Basic Neuroimmunology

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Outline

• Essential immunology (innate + adaptive) for neurologist with clinical correlation to neurological disease
• Immunity control: tolerance and immune-homeostasis
• General concept of autoimmune disease
• Pathophysiology of immune mediated disease in CNS & PNS
• General concept for treatment & monitor patients with immune mediated disease
Innate system works first & fast to recognize foreign subjects

Innate immune

• Initial response to infection or damage
• Macrophage, dendritic cells, neutrophils, NK cell are triggered by damaged or dying cell
  • Host cell damage → cellular debris DAMPs (damage-associated molecule patterns)
  • Pathogen attacks cause common molecular structures on cell surface → PAMPs (pathogen associated molecular pattern)
  • Both DAMPs & PAMPs are recognized by “pattern-recognition receptors” such as TLR, NLR, NK receptor
• Complement activation
Innate mechanism

Pattern recognition mechanism
by PRR (TLR, NLR, NK rec)

Complement mechanism

Complement system

Eculizumab: drug that binds to C5 and inhibit the cleavage of C5 by C5 convertase
Innate immunity in CNS

- Microglia: phagocytose & produce trophic factors, chemokines, cytokines, complement protein, ROS, NO
- Play an important role in neurodegenerative disease (ALS, PD, AD)

Adaptive immune response

1. Specificity
2. Diversity: total number of antigenic specificities of lymphocytes in an individual = repertoire
3. Memory
4. Clonal expansion
5. Specialization
6. Homeostasis
7. Non-reactive to self: tolerance

Abbas et al: Cellular and Molecular Immunology, Updated Fifth Edition. Copyright © 2009 by Saunders, an imprint of Elsevier, Inc. All rights reserved.
Many types of lymphocytes

**B lymphocyte:**
- Ab production
- Ag presentation

**Helper T lymphocyte:**
- Th1 → Activation of macrophage
- Th2 → Help B cell in Ab production
- Th17 → Granulocyte recruitment
- Treg → control immune

**Cytotoxic T lymphocyte:**
- Cellular cytotoxicity

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Abbas et al. Cellular and Molecular Immunology, Updated 6th Edition. Copyright © 2009 by Saunders, an imprint of Elsevier, Inc. All rights reserved.
Duration of immune process $\rightarrow$ usually within 2-3 weeks

**Antigen specificity** $\rightarrow$ antibodies bind to specific antigenic expression along neural axis

**Marker of immune response:** antibodies, activated T cell, inflammatory cytokines

**Self remitting**

**Relapsing**

**Peripheral lymphoid organs:**
Where Innate (APC) activates Adaptive (lymphocytes)
S1P and its receptors

Afferent naive T cells migrate through lymph nodes, are activated & egress through an S1P-S1P₁ receptor gradient (low in lymph node, high in the circulation) → induce migration of lymphocytes from lymph node into circulation

S1P and its receptors

Fingolimod is phosphorylated in vivo after oral ingestion → initially act as an agonist of S1P₁ receptor → becomes a highly potent functional antagonist → internalization of S1P₁ receptors on lymph-node T cells → lymphocytes no longer respond to the gradient of S1P & remain sequestered in the lymph node.
Antigen presenting cell: key of adaptive immune response initiation

Antigen processing:
1. Extracellular protein → MHC II → CD4+ T cell
2. Intracellular protein → MHC I → CD8+ T cell
3. Extracellular protein (tumor cell Ag) → MHC I (cross presentation) → CD8+ T cell
Cross presentation:

Unique characteristic of dendritic cell: present antigen from another cell type (tumor cell or viral infected cell) to T cells that specific for these antigen

T cell recognize:

peptide + MHC + Co-stimulator
T cell & B cell interaction in lymph node

Step of B cell activation:

1. Dendritic cell presents [Ag + MHC II + B7-1,2] to Helper T cell (TCR + CD28)
2. Helper T cell recognize [Ag + MHC II + B7-1,2] , then express CD40 ligand + secrete cytokine
3. CD40 ligand on activated T cell binds CD40 on B cell → B cell proliferation & differentiation
Cytokines in immune response

