Association of common variable immunodeficiency and rare and complex connective tissue and musculoskeletal diseases. A systematic literature review

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ABSTRACT

Objective. *To perform a systematic literature review (SLR) on the association of common variable immunodeficiency (CVID) and rare and complex connective tissue and musculoskeletal diseases, namely systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), idiopathic inflammatory myopathies (IIM), systemic sclerosis (SSc), relapsing polychondritis, antiphospholipid syndrome, immunoglobulin (Ig) G4-related disease, as well as undifferentiated and mixed connective tissue disease.*

Methods. *An SLR on studies and cases about the association of CVID and rare and complex connective tissue and musculoskeletal diseases was performed. Animal studies were excluded.*

Results. *170 publications fulfilled the inclusion criteria. Sjögren's syndrome was the most frequent connective tissue disease in CVID-patients. Most case reports exist on SLE and CVID with SLE mostly preceding the manifestation of CVID. Multiple cases were published reporting the concurrence of CVID and inclusion body myositis and single cases were found on CVID and antisynthetase syndrome, polymyositis, limited SSc and relapsing polychondritis, respectively. There are no cases of CVID and antiphospholipid syndrome, IgG4-related disease, as well as undifferentiated and mixed connective tissue disease.*

Conclusion. *The concurrence of CVID and complex connective tissue and musculoskeletal diseases, especially SS, IIM, SSc and relapsing polychondritis is rare but relevant. The measurements of Ig-levels should be performed before the initiation of immunosuppressive therapy to allow for the differentiation of primary and secondary Ig-deficiency and substitute IG if necessary.*

Introduction

Common variable immunodeficiency (CVID) is among the clinically most severe primary immunodeficiencies and the second most common one after selective IgA deficiency. It encompasses a heterogeneous group of diseases that is characterised by hypogammaglobulinaemia and a poor or absent immunologic response after exposure to pathogens or immunisation. Patients with CVID have markedly reduced concentrations of immunoglobulin (Ig) G, IgA and/or IgM. They suffer from frequent, mostly respiratory and gastrointestinal infections, as well as from autoimmune phenomena and cancer predisposition (1). Common other clinical manifestations are splenomegaly, lymphadenopathy, granulomatous disease, and other gastrointestinal complications.

Its prevalence is estimated at 1:25,000 with men and women being equally affected. The age of onset is variable, most patients are diagnosed in childhood or between the ages of 20 and 40 years.

In recent years, some of the genetic defects underlying CVID have been described, so far they affect however maximally 20% of the patients.

About 20% of patients with CVID present with autoimmune features, most commonly autoimmune cytopenias, followed by rheumatic disorders, such as inflammatory arthritides as the most common manifestation, followed by Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE) in 6% of all patients with CVID (2, 3). Autoimmune diseases were observed in 17.4% of patients before CVID diagnosis, being the only clinical manifestation in 2.3% of the cases (4).

Autoimmunity usually presents before the diagnosis of CVID, leading to the diagnostic challenge to differentiate hypogammaglobulinemia due to im-

munosuppressive therapies from CVID. Since patients with CVID may suffer from a variety of manifestations that unrecognised might lead to severe complications, it is important to establish the diagnosis and arrange appropriate monitoring. However, knowledge about the association of CVID and rheumatic diseases is still lacking. This review aims at assessing the frequency of rare and complex connective tissue and musculoskeletal diseases (ReCONNET), summarising the features of reported cases and establish management advice.

Methods

A literature search was conducted in July 2021 in MEDLINE via PubMed and Cochrane CENTRAL Register of Controlled Trials, without language restrictions and comprised until July 10, 2021. No restrictions were made regarding the earliest publication date. Manuscripts published after July 10, 2021 were not included. Details on complete search strategies are provided in the supplement. The literature review addressed the association of CVID and autoimmune diseases of European Reference Network (ERN) ReCONNET spectrum, more precise antiphospholipid syndrome, IIM, IgG4-related disease, mixed connective tissue disease, relapsing polychondritis, SS, SLE, systemic sclerosis (SSc) and undifferentiated connective tissue disease (UCTD). Cohort studies, clinical trials and retrospective analyses as well as case reports and case series were included. No age restriction of the participants was applied and manuscripts on both juvenile and adult patients were included. Animal studies were excluded.

