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Sinus bradycardia in a patient with bacterial meningitis in therapy with IVIg: a case report

F. D'Andrea[1], M. Ceccarelli[1,2], A. Facciolà[1], I. Paolucci[3], D. Maranto[3], M.R. Lo Presti Costantino[3], D. Spicola[4], D. Larnè[1], E. Venanzi Rullo[1,2], P. Mondello[3], G. F. Pellicanò[5]

[1]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[2]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA
[3]Unit of Infectious Diseases, "G. Martino" University Hospital, Messina, Italy
[4]Unit of Infectious Diseases, A.R.N.A.S. "Civico di Cristina Benfratelli", Palermo, Italy
[5]Department of Human Pathology of the Adult and the Developmental Age "G. Barresi", University of Messina, Messina, Italy

ABSTRACT:

Objective: Mortality as a result of sepsis and septic shock is still high despite the use of anti-microbial agents. Intravenous Immunoglobulins (IVIgs) have been proposed as adjuvant therapy for sepsis even though their efficacy in this setting has long been debated. We describe the case of a patient with sepsis treated with IVIgs developing bradycardia. Bradycardia progressively improved with the IVIgs washout, and spontaneously resolved after two days from the end of the treatment. Further studies are needed to ascertain this possible link.

Keywords: Sinus bradycardia, Infection, Meningitis, *Streptococcus Pneumoniae*, Intravenous Immunoglobulin, IVIg, Sepsis.

INTRODUCTION

Sepsis is the inflammatory response of the body to severe infection caused by a variety of micro-organisms[1]. Mortality as a result of sepsis and septic shock is still high despite the use of anti-microbial agents[2]. Therefore, other agents have been considered to help fighting the effects of sepsis, such as Intravenous Immunoglobulins (IVIgs). IVIgs are blood products, therapeutic preparations of polyclonal immunoglobulin G, extracted from the plasma of thousands of donors[3].

Initially introduced as replacement therapy for patients with immune deficiencies, IVIgs are now used for the treatment of many autoimmune and systemic inflammatory diseases[4-6].

Because of their immunomodulatory and anti-inflammatory effects, they have been proposed as adjuvant therapy for sepsis even though their efficacy in this setting has long been debated[6-8]. In fact, clinical studies demonstrating their efficacy and safety are relatively small[9]. In sepsis, the use of IVIGs represents a therapeutic weapon to positively modulate the immune response by several mechanisms, like modulating cytokine responses, interfering with complement activation, reducing pro-inflammatory mediators, enhancing phagocytic function and neutralizing endo- and exo-toxins[10].

De Simone et al[11]. used IgG solution in patients with severe sepsis and obtained reductions in hospitalization and number of days on antibiotics, as well as in the number of positive cultures; however, the mortality rate (75% control *vs.* 58% IVIgG) was unchanged.

Similarly, Just et al[12] and Jesdinsky et al[13] were also not able to demonstrate reductions in mortality rate by IVIg application to intensive care patients with sepsis.

Dominioni et al[14] showed that the mortality rate was reduced by administration of the IgG solution from 67% to 38% in postoperative septic patients.

IVIgs are generally well tolerated but they are not free from side effects. They include aseptic meningitis, headache, fever, nausea, diarrhea, blood pressure changes, tachycardia, renal failure, thromboembolic events and anaphylactic reactions[15].

Corresponding Author: Flavia D'Andrea, MD; e-mail: flavia.dandrea91@libero.it

The purpose of this case report was to highlight the possible role played by IVIgs in the onset of bradycardia in a patient with sepsis.

CASE REPORT

A 47-year-old woman, obese, with no previous medical history, was accompanied to the Emergency Room (ER) of the "G. Martino" University Hospital in Messina (Messina, Italy) because of a progressive loss of consciousness during the previous six hours. Her relatives referred fever (maximum temperature 38.2°C) and otalgia, vomit and headache progressively worsening over the previous 4 days.

Upon arrival, physical examination revealed that the patient was non responsive to verbal stimuli and had miotic pupils non-reacting to the light. Voluntary motility was preserved in the upper left and lower limbs. She underwent a brain CT scan and a following brain MRI, which showed the presence of a thrombosis of the superior sagittal sinus with a cranio-caudal extension of about 7 cm. Brain MRI also highlighted a spread hyper intensity of subarachnoid infra- and supratentorial, with an intense and widespread leptomeningeal impregnation, and bilateral otomastoiditis.