B cell development

2 phases:
- **Maturation phase**: HSC → naïve B cell (controlled by cytokines & foreign Ag independent)
- **Differentiation phase**: activation by foreign Ag + generation of plasma cell & memory B cell

Whittam DH, 2018
B cell marker in each stage

- CD19 & CD20 are B cell transmembrane protein
- Both are absent in plasma cell
- CD19+CD27+ is specific to memory B cell

Rituximab: anti-CD20 is widely use for autoimmune disease & B cell lymphoma

Immunoglobulin

- 2 Heavy (H) + 2 Light (L) chains
- Variable (V) & Constant (C) domains
- H: 1 V_H + 3 C_H
- L: 1 V_L + 1 C_L

Fab = fragment antigen binding
Fc = fragment crystallisable
CDR = complementary determining region

Fc receptors activation
H & L chain isotype

<table>
<thead>
<tr>
<th>Basic structure</th>
<th>Heavy chain isotypes</th>
<th>Heavy chain domains</th>
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<tr>
<td>IgG</td>
<td>μ</td>
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<tr>
<td>IgD</td>
<td>δ</td>
<td>Cδ1-3</td>
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<tr>
<td>IgE</td>
<td>γ1, γ2</td>
<td>Cγ1-3</td>
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<tr>
<td>IgA</td>
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<td></td>
<td>Mouse 5</td>
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<td>λ</td>
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Immunoglobulin property

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<td>Binding to:</td>
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<td>Lymphocytes</td>
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<td>2.5</td>
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<td>Synthesis mg/kg/day</td>
<td>25 ? 3.5 ?</td>
<td>24 ? 7</td>
<td>0.4</td>
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Function of immunoglobulin

- **Neutralization**: secreted Ab bind to virus, toxin → protect host cell from being attracted
- **Classical complement activation**: IgM, IgG1, IgG2, IgG3
- **Opsonization**: Ag is coated by IgG1, IgG3 → enhance recognized by phagocytic cells [Fc mediated]
- **Antibody-Dependent Cell-Mediated cytotoxicity (ADCC)**: Fc mediated through FcR on NK cell → release cytotoxic granule

T cell expansion & differentiation
NMOSD pathogenesis: IgG mediated astrocytic injury

Davoudi V, 2016

NMO pathogenesis

Obermeier et al 2013
Tolerance: key control of self immunity

- **Tolerance** begins at the very beginning step of lymphocyte development
- For T cell: *thymic education* is the main mechanism for protecting from self-immunity
- Only **1%** of precursor cell entering thymus (thymocytes) leave as mature T cells
- Thymic education = selection process → Central tolerance (major tolerance mechanism)

Central tolerance: *thymic education*

- **[Thymic cortex]:** T cell with TCR able to bind host MHC are survive
- **[Thymic cortex]:** T cell with low affinity binding to *self Ag*, but high affinity binding with *foreign Ag* are selected → positive selection (protective immunity)
- **[Thymic medulla-AIRE]:** T cell with high affinity binding to *self Ag*, are deleted → negative selection (autoimmunity)

*AIRE gene produce tissue-restricted Ag (TRA) such as insulin*

Normally some autoreactive T cell may survive from this process. **Failure of central tolerance may induce autoimmunity**
Peripheral tolerance

1. Anergy: Exposure of mature CD4+ T cell to Ag in the absence of costimulation or innate immunity → incapable of responding to that Ag

2. Suppression by Regulatory T cell (Treg): subset of CD4+ suppress immune response & maintain self-tolerance. This cell express high level of IL-2 receptor (CD25) + FoxP3 (transcription factor)

3. Deletion of T cells by apoptotic cell death: T cell that recognize self Ag with high affinity or are repeatedly stimulated by Ags → apoptosis

