

Juvenile Idiopathic Arthritis (JIA) Presenting as Temporomandibular Joint Arthritis in Patients with Common Variable Immunodeficiency (CVID)

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Abstract

CVID is the most common clinically encountered primary antibody deficiency disorder and can be associated with autoimmune complications. We report 2 children with CVID who developed joint symptoms several years after initial diagnosis and were referred to a pediatric rheumatologist, who suspected temporomandibular joint arthritis clinically. Both patients underwent MRI imaging with contrast administration, which confirmed temporomandibular arthritis. They were successfully treated with intra-articular steroid joint injections. Juvenile idiopathic arthritis (JIA) can be one of the autoimmune associations with CVID, but temporomandibular arthritis as the primary manifestation is uncommon, difficult to detect clinically and has not been described previously in CVID. Although jaw pain and discomfort on chewing might indicate underlying temporomandibular joint arthritis, these symptoms might not necessarily be present. If not promptly identified and treated, arthritis of JIA can cause joint damage/disability and therefore needs specialist multidisciplinary management under a pediatric rheumatologist. JIA may not respond to steroid injections alone and might require escalation in therapy with systemic immunosuppressive agents. Little is known about the intricacies of systemic immunosuppressive therapy in patients with CVID who develop JIA.

Conclusion: In relation to CVID, juvenile idiopathic arthritis (JIA) can be an associated autoimmune manifestation. JIA presenting as temporomandibular joint arthritis as the first manifestation is unusual but can occur and might be potentially difficult to detect clinically. Pediatricians should be aware of the possibility of JIA in a child with CVID and refer to a pediatric rheumatologist for appropriate management. If not treated promptly, JIA can cause joint destruction and disability.

Keywords: Common variable immuno deficiency; Pediatric; Autoimmune; Juvenile idiopathic arthritis; Temporomandibular joint arthritis

Abbreviations:

CVID: Common Variable Immuno Deficiency; JIA: Juvenile Idiopathic Arthritis; TMJ: Temporomandibular Joint; ICOS: Inducible Co-Stimulator; TACI: Transmembrane Activator and Calcium-modulator and Cyclophilin ligand Interactor; BAFF: B cell Activating Factor; CD: Cluster of Differentiation; MRI: Magnetic Resonance Imaging; ANA: Anti-Nuclear Antibody; ENA: Extractable Nuclear Antibody

Introduction

Common Variable Immunodeficiency is the most common symptomatic primary antibody deficiency in children affecting both sexes equally and characterized by hypogammaglobulinaemia. CVID is mostly sporadic, although familial patterns of inheritance are seen in ~20–25% of cases [1]. Typically, patients present with recurrent bacterial infections of the respiratory and gastrointestinal tract. They may also develop malignancies, inflammatory and autoimmune complications [2-4]. The depletion of switched memory B cells as well as attenuation of regulatory T cells have been shown to be associated with autoimmune disease in patients with CVID [5]. Identification of

monogenic defects (ICOS, TACI, CD19, BAFF-R, CD20, CD81) has demonstrated that the genetic basis of CVID is highly variable. Of all genetic defects associated with CVID, certain alterations in TACI, CD19 and CD81 have most often been associated with autoimmune manifestations [6]. Recent studies have tried to address demographic/genetic associations and functional aspects of memory B-cells in relation to CVID, with proposed implications on classification and therapy [7,8]. With the advent of immunoglobulin therapy, mortality from CVID has reduced over the last decade [9]. We report two pediatric patients with CVID, who developed temporomandibular joint arthritis as the first manifestation of associated Juvenile Idiopathic Arthritis (JIA).

Case-series of Two Patients

Patient 1: A 12 year old girl was diagnosed with CVID at the age of 6 years. She had been unwell with recurrent episodes of otitis media and severe bacterial chest infections since six months of age. She developed a BCG abscess post-immunisation. Paternal grandfather had bronchiectasis and recurrent pneumonias. A maternal cousin had lupus and maternal grandmother had rheumatoid arthritis.

