



A Case of Refractory Chronic Cough that Resolved Completely with Long-Term Low-Dose Gabapentin

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Abstract

A 61-year-old man visited our outpatient office with a 3-month history of refractory cough that had proven resistant to >1-month treatments with codeine phosphate, inhaled budesonide/formoterol combination, one of inhaled corticosteroid/long acting beta-agonist combinations (ICS/LABA combinations) and omeprazole. We attempted treatment with other ICS/LABA combinations (fluticasone/vilanterol combination), inhaled long-acting muscarinic agonists, proton pump inhibitors, macrolide antibiotics (roxithromycin) and codeine, but cough remained. Gabapentin was started at 200 mg, twice daily. Remission of cough began from day 10 of administration, and after 1 month, scores from all indices of cough Visual Analogue Scale (VAS) decreased to about one-quarter of scores on presentation. The gabapentin regimen was maintained for 3 months, and then reduced to 200 mg/day. Five months after reducing the dose, no exacerbation of cough or cough VAS scores was seen. We reduced gabapentin further, completely ending treatment 10 months after beginning gabapentin. No recurrence of cough has been seen as of 6 months after ending gabapentin. The present clinical experience of complete remission of intractable cough by gabapentin implies that some cough mainly involves neural dysfunction. Further studies are required to determine suitable biomarkers, doses, and durations of pharmacotherapy.

Keywords: Gabapentin; Chronic cough; Cough hypersensitivity syndrome

Introduction

Refractory cough is defined as cough continuing for a long period and remaining unimproved even with treatments targeting allergic, infectious and/or gastro-esophageal regurgitation pathophysiologies of the upper and lower airways. Recently, in terms of pathophysiology, impairment of the nervous system involved in cough reflex has been considered. Gabapentin modifies nervous system function, and has been shown to be effective against refractory cough [1-3]. However, the optimal dose and period of administration and whether complete remission of cough is achieved have yet to be clarified. Further accumulation of clinical experiences and studies is thus necessary.

We report herein a case of refractory cough in which administration of low-dose gabapentin for 11 months proved effective, with no recurrence even after termination of therapy.

Case Presentation

A 61-year-old man visited our outpatient office with a 3-month history of refractory cough. Cough appeared all day long, especially after abnormal throat sensations or short conversation, and also affected sleep at night. The patient had smoked 1 pack of cigarettes a day for 11 years, but had quit 8 years earlier. He drank socially, but alcohol did not induce cough. His medical history included hypertension, diabetes mellitus and hyperlipidemia, and he had been taking the following pharmacotherapies for 10 years: metformin hydrochloride; amlodipine besilate; pioglitazone hydrochloride; sitagliptin phosphate; telmisartan/hydrochlorothiazide; and glimepiride. Furthermore, for 1 month before presenting to our clinic, he had been prescribed codeine phosphate, inhaled budesonide/formoterol combination (DPI), and omeprazole, none of which had proven effective.

Physical and laboratory data on the first visit are shown in Table 1. Analyses of peripheral blood revealed a slight increase in eosinophils (total white blood cell count, 5100/ μ l; eosinophils, 7%), but no abnormalities were seen in serum titers of total immunoglobulin (Ig)E or specific IgE for any antigens. Markers of infection, antibody titers of *Mycoplasma*, *Chlamydomphila* and pertussis, and Cold Hemagglutinin titer (CHA) were all negative.

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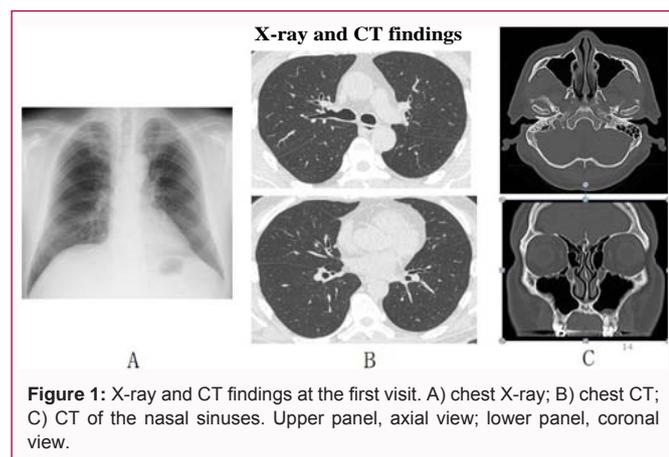
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Table 1: Results of clinical examinations at the first visit.