Mechanism of Anergy

- CTLA-4: competitive inhibitor of CD28 & reduces the availability of B7 for the CD28 receptor
- PD-1: another inhibitory receptor of CD28; PD-1 recognizes 2 ligands PD-L1 & PD-L2 (expressed on APC)
Drugs that block CTLA-4 or PD-1 pathway

- Since tumors can produce PD-1 ligand (PD-L1) → inhibit tumor specific activated T cell to kill tumor
- Drugs that block CTLA-4 or PD-1 pathway → promote activated T cell to kill tumors
- PD-1 checkpoint inhibitor: can produce autoimmune disease

Suppression by Tregs

Three mechanisms of Tregs:
1. Production of immunosuppressive cytokines IL-10 & TGF-β
2. Reduced ability of APCs to stimulate T cells
3. Consumption of IL-2

- FoxP3 gene mutation → absence of Tregs → IPEX
- Drugs that have similar effect of IL-2 or promote binding of CD25 → activate Tregs → Rx autoimmune disease
B cell tolerance

- Necessary for maintaining unresponsiveness to thymus-independent self-Ag
- Preventing Ab responses to protein Ag
  - **Central B cell tolerance**: immature B cell that recognizes self Ag in BM with high affinity → changed their specificity or are deleted
  - **Peripheral B cell tolerance**: mature B cell that recognize self Ag in peripheral tissues in the absence of specific Th → functionally unresponsive or apoptosis
Restoring immune tolerance therapy

Peptide-induced tolerance: excess Ag administer → burst proliferation of autoreactive T cell → activation induce cell death [Vaccine]

Antigen-couple-cell induce tolerance: activation without costimulation signal → anergy or activate through Treg → suppress immune response

Alter-peptide ligand: change amino acid in peptide → Th2/Treg stimulation [Glatiramer acetate]

New Rx in NMO

<table>
<thead>
<tr>
<th>Tolerance strategy</th>
<th>Material source</th>
<th>Biological source</th>
<th>Primary target</th>
<th>Animal studies</th>
<th>Example study outcomes</th>
<th>Human studies</th>
<th>Example study outcomes</th>
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<tr>
<td>Inverse DNA vaccine</td>
<td>Heterologous</td>
<td>Engineered</td>
<td>APC, Tc, and Bc subsets</td>
<td>Yes**</td>
<td>Induction of tumor suppression</td>
<td>Yes**</td>
<td>Reduction in proinflammatory CD8+ T cells</td>
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<tr>
<td>Autoreactive Tc vaccine</td>
<td>Autologous</td>
<td>Natural</td>
<td>Autoreactive Tc</td>
<td>Yes**</td>
<td>Mortality reduced from 50% to 0% in SJL/J mice</td>
<td>Yes**</td>
<td>Induction of CD8+ Tc-attenuated T2D severity</td>
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<tr>
<td>Dendritic cell vaccine</td>
<td>Autologous</td>
<td>Natural</td>
<td>AQP4 presentation</td>
<td>Yes**</td>
<td>Tolerogenic DC vaccine protective in EAE model</td>
<td>Yes**</td>
<td>Mixed outcomes of Ag-specific DC in T2D</td>
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<tr>
<td>Ap-coupled presentation</td>
<td>Autologous</td>
<td>Engineered</td>
<td>AQP4 presentation</td>
<td>Yes**</td>
<td>Expansion of Ap-specific CD4+ and CD8+ Tc</td>
<td>Yes**</td>
<td>Treg reactivity to myelin Ag peptide in patients with MS</td>
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<tr>
<td>Tc receptor engineering</td>
<td>Autologous</td>
<td>Engineered</td>
<td>Autoreactive Tc</td>
<td>Yes**</td>
<td>Induction of Treg subset in mouse EAE model</td>
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<td>Moderate efficacy in human malignancies</td>
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<td>Regulatory Tc induction</td>
<td>Autologous</td>
<td>Natural</td>
<td>Proinflammatory cell pathways</td>
<td>Yes**</td>
<td>Treg induction in various preclinical models</td>
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<td>Expansion of Treg subset attenuates inflammation</td>
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<tr>
<td>Regulatory Bc induction</td>
<td>Autologous</td>
<td>Natural</td>
<td>Proinflammatory cell pathways</td>
<td>Yes**</td>
<td>Suppression of Tc autoreactivity, binding immunoglobulin protein induces Breg</td>
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<td>No NA</td>
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<td>Oral/mucosal tolerization</td>
<td>Recombinant</td>
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<td>APC, Tc, and Bc subsets</td>
<td>Yes**</td>
<td>CD4+CD25+Foxp3+LAP+ Treg induction in various preclinical models</td>
<td>Yes**</td>
<td>Lower TNFα, higher IL-10 induction by Ag-specific Tc; allergic desensitization</td>
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<tr>
<td>Adaptive transfer</td>
<td>Autologous or HLA-matched</td>
<td>Conditioned natural</td>
<td>APC, Tc, and Bc subsets</td>
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<td>Modest efficacy in murine arthritis and lupus</td>
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<td>Efficacy in GVHD</td>
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<td>Pathogenic Ab</td>
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<td>Anti-idiotypic induction in NOD mouse model</td>
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<td>Passive tolerization</td>
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<td>Either</td>
<td>Pathogenic Ab</td>
<td>Yes**</td>
<td>Passive aquaporinmab efficacy in EAE model</td>
<td>Yes**</td>
<td>No NA</td>
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</table>

