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New Diagnosis Criteria for Common Variable Immunodeficiency Exploration Systematic Review and Current Perspectives

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Abstract:- Common variable immune deficiency (CVID) is the most common symptomatic immune deficiency in adults. It is defined by primary hypogammaglobulinemia with B-cells (CD19) present. It is a heterogeneous syndrome clinically characterized by recurrent bacterial infections (almost a constant feature), the frequency of auto-immune and/or granulomatous manifestations and the presence of a lymphoproliferative syndrome (follicular hyperplasia, lymph nodes…). The recurrence of these infections should point to the diagnosis, which will be confirmed by proteins electrophoresis and immunoglobulin tests. The treatment of CVID is based on regular substitution of polyvalent immunoglobulins, using intravenous or subcutaneous injections. The disease physio-pathology is poorly understood, but the immun-ological studies on lymphocyte subpopulations, particularly B lymphocytes, and recent genetic defect studies have improved our understanding. This review aims to describe the latest clinical and immunological characteristics of CVID, as well as its genetic and physio-pathogenic advances, in order to propose new criteria to explore this pathology and rule out other possible causes of hypogamma-globulinemia, hence allowing a better therapeutic care for the patients affected.

Keywords:- *CVID, Immunodeficiency, Hypogamma-Globulinemia, B Cell*

I. INTRODUCTION

Common Variable Immunodeficiency Disorder (CVID) is the most common symptomatic primary immunodeficiency in adults. It is clinically characterized by recurrent severe infections, and/or autoimmunity and an increased risk of malignancy. Current studies estimate a prevalence of 1 in 25,000 approximately in the general population [1]. Significant ethnic variations exist and the frequency may be lower in some populations such as North-East Asia. Diagnosis is usually made in the second or third decade of life [2,3]. CVID is defined by significantly reduced IgG levels, usually associated, but variably, with decreased IgA and IgM levels. It is sometimes associated with impaired vaccine responses [4,5]. The blood lymphocyte populations phenotype is variable. The number of circulating B lymphocytes is either normal or decreased. Qualitative and quantitative abnormalities of T-cell immunity are observed in some of patients. Up to date, the genetic basis of CVID has not been identified in the majority of individuals; yet, it is now accepted that it is a polygenic syndrome. Patients with monogenic defects have been identified in rare cases [6].

The objective of this article is to describe the clinical and immunological features of CVID based on the latest immuno-phenotypic classification ”EUROCLASS”, to propose an exploration and diagnosis strategy, and finally, to highlight the genetic and physio-pathogenic advances concerning this immune deficiency.

II. CLINICAL SYMPTOMATOLOGY

The symptomatology of CVID is multifaceted, but recurrent respiratory tract and ENT infections are commonly present in more than 90% of patients. A number of patients are also thought to have an autoimmune disease, most often autoimmune cytopenia, which may begin several years before the diagnosis. Granulomatosis, particularly of the lungs or digestive tract, may also occur in some patients, leading to sarcoidosis-like symptoms.

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Follicular lymphoid hyperplasia may also develop, particularly in the lymph nodes, liver or spleen, and more rarely in the gastrointestinal tract. An increased risk of digestive and hematological cancers, has also been noted, and constitutes an important cause of death. CVID patients with at least one non-infectious complication have a higher morbidity/mortality risk than patients with only infectious complications [5,6].

III. DIAGNOSIS APPROACH OF HYPOGAMMAGLOBULINEMIA

Serum protein electrophoresis is the key test for the diagnosis of any hypogammaglobulinemia (Figure 1), and the first step in the CVID diagnosis. It is the only routine quantitative and relatively specific test to determine the global concentration of gamma globulin. This analysis can reveal hypo/hyper gammaglobulinemia, a potential presence of a narrow immunoglobulin peak, and even other qualitative abnormalities.

Furthermore, this test gives an accurate evaluation of albuminemia, which is an important element in the etiological diagnosis of hypogamma-globulinemia. The protein electrophoresis is often wrongly replaced by proteins profiling in routine. It allows by nephelometric analysis, a quantitative estimation of a large number of biological parameters (CRP, C3 and C4 complement fractions, orosomucoid, haptoglobin, albumin, IgG, IgA and IgM), but with insufficient precision concerning albuminemia and especially serum immunoglobulin concentrations. The diagnosis of hypogamma-globulinemia, is sometimes suspected with the presence of a decrease of one or more immunoglobulin fractions on the protein profile, and it should be confirmed by the serum protein electrophoresis.

