Williams–Campbell syndrome case series and discordant twins

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To the Editor:

Williams–Campbell syndrome (WCS) is a rare pulmonary disorder encompassing aspects of both bronchiectasis and obstructive lung disease. First described by Williams and Campbell in 1960 [1], this syndrome is characterised by the absence of bronchial cartilage, leading to bronchiectasis and recurrent respiratory infections [2, 3]. Due to its rarity, WCS poses significant challenges in terms of diagnosis and management.

A diagnosis is made through the typical radiological presentation and exclusion of other aetiologies. Advancements in imaging technologies, such as high-resolution computed tomography and bronchoscopy, have yielded valuable insights into the structural abnormalities associated with WCS [2, 3], enabling more precise diagnoses and assessments of disease severity.

Moving beyond the diagnostic phase, the management of WCS demands a multidisciplinary approach that is aimed at identifying treatable traits, such as infection (*Pseudomonas aeruginosa* or otherwise), mucus hypersecretion or airway obstruction [4, 5]. A combination of prevention of respiratory infections, swift intervention and improvement of respiratory function are employed to mitigate complications.

There is considerable debate around the underlying cause of WCS. Both genetic and as environmental causes have been proposed; genetic causes for children with congenital absence of bronchial cartilage [6, 7] and environmental causes for adults diagnosed with WCS later in life [8, 9].

The rarity of WCS leads to a scarcity of scientific literature for healthcare professionals, researchers and educators. By presenting a case series of WCS patients, including the healthy monozygotic twin of one patient, this report seeks to increase our knowledge about this rare syndrome as well as stimulate debate about the environmental and/or genetic causes of this pulmonary condition.

WCS patients were identified from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) registry [10]. In addition, we identified WCS patients observed in the LMU University Hospital (Munich, Germany). WCS cases were diagnosed by imaging studies and interdisciplinary clinical workup with exclusion of other causes. One of the WCS patients seen at the LMU University Hospital has a healthy monozygotic twin brother who requested clinical workup and was subsequently also included in the study. Demographic and clinical data including age, sex, smoking history, pulmonary comorbidities, sputum production, bacterial colonisation, antibiotic usage, bronchiectasis-specific medication and lung function parameters were collected for all WCS patients and the healthy monozygotic twin (table 1). All patients gave informed consent for participation in this study. We reported numerical variables as median and range, and categorical variables as absolute and relative frequencies.

A total of five patients diagnosed with WCS were extracted from the 16 963 bronchiectasis patients (0.03%) included in the EMBARC registry. Two more patients were identified retrospectively in the databases of the LMU University Hospital. We also included the healthy monozygotic twin of one WCS patient. The mean±SD age at study consent was 42.9±9.7 years and five patients (71%) were male (these numbers exclude the healthy monozygotic twin brother). All patients for whom the years since diagnosis of bronchiectasis were available were diagnosed in adulthood. One of the seven patients (14%) was diagnosed with comorbid asthma, while none showed other pulmonary comorbidities.

Shareable abstract (@ERSpublications)
Williams–Campbell syndrome (WCS) presents diagnostic challenges. This case series highlights clinical complexities and genetic/environmental interplay, and underscores the need for personalised treatment approaches. #WCS #RareDisease https://bit.ly/3Xqze8x

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TABLE 1 Overview of demographic and clinical characteristics

Patient	Age at consent (years)	Years since bronchiectasis diagnosis	Sex	BSI score	mMRC score	Regular sputum	Colonisation with PA	Other colonisation	Inhaled antibiotic	Macrolide	Exacerbations	Exacerbations requiring hospital admission/ secondary care	FEV_1 (% pred)	FVC (% pred)
WCS-1	55	Unknown	Female	17	3	Yes	Yes	Yes	No	No	6	3	52.5	71.2
WCS-2	41	<5	Male	3	0	No	No	No	No	No	0	0	43.9	83.6
WCS-3	56	10–15	Male	6	0	Yes	No	Yes	No	No	0	0	46.9	75.5
WCS-4	43	Unknown	Male	6	0	No	No	Yes	No	No	2	1	95.5	107.8
WCS-5	34	10–15	Male	6	3	Yes	No	No	No	No	1	1	28.5	46.1
WCS-6	27	<5	Female	3	1	No	Unknown	Unknown	No	No	0	0	39.0	74.0
WCS-7	44	10–15	Male	5	0	Yes	No	Yes	No	Yes	3	0	79.0	92.0
HMT	44	NA	Male	0	0	No	No	No	No	No	0	0	110.2	111.6

BSI: Bronchiectasis Severity Index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; HMT: healthy monozygotic twin; mMRC: modified Medical Research Council; PA: *Pseudomonas aeruginosa*; WCS: Williams–Campbell syndrome.

