Enuresis nocturna, defined as involuntary urination while asleep, at an age at which bladder control is expected, understandably causes emotional stress. Important causes of bedwetting in patients who were previously continent include urinary tract infections or anatomic malformations, emotional disturbances, epilepsy, sleep apnea, and certain medications. Recommendations concerning the diagnostic workup of secondary enuresis nocturna address this differential diagnosis list accordingly.2–5

We recently became aware of a case of an adolescent with bedwetting. The case ended, tragically, in nocturnal sudden death. We were appalled by the fact that the possibility of nocturnal arrhythmias as the underlying cause of bedwetting was never considered by the treating physician. Therefore, we presented the case to an eminent expert in enuresis (TMJ) and also conducted a survey of family physicians and internists who (because of their line of work) are likely to encounter a case such as this one. They were asked to enter the diagnostic tests they would perform in a case identical to ours. We believe the facts and thoughts presented here should drive a paradigm shift in the diagnostic approach to enuresis nocturna.

The young girl with bedwetting

The research reported in this report adhered to the CARE Case Reports Guidelines. A young and ostensibly healthy female was referred for evaluation following two episodes of unexplained bedwetting that occurred 2 years apart, at 18 and 20 years of age. On both occasions she reported awakening feeling well, only to notice she had passed urine in bed during sleep. She had no other symptoms. She was not taking any medications and denied consuming alcohol or illegal substances. Urine tests and an abdominal ultrasound were normal. On both occasions, she received empiric antibiotic therapy for presumed (yet unconﬁrmed) urinary tract infection. She died suddenly in her sleep at the age of 23 years, 3 years after her most recent event of unexplained bedwetting. Her mother was then referred to us for cardiac evaluation (as cascade screening of familial sudden death). In response to direct questioning, the mother mentioned that 2 additional family members had died suddenly at a young age. The mother’s own cardiac evaluation was normal except for her electrocardiogram, which displayed a prolonged QT interval with T-wave morphology suggestive of congenital long QT syndrome type II (Figure 1).6 Provocative tests further supported the diagnosis (Figures 1B and 1C).7–9 Finally, genetic evaluation with an expanded gene panel of arrhythmia and cardiomyopathy genes (including 168 genes) conﬁrmed the diagnosis of congenital long QT syndrome type II by identifying a pathogenic mutation in KCNH2, the gene that, based on the phenotype, was expected to be disease-causing [KCNH2: c.2699_2760dup (p.Gly921Serfs*74)].

Physicians’ survey

An anonymous electronic survey was loaded onto an online survey platform (https://www.surveymonkey.com/), and its link was sent by e-mail to pediatricians, family physicians, and internal medicine physicians. Participating physicians were asked to select the diagnostic test(s) they would perform on a 20-year-old female with 2 episodes of unexplained bedwetting that occurred 2 years apart without other symptoms. The invitation to fill the questionnaire was send to physicians via their respective professional society. The questionnaire included 18 items covering potential choices for initial diagnostic workup for a case identical to the case presented here.
Each physician had the option of selecting an unlimited number of diagnostic tests among the following options: blood tests (complete blood count, basic metabolic panel, or HbA1c serum levels); an oral glucose tolerance test; urine tests (urinalysis and urine culture); imaging tests (ultrasound of kidneys and urinary tract, radiography of abdomen and pelvis, computerized tomography or magnetic resonance imaging of the abdomen and lumbar or sacral spine); electrocardiogram; electroencephalogram; dynamic studies such as uroflowmetry; referral for urologist and/or nephrologist consultation; and referral for psychiatric assessment. Physicians also could enter a free-text response regarding additional diagnostic tests. Associations between tests proposed by physicians in response to the survey and their medical field and experience level were tested using the $\chi^2$ test, univariate and multivariate logistic regression models with the above categorical variables, with and without interaction terms. The 95% and 99% confidence intervals (CIs) for the proportions of specific responses were calculated using the Clopper-Pearson method. All analyses were done in the R programming language, Version 4.0.2 (The R Foundation).

A total of 346 physicians (102 pediatricians, 73 family physicians, 57 internal medicine specialists, 35 residents in internal medicine, 37 interns, and 42 advanced medical students) responded to the survey; 114 were senior physicians with $\geq$ 3 years of experience. Their response to the survey, in terms of diagnostic workup for our case, did not differ by medical field specialty or number of years in medical practice. The distribution of diagnostic tests recommended is shown in Figure 2. Only 4 responders (1.1% (95% confidence interval $\leq$ 3.3%; 99% confidence interval $\leq$ 3.7%) proposed performing an electrocardiogram, the only diagnostic test that was likely to unravel the correct diagnosis in this case, as part of the diagnostic workup. Referral rates to electrocardiographic testing was not associated with the responders’ medical specialty or experience level. Interestingly, 19% physicians (95% confidence interval 14.8%–23.3%) mentioned that an encephalogram should be included in the diagnostic workup for our enuresis case.

**Clinical problem-solving by the expert**

The step-by-step case presentation to our expert is given in the Supplemental Appendix. The expert noted that the case did not fit well with the “idiopathic bedwetting” category of adults because of her age and the highly sporadic nature of bedwetting events. His differential diagnosis included...

