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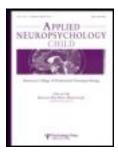
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CASE STUDY

An 11-Year-Old Girl With up to 19,200 Coughs per Day: Broadening Therapeutic Strategies

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An 11-year-old girl was transferred to the Universidad de Chile Clinical Hospital after 2.5 months of persistent and unresponsive treatment for coughlike spasms. On arrival, the frequency of symptoms was 1 cough every 4 s, which disappeared during sleep. A multidisciplinary examination excluded allergic, viral, respiratory, epileptic, and other more usual causes of similar conditions. Two diagnoses (psychogenic cough and transient vocal tic disorder) and a mixed intervention were proposed leading to resolution in 12 days of treatment. No recurrence of symptoms was observed during several evaluations within 12 months of medical follow-up. An association between the 2 diagnoses is proposed and discussed.

Key words: psychogenic cough, single-case experiment, somatoform, tic disorder

Pediatric coughing is divided into acute (less than 2 weeks), subacute (2 to 4 weeks), and chronic (more than 4 weeks; Ramanuja & Kelkar, 2009). Possible etiologies for chronic coughing in children include cough variant asthma, protracted bronchitis, upper-airway cough syndrome, gastroesophageal reflux, postinfection cough, allergic cough, and functional illnesses as differential diagnoses (Asilsoy et al., 2008; Linz, Daniels, & Fallon, 2007; Zhang & Nong, 2011). Such states can predispose or overlap with symptoms of somatoform respiratory disorders (Gruber, Lehmann, Weiss, & Niggemann,

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2012). Additionally, it has been considered a type of focal epileptic crisis (Kofman, 1964); however, it generally occurs together with other epileptic signs (Grant & Roter, 1994).

It has been established that about 46% of the patients with chronic cough seek secondary care due to unclear causes of their symptoms despite extensive examination (Pavord & Chung, 2008), and the neurological symptoms are psychologically based on 1% to 9% of the general population (Lempert, Dieterich, Huppert, & Brandt, 1990). These cases need a different approach that involves a psychoneurological or psychosocial perspective. Psychogenic and habit cough are the most-used terms (Irwin, Glomb, & Chang, 2006) to refer to a chronic dry cough without evidence of organic base that does not respond to antitussive pharmacotherapy.

Psychogenic cough disappears during sleep (Shuper, Mukamel, Mimouni, Lerman, & Varsano, 1983), which suggests psychogenic etiology. Additionally, the patient's behavior suggests a conversion disorder (Gay et al., 1987), which commonly presents when children are aged 6 to 14 years old and is frequently associated with psychosocial stress (Irwin & Madison, 2002), "la belle indifference" to symptoms (Irwin et al., 2006), and extremely worried parents (de Jongste & Shields, 2003). Psychogenic cough disrupts social activities and decreases with pleasurable activities, which indicates secondary gain. The cough worsens in the presence of health care providers, and a family history may indicate patterning in the child's symptoms. It is preceded by an upper-respiratory tract infection and expresses a need for attention (Irwin et al., 2006). These preceding infections are proposed as a model for the upcoming symptoms (Gay et al., 1987) and suggest psychological pathways. Additionally, it has been reported as having phonetic components (Weinberg, 1980). However, the level of effort a patient puts forth on a neurological task has been highlighted as an important factor for the evaluation of psychogenic-based symptoms. This does not imply intention to fail (Drane et al., 2006; Kalogjera-Sackellares & Sackellares, 1999) but a neuropsychological profile that needs to be included to evaluate noncredible cognitive performance (Heintz et al., 2013).