The immunoglobulin and possibly the IgG subclass determination (Tables 1 and 2) should be requested in order to clarify the characteristics of hypo-gammaglobulinemia, as the different Ig classes and IgG subclasses are variably affected from a patient to another. To establish a hypogammaglobulinemia diagnosis, serum protein electro-phoresis should indicate a gamma globulin concentration below the lower limit of normal in at least two successive tests. This is usually between 6 and 8 g/l in adults but may differ depending on laboratories (Figure 1).

IV. ETIOLOGICAL DIAGNOSIS OF HYPOGAMMAGLOBULINEMIA

It is important to note that CVID diagnosis remains a diagnosis of elimination, which always requires the exclusion of other causes of hypogammaglobulinemia before holding a CVID diagnosis (Table 3). A rigorous etiological approach is necessary to any hypogammaglobulinemia, which will be guided by the clinical features and standard hematological and biological examinations, that should be completed by a serum protein electro-phoresis (Table 1).

Hypogammaglobulinemia associated to hypoalbuminemia.

If hypoalbuminemia is less than 30 g/l, it is important to search for a protein loss of renal origin (nephrotic syndrome) or less frequently, of digestive origin (exudative enteropathy). However, etiologies where hypoalbuminemia is associated to hypogammaglobulinemia are not limited to extra-corporeal protein leakage alone. Hypoalbuminemia may be observed transiently during an acute infectious episode. The association of hypogamma-globulinemia with transient hypoalbuminemia may also occur during the exceptional paroxysmal capillary hyperpermeability syndrome (acute episodes of severe collapse associated with hemoconcentration and hypoprotidemia/hypo-albuminemia) [7].

In addition, chronic hypoalbuminemia may be indicative of a long-lasting inflammatory process or undernutrition in a patient who already has hypo-gammaglobulinemia. Hypoalbuminemia may also occur in certain forms of multiple myeloma and may indicate a poor prognosis in these forms. It is important to remember that some patients with CVID may also have permanent hypoalbuminemia with no detectable cause in some cases (not explained by exudative enteropathy).

A. Hypogammaglobulinemia Without Hypo-Albuminemia

It is mainly classified into two major etiological groups: primary immunodeficiencies (PIDs) and lymphoid hematological diseases.

- *Primary Immunodeficiencies (Pids)*

- *Agammaglobulinemia*

In addition to CVID, other PIDs are associated or characterized by hypogammaglobulinemia. These are primarily agammaglobulinemia (Table 4) [8,9]. They are defined by less than 1g/L of gamma globulin serum concentrations and a major decrease or absence of circulating B-lymphocytes [10,11]. The most common form (90% of cases) is X-linked agammaglobulinemia (Bruton type), resulting from a mutation in the gene coding for BTK, a member of the tyrosine kinase family [12]. Autosomal forms (10% of cases) are usually the result of mutations in genes coding for one of the components of the pre-B receptor. The clinical picture is characterized primarily by recurrent neuro-meningeal, ENT, respiratory or digestive infections.

- *X-Linked Lymphoproliferation Syndrome (XLP or Purtilo Syndrome):*

In Purtilo syndrome, Male patients are generally healthy (although small abnormalities of immunity can be early detected) until a primary infection with Epstein Barr Virus (EBV), resulting in a severe mononucleosis infection associated to hemophagocytosis, that can be fatal. Survivors usually develop a severe hypogammaglobulinemia or non-Hodgkin's lymphoma type B. Recent studies have shown that mutations in the gene coding for the adaptor DSHP or SAP (signaling lymphocyte activating molecule associated protein) could be responsible for some cases of XLP. [13,14].

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- *Hyper-IgM Syndrome:*

Hyper IgM syndrome results in normal or elevated serum polyclonal IgM (and IgD) concentrations, in contrast with a significant decrease in other classes of immunoglobulins, suggesting an isotypic switching defect. Levels of gamma globulins determined by serum protein electrophoresis are variable, depending on IgM elevation. In the X-linked form, there is a mutation in the gene coding for CD40 ligand (CD154) [15,16]. These patients develop infections of the respiratory tract, gastrointestinal tract, biliary tract and central nervous system, including atypical germs infections [15,16].

- *Other Primary Immunodeficiencies:*

Hypogammaglobulinemia may occur in a variety of other DIPs: immunodeficiencies associated to growth hormone deficiency, ataxia telangiectasia (ATM gene mutation) [17], and various severe combined immunodeficiencies (SCID) whose clinical expression is usually dominated by a defect in cellular immunity [18,19]. In these patients, immunoglobulin production defect can be masked in the first months of life, by maternal IgG.

