Resolution of Chronic Cough Following Treatment for Iron Deficiency Anemia

Eric Mull[1], Swati Jayaram[1], Ethan Bassett[1], Amanda Jacobson-Kelly[1], and Rebecca Scherzer[1]

[1]Nationwide Children's Hospital

August 12, 2023

Abstract

A previously healthy 4-year-old female presented for a cough that was not responsive to treatment of inhaled corticosteroid (ICS). Pertinent history included meconium aspiration with no respiratory support required and a course of confirmed SARS-CoV-2 with fever and mild respiratory symptoms of a cough, that resolved in 2-3 weeks. Child was seen in Allergy clinic 2 months before first Pulmonary clinic appointment with a compliant of cough that redeveloped. Cough was dry, associated with strenuous activity, and noticeably present at night. She was started on albuterol 2 puffs every 4 hours, as needed.

Resolution of Chronic Cough Following Treatment for Iron Deficiency Anemia

A previously healthy 4-year-old female presented for a cough that was not responsive to treatment of inhaled corticosteroid (ICS). Pertinent history included meconium aspiration with no respiratory support required and a course of confirmed SARS-CoV-2 with fever and mild respiratory symptoms of a cough, that resolved in 2-3 weeks. Child was seen in Allergy clinic 2 months before first Pulmonary clinic appointment with a compliant of cough that redeveloped. Cough was dry, associated with strenuous activity, and noticeably present at night. She was started on albuterol 2 puffs every 4 hours, as needed.

At the one month follow up in Allergy clinic, cough remained present with a mixed response to bronchodilator therapy. Given her history of worsening cough at night and symptoms with activity, as well as a minor family history of asthma, the patient was started on fluticasone 44 mcg, 2 puffs twice a day (BID). At that time, she was also referred to pulmonary division for further workup and evaluation.

History obtained during pulmonary visit reaffirmed that obtained from the patient's previous allergy visits. In addition, there were no reports of wheezing and whenever evaluated by a medical professional, the child always sounded "clear." Vitals were within normal limits with a saturation of peripheral oxygen (SpO2) of 96%. A chest x-ray was obtained showed nonspecific findings of reactive or viral airway disease (Figure 1). Given that there was no improvement on the standard dose ICS and the patient was too young to perform spirometry or fraction exhaled nitric oxide (FENO) accurately, her therapy was altered to combination ICS with long acting beta2-agonist (LABA). Mometasone/formoterol 100/5 mcg 1 puff BID.

Four months later, there was almost complete resolution of nocturnal cough and activity intolerance. However, she continued to have a frequent dry cough during the daytime. As the patient was scheduled for a direct laryngoscopy within the week of her pulmonary clinic visit, a flexible bronchoscopy with bronchoalveolar lavage (BAL) was added with blood work under sedation for a severe asthma workup, which included a complete blood count (CBC) with differential and immunoglobulin E (IgE).

Flexible bronchoscopy was unremarkable for visual findings other than pale mucosa (Figure 1). Cultures showed no growth. Cytology showed a neutrophil predominance of 50%, followed by macrophages at 33%,

and lymphocytes at 17%. Due to the fact lipid-laden macrophage index of 6 out of 200 and the absence of findings of cobblestone mucosa, aspiration and reflux were unlikely to be attributing to her symptoms. Her blood work resulted showing IgE of 66 [IU]/mL (Reference Range [RR] 0-75). The CBC was concerning for microcytic anemia with a hemoglobin (Hgb) of 10.4 g/dL (RR 11.5-13.5 g/dL) and a hematocrit (Hct) of 32.6% (RR 34.0-40.0%). The mean corpuscular volume (MCV) was low at 68.5 fL (RR 75.0-87.0 fL) and she had a basophilia of 1.8% (RR 0.1-1.1%).

Ultimately, she was referred to hematology and was started on oral ferrous sulfate at 3 mg/kg daily after finding her low ferritin of 4 ng/mL (RR 7-142 ng/mL). After 2 months of therapy, her symptoms of cough completely resolved and family weaned her from the ICS+LABA. Within 3 months after that, she had normalized blood work. This included a Hgb 4.3 g/dL, Hct 43.8%, MCV 82.8 fL, and a ferritin of 52. She was then transitioned to a multivitamin. At her follow up in pulmonary clinic two months after discontinuing ICS+LABA, there were no respiratory complaints.

Cough is a common presenting symptom in pediatrics[1]. This natural process that protects the airways and occurs spontaneously or voluntarily. If lasting longer than 4 weeks in the pediatric population, it is considered chronic[2]. Common etiologies in children include: asthma, protracted bronchitis, tracheomalacia, habit cough, and various systemic disorders[2]. This case is unique due to reported resolution of cough and ability to tolerate weaning off of ICS+LABA following the identification and correction of iron deficiency anemia (IDA).

