Common Variable Immunodeficiency

Common variable immunodeficiency (in abbreviation **CVID**) is the most common primary immunodeficiency, which affects antigen specific immunity. As the term says, its clinical manifestation is very miscellaneous, but distinctive is **decreased level of immunoglobine's class IgG** (under 3 g/l), **IgA** (under 0,05 g/l) and half of the patients have decreased level of IgM class and disorder in T lymphocyte system. Number of **B lymphocyte** remains commonly **unchanged**.

Onset

Although **onset** of first symptoms is **between first and fifth year**, disease usually fully manifest in the age of sixteen to twenty, or later in adulthood, when two thirds of patients are diagnosed. Because of this reason, the disease was for a long time considered as a secondary immunodeficiency – **acquired adult hypogammaglobulinaemia**.

Clinical Features

Among the clinical symptoms of CVID are **infections of** upper and lower **respiratory tract**, particularly recurrent pneumonia otitis and frequent is recurrent sinusitis and bronchitis. Encapsulated bacteria dominate as a causal agent - *Haemophilus influenzae*, *Streptococus pneumoniae* a *Moraxella catarrhalis*. In addition to respiratory infections, patients can suffer from **chronic diarrhea** caused by intestinal infection, where etiological agent is flagellate *Giardia Lamblia*. This in children's case may have impact on not putting on weight and delayed growth. In isolated cases septicaemia and meningitis emerged. Patients are, however, not substantially susceptible to viral or fungal infections then common population. Exceptions are recurrent **viral infections** of *herpes simplex*, *cytomegalovirus* and *enteroviruses*.

Associated conditions

More than 30% of patients develop autoimmune disease; most frequently **haemolytic anaemia** and **thrombocytopenia**. Among the others less frequent are rheumatic arthritis, thyreopathy and systemic lupus erythematosus. The risk of certain malignancies is high. Particular concern is **lymphoma** affecting gastrointestinal tract and there is 50 times greater risk of a **gastric adenocarcinoma** as well.

Aetiology

Despite the 40 years long research, the exact etiological **cause** remains largely **unknown**. Part of the problem is heterogeneity of the disease. So far, there are three known causal genes responsible for up to 20-25% of cases of CVID, all having locus on various chromosomes. Inductive co-stimulating molecule *ICOS* important in the process of T lymphocytes activation and other B lymphocytes antigens - *TACI* and *CD19*. 20% patients have first degree relative with selective IgA deficiency. This finding indicates connection between genes.

Diagnosis

Diagnosis does not differ between men and women as the disease affects them equally and it is based on anamnesis of overcome infections, results of microbiological diagnosis and description of success rate of treatment. Laboratory tests necessarily include blood image with differential white cell count and biochemical screening of IgG, IgA, IgM concentrations. The second stage of diagnosis is dermal test of delayed type hypersensitivity, e.g. tuberculin or candida intradermal test, which point on T lymphocytes functional condition. The third stage is examination in highly specialized centres with utilization of genetic and molecular methods or flow cytometry.

Diagnostic criteria

Diagnostic criteria for definite diagnostics do not exist. Valid diagnostic criteria for probable diagnosis approved *European Society for Immunodeficiencies* (ESID)[1]. Male or female patient who has a marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and fulfills all of the following criteria:

1. Onset of immunodeficiency at greater than 2 years of age
2. Absent isohemaglutinins and/or poor response to vaccines
3. Defined causes of hypogammaglobulinemia have been excluded

Secondary causes of hypogammaglobulinemia

- Hematological diseases

chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia, myelomatosis, lymphomas, primary amyloidosis

- Drug induced

antimalarial agents, captopril, carbamazepine, glucocorticoids, fenclofenac, gold salts, penicillamine, phenytoin, sulfasalazine

- Infectious diseases

HIV, congenital rubella, CMV, Epstein-Barr virus, congenital infection with Toxoplasma gondii

- Excessive loss of immunoglobulins

enteropathy with protein losses (nephritic syndrom, severe burns, lymphangiectasia, severe diarrhea)

- Splenoctomy
- Transplantation
- Genetic disorders

some metabolic disorders, chromosomal Anomalies, chromosome 18q-Syndrome, monosomy 22, trisomy 8, trisomy 21

FACS - Fluorescence-activated cell sorting (flow cytometer)

Prognosis and treatment

Prognosis depends upon on-time detection of disease. Delayed diagnosis leads to a high sickness rate, bad quality of life, but particularly leads to irreversible tissue damage like bronchiectasis, pathologic dilatation of bronchi, which can lead to right-sided heart failure. Among the others is lymphoma, which risk is 300 times higher than in common population. Treatment consists of **immunoglobulin replacement therapy** to provide protective antibodies in 4-weeks intervals. Very important is treatment of progressing bacterial infections by **administration of antibiotics**, in some cases prophylactically as well. At early diagnosis is life expectancy similar to a healthy one.

Differential diagnosis

Differential diagnosis of CVID involves predominantly X-linked agammaglobulinemia and X-linked lymphoproliferative disease:

- **X-linked agammaglobulinemia** is characterized by a marked reduction in all classes of serum Ig similarly to CVID, but also by absent B cells in addition. It is caused by mutation of Bruton's tyrosine kinase (BTK).
- **X-linked lymphoproliferative disease** includes dysgammaglobulinemia creating CVID-like picture. But other distinctive feature is inappropriate immune response to Epstein-Barr virus and lymphoproliferative disorders like high grade B-cell lymphomas. Of course it is caused by different mutation in SH2D1A protein.

Epidemiology

Prevalence of disease is estimated 1:50 000 worldwide, similar to Czech Republic, but readings from various sources are not very uniform. Values vary from 1:10 000 to 1:400 000. *Institute of Health Information and Statistics of the Czech Republic* states 14 681 patients (1:25 000) in the year 2010.

Links

Related Articles

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1. www.esid.org