Review paper

Common variable immunodeficiency

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Abstract

This article presents basic information about Common Variable Immunodeficiency and enumerates the characteristic signs of this disease.

Key words: *Common variable immunodeficiency, diagnostics, treatment.*

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Introduction

Common variable immunodeficiency (CVID) is one of the most frequent forms of primary immunodeficiency and it comprises an array of different immunological disturbances. Characteristic traits found in all patients are [1]:

- A deficit of two main IgG classes in serum (the level of definite serum Ig is two standard deviations below the level for the age).
- No isohemagglutinins and/or weaker response after vaccination (decreased synthesis of specific antibodies after vaccination, e.g. to tetanus anatoxin).
- The disease begins after the second year of life.

Because of the late onset of CVID, there are some other (rarer) names for it, such as adult-onset agammaglobulinemia, late-onset hypogammaglobulinemia, and acquired agammaglobulinemia. This disease appears both in men and women. CVID frequency is from 1 in 10,000 to 1 in 50,000 persons. The first clinical symptoms, such as recurrent severe or mild infections, can appear at any age: after the second year of life, during adolescence, or in adulthood, most often between the ages of 20 and 30 [2, 3]. In diagnosing CVID it is mandatory to exclude other causes of decreased antibody synthesis. Figure 1 resents some of these.

CVID can have different courses, which is why there are so many theories about its etiology and the familial and genetic factors predisposing to the disease. The very different modes of CVID inheritance attest to the heterogeneity of this disease [4]. Autosomal recessive, autosomal dominant, and also X-linked inheritance have been found in some cases. In patients with CVID, HLA:-DR3, -B8, and -SCO1 are more frequent, which suggests a role of genetic factors in its pathogenesis [5]. Other immunodeficiencies are common in family members of CVID patients, for example IgA deficit and higher predisposition to malignant cancers [6]. A lack of expression of ICOS genes was recently discovered in some homozygote persons, this causing a very specific presentation of CVID with patients with decreased B lymphocyte levels (at about 3%) without splenomegaly and no autoimmunological diseases [7, 8]. In these families there was autosomal recessive CVID inheritance. In other studies, genes responsible for CVID predisposition were shown in the of MHC class III region, also with TNF-alpha and TNF-beta genes.

T-helper lymphocytes responsible for B lymphocyte initiation in lymph nodes could disturb antibody synthesis in some cases. Disrupted Th1-lymphocyte function causes greater cytokine synthesis, especially of IFN-gamma [9, 10]. In patients with decreased B lymphocyte levels, a lack of Pax5 gene expression is observed, which encodes a protein which affects B-cell activity [9, 10].

These quite varied disturbances in immunological parameters [11-17], as shown in table 1, were applied in an attempt to create a list of CVID types. IgG and IgM production by B lymphocytes was measured after antibody for superficial IgM and Il-2 stimulation. On this basis the following CVID types were described:

- lack of B lymphocytes (difficult to differentiate from Bruton agammaglobulinemia),

