Diagnostic and therapeutic difficulties in hypogammaglobulinemia in adults

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Abstract

Patients with rheumatic diseases have various abnormalities in immune system. One of these is hypogammaglobulinemia, that can be caused by different factors (medicines, genetic defects, infectious diseases, secondary immune deficiencies, neoplasms). Patients with primary immunodeficiency have higher incidence of autoimmune diseases. We report on clinical cases of hypogammaglobulinemia as a result of treatment with gold salts and hypogammaglobulinemia in a patient with spondyloarthropathy.

Key words: *hypogammaglobulinemia, common variable immunodeficiency, autoimmune disorders.*

(Centr Eur J Immunol 2007; 32 (1): 11-14)

Introduction

Patients with rheumatic diseases have various abnormalities in immune system. One of these is hypogammaglobulinemia, that can be caused by different factors (table 1). We aim at present patient cases with rheumatologic diseases with coexistent hypogammaglobulinemia.

Case 1: Hypogammaglobulinemia after treatment with gold salts

Fifty year old woman with rheumatoid arthritis diagnosed 5 years earlier was treated with sulfasalazine, D-penicilamine and glucocorticosteroids (prednisolon 5-7,5 mg/day). Because of high disease activity gold salts were started (injectable form – disodium aurothiomalate) which were continued for 18 months. Cumulative dose of gold salts was 1500 mg. Initially the therapy was well tolerated. After 5 months 50% improvement according to ACR was reached, which was sustained till the cessation of treatment. During the last 3 months of therapy patient had several infections of upper respiratory tract. Diagnostic tests showed gradual decrease of serum immunoglobulin levels, especially IgG, what was the reason why gold salts were stopped (table 2). Following treatment consisted of leflunomid. Four months later control serum tests were made, which showed the increase of immunoglobulin levels and there was no need for substitute therapy with IVIG.

Case 2: CVID and spondyloarthropathy

47year old woman was admitted to rheumatologic department because of ankle joints arthritis. She had a history of recurrent angina and bilateral uveitis. She had increased ESR (24 mm Hg) and positive test for chlamydia trachomatis from urethra and eye swab. She was diagnosed with reactive arthritis and treated with doxycycline and sulfasalazine. Treatment brought about partial improvement in arthritis, but 7 months later she was admitted again with polyarthritis and psoriatic skin changes. Chlamydia trachomatis was then negative. There was limited mobility of the spine. She was continuously treated with sulfasalasine and NSAID for 2 years.

At the age of 51 she was admitted again because of acute polyarthritis and fever to 39°C and swelling and erythema of eyelids. Laboratory evaluation showed an ESR of 76 mm Hg, CRP – 4,7 mg%, WBC 5900/mm^3 (13% lymphocytes). Lymphocyte T count was 284 and lymphocyte B – 138. HIV infection was excluded. Serum protein electrophoresis showed normal total protein level but only 6.4% gammaglobulin and decreased level of IgG, IgA and IgM.

IgG level was 393 mg%, IgA 33 mg% and IgM 36 mg%. There was neither rheumatoid factor nor ANA

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Table 1. Reasons of immunoglobulins deficits

Primary hopogammaglobulinemia	X-Linked Agammaglobulinemia Selective IgA deficiency Common Variable Immunodeficiency Hiper – IgM Syndrome (not related with chromosome X)
Hypogammaglobulinemia induced by drugs	Antimalarial drugs Captopril Carbamazepin Phenytoin Steroides Aurom salts Penicillamin Sulfasalazin
Secondary immunodeficiencies	Immunodeficiencies with increased immunoglobulins catabolism Immunodeficiencies with protein deficit-syndroma nephroticum Severe burns, lymphangiectasies Severe diarrhea
Infectious diseases	HIV infection Congenital roseola Congenital CMV infection Congenital Toxoplasmosis EBV infection
Cancers	Chronic limphocytic leucaemia Immunodeficiency with thymoma Non-Hodgkin lymphomas Plasmocythoma
Chromosomal disorders	Monosomia 22, Trisomia 8, Trisomia 2
Genetically determined diseases	Ataxia-Teleangietasia Autosomal SCID Hiper-IgM Syndrome Transcobolamin II deficit Brunon Disease X-limpho-proliferative syndrome (with EBV infection) Some of metabolic diseases

antibodies. Complement level was 128 UI/ml (N;66-146). In lymphocyte T test there was 20% T1 – early lymphocytes and 37% T2-late lymphocytes. Fluorescence method showed 18% B lymphocytes.

Blood and urine cultures were sterile. She was treated with amoxicilline – clavulonic acid, biodacine and with IVIG which caused disappearance of fever and remission of clinical symptoms. She was diagnosed with spondyloarthropathy and CVID. For the next 6 months she was treated with six doses IVIG. Control blood tests showed normal levels of inflammatory parameters, control test for Chlamydia trachomatis was negative. Clinically there persisted mild arthralgia and swelling of PIP and left ankle joint. There were no active psoriatic skin lesions. Because of recurrent anterior uveitis she was treated with local steroids.

Discussion

Case 1.

Many disease-modifying antirheumatic drugs, including gold, D-penicillamine, sulfasalazine, azathioprine, and cyclophosphamide, cause symptomatic hypogammaglobulinemia in some patients [1]. The exact mode of gold action in rheumatoid arthritis is unknown. Gold compounds alters macrophage and complement functions. Therapeutic effects include: inhibition of signal transduction, NF kappa B activation, inhibition of B cell activation, increase of IL-1ra production. About 40% of patients experience some toxicity. The most common reaction is dermatitis and proteinuria. Hematologic abnormalities occur in 1-2 % of patients – the most common is thrombocytopenia and leucopenia. When hematological adverse reactions occur gold should not be restarted. Parenteral gold was first associated with a significant decrease in serum gammaglobulin levels in 1973 by Strong et al. [2]. Hypogammaglobulinemia usually occurs in the first few months of therapy, affects patients of any age and has been associated in the majority of cases with recurrent bacterial infections.

