Paediatric Respiratory Reviews 19 (2016) 56–61

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Review

Respiratory manifestations and management in children with Common Variable Immunodeficiency

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EDUCATIONAL AIMS THE READER WILL COME TO UNDERSTAND:

- The broad clinical phenotypes in children with common variable immunodeficiency (CVID)
- The importance of early diagnosis and management of respiratory morbidity in CVID
- The role of other treatment options such as prophylactic antibiotics, anti-inflammatory medications and muco-ciliary clearance in delaying respiratory progression in CVID

ARTICLE INFO

Keywords:
Common variable immunodeficiency
Diagnosis
Respiratory management

SUMMARY

Common variable immunodeficiency is an antibody deficiency that usually presents in childhood with recurrent sino-pulmonary infections. Diagnostic delay is frequent and thus respiratory morbidity is common, ranging from recurrent suppurative bronchitis to bronchiectasis. Immunoglobulin replacement therapy is the mainstay of treatment, whilst prophylactic antibiotic therapy and muco-ciliary clearance are additional treatment options. This review examines the diagnosis and management of respiratory issues in children with CVID.

INTRODUCTION

Common variable immunodeficiency is a heterogeneous group of immunodeficiency disorders characterized by dysfunctional antibody production resulting in a spectrum of clinical disease most commonly associated with recurrent sino-pulmonary infections [1]. A small number of patients initially present with autoimmune or auto-inflammatory conditions, but eventually develop recurrent infections. It is the second most frequent primary immunodeficiency (PID) with an estimated prevalence from 1 in 10000 to 1 in 50000. It is characterized by a bimodal presentation of age, usually presenting in early childhood or in young adult years [1–3].

The European Society of Immune Deficiencies (ESID) revised their definition of CVID in 2014 (Table 1) [4]. Essentially, a diagnosis of CVID can be made in a person > 4 years of age with clinical features of immune dysfunction (i.e at least one of recurrent infections, autoimmunity, granulomatous disease and/or unexplained polyclonal lymphoproliferation) and laboratory evidence of B-cell dysfunction (i.e. marked reduction in IgG and IgA levels 2 standard deviations below normal with/without reduced IgM levels and either poor dynamic antibody responses to vaccines and/or low switched memory B-cells). CVID is a diagnosis of exclusion, such that other causes of hypogammaglobulinaemia and profound T-cell deficiency need to be excluded before a diagnosis can be made. Although hypogammaglobulinemia and therefore sino-pulmonary infections are the defining feature of CVID, the complex and heterogenous pathogenesis of CVID results in many extra-pulmonary manifestations. In this review, we focus on the respiratory manifestations of CVID, and highlight the importance of early diagnosis and treatment.

Pathogenesis of CVID

CVID is not a monogenic immunodeficiency, but instead a collection of heterogeneous disorders linked by T-B-cell dysregulation resulting in defective antibody production.

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http://dx.doi.org/10.1016/j.prrv.2015.12.003

Table 1
Revised ESID (2014) diagnostic criteria for CVID

At least **one** of the following:
• Increased susceptibility to infection
• Autoimmune manifestations
• Granulomatous disease
• Unexplained polyclonal lymphoproliferation
• Affected family member with antibody deficiency
AND marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2 SD of the normal levels for their age);
AND at least one of the following:
• Poor antibody response to vaccines (and/or absent isohemagglutinins); i.e.
absence of protective levels despite vaccination where defined
• Low switched memory B cells (<70% of age-related normal value)
AND secondary causes of hypogammaglobulinemia have been excluded
AND diagnosis is established after the fourth year of life (but symptoms may be present before)
AND no evidence of profound T-cell deficiency, defined as two out of the following (y = year of life):
• CD4 numbers/microliter: 2–6 y < 300, 6–12 y < 250, >12 y < 200
• % Naive CD4: 2–6 y < 25%, 6–16 y < 20%, >16 y < 10%
• T-cell proliferation absent

http://esid.org/Working-Parties/Registry/Diagnosis-criteria.

