# Congenital Insensitivity to Pain, with Impaired Pulmonary Functions, and Diminished Cough Reflex.

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To the editor:

Despite being an undesirable feeling, pain is one of the important protective and defense mechanisms of the human body. Disorders that affect pain sensation are associated with either increased or decreased pain perception. Decreased pain perception could be acquired such as diabetic peripheral neuropathy, syringomyelia, and infection (e.g. leprosy); or congenital such as Hereditary Sensory Autonomic Neuropathies (HSAN). (1). Congenital insensitivity to pain with anhidrosis (CIPA) is characterized by insensitivity to pain and temperature, decrease or absent sweating, hyperpyrexia, intellectual disability, and self-mutilation which leads to variable injuries, due to the involvement of the autonomic and sensory nervous system (2). Despite most of the case reports were concerned with the orthopedic or other conditions related to pain such as Anesthesia; there was no adequate reporting of the respiratory disorders in such patients. Here, we describe a 13-year-old girl presented with swelling of her right ankle joint and foot (Figure 1). The swelling increased over the last few days. The parents also complained that she was sleepy in the last few days. She

was previously diagnosed to have CIPA due to mutation of the neurotrophic tyrosine kinase receptor type I (NTRK1) gene [homozygous variant c.1842_1843insT (p. Pro6155ersf*12)].

Her past history revealed that she had frequent trauma either accidentally or self-mutilated, with a history of a fracture in the right foot 2 years ago to which she had posterior slab support. She had also a history of recurrent episodes of high fever without sweating especially with hot weather which usually calmed down after a bath or cooling with a wet towel since birth. The family history showed that the girl was the product of consanguineous marriage, with her sister and maternal uncle have the same condition. Both parents are heterozygous carriers of the same mutation (Figure 2).

She presented for consultation because of painless swelling of her right ankle. Previous plain X-ray of the right foot and ankle did not show a fracture. Her weight, height, and body mass index were 33 kg, 147.5 cm, and 15.1 $Kg/m^2$ respectively. General physical examination revealed that she was conscious but not active like every day, her Oxygen saturation was 90% on room air. Her gag reflex was absent. Chest examination showed diffuse sibilant rhonchi all over the chest with prolonged expiration. The parents denied the presence of a cough at all and the child did not complain from any difficulty of breathing. The chest X-ray was normal. Spirometry was done and showed reduced forced expiratory volume in one second [$FEV_1$] (54% of predicted), forced vital capacity [FVC] (77% of predicted), and reduced FEV1/FVC (57% of predicted). After salbutamol inhalation, spirometry was repeated which showed improvement of FEV1 (72%), FVC (83%), and $FEV_1$/FVC (69%).

After stabilizing her condition, we did an ultrasound of the right ankle with Duplex. It showed diffuse asymmetrical swelling of the right ankle with mild joint effusion and marked subcutaneous soft tissue edema with trabeculation. Magnetic resonance imaging (MRI) complemented with computerized tomography (CT) scan of her right ankle joint showed skeletal immaturity with diffuse osteopenia. Within the distal tibia, there were sequelae of old trauma to the distal tibia. There were deformity and remodelling of the subtalar joints and the joints of the midfoot. These findings were a combination of neuropathic changes and altered foot and ankle mechanics. There were stress fractures within the navicular, cuneiforms, cuboid, and several metatarsals, which explains the foot swelling. There was no MRI evidence of osteomyelitis or septic arthritis.

The child was prescribed Fluticasone dipropionate /salmeterol (125/25) Evohaler; 2 puffs twice daily. She was also on physiotherapy, oral anti-inflammatory Naproxin 250 mg twice daily for 5 days and advised for limited weight-bearing until the swelling subsides. She came after 1 week, the swelling subsided completely, and her $O_2$saturation was 95% on room air. After 1month, her pulmonary functions were normalized.

The cough reflex protects the airways and lungs from aspiration, inhaled irritants, particulates, and pathogens. It also clears the air spaces of accumulated secretions. Cough is initiated by the activation of vagal afferent nerves. Pain, dyspnoea, and cough share some important features. Each of these symptoms is very common, can be profoundly uncomfortable, and can strongly worsen the quality of life. Despite being undesirable symptoms, both pain and cough are part of the protective mechanism for the human body (3). At the level of the primary afferent nerves, pain and cough pathways are remarkably analogous. As with pain, cough can be evoked in experimental animals by stimulation of nociceptive C-fibers as well as by faster-conducting Aδ-fibers. Cough reflex can be impaired due to a wide variety of causes. In some diseases of the central nervous system, there is a complete depression of the cough reflex. Cough reflex sensitivity is also diminished in smoking, pulmonary coccidioidomycosis and could be drug-induced as with Baclofen-induced cough suppression (4).

As the cough reflex has type A and C fibers as an afferent limb; cough reflex could be also affected in CIPA. According to the best of our knowledge, unfortunately, we did not find any previous report describing impaired pulmonary functions or diminished cough reflex in CIPA. However, absent cough reflex was previously described in a female named Ashlyn Blocker which gives the CIPA the name of Ashlyn congenital condition. This girl was described that she had never sneezed and never coughed (5). The importance of this report is to emphasize the need for a high level of suspicion for the conditions presented with the cardinal symptoms of pain, cough, or dyspnoea. Absence of these alarming symptoms/signs in patients with CIPA should not

let the physician underestimate their clinical status; as serious conditions for instance severe asthma, acute appendicitis, or even acute chest conditions could present without its cardinal alarming signs. In all cases, we must ask ourselves what should we treat: a symptom, a sign, or a disease?

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**Legends**

**Figure 1: Right ankle and foot swelling:**

There is a swelling at the ankle joint that was painless and lasting for 3 months on and off, increased over the last few days.

**Figure 2: The family pedigree of the patient** showed that her parents are carriers and her sister and maternal uncle were affected with the same mutation (in red).

**Figure 3: The MRI and CT of the right ankle**

Sagittal CT reformate (A) and Sagittal PDFS MRI (B) images demonstrating “bone within bone” appearance in the distal tibia (yellow arrows) suggesting previous traumatic insult. There is also irregularity with sclerosis and remodelling of the subtalar joints (red arrows), indicating altered foot mechanics due to neuropathy. Long axis PDFS MRI image (C) demonstrating marrow edema within the tarsal bones, along with multiple small fracture lines (blue arrows. PDFS: fluid-sensitive fat-saturated.