

Respiratory symptoms in children with Ehlers-Danlos syndrome

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Clinical Implication

- Children with Ehlers-Danlos syndrome can present with recurrent respiratory symptoms related to their underlying connective tissue disease that may be inaccurately attributed to asthma.

TO THE EDITOR:

Ehlers-Danlos syndrome (EDS) is a connective tissue disorder characterized by hypermobility, skin laxity, and tissue fragility. EDS is classified based on clinical manifestations, inheritance pattern, and genetic defects. The 6 subtypes per the 1997 Villefranche classification include classic, hypermobility, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis.¹ Hypermobility type EDS is characterized by generalized joint hypermobility and the presence of minor skin involvement, including hyperextensibility and/or smooth velvety skin. This subtype remains a diagnostic challenge given the lack of biomarkers and known genetic defect. In contrast, the classic type EDS is linked to a defect in type V collagen, and the 3 major diagnostic criteria are skin hyperextensibility, widened atrophic scars, and joint hypermobility. EDS case reports discuss the increased prevalence of chest wall deformities, mild hearing impairment, dysphonia, vocal cord abnormalities, and swallowing difficulties.²⁻⁶ A recent report indicates increased atopy and asthmatic symptoms in adult patients with this syndrome.⁷ Data are lacking in the pediatric literature. We report respiratory symptoms in children with EDS that were misdiagnosed as asthma or that accompanied this disease.

Our series of 5 children with EDS presented to the allergy clinic with a previous diagnosis of asthma (Table I). All the patients underwent spirometry and assessment of albuterol response. Pulmonary function measurements included a forced expiratory volume in 1 second (FEV₁) of 96%-124% predicted, and an FEV₁ to forced vital capacity (FVC) ratio of 77% to 89%. Because the FEV₁ was not reduced in association with a normal or increased FEV₁/FVC ratio, there was no apparent restrictive component that may be related to a chest wall or skeletal deformity. For further evaluation of airway hyperreactivity, 1 patient underwent a methacholine challenge, which was negative. Only 2 patients had confirmed asthma with reversible airway obstruction with albuterol or exercise pulmonary function tests with a fall of the FEV₁ by at least 10%.

Patient no. 1 was a 9-year-old boy with classic EDS and with a history of gastroesophageal reflux (GER) status-post fundoplication, platelet function disorder, irritable bowel syndrome, and kyphoscoliosis who presented with dyspnea and chest tightness with exercise. He was taking a bronchodilator and an inhaled corticosteroid for asthma. This patient had normal spirometry, with no response to a bronchodilator. Airway fluoroscopy was

normal, and radioallergosorbent test (RAST) for common food allergens was negative. He was diagnosed with vocal cord dysfunction after a videostroboscopy demonstrated significant paradoxical vocal fold movement.

Patient no. 2 was a 10-year-old boy with hypermobility type EDS who presented with nocturnal dyspnea, intermittent stridor, and cough. His asthma was being treated with a bronchodilator and montelukast. Other medical history information included GER, failure to thrive, scoliosis, recurrent croup, and bicuspid aortic valve. Spirometry was normal, without reversibility from a bronchodilator. Allergy scratch testing was positive for several common environmental and airborne allergens. The patient also had a positive RAST to egg. The patient underwent a direct laryngoscopy and rigid bronchoscopy with bronchial alveolar lavage given the concern for anatomic abnormality. He was found to have distal tracheal compression, greater than 50% at the level of the carina, with a pulsatile appearance. A subsequent angiogram chest computed tomography demonstrated a dilated ascending aorta and right innominate vessel leading to tracheal compression (the trachea was 6 mm in diameter at the level of greatest involvement) (Figure 1).

Patient no. 3 was an 11-year-old girl with hypermobility type EDS and history of failure to thrive, pancreatitis, dysautonomia, GER status-post fundoplication, and anxiety who presented with dyspnea on exertion, cough, and chronic nasal congestion. Food and drug allergies were present based on clinical history. Allergy scratch testing to common indoor and outdoor allergens was negative. Her spirometry demonstrated mild obstruction with reversibility from a bronchodilator, which confirmed a diagnosis of asthma. A flexible laryngoscopy demonstrated 100% choanal obstruction by adenoid tissue and normal vocal cord mobility. A polysomnogram was normal, without evidence of obstructive sleep apnea. She underwent an adenoidectomy without much improvement to her cough and snoring. A methacholine challenge and videostroboscopy were recommended but not done.

Patient no. 4 was a 13-year-old girl with classic EDS and is the sibling of patient no. 1. She had a history of ichthyosis, GER, scoliosis, and irritable bowel syndrome, and presented to the clinic with dyspnea on exertion, cough, and "throat clearing." Her asthma was treated with a bronchodilator and montelukast but with minimal effect on the symptoms. Her spirometry was normal, without significant change with bronchodilator administration. Skin testing was not performed due to ichthyosis, but RAST was negative for common environmental allergies. A methacholine challenge was negative, and an airway fluoroscopy was normal. A laryngoscopy was unable to confirm vocal cord dysfunction but this diagnosis was probable based on her symptoms and improvement with breathing exercises provided by speech therapy.

