ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 8| Issue: 9| September 2022|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2022: 8.205 || ISI Value: 1.188

HEADACHE AS AN ADVERSE EFFECT OF IMMUNOGLOBULIN ADMINISTRATION FOR SELECTIVE IMMUNOGLOBULIN G DEFICIENCY

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Article DOI: https://doi.org/10.36713/epra11187
DOI No: 10.36713/epra11187

SUMMARY

INTRODUCTION: *IgG subclass deficiency was described by William Terry in a patient with recurrent infections. Selective IgG subclass is defined as a significant decrease in serum concentration of 1 or more IgG subclasses with normal total IgG, IgA and IgM levels. Persistent low serum levels of one or more immunoglobulin G (IgG) subclasses may be found in a high proportion of adult patients with increased susceptibility to infections (17). This deficiency has been described in association with other primary immunodeficiencies, including: selective IgA deficiency, selective IgM deficiency and Ataxia-Telangiectasia, growth hormone deficiency, Down syndrome, cystic fibrosis, among others (1).*

CLINICAL CASE:*We present the clinical case of a 28-year-old female patient with a history of selective immunodeficiency to IgG immunoglobulin, repeated urinary tract infections, repeated vaginal infections and herpes simplex II infection, all of which have been treated, She went to a hospital in Morona Santiago three days ago for presenting, as the apparent cause, administration of immunoglobulin for a basic illness, a mild holocranial headache that evolved into a severe headache, accompanied by nausea that led to vomiting on one occasion, for which she was admitted to the hospital for pain management. Complementary examinations showed that there was no metabolic alteration or neurological deterioration, which is why she was classified as an adverse effect of the administration of immunoglobulin 3 days earlier.*

EVOLUTION:*The patient was admitted for pain management due to severe headaches, multiple analgesics were administered without adequate response, so it was decided to start a tramadol infusion pump. During the following hours of hospitalization she remained with a feeling of nausea and weakness, however, the headache gradually subsided and it was decided to discontinue analgesic medication to assess the response of the clinical picture, and she was discharged 24 hours after admission with a favorable evolution.*

CONCLUSIONS: *IgG subclass deficiency is a pathology characterized by the fact that it occurs in women over 16 years of age, with a very low prevalence; the presence of respiratory pathologies gives rise to the suspicion of this disease. The treatment of this pathology is based solely on the intravenous or subcutaneous administration of Immunoglobulin G, together with the concomitant treatment of the infections that the patient presents. Adverse effects should always be taken into account, as they are temporary, but quite disabling.*

KEYWORDS: *Headache, Immunoglobulin G, Urinary Tract Infections, Herpes Simplex*

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INTRODUCTION

Usually, IgG subclass deficiency is characterized by frequent or severe upper or lower respiratory tract infections, which are not explained by other causes. The disease predominates in females, starting in those over 16 years of age; its frequency is 1 per 10,000 persons. The IgG1 and IgG2 subclasses are determinants that are generally found to be abnormal in adults. Factors associated with this pathology are: age at diagnosis, female sex, autoimmune conditions, atopy, serum IgG, IgA and IgM levels (3)(16). Infectious complications, especially repeated viral infections, are the most common manifestations, followed by lower respiratory tract infections, such as pneumonia. In some studies, it has been associated with bronchiectasis and increased hospitalisations for chronic obstructive pulmonary disease (4). This disease results in susceptibility to respiratory tract infections, such as pneumonia, recurrent sinusitis. However, non-infectious complications may occur due to the B-cell phenotype (11).

Measurement of immunoglobulin G subclasses has been used for screening patients with chronic diseases. A study by De Vries has suggested that measurement of the immunoglobulin G subclass be measured after measurement of total IgG, IgA and IgM if IgG is greater than 4 gr/L. IgG assessment is useful as part of the evaluation in the study of patients with a history of repeated infections. In addition, this test is requested in patients with low IgA and should be monitored in IgG deficient patients with progression to a common variable immunodeficiency. In general, measurement of the IgG subclass is an important test that provides a comprehensive picture of the humoral system. IgG concentrations are usually measured on the basis of radial immunodiffusion and by ELISA. All methods provide a quantitative measurement of IgG subclass concentrations and with a high sensitivity of detection of IgG subclass concentrations. For the diagnosis of this pathology, 1 or more IgG subclass concentrations lower than the fifth percentile are required in the presence of normal IgG, IgA and IgM concentrations. Abnormal concentrations should be confirmed at least 1 month after the first test (6).

