike wave activity as seen in CSWS.

CSWS is often refractory to treatment. Prednisone, benzodiazepines, sulthiame, leviteracetam, valproate, clobazam and ethosuximide have all been shown through anecdotal and retrospective studies to be, at times, effective in controlling CSWS. A published review of the literature suggests that longterm steroids and

benzodiazepines are the most impactful treatments [2], but they are potentially associated with significant harmful side effects. Surgical treatment in refractory lesional cases has been reported successful in appropriately selected cases. Outcomes are variable and depend on etiology, age of onset, the spike burden and refractoriness of the seizures and spikes to treatment amongst other factors.

To manage the CSWS in our patient we increased the dose of levetiracetam to 60 mg/kg and valproate was subsequently added without effect. Subsequently, the patient was admitted for a trial of high dose diazepam given during continuous EEG monitoring which was also ineffective.

Our next step was to discontinue the valproate and start ethosuximide as an outpatient given the MRI showing thalamic abnormalities and that there was no definitive history of cognitive deterioration therefore the risk of steroids outweighed the benefits. Ethosuximide is a T-type calcium channel antagonist used to treat absence epilepsy- a thalamocortical network disorder.

A 24-hour ambulatory EEG done 3 months later was normal. She has since had 5 subsequent EEGs of which 3 were prolonged; all of which were normal. The patient is now 16 years old seizure free off medications and doing well in school.

Final Diagnosis or Most Likely Diagnosis

Epileptic encephalopathy with continuous spike wave during sleep.

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Case 46. Breathing Is Not the Complete Story

46

Alcibiades J. Rodriguez

History

A 68-year-old man presented to the sleep clinic with frequent awakenings, difficulties staying sleep, loud snoring, acting out dreams and restless sleep.

He was diagnosed with obstructive sleep apnea (OSA) elsewhere 9 years ago. His polysomnogram (PSG) showed an apnea-hypopnea index (AHI) of 39.6/h, respiratory disturbance index (RDI) of 79.4/h. His minimal oxygen saturation was 74%. His periodic limb movements of sleep (PLMS) index was 18.9/h. There was no definite REM sleep without atonia (RSWA) according to report, but only 16 min of REM sleep stage was recorded.

A continuous positive airway pressure (CPAP) study was recommended. He did well at 13 cm of water with resolution of all his respiratory events. His PLMS index was 106.3/h. The total sleep time was 390 min. He had 111 min of REM sleep stage, which did not show RSWA or dream enactment behavior. The EEG showed "extended spike and slow wave distribution bilaterally" as per report.

He did well for 2 months, but had a gradual return of his symptoms. He feels his pressure is too low and has barely used CPAP device since. He continues to have restless sleep, with frequent awakenings and kicking and moving, which may or may not be associated with dreaming. He sleeps alone and he does not remember punching or falling from bed. He reports that most of the restlessness in his legs occurs at night, with minor and manageable symptoms during the day. Moving of

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/978-3-031-18374-4_46.

A. J. Rodriguez (✉)
Department of Neurology, NYU Langone Comprehensive Epilepsy Center-Sleep Center, New York, NY, USA
e-mail: Alcibiades.rodriguez@nyulangone.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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his legs provides some temporary relief. He reports that treatment with ropinerole (unknown dose) in the past was unsuccessful. His Epworth Sleepiness Scale was 9/24.

He has a past medical history of anxiety, coronary artery disease, restless legs syndrome (RLS), benign prostatic hypertrophy and systemic hypertension. He never had a seizure or risk factors for epilepsy, such as, traumatic brain injury, febrile seizure, traumatic birth, or family history of seizures. Medications include amlodipine, aspirin, carvedilol, clopidrogel, rosuvastatin, sertraline and tamsulosin.

Examination

Weight: 225 lbs.

Height: 64 in.

Body mass index (BMI): 38.62 kg/m^2.

General physical and neurological examination was normal. There was no significant weight change since 9 years ago.

Investigations

A CPAP titration study showed complete resolution of respiratory events with Bi-level PAP at 18/11 cm of water. He had a PLMS index of 111.3/h, which occurred exclusively during NREM sleep (see Fig. 46.1a). The movements involved all four extremities and torso, at times, with minor vocalizations. There was also events of gasping for air that involved vocalizations. Sometimes, the legs movements were closely associated with the respiratory events. The arousal index was 42.4/h (related to breathing and PLMS). The total sleep time was 220.5 min with 35 min of REM sleep. There was normal muscle atonia during REM sleep stage with no dream enactment behavior. PLMS stopped during REM sleep stage (see Fig. 46.1b).

The patient had troubles falling and staying asleep, showing restlessness in the middle of the night (see Video 46.1) and markedly brisk limb movements even after complete CPAP titration (Video 46.2).

Brain magnetic resonance imaging (MRI) and video electroencephalogram (EEG) were normal. His ferritin level was 138 ng/mL, total iron was 142 UG/DL, Total iron binding capacity (TIBC) was 368 µg/dL, percentage of iron saturation was 39% and transferrin was 284 mg/dL.