Lastly, patient no. 5 was a 14-year-old girl with hypermobility type EDS who was taking a bronchodilator and inhaled corticosteroid for her asthma. She presented with dyspnea on exertion and cough. Her medical history included anomalous right coronary artery and attention deficit hyperactivity disorder. Asthma was confirmed with spirometry, which showed a mild obstructive pattern with clinically significant bronchodilator response in symptoms and FEV₁. Allergy scratch testing to

TABLE 1. Patient characteristics

Patient no.	Age (y)/sex	EDS type	Symptoms	Medical history	FEV ₁ , %	FEV ₁ /FVC, %	Allergy testing	Diagnosis
1	9/boy	Classic	Dyspnea, chest tightness with exercise	GER status-post fundoplication, kyphoscoliosis, platelet function disorder, irritable bowel syndrome	102	83	RAST to aeroallergens negative	Vocal cord dysfunction, GER
2	10/boy	Hypermobility	Nocturnal dyspnea, cough, choking sensation	Failure to thrive, GER, pyloric web, gastrostomy tube placement, recurrent croup, scoliosis, bicuspid aortic valve	124	89	Scratch test positive to several common aeroallergens; RAST positive to egg	Vascular tracheal compression, allergic rhinitis, drug allergies, food allergy, GER
3	11/girl	Hypermobility	Dyspnea on exertion, cough, chronic nasal congestion	Failure to thrive, umbilical hernia, hiatal hernia, pancreatitis, dysautonomia, febrile seizure, GER status-post fundoplication, gastrostomy tube placement, anxiety	109	87	Scratch test to aeroallergens negative	Asthma, drug and food allergies, adenoid hypertrophy, GER
4	13/girl	Classic	Dyspnea on exertion, cough, throat clearing	Ichthyosis, atopic dermatitis, GER, scoliosis, irritable bowel syndrome	96	83	RAST to aeroallergens negative	Probable vocal cord dysfunction, GER
5	14/girl	Hypermobility	Dyspnea on exertion, cough	Anomalous right coronary artery status-post unroofing procedure, ADHD	101	77	Scratch test to aeroallergens negative	Vocal cord dysfunction, asthma

ADHD, Attention deficit hyperactivity disorder; EDS, Ehlers-Danlos syndrome; FVC, forced vital capacity; GER, gastroesophageal reflux; RAST, radioallergen sorbent test.



FIGURE 1. Angiogram chest computed tomography of patient no. 2, demonstrating dilatation of the ascending aorta and subsequent tracheal compression.

common airborne allergens was negative, and videostroboscopy was diagnostic for vocal cord dysfunction.

To our knowledge, this is the first case series of patients with EDS to describe recurrent respiratory symptoms in the pediatric population. Despite all 5 patients being previously diagnosed with asthma, this was confirmed in only 2 patients, and alternate explanations were found. A study of adult patients with EDS described increased respiratory symptoms of cough, dyspnea, and nocturnal cough or wheeze, with results statistically significant compared with controls.⁷ The prevalence of asthma was increased in patients with EDS (23%) versus controls (14%) based on pulmonary function tests; however, this was not statistically significant. As in this reference, similar findings of asthma in our patients may not entirely account for their respiratory symptoms.

With 2 confirmed and 1 probable case of vocal cord dysfunction in our series, this suggests an association with their underlying connective tissue disease. One review of patients with hypermobility type EDS discussed findings of incoordination or hypotonia of vocal cords in all patients who underwent fibroscopy.⁴ However, the article failed to mention the number or age of the patients who had this diagnostic test. Dysphonia symptoms rather

than respiratory symptoms led to the diagnosis of vocal cord dysfunction. This series of 21 patients did not describe any respiratory or pulmonary symptoms as manifestations of EDS. No patients in our series experienced dysphonia. Our 1 patient with swallowing difficulties characterizes a fairly common symptom of choking in EDS based on a recent report. A survey of 411 patients with EDS (range, 1-80 years old) self-reported swallowing difficulties in 39%, which included difficulty clearing the throat, tightness in the throat, and globus sensation.⁵

We found no report that described vascular tracheal compression in EDS. Airway collapse has been described, and EDS may lead to increased airway distensibility, with inadequate connective tissue to support small airways.⁷ There is a case report of a 19-year-old woman who presented with stridor and hemoptysis, and she was eventually diagnosed with EDS. Fluoroscopy of the neck demonstrated intermittent airway occlusion.⁸ Vascular anomalies such as aortic dilation and dissection are reported in EDS, especially with the vascular subtype. A recent article by Atzinger et al⁹ describes cardiac findings in hypermobile and classic EDS. Seven patients had dilated aortas before age 14, and only 1 child continued to show dilatation after this age. Interestingly, no one developed aortic dilatation as an adult. This study concluded that aortic root size is increased in EDS in 6% of the classic subtype and 12% of the hypermobile subtype but tends to be of little clinical significance.

Children with EDS can have recurrent respiratory symptoms due to many etiologies, including paradoxical vocal cord dysfunction and potential airway compression, which may be erroneously attributed to asthma and possibly related to their underlying connective tissue disease.

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