

Recurrent Septic Shock and Syncope: An Unusual Combination

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Abstract

Immunoglobulin G (IgG) deficiency disorder is a form of dysgammaglobulinemia, where proportional levels of immunoglobulin G isotype is reduced as compared to other immunoglobulin isotypes. Common clinical presentations of IgG deficiency disorder are recurrent sinusitis and/or lower respiratory infections. However, IgG deficiency manifesting as recurrent septic shock in absence of upper and lower respiratory infection has never been reported, in our search for literature from world over. With this rare case, we highlight the importance of investigating IgG levels in clinical scenarios of recurrent sepsis with no known or traceable infective focus.

Introduction

Primary humoral immunodeficiencies are disorders resulting from impaired antibody production, because of molecular defect intrinsic to B cells or a failure of interactions between B and T cells.¹ Although majority of them become evident in childhood they can manifest at any age.²

We are presenting a rare case scenario of a patient with recurrent septic shock who was in due course found to have underlying primary humoral immunodeficiency disorder.

Case

A gentleman, aged 32 years presented to our ER with giddiness, vomiting and calf pain of one day duration. There was no history of loose stools, abdominal pain, breathlessness, cough with expectoration, headache, chest pain or altered behavior. On physical examination, he was hypotensive (BP-60/40 mm Hg), in tachycardia (Heart rate-150/m), afebrile and had severe diaphoresis. Systemic examination was unremarkable except for tenderness in calf muscles of both legs. He was shifted to MICU for further management, where he was found to have low central venous pressure (CVP-1 cm H₂O). Laboratory parameters revealed: polycythemia (haemoglobin-20.2 g/dl), leukocytosis (total leucocyte count-35000/cumm) with neutrophilia (Differential count: Neutrophils-76, Lymphocytes-18, Monocytes-6), deranged kidney functions (Urea - 80 mg/dl, Serum Creatinine: 2.1

mg/dl) Dyselectrolytemia (Serum sodium - 132 mEq/L, Serum Potassium - 6.2 mEq/L), elevated transaminases (SGOT - 234mg/dl, SGPT - 599 mg/dl) with insignificantly raised C-reactive protein levels (34mg/dl). Chest x-ray and ultrasound whole abdomen were normal. Electrocardiogram showed no abnormality. 2-D echocardiogram showed collapsed inferior vena cava with normal ejection fraction. Colour doppler study of lower limbs was normal. Patient was managed with intravenous fluids, ionotropes, and broad spectrum parental antibiotics along with steroids. He was given a total of ten litres of intravenous fluids on the first day. Serial monitoring of creatinine phosphokinase (CPK) level (236 mg/dl on day 1 to 44133 mg/dl on day 5) until fifth day followed by gradual decline after that. His general condition improved; blood pressure normalized; TLC decreased to 11240/cumm; serum creatinine level improved to 1.3mg/dl and was shifted to ward, where he developed numbness and weakness of limbs. Nerve conduction study revealed sensori-motor neuropathy and he was discharged in stable condition.

He suffered a syncopal attack 3 months later while riding on a motorbike but he recovered unhurt. A few days later he was brought to the casualty where was found to have severe hypotension (systolic BP-50 mm Hg) and tachycardia (HR-140/m). His CVP was very low. He was resuscitated with large volume intravenous fluid administration, and

ventilatory support was provided in view of poor general condition. He was started on ionotropes and broad spectrum antibiotics. Laboratory parameters showed Haemoglobin - 18 g/dl, total leucocyte count - 40000/cumm, and serum creatinine-2.5gm/dl, albumin-1.9gm/L with normal serum electrolytes, transaminase and CPK levels. A profile similar to the earlier profile. Blood and urine cultures were sterile. Routine Viral markers were nonreactive. Computed tomography of chest and abdomen were normal except left kidney showed irregular outline suggestive of old injury or chronic pyelonephritis. MRI brain was normal. Urine for porphobilinogen, 5-hydroxy indole acetic acid, 24 hr urine catecholamines and metanephrines were normal. He improved over 72 hours; was weaned off the ionotrope and ventilatory support; laboratory parameters normalised. A drop of 30 mm Hg was noted in systolic BP after the patient was shifted to ward with normal heart rate variability on standing from supine position with inability to perform valsalva manouver. ANA & dsDNA were normal. In view of two episode of life threatening sepsis his IG and complement levels were sent. Complement 3 level was low but complement 4 was normal. Immunoglobulin profile and immunodeficiency panel showed normal T cell and B cell counts but decreased IgG levels- 341 (Ref Range:694-1618 mg/dl). IgG subclass assay could not be done because of logistic problems. Patient then developed a nosocomial pneumonia and he was given a full dose of intravenous immunoglobulin therapy upon which he recovered and was discharged from hospital. He was advised monthly IG injections but was not able to afford and opted for alternate medicine, is now on follow up visits.