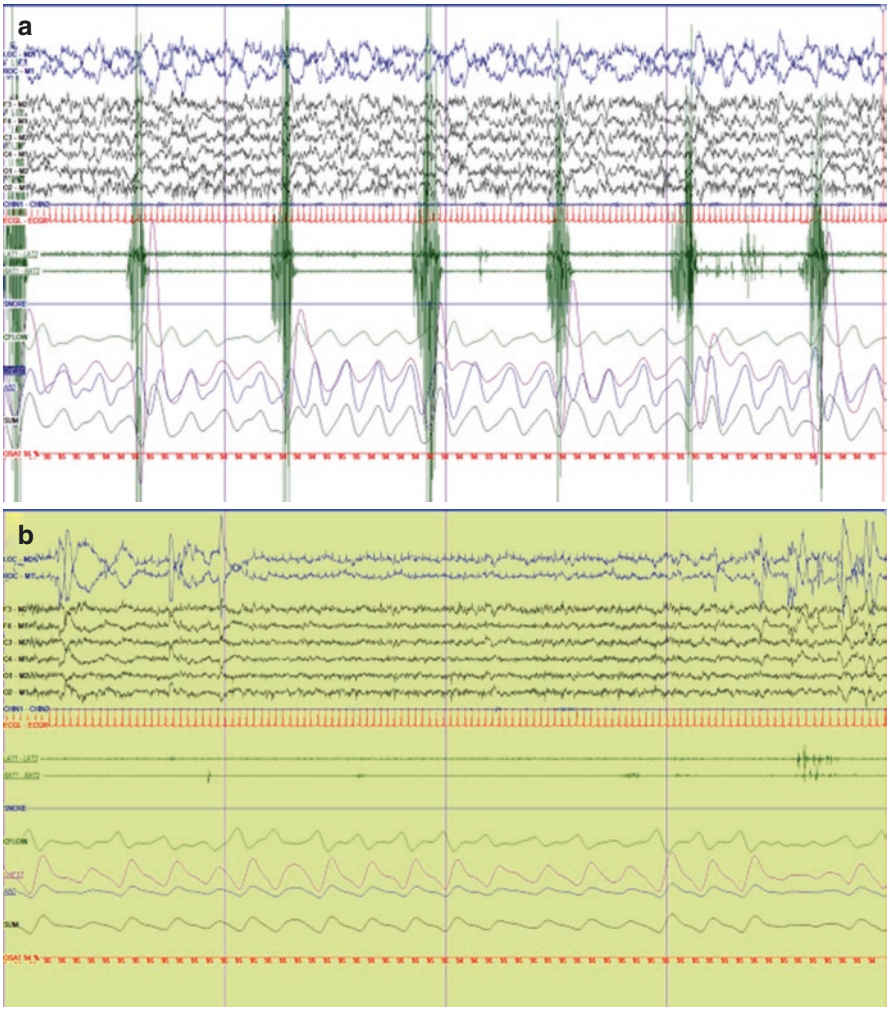

Fig. 46.1 Two-minute-epoch on NREM sleep stage showing frequent, high amplitude periodic leg movements (**a**) and two-minute-epoch of REM sleep stage showing normal muscle atonia (**b**). Electroencephalogram (EEG) and Electro-oculogram (EOG) referenced to left mastoid (M1) and right mastoid (M2) electrodes. EOG: LOC-M2, left eye; ROC-M1, right eye. EEG: F3-M2 (left frontal electrode), F4-M1 (right frontal electrode), C3-M2 (left central electrode), C4-M1 (right central electrode), O1-M2 (left occipital electrode), O2-M1 (right occipital electrode). CHIN1-CHIN2: Chin surface electromyogram (EMG) electrode. ECGL-ECGR: Electrocardiogram. LAT1-LAT2: left anterior tibialis surface EMG. RAT1-RAT2: right anterior tibialis surface EMG. Snore channel. Cflow: continuous positive airway pressure (CPAP) Pressure flow. Chest: Chest belt. Abd: abdominal belt. Sum: summary of belt and abdominal belts signal. OSAT: oxygen saturation

Differential Diagnosis

The patient presented with untreated severe sleep apnea due to poor compliance, restless sleep, possible dream enactment behavior and frequent awakenings. Previous attempts to treat his sleep apnea failed. Insomnia, due in part to his RLS, in some measure was responsible for his non-compliance. In addition, there was the possibility of REM sleep behavior disorder (RBD). Most patients with idiopathic RBD eventually develop a α-synucleopathy, such as, Parkinson's disease, dementia of Lewy bodies or multi system atrophy. Patients with severe OSA may present with a history that may resemble RBD. In addition, there have been reports of severe PLMS that can also mimic RBD. Of course, all these disorders may co-exist at the same time, which could make the management more challenging.

During the first CPAP titration there was also the suggestion possible epileptiform spikes, however, the study was done without a full EEG montage. The patient has no history of seizures or risk factors for epilepsy.

Discussion and Management

The first step was to proceed with a proper PAP titration to be sure he was getting the appropriate pressure to control his severe OSA. The final pressure was high and Bi-level PAP was used. During the titration, he demonstrated severe difficulties falling and staying asleep. At some point, the patient was out of bed checking his phone and very restless (Video 46.1). The PLMS index was very high at 111.3/h, many related to arousals. These movements were stereotyped, periodic and vigorous, involving fours limbs and trunk, and occurred exclusively during NREM sleep stage. Respiratory events were also associated with violent movements as the patient was gasping for air. After all the respiratory events were under control, the patient reached REM sleep stage and normal muscle atonia was observed with no PLMS or dream enactment behavior. This case shows severe, brisk PLMS and OSA contributing to abnormal sleep behaviors, which may have been misinterpreted as RBD, also known as pseudo-RBD [1, 2].

Nocturnal seizures may have a motor component, are usually stereotyped, may occur multiple times a night and be associated with confusion afterwards. An overnight video EEG that was normal may not totally exclude epilepsy, but the patient's clinical history is not suggestive of a seizure disorder.

The patient was placed on PAP therapy and started on gabapentin 300–600 mg every night. He thought it was causing binge eating at night and he discontinued it. Pregabalin was started and he reported headaches. Gabapentin was re-introduced at 200 mg at night. Upon his last visit, he reports sleeping 5 h at night with no side effects related to medication. He uses PAP every night on average 3 h and 26 min with a residual AHI of 1.4/h. He feels more rested and energetic. Medications were reviewed, but due to anxiety he was advised to continue sertraline, which may contribute to PLMS.

The treatment of sleep apnea could be cumbersome to many and even more in the presence of other sleep disorders such as RLS with PLMS (which could be the

cause of secondary insomnia), as seen in this case. The certainty of the diagnosis of idiopathic RBD is extremely important, since its presence may indicate the patient may progress to a neurodegenerative disorder. The patient has achieved better sleep and hopes for continued improvement with time and medication adjustments.

Final Diagnosis

Severe OSA and RLS with PLMS, contributing to insomnia and mimicking RBD.

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Case 47. Rapidly Worsening Obstructive Sleep Apnea

47

Boris Chernobilsky

History

Sixty-three years old female who presented to otolaryngology-head and neck surgery for evaluation of nasal obstruction at the request of her pulmonologist. She had a history of nasal trauma and was noted to have nasal obstruction on exam. The patient states she had rapidly worsening snoring, sleep disturbance and daytime somnolence over the last several months. She had two sleep studies in the past: one negative for obstructive sleep apnea (OSA) and the other showing mild OSA for which she had received a mandibular advancement device (MAD). She did not use it because she did not feel that her sleep was that disturbed and she did not feel better with the MAD at the time. She complained to her primary care physician (PCP) and pulmonologist that her snoring had rapidly worsened and her sleep significantly deteriorated in the last month prompting a new sleep study which showed severe sleep apnea. She was supposed to start continuous positive airway pressure (CPAP), but had not, stating she was "not ready and could not understand how things worsened so quickly." The patient denied any changes in weight or significant tobacco, alcohol or illegal drug use.

On review of systems, the patient reported that her right ear has been "bothering" her for 6 weeks and a soreness that radiated down her right neck. Her PCP had examined her and gave her azelastine nasal spray which provided no relief. She denied dizziness, tinnitus, or hearing change. She also described intermittent odynophagia for approximately 6 weeks. She also stated she is under a significant amount of stress lately with family issues. She uses amphetamine salts sparingly, a few times a month and alprazolam about once a week. Past medical history was positive for hypothyroidism, oral herpes, depression, fatty liver and anxiety.

B. Chernobilsky (✉)
Otolaryngology - Head and Neck Surgery, NYU Langone Health, New York, NY, USA

Internal Medicine, NYU Langone Health, New York, NY, USA
e-mail: boris.chernobilsky@nyulangone.org

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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Examination

Obese female in no acute distress with a body mass index (BMI) of 35 kg/m^2. Examination was significant for left septal deviation. Oral exam revealed a large, scalloped tongue with deviation to the right. Severe wear facets on teeth from bruxism were noted. The patient had difficulty opening her mouth with some significant guarding making the oropharyngeal exam difficult. With significant effort by manually depressing the tongue base, the oropharynx could be inspected. Right base of tongue and tonsillar pillar fullness was noted. An ulceration was noted in the right anterior tonsillar pillar. The neck exam was supple, without lymphadenopathy although a large thyroid was palpated. Flexible nasolaryngoscopy confirmed significant tongue base fullness.

Investigations

The patient's unattended peripheral arterial tonometry (PAT), WatchPat® (Itamar Medical) sleep study revealed severe obstructive sleep apnea (OSA):

PAT apnea-hypopnea (pAHI) at 4%: 38.8/hr.