Psychogenic or habit cough can be difficult to diagnose in daily clinical practice. Therefore, it can be difficult to treat, and the patient may be subject to increasingly invasive examinations and/or treatments, leading to higher parental anxiety as well as increased medical and hospital expenses (Cohlan & Stone, 1984). Additionally, it is difficult to establish a clear differential diagnosis between an organic-based cough versus a nonorganic-based cough. A strong body of research has started to broaden scientific understanding from a dualistic (mind/brain) model to a psychoneurological integrative approach where neuropsychological interactions have been documented in patients diagnosed with neurological deficits without organic neurological lesions (Bremner et al., 2003; Montoya, Price, & Lepage, 2006; Yamasue et al., 2003). Nevertheless, further research is needed to fully understand these interactions and to systematically use this knowledge in clinical practice.

The objective of this article is to present a clinical case that may help general practitioners and specialists to consider alternative etiologies and treatment strategies when facing a similar case.

This revision was approved by the Universidad de Chile Clinical Hospital Ethical Committee (Folio OAIC: 224/22-09-2011). Informed consent was signed by the patient's legal guardian.

Evaluation Strategies

The approach was based on the analytic-functional diagrams for clinical cases (Haynes & O'Brien, 2000).

Multidisciplinary approach included: physical (medical examination, provided by medical doctors [neurologist, immunologist, and otorhinolaryngologist]), biological (laboratory analysis), and psychological (personality factors, recent environmental stressors, and family history, provided by medical doctors [psychiatrist and interns] and a PhD [psychologist]) examination.

CLINICAL CASE

An 11-year-old girl presented an extremely high rate of unresponsive-to-treatment and nonproductive coughlike spasms for 2.5 months, which disappeared during sleep. Before admission into the Universidad de Chile Clinical Hospital (HCUCh, from Spanish acronym), the patient had obstructive bronchitis with respiratory symptoms, was being treated with bronchodilators, and responded positively after 4 days of treatment at the end of April. However, the patient started the observed coughlike spasm at the beginning of May. After that, the patient was unsuccessfully treated for allergic rhinitis with firstline antihistaminic, for obstructive bronchitis with inhalants, and for subglottic pharyngitis with second-line antihistaminic. Additionally, acupuncture, biomagnetism, and herbal therapy were attempted. At this point (mid-July), the HCUCh was contacted to evaluate the child.

On initial examination, the patient was in good general condition, though presented eating difficulties because of recurrent coughing. The patient had dry, non-productive coughlike spasms, calculated at an average of 15,360 per day. Symptoms increased before going to sleep and in the presence of medical staff and disappeared while sleeping. Several evaluations were made by various professionals.

- Physical examination: normal march, oriented, and attentive, adequately nourished and hydrated; highlights sweaty and cold skin. Trigeminal (V) and facial (VII) nerves had no alteration, corneal reflex and photomotor reflex +/+, nose had no secretions, external mild erythema was on the nose. Blood pressure, pulse, heart sounds, temperature, otoscopic, and nasopharyngeal examinations were normal; respirations and lungs auscultation were normal.
- Laboratory analysis: Hematologic, biochemical, kidney, and lipid profiles were normal (Table 1). Chest X-rays, electroencephalogram, magnetic resonance imaging, antistreptolysin 0, and anti-DNase B antibodies, nasal eosinophil count, protein electrophoresis, prick test, and cryoglobulins results were normal.
- Neurological analysis: Highlights included reduced skin sensitivity on the left leg, the dorsum of the left foot, plantar region of the right foot, posterior right and left arm, palm of the right hand, and left anterior forearm.