Blood Analyses		
WBC	5100/ μ l	
Neut	62.00%	IgE 67.5 IU/ml (<173)
Ly	27.00%	Antigen-specific IgE; not detected
Mono	4.00%	Mycoplasma antibody (HI); <X20 (<X40)
Eo	7.00%	CHA titer; X8 (<32)
Baso	1.00%	Chlamydomphila pneumonia antibodies
RBC	486×10^4 / μ l	
Hb	15.4 g/dl	IgG (\pm), IgA (-), IgM (-)
Plt	24.7×10^4 / μ l	
Alb	4.2 g/dl	Pertussis antibody : PT-IgG 20 EU/ml
AST	29 IU/l	[Pulmonary functions]
ALT	44 IU/l	FVC 3.92L
LDH	200 IU/l	%VC 99.2%
UN	27.3 mg/dl	FEV1 3.36L
Cre	1.30 mg/dl	FEV1/FVC 84.0%
Glu	96 mg/dl	%FEV1 99.6%
CRP	0.10 mg/dl	Feno 16ppb

**Figure 1:** X-ray and CT findings at the first visit. A) chest X-ray; B) chest CT; C) CT of the nasal sinuses. Upper panel, axial view; lower panel, coronal view.

Pulmonary function testing revealed no obstructive or constrictive abnormalities, and fractional exhaled nitric oxide (FeNO) was also within the normal range (<22 ppb). We evaluated Bronchial Hyperresponsiveness (BHR) using inhaled Acetylcholine (ACh). Inhalation of 1250 μ g/ml ACh produced severe coughing and throat pain, disabling from the determining of the BHR. At this point, Forced Expiratory Volume in 1 second (FEV1) was decreased by 10% compared with baseline FEV1 during saline inhalation. We were thus unable to identify whether BHR was present (Table 2).

Chest X-ray and CT of the chest and nasal sinuses revealed no abnormalities (Figure 1). Otolaryngological examinations showed no redness of the laryngeal mucous membranes and gastroesophageal regurgitation was considered unlikely.

Clinical Course

At the time of visiting our outpatient office, the patient had post-nasal drip as well as refractory cough, so we started with administration of Roxithromycin (RXM) at 300 mg/day, dextromethorphan at 90 mg/day and carbocysteine at 1500 mg/day, as well as tulobuterol patch (2 mg/day) confirming that the patient performed an exact

Table 2: Bronchial hyperresponsiveness to inhaled acetylcholine.

Concentration of Ach (mg/ml)	FEV1.0 (L)	Symptoms
Saline (Control)	3.00	Coughing
39	2.91	Coughing and abnormal throat sensation
78	3.02	Abnormal throat sensation
156	3.00	Abnormal throat sensation
312	2.85	tickles
625	2.82	Coughing, abnormal throat, tickles
1250	2.74	Severe coughing and throat pain:
2500		
5000		
10000		

	Actual	Predicted	%predicted
FVC(L)	3.79	3.51	108
FEV1.0(L)	3.02	2.78	108.6
FEV1.0(%)	79.7	68.7	116.1
80%FEV1.0	2.42		
90%FEV1.0	2.72		

Inhalation of 1250 μ g/ml Acetylcholine (Ach) produced severe coughing and throat pain, leading to abandonment of examination. At this point, FEV1 was decreased by 10% compared with control FEV1 under saline inhalation

using of these medicines (Figure 2).