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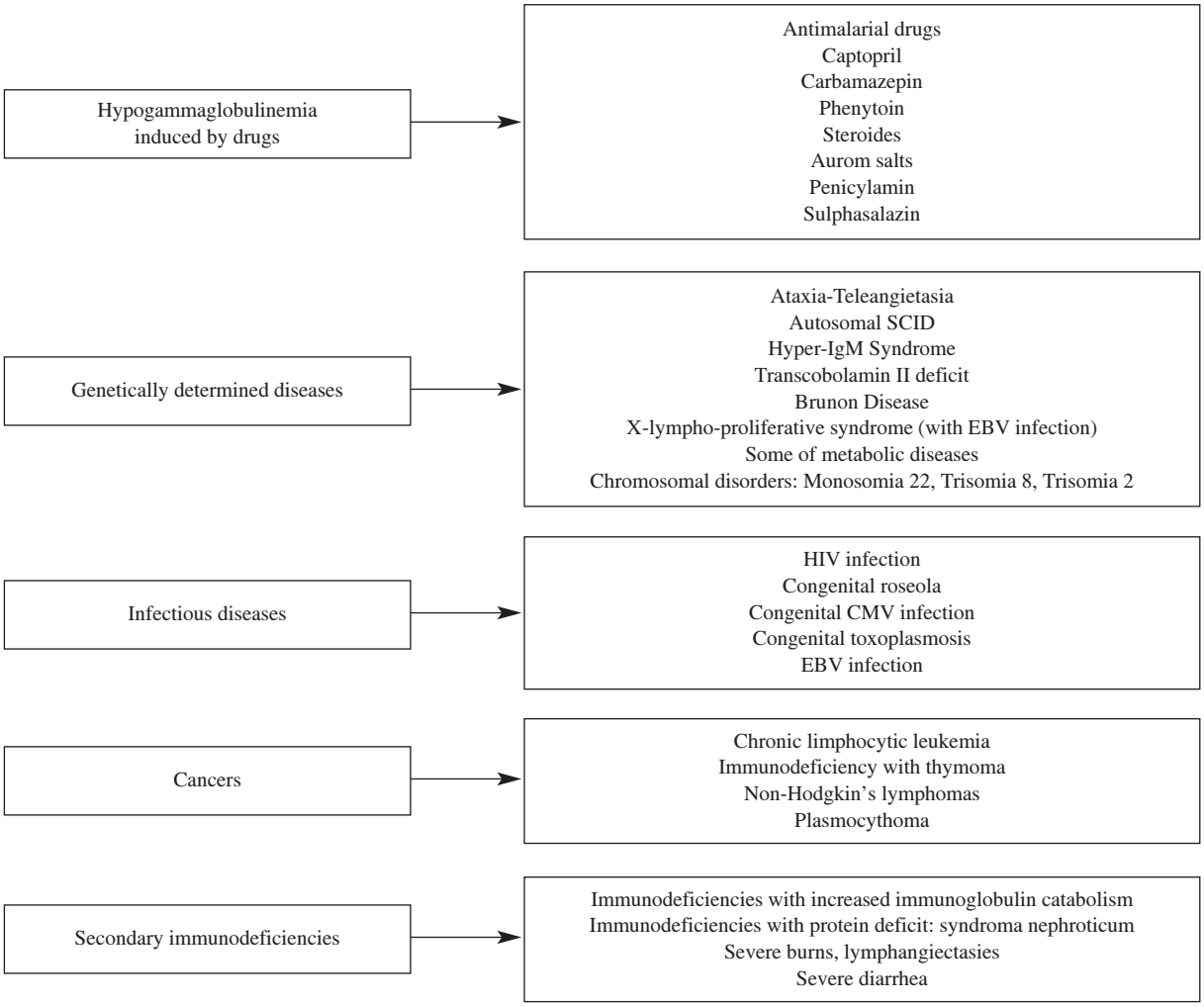

Fig. 1. Reasons other than CVID for immunoglobulin deficits and specific antibodies which need a differential diagnostics

- decreased B-lymphocyte count; they produce neither IgG nor IgM,
- B lymphocytes present, IgM synthesis active, IgG synthesis disturbed,
- proper B-lymphocytes count, normal IgG and IgM synthesis, but specific antibody synthesis is disrupted [18].

Clinical symptoms

Because of the different immunological disturbances and modes of inheritance, CVID patients suffer from a plethora of complaints and diseases, some of which are collected in figure 2. Recurrent infections are mainly characteristic of CVID. In most cases, recurrent respiratory (lungs, bronchi) infections appear first (98% of cases), causing chronic inflammation, fibrosis, and lung tissue destruction (bronchiectasis) [19]. Alimentary tract infections are also frequent, including those of difficult to treat *Giardia lamblia* (3.2%) and *Camphylobacter enteritis* (1.2%), which Cunningham-Rundles et al. observed [20, 21]. Other etiological factors causing severe infections in CVID are *Herpes viruses* (3.6%), *Pneumocystis carini* (2.8%), and *Mycoplasma pneumoniae* (2.4%). Sepsis caused by the bacteria *Pseudomonas*, *Pneumococci*, *Haemophilus influenzae* is observed in 1.2% of patients.