Two reviewers (JM and MS) independently screened titles and abstracts, and if necessary, the full text, for eligibility. Disagreements were discussed until consensus was achieved and involvement of a third reviewer was not necessary.

Results

Of a total of 170 references, 27 were included. Among these were 24 case reports, 2 cohort studies and one retrospective analysis. Data was retrieved on CVID and SLE, SS, inclusion body myositis, SSc and relapsing polychondritis. No association was reported between CVID and antiphospholipid syndrome, IgG4-related disease, undifferentiated and mixed connective tissue disease.

Due to the low frequency of CVID and rare connective tissue and musculoskeletal diseases, reliable prevalence rates do not exist. A recent retrospective analysis of 870 paediatric and adult patients with CVID from the United States Immunodeficiency Network (USIDNET) found physician-reported CVID in 5.9%. Of these, the majority (n=18; 35.3%) presented with inflammatory arthritis, 21.6% (n=11) had SS, 15.7% (n=8) suffered from SLE and 3 patients (5.9%) had mixed connective tissue disease (3). A total of 18 patients with CVID-associated rheumatic disorders (35%) had an additional inflammatory manifestation such as organ-specific autoimmunity (optic neuritis, uveitis, inflammatory bowel disease and autoimmune cytopenias), other inflammatory manifestations (granulomatous disease, inflammatory lung disease) or cancer. Patients with CVID and rheumatic diseases were of older age at CVID-diagnosis than patients with CVID only.

No immunophenotypic differences were found between patients with CVID-associated disease and those with non-inflammatory CVID regarding CD19+ B-cells, the median CD4/CD8 ratio and median IgA or IgM levels. A tendency of lower memory B-cells and especially IgM+ memory B-cells in CVID patients with rheumatic diseases compared to CVID patients only. However, the number of available B-cell observations was too low for a definite statement (3).

CVID and SS

As stated above, SS has been reported to be the second most frequent rheumatic manifestation in CVID patients (3). In another cohort of patients with CVID referred to a haematology/oncology practice, mainly by rheumatologists, 7% had SS (5). No case was described in detail and no information exists regarding the manifestations and findings the diagnosis of SS was based on.

CVID and SLE

Reviewing the literature, we identified 15 cases with concurrent SLE and CVID (6-17) of which 12 have been summarised in a recently published review (18). In most cases, the diagnosis of SLE preceded the diagnosis of CVID with a mean age of 20.4 years (standard deviation (SD) 9.7) at SLE diagnosis and 29.9 years (SD 18.1) at CVID diagnosis. CVID diagnosis was based on low Ig-levels and recurrent infections. In few cases, the diagnosis was further corroborated by poor response to vaccination. At the time of diagnosis, 93% were ANA positive, in 73% a positive dsDNA-antibody was reported. All patients received glucocorticoids (GC) as SLE treatment, 11 cases received one or more additional immunosuppressive therapies such as antimalarials (n=4), azathioprine (n=6), cyclophosphamide (n=3), methotrexate (n=1), mycophenolate mofetil (n=1), tacrolimus (n=1) and plasmapheresis (n=1). Onset of CVID was typically marked by recurrent, mostly sinopulmonary infections. Isolated cases of enteritis, urinary tract infection, meningitis and cellulitis were reported, too. All patients received IVIG as therapy for CVID, in one case, treatment was not reported. Of the 11 cases with reported ANA and dsDNA-levels, 7 had normalised ANA titres and 8 had normalised dsDNA titres within a few months after the diagnosis of CVID and no symptoms of SLE. Only one case had severe SLE disease activity after diagnosis of CVID (14).