TABLE 1
Patient's Laboratory Analysis

| Analysis | Value | Values | Unit |
|----------------------|---------|---------------|-------|
| Hematologic | | | , |
| aPTT | 28.1 | 26-36 | seg |
| Hematocrit | 39.2 | 34-44 | % |
| MCV | 81.7 | 82-95 | fl |
| Leucocytes | 7,820 | 5,000-13,500 | /uL |
| Platelets | 387,000 | 15,000-40,000 | /uL |
| Hemoglobin | 13.7 | 11.6-15 | g/dL |
| VSG | 17 | 0-25 | mm/hr |
| Segmented | 58 | 54-62 | % |
| Eosinophils | 3 | 1–3 | % |
| Monocytes | 4 | 3–7 | % |
| Lymphocytes | 35 | 25-33 | % |
| Biochemical | | | |
| Glucose | 76 | 75–100 | mg/dL |
| BUN | 15 | 6.9 - 16.7 | mg/dL |
| Calcium | 10.1 | 8.7-10.3 | mg/dL |
| Phosphorus | 4 | 3.75-5.62 | mg/dL |
| Total protein | 6.7 | 6.3-8.6 | g/dL |
| Albumin | 4.3 | 3.7-5.6 | g/dL |
| Kidney | | | |
| Na | 141 | 137-145 | mEq/L |
| K | 4.2 | 3.5-5.1 | mEq/L |
| Cl | 109 | 98-107 | mEq/L |
| Hepatic | | | |
| Bilirubin | 0.3 | 0.2 - 1.3 | mg/dL |
| Alkaline phosphatase | 250 | 130-560 | U/L |
| GGT | 16 | 17-28 | U/L |
| Lipid | | | |
| Total cholesterol | 188 | <170 | mg/dL |
| HDL | 50 | 40-60 | mg/dL |
| LDL | 117.6 | 0-140 | mg/dL |
| Triglycerides | 102 | <150 | mg/dL |

aPTT=Activated Partial Thromboplastin Time; MCV=Mean Corpuscular Volume; ESR=Erythrocyte Sedimentation Rate; BUN=Blood Urea Nitrogen; GGT=Gamma glutamyl transferase; HDL=high-density lipoprotein; LDL=low-density lipoprotein.

• Psychosocial analysis: (a) Clinical observation: The patient answered all questions; however, most of her responses were monosyllabic, while she searched for something to play with, looked at the window, and avoided eye contact. Her language was clear and she did not seem to be frightened by the interview. The patient said she was bored of repeating the speech about her symptoms, which may explain this lack of interest during the interview. The patient's use of expressive language, though interrupted by the cough, was articulated and logically structured; the patient could easily understand, recall, and follow orders when asked to perform basic activities, to remember previous instructions, and to perform the psychological tests. The patient achieved good academic results (within the top of her class) and had no behavioral problems at school. Lack of concern about the symptoms was observed (la belle indifference), and symptoms reduced when pleasant

activities were performed, such as listening to music or talking about a topic of her interest. This observed behavior indicated conserved social and intellectual skills and suggested an underlying conversion disorder. During the first psychological evaluation, the patient complained about nose, throat, and abdominal pain, paresthetic sensations in both hands (thumb and little finger), and a lack of sensation in her upper lip; these sensations became intermittent and lacked a clear trigger. Other similar sensations (in the nose and right part of her forehead) were easily induced during the interview, suggesting a hysterical base. No previous reports of such paresthetic sensation have been found in the literature. Stereotyped, repetitive, and involuntary movements were observed before and after each cough (rising of the right arm, eye squinting, and scratching of the nose). (b) Psychological test: To confirm the clinical observation of the psychologist and psychiatrist, two psychological tests (Rorschach test and the Hospital Anxiety and Depression Scale [HADS]) were used. High levels of anguish, critical and perfectionist thinking, and anxiety (HADS Anxiety score = 14, which indicates definite anxiety; Depression score = 2, which indicates unlikely depression) and some obsessive and hysterical traits were observed (see details in Table 2). This coexistence of psychogenic cough, anxiety, and conversion disorder has been previously reported (Bhatia, Chandra, & Vaid, 2002; Gay et al., 1987). The Rorschach test historically has generated opposite opinions regarding its utility and validity; a complete revision of this topic can be found in Bornstein (2012). However, several studies support its utility on personality research (Cogswell, 2008; Fowler, Brunnschweiler, Swales, & Brock, 2005; Mihura, Nathan-Montano, & Alperin, 2003) and psychopathology (Baity, Blais, Hilsenroth, Fowler, & Padawer, 2009; Dao & Prevatt, 2006). The HADS (Zigmond & Snaith, 1983) has been validated

