Lifelong immunoglobulin replacement is not always necessary: A case description of a patient with recurrent infections and hypogammaglobulinemia

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Abstract

Humoral immunodeficiency with accompanying infections is an indication for human immunoglobulin replacement therapy. Whether treatment will be lifelong or necessary only temporarily depends on the nature of deficiency: primary (persistent) or secondary (persistent or transient). It is not always easy to distinguish between primary and secondary immunodeficiency, especially in adults. The article presents a case of a 39-year-old patient with anamnesis and medical tests results that suggested primary humoral immunodeficiency. The deficiency was diagnosed for the first time at the age of 38, when the patient was pregnant. The patient was qualified for immunoglobulin G replacement therapy. Clinical improvement was achieved. After the end of pregnancy, systematic improvement in immunological parameters was observed, suggesting the resolution of immunodeficiency. A decision was made to discontinue immunoglobulin replacement. Due to the ability to respond to vaccine, confirmed during diagnosis, preventive vaccines were recommended. There was no recurrence of serious infections. The clinical course finally enabled a diagnosis of secondary immunodeficiency. The presented case shows the importance of an active approach to the diagnostic and therapeutic process, constant assessment of clinical course, monitoring of IgG concentrations, and the awareness that in the situation when we do not have a genetic confirmation of the disease, the diagnosis may change.

Keywords

Introduction

The replacement of human immunoglobulin IgG is a treatment method used in the case of a deficiency of this antibody class. In the case of primary immunodeficiency (PID), treatment has to be continued lifelong. Such a situation takes place, among others, in common variable immunodeficiency (CVID) or X-linked agammaglobulinemia (XLA). In some cases, replacement is indicated at normal IgG concentrations, but with a deficiency of IgG subclasses or selective polysaccharide antibody deficiency (SPAD), especially when these deficiencies occur

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with problematic infections. In secondary humoral immunodeficiencies, which are accompanied by infections, there are often indications only for temporary replacement of human immunoglobulins.[1] At the time of diagnosis, it is not always easy to distinguish whether the immunodeficiency is primary or secondary. Therefore, it is highly important to perform necessary tests before starting immunoglobulin supplementation, and if this is not possible, preserve the blood for the analyses that will be conducted at a later time. There are numerous tests that cannot be performed during immunoglobulin supplementation, for example, assessment of the ability to produce specific antibodies, and their results could facilitate the decision concerning possible discontinuation of the replacement therapy.

The case presented below shows that in spite of the anamnesis and results of medical tests suggesting PID, it is important to monitor the patient's condition, clinical course of deficiency as well as immunoglobulin concentration during treatment. When we do not have a genetic confirmation of the disease, the diagnosis should always be considered as "possible" or "probable," which means that it can be changed. Discontinuation of immunoglobulin replacement is the consequence of changing the diagnosis and resolution of the deficiency. It has to be remembered that in many cases they are drugs of choice and save lives; however, they are not free from side effects. Therefore, their use, especially long-term, must be justified.

Materials and methods

The patient gave her informed and signed consent to participate in the study.

Case report

A 39-year-old woman diagnosed with hypogammaglobulinemia with deficiency of IgG1 and IgG2 subclasses found a year earlier, when the patient was at 28 weeks of gestation (second pregnancy). PID was suspected because of outpatient unsuccessful treatment of left-sided pneumonia accompanied by acute bronchitis and a history of infections. The patient has experienced an increase in the incidence of recurrent sinusitis (several times a year), four episodes of pneumonia, and bronchitis in the last 2 years. Before pregnancy, the patient had been professionally active (working in a cold store). She underwent appendectomy at the age of 13 and had not taken any medicines. She had given birth to one healthy child. Also in childhood, the patient suffered from upper respiratory tract infections and bronchitis, and until the appearance of the previously mentioned problematic infections, she had severe sinusitis periodically. Additional tests revealed leukocytosis and elevated C-reactive protein (CRP) level. The treatment included antibiotic therapy (cefuroxime), nebulization (budesonide), a probiotic, and paracetamol on demand. There was no satisfactory improvement: a tiring cough and shortness of breath persisted. Therefore, after 5 days, another medical consultation took place. Because the consultant internist was also a clinical immunologist, he took a detailed medical history for infections and recommended wider diagnosis for humoral immunodeficiency and modification of treatment: systemic steroid therapy (hydrocortisum); increased the frequency of budesonide inhalation; in case of dyspnoea, 1–2 puffs of salbutamol were recommended; and antibiotic therapy was modified (cefuroxime was discontinued and erythromycin was given).