CVID and IIM

A total of 8 cases with concurrent CVID and IIM were identified in the literature, 5 cases suffering from inclusion body myositis (19-21), two cases with polymyositis (PM) and one case with antisynthetase syndrome (ASS) (22, 23) (Table I). In contrast to patients with CVID and SLE, CVID was diagnosed before the onset of IBM in all cases. However, mean age at IBM diagnosis was 39.2 (SD 9.8) years, earlier than in patients with sporadic IBM (usually >50 years of age) (24). In a case series of 18 patients with IBM, two cases had CVID (19). In both cases, CVID was diagnosed before IBM, however, pa-

Table I. Patients with concurrent CVID and idiopathic inflammatory myopathy.

Pt	Sex	IIM	Age at CVID diagnosis in years	Age at IIM diagnosis in years	CK-levels in U/L	IgG in mg/dL	IgA in mg/dL	IgM in mg/dL	Treatment for CVID	Treatment for IIM	Improvement with treatment?	Reference
1	F	IBM	51	55	612	35	< 0.5	< 0.5	IVIG	prednisone, CSA	Death 14 years after IBM diagnosis	(19)
2	F	IBM	24	39	660	20	< 0.5	< 0.5	IVIG	prednisone, CSA	Short improvement	(19)
3	M	IBM	13	36	normal	0	0	17	IVIG	IVIG	No	(20)
4	M	IBM	13	28	normal	31	5	24	IVIG	IVIG	Yes	(20)
5	M	IBM	34*	38	199	0	0	72.4	IVIG	IVIG, prednisone, azathioprine	No	(21)
6	F	PM	64	57**	elevated	636	49	68	IVIG	methylprednisolone, methotrexate, azathioprine	Yes	(22)
7	M	PM	23*	33	1094	7	25	180	antibiotics	eperisone hydrochloride	Stable disease	(23)
8	M	ASS	52	40	556	417	NR	16	IVIG	methylprednisolone, cyclophosphamide, azathioprin	Death due to respiratory insufficiency related to disease progression	(22)

*onset of CVID marked by recurrent infections. **onset of myopathy.
ASS: antisynthetase syndrome; CK creatin kinase; CSA: cyclosporine; CVID: common variable immunodeficiency; IBM: inclusion body myositis; Ig: immunoglobulin; IIM: idiopathic inflammatory myopathy; IVIG: intravenous immunoglobulins; pt: patient.

tient 1 already presented with symptoms of IBM at CVID-diagnosis. The phenotype of both patients did not differ from the other 16 reported cases and both showed a deterioration in muscle function despite treatment with cyclosporine and IVIGs. Patient 1 died 14 years after the diagnosis due to respiratory insufficiency secondary to muscle weakness. In 2 patients reported by Dalakas and Illa, 2 patients with IBM and CVID endomysial cell analysis showed an increased number of natural killer (NK) cells compared to patients with sporadic IBM (8.5 to 9.5% vs 1%) (20). NK cells seemed to invade muscular fibres negative for major histocompatibility complex (MHC) class 1. In general, and contrary to sporadic IBM, MHC class I was only weakly expressed in muscle fibres surrounded by CD8+ cells. In one patient, NK-cells normalised with IVIG therapy, and his strength improved.

In one case with PM, the diagnosis of PM was made 7 years before the diagnosis of CVID, in the other case (22), the patient had suffered from recurrent infections in the ten years preceding the diagnosis of PM. In the patient with ASS, the IIM was diagnosed 12 years before CVID (22). While the PM-patients reached a state of controlled disease (one case with GC and methotrexate, the other case without immunosuppressive treatment), the patient with ASS died from ASS-complications.