TREATMENT

For most patients, administration should be every 3 to 4 weeks. The dose to be used is 0.3 to 0.5 g/kg every 3 weeks or 0.4 to 0.6 g/kg every 4 weeks. Generally in initial doses, a loading dose of 1 g/kg is given. Thrombotic risk, haemolysis and renal complications are exacerbated by high and rapid infusion doses. Sometimes, administration of this medication leads to anaphylactic reactions in patients with IgA deficiency (10). Monthly IVIG significantly improved quality of life, decreased the number of infections and the need for antibiotics, and improved IgG subclass and serum antibody levels (18).

To produce the immunoglobulins to be administered, as many pathogens, especially viruses, are removed. However, there is a small risk of transmission of these pathogens. All available immunoglobulin replacement products contain more than 95% immunoglobulins with all IgG subclasses. Most products do not contain IgM (to avoid large complexes generating adverse reactions) and contain a small amount of IgA. Thanks to early diagnosis, IgG treatment has become more effective; along with survival, which has improved considerably in the last decade, leading to a reduction in the frequency and severity of infections. However, patients with autoimmune complications and neoplasms remain with a low life expectancy. Initiation of IgG replacement is with IgG levels less than 2 g/L, in patients with recurrent infections, and specific antibody deficiency with IgG levels between 2 and 5 g/L; and patients with IgG greater than 5 g/L with recurrent and severe infections. The initial dose should be considered between 400 mg/kg/month and 100 mg weekly. Levels should be greater than 3 g/L compared to baseline (9).

COMPLICATIONS

As mentioned above, the most frequent complications are lung diseases. Therefore, most of them should be evaluated with high-resolution computed tomography. The most frequent complications to be found are: Bronchiectasis, bronchospasm, obstructive lung disease and granulomas. The risk of developing cancer is between 4 and 25%, with an estimated incidence of malignant neoplasms of 10% (Hodgkin's lymphoma and gastric carcinoma) (15).

ADVERSE EFFECTS OF IMMUNOGLOBULIN G TREATMENT

About 40% of patients receiving immunoglobulin infusion are accompanied by adverse effects within 72 hours. These symptoms include headache, nausea, musculoskeletal pain, tachycardia, flushing, chills and fever (8). These adverse effects can be managed by decreasing the infusion or stopping it. Symptoms may be relieved by acetaminophen, NSAIDs or antihistamines. In some patients, corticosteroids may be needed. To avoid these adverse effects, you can start with a slow infusion and gradually increase the infusion. In general, the infusion rate should not exceed 0.08 ml/kg/min of the 10% IgG solution. With repeated administration of the immunoglobulins, these reactions decrease in severity. Headache is the most common adverse effect, and the most commonly reported. This symptom begins 24 to 48 hours after the immunoglobulin infusion. Most headaches resolve within 24 hours, but severe headaches last up to 72 hours. In a small number of patients, particularly with a history of migraine, it is usually accompanied by nausea and vomiting. Occasionally, headaches may be accompanied by fever. Generally, severe headache is more frequent in patients with high doses of immunoglobulin (1 - 2 g/kg); sometimes, it can lead to meningeal irritation. In cases of migraine, the use of anti-migraine preparations is suggested, which can be used again in case of recurrence. In addition, there is evidence of benefit from the administration of glucocorticoids (0.5 - 1 mg/kg prednisone or equivalent) (5).

CLINICAL CASE

A 28-year-old female patient with a history of selective immunodeficiency to IgG immunoglobulin, repeated urinary tract infections, repeated vaginal infections and herpes simplex II infection, all of which have been treated, attended a hospital in Morona Santiago on 28/5/2021 because she had

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presented for the last 3 days and as the apparent cause, administration of immunoglobulin for a basic illness, a picture of mild holocranial headache (3/10 on the VAS scale), which evolved 24 hours later, She had been receiving immunoglobulin for her underlying disease for three days and had a mild (3/10 on the VAS scale), pulsatile holocranial headache, which progressed 24 hours later to a severe headache (8/10 on the VAS scale), for which she self-medicated with paracetamol and diclofenac with partial improvement. However, 10 hours before her admission, she again presented a picture of severe headache, which increased on movement and was accompanied by nausea leading to vomiting on 1 occasion, for which she was admitted to the hospital for pain management.

PERSONAL BACKGROUND

1. Primary selective IgG immunodeficiency, since 3 months, with treatment started on 25/5/2021 with 30 grams of immunoglobulin to be administered monthly.
2. Recurrent urinary tract infection, approximately every 20 days. Last episode was 3 months ago. Current treatment with Trimethoprim + Sulfamethoxazole 800/160 milligrams orally every day.
3. Repeated vaginal infections, last episode 1 month ago treated with cefuroxime.
4. Herpes simplex type II infection, last episode 4 months ago. Treated to date with acyclovir 400 milligrams orally every day.

