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Common Variable Immunodeficiency Presenting as Juvenile Spondyloarthritis: Concerns about Increased Risk of Infections Associated with Immunosuppressive Agents

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ABSTRACT

Common variable immunodeficiency (CVID) is a disorder characterized by defective B cell function leading to impaired immunoglobulin production. Although symptoms typically manifest between the second and fourth decades of life, they can emerge in childhood, with heterogeneous clinical manifestations such as recurrent infections, chronic lung disease, autoimmune disorders, gastrointestinal disease, or increased risk of malignancy. We report the case of a 17-year-old male with a personal background of rhonchopathy and recurrent otitis until the age of five, when he undergone adenoidectomy and bilateral tympanostomy with ventilation tubes. He remained asymptomatic until the age of 13, when he developed arthralgia affecting the spine, sternum, hips and knees. After clinical evaluation, he was diagnosed with CVID and juvenile spondyloarthritis (JSpA). He is under multidisciplinary care, including immunodeficiency, rheumatology, pneumology and medical genetics. His current treatment includes subcutaneous immunoglobulin and a selective COX-2 inhibitor.

This case highlights the clinical presentation of CVID in pediatric patients, focusing on diagnostic approach and treatment strategies.

Keywords: CVID; Juvenile spondyloarthritis; Pediatric

ABBREVIATIONS

ANAs, antinuclear antibodies; AS, ankylosing spondylitis; CMV, cytomegalovirus; CVID, common variable immunodeficiency; DMARDs, disease-modifying anti-rheumatic drugs; ESID, European Society for Immunodeficiencies; GLILD, granulomatous-lymphocytic interstitial lung disease; HIV, human immunodeficiency virus; HLA-B27, human leukocyte antigen B27; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IGRA, interferon-gamma release assay; IgRT, immunoglobulin replacement therapy; IL, interleukin; IVIG, intravenous immunoglobulin; JIA, juvenile idiopathic arthritis; JSpA, juvenile spondyloarthritis; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells;

NFKB1, nuclear factor kappa b subunit 1; NSAIDs, nonsteroidal anti-inflammatory drugs; PID, primary immunodeficiency disorder; RF, Rheumatoid factor; TNF, tumor necrosis factor

INTRODUCTION

Common Variable Immunodeficiency (CVID) is a primary immunodeficiency disorder (PID) characterized by dysfunction in B cells, T cells, and dendritic cells, leading to impaired antibody production. However, the precise physiological mechanisms underlying this dysfunction remain poorly understood. To date, mutations in approximately 60 genes have been linked to CVID, with some predisposing individuals to develop the condition, while others are directly responsible for the disease.[1] The latter are categorized as CVID-like disorders.

CVID is diagnosed, according to the European Society for Immunodeficiencies (ESID),[2] when at least one of the following clinical features is present: increased susceptibility to infections, autoimmune manifestations, granulomatous disease, unexplained polyclonal lymphoproliferation, or a family history of antibody deficiency. Furthermore, the diagnosis requires all of the following criteria: a significant decrease (≥ 2 standard deviations bellow the age-specific mean) in immunoglobulin G (IgG) and immunoglobulin A (IgA) levels, with or without low immunoglobulin M (IgM) levels; diagnosis after the fourth year of life (although symptoms may be present earlier); exclusion of profound T cell deficiency; absent of isohemagglutinins, poor response to vaccines, or both; and exclusion of other causes of hypogammaglobulinemia.

CVID management includes immunoglobulin replacement therapy, prophylactic and therapeutic antibiotics and complementary vaccinations with inactive antigens.

Although infectious manifestations are the most common in children with CVID, autoimmune and inflammatory manifestations have been increasingly recognized as distinguishing features of this condition.[3]

Juvenile spondyloarthritis (JSpA) is a group of human leukocyte antigen B27 (HLA-B27) associated disorders that begin in children under 16. In contrast to adult-onset spondyloarthritis, JSpA often starts with inflammation of peripheral joints and entheses, with sacroiliitis and spondylitis potentially developing years later. Treatment options for JSpA include physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), tumor necrosis factor (TNF) inhibitors or disease-modifying anti-rheumatic drugs (DMARDs).

This case report presents a pediatric patient diagnosed with CVID and JSpA. It emphasizes the importance of early diagnosis, the potential benefit of immunoglobulin replacement therapy, and the cautious use of immunosuppressive agents in managing such cases.

CASE PRESENTATION

A 13-year-old male adolescent was referred to pediatric rheumatology due to recurrent arthralgias involving the spine, sternum, hips and knees, with symptoms alternating between the left and right sides. The patient had no significant prior medical history, except for undergoing adenoidectomy and myringotomy with tympanostomy tube placement at the age of 5 due to roncopathy and recurrent otitis media.