The following mechanisms are considered:

- direct effect of gold on the humoral compartment of immunity [3],

Table 2. Serum immunoglobulin levels during therapy with gold

	Before therapy	4 month	18 month	4 month after therapy with gold
IgG mg%	727	598	552	682
IgA mg%	315	243	221	289
IgM mg%	78.8	38.4	29	67

- dysfunction of the regulatory monocyte-macrophage system [4],
- partial blockade of B-cell maturation at the early pre-B stage, with no apparent interference of serum factors [5].

In some cases hypogammaglobulinemia disappears after the treatment is stopped, in other substitute IVIG are needed. Other drugs which can potentially cause drug-induced hypogammaglobulinemia are sulfasalazine, D-penicillamine, azathioprine or cyclophosphamide. Hypogammaglobulinemia during treatment with DMARD is not prompting to stop this unless there are recurrent infections. The same holds true for IVIG treatment. These patients should however be closely monitored.

Case 2.

Reiter's syndrome, psoriatic arthritis, and the related spondyloarhropathies, have been reported to occur at greater than expected prevalence among HIV-positive individuals.

There are however only single case reports on coincidence of primary hypogammaglobulinemia, including CVID and spondyloatrhropathy.

Common variable immunodeficiency is a group of syndromes characterized by defective antibody formation and decreased serum antibody concentrations in at least two immunoglobuline isotypes. CVID has different course, that is why there are so many theories about its etiology, family and genetic factors predisposing to the disease. The diagnosis is made upon exclusion of other cause of humoral immune defects. CVID affects both genders equally, and often presents in young adulthood. Patients have recurrent bacterial infections, most often of the upper and lower respiratory tracts.

Among the 103 CVID patients observed by Cunningham -Rundles 22% had simultaneously autoimmune disorders. Before diagnosis of CVID two of them had colitis (in one case autoimmune colitis, in other ulcerative colitis). In one patient sacroilitis was found [6]. Ardenis et al describe a patient with CVID and arthritis due to Chlamydia pneumoniae. The patient had a history of recurrent respiratory tract infections, and the latest exacerbation was followed by arthritis. Chlamydia pneumoniae was detected in synovial fluid specimens by cell culture technique. Her nasopharyngeal swab and sputum culture specimens were also positive for this pathogen. Chlamydia pneumoniae should be kept in mind as a causative pathogen in patients with CVID and arthritis [7]. Patients with selective IgA deficiency are prone to developing seronegative spondylarthropathies, including ankylosing spondylitis [8]. Several patients have coexistent ankylosing spondyloarthropathy and symptomatic IgA deficiency [9]. In differential diagnostic in the case of our patient one should consider the decrease of immunoglobulin levels as a result of sulfasalazine treatment. Unfortunately immunoglobulin levels were not checked before the first administration of sulfasalazine. It should be emphasized that joint pain and arthritis present in the course of CVID are not especially responsive to DMARD treatment but disappear after treatment with intravenous immunoglobulins. This was also the case in our patient.

Conclusions

1. In diagnostics of patients with recurrent infections, especially bacterial, and joint pain one should always consider immune deficiencies.
2. In differential diagnostics of hypogammaglobulinemia one should consider secondary causes of decreased immunoglobulin levels:

- medication,
- autoimmune disorders,
- neoplasms,
- infections,
- states with protein loss [10].

References

1. Lee AH, Levinson AI, Schumacher HR Jr (1993): Hypogammaglobulinemia and rheumatic disease. Semin Arthritis Rheum 22: 252-264.
2. Strong JS, Bartholomew BA, Smyth CJ (1973): Immunoresponsiveness of patients with rheumatoid arthritis receiving cyclophosphamide or gold salts. Ann Rheum Dis 32: 233-237.
3. Stuckey BG, Hanrahan PS, Zilko PJ, et al. (1986): Hypogammaglobulinemia and lung infiltrates after gold therapy. J Rheumatol 13: 468-469.
4. So AK, Peskett SA, Webster AD (1984): Hypogammaglobulinaemia associated with gold therapy. Ann Rheum Dis 43: 581-582.
5. Guillemin F, Bene MC, Aussedat R, et al. (1987): Hypogammaglobulinemia associated with gold therapy: evidence for a partial maturation blockade of B cells. J Rheumatol 14: 1034-1035.
6. Cunningham-Rundles C (1989): Clinical and immunologic analyses of 103 patients with common variable immunodeficiency. J Clin Immunol 9: 22-33.
7. Ardeniz O, Gulbahar O, Mete N, et al. (2005): Chlamydia pneumoniae arthritis in a patient with common variable immunodeficiency. Ann Allergy Asthma Immunol 94: 504-508.

8. Pipitone N, Fioravanti A, Marcolongo R, et al. (2001): Articular involvement in the course of primary hypogammaglobulinemia. Recenti Prog Med 92: 63-67.
9. Herrero-Beaumont G, Armas JB, Elswood J, et al. (1990): Selective IgA deficiency and spondyloarthropathy: a distinct disease? Ann Rheum Dis 49: 636-637.
10. Swierkot J, Lewandowicz-Uszynska A, Jankowski A, et al. (2005): The arthritic pathologies accompanying primary immunodeficiencies with antibody synthesis disturbances. Postepy Hig Med Dosw (Online) 59: 219-223.