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## Clinical spectrum and cellular and synaptic mechanisms of forms of autoimmune synaptic encephalitis

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## 1. Summary of the Project

Our work has revealed a new category of potentially lethal autoimmune encephalitides that are curable if recognized and treated. Patients with these syndromes were previously diagnosed incorrectly or not known to have a treatable autoimmune process. We showed that these patients had autoimmune responses characterized by the presence of antibodies against extracellular epitopes of neuronal cell surface or synaptic receptors. We postulated and have since shown in some cases that the antibodies caused dysfunction of the target antigens resulting in alterations in synaptic transmission and excitability. In addition to providing a definitive diagnosis for patients that directs appropriate therapy with immunosuppressants, the identification of the target antigen(s) is used to develop highly specific blood tests that facilitate diagnosis. In this project we aimed to study 3 syndromes for which we had evidence of autoimmunity but for which the specific antibodies and target antigens had not been identified (Specific Aim 1). We also planned to continue studies on several previously identified novel autoimmune syndromes (Specific Aim 2). Finally in Specific Aim 3 we planned to investigate the effects of patients' antibodies on neuronal function.

## 2. Results

Aim 1- To determine the range of symptoms/syndromes associated with NMDA, AMPA and GABAB receptor antibody related encephalitis

Global Summary: Over the 3 years of this grant we determined the range of symptoms and syndromes associated with NMDA, AMPA and GABAB receptor encephalitis. As detailed below this work has provided the clinical descriptions of these 3 syndromes that allow for prompt recognition and diagnosis, and has provided

guidelines for treatment. We have further characterized the associated immune responses and are in the process of developing serologic tests (not an aim of the study). Importantly, we have shown that these autoimmune encephalitis syndromes are not uncommon and represent an expanding group of potentially treatable disorders that should be included in the differential diagnosis of any type of encephalitis [1,2].

NMDA receptor encephalitis.

Our studies, including one of 577 patients with NMDA receptor encephalitis [3], have established the full clinical spectrum of this disorder, response to treatment and prognostic factors for long-term outcome. We have also characterized the clinical spectrum, response to treatment and outcome of NMDA receptor encephalitis in the pediatric and older aged populations [4-6]. We have also demonstrated that although rare, patients can present with partial syndromes such as isolated psychiatric presentations [7]. In some of these cases the patient were initially diagnosed with new onset psychosis or schizophrenia. We have uncovered a novel EEG pattern specific to this disorder that we have labeled extreme delta brush [8], and we have studied a variety of antibody testing methodologies and outlined optimal antibody testing strategies [9,10].

Our studies of this disorder have uncovered several new clinical-immunological associations. For example we have found that anti-NMDA receptor encephalitis can be triggered by a prior viral infection with herpes simplex virus and results in a syndrome previously described as non-viral choreoathetosis post-herpes encephalitis [11-15]. We have also shown that patients can develop overlapping autoimmune syndromes such as NMDA receptor encephalitis and a demyelinating disorder [16,17]. Recognition that these 2 disorders can co-exist is important because treatment and responses of each disorder are different.

AMPA receptor encephalitis.

We first described this disorder in 2009 as mostly cancer associated, with seizures and memory deficits and primarily affecting adult women. We have now developed an improved screening method for these antibodies that facilitates this diagnosis [18]. The identification of additional cases suggests a broader clinical picture and although older women are more often affected than men, this disorder does rarely occur in young patients and men.

GABAB encephalitis.

We first reported this encephalitis in 2010 in 10 patients. We have now studied additional patients and published the findings of 20 of these patients [19]. This work confirmed the GABAB receptor as an autoantigen of paraneoplastic and non-paraneoplastic limbic encephalitis, and expanded the phenotype of the syndrome to include ataxia, opsomyoclonus and status epilepticus. We also showed that long-term prognosis is dictated by the presence of a tumor. Our studies facilitate recognition of this disorder, which is important because these patients usually respond to treatment.

Aim 2- To identify novel autoantigens of the indicated subgroups noted below of encephalitis using highly sensitive methods for the presence of antibodies to cell surface proteins:

- Non-paraneoplastic limbic encephalitis
- Rapidly progressive neuropsychiatric and autistic-like syndromes with CSF pleocytosis
- Brainstem encephalitis/cerebellitis with opsomyoclonus and other eye movement disorders.

Global Summary: We have identified a novel autoantigen associated with one of the indicated subgroups (non-paraneoplastic limbic encephalitis) that lead to the description of a previously unknown autoimmune encephalitis (anti-DPPX encephalitis). We have found that patients in the second subgroup, rapidly

progressive neuropsychiatric and autistic-like syndromes with CSF pleocytosis, in fact, often have anti-NMDA receptor encephalitis despite the unusual presentation. Finally we have shown that patients in the 3rd subgroup, brainstem encephalitis/cerebellitis with opsomyoclonus and other eye movement disorders, are often young women with ovarian teratoma, without autoantibodies and that this disorder responds to immunotherapy. Additionally, we have discovered several novel autoimmune encephalitis syndromes as noted below in further detail. In sum, with the completion of the work of this Aim, as with Aim 1, we have provided physicians with clinical descriptions that help them to recognize these treatment-responsive autoimmune conditions and are providing them with specific diagnostic tests.