She was then admitted to the Infectious Diseases ward with the diagnosis of meningitis. Physical examination was repeated, for the rapidly worsening condition of the patient. At the admission, she was comatose, with a Glasgow Coma Scale (GCS) score of 7, defined as no eye opening (1), no verbal response (1) and localizing pain (5). Quick Sepsis-related Organ Failure Assessment (qSOFA) score was 2, defined as respiratory rate > 22 (1) and GCS < 15 (1). She was not febrile (temperature 36.0°C), her heart rate (HR) was 88 beats per minute (bpm) and her blood pressure (BP) 130/70 mmHg. Blood tests performed at the ER showed a white blood cell (WBC) count of 33,200 cells/µL, with 84% of neutrophils and elevated procalcitonin (PCT, 14.4 ng/ml, normal values < 0.1 ng/mL) and C Reactive Protein (CRP, 30.5 mg/dL, normal values < 0.5 mg/dL). Renal and liver function tests were normal (creatinine 0.6 mg/dL, normal values 0.5-1.2 mg/dL; total bilirubin 1.1 mg/dL, normal values < 1.2 mg/dL; aspartate aminotransferase, AST, 15 U/L, normal values < 42 U/L; alanine aminotransferase, ALT, 15 U/L, normal values < 50 U/L). Complete blood tests revealed a high concentration of blood glucose (201 mg/dL, normal values 65-110 mg/dL).

Antimicrobial therapy with vancomycin 1 g tris in die (tid), ceftriaxone 2 g bis in die (bid) and dexamethasone 8 mg bid was promptly started, according to guidelines. Low molecular weight heparin (enoxaparin) 6,000 UI bid was started for the thrombosis of the superior sagittal sinus.

Lumbar puncture, blood and urine cultures were performed after the first dose of the antimicrobial therapy. Lumbar puncture revealed the presence of turbid cerebral-spinal fluid (CSF), which examination highlighted an elevated content of proteins (686 mg/dL, normal values <12 mg/dL), a low concentration of glucose (8 mg/dL, normal values 65-110 mg/dL) and an important presence of leukocytes (41,750/µL, normal value: absence). These results were consistent with bacterial meningitis. A test for the early antigen of Streptococcus pneumoniae resulted positive, and cultures confirmed the etiology. Both blood and urine cultures resulted negative.

Vancomycin was then stopped and rifampicin 600 mg quondam die (qd) was started. For the severity of the general conditions of the patient, it was then decided to start the infusion of IVIgs (Pentaglobin™, Biotest Pharma Gmbh, Dreieich, DE) after an allergist evaluation, at 16 mL/h speed, 0.25 mg/kg weight qd per 3 consecutive days. After the second infusion, we started to notice a lower bpm (HR 54 bpm), which after the third, and last, was a full-blown sinus bradycardia (HR 36 bpm), confirmed by the electrocardiogram (EKG, Figure 1).

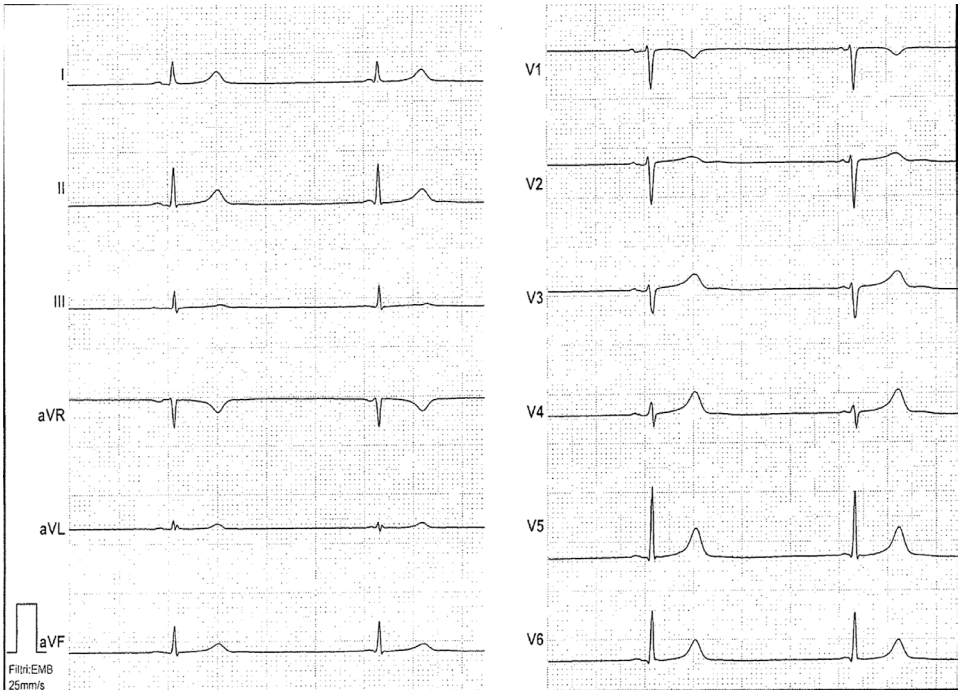

Figure 1. EKG tracing after the third and last dose of IVIgs. It can be noticed that the heart rate is profoundly decelerated, but it maintains the sinus rhythm.