REM pAHI(4%): 30.5 per hour

NREM pAHI(4%): 40.7 per hour

PAT respiratory disturbance index (pRDI): 39.8 per hour

Lowest oxygen saturation: 74%

Cumulative oxygen desaturation <=88: 26.4 minutes

Impression: Severe obstructive sleep apnea.

Computed tomography (CT) scan of the neck:

Aerodigestive structures: There is a 3.6 × 2.1 × 2.2 cm enhancing, irregular mass involving the right base of tongue, right glossotonsillar sulcus and tonsillar fossa. The mass extends laterally to the parapharyngeal space and superiorly to the soft palate. Anteriorly, there is involvement of the posterior aspect of the right hyoglossus muscle.

Lymph nodes: 1.3 cm right level 2A lymph node with central hypodensity.

Differential Diagnosis

Severe Obstructive Sleep Apnea.
Oropharyngeal Tongue Base Malignancy with neck metastasis.
Anxiety and Maintenance Insomnia.

Discussion and Management

The patient was sent for fine needle aspiration of her neck mass, which revealed metastatic squamous cell carcinoma, keratinizing in the lymph node, and right cervical, level 2A. The neoplastic cells were positive for p63. Approximately 15–20% of the tumor cells show strong nuclear and cytoplasmic staining with p16. Positron emission tomography (PET)/CT and magnetic resonance imaging (MRI) confirmed initial workup and no distant metastases were noted although the mass measured larger at 4.3 × 2.6 cm (see Figs. 47.1 and 47.2). She was referred for chemotherapy and radiation for metastatic human papilloma virus (HPV) related squamous cell carcinoma.

This case demonstrates several important principles. First and foremost, the need for a good head and neck examination for obstructive sleep apnea. The patient had a difficult airway because of the bulk of the lesion and trismus from infiltration of her parapharyngeal musculature, however visualization was possible with effort in the office. Second, a multidisciplinary approach to the patient's OSA results in a more complete understanding of the patient's underlying anatomic and pathophysiologic process. Most patients undergo evaluation by pulmonology and otolaryngology at our center. Third, careful history demonstrated several "red flags" in this patient: persistent right sided ear pain with a normal ear exam and chronic intermittent sore throat. Finally, patient attribution is also very important. Her rapidly worsening night time sleep disordered breathing in the span of about

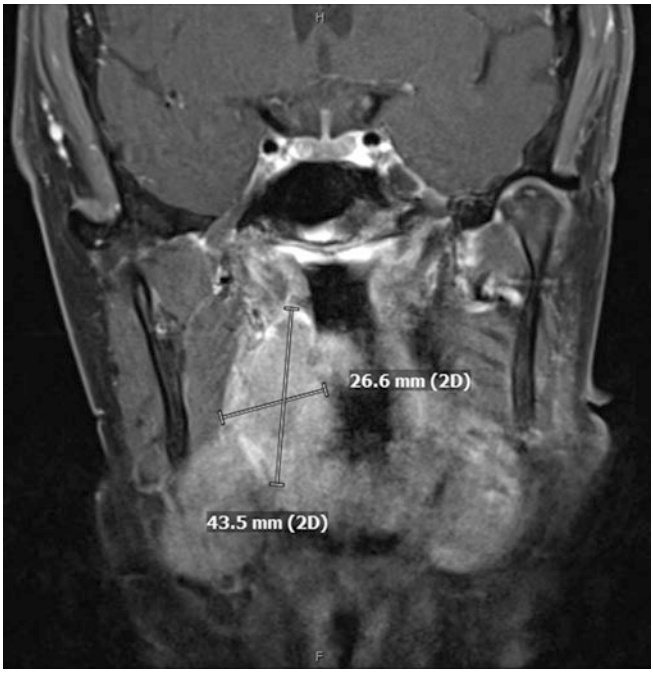

Fig. 47.1 Coronal MRI view (T1 fast spin echo, small field of view post-contrast) showing a large, enhancing mass 4.3 × 2.6 cm occupying the right base of tongue extending to the nasopharynx

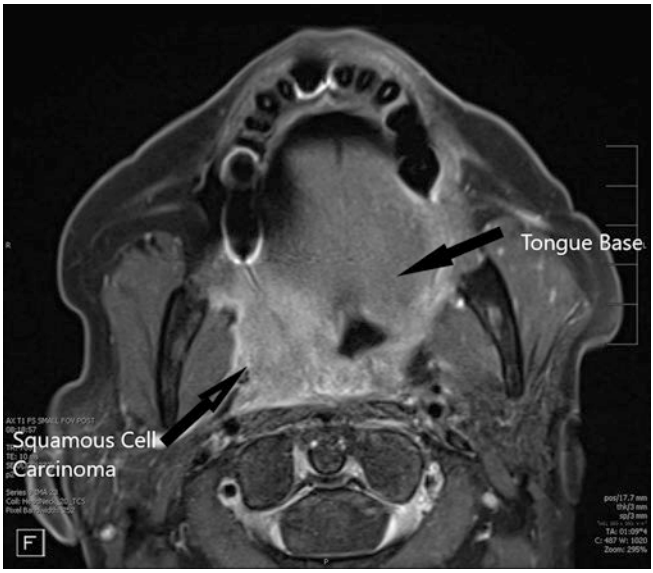

Fig. 47.2 Axial MRI view (T1 fast spin echo, small field of view post-contrast) showing large, enhancing mass obstructing the right oropharynx

6–8 weeks without any other changes led the patient to believe "something was wrong" and resulted in her resistance to initiating CPAP therapy. The rapid growth and the large bulky size of the tumor led to significant progressive airway obstruction during sleep. While OSA is a rare presentation of oropharyngeal squamous cell carcinoma, the sleep provider must be vigilant for space occupying masses as a cause of OSA for appropriate and timely treatment [1].

Final Diagnosis

Obstructive Sleep Apnea secondary to space occupying malignancy of the oropharynx.

Reference

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Case 48. Unusual Cause of Worsening AHI on CPAP Download

48

John G. Park

History

A 20-year-old patient with a history of intellectual disability with Lennox-Gastaut syndrome, intractable epilepsy, progressive neuromuscular scoliosis, and obstructive sleep apnea [apnea-hypopnea index (AHI) of 10 and 38% of the night with end-tidal CO_2 (EtCO2) > 50, during full-night diagnostic testing with exclusively supine sleep and 31% REM sleep recorded, 4 years previously], presents for a continuous positive airway pressure (CPAP) follow-up. Although his mother reports improvements (though not resolution) in his daytime functioning and reduction in his daytime seizure frequency, download suggests poor adherence with only 42% of the night used >4 h, the average time in a large leak of 4 min, and residual AHI of 13/h on his auto-titrating CPAP (set between 4–12, with a mean pressure of 6 cm H_2O and 9 cm $H_2O \leq 90\%$ of the time).

Examination

Body mass index (BMI) was 14.8 kg/m^2 and neck circumference was 31 cm. Presents in a wheelchair with non-purposeful movements with low axial and truncal tone.

J. G. Park (✉)
Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA
e-mail: park.john@mayo.edu

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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Investigations

Repeat split-night polysomnogram revealed:

Diagnostic	
Total sleep time	134.5 min
Sleep efficiency	81%
AHI	15.2/h
Obstuctive	0/h
Central	9.4/h
Hypopnea	5.8/h (mostly central hypopnea)
Mean saturation	93.8%
Nadir saturation	87%
Therapeutic (CPAP)	
AHI	17.8/h
Obstructive	0/h
Central	16.5/h
Hypopnea	1.3/h

Differential Diagnosis

Worsening AHI on the CPAP download may be due to inadequate pressure, excessive leak, treatment-emergent central sleep apnea, or misdiagnosed obstructive sleep apnea (OSA) due to misclassification of hypopnea as obstructive and not central. One must also consider the progression or development of other medical conditions which may now precipitate the onset of central sleep apnea that was not present at the time of the previous test. Examples of such disorders include the development of congestive heart failure, stroke, initiation of certain medications including narcotics, or other neurologic disorders.