Iron deficiency (ID) and IDA are very common diagnoses worldwide, impacting 1-2 billion individuals a year. Occurring predominantly in children, especially in low- to middle income families[3]. Classically, ID is characterized with fatigue, lethargy, difficulty concentrating, dizziness, tinnitus, pallor, and headache[4]. While a cough hasn't been directly associated with ID, there is an association with nitric oxide (NO) production[5], which is a modulator of type 2 inflammation. It is increased in the exhaled breath of many asthmatics with its concentrations widely recognized as a marker of airway inflammation and measured via fractional concentration of exhaled nitric oxide (FENO)[6,7]. Other than occurring in patients with asthma, NO is known to be an important pathogenic effector in pertussis and other respiratory tract diseases that are caused by inflammation[8,9].

There are currently published reports of iron supplementation being beneficial in the treatment of a cough associated with angiotensin converting enzyme inhibitor (ACEI). This is due to decreased ACEI induced generation of NO in bronchial epithelial cells. Iron has the ability to inhibit the activity of NO synthase (NOS), the heme-related enzyme involved in NO production[10]. Thus, suggesting that iron supplementation reduces the generation of NO and may consequently abolish a dry cough[6].

Although other mechanisms by which ID may favor a lingering cough are unknown, there have been findings of reduced epithelial airway thickness in subjects with ID that suggests a cough could be favored by increased mucosa permeability to irritative stimuli[10]. In addition, plausible explanation includes ID acting to impair the defense mechanisms of airway mucosa via physiologic changes[11]. It is known that ID weakens the defensive response to injuries by impairing immune function, such as the production of interleukin-2, a cytokine, which plays an important role in maintaining the normal immune response[12].

In summary, while ID and IDA direct mechanisms for cough production are unknown, there are known associations with physiologic changes in the respiratory tract that may promote and extend the length of time for a cough to persist. When the targeted therapy directly addressed to the symptoms is not responding, there may be utility in the differential assessment of standard blood work.

Swati Jayaram, MD[a], Ethan Bassett, MD[c], Amanda Jacobson-Kelly, MD[bd], MSc[d], Rebecca Scherzer, MD[be], Eric S. Mull, DO[ab]

[a]Division of Pulmonary Medicine;[b]Department of Pediatrics; [c]Division of Otolaryngology; [d]Division of Hematology/Oncology;[e]Division of Allergy and Immunology

Columbus, Ohio

Institution: Nationwide Children's Hospital; Columbus, OH

Funding Source: None

Financial Disclosure: None

Conflicts of Interest: None

Reference:

1. Chang AB, Oppenheimer JJ, Irwin RS; CHEST Expert Cough Panel. Managing Chronic Cough as a Symptom in Children and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest. 2020 Jul;158(1):303-329.
2. Weinberger M, Hurvitz M. Diagnosis and management of chronic cough: similarities and differences between children and adults. F1000Res. 2020 Jul 22;9:F1000 Faculty Rev-757.
3. Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW. Iron deficiency. Lancet. 2021 Jan 16;397(10270):233-248.
4. Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW. Iron deficiency. Lancet. 2021 Jan 16;397(10270):233-248. doi: 10.1016/S0140-6736(20)32594-0. Epub 2020 Dec 4. PMID: 33285139.
5. Choi JW, Pai SH, Kim SK, Ito M, Park CS, Cha YN. Iron deficiency anemia increases nitric oxide production in healthy adolescents. Ann Hematol. 2002 Jan;81(1):1-6.
6. Lee SC, Park SW, Kim DK, Lee SH, Hong KP. Iron supplementation inhibits cough associated with ACE inhibitors. Hypertension. 2001 Aug;38(2):166-70.
7. Loewenthal L, Menzies-Gow A. FeNO in Asthma. Semin Respir Crit Care Med. 2022 Oct;43(5):635-645.
8. Flak TA, Goldman WE. Autotoxicity of nitric oxide in airway disease. Am J Respir Crit Care Med. 1996 Oct;154(4 Pt 2):S202-6.
9. Heiss LN, Lancaster JR, Corbett JA, Goldman WE. Epithelial autotoxicity of nitric oxide: role in the respiratory cytopathology of pertussis. Proc Natl Acad Sci U S A. 1994 Jan 4;91(1):267-70.
10. Bucca C, Culla B, Brussino L, Ricciardolo FL, Cicolin A, Heffler E, Bugiani M, Rolla G. Effect of iron supplementation in women with chronic cough and iron deficiency. Int J Clin Pract. 2012 Nov;66(11):1095-100.
11. Rennie JS, MacDonald DG, Dagg JH. Quantitative analysis of human buccal epithelium in iron deficiency anaemia. J Oral Pathol. 1982 Feb;11(1):39-46.
12. Bergman M, Bessler H, Salman H, Siomin D, Straussberg R, Djaldetti M. In vitro cytokine production in patients with iron deficiency anemia. Clin Immunol. 2004 Dec;113(3):340-4.

Hosted file

`IDA and Cough Figure.docx` available at https://authorea.com/users/326440/articles/659645-resolution-of-chronic-cough-following-treatment-for-iron-deficiency-anemia