The physical exam showed painful mobility of the hips and knees. There were no signs of inflammation in the other joints, and the remaining examination was unremarkable.

Imaging studies, including radiographs of the pelvis and knees and a hip ultrasound showed no significant abnormalities.

The patient was initially managed with ibuprofen on an as-needed basis. Laboratory analysis revealed hypogammaglobulinemia (Table 1). Rheumatoid factor (RF), antinuclear antibodies (ANAs) and HLA-B27 were negative.

Repeat laboratory tests confirmed continued low immunoglobulin levels, including decreased immunoglobulin subclasses (Table 2). Additionally, he demonstrated a poor response to the 23-valent pneumococcal vaccine. Flow cytometry showed normal B and T cell subsets. Acquired causes of hypogammaglobulinemia were ruled out, namely the human immunodeficiency virus (HIV) infection. The cytomegalovirus (CMV) antibodies and the interferon-gamma release assay (IGRA) were negative.

Given the suspicion of CVID, genetic testing was performed and revealed a heterozygous variant in the NFKB1 (Nuclear Factor Kappa B Subunit 1) gene.

At age 15, he contracted COVID-19, presenting with mild symptoms and requiring no hospitalization. A thoracic CT scan was subsequently performed, revealing ground-glass opacities in the middle lobe and lingula in a centrilobular distribution, without evidence of bronchiectasis, suspicious nodules, pleural effusion, or lymphadenopathy. Pulmonary function testing, including a bronchoprovocation test, revealed normal results. In view of the known association between CVID (and CVID-like disorders) and granulomatous-lymphocytic interstitial lung disease (GLILD), he was referred to pediatric pneumology.

At age 16, despite being without infectious diseases, the patient was started on intravenous immunoglobulin (IVIG) therapy due to worsening hypogammaglobulinemia and the previous CT findings.

During this period, he experienced a recurrence of right-sided lumbosacral pain and arthralgia affecting the hips and knees. Physical examination revealed a positive Patrick's test at the right side. A pelvic radiograph (Figure 1) revealed subchondral sclerosis of the sacroiliac joints. Lumbar spine magnetic resonance imaging (MRI) was normal, but pelvic MRI (Figure 2) demonstrated marked bone marrow edema in both sacroiliac joints, articular surface irregularities and bilateral subchondral sclerosis. These findings supported a diagnosis of spondyloarthritis, and treatment with naproxen was initiated, once patient should avoid DMARDs. Due to the development of thrombocytopenia, switching from naproxen to etoricoxib was a viable alternative.

At the time of this report, the patient continues under multidisciplinary follow-up, on subcutaneous immunoglobulin therapy (with a recent IgG level over 800 mg/dL and without infectious complications), presenting arthralgias well-controlled and no evidence of GLILD.

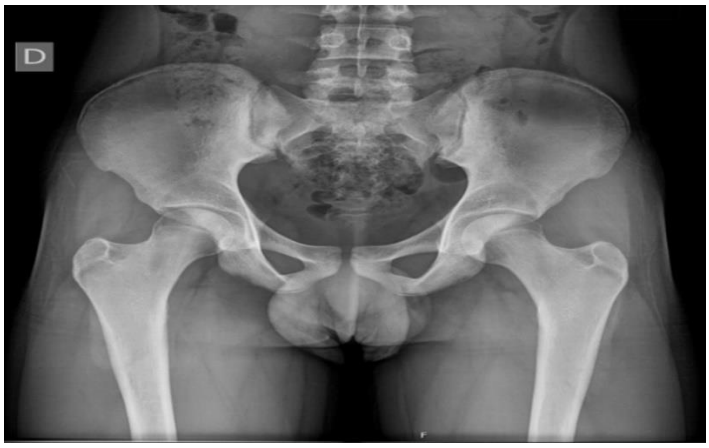

Figure 1: Pelvic x-ray showing subcondral sclerosis of the sacroiliac joints.

