PARTICULAR DIAGNOSIS AND TREATMENT FEATURES OF A CASE OF COMMON VARIABLE IMMUNOGLOBULIN DEFICIENCY ASSOCIATED WITH GLUTEN INTOLERANCE AND SEVERE MALABSORPTION SYNDROME

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Abstract. The authors present the case of a Common variable immunoglobulin deficiency (CVID) patient who has hypogammaglobulinemia, bowel involvement and severe malabsorption syndrome. Various problems related to positive and differential diagnosis are discussed within the framework of a very severe progression due to malabsorption syndrome with cachexia, numerous intercurrent pulmonary, intestinal, genital and skin infections and thrombophilia secondary to malabsorption. Eventually the course of disease is favourable partially thanks to the multidisciplinary approach undertaken.

Keywords: immunodeficiency, enteropathy, gluten, malabsorption, thrombophilia

Introduction

Specific to the common variable immunoglobulin deficiency syndrome (CVID) is the low level of serum immunoglobulins despite the normal number and morphology of the B lymphocytes. The incidence of the disease varies widely between 1:10,000 and 1:200,000, having an equal distribution among sexes [1, 2]. The late onset of intercurrent infections, usually in adolescence lead to the term “acquired hypogammaglobulinemia” although the conditions seems to have genetic origins causing altered lymphocyte B functionality [1,3]. Besides recurrent infections, oftentimes with opportunistic germs, the disease can involve various organs and systems; it can be associated with numerous autoimmune and granulomatous conditions and is quite often seen together with cancers of the hematopoietic system and the digestive tract, thus creating difficult differential diagnosis problems [4,5]. In spite of severe infections and organ complications, the diagnosis is established late most of the times, 1-10 years after the initial symptoms [5].

A multidisciplinary approach is necessary in order to diagnose and treat these patients in an effective manner [1].

Case report

Male patient, aged 32, presented with serious weight loss over the last year (10 kg) and diarrheic, liquid stools. No immunodeficiency or celiac sprue was present in family members. The patient suffered from viral hepatitis A one year ago, and repeated respiratory infections over the last years in the absence of smoking or alcohol as risk factors.

The physical examination showed a cachectic patient (Body mass index - BMI 12.7), hyperpigmentation of the skin, missing subcutaneous adipose tissue, calf oedema, no peripheral adenomegaly palpable liver and spleen.

The initial biological evaluation showed light anaemia, (hemoglobinemia: 121 g/L), with low serum iron levels (6.26 µmol/L) but normal mean cell volume (MVC 91.3 fL), white blood cell count 8420/mm³ with a normal leukocyte formula, normal morphology on the peripheral blood smear test, thrombocytes 153,000/mm³, low levels for the serum immunoglobulins: IgG 20 UI/ml, IgM 16 UI/ml, IgA undetectable. Immunophenotyping the leukocytes in peripheral blood flow shows no decrease of B: CD19+ 8%, CD56+ 2%, CD3+ 88% (30% Th, 58%Tc; Th/Tc 0.58), CD4 34.50%, CD4/
DNA undetectable, HCV ARN undetectable. Bac-
Ac HIV1,2 negative, HIV PCR undetectable, HBV
70, normal levels of plasma cortisol. Virology:
mg%, GOT 65 Ul, GPT 55 Ul, GGT 67 Ul, ALP
min 3.1 g%, cholesterol 78 mg%, triglycerides 45
70, SSA, SSB, ADN2C, RNP . Biology: serum albu-
negative, lack of anticentromere antibodies, SCL
HLA DQ typing: DQ alpha 1 negative, DQ beta 1
tissue transglutaminase Ab negative, CD8 0.67. Immunology: endomisium IgA Ab, IgG
by recurrent respiratory infections.
Diarrheic syndrome and nutrition overall aggravated
The evolution was positive, an improvement of the
manifestations caused by CVID the patient was
given oral corticotherapy, Prednisone 15mg/day.

The patient was soon started on iv immunoglobu-
ln until the low end of the range was reached, then
maintained for 6 months; metronidazole to treat the
Giardia lamblia infestation, without improvement –
malabsorption syndrome and diarrhoea were still
present. Then we considered gluten enteropathy as
a possibility, making the change to a gluten free
diet without any obvious subjective improvement
over the following 6 months but with a slight his-
tological one. Given the lack of response to therapy
for the celiac disease and the bowel autoimmune
manifestations caused by CVID the patient was
given oral corticotherapy, Prednisone 15mg/day.
The evolution was positive, an improvement of the
diarrheic syndrome and nutrition overall aggravated
by recurrent respiratory infections.

The low compliance to gluten free diet led after
2 years of steady progress to deterioration in the
nutritional status and repeated respiratory infec-
tions, the most common agents that were isolated
being Haemophilus influenzae, Pseudomonas ae-
ruginosa, Klebsiella pneumoniae. The antibiotic
therapy worked well, no secondary bronchiectasis
developed. Other infectious episodes included
orchiepididymitis, otitis media, leg skin infections
suggesting a streptococcal agent, enteric infections
caused by Giardia lamblia each time.