#### Novel autoimmune encephalitis discovered in this grant

Encephalitis with antibodies to the GABAA receptor: Patients with this syndrome are children and adults who develop a rapidly progressive encephalopathy with refractory seizures, status epilepticus and/or epilepsy partialis continua. The disorder appears to be responsive to immunotherapy although the seizures often require pharmacologically induced coma until improvement [20].

Encephalitis with antibodies to IgLON5: These patients develop non-REM and REM parasomnias and sleep breathing dysfunction with stridor. The patients are often initially misdiagnosed with obstructive sleep apnea [21]. This disorder is associated with neurodegeneration and a novel tauopathy and thus provides a possible link between autoimmunity and neurodegenerative diseases.

Encephalitis with antibodies to DPPX: This is a rapidly, progressive encephalitis, characterized by agitation, delusions, hallucinations, and myoclonic jerks and in most patients by severe diarrhea [22].

Brainstem encephalitis/cerebellitis with opsomyoclonus and other eye movement disorders. This disorder primarily occurs in young women with ovarian teratoma without autoantibodies to the neuronal cell surface [23]. Patients often respond to immunotherapy.

Encephalitis with antibodies to Homer-3. These patients develop acute cerebellar ataxia [24].

Encephalitis with antibodies to carbonic anhydrase: These patients developed a pan-cerebellar syndrome in association with a systemic cancer [25].

Aim 3- To determine the effects of patients' antibodies on the antigens and synapses in neuronal cultures.

Global Summary: Our work has confirmed that the antibodies associated with autoimmune encephalitis are pathogenic. For example, for anti-NMDA receptor encephalitis we have proved that major mechanism of neuronal dysfunction is due to antibody mediated loss of NMDA receptors due to IgG-mediated cross-linking and internalization [26]. The antibody-mediated down-regulation of surface NMDARs was shown to engage homeostatic synaptic plasticity mechanisms. For anti-AMPA receptor encephalitis we have shown that patient antibodies selectively eliminate surface and synaptic AMPARs, resulting in a homeostatic decrease in inhibitory synaptic transmission and increased intrinsic excitability [18]. The implications of these findings extend beyond the autoimmune encephalitis under study in this application. For example, homeostatic responses to altered levels of neuronal activity have been found or hypothesized to occur in several neurological disorders, including epilepsy, myasthenia gravis, Alzheimer's disease, and schizophrenia. In schizophrenia, and NMDA hypofunction models, loss of inhibition may contribute to symptom profile and disease progression. Thus our findings add to the general understanding of the

mechanisms that drive synaptic circuit-level changes that underlie behavioral and neurological symptoms and may provide an important link between the pathophysiological events of anti-NMDAR encephalitis with those of other disorders with similar neuropsychiatric manifestations.

### **3. Relevance and possible implications**

Our work has directly impacted patient care in several ways.

- 1- The identification of new autoimmune encephalitis has reclassified syndromes of unclear pathogenesis (e.g. patients previously diagnosed with idiopathic disorders, or viral related diseases even when no viruses were found). We now know that many of these patients have autoimmune encephalitis and are potentially responsive to immunotherapy.
- 2- Our detailed description of the clinical characteristics of these disorders helps to diagnose patients with atypical syndromes that did not fit well with any one particular disorder. For example, by revealing that some patients develop overlapping syndromes, patients that were previously considered as simply having an atypical presentation of one disease are now known to have 2 concurrent disorders (e.g. anti-NMDA receptor encephalitis and a demyelinating disease) that each require different treatment.
- 3- We have developed simple diagnostic tests that are in clinical use.
- 4- Our studies of these patients (in particular anti-NMDA receptor encephalitis, which is the most frequent) have demonstrated prognostic and predictive factors for response to treatment and outcome that directs management of these patients.

5- Our studies of different antibody testing methods have demonstrated which method is the most sensitive and specific.

On a basic level our work has the following relevance and impact.

1- By examining antibody-induced changes of the structure and function of the target receptors our work has revealed novel and important mechanisms that link synaptic function with alterations in memory, behavior, seizures, movement disorders and sleep disturbances, among others.

2- Knowledge of how antibodies affect receptor function has provided a new framework for analyzing and understanding synaptic health and function.

3- Understanding how antibodies cause symptoms will lead to strategies to block their effects.

Our findings will improve the understanding of the neuronal basis of symptoms in other disorders (e.g. NMDAR hypofunction hypothesis of schizophrenia or the decrease of synaptic GABA<sub>A</sub>R and status epilepticus).