V. HYPOGAMMAGLOBULINEMIA ASSOCIATED WITH LYMPHOID MALIGNANCIES

➢ *Example of Chronic Lymphocytic Leukemia "CLL".*

In 20-25% of CLL cases, there is initially significant polyclonal hypogammaglobulinemia (<5 g/L) with or without monoclonal immunoglobulin [20,21]. Mostly, it remains asymptomatic, but when levels are below 3 g/L and IgG levels below 2 g/L, recurrent infections, especially bronchopulmonary infections may occur, requiring a therapeutic substitution with intravenous immunoglobulins.

Hypogammaglobulinemia may occur at the diagnosis of some non-Hodgkin's malignant lymphomas at a lower prevalence than in CLL.

In general, the presence of monoclonal immunoglobulin associated with a decrease in polyclonal fractions should imply a search for CLL type lymphoid malignancy, non-Hodgkin's lymphoma or myeloma. However, in a significant number of patients with PIDs, especially CVID, a monoclonal component may be observed, which implies the search for malignant lymphoplasmacytic disease. CVID diagnosis should be hold based on age of onset, clinical picture and in the absence of any underlying malignant clonal lymphoproliferation. Nevertheless, follow-up is always necessary in these cases, in order to detect any possible hematological malignancy.

➢ *Transient Hypogammaglobulinemia*

Hypogammaglobulinemia may occur in some cases with prolonged treatment with immunosuppressants or cancer chemotherapy, it is sometimes difficult to know whether it reflects an unknown underlying immune deficiency revealed by the treatment or whether the deficiency is entirely induced by the therapy.

Some hypogammaglobulinemia, such as IgA deficiencies, can be induced in children, especially newborns, by various viral infections (CMV infection, measles, rubella, HIV...) [8]. Transient hypogammaglobulinemia, usually mild, may occur in children. [9].

VI. GOOD'S SYNDROME

Good's syndrome (GS), or thymoma-associated immune deficiency, is a rare disease usually affecting adults between 40 and 70 years old. These patients typically have decreased or absent B and T cells, an inverted CD4+ and CD8+ T cell ratio, and reduced T cell response to mitogen [22].

VII. DIAGNOSIS CRITERIA FOR CVID

Various diagnosis criteria have been proposed. The definition published by the European Society for Immunodeficiency Diseases (ESID) and the Pan American Group for Immune Deficiency (PAGID) is commonly used [23,24]. The ESID/PAGID diagnosis criteria consist on three items (Table 5).

(http://esid.org/Working-Parties/Registry/Diagnosis-criteria, table5)

However, these criteria have many limitations: the first criterion requiring immunoglobulin levels to be two standard deviations below the average, can be met filled only in 2.5% of the general population. In clinical practice, patients with slightly reduced IgG levels would rarely be explored [25,26].

VIII. EUROCLASS CLASSIFICATION

In 2002, European studies suggested a “EUROclass” classification by flow cytometry in patients with CVID, according to the B cell phenotype [27,28]. This EUROclass trial involved a large cohort of patients with CVID from 8 European immunodeficiency centers, and aimed to determine a clinical and immunological phenotype of the CVID patients in Europe, and improve and standardize the classification system. The heterogeneity of common variable immunodeficiency (CVID) calls for a classification considering pathogenic mechanisms as well as clinical relevance. This European multicenter trial was initiated to develop a consensus of two existing classification schemes based on flow cytometric B cell phenotyping and the clinical features. The clinical evaluation of CVID diagnosed patients demonstrated a significant co-occurence of granulomatous disease, autoimmune cytopenia, and splenomegaly. Phenotyping of B-cell subpopulations confirmed a severe reduction of switched memory B cells in most of the patients that was associated with a higher risk of splenomegaly and granulomatous disease. An expansion of CD21 low B cells marked patients with splenomegaly. Lymphadenopathy was significantly linked with transitional B-cell expansion. Based on these findings and pathogenic consideration of B-cell differentiation, we suggest an improved classification for CVID (EUROclass), separating patients with nearly absent B cells (less than 1%), severely reduced switched memory B cells (less than 2%), and expansion of transitional (more than

9%) or CD21 low B cells (more than 10%). Whereas the first group contains all patients with severe defects of early B-cell differentiation, severely reduced switched memory B cells indicate a defective germinal center development as found in inducible constimulator (ICOS) or CD40L deficiency. The underlying defects of expanded transitional or CD21 low B cells remain to be elucidated [29].