Immunological tests revealed deficiency of total IgG and IgG1 and IgG2 subclasses. The results were as follows: IgG=488 mg/dL (N: 700–1600 mg/dL), IgG1=333 mg/dL (N: 405–1011 mg/dL), and IgG2=141 mg/dL (N: 169–786 mg/dL). IgA and IgM concentrations were normal. The total protein concentration was low at 4.88 g/dL (N: 6–8 mg/dL). The concentration of anti-tetanus toxoid antibodies in the IgG class was normal, indicating the preserved ability to vaccine response. Unfortunately, despite the importance of the determination of antibodies against *Salmonella typhi* in the IgG class in the diagnosis of PID, this test was not available in the hospital where the patient was staying. A preliminary clinical diagnosis was established: "Hypogammaglobulinemia with deficiency of IgG1 and IgG2 subclasses. Suspected primary immunodeficiency." According to the European Society for Immunodeficiencies (ESID), the patient met the criteria of unclassified antibody deficiency. A preparation of human intravenous immunoglobulin (IVIG) was given at 0.4 g/kg body weight. After clinical improvement, the patient was discharged home, and continuation of immunoglobulin replacement every 3–4 weeks was recommended as well as IgG monitoring prior to each IVIG infusion. In the 34th week of pregnancy, the patient was admitted to the obstetrics clinic due to a threat of premature delivery. The patient had a natural delivery

and gave birth to a premature daughter with birth weight of 1840 g, the Apgar score 9. Despite the IVIG infusion performed 2 weeks earlier, the concentrations of IgG and IgG1 and IgG2 subclasses were lower than before the infusion (381, 245, and 123 mg/dL). Again, before delivery, IVIG was given, hoping for the chance of transferring immunoglobulins to the fetal circulation.

After delivery, IVIG infusions were continued every 4 weeks. In addition, the patient was diagnosed with bronchial asthma (in spirometry with a histamine challenge, reduction of FEV1 by 23%). Inhaled glucocorticosteroids and beta-2 mimetics were continued. During the third hospitalization, it was noticed that the IgG concentration before the administration of the next dose of immunoglobulins increased significantly and amounted to 1170 mg/dL, and in the following month, it was 1010 mg/dL. A decision was made to discontinue immunoglobulin replacement and give additional immunizations due to the correct vaccine response observed at the time of diagnosis. The patient completed pneumococcal vaccination (PCV 13), *Haemophilus influenza*, and meningococcus (Men ACYW and Men B) vaccines. The vaccination against influenza virus was recommended every year. Follow-up concentrations of immunoglobulins in the main classes and IgG 1–4 subclasses 2 and 5 months after discontinuation of immunoglobulins were within normal range. Infection problems resolved. Finally, a secondary humoral immunodeficiency was diagnosed due to a correct vaccination response and normalization of immunoglobulin concentrations.

Discussion

To facilitate the diagnosis, Jeffrey Model Foundation developed 10 warning signs of PID in adults.[2] Symptoms include two or more sinusitis (without allergy symptoms) and one incident of pneumonia within a year. The patient met both of these criteria. Also in childhood, the patient suffered from upper respiratory tract infections and bronchitis, and until the appearance of the previously mentioned problematic infections, she had severe sinusitis periodically. In addition, the patient had a marked decrease of concentration of total IgG, did not take any drugs that could affect the concentrations of antibodies, *and* T lymphocyte disorders were excluded. She did not have any other chronic diseases. Therefore, a

PID was suspected.[3,4] A preliminary clinical diagnosis was established: "Hypogammaglobulinemia with deficiency of IgG1 and IgG2 subclasses. Suspected primary immunodeficiency." According to the guidelines of ESID, the patient met the criteria of unclassified antibody deficiency.[5]

One of the diagnostic tests performed in order to diagnose PID is the assessment of vaccine response, both after the administration of protein antigens[6] as well as polysaccharide ones.[7] It is important to perform this test before the first administration of immunoglobulins, since they are present in these preparations.[8] A correct vaccine response excludes some immunodeficiency and also allows the use of preventive vaccination for immunostimulation, and as a result, there may be no indications for immunoglobulin replacement. However, for most vaccines, gestation is a temporary contraindication to their use (lack of tests confirming their safety for the mother and the fetus). The exception is vaccination against influenza and pertussis.[9]

It has been shown that decreased IgG values are associated with a higher risk of serious infections and their complications. However, in some cases, supplementation should be given at even normal IgG concentrations (among others, in the absence of a vaccine response). The most important criterion for the human immunoglobulin replacement is the clinical condition of the patient and vaccination response.[10]

Primarily due to the clinical picture and additional reduction of total IgG concentration in the presented case, a decision was made to give human immunoglobulin preparation at a supplementation dose of 0.4 g/kg of body weight.[1] Because PID was suspected, the patient was qualified for permanent replacement of human immunoglobulins. The only parameter that raised doubts was the reduction in total protein concentration. The patient, however, was not diagnosed with any diseases that could cause defects in protein synthesis.[3,4] So far, there were also no studies available that would confirm that such low levels of IgG can be the result of only pregnancy.

Because 3 months after delivery, the concentration of IgG before the next transfusion was significantly higher, an effective attempt to discontinue treatment was made. Concentrations of IgG and IgG subclasses 2 were normal 5 months after IVIG withdrawal. The half-life of serum IgG is 23.1 days on average.[11] Thus, the normal high immunoglobulin values before

drug administration in the third and fourth month of replacement and correct IgG levels after discontinuation of therapy were the result of the patient's normal production of endogenous antibodies. Therefore, the diagnosis of humoral immunodeficiency was verified from primary to secondary.