Coughing had seemed to decrease slightly with these medicines, but strong cough recurred after 1 month. Inhaled fluticasone at 200 μ g/day and vilanterol at 60 μ g/day combination, one of Inhaled Corticosteroid and Long Acting Beta-Agonist combinations (ICS/LABA combinations) was added instead of tulobuterol patch, but hoarseness and cough triggered by irritation from inhalation therapy led to cessation of this treatment and a return to the tulobuterol patch. We added 1% codeine phosphate (6 g/day) for 1 month, achieving no improvement. We next prescribed inhaled tiotropium (18 μ g/day) as a Long-Acting Muscarinic Agonist (LAMA), but this was again unsuccessful for improving cough. The next month, nasal drip therapy with fluticasone furoate was added while restarting omeprazole (10 mg/day), since rhinorrhea and post-nasal drip sensation with epigastric discomfort appeared. These symptoms improved but coughing remained, especially after meals or when the patient was out.

No standard treatments for chronic cough (i.e., ICS/LABA, LAMA, PPI or codeine) proved effective for the refractory cough, so gabapentin (400 mg/day, as 200 mg twice daily) was started 5 months after the first visit. Improvements in cough began from around 10 day after starting gabapentin administration. After 1 month, scores from all indices of cough VAS (influences on sleep, daily life, and degree of cough) decreased to about one-quarter of the scores seen at the first visit, and frequency of cough improved. Cough recurred when the patient tried to quit using gabapentin for a few days and improved on restarting this agent. Since gabapentin was effective at 400 mg/day, this dose was continued for a further 3 months, and then was reduced to 200 mg/day.

Even 5 months after reducing the dose, cough showed no exacerbation. VAS scores for cough likewise did not deteriorate. The gabapentin dose was further reduced to alternate-day administration at 200 mg/day, but symptoms continued to improve and resolve. In