Four of our seven WCS patients showed chronic bacterial infection: one with *P. aeruginosa* and *Enterobacteriaceae*, one with *Haemophilus influenzae*, one with *Staphylococcus aureus* and one with an unknown pathogen. Three patients showed no chronic colonisation. The median number of exacerbations over the past 12 months was 1 (range: 0–6 exacerbations). A median of 0 exacerbations (range: 0–3 exacerbations) requiring hospital admission were recorded in the 12 months preceding inclusion.

Medication was very variable between the seven WCS patients. Among inhaled medication, long-acting beta-agonists (LABAs) were the most frequently prescribed agent (five of seven patients, 71%), followed by long-acting muscarinic antagonists (LAMAs) (three of seven patients, 43%), inhaled corticosteroids (ICS) (two of seven patients, 29%), and short-acting beta-agonists, short-acting muscarinic antagonists, and isotonic and hypertonic saline (one of seven each, 14%). Only one patient (14%) received long-term antibiotic treatment, this being oral macrolides.

The median forced expiratory volume in 1 s (FEV_1) of the seven WCS patients was 46.9% predicted (range: 28.5–95.5% pred). Forced vital capacity (FVC) was less variable and overall higher than FEV_1 % pred, with a median of 75.5% pred (range: 46.1–107.8% pred). Diffusing capacity of the lung for carbon monoxide (D_{LCO}) was only available for five of seven patients. This parameter was quite variable, with a median D_{LCO} of 25.5% pred (range: 14.2–117.3% pred). All patients showed signs of COPD; four of seven patients were in Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups 3 or 4.

The twin pair (consisting of one twin with WCS and one healthy twin) reported both having had pneumonia at the age of 13 years, with only one of the two subsequently developing recurrent respiratory infections and a diagnosis of WCS. Both reported not having frequent respiratory exacerbations before this event.

The results of our study provide valuable insights into the clinical characteristics and management of patients with WCS. Our patient cohort, comprised of seven individuals with WCS and one monozygotic healthy twin brother, contributes to the limited existing literature on this rare pulmonary disorder.

Our findings reveal a spectrum of bacterial colonisation among WCS patients, with four individuals showing chronic infection, including *P. aeruginosa*, *Enterobacteriaceae*, *H. influenzae* and *S. aureus*. The presence of chronic colonisation underscores the challenges posed by recurrent respiratory infections in WCS [11, 12]. The median number of exacerbations over the past 12 months was 1, with a subset requiring hospitalisation. No estimates for exacerbation frequency in WCS exist; however, our numbers are comparable with previously published exacerbation frequencies for bronchiectasis as a whole [10]. This emphasises the clinical burden of WCS and the importance of proactive management strategies to prevent exacerbations.

The variability in medication usage among WCS patients highlights the lack of standardised therapeutic approaches. LABAs were the most frequently prescribed agents, followed by LAMAs and ICS. Antibiotic usage was low, with only one patient receiving chronic inhaled or oral antibiotics in the form of regular macrolides. Other authors have described their patients to have been treated with antibiotics as needed [3]; however, our report is the first to describe use of anti-muscarinics or beta-agonists. This heterogeneity in medication patterns underscores the lack of evidence-based treatment guidelines as well as the need for personalised treatment regimens tailored to the individual needs of WCS patients.

The lung function parameters of our WCS cohort demonstrated significant variability. The median FEV_1 was 46.9% pred, reflecting the obstructive nature of the disease. FVC data were less variable, with a median of 75.5% pred. COPD was evident in all patients, with four falling into GOLD groups 3 or 4, indicating moderate to very severe airflow limitation. This heterogeneity ranging from normal lung function to strong obstruction was in line with other published cases [6, 11, 13]. These results underscore the impact of WCS on pulmonary function and the need for interventions targeting treatable traits to preserve lung function.

The examination of a singular case involving WCS in an individual alongside his healthy monozygotic twin brother provides an opportunity for a nuanced exploration of the interplay between genetic and environmental factors in this rare pulmonary disorder. WCS has been suggested to be either congenital or caused by infection, specifically adenovirus infection [14, 15]. The twin pair in this study reported no history of recurrent respiratory infections before both contracting pneumonia at the age of 13 years, hinting at a potential contribution to WCS development. However, imaging confirming the presence of WCS was unavailable until the patient reached the age of 34 years. Surprisingly, despite both twins contracting pneumonia, only one of them subsequently developed WCS. This observation suggests that a purely genetic or environmental cause is less likely, highlighting the complexity of WCS aetiology.

In conclusion, our study contributes valuable data to the limited pool of knowledge surrounding WCS. The observed variability in clinical presentation, bacterial colonisation, medication patterns and lung function parameters underscores the complexity of managing this rare pulmonary disorder. Moving forward, collaborative efforts and larger-scale studies are essential to refine diagnostic and therapeutic strategies for improved outcomes in individuals affected by WCS.

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