Review Article

The Clinical Manifestations, Diagnosis and Management of Williams-Campbell Syndrome

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Abstract

Williams-Campbell syndrome is a rare congenital syndrome characterized by the absence of cartilage in subsegmental bronchi leading to formation of bronchiectasis distal to the affected bronchi. The differential diagnosis of bronchiectasis is broad and the rarity of the disease poses a diagnostic and management challenge for clinicians. This present review aims to help the understanding of the clinical manifestations, pathophysiological features, diagnostic modalities, management and differential diagnosis of Williams-Campbell syndrome. A MedLine/PubMed search was performed identifying all relevant articles. No restrictions were used for publication dates. The author used the keywords "Williams-Campbell syndrome," "non-cystic fibrosis bronchiectasis" and "congenital bronchiectasis" finding 503, 195 and 489 articles, respectively.

Keywords: Bronchiectasis, Bronchomalacia, Williams-campbell syndrome

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Introduction

Williams-Campbell Syndrome (WCS) is a rare congenital syndrome characterized by defective or completely absent bronchial wall cartilage in subsegmental bronchi, leading to distal airway collapse, producing a mechanical abnormality that may contribute to the formation of bronchiectasis distal to the collapsed bronchi.[1] The defect usually is between the fourth and sixth order bronchial divisions,[2] but it may extend between first to eight generations of proximal bronchi.[1] The deficiency in cartilage occurs early in life when the lungs are still developing and growing. The exact mechanism is still not well understood. There is no evidence suggesting that cartilage deficiency occurs outside of the lung. Affected patients have normal caliber trachea and central bronchi. The symptoms and prognosis ultimately depend on the extent of cartilage maldevelopment of the bronchi. Although the syndrome has been best described in children[1,3] with recurrent pneumonia and broncho-obstructive symptoms such as coughing and wheezing, there have been case reports in adults diagnosed late, mainly because of misdiagnosis with other more common pathologies. Nevertheless, adult cases have been diagnosed without pathologic confirmation.[4,5]

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WCS was first described by Williams and Campbell *et al* in 1960 as a rare form of congenital bronchiectasis. They described a case series of five children with similar clinical and radiological symptoms. It was proposed that the abnormal development of cartilage in bronchial tree was responsible for this presentation.[2]

Other anatomic features of the syndrome include absence or destruction of other (non-cartilaginous) bronchial wall structures by inflammation and a relatively uniform, bilateral distribution of the process.[1,6] There is also early development of clubbing because of recurrent suppurative infections and extensive radiological changes of saccular bronchiectasis.

In 1976, the first report of the occurrence of familial bronchiectasis in siblings was published and supported

the theory that WCS was congenital, based on the uniformity of the cartilaginous defect.[6-8] It may be possibly the result of an autosomal recessive mechanism, but genetic studies have not identified the specific gene so far. Although most described cases presented sporadically in early childhood, subclinical cases maybe diagnosed as late as in adulthood.[3,4,9]

Some authors have classified WCS in congenital and acquired forms. The congenital form is usually found in children and is associated with congenital anomalies such as polysplenia, malrotation of the abdominal viscera, thorax piriformis, congenital cardiac diseases and bronchial isomerism.[10-12] Other authors support the acquired hypothesis, in which bronchiectasis is secondary to adenovirus infections that cause bronchomalacia.[13]

Diagnosis

Diagnosis requires an appropriate clinical history, the characteristic expiratory airway collapse on radiological investigation, and exclusion of other causes of congenital and acquired bronchiectasis.

Pathology of the affected bronchi by bronchoscopy showing the deficiency of cartilaginous plates in the bronchial wall is the confirmatory test. However, lung biopsy has several complications and is not always diagnostic. Early reports relied on bronchography and fluoroscopic visualization, which did not offer good quality images. Fiberoptic bronchoscopy on the other hand is often non-diagnostic and not all patients are good candidates for these procedures. During the 1990s, CT became the radiological investigation of choice.[14] In 2006, Di Scioscio *et al*. described a case of WCS using inspiratory and expiratory CT imaging, which showed inspiratory ballooning of bilateral cylindrical/cystic bronchiectasis distal to the third-generation bronchi with hyperinflation of the lung. On expiration phase, there was a complete collapse of the bronchiectasis, suggesting the absence of cartilaginous plates in the subsegmental bronchi.[15] George *et al*. on the same year used in addition to conventional CT, a three-dimensional reconstruction of the bronchial tree. This imaging technique is termed virtual bronchoscopy. The case described by them showed collapsed subsegmental bronchi on conventional CT, but on CT bronchoscopy, images appeared deficient of cartilage rings (absence of ring impressions) from the main stem to the subsegmental level, which could be of great significance, especially if lung transplant is considered as a treatment option.[16] Therefore, considering its non-invasive methodology, facility of execution, and good patient tolerance, multi-slice spiral CT or CT bronchoscopy should be the test of choice to study cystic lung diseases in particular WCS.