TABLE 2
Psychological Analysis: Main Results of the Rorschach Test

- Reduced emotional contact with the current situation
- · Efforts to fully comply with all instructions
- Meticulous, showing anxiety signs to the situation
- · Extremely rational behavior without much emotional integration
- · Persecutory separation anxieties
- Difficulties to experience needs of affection and sensorimotor contact
- Severe distortions in the configuration of the psychological and bodily self
- · Emotionally demanding on her relationships
- · Very immature primary needs
- Tendency to have a critical perception of herself and her environment
- Borderline personality structure with childlike, hysterical, dependent, and obsessive features
- Use of defensive mechanism such as repression, rationalization, dissociation, fragmentation, projection, and denial

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- in several studies (Bjelland, Dahl, Haug, & Neckelmann, 2002), and it has been also validated for use in adolescents (White, Leach, Sims, Atkinson, & Cottrell, 1999).
- Family/historical data: The parents were nonsmokers.
 One year and 6 months after birth, the patient suffered a life-threatening episode of pleuro-pneumonia.
 After this episode, the parents were very cautious in observing any sign of coughing or flulike symptoms in their daughter. Despite the latter and due to occupational duties, the parents reported a lack of family time.

Treatments

Different treatment strategies for psychogenic cough have been reported, including several distractors such as nebulized lidocaine therapy (Sherman, 1997), throat lozenge (Mastrovich & Greenberger, 2002), or prevention of mouth breathing by placing a button between the patient's lips (Bernstein, 1963). In this case, signs of a psychogenic base for the cough, inducible paresthetic sensations, and stereotyped and repeated movements before and after each cough guided us to mix drugs and psychological treatment instead of other more invasive strategies described on the literature such as pressure on the chest, bronchoscopy, or even electroshock therapy. Therefore, and based on suggestion therapy, the treatment strategy intended to psychologically influence her ideas about the cough and her behavior. The psychological approach included initial separate interviews with the parents and the patient. This evaluation focused on: (a) personality factors that could predispose the patient to convert psychological distress into physical symptoms; (b) recent environmental stressors that might act as trigger mechanisms and exacerbate the patient's illness; and (c) family history events that might be related to the current event.

Individual psychotherapy (1 h. each day) based on influencing ideas, together with an atypical neuroleptic drug (quetiapine) administered in a low dosage (37.5 mg/day, increasing to reach 75 mg/day during a 7-day lapse [common dosage: 200 mg/day to 800 mg/day (Stroup et al., 2003)]) were initiated. The patient was told that the drug would definitely but gradually reduce cough recurrence and intensity and would definitely and increasingly allow her to control the symptoms. Such suggestion therapy immediately modified the patient's paresthetic sensations and the ability to control the cough, which decreased considerably (Figure 1). During sessions, the patient was encouraged to voluntarily suppress the cough and it was reaffirmed that the drug would definitely help her in that purpose and that later on she would be able to suppress it herself. Additionally, respiration (deep or diaphragmatic breathing) technique and progressive muscular relaxation technique were taught and practiced daily in different sessions.

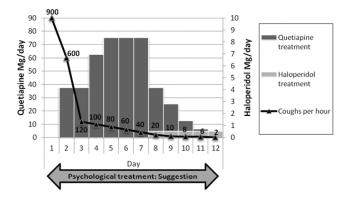


FIGURE 1 Treatment schedule. Multidisciplinary approach: suggestion therapy and drug scheme (quetiapine from 37.5 mg/day to 75 mg/day and haloperidol 0.5 mg/day).

In parallel and in daily sessions, the patient's parents were trained to reduce anxiety due to the situation and were guided to effectively manage their child's need for attention and the relationship of their behavior with the patient's observed symptoms. They also were educated on how to focus their attention on the patient's matters and interests, more than on her symptoms.

Results

The patient had a frequency of coughs—to our knowledge, not previously reported—on average of 15,360 (range = 11,520–19,200) coughs/day. This calculates to a cough every 3 s to 5 s, which excludes 8 h. for sleep. The family reported an initial rate of one cough every 1 s to 2 s (end of May).