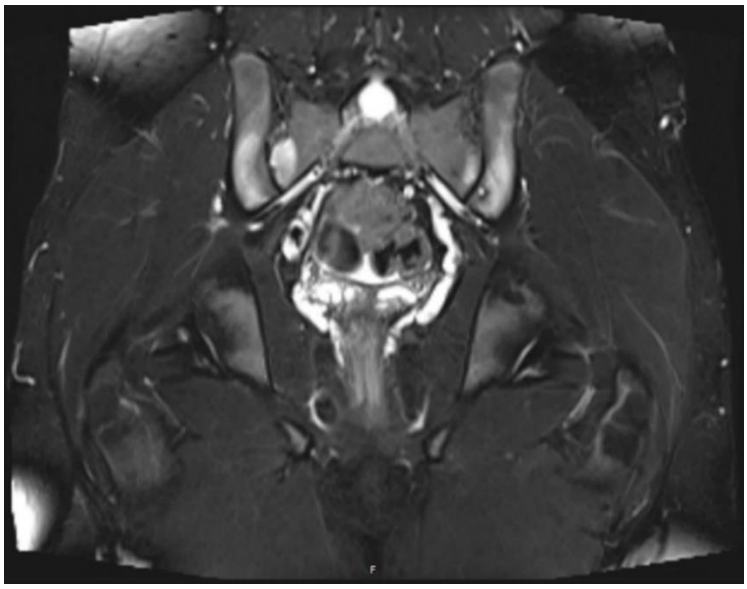

Figure 2: Magnetic Resonance Imaging (MRI) of the pelvis, with fat saturation following gadolinium contrast administration, showing bone marrow edema, subchondral sclerosis and irregularity of the articular surfaces of both sacroiliac joints.

Table 1: Hypogammaglobulinemia

		Normal range
Immunoglobulin A	10 mg/dL	63 – 484 mg/dL
Immunoglobulin G	378 mg/dL	540 – 1822 mg/dL
Immunoglobulin M	20 mg/dL	22 – 240 mg/dL

Table 2: IgG Subclasses deficiency

		Normal range
Immunoglobulin G subclass 1	182 mg/dL	402 – 715 mg/dL
Immunoglobulin G subclass 2	5 mg/dL	216 – 523 mg/dL
Immunoglobulin G subclass 3	16 mg/dL	36 – 139 mg/dL
Immunoglobulin G subclass 4	< 1 mg/dL	9 – 104 mg/dL

DISCUSSION

We report a case of hypogammaglobulinemia due to a pathogenic NFKB1 variant, diagnosed first with JSpA. Loss-of-function NFKB1 variants are the most common monogenic cause of CVID in European populations.[4] The NFKB1 gene encodes the transcription factor NF-κB1, which plays a critical role in cell proliferation and survival, inflammation, and immune response. Dysregulated NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) signaling has been implicated in a wide range of pathologies, including increased susceptibility to infections, autoimmune disorders, granulomatous diseases, lymphoproliferative disorders, and neoplasms.[5]

Our patient exhibited recurrent infections only at an early age and during adolescence he contracted COVID-19 but did not require hospitalization.

Chest CT findings, along with the association between GLILD with CVID, prompted ongoing monitoring due to the significant impact of GLILD on prognosis. To date, the patient has shown no clinical signs of GLILD and has normal pulmonary function tests, despite a worsening in the number and extent of ground-glass opacities.

Otherwise, inflammatory joint symptoms were more prominent, affecting the axial skeleton and peripheral joints.

Autoimmune and inflammatory complications are increasingly recognized as the second most common manifestation of CVID and CVID-like disorders, following infectious complications.[6] Inflammatory arthritis has been reported in 1% to 15% of pediatric and adult patients with these conditions.[7] Early recognition of CVID in these patients is crucial, as the use of immunosuppressive therapy may increase the risk of severe or opportunistic infections. Previous studies have demonstrated that enhanced activity in the NF-kB pathway, along with TNF-α and IL-23/IL-17 pathways, is associated with a higher risk of ankylosing spondylitis (AS) in adults.[8] Given the pathophysiological overlap between AS and JSpA, these findings may also have relevance in the pediatric context.

The cornerstone of treatment in CVID is immunoglobulin replacement therapy (IgRT), administered either intravenously or subcutaneously. IgRT should be initiated as early as possible following a comprehensive immunological evaluation. The treatment goal is to maintain serum IgG levels above 700 mg/dL.[9] Most pediatric patients experience significant benefits from IgRT, including reduced frequency and severity of infections, fewer hospitalizations, decreased antibiotic use, and improved growth and development outcomes.[9-10]

The patient was managed with NSAIDs on an as-needed basis, since could not use DMARDs. While the role of IgRT in modulating autoimmune or inflammatory symptoms remains incompletely understood, our patient improved significantly after reaching target IgG levels. This observation suggests a possible link between IgRT and modulation of inflammatory activity in JSpA, warranting further investigation.

CONCLUSIONS

The rarity and limited awareness of CVID often lead to underdiagnosis. Its clinical presentation is notably heterogeneous, with recurrent respiratory tract infections being the most common manifestation in pediatric patients. However, autoimmune and inflammatory features, as illustrated in this case report, should also be considered.

Early recognition of CVID is crucial for prompt diagnosis and initiation of immunoglobulin therapy.

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CONFLICTS OF INTEREST

The authors have no conflict of interest.

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