FAMILY HISTORY: Does not refer

PHYSICAL EXAMINATION

Blood Pressure: 110/60 mmHg, Heart Rate: 110 bpm, Respiratory Rate: 24 rpm, Temperature: 36.7 C, Capillary refill 2 seconds, O2 Sat: 93%,

General appearance regular, atraumatic head, normal implantation of hair, presence of positive time points, eyes: isochoric sclerae, light reactive.

Mouth: oral mucous membranes moist, oropharynx not congestive, chest with preserved vesicular murmur, preserved frémito, no added sounds, abdomen with active hydro-aerial sounds, pain on deep palpation in the mesogastrium, symmetrical limbs, strength and tone preserved. Neurological examination: vigil, oriented in time, space and person, no neurological alteration is evident. Absence of nuchal rigidity, negative Kernig and Brudzinski signs, coordination without alteration.

DEVELOPMENTS

Patient admitted on 28/5/2021 for pain management due to severe headaches, multiple analgesics are administered, including: Tramadol 300 milligrams diluted in 250 milliliters of sodium chloride 0.9%, going to 4 milliliters/hour, Ketorolac 30 milligrams via venous every 8 hours, Paracetamol 1 gram orally every 8 hours, Metoclopramide 10 milligrams via venous every 8 hours, and her basic medication. Laboratory tests were carried out, and there was no evidence of infection or metabolic alterations. During the following hours of hospitalization, she remained with a feeling of nausea and weakness of lesser intensity, and her headache gradually subsided, so it was decided to discontinue analgesic medication to assess the response of the clinical picture, and she was discharged 24 hours after admission with a favorable evolution with a diagnosis of drug-induced headache and selective deficiency of subclasses of immunoglobulin G. She was sent home with signs and symptoms of headache. She was sent home with indications of alarm signs, Diclofenac 50 milligrams orally every day and Tramadol 50 milligrams orally for necessary reasons.

Table 1. Blood Biometry

Leukocytes	5480
Neutrophils	78
Lymphocytes	
Platelets	259000
Haematocrit	39.3
Haemoglobin	12.7

Source: Morona Santiago Hospital

Table 2. Blood Chemistry

Glucose	77.9
Urea	15.8
Creatinine	0.64
Cholesterol	126
Triglycerides	51.6
LDL	
TGO	11.5
TGP	7.40
Total protein	6.39
Albumin	3.9
Globulin	2.49

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PCR	2.2
Potassium	
Sodium	
Chlorine	106.8
Uroanalysis	Negative

Source: Morona Santiago Hospital

DISCUSSION

One of the factors studied in a review of 2020 showed that the age at diagnosis, the predominance of the female sex and the presence of recurrent infections, especially respiratory infections (although not only of the respiratory tract), atopy, allergies, autoimmune conditions, are the determinants of the diagnosis of this disease. In our patient, age, female sex and the frequency of genitourinary tract infections led to the suspicion of this disease (12)(13).

In a study conducted in 2021 with 20 patients analyzed, it was reported that 10 patients had rash, 3 patients had headache, 3 patients had pain at the puncture site, 2 patients had chills and 2 patients had fever (7). In the present clinical case, there was evidence of mild headache that increased in intensity over the hours until it became intolerable 72 hours after administration of immunoglobulin G; the condition was accompanied by nausea that led to vomiting on 1 occasion. Therefore, the patient was managed with strong analgesics and antiemetics.

A study conducted in 2020 compared the frequency in subgroups of 269 patients with selective IgG deficiency. The association of HLA-A and B with the frequency of IgG deficiency in patients was found (2). Because the patient was seen in a basic hospital, limited testing was a major limitation in arriving at the association of this patient with HLA-A or HLA-B types.

In a 2003 study, which reported adverse effects in 955 patients after IgG infusion, 4.7% of patients had headache (although they did not report whether the infusion rate was high or low) (14). In our patient, the diagnostic suspicion of IgG post-infusion headache was made because of the multiple history of infections and the frequency with which this symptom is present after immunoglobulin administration (24-72 hours).

CONCLUSIONS

IgG subclass deficiency is a pathology characterized by the fact that it occurs in women over 16 years of age, female, and with a very low frequency; the presence of respiratory pathologies gives rise to suspicion of this disease. The treatment of this pathology is based solely on the intravenous or subcutaneous administration of Immunoglobulin G, together with the concomitant treatment of the infections that the patient presents. Adverse effects should always be taken into account, as they are temporary, but quite disabling. There is sometimes a need to control adverse effects, and in some cases, to prevent them with appropriate and slow administration of Immunoglobulin G.

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Volume: 8| Issue: 9| September 2022|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2022: 8.205 || ISI Value: 1.188

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