#### **4. Publications Produced (53)**

Relevant presentations at national and international meetings: 28

Armangue T, Leyboldt F, Dalmau J. Autoimmune encephalitis as differential diagnosis of infectious encephalitis. *Curr Opin Neurol* 2014;27(3):361-368.



Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. *Clin Infect Dis* 2012;54(7):899-904.

Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013;12(2):157-165.

Titulaer MJ, McCracken L, Gabilondo I, Iizuka T, Kawachi I, Bataller L, et al. Late-onset anti-NMDA receptor encephalitis. *Neurology* 2013;81(12):1058-1063.

Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. *J Child Neurol* 2012;27(11):1460-1469.

Armangue T, Titulaer MJ, Malaga I, Bataller L, Gabilondo I, Graus F, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013;162(4):850-856.

Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti-N-methyl-d-aspartate receptor encephalitis. *JAMA Neurol* 2013;70(9):1133-1139.

Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012;79(11):1094-1100.

Gresa-Arribas N, Titulaer MJ, Torrents A, Aguilar E, McCracken L, Leypoldt F, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol* 2014;13:167-177.

Hoftberger R, Dalmau J, Graus F. Clinical neuropathology practice guide 5-2012: updated guideline for the diagnosis of antineuronal antibodies. *Clin Neuropathol* 2012;31(5):337-341.

Armangue T, Leypoldt F, Malaga I, Raspall-Chaure M, Marti I, Nichter C, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. *Ann Neurol* 2014;75:317-323.

Leypoldt F, Titulaer MJ, Aguilar E, Walther J, Bonstrup M, Havemeister S, et al. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. *Neurology* 2013;81(18):1637-1639.

Titulaer MJ, Leypoldt F, Dalmau J. Antibodies to N-methyl-D-aspartate and other synaptic receptors in choreoathetosis and relapsing symptoms post-herpes virus encephalitis. *Mov Disord* 2014;29(1):3-6.

Hoftberger R, Armangue T, Leypoldt F, Graus F, Dalmau J. Clinical Neuropathology practice guide 4-2013: post-herpes simplex encephalitis: N-methyl-D-aspartate receptor antibodies are part of the problem. *Clin Neuropathol* 2013;32(4):251-254.

Pruss H, Finke C, Holtje M, Hofmann J, Klingbeil C, Probst C, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol* 2012;72(6):902-911.

Titulaer MJ, Hoftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, et al. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol* 2014;75(3):411-428.

Cobo-Calvo A, Izquierdo GC, Quinones SM, Torro CM, Saiz A, Dalmau J, et al. Optic neuritis in the setting of NMDA receptor encephalitis. *J Neuroophthalmol* 2014;34(3):316-319.

Gleichman AJ, Panzer JA, Baumann BH, Dalmau J, Lynch DR. Antigenic and mechanistic characterization of anti-AMPA receptor encephalitis. *Ann Clin Transl Neurol* 2014;1(3):180-189.

Hoftberger R, Titulaer MJ, Sabater L, Dome B, Rozsas A, Hegedus B, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. *Neurology* 2013;81(17):1500-1506.

Petit-Pedrol M, Armangue T, Peng X, Bataller L, Cellucci T, Davis R, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABA<sub>A</sub> receptor: a case series, characterization of the antigen, and analysis of the effects of antibodies. *Lancet Neurol* 2014;13:276-286.

Sabater L, Gaig C, Gelpi E, Bataller L, Lewerenz J, Torres-Vega E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol* 2014;13:575-586.

Boronat A, Gelfand JM, Gresa-Arribas N, Jeong HY, Walsh M, Roberts K, et al. Encephalitis and antibodies to dipeptidyl-peptidase-like protein-6, a subunit of Kv4.2 potassium channels. *Ann Neurol* 2013;73(1):120-128.

Armangue T, Titulaer MJ, Sabater L, Pardo-Moreno J, Gresa-Arribas N, Barbero-Bordallo N, et al. A novel treatment-responsive encephalitis with frequent opsoclonus and teratoma. *Ann Neurol* 2014;75(3):435-441.

Hoftberger R, Sabater L, Ortega A, Dalmau J, Graus F. Patient with homer-3 antibodies and cerebellitis. *JAMA Neurol* 2013;70(4):506-509.

Hoftberger R, Sabater L, Velasco F, Ciordia R, Dalmau J, Graus F. Carbonic anhydrase-related protein VIII antibodies and paraneoplastic cerebellar degeneration. *Neuropathol Appl Neurobiol* 2014;40(5):650-653.

Moscato EH, Peng X, Jain A, Parsons TD, Dalmau J, Balice-Gordon RJ. Acute mechanisms underlying antibody effects in anti-N-methyl-D-aspartate receptor encephalitis. *Ann Neurol* 2014;76:108-119.