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Neurocysticercosis: Autoantibodies, Another Cog in the Wheel of Its Variable Pathogenicity

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Abstract

Neurocysticercosis (NC) presents a spectrum of clinical symptoms, with two broad clinical entities based on the CNS location of the parasite: parenchymal (P-NC) or extraparenchymal (EP-NC). In view of the importance of inflammation in the pathogenesis of NC, it is surprising that the possible occurrence of anti-brain autoantibodies in NC has not been explored until recently. In this study the presence of autoantibodies to nine ubiquitous intracellular proteins from extraparenchymal (EP-NC) was reported. Levels of these autoantibodies were greatly reduced or absent in P-NC, an observation consistent with our understanding of the immunological potential of these two distinct anatomical areas of the brain. In more recent work, we similarly observed autoantibodies to tubulin and MOG in the CSF of EP-NC, but not P-NC patients. In addition to the evident importance of the early inflammatory response, the identification of autoantibodies to the neuronal surface protein MOG (and perhaps other anti-neuronal autoantibodies) provides a potentially critical role in the pathogenesis of NC through their predicted potential for antibody mediated cytotoxicity and the subsequent release of intracellular proteins which, in turn, would stimulate a cascade of more autoantibodies to the liberated intracellular proteins. These, together with antibodies to metacestode proteins may be expected to play an important role in the continuously evolving and variable pathogenesis of NC, as is summarized in the hypothetical model presented.

Keywords: Neurocysticercosis; Anti-brain autoantibodies; Tubulin; MOG; Extraparenchymal; Parenchymal

Neurological diseases are a major cause of disability and the second cause of death today [1]. This reality has stimulated the search for predictive biomarkers facilitating early diagnosis and the design of appropriate treatments. One source of such biomarkers for inflammatory neuropathologies is autoantibodies. Indeed, of the 5.7% of the world's population with autoantibodies, 3% have been demonstrated to be anti-brain autoantibodies associatedy with a wide range of nervous system diseases, typically in individuals with Blood-Brain Barrier disruption [2].

In addition to non-infectious diseases, previous studies have suggested that parasites may also trigger activation of both cellular and serological anti-brain autoimmune mechanisms [3]. Such autoantibodies have been explained by (1) Molecular mimicry between host and

parasite molecules [3-5] and (2) The release of parasite immunogenic antigens normally "invisible" to the immune system directly or through the induction of an exacerbated inflammatory response mediated cell lysis. The relative contribution of these two mechanisms to various autoimmune neurological diseases requires further studies [6]. A crucial question for the future is to define mechanisms of molecular mimicry that exist between *Taenia solium* and neuronal antigens. At present, the only relevant observations are tenuous: (1) "Glycan mimicry" in many helminths, including *Echinococcus granulosus* and *T. solium* [7], (2) 94 tapeworm protein sequences with bioinformatic similarities to stickleback proteins [8] and (3) False positive ELISA's for *E. granulosus* with patients presenting with an undifferentiated embryonic sarcoma of the liver, interpreted as evidence for the molecular mimicry hypothesis [9].

Neurocysticercosis (NC), infection of the human Central Nervous System (CNS) by the larval phase of the cestode parasite *T. solium*, is a neglected zoonotic [10] and usually poverty-related disease of high public health importance that is still a cause of unacceptable morbidity and mortality, not only in endemic lower-income Latin America countries, Africa, and Asia, but also increasingly in high-income countries due to migration [11,12]. As the most common parasite of the CNS worldwide [13], and a major cause of seizures in endemic countries [14], NC is not a single entity. It is a "spectral" disease covering a wide range of clinical symptoms, ranging from benign to frankly life threatening, depending on the number, localization and physiological state of the parasite and the corresponding host inflammatory response. Operationally, NC presents two broad clinical entities reflecting the CNS location of the parasite; parenchymal (P-NC) and extraparenchymal (EP-NC). When the parasite is located in the cerebral parenchyma or in the sulci, the clinical picture is relatively benign and in most cases the parasites are destroyed without major symptoms. The extraparenchymal localization of the parasite in the subarachnoid space or the ventricles is clearly associated to the most severe clinical manifestation; intracranial hypertension caused by hydrocephalus as a result of mechanical obstruction of cerebrospinal fluid (CSF) flow. These patients were more likely to require a ventriculoperitoneal shunt to prevent severe complications from intracranial hypertension resulting from exacerbated inflammation [15]. EP-NC frequently required high doses of intravenous glucocorticoids, to reach therapeutic doses in the CNS and ultimately control neuroinflammation. Indeed, the cysticidal treatment must be administered in conjunction with high doses of glucocorticoids that have to be sustained both during and after the duration of the cysticidal treatment. In view of the importance of inflammation in the pathogenesis of NC, it is therefore surprising that the possible occurrence of anti-brain autoantibodies in the NC has not been explored until this year [16].