This has become increasingly more apparent with the advent of next generation sequencing, which has allowed immunologists to identify previously known mutations in the group of patients presenting with a CVID phenotype. For example, children with monogenic mutations that cause severe combined immune deficiency (SCID) can present atypically with a CVID phenotype, especially if the mutation is hypomorphic and some function of the affected protein is preserved [5]. Genetic defects known to cause familial hemophagocytic lymphohistiocytosis (HLH) can also lead to a clinical phenotype of "CVID", before the catastrophic presentation with hemophagocytic syndrome [6]. Next generation sequencing has also allowed the identification of new genes within the CVID group. Recent examples include CTLA-4 loss of function [7] and PI3K gain of function [8] mutations, along with other previously identified genes such as CD19, TACI and ICOS. However, < 5-10% of all CVID cases currently have a genetic explanation, and multiple centres are currently conducting trials to better delineate genetic mutations leading to a CVID phenotype [9–11].

SPECTRUM OF PULMONARY DISEASE

Age of presentation

Age of presentation can range from 3 years to 71 years of age with studies identifying 2 peaks, between 6 and 10 years of age and in young adulthood (between 26 and 40 years) [1,14–16]. In both the US and France national studies, nearly 15% of all the patients presented between 4 to 10 years of age [1,15]. A small number of patients (<5%), do not have recurrent infection but rather come to attention initially due to presence of inflammatory or autoimmune complications, but overtime develop recurrent suppurative infections [16]. The primary defect in CVID is usually insufficient production of IgG and IgA antibodies to pathogens. Consequently, patients suffer from frequent or persistent upper respiratory tract infections, especially in the pre-school age [12]. As recurrent infections are common in children, and patients with CVID present with typical symptoms of wet cough and ear infections, diagnostic delay is not infrequent. In one study the average diagnostic delay was 2.5 years for children and 5.5 years for adults [13]. Early diagnosis and optimal management are likely to result in improved clinical and quality-of-life outcomes for patients with CVID.

Upper respiratory tract infection

Recurrent or chronic otitis media, sinusitis and bronchitis, in isolation or in combination, are the most common presenting features in children and adults with CVID [1,14]. Ear and chest infections are common in immunocompetent children, particularly in the first 2 years of life. Antibody defects, such as CVID, however must always be considered if a patient is presenting with recurrent or chronic bronchitis, sinusitis and otitis media with ottorrhoea [17]. A patient who presents with recurrent episodes of rhinorrhoea, wheeze, and cough who is well in between episodes is much more likely to be immune competent and have recurrent viral upper respiratory tract infections compared to a patient with recurrent or persistent antibiotic responsive wet cough and/or purulent otitis media. Culture of sputum or ear discharge in such circumstances is useful, since an antibody defect is more likely if encapsulated bacteria are isolated.

Recurrent pneumonia

Almost three quarters of patients with CVID would have had at least one episode of pneumonia requiring antibiotic therapy before diagnosis, with some children having had multiple episodes of pneumonia [15]. Pneumonia can be severe requiring hospitalization and can also be associated with complications including empyema, pneumatocoeles and lung abscess. Watts et al described 28 (87.5%) out of 32 patients who had an average of 3 or more episodes of pneumonia [18]. Different lobes of the lung are often involved but rarely the same lobe can be affected. This can then progress to bronchiectasis which may require lobectomy in later years. Encapsulated bacteria are the predominant organisms isolated in children with CVID. These include *streptococcus pneumoniae and haemophilus influenzae*. Staphylococcus aureus has also been frequently isolated [19,20]. Any patient presenting with two or more episodes of pneumonia needs to be investigated for an antibody defect.

Asthma

Patients with CVID may have recurrent wheezing requiring treatment with bronchodilators for relief. The incidence of asthma has been reported to be between 9% and 15% [21,22]. This may be attributed to intrinsic asthma which is IgE independent and may also be secondary to increased inflammation, producing reversible obstruction and clinical wheezing. Asthma symptoms are likely to delay diagnosis by masking the underlying symptoms of immunodeficiency and therefore any patient presenting with a chronic or recurrent bronchitis with wheeze should be assumed to have an antibody defect until proven otherwise. Such patients must have a full blood count and antibody levels (IgG, IgA and IgM) measured as a minimum, prior to any escalation of asthma medications.