Myocardial necrosis enzymes were negative. We then decided to consult both the anesthesiologists and the cardiologists and begin therapy with atropine 1 mg diluted in 5 mL of saline solution (0.9%), 1 mL every 2 minutes. The therapy was effective, but during the night a new episode of sinus bradycardia (HR 35 bpm) led to a second administration of atropine 1 mg in 100 mL of saline solution (0.9%), once again with only a transient efficacy in restoring a normal HR. Bradycardia progressively improved with the IVIgs washout, and spontaneously resolved after two days from the end of the treatment.

Her general conditions progressively improved. After seven days from the admission, the patient was alert, oriented in time and space, collaborative, afebrile and eupneic. Her cardiac activity was rhythmic and her HR was within normal values. A brain MRI performed on the 6th day of the admission showed that the widespread intense meningeal impregnation previously highlighted in both hemispheres of the brain was not appreciable anymore.

We discharged the patient after 14 days of admission in good clinical conditions, with a normal blood count (WBC 6,800/µL, with 48% of neutrophils) and normal CRP (0.50 mg/dl) and PCT (0.08 ng/ml). There was no recurrence of the bradycardia during follow-up.

The patient was later revealed affected by a homozygotic C677T mutation of the MTHFR gene, which led to the severe thrombosis during the general inflammatory status. She is still in follow up for this coagulation disorder.

DISCUSSION

Despite the development of new therapeutic strategies and antibiotic regimens, mortality of sepsis and septic shock is still high. Administration of intravenous immunoglobulin (IVIg) seems to be promising in clinical practice because of the possibility of neutralizing endotoxin, modulating cytokine responses, interfering with complement activation and reducing pro-inflammatory mediators. Moreover, IVIgs administration is generally well tolerated. Side effects include aseptic meningitis, headache, fever, nausea, diarrhea, blood pressure changes, tachycardia, renal failure, thromboembolic events and anaphylactic reactions[15]. The use of IVIgs has been extensively studied in the setting of sepsis and septic shock, at all ages. In their Cochrane database review, Alejandria et al[1] concluded that the use of IVIgs seems to be effective among adults with sepsis. However, this result was only true for studies that presented medium-high risk of biases, so their suggestion was to maintain the use of IVIgs experimental.

In 2014, a study by Bermejo-Martín et al[16] showed that low levels of IgG1, IgM and IgA in plasma were associated with a higher risk of mortality in the setting of sepsis. Moreover, in a case-control study, Ishikura et al[17] showed a statistically significant correlation between the use of IVIgs and sepsis-related organ failure assessment (SOFA) score. The same study also showed a quicker and more important decrease of the inflammation markers (CRP, PCT and interleukin-6) in the group using IVIgs vs the group not using them. This evidence brought Ishikura to suggest the use of IVIgs in patients affected by severe sepsis and septic shock[17].

In our case, the choice to start a therapy with IVIgs was led by the critical conditions of the patient after the second day of antimicrobial treatment with an effective regimen, which seemed to indicate a possible negative outcome. Despite the contraindications to the use of IVIgs represented by the patient being overweight and the presence of a thrombosis of the sagittal sinus, we assessed risks and benefits for this particular case and decided to proceed. Bradycardia has been previously described in pediatric studies as a side effect of the simultaneous administration of IVIgs and corticosteroids, especially in the setting of Kawasaki disease [18,19]. Moreover, Raheja et al[20] reported about a case of profound sinus bradycardia in a 33-year-old patient affected by idiopathic thrombocytopenic purpura treated with IVIgs that, similarly to our case, spontaneously resolved after the suspension of the treatment. Like in Raheja et al[20], the strict temporal dependence between bradycardia and IVIgs therapy, and the spontaneous solution after suspension, seems to provide strong evidence for a causal relationship in our case. However, further studies are needed to ascertain this kind of direct link since, in our case, the simultaneous treatment with dexamethasone and the antimicrobial therapy could be confounding factors. Finally, the critical conditions of our patient and the central nervous system involvement may have determined the onset of central bradycardia, regardless of the administration of IVIgs.

CONCLUSIONS

In our limited experience, treatment with IVIgs in the case of sepsis has provided benefits. However, strict monitoring of general conditions and vital signs during treatment is recommended for the possible causal link between IVIgs and bradycardia, especially in the case of simultaneous administration of corticosteroids. Further studies are needed to verify this relation.

Conflict of Interest:
The authors declare no conflict of interest.

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