Another very common problem in CVID is the higher predisposition to autoimmunological diseases [22, 23], for which the risk in CVID patients is about 20 times higher than in healthy persons. That is why there are so many clinical symptoms in different organs and systems. Cancer appears more frequently in CVID patients. A 50-times higher risk of stomach cancer and a 34-times higher risk of B-cell lymphoma have also been noted [24, 25].

The mean life expectancy of persons with CVID is 55 years for women and 29 years for men. The most common causes of death are cancer diseases, especially non-Hodgkin's lymphoma and stomach cancers, and infectious complications causing organ lesions (in the lung, liver, and alimentary canal).

Respiratory tract

Infections characteristic of CVID involve the ears, sinuses, bronchi, and lungs, and they are recurrent, causing sino-bronchial syndrome. In the mornings, patients have a wet cough with mucopus sputum in large amounts, which suggests a chronic bacterial infection. Infections which recur can also cause bronchial wall damage, which leads to bronchiectasis. The most common pathogens are *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. There are also infections of *Herpes* and *Pneumocystis carinii*. Chronic interstitial pneumonias are frequent enough in CVID to cause fibrous changes which are difficult to cure [26-28]. This leads to progressive respiratory insufficiency, severely limiting these patients' activity.

Alimentary tract

In CVID patients there are persistent *Giardia lamblia* intestinations, often together with malabsorption of lipids and some saccharides. Sometimes celiac disease-like symptoms are observed. There can be abdominal aches, tympanites, vomitus, chronic diarrhea causing electrolyte imbalance, lack of protein, and cachexia. *Camphylobacter jejuni* and *Cryptosporidium* are also commonly found. In some patients, atrophic gastritis appears, leading to achlorhydia and megaloblastic anemia. Lympho-proliferation processes are activated in the intestine wall, showing a characteristic picture of nodular lymphoid hyperplasia (hypertrophy of the lymph nodes). CVID often exists together with *Colitis ulcerosa*, and stomach and ileum cancer is much more frequent than in the general population [29, 30].

Hemopoietic system

Some CVID patients, despite immunoglobulin deficit and disturbed antibody synthesis, can have auto-antibodies to leukocytes, erythrocytes, and thrombocytes, causing their degradation and leading to leukopenia, erythrocytopenia, and thrombocytopenia [31, 32]. The result of such damage is splenomegaly (1/3 CVID cases), and splenectomy is sometimes necessary.

Lymphatic system

Lymphadenopathy of the neck and abdomen is very common in CVID patients.

Table 1. Different immunological disturbances fund in CVID

Type of disturbance		
IgG level		↓=
IgA level		↓=
IgM level		↓=
Synthesis of specific antibodies (**e.g. to** tetanus anatoxin)		↓
Izohemagglutinins		no
Lymphocyte B number		↓=
Lymphocyte T number		↓=
CD4-lymphocyte number an activity deviations	[10]	↓=
Lymhocyte CD4/CD45RA number		↓=
Lymphocyte Ts function disturbances	[11]	↓=
CD4:CD8		↓
Mikrogobulin β_2		↑
Solube CD25		↑
CD40 Ligand	[12]	↓
INF-γ	[7]	↑
Prolypheral response of lymphocytes to antigens	[13]	↓=
IL-2	[10]	↓
IL-4		↓
Lymph. B spontaneus apoptosis		↑
CD95 (APO-1/Fas)		↑
ADA level	[14]	↓=
PNP level	[14]	↓=

↓ *below,* ↑ *higher, = normal rate.*

Osteoarticular system

Arthritis is often the first sign of CVID. In some patients, septic arthritis caused by *Mycoplasma pneumoniae*, *Mycoplasma hominis*, and *Ureaplasma urealiticum* appears. Rarer etiologic factors are *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Hemophilus influenze*. Some arthritis is caused by viral infections, especially by adenovirus type 1 and echovirus type 11. Frequent infections lead to chronic arthritis, causing arthropathy and amyloidosis very quickly. CVID also provokes such autoimmunological diseases as lupus systemicus, scleroderma, inflammation involving many muscles, Sjögren's Syndrome, and rheumatoid arthritis (RA) [33-35]. RA during CVID is often treated as aseptic arthritis, and very characteristic is that a few or several symmetric joints are involved in the inflammation, e.g. knees, ankles, wrists, and hand joints, usually without bone erosion. In articular liquid there is no