The patient underwent quetiapine (in low dosage) and suggestion therapy for 7 days and achieved a total cough reduction of 95.83%; after these 7 days of treatment, the cough rate decreased from 960 coughs per hour to 40 coughs per hour. The rate reduction proved the efficacy of the first strategy; however, the symptoms did not disappear and a change of drug treatment was decided: Haloperidol (0.5 mg/day). Quetiapine doses were reduced until withdrawn after 4 days. The symptoms continued to reduce, and by Day 12, the cough decreased to 2 per hour (Figure 1). The treatment resulted in a cough reduction of 99.8% (details in Figure 1). Upon discharge, an appointment schedule was given to the patient's family for medical follow-up: The patient was evaluated at 1 week, 1 month, 2 months, and 6 months after discharge; no further coughing episodes were observed. After 12 months, the patient remained free of coughing episodes.

DISCUSSION

The event of pneumonia and her parents' reaction after such an episode, the reduced time for family interaction, the patient's behavior with regard to the symptoms, and the findings of the psychological evaluation suggested pathways between these events and the observed symptoms.

The difficulty implied by a differential diagnosis between psychogenic or organic-based tics is because from an organic viewpoint, tics involve a malfunction of the basal ganglia, mediated by the liberation of the corpus striatum and the participation of dopamine receptors (D2), which are the target of drug therapy. On the other hand, involuntary movements increase with anxiety and disappear during sleep. Tics can be also momentarily suppressed by distracting strategies. These characteristics make a differential diagnosis with a conversion disorder difficult, excluding comorbidity between both phenomena. Therefore, a neuropsychological base is proposed for this case and this opens the discussion to a multicausal paradigm rather than an organic versus psychological dichotomy.

Neuropharmacological Analysis

Quetiapine and its metabolite (norquetiapine) act as dopaminergic antagonists (mainly D2), and it is through this pathway that they aim at tic control. On the prefrontal cortex, there is a high density of norepinephrine (NE) transporters and low density of dopamine (DA) transporters, because NE transporters are the main DA reuptakers. Once NE transporters are inhibited by norquetiapine on the prefrontal cortex, the synaptic availability of both NE and DA rises. As a consequence, norquetiapine may have a direct antidepressant effect. Additionally, norquetiapine is an inhibitor of the presynaptic alpha-epinephrine receptors, which are another pathway for increasing NE in the synaptic space (Jensen et al., 2008; Stahl, 2008). Likewise, both quetiapine and norquetiapine have an effect over serotoninergic receptors, specifically the antagonist of the 5-HT_{2A} receptors. This also leads to an increase of the extracellular DA concentrations over the prefrontal cortex and of serotonin in the synaptic space. Therefore, the final effects over these neurotransmitters (DA and serotonin) have a positive influence over anxiety regulation. Moreover, due to the antihistaminic action, it has a sedative effect, which may reduce tics (Prieto, Mico, Meana, & Majadas, 2010). Thus, it is theoretically possible that the patient's initial recovery might have been due to the antidepressant-anxiolytic-sedative effect of the drug rather than the antagonism for the D2 receptors of the basal ganglia. This might be possible; in fact, norquetiapine has been used in schizophrenia (Arvanitis & Miller, 1997; Lee et al., 2010), obsessive-compulsive disorder (Fineberg, Sivakumaran, Roberts, & Gale, 2005), acute mania (Vieta, Goldberg, Mullen, Vagero, & Paulsson, 2007), and depression (Goldberg et al., 2008; Vieta, Calabrese, Goikolea, Raines, & Macfadden, 2007). Nevertheless, all these studies coincided in a minimum of 150 mg/day and an optimal of 300 mg/day to 400 mg/day to achieve significant effects, and there is no evidence about the real effect of the dosage used on our patient (37.5 mg/day, increasing to reach 75 mg/day during a 7-day lapse).