Discussion and Management

Polysomnogram (PSG) with a full electroencephalogram (EEG) montage clearly shows the onset of central sleep apneic event during an electrographic seizure episode (see Figs. 48.1 and 48.2). In this patient with intractable seizures, it is most likely that his improved, but persistent electrographic seizures during his sleep are the cause of the apparent central sleep apneic events. While OSA is more common, one study estimates that 10% of epilepsy patients have central apneic events during their PSG [1]. Another study suggested the presence of central apneas during seizures in 59% of patients with epilepsy [2]. While it is commonly accepted that untreated OSA may lead to increased seizure activity, this association with central sleep apnea (CSA) remains unclear. This case illustrates that it may be the electrographic seizures that precipitate the central apneic events. The mechanism of this interaction remains speculative, in that, the seizure activity may directly or indirectly affect the respiratory center which results in the disturbance of respiratory control.

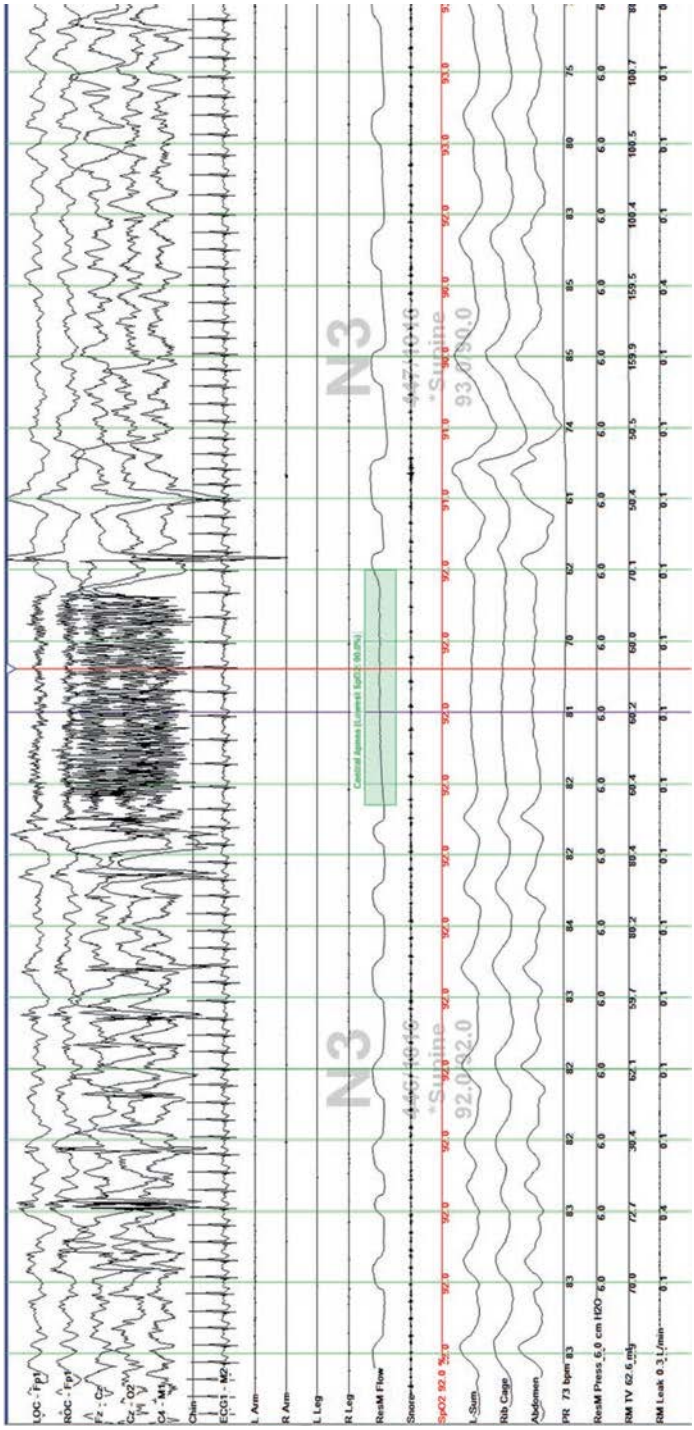

Fig. 48.1 60-second Epoch during the diagnostic study

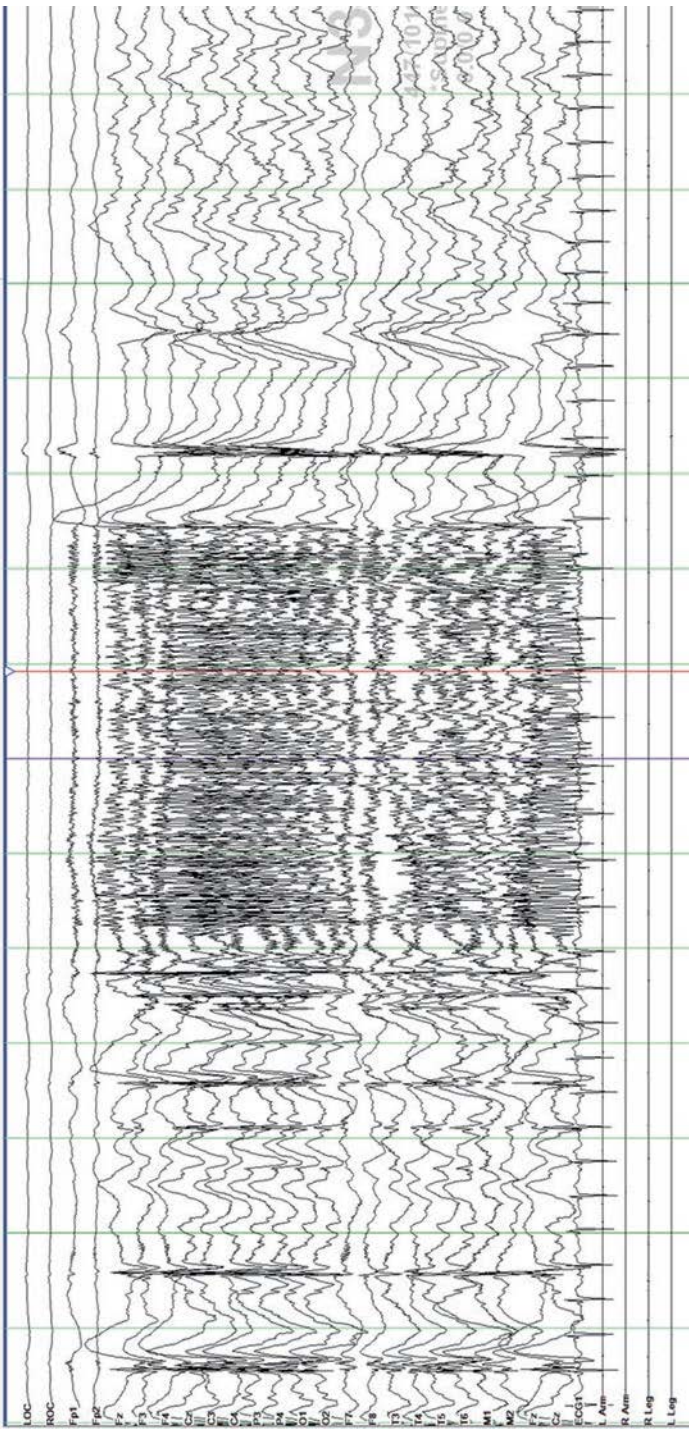

Fig. 48.2 16 channel 10- second Electroencephalogram showing paroxysmal fast activity (PAF) seizure discharge corresponding with previous 60-second epoch in Fig. 48.1

In this case, while his CSA was controlled with a bi-level device, further control of his underlying seizure disorder would better control his sleep-related breathing disorder.