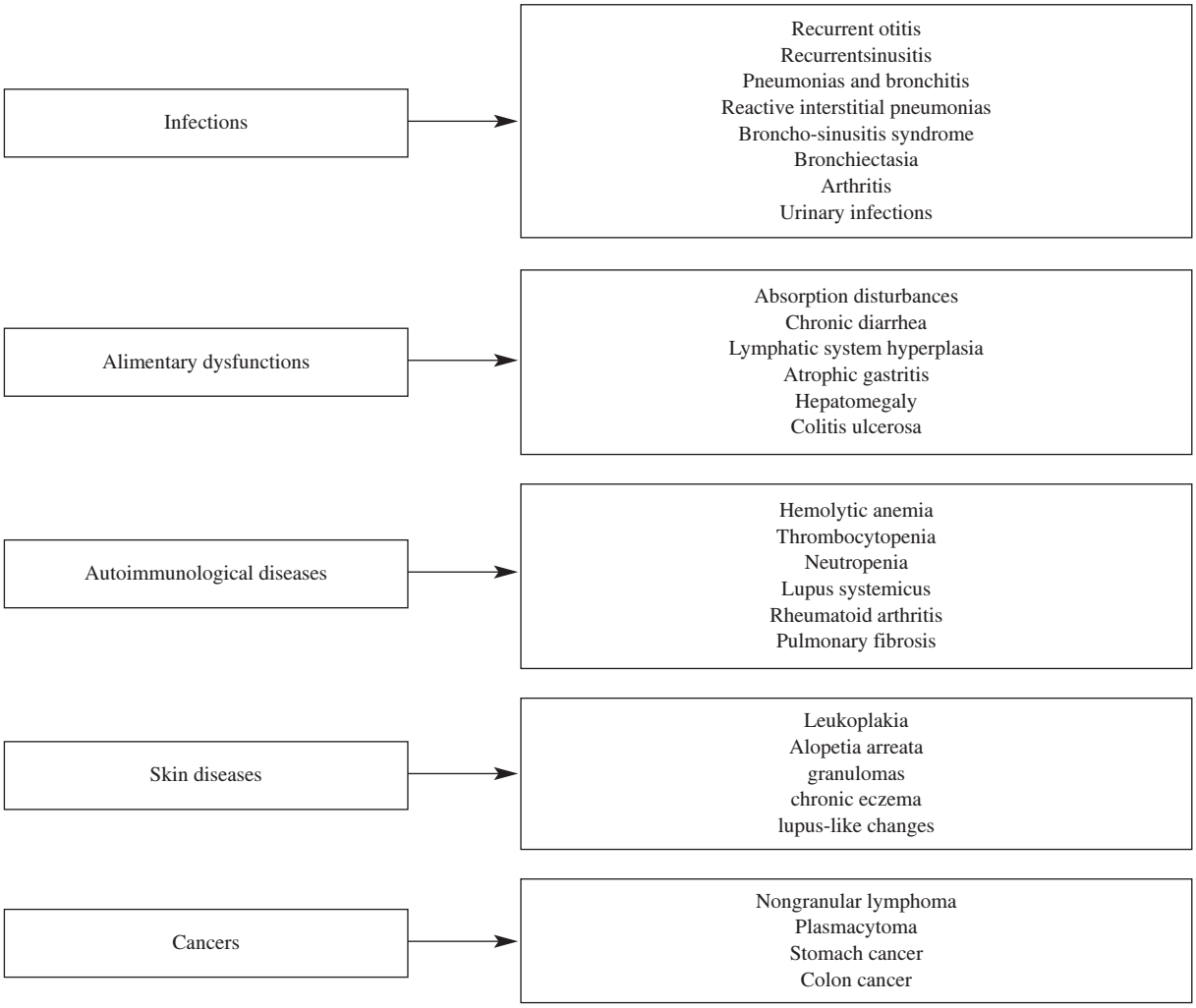

Fig. 2. The most common diseases existing in CVID

rheumatoid factor (RF). The signs of arthritic inflammation are alleviated or even disappear with IVIG substitution.

