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Case Report

Phenytoin-induced isolated chronic, nocturnal dry cough

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ABSTRACT

We report a 72-year-old man with a four-year history of dyscognitive seizures (with occasional secondary generalization) who developed isolated, nocturnal dry cough immediately after being started on PO phenytoin. The cough was not accompanied by any other symptom or sign as his physical exam was completely normal. Further investigation with chest CT and spirometry was unremarkable. This symptom persisted for six months and did not resolve until we weaned him off of phenytoin. According to the Naranjo Adverse Drug Reaction Probability Scale, his cough was classified as being probably (score +6) related to the use of this antiepileptic drug. To our knowledge, there has been only one study that reported phenytoin-triggered cough. It described a postoperative patient who developed cough and bronchospasm after receiving IV phenytoin. By reporting our case and discussing the literature on this specific topic, we have essentially two goals. First, we intend to remind clinicians that isolated persistent cough can be an adverse reaction to phenytoin. Second, we hope to encourage further studies that will be able to elucidate the association presented herein.

We report a 72-year-old man, with no personal or family history of seizures, who started having dyscognitive seizures – with occasional secondary generalization – at the age of 68 years. Seizure onset occurred four months after he had undergone uneventful prostatectomy for the treatment of prostatic adenocarcinoma in situ. The dyscognitive seizures were characterized by hand and mouth automatisms in association with impairment of consciousness; each of the seizures lasted for a few seconds only, and most of them were followed by postictal confusion and tiredness. He also had positive hepatitis C serology, a previous endovascular treatment of an unruptured intracranial aneurysm, chronic headaches, lower extremity pain, hypertension, hypothyroidism, dyslipidemia, and ulcerative colitis. For the last four conditions just mentioned, he was using losartan, levothyroxine, simvastatin, and mesalazine — respectively. In terms of neurological investigation, brain MRI was normal, while EEG study showed minimally reactive slow background activity without epileptiform abnormalities. Several antiepileptic drugs (AEDs) were tried: carbamazepine, oxcarbazepine, valproate, topiramate, lamotrigine, and lacosamide — all of which needed to be discontinued because of side effects. Seizure freedom was not achieved until he was started on phenytoin. Initially, the phenytoin was given at a dose of 300 mg/day. However, the dose had to be gradually decreased because of complaints of unsteadiness and poor balance. This AED was then kept at 100 mg/day, which showed to be the maximum tolerated dose by this patient. Of note, the phenytoin prescribed was the brand name Hidantal®, manufactured by the pharmaceutical company Sanofi-Aventis. Its excipients are comprised of starch, magnesium stearate, lactose monohydrate, talc, and povidone K30.

Four days after being initiated on phenytoin, however, he began to experience isolated, nocturnal dry cough. On examination, there was not any abnormal pulmonary finding whatsoever. Our first intervention was to switch his losartan to amlodipine because the former has been previously associated with cough [1]. Despite this change, his cough persisted, which prompted further investigation with chest CT and spirometry — both of which were normal. Six months after, still without resolution of the cough, phenytoin was weaned off and replaced with phenobarbital at 100 mg/day. Within the following day, the patient's chronic cough was completely resolved. Importantly, he was not rechallenged with phenytoin as per his desire. Presently, at 3-month follow-up, our patient remains cough-free.

Phenytoin-induced respiratory involvement can be essentially divided into two groups: (1) drug-induced interstitial pneumonitis (as part of a generalized hypersensitivity reaction) and (2) isolated cough and/or bronchospasm. While the former has been consistently reported [2], rarely has phenytoin been linked to isolated cough and/or bronchospasm. In fact, to our knowledge, there has been only one study that described phenytoin-induced isolated cough and bronchospasm. This study reported a postoperative neurosurgical patient who developed cough in association with bronchospasm immediately after rapid IV infusion of phenytoin. The authors ruled out anaphylaxis as a cause of the event based on the absence of any hemodynamic change as well as the

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Table 1
Reported patient's isolated chronic, nocturnal dry cough while on PO phenytoin (100 mg/day) as assessed by the Naranjo Adverse Drug Reaction Probability Scale.
Modified from Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981 Aug; 30(2):239–245.

Question	Yes	No	Unknown	Patient's score
Are there any previous conclusive reports of this reaction?	+1	0	0	+1
Did the adverse event appear after the suspected drug was given?	+2	−1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	+1
Did the adverse reaction appear when the drug was readministered?	+2	−1	0	0
Are there alternative causes that could have caused the reaction?	−1	+2	0	+2
Did the reaction reappear when a placebo was given?	−1	+1	0	0
Was the drug detected in any body fluid in toxic concentrations?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	0
Patient's total score				+6

Scoring algorithm: >9 = definite ADR, 5–8 = probable ADR, 1–4 = possible ADR, 0 = doubtful ADR. ADR, adverse drug reaction.

uneventful use of PO phenytoin prior to the surgical procedure. Finally, they postulated that this patient's cough and bronchospasm were generated by a phenytoin-triggered central sympathetic inhibition with vagal predominance [3].

Regarding our patient, we believe that his chronic, isolated cough was secondary to the phenytoin use mainly based on the temporal relationship between drug exposure and symptom onset as well as its complete resolution immediately after drug discontinuation. Moreover, the absence of other potential causes, as well as the previous published report describing similar reaction, further supports the abovementioned hypothesis. An alternative hypothesis would be that our patient's cough was, in fact, periictal [4,5]. This is highly unlikely mainly because (i) our patient's seizures (including ictal and postictal periods) were never accompanied by cough or any other vegetative symptom, and (ii) each of his bouts of cough lasted approximately an hour, which is not consistent with periictal cough — which occurs, by definition, sometime between the beginning of a seizure and a few minutes after it ends [4,5].

Finally, it should be noted that none of the drug excipients (which were described above) have ever been associated with pulmonary adverse effects. By estimating the probability that phenytoin caused the reported patient's chronic cough through the scoring system proposed by Naranjo et al. [6], we obtain a total score of +6 (Table 1). Scores from +5 to +8 indicate that the adverse drug reaction is probable.

In summary, we report a patient with epilepsy who developed isolated chronic, nocturnal dry cough while on therapy with PO phenytoin. Based on the Naranjo Adverse Drug Reaction Probability Scale [6], we can define this symptom as probably generated by the phenytoin use. In light of the data presented herein, we conclude that, irrespective of the drug formulation and vehicle, cough – whether in association or not with bronchospasm – appears to be an uncommon but specific phenytoin-related side effect. Therefore, clinicians should be familiar with this knowledge when facing patients on phenytoin who develop cough, with or without bronchospasm, of unclear etiology. Lastly, we hope to encourage further studies that will be able to elucidate the association presented in this report.

Conflict of interest

There is no conflict of interest.

Author contributions

Fábio A. Nascimento, MD, contributed to the study design, acquisition of data, data analysis and interpretation, and drafting of the manuscript and accepts responsibility for conduct of the research.

Bruno Takeshita, MD, contributed to the acquisition of data and data analysis and interpretation.

Pedro A. Kowacs, MD, contributed to the study concept and design, study supervision, manuscript revision, and final approval and accepts responsibility for conduct of the research.

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Ethics

Informed consent was obtained from the participant — this is on file, in case it is requested. The work described herein is consistent with *Epilepsy & Behavior*'s guidelines for ethical publication.

Disclosure

All authors report no disclosures.

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