IX. GENETICS

The CVID is highly heterogeneous phenotypically and genetically. Unlike many other PIDs, monogenic forms are reported only in 2-10% of patients with CVID. Genes that have been implicated in monogenic CVID include: ICOS, TNFRSF13B (TACI), TNFRSF13C (BAFFR), LRBA, TNFSF12 (TWEAK), CD19, ILCR2 (CD21), MS4A1 (CD20), TNFRSF7 (CD27), IL21R, CTLA4, PRKCD, PLCG2, NFKB1, NFKB2, PIK3CD, PIK3R1, CD81, VAV1, RAC2, BLK, IKZF1 (IKAROS) and IRF2BP2.

Due to the increasing number of these genes, it has become clear that many of these genetic defects cause distinct disease entities of CVID, whose diagnosis is confirmed by genetic analysis. In addition, evidence based studies show that at least one subgroup of CVID patients has a complex rather than monogenic inheritance [30,31].

X. PROPOSAL OF AN EXPLORATION STRATEGY IN CASE OF SUSPICION OF CVID

Patient's personal and family history collection is a very important step, and provides necessary elements such as repeated infections (sinusitis, bronchitis…), history of malignant or autoimmune diseases. The clinical examination seeks for lymphoproliferation (splenomegaly, hepatomegaly and peripheral lymphnodes) and signs in favor of an autoimmune or granulomatous disease.

Searching for target organs involvement is a systematic step. Thus, respiratory exploration will be realized by functional respiratory exploration and CT scan sections of the sinuses and lungs. The digestive exploration is essential in case of signs of digestive involvement.

When CVID is suspected, the first-line evaluation will include a blood test, 24-hour proteinuria, IgG, IgA, IgM or at least serum protein electrophoresis. After confirmation of hypogammaglobulinemia, the second-line test will consist on a quantitative analysis by flow cytometry of B, T and Natural Killer lymphocytes, combined with vaccine response tests. If a patient with recurrent infections has only IgA deficiency, IgG subclass testing may be done.

A third level of exploration is conducted by reference centers, such as the switched (CD27+IgD-IgM-) and unswitched (CD27+IgD+IgM+) memory B cells tests and other subgroups of B lymphocytes such as low CD21. Genetic analysis remains optional, it is not recommended to do it systematically, but usually, it is performed in research centers.

Currently, we are working on a classification procedure study based on B lymphocyte, to a better exploration of this disease.

XI. CONCLUSION

CVID is a heterogeneous syndrome, mainly due to a deficiency of antibodies, which makes the diagnosis and exploration easier following a methodical diagnostic approach. In the majority of cases, the disease is polygenic and multifactorial. Several trials have been attempted to classify CVID into several subgroups according to characteristic clinical and immunological criteria, using flow cytometry and functional B-cell memory assay. Different groups were identified and appear to have different clinical expression and prognosis, which would probably allow future management to be adapted for each of these groups. A comprehensive and more precise approach CVID classification by combining clinical-immunological and genetic data is being investigated.

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Table 1 Serum Contraction Values of Igg, Iga and Igm Determined by Nephelometry

	IgA	IgG	IgM
1-5 Days	0.07-0.22	7.00-13.00	0.04-0.20
5-10 Days	0.07-0.22	6.30-11.50	0.10-0.30
15-30 Days	0.10-0.30	4.60-8.60	0.20-0.65
1-6 mouths	0.10-0.62	3.00-4.50	0.30-0.80
6-12 mouths	0.30-0.86	2.80-5.50	0.40-1.20
1-3 years	0.40-1.22	4.50-8.00	0.50-1.50
3-7 years	0.45-1.50	5.30-10.00	0.50-1.50
7-10 years	0.50-1.60	6.00-12.00	0.50-1.5
10-12 years	0.60-2.00	6.30-12.00	0.50-1.50
Adult M (Men)	0.75-3.50	6.75-12.80	0.50-1.5
Adult W (Women)	0.70-2.60	6.70-12.35	0.70-1.50

Table 2 Value of Serum Contractions of Igg Subclasses

Age (years)	1-1.9	2-2.9	3.3.9	4-5.9	6-7.9	8-9.9	10-12.9	13-17	Adults
IgG1	3.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
IgG2	0.30	0.30	0.35	0.40	0.45	0.50	0.50	0.60	0.60
IgG3	0.12	0.13	0.15	0.16	0.17	0.17	0.17	0.17	0.17