In this first study the presence of autoantibodies to brain proteins in CSF from extraparenchymal (EP-NC), but not parenchymal (P-NC) patients was reported using quantitative immunoblot methodology. There was striking correlation between the level of autoantibodies and the levels of the secreted metacestode glycoprotein HP-10, suggesting that the level of stimulation of the autoantibody response may be a function of the number of viable parasites. Examination of the immunoblot profiles of the EP-NC CSF samples revealed considerable heterogeneity between them. However, a total of nine proteins were identified by mass spectroscopy in at least 60% of the CSF samples from cases of EP-NC and thus may be provisionally considered to be possible common auto-antigens and worthy of further investigation. Gene-ontology enrichment revealed these 9 proteins to be ubiquitous intracellular proteins (Clusterin (CLU), Transthyretin (TTR), Haptoglobin (HP), Ceruloplasmin (CP), Alpha-2-Macroglobulin (A2M), CARD9 (CARD9), Cytostatin C (CST3), Angiotensin (AGT), 60S ribosomal protein L27a (RP27A)), with the majority secreted and/or involved in the immune effector process or the defense response.

Similarly, a recent study in multiple sclerosis patients found the targets of these antibodies to be ubiquitous intracellular proteins rather than brain-specific self-antigens, suggesting a nonspecific secondary response, for example to damaged/dead cells, rather than a direct pathogenic involvement [17]. Other examples of autoantibodies to ubiquitous intracellular proteins associated with cerebral disease include autism [18] and pesticide induced neurotoxicity [19].

In contrast, other authors suggest direct pathogenic effect of the CSF anti-brain antibodies in other infectious and non-infectious diseases of the brain. For example, autoantibodies to CNS neuronal surface antigens have been described in association with autoimmune encephalopathies which notably feature psychiatric in addition to neurological symptoms [20,21]. Similarly, in systemic lupus erythematosus, antibodies to double stranded DNA that cross react with the neuronal N-methyl– aspartate receptor, have recently been linked to neurocognitive dysfunction [22,23]. Infection of the CNS with herpes simplex virus can trigger anti-CNS autoimmunity associated with anti-GABA antibodies that can modify the normal activity of this neurotransmissor [24]. Anti-neural autoantibodies have been implicated in the pathogenesis of nerve damage in leprosy patients. Thus, leprosy patients are more likely to be seropositive for peripheral auto-antibodies against spinal cord than normal controls (25% vs 7%). Later on, autoantibodies against intracellular cerebroside sulphate (sulphatide) were also reported and their participation has been proposed to be involved in pathology during periods of inflammation, particularly in multibacillary patients [25].

Clearly, autoantibodies to ubiquitous intracellular proteins would only occur after autoanti-brain antibody mediated or brain injury induced cell death, often in the context of blood-brain barrier disruption and the impact of the host inflammatory response. The consequent damage in the CNS would release intracellular host proteins that could stimulate autoantibody synthesis in peripheral lymph nodes. The resulting autoantibodies in the peripheral blood could then return to the brain through the circumventricular organs or the choroid plexus, structures in the brain linked to the ventricular system and lacking a blood-brain barrier [26]. An additional possibility, facilitated by the initial inflammatory response to the extraparenchymal metacestodes, is the intrathecal synthesis of autoantibodies.

Finally, antibodies to metacestode proteins, released because of inflammation mediated damage would also be similarly generated. These, together with autoantibodies to neuronal cell surface and intracellular proteins, would be predicted to influence the progressive pathogenesis of NC

Our failure to demonstrate autoantibodies to neural cell surface proteins in this first study stimulated a more direct approach, the ELISA examination of Mexican CSF samples with clinically defined cases of EP-NC and P-NC for autoantibodies to the Major Oligodendrocyte glycoprotein surface protein (MOG) and the ubiquitous intracellular protein tubulin (Parkhouse et al., unpublished work). In this study, we also observed the presence of similar and significant levels of autoantibodies recognizing both tubulin and MOG in the CSF from some, but not all, cases of EP-NC. In contrast, such autoantibodies were greatly reduced or absent in the CSF from patients with P-NC, once again an observation consistent with differences in the immunobiology of the extraparenchymal versus parenchymal compartments. Specifically, extraparenchymal cysts are surrounded by CSF, which interacts with the peripheral immune system through its afferent and efferent connections through the dural sinuses to the deep cervical lymph nodes [27]. This communication with the peripheral immune system allowing immune-cell trafficking is much more efficient for this compartment than for the parenchymal one [28]. Moreover, most patients with parenchymal NC do not have an inflammatory CSF. Thus, it is highly relevant that we observed a statistically significant correlation between the number of cells in the CSF and the autoantibody response to MOG (R=0.68; P=0.0001) and to tubulin (R=0.72; P=0.0001) in patients with extraparenchymal NC. CSF protein titers were also significantly associated with autoantibodies titers. (R= 0.51, P=0.008 for tubulin, and R=0.48, P=0.012 for MOG). Moreover, CSF proteins closely correlate with CSF cellularity. Thus, we decided to report the relation of autoantibodies with CSF cellularity as it is a parameter more clearly involved with acute inflammation and more frequently used for this purpose.

