Neutralizing Anti-Interleukin 6 Autoantibodies in a Patient with Recurrent Aseptic Meningitis

Davenport K[1,2], Tuite H[2], Fleming C[2], Tormey V[1], Lee-Brennan C[1]

[1]Department of Immunology, Galway University Hospitals, Galway, Ireland
[2]Department of Infectious Diseases, Galway University Hospitals, Galway, Ireland

Case Importance

- Interleukin-6 (IL6) is a cytokine produced in response to noxious stimuli such as infections[1].
- Activation of the IL6 receptor triggers a signalling cascade leading to production of acute phase reactants, e.g. C-reactive protein (CRP), which in turn promote innate immune responses including opsonisation, phagocytosis, chemotaxis and complement activation[1].
- Defects in this pathway are associated with recurrent bacterial infections characterised by an absent acute phase response[1].
- To date, there are no published reports of significant recurrent viral infections in patients with defects in the IL6 signalling pathway[1].

Case Description

- 50-year-old lady with history of three episodes of aseptic meningitis (1997, 2008, 2018) presenting with fever, headaches, neck stiffness and photophobia, with no features of encephalitis.
- Erythrocyte sedimentation rate was 2 mmHg/h on the first occasion, and CRP <1mg/L on the subsequent two.
- On all occasions, cerebrospinal fluid (CSF) demonstrated lymphocytic pleocytosis, raised protein, marginally low glucose, and negative microscopy and bacterial/ mycobacterial cultures. *Herpes simplex virus 2* (HSV2) DNA was detected in CSF on one occasion, other bacterial/ viral targets were not detected.
- Serum HSV2 IgG was positive in the absence of clinical history of herpetic lesions.
- Past medical history was otherwise unremarkable. Normal Bacillus Calmette-Guérin vaccination scar was present. Mantoux test and HIV serology were negative.
- Immunological investigations demonstrated normal immunoglobulins and IgG subclasses, adequate specific antibody responses to *Streptococcus pneumoniae*/ tetanus/ *Haemophilus influenzae B*, and normal extended T and B lymphocyte subsets. Complement activity was normal for both classical and alternative pathways.

Methods

- Cytokine studies were undertaken in search for defects associated with susceptibility to herpetic infections. Analyses were carried out using in-house assays in the Department of Clinical Biochemistry and Immunology, Addenbrooke's Hospital, Cambridge, UK.
- ➢ Whole blood was activated with interleukin-2 (IL2), interleukin-12 (IL12), interferon gamma (INFγ), lipopolysaccharide (LPS), mitogenic anti-CD3 antibodies, phytohaemagglutinin and phorbol myristate acetate .
- ➢ Secretion of interleukin-1β (IL1β), IL2, interleukin-10 (IL10), IL12, interleukin-17 (IL17), INFγ and tumour necrosis factor α (TNFα) was measured from the recovered whole-blood supernatants using ELISA technology.
- ➢ Anti-IL6 serology testing and functional analysis of peripheral blood monocytes (PMBCs) with and without autologous serum were performed.
- Data were analysed using Microsoft Excel 2010 and GraphPad Prism 4.

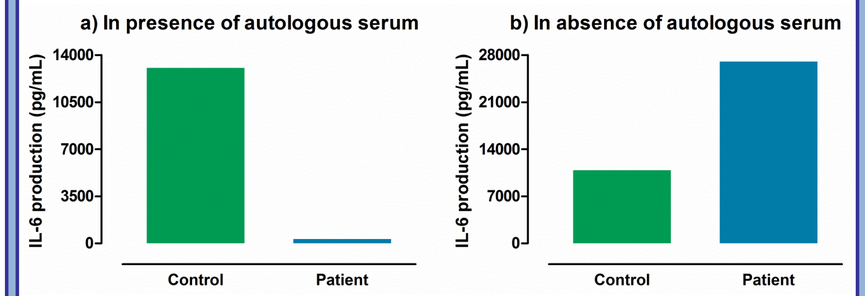
Results

- Production of IL6 was severely and selectively impaired to all tested stimuli (Figure 1a) compared to healthy control.
- Testing for presence of anti-IL6 antibodies in patient's blood was positive.
- Functional testing of PMBCs in the absence of autologous serum demonstrated normalization of the IL6 response to levels comparable to control (Figure 1b).
- Induction of other tested cytokines was normal in response to LPS, IL12, INFγ and polyclonal T-cell stimulation ruling out defects in these pathways.

References

1. Ku CL *et al*. Autoantibodies against cytokines: phenocopies of primary immunodeficiencies? *Hum Genet* 2020;139(6-7):783-794.
2. Winthrop KL *et al*. ESCMID study group for infections in compromised hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clin Microbiol Infect* 2018;24(Suppl 2):S21-S40.

Figure 1



Discussion

- Herein we describe a case of severely impaired IL6 response due to presence of neutralizing anti-IL6 autoantibodies in a patient presenting with recurrent, likely viral, meningitis.
- Inhibited IL-6 function explains her inability to mount an acute phase response, and may well have contributed to the recurrent nature of infections.
- This is line with previous reports implicating defects in the IL6 signalling pathway, both in the setting of primary immunodeficiencies and anti-cytokine autoantibodies, to be associated with severe pyogenic infections[1]. Similarly, infections commonly seen in patients on IL6-targeted therapies are mostly bacterial in nature[2].
- Our patient expands the hitherto described phenotype to include susceptibility to viral infections such as HSV2.

Conclusion

- This is a first report of significant recurrent viral infections in the setting of presence of neutralizing anti-IL6 autoantibodies .
- Concept of autologous anti-IL6 antibodies is of particular interest in the context of current COVID-19 pandemic and pharmacological use of a monoclonal antibody against IL6, tocilizumab.