LETTER TO THE EDITOR

Reply: In vitro effects of a human monoclonal antibody against the N-methyl-D-aspartate receptor

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Sir,

We thank Professor Dalmau for the stimulating thoughts on our work (Dalmau, 2016). We fully agree that—already before our study—the fundamental experimental data acquired by his and further groups using human immunoglobulins from patients with N-methyl-D-aspartate receptor (NMDAR) encephalitis provided solid evidence that the clinical symptoms relate to dysfunction of NMDA receptors caused by the antibodies contained in human samples (Dalmau, 2008; Hughes et al., 2010; Prüss et al., 2010; Moscato et al., 2014; Planaguma et al., 2015, 2016). Effects in primary neuronal cell cultures mimicked the phenotype in laboratory animals and were thus designated as surrogate markers of the pathophysiology. Therefore, in this first paper using monoclonal human NMDAR autoantibodies, we focused on the established surrogate effects. Ongoing work with in vivo models will eventually confirm whether similar effects result from these (and only these) antibodies. In addition to this, the scientific community is most welcome to use these antibodies in their areas of expertise, ranging from high-resolution imaging to animal models to synaptic remodelling. In our opinion, the main achievement of the present work is not recapitulating antibody effects, but rather showing that monoclonal antibodies can be cloned from encephalitis patients and be used for biochemical and electrophysiological assays in exactly determined concentrations of the disease-specific immunoglobulin, which is impossible with human samples. We feel that this increase in availability and standardization will become a gold standard in future papers on human encephalitis autoantibodies. More importantly, precisely determined concentrations, known epitopes and antibody affinities, reproducible conditions between laboratories and many more are advantages of disease-specific monoclonal antibodies and will eventually also solve the controversial literature on the relevance of non-IgG isotype antibodies (Prüss et al., 2012; Dahm et al., 2014; Doss et al., 2014; Dalmau, 2016).

We respectfully disagree that co-existence of other antibodies is rare. As outlined in detail in the paper, we found in all patients live plasma cells that produced antibodies against further, mainly not yet specified brain epitopes. Plasma cells are continuously releasing antibodies at the rate of several thousand immunoglobulin molecules per second (Alberts et al., 2002). We agree, though, that this amount might not reach the detection threshold in clinical routine assays. In turn, low antibody levels certainly do not exclude a participation in the disease process. Unfortunately, immunoadsorption of patients’ CSF with HEK cells expressing the NMDAR (Planaguma et al., 2016) cannot unambiguously exclude the participation of further low-level antibodies. Here, ~10% of our monoclonal non-NR1 antibodies strongly bound to HEK cells and would therefore be similarly removed.

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Interestingly, our ongoing attempts to identify the target epitopes of the non-NRI monoclonal antibodies, using immunoprecipitation and mass spectrometry, resulted in attractive first candidates, such as ryanodine receptor 2 (RYR2). RYR2 antibodies are not only discussed as being pathogenic in humans (Gilhus et al., 2016), genetic dysfunction of RYR2 results in fatal cardiac arrhythmias and asystole (Meli et al., 2011). Indeed, the young NMDAR encephalitis patient from whom we cloned this antibody suffered from repeated asystole and required a transient pacemaker during her intensive care unit stay. We feel that the most interesting question emerging from this controversy is not whether further antibodies are present, but why and when some of these antibodies (AQP4, MOG, AChR, GFAP) rise to detectable levels and lead to overt symptoms (Leite et al., 2012; Titulaer et al., 2014; Fang et al., 2016), then classified as co-existing autoimmune entities, such as NMDAR encephalitis, neuromyelitis optica (NMO)-spectrum disorder or myasthenia gravis.

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**References**


Dalmau J. *In vitro* effects of a human monoclonal antibody against the N-methyl-d-aspartate receptor (Letter to the Editor). Brain 2016, in press.