A thorough analysis of the anamnesis revealed that the patient worked in a cold store, that is, variable temperature conditions, which could have contributed to an increase in frequency and severity of infections. Due to the undiagnosed, and thus untreated, bronchial asthma, additional immunoglobulin binding could have occurred as a result of an active inflammation.[3,4] Another, and it seems that the most important, reason for the reduced IgG concentration was pregnancy and the transport of immunoglobulins to the fetal circulation, because only this class of antibodies crosses the placenta. This transport is dependent on total IgG concentration and specific maternal antibodies, gestational age, placental integrity, IgG subclass, and the nature of antigen. This concerns both endogenous and exogenous immunoglobulins transfused during pregnancy.[12] Intravenous glucocorticosteroids were used to treat pneumonia and bronchitis, which could have additionally contributed to the lack of expected improvement after the first IVIG transfusion. Significant influence of systemic steroids on the production of immunoglobulins has been confirmed in many studies.[3,4]

Changing environmental conditions (giving up work in a cold store), correct treatment of bronchial asthma, termination of pregnancy, and recommended vaccinations after discontinuation of immunoglobulin supplementation probably contributed to the resolution of infection problems in the patient.

The presented case shows that immunoglobulin replacement in patients with humoral immunodeficiencies manifested by recurrent respiratory infections should always be approached with great caution. Evaluation of the vaccine response before starting immunoglobulin supplementation is not only a criterion for exclusion of some PID but also may facilitate a decision about the need to begin, continue, or stop immunoglobulin supplementation.

We must always remember about secondary immunodeficiencies, even if the anamnesis suggests a congenital background of the disorder. Lack of monitoring the treatment or misinterpretation of results may lead to unnecessary lifelong supplementation, and this increases the risk of complications and causes restrictions in the patient's life. In the absence of a definitive PID diagnosis, which is possible with the genetic confirmation of the defect, it should always be remembered that the diagnosis may change and, as a consequence, indications for immunoglobulin replacement may subside. Although immunoglobulins are, in many cases, the drug of choice, also in secondary immunodeficiencies, they are not free from side effects. The cost of therapy is also very high. Therefore, their use, especially long-term, must be fully justified. It should be remembered that the indications should be re-evaluated systematically depending on the nature of deficiency (primary or secondary).

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References

1. Pecoraro A, Crescenzi L, Granata F, et al. (2017) Immunoglobulin replacement therapy in primary and secondary antibody deficiency: The correct clinical approach. *International Immunopharmacology* 52: 136–142.
2. Jeffrey Modell Foundation (2013) 10 warning signs. Available at: http://www.info4pi.org/aboutPI/index.cfm?section=aboutPI&content=warningsigns
3. Srivastava S and Wood P (2016) Secondary antibody deficiency—Causes and approach to diagnosis. *Clinical Medicine* 16(6): 571–576.
4. Dhalla F and Misbah SA (2015) Secondary antibody deficiencies. *Current Opinion in Allergy and Clinical Immunology* 15(6): 505–513.
5. ESID Registry 2017. Available at: https://esid.org/Working-Parties/Registry/Diagnosis-criteria
6. Nobre FA, Gonzalez IG, Simao RM, et al. (2014) Antibody levels to tetanus, diphtheria, measles and varicella in patients with primary immunodeficiency undergoing intravenous immunoglobulin therapy: A prospective study. *BMC Immunology* 15: 26.
7. Parker AR, Bradley C, Harding S, et al. (2018) Measurement and interpretation of *Salmonella typhi* Vi IgG antibodies for the assessment of adaptive

immunity. *Journal of Immunological Methods* 459: 1–10.

8. Novaretti MCZ and Dinardo CL (2011) Immunoglobulin: Production, mechanisms of action and formulations. *Revista Brasileira de Hematologia e Hemoterapia* 33(5): 377–382.

9. O'Shea A, Cleary B, McEntee E, et al. (2018) To vaccinate or not to vaccinate? Women's perception of vaccination in pregnancy: A qualitative study. *BJGP Open*. Epub ahead of print 4 April. DOI: 10.3399/bjgpopen18X101457.

10. Jolles S, Chapel H and Litzman J (2017) When to initiate immunoglobulin replacement therapy (IGRT) in antibody deficiency: A practical approach. *Clinical and Experimental Immunology* 188(3): 333–341.

11. Fokkink W, Koch B, Ramakers C, et al. (2017) Pharmacokinetics and pharmacodynamics of intravenous immunoglobulin G maintenance therapy in chronic immune-mediated neuropathies. *Clinical Pharmacology and Therapeutics* 102(4): 709–716.

12. Palmeira P, Quinello C, Silveira-Lessa AL, et al. (2012) IgG placental transfer in healthy and pathological pregnancies. *Clinical and Developmental Immunology* 2012: 985646.