Final Diagnosis

Central sleep apnea due to persistent electrographic seizures.

References

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Case 49. The Therapeutic Labyrinth of Multimorbidity

49

Diego Garcia-Borreguero and Carolina Miranda-Castillo

History

A 64-year-old man presented with discomfort in the lower limbs localized mostly in his calves. He described it as an urge to move his limbs that necessitated standing up and walking around. While this urge could occur throughout the day it was more pronounced during periods of prolonged rest and at night. Furthermore, this need to move his legs caused him to wake up as many as 10 times a night and he complained of not being able to go back to sleep afterwards.

His symptoms had started 4 years before the consultation. He was diagnosed with restless leg syndrome (RLS) and treated with pramipexole. He also suffered from excessive daytime sleepiness, hypnagogic hallucinations, sleep paralysis, and cataplexy, and had been diagnosed with narcolepsy at the age of 18 years. In addition, he suffered from obstructive sleep apnea and underwent treatment with continuous positive airway pressure (CPAP) at 7 cm H_2O. Sleep-related medications at the time of the initial consultation at our clinic were: pramipexole 2 mg/day for the last 3 years, clomipramine 75 mg/day, pregabalin 150 mg/day, modafinil 200 mg/day, levodopa-benserazide 200 mg/50 mg a day, and quetiapine 25 mg/day.

D. Garcia-Borreguero (✉)
European Sleep Institute, Santiago de Chile, Chile
e-mail: dgb@iis.es

C. Miranda-Castillo
Sleep Research Institute, Madrid, Spain
e-mail: acmiranda@hospitalreyjuancarlos.es

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_49

Examination

The neurological examination was normal. His Epworth Sleepiness Scale score was 21/24 and the International RLS rating scales core was 35/40 (very severe: 31–40 points).

Investigations

The polysomnogram showed a total sleep time of 311.5 min, with a sleep latency of 2.5 min, a rapid eye movement latency of 47.5 min, a periodic leg movement during sleep index of 67.8/h, and an apnea/hypopnea index of 19.3/h. A multiple sleep latency test showed an average sleep latency of 4.7 min with four episodes of sleep-onset rapid eye movements.

Parenchymal transcranial sonography reported an echogenicity of the substantia nigra (SN) of 0.188cm^2. The echogenicity was determined by taking five measurements of each side of the SN to get the average of each side. The SN is considered hypoechogenic if the sum of both sides is below 0.21cm^2 (see Fig. 49.1). The iron status investigation showed a serum ferritin of 815 ng/mL and a serum transferrin saturation of 43%. Following a repeat assessment of iron parameters, these abnormally high values were confirmed and we decided to perform a genetic test for hemochromatosis; the patient was found to be heterozygote for allele H63D.

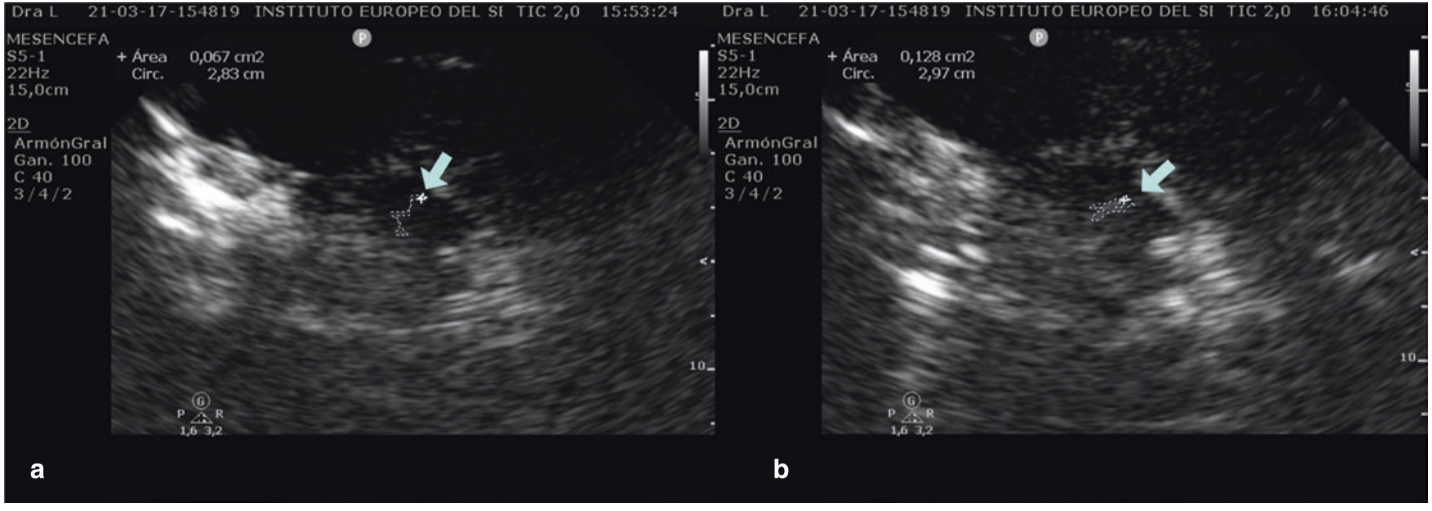

Fig. 49.1 The midbrain is observed through transcranial ultrasound, the substantia nigra is measured on the left side (**a**) with an area of 0.067 cm^2 and on the right side (**b**) with an area of 0.128 cm^2. SN is pointed out in both sizes with blue arrows. The result confirms hypoechogenicity of the substantia nigra due to low brain iron deposits

Differential Diagnosis

Peripheral neuropathy, akathisia, nocturnal leg cramps, idiopathic hypersomnia, post-CPAP residual drowsiness, REM behavior disorder.

Discussion and Management

RLS is a common neurological disorder. Its diagnosis is based on a clinical history in which five essential criteria must be met: (1) An urge to move the legs usually associated with an uncomfortable sensation in the legs; (2) the urge to move the legs begins or worsen during inactivity; (3) the uncomfortable sensations are partially or completely relieved by movement; (4) the sensations and the urge to move occur or are worse at night; (5) the symptoms cannot be explained by any other disease. The first line of treatment for RLS is either dopaminergic agonists (pramipexole, ropinirole, rotigotine) or α2δ-ligands (pregabalin, gabapentin and gabapentin enacarbil) [1]. However, treatment with dopaminergic agents frequently leads tolerance and over time, to dopaminergic augmentation of symptoms. Augmentation is defined as a long-term iatrogenic worsening of symptom severity when compared to before treatment initiation. Its main features are an earlier onset of symptoms in the afternoon, a spread to additional body parts, and a shorter latency to symptom onset when at rest. During augmentation, there is usually a worsening of symptoms when higher doses of the dopaminergic agent are used, and relative improvement some time after dose reduction.

