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Letter to the Editor

Does intravenous immunoglobulin therapy in Guillain-Barré syndrome patients interfere with serological Zika detection?

Guillain-Barré syndrome (GBS) is a rare neurological autoimmune disease that targets peripheral nerves [1,2]. The yearly new incidence of the disease is ranging from one to two cases per 100,000 people. Pathogen mimicry has been long suggested to be one of the causes for triggering this autoimmune disease as in many cases patients had recent bout of infectious diseases before the appearance of GBS. Incidentally recent outbreaks of Zika virus, a member of the *Flaviviridae* family in South America and other tropical countries not only lead to severe neurological complications in adults, microcephaly in neonates but also pre-disposed the affected population for GBS [3–6].

Therefore, we wanted to test at laboratory level whether new cases GBS patients in France (excluding offshore territories) are associated with Zika virus infection. We analyzed the plasma of seven fresh cases of GBS (2015–2016) in two French centers (Limoges and Paris) for anti-Zika IgG and IgM, using the ELISA kit from Euroimmun Medizinische Labordiagnostika AG (Germany). Patients were aged 67.4 ± 13.9 years (ranging from 49 to 88 years) and relevant ethical approval (84-2012-08, CHU Limoges, France) was obtained before the collection of plasma samples.

The relative units (RU) of anti-Zika IgG in these patients were 1.65 ± 0.67 (mean ± standard deviation, ranging from 0.8 to 2.9) and were way below the recommended relative units of ≥22 for positive Zika virus infection (Fig. 1A). Similarly, semi-quantitative IgM ELISA also indicated absence of Zika infection in our cohort of GBS