Unfortunately, we included only 5 patients with parenchymal NCC, 4 of them with multiple parasites. In extraparenchymal, all the patients included presented parasites in the subarachnoid space, and all but one has multiple parasites. In this situation, it was impossible to make any statistical analysis. It is clear that complementary studies with more patients are necessary to better understand the relation between autoantibodies and pathogenicity.

Both tubulin and MOG have been recognized as targets for autoantibodies in a variety of cerebral neuropathologies. Examples of autoantibodies to ubiquitous intracellular proteins such as tubulin include Behcet's Disease [29], Systemic Lupus Erythematosus [30] and Sydenham's Chorea [31]. Significantly, intrathecally synthesized anti-tubulin autoantibodies have also been identified as a potential risk factor in the latter three reports and appear to be related to axonal damage [32]. While antibodies to MOG were originally thought to be involved in multiple sclerosis, over the last decade, a robust association of autoantibodies to MOG with optic neuritis, brainstem encephalitis, and acute disseminated encephalomyelitis has been demonstrated. However recent reports consider MOG-associated a disease entity in its own right, immunopathogenetically distinct from classic multiple sclerosis and neuromyelitis optica spectrum disorders [33]. The extent of CNS inflammatory diseases has recently broadened to include a new condition associated with pathogenic serum antibodies against MOG, which has been recognized as a distinct clinical disorder with a different treatment [34,35]. Indeed, new studies encountered patients with seizures associated with MOG-IgG disease [36].

From the practical point of view, autoantibodies in NC may provide novel strategies for the management and therapy of NC; for example, autoantibodies in NC patients might serve as a "biomarker" indicating the intensity of inflammation, which is a crucial factor to consider for the design of the anti-inflammatory therapeutic scheme associated to cysticidal drugs for EP-NC. EP-NC frequently required high doses of intravenous glucocorticoids, to reach therapeutic doses in the CNS and ultimately control neuroinflammation. Indeed, in EP-NC high doses of glucocorticoids must be administered both during and after the duration of the cysticidal treatment.

Furthermore, this work raises two other rational clinical possibilities: immunosuppressive therapy and the blocking of potentially pathogenic autoantibodies and other pro-inflammatory factors through the administration of normal immunoglobulin, as indeed has been reported in cases

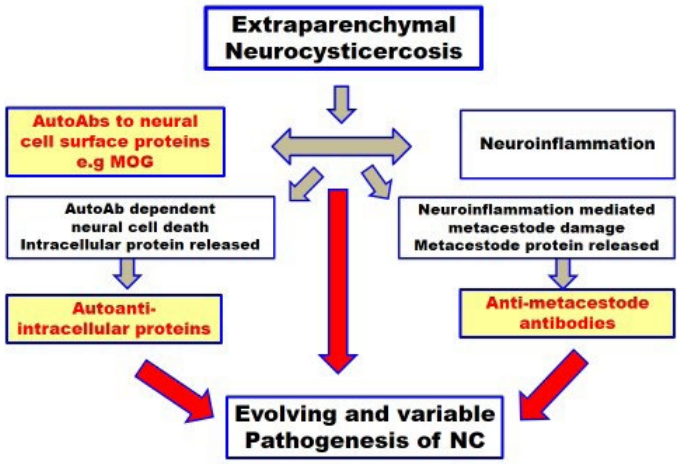

Figure 1: A hypothetical model correlating the contribution of inflammation, autoantibodies and anti-metacestode antibodies to the pathogenesis of Neurocysticercosis.

of lupus erythematosus [37] and various neurological, in particular neuro-inflammatory, conditions, such as, intractable autoimmune epilepsy, paraneoplastic syndrome, and autoimmune encephalitis [38,39], as well as the administration of monoclonal antibodies for the therapy of emerging infectious diseases [40].

In conclusion, the finding of significant levels of autoantibodies in the CSF of EP-NC, but not P-NC, patients is consistent with our understanding of the immunological potential of these two distinct anatomical areas of the brain, and highlights the need for further studies explaining the relationships between autoimmunity, neuro-inflammation and NC. In addition to the evident importance of the early inflammatory response, the identification of autoantibodies to the neuronal surface protein MOG (and perhaps other anti-neuronal autoantibodies) provides a potentially critical role through their predicted antibody mediated cytotoxicity mediated liberation of intracellular proteins which, in turn, would stimulate a cascade of more autoantibodies to the liberated intracellular proteins. These autoantibodies, together with antibodies to metacestode proteins, may be expected to play an important role in the continuously evolving and variable pathogenesis of neurocysticercosis, as is summarized in the hypothetical model presented in Figure 1.

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