Treatment

No specific treatment exists for WCS. Prophylaxis from exacerbations remains the basis of treatment. Prophylaxis can be achieved if an oral or intravenous antibiotic is given for 7-10 days or until sputum production decreases. For severe cases, several different antibiotics may be used sequentially in a continuous regimen to minimize bacterial resistance.

In 2011, Hacken *et al*. conducted a systematic review, aiming to answer what are the effects of treatments in people with bronchiectasis but without cystic fibrosis.[17] The following treatment recommendations were given: Exercise or inspiratory muscle training may improve quality of life and exercise endurance in people with bronchiectasis but without cystic fibrosis. Prolonged use of antibiotics improves clinical response rates and may improve quality of life and reduce time to first exacerbation, but it may not reduce exacerbation rates or improve lung function. Inhaled corticosteroids may reduce sputum volume and improve dyspnea, but have not been shown to reduce exacerbations. There are not enough studies to prove if bronchopulmonary hygiene, physical therapy, mucolytics, inhaled hyperosmolar agents, oral corticosteroids, leukotriene receptor antagonists, short-acting beta 2 agonists, long-acting beta 2 agonists, or anticholinergic therapy is beneficial.[17]

There are case reports that domiciliary non-invasive positive pressure ventilation (NPPV) may have an advantage in adult patients with WCS who have severe respiratory failure and recurrent pulmonary infections.[18]

WCS is an obstructive disorder that shares some similarities with chronic obstructive pulmonary disorder (COPD). NPPV has been reported to improve chronic respiratory failure in patients with bronchiectasis. NPPV combined with long-term home oxygen therapy decreases carbon dioxide retention and improves dyspnea in hypercapnic COPD. Moreover, long-term NPPV may decrease acute exacerbation and recurrent hospitalization.

Surgery is often considered for people with extreme damage to one or two lobes of the lung who are at risk of severe infection or bleeding. However, surgery in two patients, one given a triple lobectomy and the other a right upper lobectomy, resulted in severe respiratory failure.[8]

Transplantation has been reported in a patient with severe respiratory symptoms from WCS, but the patient died a year later. Upon postmortem examination, it was observed that the main bronchi had bronchomalacia, which was attributed to a respiratory infection during the post-surgery period.[7]

Given the rarity of the disease, 2006 guidelines from the International Society for Heart and Lung Transplantation give no specific recommendation on selection of patients for lung transplantation, but state that with non-CF bronchiectasis the lung transplant community has generally followed the guidelines used for CF patients. As per these recommendations, the transplant window can be established when FEV1 reaches 30% of predicted or with rapid deterioration of FEV1, with increasing frequency of exacerbations or an ICU stay, refractory/recurrent pneumothorax and hemoptysis not controlled by embolization.[19]

Differential diagnosis

Bronchiectasis is characterized by irreversible widening of medium-sized airways, with inflammation, chronic bacterial infection and destruction of bronchial walls.

The diagnosis of WCS requires an appropriate clinical history, characteristic expiratory collapse of airways, and exclusion of other causes of congenital or acquired bronchiectasis.

There are numerous etiologies that can induce or contribute to the pathophysiologic processes that result in bronchiectasis. They include airway obstruction (e.g., foreign body aspiration), defective host defenses, cystic fibrosis, Young's syndrome, rheumatic and systemic diseases, dyskinetic cilia, pulmonary infections, allergic bronchopulmonary aspergillosis and cigarette smoking.[20,21]

The initial evaluation of a patient with bronchiectasis should include a complete blood count with differential, immunoglobulin quantization (IgG, IgM and IgA), and sputum culture and smear for bacteria, mycobacteria and fungi.

The distribution of bronchiectasis may be important diagnostically. A central distribution is suggestive of allergic bronchopulmonary aspergillosis; predominant upper lobe distribution is characteristic of cystic fibrosis; middle and lower lobe distribution is consistent with primary ciliary dyskinesia; middle lobe and lingular segment of the left upper lobe involvement is characteristic of non-tuberculous mycobacteria; and lower lobe involvement is typical of idiopathic bronchiectasis.[22,23]

Conclusion

WCS is an uncommon congenital cystic lung disease. The diagnosis of WCS is made by exclusion, after detailed work-up and exclusion of the other common causes of bronchiectasis. CT bronchoscopy should be ordered before trying more invasive procedures for diagnosis.

When patients' signs and symptoms include recurrent respiratory infections and diffuse bronchiectasis, WCS should be included in the differential diagnosis.

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