It is known that a placebo effect may facilitate patients' recovery. Involuntary movements increase with anxiety and disappear during sleep. However, the authors are not certain that such a placebo effect is the only explanation for the patient's recovery. Therefore, and based on the previous psychopharmacological analysis, the combined drug and psychological treatment is proposed to have played the main role in the elimination of the coughing episode.

Diagnostic Possibilities

Simple motor and vocal symptoms, together with the lack of evidence of underlying neurologic disorders and symptom clearing during sleep, support the diagnosis of an episode of transient vocal tic disorder (*Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition, Text Revision [DSM-IV-TR]). The patient had multiple motor and vocal tics (Criterion A) that presented for 2.5 months (Criterion B), significant impairment in social areas (Criterion C), was 11 years old (Criterion D), and had no direct physiological effects of substances or another organic condition (Criterion E) that can explain the symptoms in the absence of another possible neuropsychological diagnosis (Criterion F).

On the other hand, a somatoform disorder is also plausible, specifically a conversion disorder in the form of psychogenic cough. This diagnosis can be made only after ruling out biological and genetic tic disorders associated with coughing (Irwin et al., 2006). The symptoms affected voluntary motor and sensory function suggesting a neurological condition (Criterion A); psychological factors were reasonably associated with the symptoms (short time spent with family; Criterion B); the symptoms were not intentionally produced or feigned (Criterion C); the symptoms cannot be explained by a general medical condition or by the effects of a substance (Criterion D); the symptoms caused social impairment and warranted medical evaluation (Criterion E); and the symptoms were not limited to pain and were not better accounted for by another mental disorder (Criterion F).

Conclusions

As shown, different features of the patient's behavior and symptoms were consistent with neurologic and conversion disorders. In this case a clear secondary gain was seen; parents spent all their time on patient's matters. Additionally, the pattern for the current symptoms (coughs) was not only due to obstructive bronchitis, but also the parent's reaction after the episode of pleuro-pneumonia during early childhood. This, added to the lack of family time

admitted by both parents and children, defines a context where the symptoms can be psychologically based. All these features have been previously described in similar cases (Gay et al., 1987).

Therefore, based on routine treatment failure, incessant symptoms during the day that are absent during sleep, the characteristics and development of the observed symptoms, and the response to treatment strategies (Ishizaki, Kobayashi, & Kino, 2008), two diagnoses seem plausible: psychogenic cough and transient vocal tic disorder. However, the International Classification of Diseases-10th Revision sustains that there is no clear division between a tic disorder with some associated emotional disturbance (World Health Organization, 2008, p. 283). As shown, all the DSM-IV-TR criteria for the proposed diagnoses can be observed in the patient. Based on clinical observation and the described biochemical interaction between drug treatment and psychological symptoms, it is argued that an interaction between psychological and organic processes may have led to a scenario where a combination between tic disorders and conversion disorders might represent a better etiological explanation to cases where some components overlap and mutually influence one another (Linz et al., 2007).

Similar cases have been reported (Ojoo, Kastelik, & Morice, 2003), and in concordance with successfully applied strategies (Lokshin, Lindgren, Weinberger, & Koviach, 1991; Weinberger, 2003), suggestion therapy together with drug treatment were used for this case. Additionally, the authors propose a closer connection between the psychosocial factors underlying this case; life events (as the episode of pleuro-pneumonia) and psychosocial factors might have predisposed the patient to the conversion of psychological anxiety into physical symptoms based on an obsessive personality with hysterical traits. Differential diagnosis between psychogenic and functional symptoms is a key factor to prevent stigmatization, symptoms fixation, normal life interference, and unnecessary medical procedures (Niggemann, 2010). Nevertheless, a strong body of research on the psychoneuroimmunology field confirms organic and psychological interactions that support a holistic approach for treatment. In this way, the understanding of biopsychosocial interactions can broaden therapeutic strategies and increase possibilities for rapid success in cases such as the one presented.

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