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**Figure 1**  Electrocardiogram of the mother of the sudden death victim. **A:** Resting electrocardiogram of the mother, recorded after the sudden death of her daughter. Sinus rate is approximately 60 bpm. QTc = 482 ms. This value represents the 99.8th percentile of the QTc of healthy females and the 65.6th percentile of the QTc of females with congenital long QT syndrome. This denotes a prolonged QT in the context of familial sudden death. The T waves are slightly broad, suggesting long QT syndrome type II. **B:** Electrocardiogram during a quick-standing test. As the patient stands quickly, her sinus rate accelerates, but her QT fails to shorten adequately and the QTc increases to 588 ms (a pathologic response). **C:** Electrocardiogram recorded a few seconds later. As the sinus rate begins to return to baseline, the abnormal T-wave notching (arrows) characteristic of long QT syndrome type II becomes evident.

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the use of medications (from diuretics used for “dieting purposes” to sedatives slipped into her drink by others). Candidate causes of nocturnal polyuria were discussed and dismissed. Diagnostic tests proposed included cystometry for pressure filling/sensation abnormality, polysomnographic studies to evaluate the possibility of sleep disorders, and magnetic resonance imaging to rule out neurological disorders such as multiple sclerosis. However, even an expert in adult-related enuresis did not consider the possibility of underlying cardiac disease.

It is time for a paradigm shift in the minimal diagnostic evaluation of enuresis

This tragic case of nocturnal sudden death at the age of 23 years was most likely an arrhythmic death due to a congenital long QT syndrome. It follows that her preceding bedwetting events were most likely caused by self-terminating ventricular tachyarrhythmias, leading to cerebral hypoperfusion and resulting in urine incontinence. The highly sporadic nature (years apart) of her bedwetting episodes should have raised the suspicion of underlying arrhythmias because bedwetting among youngsters tends to occur on a weekly/monthly basis.

Urine incontinence often occurs during daytime syncope. It is almost 5 times more common during arrhythmogenic syncpe than during benign vagal syncpe, probably because the former leads to deeper and longer cerebral hypoperfusion. Indeed, 40% and 45% of daytime syncopal events due to long QT and Brugada syndromes involve involuntary urination. Arrhythmogenic syncpe striking during sleep triggers “nocturnal seizures.” Here, the transient cerebral anoxia causes strenuous breathing, loud enough to awaken a sleeping partner. This witness will then report that the victim initially was “stiff,” only to eventually become apneic and flaccid, often with urinary incontinence and subsequent confusion. When such nocturnal seizures remain un-witnessed (when the victim sleeps alone), bedwetting may be the only clue remaining from the dramatic event.

Nocturnal arrhythmic events, causing either nocturnal seizures or sudden death during sleep, are a typical feature of the long QT (types II and III) syndrome and Brugada syndrome. Both diseases can be recognized from the electrocardiogram in combination with clinical and family history.

Neither the family physician treating this patient in real life nor the renowned expert presented with the case considered the possibility of arrhythmias as a potential cause for enuresis, asked the patient about a family history of sudden death, or referred the patient for a simple electrocardiogram. Furthermore, only 1% of the physicians who responded to our survey thought that an electrocardiogram should be part of the diagnostic workup of a young adult patient with unexplained bedwetting. The upper boundary of the 99% confidence interval for this result is <4%. This suggests that additional surveys, involving a much larger sample of similar physicians, likely would demonstrate that physicians do not generally consider arrhythmogenic syncope during the differential diagnosis of bedwetting. We believe that these results are representative of physicians’ conceptions worldwide. Neither textbooks on internal medicine, family medicine, and pediatrics nor guideline documents endorse performing an electrocardiogram during the evaluation of bedwetting. Physicians are not asked to consider arrhythmogenic syncope during the evaluation of enuresis in the Bedwetting in Under 19s clinical guideline from the National Institute for Health and Care Excellence (NICE) or in the Bedwetting in Teenagers and Young Adults document from the Continence Foundation of Australia.

Interestingly, 19% of physicians surveyed would perform an encephalogram, demonstrating that they considered the possibility of nocturnal epilepsy, but not nocturnal arrhythmias, as a possible cause of bedwetting. Publications targeting family physicians do mention epilepsy, but not arrhythmias, as a potential cause for enuresis.

We are not suggesting that every child with bedwetting should undergo electrocardiographic recording, as this would likely lead to significant overdiagnosis. However, inquiring about a familial history of sudden death should be part of every medical consultation. Performing an electrocardiogram is considered an essential (quasi-mandatory) step in the evaluation of syncope because patients who present...
with cardiogenic syncope but remain unrecognized and untreated have a very high mortality risk. Notwithstanding its anecdotal nature, our report supports similar recommendations for the evaluation of enuresis in selected cases, similar to the one presented here (a young adult with highly sporadic, unexplained events of bedwetting). The American Academy of Neurology emphasizes that nocturnal seizures represent a risk factor for sudden unexpected death in epilepsy. It is now recognized that patients with long QT syndrome who present with arrhythmic seizures too often are misdiagnosed as suffering from “epilepsy.” It is time to raise awareness among primary physicians that potentially lethal arrhythmic conditions can present with sporadic nocturnal enuresis. These conditions are detectable via family and clinical history in combination with an electrocardiogram.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2022.01.031.

References