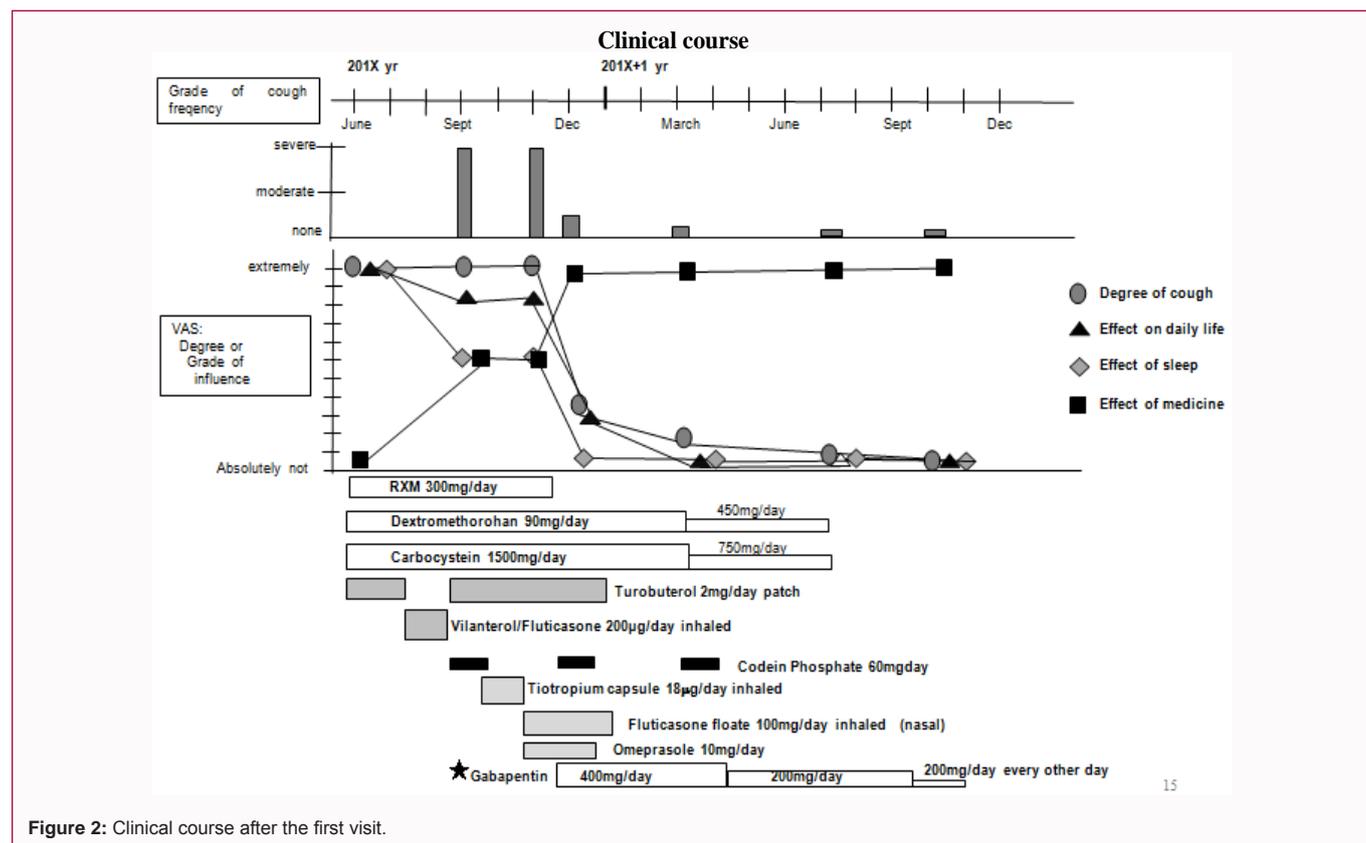


Figure 2: Clinical course after the first visit.

the meantime, cough was recognized occasionally due to an upper respiratory tract infection, but improved again within a short period following administration of L-carbocysteine, dextromethorphan, and azithromycin.

Ten months after starting gabapentin treatment stopped, but the cough did not reoccur within the next 6 months. We thus judged the refractory cough as completely cured.

Discussion

Gabapentin is a derivative of the γ -Amino Butyric Acid (GABA). Voltage-dependent Ca^{2+} channel inhibition and brain GABA increase without binding to GABA receptors, and this has been speculated as the mechanism of action in the central nervous system. GABA acts to prevent the release of neurotransmitters such as substance P by combining with voltage-dependent Ca channels in peripheral nerves. Pregabalin, a precursor of gabapentin, shows similar effects to gabapentin.

Recently, the concept of Cough Hypersensitivity Syndrome (CHS) has been advocated to explain the pathophysiology of refractory cough [4-7]. CHS is a condition in which the cough threshold drops and is attributed to hyperirritabilities along the nerve pathway of the cough reflex, including cough receptors. For example, in the pathophysiology of laryngeal sensory neuropathy, some impairments occur in afferent nerve fibers in the vagus nerve and/or cough receptors in the airways after viral infection of the upper respiratory tract, and excitatory inputs for cough may occur. This kind of pathophysiology usually remits, but may become intractable in some cases [8,9]. Furthermore, intractable cough is often associated with abnormal throat sensation and is induced by actions that would not usually result in cough, such as conversation and laughter. This

condition is called allotussia, and is considered to involve higher brain control in the form of Central Sensitization (CS), which has also been proposed to be involved in pain pathophysiology [10]. Actually, localization of the higher brain control involved in cough production and suppression has been confirmed using functional MRI [11,12].

Ryan et al. [3] performed a randomized control trial with gabapentin and placebo control, reporting that 12-weeks treatment with gabapentin significantly decreased the frequency and severity of cough, improving cough QOL significantly more in patients with CS than in those without CS. Furthermore, in this report, gabapentin was considered to act mainly in the central nervous system on the nerve pathways for cough, since gabapentin has been shown to have less effect on capsaicin-induced cough as a marker of cough receptor sensitivity. On the other hand, that RCT study also reported that, after stopping gabapentin, cough recurred to a degree equal to that in the placebo group. Furthermore, in that study, the dose of gabapentin was gradually increased until suppressive effects were obtained in patients, some of whom required a high dose of 1800 mg/day.

In our case, cough symptoms remitted with low-dose gabapentin (200 mg, twice daily) and no recurrence was observed after ending pharmacotherapy. This might be due to long-term administration (11 months, including the period of tapering off). In other words, the present case may be meaningful from the perspective that long-term administration of gabapentin may prove useful for complete remission of intractable cough associated with CS, in that no adverse effects occurred.