The skin

Herpes simplex infection and herpes zoster are specific to CVID and such infections are recurrent [36]. Others skin changes met with here are leukoderma, alopecia areata, and skin granulomas. Some of these are similar to lupus ones and they become harder after exposure to sunlight.

Treatment

The basic treatment method is monthly intravenous immunoglobulin (IVIG) substitution in doses chosen individually for each case [37]. This therapy might be started with a saturation dose of 500-800 mg/kg body weight and followed by a medium dose of 300-500 mg/kg. This allows maintaining an IgG serum level above 450 mg/dl. With progressed inflammatory changes in the respiratory tract (bronchiectasis) it is better to use higher doses, e.g. 600 mg/kg.

All bacterial infections should be treated intensively with wide-spectrum antibiotics. If infections occur rather often in spite of IVIG substitution, it is recommended to use antibiotics or sulfonamides as prophylactics at half the therapeutic doses. We must keep atypical bacteria infections in mind and apply the proper therapy for them. CVID patients are especially susceptible to these pathogens although they receive IVIG (IVIG products have a few specific antibodies to *Mycoplasma pneumoniae*, *Mycoplasma hominis*, and *Ureaplasma urealiticum*). It is also obligatory to eliminate mycotic

infections (Intraconazol, Diflucan, Fluconazol) and parasitic ones (Metronidazol). In patients with chronic diarrhea and malabsorption, an eliminating diet is helpful, free of gluten and disaccharides. It is also recommended to give probiotics, such as Lacidofil, Laccid, Trilac, or Enterol, which maintain theproper, natural flora in the alimentary canal.

Some patients with malabsorption or low body weight need to receive specific nutritional preparations which are easy to absorb, such as Nutridrink, Humana SL, Humana MCT, and Portagen. Patients with, for example, iron deficiency should receive it orally or, by malabsorption, parenterally.

The regular and proper treatment of CVID requires the cooperation of many specialists, as shown in figure 3. The fact that a patient requires the aid of many doctors should suggest the presence of immunodeficiency and demands that he be considered "globally", through the prism of clinical immunology.

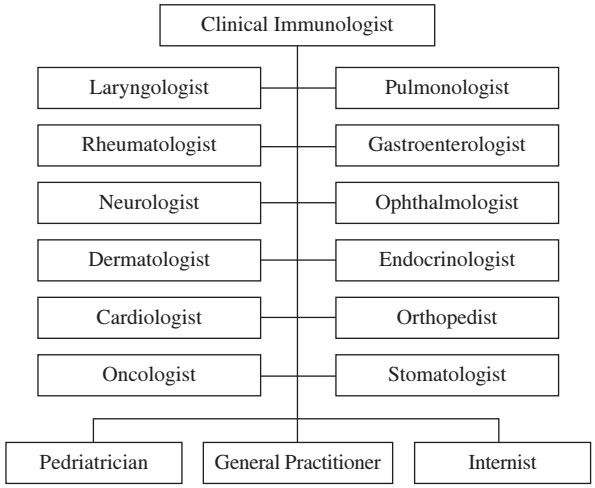

Fig. 3. Medical specialists whose cooperation in CVID treatment is mandatory

Most research workers and scholars remark on the rather long period of diagnosing the disease, often lasting some years from the appearance of the first clinical symptoms suggesting primary immunodeficiency. This is due to the multitude of signs from many organs and a pitifully poor possibility to conduct immunological tests, though it is sometimes also due to inadequate small knowledge about primary immunodeficiencies which can also appear in adults.

Conclusion

We must remember that recurrent infections as a sign of primary immunodeficiency are typical not only for children, but can also occur in adults. With this in mind, cases in adults with recurrent infections of the respiratory or alimentary tracts or urinary tract infections with the presence of autoimmunological disease, special diagnostics must be carried out to confirm or exclude common variable immunodeficiency.

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