Is EB Virus the Cause of MS? – A Way Forward

A recent paper considers molecular mimicry between EB Virus and a Glial protein, which is ultimately based on the nature of hydrogen bonding by specific, high affinity antibodies (Lanz et al.,2022, https://doi.org/10.1038/s41586-022-04432-7).

CSF oligoclonal IgG bands have been widely accepted as a biomarker for MS (circa 95%). The specificity of these bands has been extensively studied for their binding to many viruses or other antigens. The nature and specificity of the binding between any antigen and its antibody depends on the affinity mediated by hydrogen bonds. The specific affinity can be titrated by increasing amounts of sodium thiocyanate (NaSCN) which effectively chelates the shared protons that mediate any bonding. When the bond is disrupted by low concentrations of NaSCN, this signifies low affinity or non-specific binding. Conversely much higher concentrations are required to break the high affinity bond shown by antigen specific binding. Examples include measles antibody in MS compared to SSPE or herpes antibody in herpes encephalitis using immunoblotting (Chapman et al.,2007, https://doi.org/10.1016/j.jneuroim.2007.01.002) as well as earlier (Chapman et al.,2006, https://doi.org/10.1016/j.jim.2005.12.004) based on prior ELISA technology (Luxton et al.,1990, https://doi.org/ 10.1016/0022-1759(90)90199-6).

It is well known that during the natural selection of plasma cells, a process of "affinity maturation" occurs (over 7 to 10 days) with successive increases in the specificity of binding between the antigen yielding a "better fit" from the improving trials of various combinations of heavy plus light chains which then produce even tighter binding to the antigen in question.

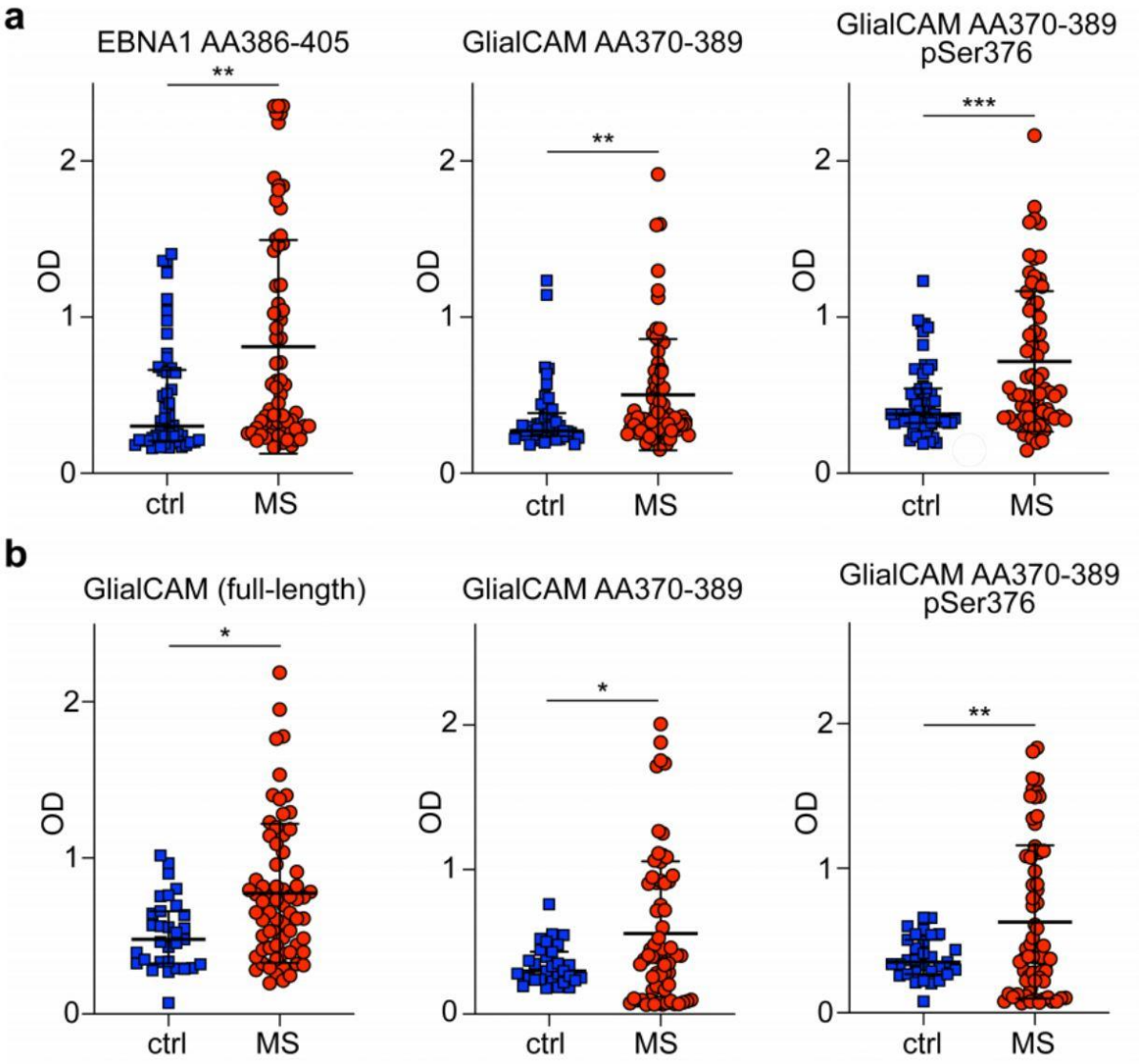
Although there is certainly statistical significance in the various comparisons to EBNA1 or GlialCAM over the range of Optical Density between 1 and 2 for MS versus Controls, however comparing the clustering of the individual dots "by eye," the majority of MS dots are present in the same range as the Controls, with only a minority of MS dots being higher and are therefore the basis for achieving significance by the final p values from this smaller number of skewed "outliers." (see Extended Data Fig 9). Parenthetically it would be of interest to know which particular "higher" dots corresponded to which individual MS "types" (CIS or RRMS ? for their two experiments, each in duplicate).

There are many limits which the Authors freely admit in their required selection criteria for a particular range of cell counts in CSF from individual patients (5 CIS, 4 RRMS, 3 Older Controls). It would be more direct and not require any particular "subset selection" on CSF cell numbers, if one were to address all of the individual oligoclonal bands from every patient using unconcentrated CSF, plus parallel serum, as previously reviewed (Giovannoni et al.,2006, https://doi.org/10.1016/j.jneuroim.2006.06.033). This would allow a more quantitative approach based on international standards of Optical Density using NIH freeware, ImageJ (Keir et al.,2008, https://doi.org/10.1258/acb.2008.007056).

A way forward would thus be to expand their studies for any given antigen using a more direct approach to further extend and complement their quite elegant studies.

See Extended Data Fig 9 on next page or as attached file: Extended-Data-Fig9.jpg

Extended Data Fig. 9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