CVID and relapsing polychondritis (RP)

Three cases of CVID and RP have been elaborated in the literature and have been summarised before (25). In the first case, the diagnosis of CVID was made in a 15-months-old boy due a positive family history for CVID (26). IVIG treatment was started at 3 years due to recurrent infections and at the age of 4, he was diagnosed with RP that was treated with local GC and methotrexate. The second case is a 32-year-old female who was diagnosed with RP and CVID at the same time (25). A newly described mutation in nuclear factor-κB2 was linked to CVID, which was also found in her daughter who already presented with low Ig-levels at the age of 2. The patients received prednisone and azathioprine as well as IVIG. The third case is a 23-year-old male who was diagnosed at 22 years with CVID and one year later with RP presenting as auricular and costal chondritis as well as bronchomalacia (27). Remission was achieved with GC- therapy and IVIG for CVID. In no case, other manifestations than recurrent infections for CVID were reported.

CVID and SSc

One case of concurrent CVID and limited systemic sclerosis was identified (28). The female patient had the diagnosis of anti-centromere-antibody positive scleroderma at 53 years and received methotrexate. CVID was diagnosed after a period of severe pulmonary infections, although she had been experiencing recurrent infections for 20 years. Treatment with IVIG and cessation of methotrexate led to a decreased episode of infection.

Discussion

While in most cases, the diagnosis of SLE precedes the diagnosis of CVID, reports of CVID and IIM are mixed, and no corresponding information exists on SS. However, measuring Ig-levels in patients with autoimmune diseases should be part of the clinical routine before the initiation of immunosuppressive therapy and later on. Diagnosis of CVID in patients with autoimmune disease does not differ from the usual diagnosis and encompasses the measurement of markedly reduced serum concentrations of IgG in combination with IgA and/or IgM, the poor or absent response to immunisations and the exclusion of other defined immunodeficiency states (29). Many patients have normal levels of circulating

B-cells however some cases show a reduced number of B-cells and 14% of adult CVID patients have less than 1% B-cells (30).

The third prerequisite poses a challenge in patients with rheumatic diseases as most immunosuppressive agents can induce secondary hypogammaglobulinemia and differentiation can be difficult (31). The most common agents associated with a reduction in immunoglobuline levels are rituximab and high-dose and long-term treatment with glucocorticoids with the latter causing mainly IgG deficiency with less impact on IgA and IgM (32). In a cohort of patients with giant cell arteritis and polymyalgia rheumatica, 25% developed persistent antibody deficiency under glucocorticoid therapy, an aspect that treating physicians should be aware of. In contrast, only a small proportion of patients receiving other immunosuppressants develops secondary hypogammaglobulinaemia (31), and genetic variants have been identified, that increase the risk of such development (33). Interestingly, a proportion of these genetic variants have been previously found in primary immunodeficiencies such as CVID, proposing an overlap between primary and secondary immunodeficiency. The disease caused by some of these mutations, such as STAT3 gain of function variants or PI3K delta, can be treated with specific inhibitors (JAK inhibitors or PI3K delta inhibitors) (34, 35). It is conceivable, that in the future co-occurrence of immunodeficiency and of autoimmunity genetic testing of selected genetic aberrations may be performed, that would pave the road to individualised treatment.

The manifestations of the evaluated rheumatic diseases do not differ between patients with or without concurrent CVID. Interestingly, in the majority of SLE-patients, ANA- and ds-DNA levels normalised, and the patient achieved remission, whereas in few cases, patients experience ongoing disease activity. No such tendency was seen in the reported IIM cases. The higher frequency of Sjogren's syndrome in patients with CVID has to be interpreted with caution as no information is available on the time of diagnosis and manifestations. Given that IVIG/subcutaneous IG often contain SS-A antibodies, some diagnoses of Sjögren's based on SS-A positivity during Ig-substitution may not be a manifest disease. Hence SS-A antibodies should be measured before the initiation of Ig-substitution. However, a recent review on Sjögren's and CVID presumes an even higher association of CVID and Sjögren's based on similar pathogenic features such as lymphoproliferation and increased risk of lymphoma, hyperexpression of B cell activating factor and an increased number of $CD21^{low/-}$ B cells. The authors conclude, that a considerable number of patients might suffer from both conditions even in the absence of specific autoantibodies (36).