Table: Potential strategies for restoring immune tolerance in NMO/SD

Miller SD, et al 2007

Privileged site of CNS & PNS

• Nervous system (CNS & PNS): privileged site, protect by BBB & BNB
• Based on
  1. There is separate anatomic separation between systemic immune (blood) & neural tissue
  2. MHC molecules are absent in normal circumstance
  3. No lymphatic drainage, but have *glymphatic pathway*
  4. Immune surveillance by T cell is lacking

Blood – Brain & Blood - CSF Barrier

Blood-brain barrier: Capillaries & Brain parenchyma
Blood-brain-CSF barrier: Capillaries-brain parenchyma-ependyma
How immune cells attack CNS

John, B et al, 2014

T cell entering CNS

α4β1 integrin on central memory T cell binds to stromal receptor in choroid plexus → T cell enter CSF

Natalizumab

α4β1 integrin on central memory T cell binds to CS1 site (fibronectin) in CNS endothelium → T cell enter brain
Autoimmunity: definition

- Host itself is attacked by immune system
- Failure or breakdown of the mechanisms normally responsible for maintaining self-tolerance in B cells, T cells, or both.
- The major factors: genetic susceptibility & environmental triggers, such as infections.
- Systemic or organ specific
- Various effector mechanisms: immune complexes, circulating autoantibodies & autoreactive T lymphocytes

Mechanism of autoimmunity

Epitope spreading: autoimmune reaction from one self Ag → release & alteration of other tissue Ag → activation of lymphocytes specific for other antigens → exacerbation of disease (chronic & progressive)
Establishing autoimmune disease (Koch’s postulate)

1. Existence of autoAb or autoreactive T cell should be demonstrated
2. Bindings of autoAb should be detectable at target structures
3. Experimentally, characteristic features of the disease should be reproducible by active immunization with putative autoantigen, passive transfer of autoAb or autoreactive T cells
4. The disease should respond to immunosuppressive/depletion therapy

Pathogenesis of autoimmune disease of the nervous system

- **Antibody recognized cell surface antigen or receptor:** Pathogenic antibody
  - Anti-NMDAR, Anti-Lgi1, Anti-GABAb etc.
  - Anti-AQP4, Anti-MOG

- **Antibody recognized intracellular antigen:** T cell mediated
  - ANNA1 (anti-Hu), ANNA2 (anti-Ri), PCA-1 (anti-Yo) etc.