He had a bout of mild chikungunya

fever just last month and went into another episode of severe shock needing hemodynamic resuscitation. Follow up IgG levels continue to be low

Discussion

Primary immunodeficiency diseases (PID) are much less common than secondary immune deficiency conditions like HIV infection, chronic kidney disease, diabetes, malnutrition or drug induced immunodeficiency. Primary immunodeficiency diseases are classified into disorders that affect one or more of four limbs of immune system (humoral immunity, cell mediated immunity, phagocytes and the complement system). Immunoglobulins have central role in humoral immunity and consists of 5 major isotypes: Immunoglobulin G, Immunoglobulin M, Immunoglobulin A, Immunoglobulin E, Immunoglobulin D. Immunoglobulin G (IgG) is further divided into 4 subclasses: IgG1, IgG2, IgG3, IgG4 and serum concentration of the subclasses directly correlate with their numerical nomenclature.

IgG deficiencies may present as isolated IgG deficiency, with normal levels of IgA, IgM, IgD, IgE or along with deficiencies of other immunoglobulin isotypes. This may occur in various conditions like common variable immunodeficiency (CVID), hyper IgM syndrome, or X-linked agammaglobulinemia.

These disorders (selective antibody deficiency or common variable immunodeficiency (CVID) or both) occur irrespective of age or gender, reminding that our patient had his first episode at 32 yrs of age. The incidence of isolated IgG deficiency is not known and deficiencies of IgG subclasses are probably more common and run familiarly as common variable immunodeficiency (CVID). The most common subtype of IgG deficiency seen in childhood is IgG2, and in adults,

is of IgG1 and IgG3 predominates. Patients with isolated IgG deficiency or deficiency of specific subclass of IgG or a combination of aforesaid, usually present with recurrent pyogenic respiratory tract infections similar to those observed in patients with B cell deficiencies. Unusually, our patient, on both occasions, had septic shock which was in due course attributed to the underlying primary immunodeficiency disorder he has. We could not find any literature on world platform which had shed light on such unusual and unexpected presentation of IgG deficiency disorder.

The clinical importance of IgG subclass deficiencies is controversial, as persons with chromosomal deletions leading to deficiencies of some IgG subclass have been reported to be healthy, and demonstration of low IgG subclass levels alone is not sufficient to diagnose antibody deficiency. One must demonstrate the deficiency of specific antibody response to documented infections and vaccine antigens.^{3,4} Amongst these, patients with selective IgG2 deficiencies with normal total IgG levels, display highest level of infectious complications generally of respiratory tract such as bronchiectasis, bronchopneumonia, bronchitis, obstructive lung disease, and hyper-reactive airways. The most common clinical presentation in any type of IgG deficiency is recurrent upper and lower respiratory tract infections. Interestingly, our patient, on both occasions, suffered life threatening septic shock with no history or features of respiratory tract infections except that he developed nosocomial pneumonia

Our patient had postural drop of 30 mm Hg in his blood pressure. He had peripheral neuropathy on NCV. Thus it is possible that he developed post infectious neuropathy with involvement of autonomic nerves leading to orthostatic hypotension and

syncope. This autonomic neuropathy is known as autoimmune autonomic neuropathy (AAN) seen in the setting of infections and paraneoplastic diseases. It is characterized by alpha A3 acetyl choline receptor antibody which is directed against autonomic ganglion.⁵ We were unable to get the antibody test done and also enterovirus antibody for the 1st episode of sepsis which could have been viral as they had to be sent to USA and not available here

The goals of therapy in IgG deficient patients are three fold. 1) treat the acute infection with antibiotics 2) introduce prophylaxis with IgG replacement 3) prevent and treat pulmonary disease. Currently, intravenous immunoglobulin (IVIg) replacement therapy is the treatment of choice for patients with IgG deficiency and also for patients of immunodeficiencies due to other causes.⁶ In last few years, home infusion of IgG administered subcutaneously (IGSC) has gained popularity and has shown higher health related quality of life as compared to hospital based treatment.⁷

References

1. Notarangelo L, Casanova JL, Fischer A, Puck J, Rosen F, Seger R. Primary immunodeficiency diseases: an update. *J Allergy Clin Immunol* 2004; 114:677-687.
2. Wood PM. Primary antibody deficiency syndrome. *Curr Opin Hematol* 2010; 17:356-361.
3. Agarwal S, Cunningham-Rundles C. Assessment and clinical interpretation of reduced IgG values. *Ann Allergy Asthma Immunol* 2007; 99:281-83.
4. Chouksey AK, Berger M. Assessment of protein antibody response in patients with suspected immune deficiency. *Ann Allergy Asthma Immunol* 2008; 100:166-168.
5. Koike H, Watanabe H, Sobue G. The spectrum of immune-mediated autonomic neuropathies: insights from the clinicopathological features. *J Neurol Neurosurg Psychiatry* 2013; 84:96-106.
6. Mandell GL, Bennet JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles & Practice of Infectious Disease. 5th ed. New York, NY: Churchill Livingstone; 2000. Vol 1:59-61.
7. Shapiro RS. Subcutaneous immunoglobulin therapy given by subcutaneous rapid push vs infusion pump: a retrospective analysis. *Ann Allergy Asthma Immunol* 2013; 111:51-5.