As one of our main objectives was to reduce dopaminergic intake, we chose to add oxycodone 10 mg as part of the RLS treatment, gradually reducing instead the intake of pramipexole and levodopa and eventually withdrawing these two medications. We also added rotigotine 4 mg to better control the RLS daytime symptoms. Quetiapine was also withdrawn since it exerts an antagonistic dopaminergic effect worsening RLS symptoms. Regarding the treatment of sleep paralysis and cataplexy, we decided to withdraw clomipramine altogether and initiate treatment with venlafaxine of 75 mg, whereby the final dose needed to be increased to 225 mg per day for sufficient symptom control.

The central role of brain iron deficiency in RLS is well documented. Indeed, current guidelines recommend that whenever brain iron is low, it should be increased for a better outcome of RLS treatment. However, iron replacement therapy (IRT) is recommended only when serum ferritin levels are <300 μg/l and transferrin saturation < 45%, to avoid the risk of iron overload [2]. Indeed, while in patients with homozygous haemochromatosis there is an absolute contraindication of IRT, such a contraindication becomes relative for the heterozygous cases and depends on the serum iron levels. In our case, as the patient was heterozygous for haemochromatosis, we performed a close follow-up of the serum iron status over a year in the hope of being able to supplement the existing iron deficit. However, so far this has not been possible (see Fig. 49.2).

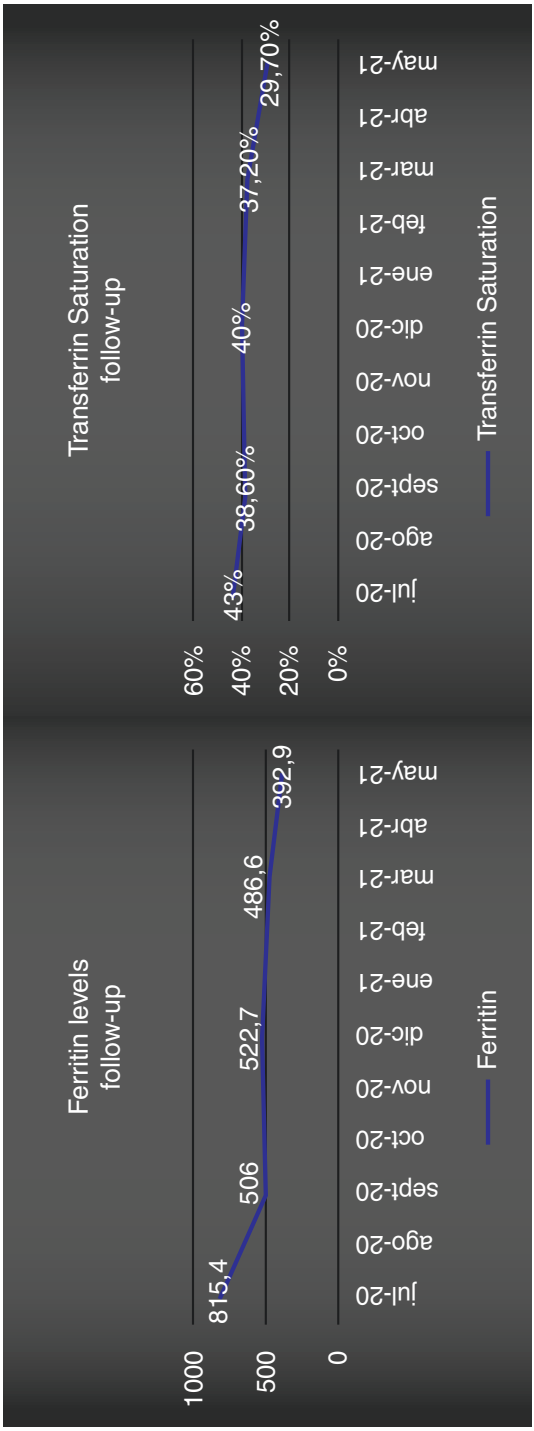

Fig. 49.2 Ferritin and transferrin saturation levels follow-up over the past year

Because the patient had an allergic skin reaction to the rotigotine transdermal patch and the dose of 10 mg oxycodone proved too low to completely substitute the remaining dopaminergic medication, we had to increase it to 30 mg at night, in addition to pramipexole 0.75 mg, venlafaxine 225 mg/day, modafinil 200 mg/day and levodopa 100 mg taken as needed (normally used three times a month). Despite this medication, the IRLS rating scale score slightly decreased to 25/40 (severe: 21 to 30 points). However, the treatment changes resulted in an improvement in nighttime symptoms and in sleep. Nevertheless, the symptoms of RLS are still present and severe, and this case is extremely difficult to manage given the associated comorbidities. An alternative treatment with methadone (replacing oxycodone and pramipexole) or even a treatment trial with transcraneal magnetic stimulation are currently being considered.

Final Diagnosis or most Likely Diagnosis

Restless leg syndrome, dopaminergic augmentation of RLS symptoms, brain iron deficiency, heterozygous haemochromatosis, narcolepsy type 1, and moderate obstructive sleep apnea.

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2. Allen RP, Picchietti DL, Auerbach M, Cho YW, Connor JR, Earley CJ, et al. Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Med. 2018;41:27–44. https://doi.org/10.1016/j.sleep.2017.11.1126; Epub 2017 Nov 24.

Case 50. My Legs Move When I Lie Down

50

Joan Santamaria

History

A 53-year-old female consulted because of a two month-history of abnormal movements in the left leg when lying down, at night. She referred episodes of repetitive movements –"like tremors"- occurring in series of up to 30 in a row, lasting 15-seconds several times, each night. There were also movements of less intensity and frequency in the left arm. The movements appeared when she lied down on the bed, between 23:00-24:00 while awake. She did not experience any urge to move the legs or in the arm nor any other sensory feeling previous or simultaneous to the movements. The movements disappeared by standing up and apparently during sleep. Treatment with oral iron during several weeks (because of low serum ferritin at 14 ng/mL) did not improve the movements. In the last few weeks, she began to experience also pain in the left leg, especially with physical efforts with no change in the abnormal movements.

She had been diagnosed at 22 years with focal onset (visual) seizures with or without awareness impairment associated to a bilateral ventricular heterotopia and been treated with phenytoin, with good control of seizures that only recurred once/twice a year. At 46 years, during a regular follow-up visit, the husband referred that she had chronic loud snoring and repeated episodes of cessation of breathing, although never mentioned it before. She also had excessive sleepiness. A sleep study showed frequent positional related obstructive sleep apnea/hypopnea events [apnea-hypopnea index (AHI) 57/h in supine while in non-supine it was 0] without oxyhemoglobin desaturations, and intermittent bursts of right hemisphere spike/wave discharges during NREM sleep, without clinical manifestations. Nasal continuous positive airway pressure (CPAP) at 7 cm of H_2O abolished completely

J. Santamaria (✉)
Hospital Clínic of Barcelona, Barcelona, Catalonia, Spain
e-mail: jsantama@clinic.cat

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
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the apnea/hypopnea events, with disappearance of snoring and improvement of sleepiness and good (8 h/night) compliance. Hypermenorrhea with low levels of serum iron and ferritin, present for several years, was treated by her family doctor intermittently with oral iron supplements. She had no other problems until present.

Examination

Normal general examination. Low implantation of the palate, (Mallampati III). Neurological examination showed increased deep tendon reflexes, with normal strength and sensory function.

