ASBAI
Arquivos de Asma, Alergia e Imunologia

Opportunity screening for inborn errors of immunity: what is calculated globulin?

Arq Asma Alerg Imunol. 2024;8(1):85-6.
http://dx.doi.org/10.5935/2526-5393.20230079-en

Dear Editor,

It is estimated that more than 100 medical appointments are necessary for patients with inborn errors of immunity (IEI), formerly known as primary immunodeficiencies, to be diagnosed.[1] This delay significantly impacts the patient, who often develops sequelae that could have been avoided with earlier detection.

Some laboratory tests are related to immunodeficiencies and can help identify patients who may have undiagnosed IEI. In this context, opportunistic screening is invaluable to reduce the diagnostic delay of IEI.[2]

Immunoglobulin G (IgG) plays a key role in the diagnosis of many IEI, and low IgG levels affect several routine medical laboratory tests, such as protein electrophoresis and the measurement of total proteins and protein fractions.

Calculated globulin (CG) is defined as the plasma total protein minus albumin and is reduced in patients with primary or secondary antibody deficiency.[3]

Recent studies in different populations have demonstrated that CG can be used as a low-cost method for screening quantitative antibody deficiency in adults, as it shows good correlation with serum IgG levels. Jolles et al.[3] examined the use of CG as a screening tool in Wales, using the Architect Biuret method for total protein and the colorimetric bromocresol green method for albumin estimation.

The cut-off value for CG was defined as < 18 g/L, with a sensitivity of 0.82 and specificity of 0.71 for an IgG < 3 g/L (or 300 mg/dL).

Yegit et al. used automated results of CG and protein electrophoresis of patients seen at a tertiary hospital for various reasons. They selected 550 patients with CG levels between 15 g/L and 25 g/L. The cut-off value for CG to predict patients with IgG < 6 g/L (or 600 mg/dL) was determined to be < 20 g/L, with a sensitivity of 83.8% and a specificity of 74.9%.[4]

In our studies using protein electrophoresis, we evaluated 886 adults and 1,215 children and adolescents seen at two allergy and immunology services. In adults, for the detection of hypogammaglobulinemia (i.e., IgG levels below the normal laboratory value of 6 g/L), the CG cut-off value of 24 g/L showed a sensitivity of 86.2% and specificity of 92%.[5]

In children and adolescents, the sensitivity and specificity of CG in detecting IgG levels below normal laboratory values were 93.1% and 81.8%, respectively. The CG cut-off values for detecting hypogammaglobulinemia were determined for patients aged 1 to 17 years and varied according to the age group studied, ranging from 23.1 g/L (1-3 years) to 24.8 g/L (4-9 years). The accuracy of this test could not be confirmed in children under 1 year of age.[6]

In clinical practice, the measurement of total proteins and protein fractions is a simple and widely used test for investigating serum protein abnormalities in general pediatrics, internal medicine, and other specialties such as gastroenterology, rheumatology, nephrology, pulmonology, oncology-hematology, and intensive care.[7-9] Additionally, the severity of the diseases serves as an alert for possible cases of immunodeficiency.[10]

Overall, CG values provide relevant data on humoral immunity, as these fractions are mainly composed of IgG.[11,12]

Strategies for implementing opportunistic screening should be encouraged and coordinated in both public and private services. The CG tool is easy to obtain and can be readily implemented in clinical laboratories. Recognizing individuals with reduced CG increases the possibility of diagnosing IEI and other causes of hypogammaglobulinemia, such as those secondary to losses and medication use, due to its close correlation

with serum IgG results. Furthermore, it serves as an additional identification method in medical services that lack immunoglobulin measurements.

References

1. Routes J, Costa-Carvalho B, Grimbacher B, Paris K, Ochs HD, Filipovich A, et al. Heath- Related Quality of Life and Health Resource Utilization in Patients with Primary immunodeficiency Disease Prior to and Following 12 Months of Immunoglobulin G Treatment. J Clin Immunol. 2016;36(5):450-61.
2. Holding S, Khan S, Sewell WAC, Jolles S, Dore PC. Using calculated globulin fraction to reduce diagnostic delay in primary and secondary hypogammaglobulinaemias: results of a demonstration project. Ann Clin Biochem. 2015;52(Pt 3):319-26.
3. Jolles S, Borrell R, Zouwail S, Heaps A, Sharp H, Moody M, et al. Calculated globulin (CG) as a screening test for antibody deficiency. Clin Exp Immunol. 2014 Sep;177(3):671-8.
4. Yegit OO, Karadag P, Eyice D, Oztop N, Beyaz S, Tüzer ÖC, et al. Calculated Globulin Is Clinically Useful as a Screening Test for Antibody Deficiency in Turkish Adult Patients. Int Arch Allergy Immunol. 2023;184(8):822-31.
5. Toledo Piza CFS, Aranda CS, Solé D, Jolles S, Condino-Neto A. Screening for Antibody Deficiencies in Adults by Serum Electrophoresis and Calculated Globin. J Clin Immunol. 2023;43(8):1873-80.
6. Piza CFST, Aranda CS, Solé D, Jolles S, Condino-Neto A. Serum protein electrophoresis may be used as a screening tool for antibody deficiency in children and adolescents. Front Immunol. 2021;12:3332.
7. Arnold DF, Wiggins J, Cunningham-Rundles C, Misbah SA, Chapel HM. Granulomatous disease: distinguishing primary antibody disease from sarcoidosis. Clin Immunol. 2008;128(1):18-22.
8. Estévez Del Toro M, Varela Ceballos I, Chico Capote A, Kokuina E, Sánchez Bruzón Y, Casas Figueredo N. Predictive factors for the development of lupus nephritis after diagnosis of systemic lupus erythematosus. Reumatol Clin (Engl Ed). 2022 Nov;18(9):513-7. doi: 10.1016/j.reumae.2021.08.003.
9. Sampaio LR, Silva MCM, Oliveira NA, Souza CLS. Avaliação bioquímica do estado nutricional. In: Sampaio LR. Org Avaliação nutricional [online]. Salvador: EDUFBA, 2012, pp 49-72. ISBN 789-85-232-1874-4.
10. Lehman H, Hernandez-Trujillo V, Ballow M. Diagnosing primary immunodeficiency: a practice approach for the non-immunologist. Curr Med Res Opin. 2015 Apr;31(4):697-706.
11. Lee AYS, Cassar PM, Johnston AM, Adelstein S. Clinical use and interpretation of serum protein electrophoresis and adjunct assays. Br J Hosp Med (Lond). 2017;78(2):C18-C20.
12. Vavricka SR, Burri E, Beglinger C, Degen L, Manz M. Serum protein electrophoresis: an underused but very useful test. Digestion. 2009;79(4):203-10.

No conflicts of interest declared concerning the publication of this letter.

Cristina Frias-Sartorelli Toledo Piza
Carolina Sanchez Aranda Lago
Maria Cândida Faria Varanda Rizzo
Ligia Maria de Oliveira Machado
Celso José Medanha da Silva
Dirceu Solé

Universidade Federal de São Paulo - Escola Paulista de Medicina, Allergy, Clinical Immunology, and Rheumatology - Department of Pediatrics - São Paulo, SP, Brazil.