Regarding the clinical features of CVID in patients with rheumatic disorders, there are no differences between patients with CVID only. The most common symptoms are recurrent upper respiratory tract infections, that require antibiotic treatment and sometimes hospitalisation. The bacteriological spectrum does not significantly differ from patients with the respective rheumatic diseases without SLE (18).

Patients with symptomatic treatment require IVIG or subcutaneous IG-therapy. IgG-levels should normalise with therapy and the rate of infection should decrease substantially. Further, the rheumatic disease may require immunomodulatory or immunosuppressive treatment.

Of note, a substantial number of patients with CVID and rheumatic diseases have additional CVID-manifestations. These include bronchiectasis, liver dysfunction often with hepatitis B and C virus infection, primary biliary cirrhosis, and granulomatous disease as well as gastrointestinal disorders. These manifestations may be severe and can mimic organ disease of the respective rheumatologic disorder. Hence careful and thorough assessment is crucial in these patients and the underlying rheumatic disease should not be held responsible for every symptom that occurs.

The molecular mechanisms of immune dysregulation underlying the association of CVID and autoimmunity and more precise rheumatic diseases, are not fully understood. The current knowledge of molecular and cellular mechanism of CVID and autoimmunity is reviewed elsewhere (37-39). On a cellular level, the inability of CVID patients to completely eradicate microbial agents due to the absence of immunoglobulins has been proposed to favour immunocomplex deposition with consequent activation of autoreactive T-cells (40, 41). In addition, abnormal regulation of immune tolerance mechanisms might decrease regulatory T-cells and isotype switched memory B-cells, expand CD21 low B-cells, reduce apoptosis of autoreactive T-cells and dysregulate cytokine production. Further, often high levels of B-cell-activating factor is found in CVID patients and may contribute to survival of autoreactive B-cells (40). Genetic defects in CVID explain 20% of the disease (42). TACI mutations seem to particularly predispose patients with CVID for autoimmunity and have been described both in SLE and CVID (43–45). Furthermore, several HLA-haplotypes and other genes such as ICOS, BAFF-R, CD19 and MSH5 have been associated with CVID.

The development of next generation sequencing techniques has enabled the identification of many genetic defects associated with primary immunodeficiencies (PID) other than CVID(46). These PID can manifest with autoimmune features due to excess immunity and can therefore benefit from immunosuppressive drugs (47). For CVID with unknown genetic causes, targeted immunosuppressive drugs have so far not been applied. However, it is to be hoped, that diagnostic tools will improve even further and tailored therapies will also be available for patients with CVID and concurrent rheumatologic disease in whom treating physicians are hesitant to start immunosuppression for fear of infectious complications.

Take home messages

- The concurrence of complex connective tissue and musculoskeletal diseases and CVID is rare but relevant in clinical practice.

- The most common manifestations are SS and SLE.
- Clinical features of the rheumatic diseases do not differ between patients with or without CVID.
- Often, especially in SLE, the rheumatic disease precedes CVID.
- Most immunosuppressive therapies can lead to secondary hypogammaglobulinemia with glucocorticoids and rituximab bearing the highest risks. Differentiation of secondary Ig-deficiency and CVID is difficult after the initiation of immunosuppressive treatment.
- Ig-levels should be measured before the initiation of treatment and throughout the disease.
- IVIG or subcutaneous IG should be started in case of recurrent infections.

Conclusion

Although the concurrence of CVID and complex connective tissue and musculoskeletal diseases is rare, it can have a relevant impact. Therefore, all patients should be assessed for concomittent hypogammaglobulinaemia at diagnosis and at regular intervals to to allow for the differentiation of primary and secondary Ig-deficiency. Advances in the identification of underlying genetic defects may enable tailored immunosuppression in cases of CVID with concurrent autoimmune features.

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