Investigations/Studies

A video-electroencephalogram (EEG) recording was performed in daytime, with the patient first semi-incorporated (45° angle) in the bed and then lying down horizontally. While she did not have any problem in the first position, shortly after adopting the supine position she presented the abnormal movements, consisting in repeated contractions of the quadriceps, simulating clonus in the rotula, then involving independently the left upper extremity, in a similar rhythmic form, in particular the left pectoral and biceps muscles. The movements disappeared again once the patient sat down. There were no epileptiform changes associated with the movements. A cervical MRI showed a C5-C6 stenosis with an associated C6-C7 hydromyelic cavity (see Fig. 50.1). An anterior cervical C5-C6 microdiscectomy was performed with resolution of the abnormal movements.

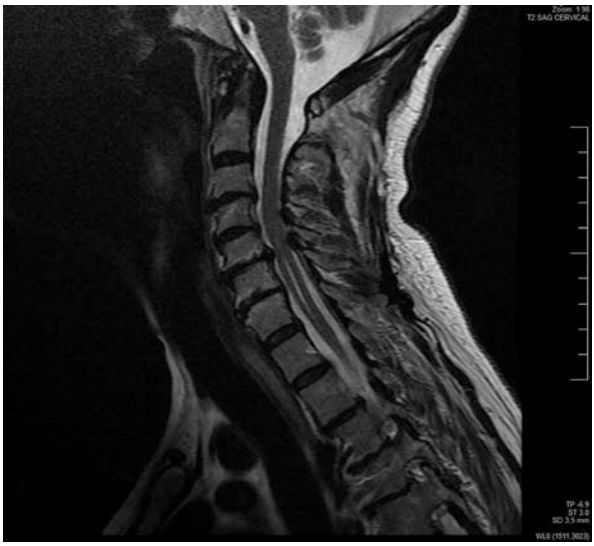

Fig. 50.1 Cervical MRI showing a C5-C6 cervical disc protrusion with focal stenosis of the spinal canal and an associated C6-C7 hydromyelic cavity

Differential Diagnosis

The abnormal left leg and arm movements in a patient with focal epilepsy suggested first the possibility of focal seizures. However, the lack of relation between the side of the movements and the side of EEG abnormalities in association with the triggering by the supine position were very atypical for epilepsy. The appearance of the movements at night, when lying down in a patient with low ferritin levels, suggested the possibility of periodic limb movements awake and perhaps continuing during sleep. However, the lack of any sensory symptoms suggesting of restless legs syndrome, the lack of response to iron supplement and the induction of the movements with the supine position at any time during the day excluded this option also. Provoking the movements and exploring the patient during the episodes suggested the possibility of a spinal cord cause.

Discussion and Management

A clinical symptom may be due to several causes. Normally, in the diagnostic process one stands out as the most likely responsible. It is less common to have a patient in whom several causes could have equal possibilities of producing the symptoms. In these cases, one needs to exclude one by one adopting a step-by-step strategy, until the final responsible appears. Spinal cord stenosis and hydromyelic cavities may have oscillations in their internal pressure in relation with orthostatic changes [1], what might have triggered the symptoms. Opening the stenosis solved the problem.

Final Diagnosis or Most Likely Diagnosis

Abnormal leg and arm movements induced by a cervical spinal cord hydromyelic cavity and stenosis.

Reference

1. Schlesinger EB, Antunes JL, Michelsen WJ, Louis KM. Hydromyelia: clinical presentation and comparison of modalities of treatment. Neurosurgery. 1981;9(4):356–65. https://doi.org/10.1227/00006123-198110000-00002.

Case 51 (Bonus Case). Sleepless Could Be Fatal

51

Marta Ros and Gemma Sansa

History

A 53-year-old man presented with a 2 month history of memory complaints. Nine months later he developed unexplained and persistent generalized pruritus. Over the next few months, the intensity of pruritus increased, appearing also severe insomnia, weight loss (over 22 lbs), weakness and dysautonomia (excessive sweating and nocturnal tachycardia). At this moment the bed-partner described abnormal nocturnal behaviors such as vocalizations, stereotyped and repetitive gestures with hands and limb myoclonus.

Examination

The patient was admitted to the hospital 16 months after the first evaluation. He presented severe disorientation, bradypsychia, and marked apathy. Neurological examination showed difficulties in verbal expression and dysarthria, increased blinking, slight horizontal nystagmus, akathisia and global hyperreflexia. There were also dyskinetic movements, intentional tremor in both arms with hyperekplexia, lower limbs dysmetria and ataxic gait. During the hospitalization, the patient deteriorated progressively presenting behavioral disorders, aphasia, generalized asymmetric myoclonus, dysphagia and respiratory disorders. He died 1 month later.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/978-3-031-18374-4_51.

M. Ros
Department of Neurology, Parc Taulí Hospital Universitari, Sabadell, Spain
e-mail: mross@tauli.cat

G. Sansa (✉)
Neurology, Hospital Parc Taulí, Barcelona, Spain
e-mail: gsansa@tauli.cat

A. J. Rodriguez (ed.), *Sleepless and Sleepy*,
https://doi.org/10.1007/978-3-031-18374-4_51

Investigations/Studies

Blood tests didn't reveal any metabolic, toxic, infectious or autoimmune remarkable abnormality. Pleocytosis and 14-3-3 protein were not noted in a cerebrospinal fluid analysis.

Brain magnetic resonance imaging (MRI) was normal. The first electroencephalogram (EEG) performed was normal but, after 10 months it showed diffuse encephalopathy with theta background activity. Neuropsychological assessment showed a very significant attentional and amnesic disorder, in addition to frontal dysfunction and psychomotor retardation. Revaluation 12 months after, we observed a worsening of attention and recent memory, visuospatial impairment, and severe psychomotor retardation.

An initial polysomnography (PSG) was performed, showing a normal sleep efficiency, with decreased ratio of REM phase (12%) and prolonged sleep latency of REM (Fig. 51.1a). Moderate sleep apnea [apnea-hypopnea index (AHI 21.2/h)] was also detected. We repeated the test 14 months later and showed a complete loss of physiological cyclic sleep organization, with a severely reduced efficiency (25%). We recorded mostly NREM sleep, with absence of sleep spindles, K complex and lack of delta activity. Rapid eye movements were detected during most of the stages, but sometimes they increased remarkably and these epochs were scored as REM. During wakefulness and sleep (including REM sleep), chin and leg electromyography activities were increased. Frequent myoclonus and complex hand movements such as grabbing objects or touching sheets were recorded (see Video 51.1). Sleep apnea was severe (AHI 44/h) (Fig. 51.1b) [1].

Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography (^{18}F-FDG PET/CT) showed diffuse supratentorial cortical hypometabolism (Fig. 51.2 left), also in cerebellum, basal ganglia and thalamus (Fig. 51.2 right), less pronounced in primary cortical sensorimotor areas [1, 2]. No images suggestive of malignancy were observed in the thoraco-abdominal study.