Few patients are satisfied with achieving milder intractable cough. In particular, patients engaged in service industries such as those frequently using the telephone, clerks at shop counters, and wait staff in restaurants desire complete relief from cough, as such work is

difficult to continue with incomplete remission of cough symptoms.

Pregabalin, a precursor of gabapentin, is also reportedly effective against intractable cough [13]. On the other hand, these kinds of drugs, including gabapentin, may have side effects such as sleepiness, depression, and suicidal ideation.

Removal of any cause in the airways is unequivocally essential for the treatment of cough. However, a recent report by Kanemitsu et al. [14] showed that cough reflex sensitivity in patients with severe asthma is linked to clinical features such as poor asthma control and higher rates of exacerbation. That report suggested that neuronal dysfunction could be considered an important phenotype for severe asthma, and novel treatments targeting excessive cough may need to target peripheral airway nerves and/or central neural pathways involved in the cough reflex [15]. Likewise, cases of chronic cough that prove resistant to standard treatments and appear associated with CS may benefit from treatment with neuromodulators.

In conclusion, given the present clinical experience with gabapentin, further studies are required to determine clinical indications, markers, and optimal duration of administration for safe and maximal efficacy.

References

- Mintz S, Lee JK. Gabapentin in the treatment of intractable idiopathic chronic cough: case reports. *Am J Med.* 2006;119(5):e13-15.
- Lee B, Woo P. Chronic cough as a sign of laryngeal sensory neuropathy: Diagnosis and treatment. *Ann Otol Rhinol Laryngol.* 2005;114(4):253-7.
- Ruan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: A randomized, double blind, placebo-control trial. *Lancet.* 2012;380:1583-9.
- Morice AH, Millqvist E, Belvisi MG, Bieksiene K, Birring SS, Chung KF, et al. Expert opinion on the cough hypersensitivity syndrome in respiratory medicine. *Eur Respir J.* 2014;44(5):1132-48.
- Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. *Lancet Respir Med.* 2013;1(5):414-22.
- Morice AH, Jakes AD, Faruqi S, Birring SS, McGarvey L, Canning B, et al. A worldwide survey of chronic cough: A manifestation of enhanced somatosensory response. *Eur Respir J.* 2014;44(5):1149-55.
- Song WJ, Chang YS, Morice AH. Changing the paradigm for cough: Does 'cough hypersensitivity' aid our understanding? *Asia Pac Allergy.* 2014;4(1):3-13.
- Bucca, BB, Bugiani M, Culla B, Guida G, Heffler E, Mietta S, et al. Chronic cough and irritable larynx. *J Allergy Clin Immunol.* 2011;127:412-9.
- Ryan NM, Gibson PG. Characterization of laryngeal dysfunction in chronic persistent cough. *Laryngoscope.* 2009;119(4):640-5.
- Gibson PG, Ryan NM. Cough pharmacotherapy: Current and future status. *Expert Opin Pharmacother.* 2011;12(11):1745-55.
- Mazzone SB, McGovern AE, Yang SK, Woo A, Phipps S, Ando A, et al. Sensorimotor circuitry involved in the higher brain control of coughing. *Cough.* 2013;9(1):7.
- Ando A, Smallwood D, McMahon M, Irving L, Mazzone SB, Farrell MJ. Neural correlates of cough hypersensitivity in humans: Evidence for central sensitization and dysfunctional inhibitory control. *Thorax.* 2016;71(4):323-9.
- Halum SL, Sycamore DL, McRae BR. A new treatment option for laryngeal sensory neuropathy. *Laryngoscope.* 2009;119(9):1844-7.
- Kanemitsu Y, Fukumitsu K, Kurokawa R, Takeda N, Suzuki M, Yap J, et al. Increased capsaicin sensitivity in severe asthmatics associated with worse clinical outcome. *Am J Respir Crit Care Med.* 2020;201(9):1068-1077.
- Satia I, O'Byrne PM. Identifying a neuro-phenotype in severe asthma. *Am J Respir Crit Care Med.* 2020;201(9):1024-5.