Table 3 Hypogammaglobulinemia Associated with Hypoalbuminemia

Hypoalbuminemia(permanent ortransient)	Normal Albuminemia
-Nephrotic syndrome - Exudative enteropathy - Paroxysmal capillary leakage -Acute Infectious Episode overlap -Prolonged inflammatory state possible - Undernutrition	Primary Immune Deficiencies Lymphatic haemopathies Immunosuppressive treatments

** Cause of hypoalbuminemia in a patient already carrying Hypogammaglobulinemia

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Table 4 Major Causes Of Hypogammaglobulinemia To Be Excluded At The Time Of Diagnosis Of An CVID

Agammaglobulinemia: - X-linked: BTK gene mutation (Bruton) - Autosomal: gene mutation λ 5 From the heavy chain gene μ from Ig From the CD79a gene From the BLNK gene
Purtilo's syndrome (SAP mutation)
Hyper IgM syndrome - X-linked (CD154 gene mutation) - Autosomal (cytidine deaminase)
DIPs associated with growth hormone deficiency - Probably heterogeneous group
Severe combined deficits: - Adenosine deaminase deficiency - Purine phosphorylase deficiency - Gene mutation Ɣc (X-linked) - JAK3 gene mutation - Mutation of chain a of the IL7 receiver - Ommen Syndrome (RAG1/RAG2 gene mutation)

Table 5 PAGID/ESID Criteria for Making the Diagnosis of CVID.

At least one of the following criteria: - Increased sensitivity to infection - Autoimmune manifestations - Granulomatous disease - Unexplained polyclonal proliferation - Family history of immunoglobulin deficiency *And* - Important decrease of IgG and IgA levels (< 2DS) with /without decreased IgM levels *And* **At least one of the following criteria:** - Vaccine responses defects or lack of isohemagglutinin - switched memory B cell deficiency (<70% of normal per age) *And* - Exclusion of secondary causes of hypogammaglobulinemia *And* - Diagnosis after the age of 4 years *AnD* Absence of a T defect defined by two of the following three criteria: - CD4 < 200/ mm³. - Naïve CD4 < 10% of T cells - Absent T cell proliferation to mitogens and antigens

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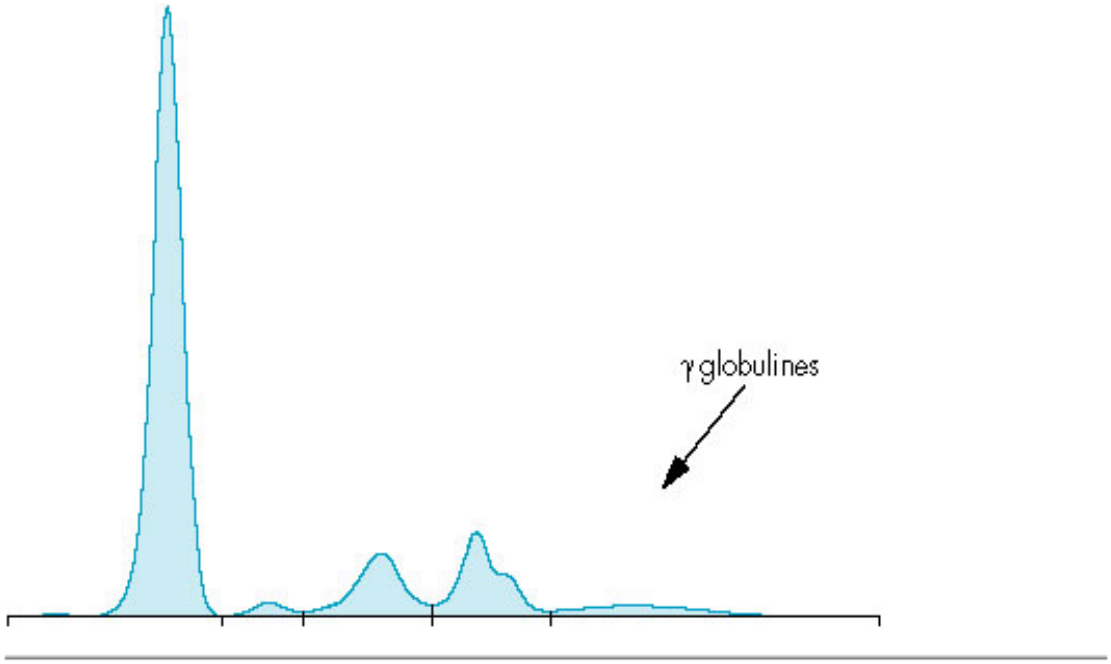

Fig 1 Serum Protein Electrophoresis Showing Hypogammaglobulinemia