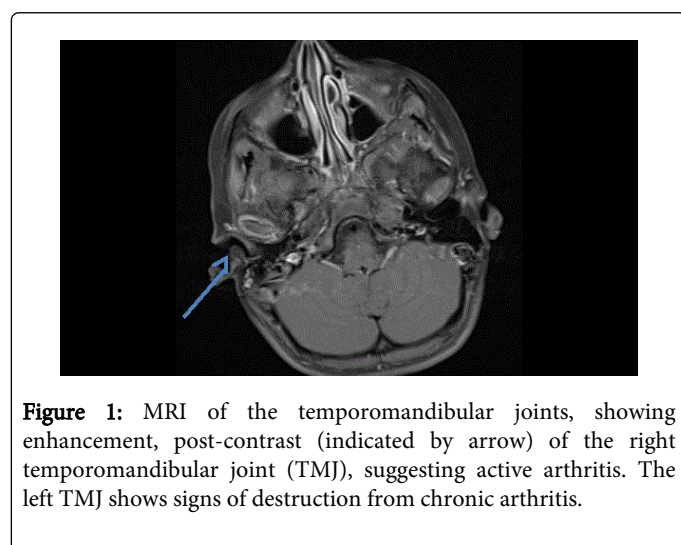
She had clubbing at diagnosis and a chest CT revealed bronchiectasis. Initial immunological investigations demonstrated hypogammaglobulinaemia with a total IgG of 3.33g/L, significantly reduced IgG subclasses (IgG1 2.76 g/L, IgG2 0.1 g/L, IgG3 0.09 g/L and absent IgG4), undetectable IgA level (<0.06 g/L) and borderline low

IgM (0.4 g/L). Flow cytometric analysis of peripheral blood lymphocytes revealed normal CD40 expression and no evidence of lymphocyte imbalance (Table 1). She had optimal responses to PMA/Ionomycin, CD3 and PHA stimulation. However, the percentage of memory B cells (CD19+CD27+) and class switch memory B cells (CD19+CD27+IgM-IgD-) was markedly reduced (2.4% and 0.25%, respectively). Furthermore, she had an inadequate antibody response to tetanus and Haemophilus influenza type B immunization (0.15IU/ML and <0.15 MCG/ML). Immunoglobulin replacement therapy and antimicrobial prophylaxis were commenced. Her course was complicated by bronchiectasis requiring repeated courses of antibiotics and an increased dose of the immunoglobulin replacement.

Lymphocyte subsets	Patient 1	Patient 2
CD3 % (10 ⁹ /L)	72 (1.79)	78 (1.93)
CD4 % (10 ⁹ /L)	43 (1.07)	54 (1.33)
CD8 % (10 ⁹ /L)	28 (0.70)	18 (0.44)
CD56 % (10 ⁹ /L)	9 (0.22)	10 (0.25)
CD19 % (10 ⁹ /L)	18 (0.45)	12 (0.30)
Total lymphocyte count 10 ⁹ /L	2.49	2.47

Table 1: Summary of T-cell and B-cell profile of the two patients at diagnosis.

Four years after diagnosis, she had an illness with fever and painful knees, followed by generalized joint pains. Although the illness subsided within a few days, non-specific joint stiffness persisted for more than 6 weeks, prompting a referral to pediatric rheumatology. Examination by a pediatric rheumatologist showed no peripheral arthritis, however, jaw deviation was demonstrable on mouth opening. Inflammatory markers including an ESR and CRP were normal and an autoantibody panel showed negative ANA, ENA and Rheumatoid factor. An MRI scan with gadolinium contrast confirmed the clinical suspicion of active right-sided temporomandibular joint arthritis (Figure 1). The left temporomandibular joint revealed signs of damage from chronic arthritis, implying arthritis of longer duration. Over the next few months her arthritis progressed, involving knee and finger joints, which responded to targeted intra-articular steroid injections.



Patient 2: A 14 year old girl was diagnosed with CVID at 2 years of age. She had endured a respiratory arrest following neonatal pneumonia and suffered from recurrent episodes of stridor, pneumonia and wheezing. Just beyond infancy, she had a further illness requiring ventilation. Immunological tests revealed a reduced total serum IgG level (2.5 g/L), low IgG2 (0.26 g/L), IgG3 (<0.17g/L) and IgG4 (<0.37 g/L) subclasses, low IgA (<0.4 g/L) and a normal IgM level (0.6 g/L). She had inadequate antibody response to childhood immunisations. Flow cytometric analysis of peripheral lymphocytes showed normal CD40 expression, normal lymphocyte subsets (Table 1) as well as normal percentage of memory B cells (19.03 %) and class switch memory B cells (9.36 %).