With a background of malabsorption and throm-
bophilia (protein S activity 33%, protein C and an-
tithrombin III normal) the patient later developed
bilateral iliofemoral deep vein thrombosis with a
good response to anticoagulants but with second-
ary necrosis in the right leg, possibly Coumadin
necrosis. The necrosis eventually led to loss of skin
covering the entire lower limb and repeated surgery,
immune and nutritional reanimation and skin grafts
with a favourable evolution – the limb recovered
its skin and function. The patient was put on low
molecular weight heparin for lack of other options
with an almost complete repermeabilization of the
deep veins in the lower limbs.

The current treatment consists of a hyperproteic,
hypercaloric gluten free diet, postural drainage
of the lower limbs and kinesiotherapy. The most
important therapeutic ingredient is intravenous
human immunoglobulin IgG (substitution therapy),
the minimal required dose in order to maintain
their serum level above the laboratory baseline be-
ing 20 grams per month, delivered on a fortnight
basis. The patient follows an immunosuppressive
treatment with prednisone 10 mg/day and anti-
coagulants – LMW heparins (enoxaparin 2x6000
UI/day). As a side effect of heparins and cortico-
therapy, osteoporotic lesions were noted that are
currently treated with bisphosphonates (ibandronic
acid 3 mg IV every 3 months), combined with al-
pha D3 1 µg/day and 1000 mg calcium salts. The
anti-infective treatment is customized to meet the
severity of the infection, its localization and the
exact nature of the agent when identified. We don't
use antibiotic prophylaxis. Tianeptine in a dosage
of 2x12.5 mg is our antidepressant of choice. Ac-
tive immunoprophylaxis is not indicated due to
insufficient antibody. Psychological counselling is
crucial to maintain compliance to diet and treat-
ment, to accept prolonged hospital stays, motor,
social, professional and family disabilities and to
allow for an increase in the overall quality of life.
The difficulties associated with getting a good
peripheral and central venous access force us to
consider a totally implanted device for long term
intravenous therapy in the near future.

**Discussions**
Our nosological framework was not accurate
since we couldn’t rule out a selective IgA deficit prior to CVID or an X-linked lymphoproliferative syndrome and we couldn’t explore the Epstein Barr infection given the lack of antibodies and the SH2D1A expression [6, 7]. We had no data to confirm gluten enteropathy, the microscopy showing lymphoid nodular hyperplasia and villi alterations without the typical findings of the celiac sprue. Glandular crypt hypertrophy and villous atrophy were to be expected in such a severe malabsorption syndrome [10]. Moreover the genetic tests for celiac disease were negative but cannot rule out the gluten enteropathy, the microscopy showing the SH2D1A expression [6, 7]. We had no data to confirm gluten enteropathy, the microscopy showing lymphoid nodular hyperplasia and villi alterations without the typical findings of the celiac sprue. Glandular crypt hypertrophy and villous atrophy were to be expected in such a severe malabsorption syndrome [10]. Moreover the genetic tests for celiac disease were negative but cannot rule out the condition. The good response to a gluten free diet strongly suggested the coexistence of CVID and gluten intolerance, extensively reported in medical literature [1, 2, 7].

A particular feature of the case is the severity of the malabsorption syndrome and of the diarrheic syndrome, responding quite well to corticotherapy and gluten free diet. The paradoxical good response to corticotherapy can be explained by the autoimmune involvement of the bowel [1, 3]. Any attempt to do without the corticotherapy led to an immediate aggravation of the condition, especially diarrhoea and malabsorption.

Despite countless infectious episodes, the response to antibiotics has always been very good. The most serious complication was the coeliac necrosis with a serious risk of losing the lower limb. We want to underline the fact that despite massive skin loss we managed to avoid infection and local suppuration by using isolation measures, asepsis, antisepsis, targeted antibiotic treatment and using the best known reparatory and reconstructive surgical techniques.

Among technical problems we should mention the very difficult IV access, the osteoporosis leading to motor inabilities and teeth loss making certain diets problematic.

Oncological monitoring was another challenge, the risk for lymphoma being 400 times bigger than in general population, and the risk for digestive cancer being also very high [1,7]. We practiced endoscopies and biopsies followed by immunophenotyping each year, also peripheral flow cytometry as often as needed and abdominal echography twice a year. We determined CA 19-9, CA 15-3, CA 72-4, AFP, CEA, tPSA on a yearly basis; in 2011 we recorded a moderate increase in CEA, CA 15-3 and CA 19-9 levels, but cannot confirm an oncologic pathology.

We consider short term prognosis to be good but the long term one remains reserved [4]. The potentially unfavourable evolution leads to suggesting biological therapy with anti TNF alpha antibodies as an option [1, 4, 7].

Conclusions
The common variable immunoglobulin deficit has a wide range of clinical manifestations including various organs and systems. There are real difficulties both regarding the positive diagnosis and treatment which has to be customized to meet the specific needs of the patient. A multidisciplinary approach is crucial in this respect. A great deal of effort is required to increase the quality of life due to the multisystem involvement caused either by disease or by therapy.

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References
6. Hammarstrom L, Vorechovsky I, Webster D. Selective IgA deficiency (SigAD) and common variable immunodeficiency (CVID). *Clin Exp Immunol* 2000; 120(2):225-231
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