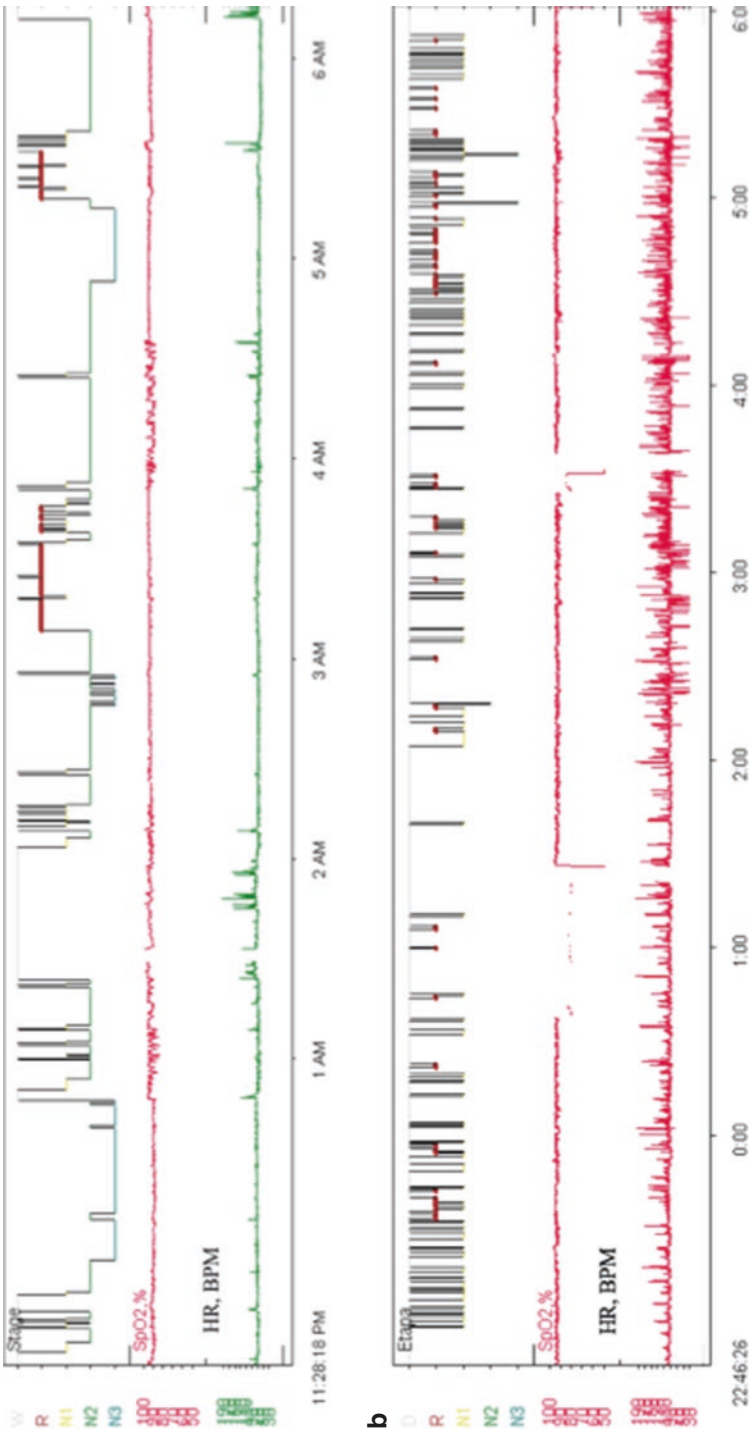

Fig. 51.1 (**a**) (Up) Basal polysomnography: Normal sleep efficiency. Heart rate (HR) 67 beats per minute (bpm). (**b**) (Down) Follow-up polysomnography (14 months later): Loss of physiological cyclic sleep organization. Nocturnal tachycardia: HR 97.6 bpm

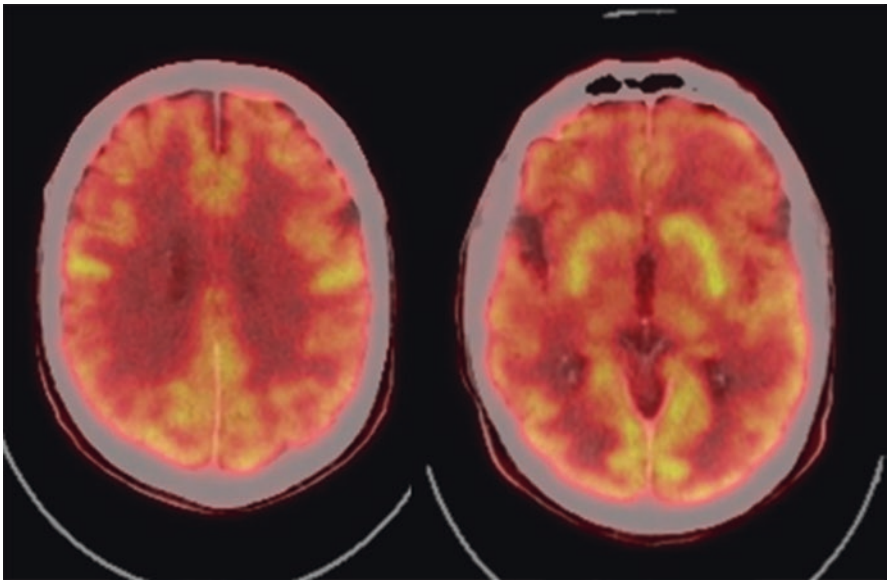

Fig. 51.2 PET-CT 18F-FDG showed diffuse supratentorial cortical hypometabolism (left), also in cerebellum, basal ganglia and thalamus (right)

Differential Diagnosis

Because of the mild cognitive complaints, initially obstructive sleep apnea-hypopnea syndrome (OSAHS) was suspected, and we indicated continuous positive airway pressure (CPAP) treatment. The symptomatology progressed despite the correct use of CPAP so the study was expanded to causes of subacute dementia. Toxic-metabolic, infectious and autoimmune causes were ruled out. Corticosteroids treatment was administered thinking on seronegative autoimmune encephalitis, with no clinical response.

The association between fronto-subcortical subacute dementia with agrypnia excitata, ataxia, myoclonus and weight loss, added to the results of ^{18}F-FDG PET/CT and PSG, with other negative examinations, oriented to fatal sporadic insomnia. There was no family history. The patient's mother died at a young age of a neoplastic disease and lost contact with part of the family.

Discussion and Management

Fatal insomnia can be challenging in early stages in patients without familial history of disease. Due to the lack of specific markers and the poor prognosis, it is mandatory to go through an extensive differential diagnosis of potentially treatable subacute dementia etiologies.

Despite being an uncommon symptom in human prion diseases [published series show 10% fatal familial insomnia (FFI) and 20% familial Creutzfeldt-Jakob disease] pruritus is a symptom to be considered in the onset of fatal insomnia. In this case, pruritus was a remarkable symptom. Periaqueductal gray matter is thought to be involved in the physiopathology of pruritus in these patients.

Final Diagnosis or most Likely Diagnosis

The brain autopsy showed marked neuronal loss associated with astrogliosis and microglial proliferation of anterior, dorsomedial and posterior thalamic nuclei and two lower olives. Only moderate superficial spongiosis was observed at the frontal, temporal, parietal and insular levels. These would be compatible with the morphological changes described in FFI.

The genetic study showed a D178N (aspartic acid to arginine) mutation in *PRNP* in combination with a polymorphism methionine at codon 129 on the mutated allele. The genotype D178N-129 M is typically seen in FFI.

Two years later, our patient's brother started uncontrollable pruritus as the first symptom of the disease. Maternal relatives were later found to be affected.

Due to family history and genetic testing, the case was finally diagnosed not as sporadic but as FFI and genetic counseling was offered to the rest of the family.

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