She was commenced on immunoglobulin replacement therapy. Apart from an episode of chicken pox a few years later, she remained well. Twelve years after the initial diagnosis, she presented with generalised joint pains, albeit with no joint swelling. There was no preceding or concurrent infection. As this was ongoing for a couple of months, a paediatric rheumatology opinion was sought, whereby reduced mouth opening with temporomandibular joint line tenderness was detected. She was systemically well and inflammatory markers (ESR, CRP) were not elevated. ANA and Rheumatoid factor were negative. An MRI scan with gadolinium contrast confirmed bilateral active temporomandibular joint arthritis. She responded well to targeted steroid joint injections. To date, she has not developed arthritis elsewhere.

Discussion

Both patients were diagnosed with CVID in early childhood. The first patient had bronchiectasis and markedly reduced numbers of class-switched memory B cells, known to be associated with increased prevalence of clinical complications, such as bronchiectasis and autoimmunity [10]. The second patient had adequate numbers of class switched memory B cells and was successfully managed on immunoglobulin replacement therapy. Both patients eventually developed JIA.

Autoimmune diseases can occur with increased frequency in CVID [2-4]. Pathogenesis of autoimmunity is unknown in CVID patients, although a loss of switched memory B cells, defective elimination of autoimmune B cells and T cell dysfunction have been implicated [10].

Chronic arthritis in a child younger than 16 years of age, after reasonable exclusion of infectious and other inflammatory causes, should raise the suspicion of JIA. JIA is predominantly a clinical diagnosis and inflammatory markers or autoantibodies are not diagnostic, but might aid in exclusion of other causes of inflammatory arthritis.

In the past, studies have shown occurrence of Rheumatoid Arthritis in 7 to 8% of patients with CVID [2]. The largest series of CVID patients had 248 cases, including both adults and children, of whom 7% developed juvenile arthritis [2].

Joint manifestation in CVID generally presents with symmetric joint involvement, most commonly of knees, ankles and hands. Autoantibodies including ANA or rheumatoid factor are typically absent due to lack of antibody production in CVID. Histologically, B cells and plasma cells are virtually absent, and T-cell infiltrate may be composed of CD8+ cells [11].

Juvenile arthritis has been reported in one of 2 siblings with CVID, but with peripheral joint arthritis as the first manifestation [12].

Isolated temporomandibular arthritis as the presenting feature in JIA is unusual but has been described previously [13]. To our knowledge, this is the first case series of pediatric patients with CVID, presenting with temporomandibular joint arthritis as the primary manifestation of associated JIA. Although jaw pain and discomfort on chewing might indicate underlying temporomandibular joint arthritis, these symptoms might not necessarily be present. This is important, as temporomandibular arthritis can be difficult to detect clinically and needs a high index of suspicion, especially if asymptomatic. In a prospective study by Weiss et al., 71% of children with newly diagnosed JIA who had acute temporomandibular arthritis were asymptomatic and 63% had normal findings on jaw examination. The authors recommend MRI as the radiological investigation of choice to diagnose temporomandibular arthritis [14]. It is imperative to have a low index of clinical suspicion for prompt detection of temporomandibular joint arthritis, as delayed recognition can lead to joint destruction with pain, asymmetry, reduced mouth opening and even micrognathia.

Furthermore, poorly controlled JIA can result in joint destruction, deformities and disability. JIA can also be associated with asymptomatic uveitis in children, which can potentially lead to visual problems including blindness if not identified and treated promptly. Although active arthritis of JIA, including temporomandibular arthritis might respond to targeted intra-articular steroid injections [15], some patients and certain subtypes of JIA will need systemic immunosuppressive medication. They also need ongoing physiotherapy input to prevent joint deformities and longstanding disease can have a wider impact on functional quality of life.

Although there is no consensus on the exact mode of immunosuppressive therapy for CVID patients with JIA, lower doses and shorter periods of treatment have been suggested [16]. More evidence is required as to how such children can be optimally managed. Pediatricians should be vigilant in children who develop chronic joint symptoms especially if they have an underlying autoimmune disease (CVID in this instance) and if appropriate, seek a pediatric rheumatology opinion for optimal management.

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