- **Antibody recognized synaptic protein or enzyme:** possible pathogenic
  - Anti-GAD65, Anti-amphiphysin
Depolarization → Action potential → excitatory transmission

Depolarization → Action potential → Muscle contraction
Pathogenesis of autoimmune disease of the nervous system

• Antibody recognized cell surface antigen or receptor: Pathogenic antibody
  • Anti-NMDAR, Anti-Lgi1, Anti-GABAb etc.
  • Anti-AQP4, Anti-MOG

• Antibody recognized intracellular antigen: T cell mediated
  • ANNA1 (anti-Hu), ANNA2 (anti-Ri), PCA-1 (anti-Yo) etc.

• Antibody recognized synaptic protein or enzyme: possible pathogenic
  • Anti-GAD65, Anti-amphiphysin
Cross presentation mechanism

CD 8+ T cell
ER
MHC I
Tumor peptide
TCR

Granzyme-mediated tumor apoptosis

T cell CD8+
Inciting event
Neuronal cell in Hippocampus (neuron express ELAVL)

T cell CD4+
B cell
Marker
Autoantibody

ANNA-1 (Anti-Hu)

BBB
Limbic encephalitis
IFN-b in MS Rx exacerbate NMO

Various proposed mechanisms:
- Induce Th17 → ↑ granulocyte recruitment
- Shift to Th2 cytokines → aggravate B cell in Ab production
- Increase expression of CD80/86 (B7.1/B7.2) costimulatory signal and IL-6 in B cell
Pathogenesis of autoimmune disease of the nervous system

- **Not definite**

- **CNS**: Autoimmune limbic encephalitis (GAD-IgG, CRMP-IgG, Amphiphysin-IgG)

- **PNS**: Immune mediated neuropathy (Ganglioside-IgG, IgM ???)

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**Ab or T cell mediated PNS demyelination: CIDP**

Koller H, et al. 2005
General approach to patients suspected autoimmune neurological disease

• Thoroughly history taking & general + neurological examination
  • PHx of autoimmune disease: DM type 1, pernicious anemia, thyroid disease, hepatitis, etc.
  • PHx or symptoms & signs suspected malignancy: unexplained weight loss, bowel habit change, etc.
  • FHx: autoimmune & malignancy

Laboratory investigation

• For confirmed diagnosis:
  • Serum + CSF for autoantibody: sensitivity depends on types of disease
    • NMOSD: serum is more sensitive (both AQP4-IgG & MOG-IgG)
    • LE: CSF is more sensitive, except in Caspr2 & some circumstance of Lgi1
  • CSF profile: lymphocytic pleocytosis, mildly elevated protein, normal sugar, OCB
    • Outlier: neutrophil predominated (neuroBechet), eosinophil (NMO), high protein if CSF blockage from spinal cord edema in NMO
    • Normal profile: NOT exclude autoimmune disease
  • Imaging study: MRI
Laboratory investigation

• For preparing patient before immunosuppressive Rx
  • Blood sugar
  • Anti-HIV
  • HBsAg
  • Anti-hepatitis C
  • CBC
  • LFT

Treatment

• Mainly immunosuppressive therapy
• Acute Rx
• Long-term Rx
Acute Rx

- **Pathogenic antibody mediated disease**
  - Immunodepletion therapy *initially*:
    Plasma exchange or IVIg or immunoadsorption
  - Then immunosuppression: High-dose steroid or rituximab or pulse cyclophosphamide:
    Methylprednisolone 1 g IV drip in 4-6 hrs X 5 days
    Rituximab 1000 mg x 2 (2 weeks apart) then q 6 mo [or 375 mg/m² weekly x 4] then FU CD19 or CD27 (keep < 0.1%)
    Cyclophosphamide 0.5-1 g/m² monthly

- **T cell mediated disease**
  - Immunodepletion therapy may have benefit (decrease inflammatory mediator), but usually not effective
  - High-dose steroid or pulse cyclophosphamide:

**Mechanism of IVIg**

- Not well understood
- Reduced inflammatory cytokines, T cell ICAM down-regulation, enhanced FcyRIIB expression, anti-idiotypic Ab or increased autoantibody metabolism

Yu Z, Lennon VA, NEJM 1999
New drug for immunodepletion in MG

Randomized phase 2 study of FcRn antagonist efgrartigimod in generalized myasthenia gravis

James F. Howard, Jr., MD, Vera Bril, MD, Ted M. Burns, MD, Renato Mantegazza, MD, Malgorzata Bilinska, MD, Andrej Szczudlik, MD, Said Beydoun, MD, Francisco Javier Rodríguez De Rivera Garrido, MD, Fredrik Piehl, MD, PhD, Mariarosa Rottoli, MD, Philip Van Damme, MD, PhD, Tuan Vu, MD, Amelia Evoli, MD, Miriam Freimer, MD, Tahseen Mozaffar, MD, E. Sally Ward, PhD, Torsten Dreier, PhD, Peter Ulbrichts, PhD, Katrien Verschuuren, MSc, Antonio Guglietta, MD, Hans de Haard, PhD, Nicolas Leupin, MD, and Jan J.G.M. Verschuuren, MD, PhD, on behalf of the Efgartigimod MG Study Group

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Long term Rx

• Depend on disease: tailor to individual

• **Monophasic (ADEM) or less likely relapse (seronegative NMO?)** → taper steroid and off within 6-9 months

• Weight between benefit & side effect

• Long term data suggests AQP4-IgG positive NMOSD trends to use life-long immunosuppression
Maintenance Rx:

- **Oral prednisolone** taper over 4-6 months then maintain low dose steroid 15-20 mg/day for > 2 years - life long + steroid sparing drugs (azathioprine 2-3 mg/kg/d or mycophenolate up to 2 g/d or methotrexate 7.5-15 mg/week)

- Monitoring for drug side effects:
  - Azathioprine, mycophenolate: CBC weekly x 4 then q 2 weeks for 2 months then monthly
  - Metabolic complication: BS, bone density, cataract, glaucoma, HT

- Other drugs supplement: Calcium + Vit D, PPI, PCP or zoster prophylaxis if indicated, vaccination

- Aware TB, parasite, Hepatitis

Use clinical as the marker for treatment; Not Ab

Paraneoplastic anti-NMDAR encephalitis: long term follow-up reveals persistent serum antibodies

Harry Alexopoulos · Michalis L. Kosmidis · Josep Dalmau · Marinos C. Dalakas

*J Neurology 2011*

Persistent Intrathecal Antibody Synthesis 15 Years After Recovering From Anti–N-methyl-D-aspartate Receptor Encephalitis

Hans-Christian Hansen, MD, Christine Klingbeil, Josep Dalmau, MD, PhD, Wenhan Li, MD, Benedikt Weißbrich, MD, and Klaus-Peter Wandinger, MD

*JAMA Neurology 2013*
MOG-IgG status predicts Rx

- Persistent of MOG-IgG (> 3 months) is the risk for relapse and justify for long term immunosuppression
- In transient MOG-IgG positive → more likely to be monophasic and may not benefit for long term immunosuppression

Lopez Chiriboga S, 2018
Pregnancy & mother immune status

- Generally immune status during pregnancy has *shift to anti-inflammation phase*
- Some of autoimmune disease activity have been modulate to low activity or at least not change to pre-pregnancy
- MS registry study shows decreased in RR during pregnancy (NMO → not change), but rebound in post partum period
- But in NMOSD, AQP4-IgG can attack AQP4 expressed in placenta → cause pre-eclampsia & abortion
IgG status in fetus & newborn

Maternal IgG can passive transfer to fetus → protect newborn afterbirth, but may transfer pathogenic Ab as well → e.g. neonatal MG (hypotonic or developing joint contracture; arthrogryposis multiplex congenital)

Clinical may recover in a few weeks or months