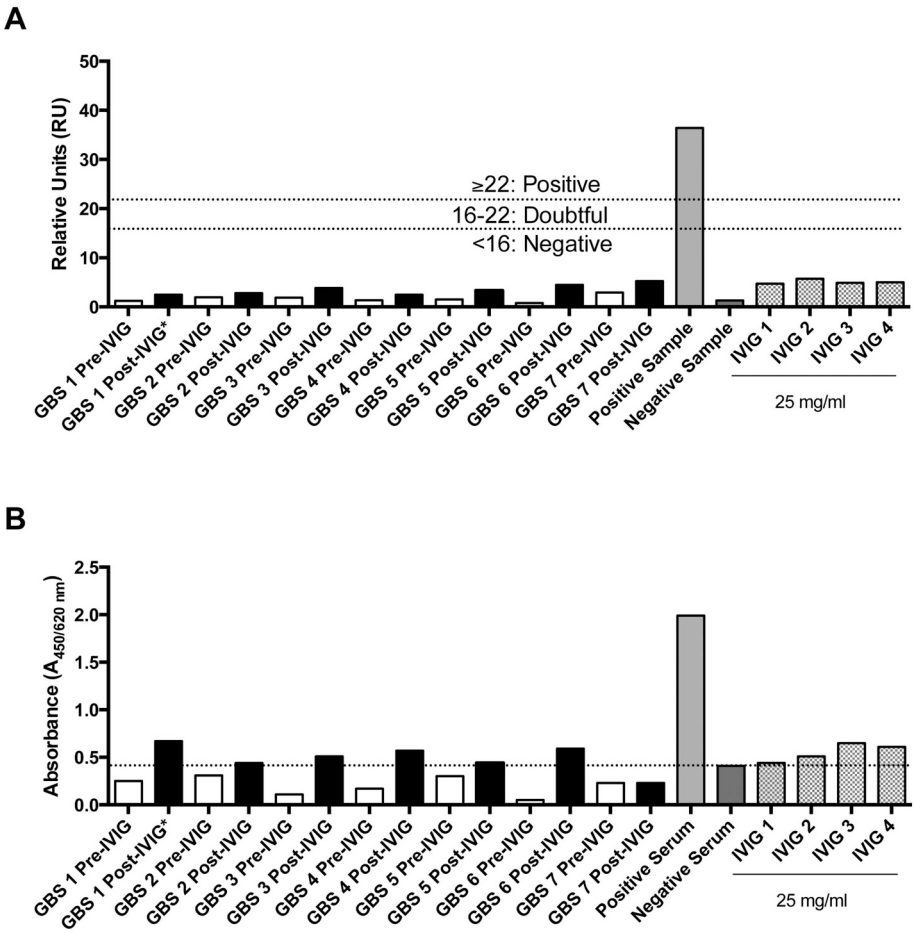

Fig. 1. Reactivity of plasma from intravenous immunoglobulin-treated Guillain-Barré syndrome patients with Zika antigens. Blood samples were collected from Guillain-Barré syndrome (GBS 1–7) patients before (Pre-IVIG) and one week post-intravenous immunoglobulin (IVIG) therapy (* except GBS 1 patient from whom blood sample was collected two weeks post-IVIG therapy). (A) Anti-Zika IgG (Relative units) to NS1 nonstructural proteins in the patients' plasma as determined by Euroimmun ELISA kit. The horizontal lines indicate recommended cut-off relevant units for the serological diagnosis of Zika virus infection. (B) Antibody titers (Absorbance values) to domain III of Zika virus E protein (EDIII) of the Asian lineage. The horizontal line depicts absorbance value of negative serum. Plasma samples were used at 1:100 dilution (100 µl/well). Four commercial IVIG preparations (IVIG 1–4) were tested for the presence of anti-zika IgG at doses equivalent of IgG reached in the patients immediately following IVIG therapy (25 mg/ml; 2.5 mg/well).

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patients. Together our data validates lack of association of Zika infection for these fresh cases of GBS in France.

Intravenous immunoglobulin (IVIG) is the treatment of choice for GBS [7,8]. IVIG is a therapeutic preparation of normal IgG obtained from the pooled plasma of several thousand healthy donors and is extensively used for the immunotherapy of autoimmune and inflammatory diseases [7–14]. Depending on the endemic nature of an infectious disease, and vaccination and infection history of the donors, IVIG contains IgG against a large number of pathogens including flaviviruses [15–17]. Therefore, serologic testing in IVIG-treated patients could create not only confusion but also false-positive serological results. In fact, false-positive viral serology tests in IVIG treated patients have been reported for hepatitis B virus, human T-lymphotropic virus and others [18,19]. In view of the association of Zika viral infection with GBS, a question that is not yet addressed in the field is whether high-dose IVIG immunotherapy (1–2 g/kg body weight) in GBS patients interferes with serological diagnosis of Zika infection by yielding false positive reactions due to the presence of possible cross-reactive antibodies.

We addressed this hypothesis by two different approaches and by using two distinct types of ELISA. First, using Euroimmun ELISA kits that detect antibodies to NS1 nonstructural proteins, we performed ELISA on plasma samples of IVIG-treated GBS patients. Plasma were collected either one week (six patients) or two weeks (one patient) post-IVIG therapy. We found that the relative units of anti-Zika IgG in the post-IVIG samples were relatively higher than pre-IVIG plasma samples (3.52 ± 1.06, ranging from 2.46 to 5.24), but remained far below the recommended positive values (Fig. 1A). Thus, our data suggested that some IgG antibodies in IVIG might show reactivity to NS1 protein. But possibly due to the low titers of these antibodies and/or low affinity, they might not provide false positive reactivity to Zika. We further confirmed this by using four different commercially available IVIG preparations of European or USA origin (lots before 2014) wherein IVIG at 25 mg/ml concentration (equivalent to IgG level reached in the plasma of patients immediately following IVIG infusion) showed relative units of anti-Zika IgG 5.08 ± 0.45 (ranging from 4.71 to 5.73) (Fig. 1A).

Next, we performed in-house ELISA using a recombinant antigen of domain III of Zika virus E protein (EDIII) of the Asian lineage expressed in eukaryotic system. Again, pre-IVIG plasma samples of GBS patients did not show positive reactivity. However, post-IVIG plasma samples as well as IVIG showed marginally higher reactivity to EDIII antigen than negative plasma control samples used in the assay (Fig. 1B).

Together, our data indicate that IVIG therapy in GBS patients does not interfere with accurate serological detection of Zika. As these IVIG lots were prepared before the outbreaks of Zika, assays need to be repeated with the perspective lots of IVIG.

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Conflicts of interests

Authors have no conflicts of interests to declare.

References

[1] van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barre syndrome. Lancet Neurol 2008;7:939–50.
[2] Esposito S, Longo MR. Guillain-Barre syndrome. Autoimmun Rev 2017;16:96–101.
[3] Parra B, Lizarazo J, Jimenez-Arango JA, Zea-Vera AF, Gonzalez-Manrique G, Vargas J, et al. Guillain-Barre Syndrome Associated with Zika virus infection in Colombia. N Engl J Med 2016;375:1513–23.
[4] Cao-Lormeau VM, Blake A, Mons S, Lastere S, Roche C, Vanhomwegen J, et al. Guillain-Barre Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet 2016;387:1531–9.
[5] Pinto-Diaz CA, Rodriguez Y, Monsalve DM, Acosta-Ampudia Y, Molano-Gonzalez N, Anaya JM, et al. Autoimmunity in Guillain-Barre syndrome associated with Zika virus infection and beyond. Autoimmun Rev 2017;16:327–34.
[6] Monsalve DM, Pacheco Y, Acosta-Ampudia Y, Rodriguez Y, Ramirez-Santana C, Anaya JM. Zika virus and autoimmunity. One-step forward. Autoimmun Rev 2017;16:1237–45.
[7] Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. N Engl J Med 2012;367:2015–25.
[8] Gilardin L, Bayry J, Kaveri SV. Intravenous immunoglobulin as clinical immune-modulating therapy. CMAJ 2015;187(4):257–64.
[9] Sala TP, Crave JC, Duracinsky M, Lepira Bompeka F, Tadmouri A, Chassany O, et al. Efficacy and patient satisfaction in the use of subcutaneous immunoglobulin immunotherapy for the treatment of auto-immune neuromuscular diseases. Autoimmun Rev 2018;17:873–81.
[10] Tenti S, Fabbroni M, Mancini V, Russo F, Galeazzi M, Fioravanti A. Intravenous Immunoglobulins as a new opportunity to treat discoid lupus erythematosus: A case report and review of the literature. Autoimmun Rev 2018;17:791–5.
[11] Perez EE, Orange JS, Bonilla F, Chinen J, Chinn IK, Dorsey M, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol 2017;139:S1–46.
[12] Sanges S, Riviere S, Mekinian A, Martin T, Le Quellec A, Chatelus E, et al. Intravenous immunoglobulins in systemic sclerosis: data from a French nationwide cohort of 46 patients and review of the literature. Autoimmun Rev 2017;16:377–84.
[13] Watad A, Amital H, Shoenfeld Y. Intravenous immunoglobulin: a biological corticosteroid-sparing agent in some autoimmune conditions. Lupus 2017;26:1015–22.
[14] Zuercher AW, Spirig R, Baz Morelli A, Kasermann F. IVIG in autoimmune disease - potential next generation biologics. Autoimmun Rev 2016;15:781–5.
[15] Bayry J, Lacroix-Desmazes S, Kazatchkine MD, Kaveri SV. Intravenous immunoglobulin for infectious diseases: back to the pre-antibiotic and passive prophylaxis era? Trends Pharmacol Sci 2004;25:306–10.
[16] Krause I, Wu R, Sherer Y, Patanik M, Peter JB, Shoenfeld Y. In vitro antiviral and antibacterial activity of commercial intravenous immunoglobulin preparations–a potential role for adjuvant intravenous immunoglobulin therapy in infectious diseases. Transfus Med 2002;12:133–9.
[17] Shopsin B, Kaveri SV, Bayry J. Tackling difficult *Staphylococcus aureus* infections: antibodies show the way. Cell Host Microbe 2016;20:555–7.
[18] Ilboudo CM, Guest EM, Ferguson AM, Garg U, Jackson MA. Misleading hepatitis B testing in the setting of intravenous immunoglobulin. F1000Res 2013;2:249.
[19] Belanger SS, Fish D, Kim J, Cohen S. False-positive human T-lymphotropic virus serology after intravenous immunoglobulin transfusion. CMAJ 2012;184:1709–12.

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