Clinical Evaluation of Neuromyelitis Optica Spectrum Disorder

Module 2: Pathophysiology
• About the Foundation

The Guthy-Jackson Charitable Foundation is a non-profit 501(c)(3) organization that promotes research to understand the causes and advance effective solutions to Neuromyelitis Optica (NMO) / Neuromyelitis Optica Spectrum Disorder (NMO/SD). The Foundation adheres to a transparent and equitable model that does not favor or endorse any particular company, institution or drug candidate.

• Clinical Position Statement

GJCF supports efforts directed at the prevention, diagnosis, treatment and cure of Neuromyelitis optica (NMO) and NMO spectrum disorders (NMO/SD). It facilitates scientific and clinical advances directed toward these goals, including educational tools developed by academic and clinical experts.

The Foundation neither performs clinical functions nor does it offer advice about the evaluation, care or treatment of patients. The GJCF does not participate in the performance, evaluation, analysis or management of clinical trials or in the interpretation of trial outcomes.

• Equal Opportunity Advocate

The Foundation functions in a transparent, neutral, and equitable manner in all of its interactions with academic experts, clinical trial sponsors, investigators, governmental and private agency or group representatives and other NMO/SD stakeholders.

For more information, please visit the Foundation website: www.guthyjacksonfoundation.org
Module 2: Learning Goals

Astrocytes & AQP4 Protein

NMO/SD Etiologic Theories

Loss of Immune Tolerance

Pathogenesis of NMO/SD

Clinical Laboratory Results
Astrocytes and Aquaporin–4

• CNS Overview:
  - Brain, optic nerves, and spinal cord
  - Two fundamental tissue types:
    - White matter: axons; oligoDCs; astrocytes
    - Gray matter: neurons; oligoDCs; astrocytes
  - Space / volume limited compartment
  - Partitioned from periphery by the BBB
  - Active monitoring by immune system
Astrocytes and Aquaporin–4

• **Astrocytes:**
  - Stellate glial cells predominant in CNS
  - Two phenotypes: $\text{FGF}_3^+$ (I) or – (II)
  - Support neuron / endothelial metabolism
  - Integral to BBB and vasomodulation
  - Regulate neurotransmitters & ion flux
  - AQP-4 expression is astrocyte-specific
  - AQP-4 enriched at end-foot processes
  - End-feet abut myelin at nodes of Ranvier
Astrocytes and Aquaporin–4

• **Aquaporin–4:**
  - 2003 Nobel Prize (aquaporins): Peter Agre
  - Hetero-tetrameric water channel protein
  - Two isoforms: M1 (full-length) vs. M23
  - Transmembrane anchor via α–syntrophin
  - Localized to abluminal / endothelium facet
  - Concentrated at pia & nodes of Ranvier
  - M23-rich tetramers form orthogonal arrays
Astrocytes and Aquaporin–4

Endothelial Cell

Aquaporin-4 Protein

Astrocyte Endfoot

Capillary Lumen

Anti-AQP4 Immunogold Conjugated MAb Stain

Nature Rev Neuroscience [2003] 4:10.1038/nrn1252
Astrocytes and Aquaporin–4

Distribution

- AQP-1
- AQP-4

Nature Rev Neuroscience
[2003] 4:10.1038/nrn1252
NMO/SD Etiologic Theories

• Etiology:

  - Unknown – hypotheses may include:
    o Polygenic: e.g. ΔAQP4; HLA; TcR
    o Loss of immune tolerance to AQP4
    o M1-M23 orthogonal array autogens
    o Molecular mimicry (e.g. microbial)
    o Ectopic AQP-4 expression (e.g. tumor)
    o Combination of the above or other
Loss of Immune Tolerance

• **Immune Tolerance:**
  - 1960 Nobel Prize: Burnet & Medawar
  - The lack of immune response to “self”
  - Central: censor autoreactive Tc & Bc
  - Peripheral: temper Tc & Bc response
    - Modulation of autoreactive Tc or Bc
    - Promotion of regulatory Tc or Bc
  - Variation over human lifespan
Loss of Immune Tolerance

• Loss of Tolerance to AQP-4:
  ▪ Immune system: AQP-4 as foreign:
    o △ antigenicity of AQP-4 protein
    o △ AQP-4 Ag presentation by APC
    o △ APC-TcR interaction / 2° signal
    o Aberrant Tc and/or Bc response
    o Insufficient immune modulation
    o Combination of above or other
Pathogenesis of NMO/SD: 1

• **Sero+ Pathogenesis:**
  
  - Basic loss of immune tolerance to AQP-4
  - APC + TcR + BcR recognition ➔ NMO-IgG
  - NMO-IgG targeting to astrocyte AQP-4
  - Complement fixation & chemoattraction
  - Direct C’–mediated astrocyte damage
  - Ensuing granulocyte & MΦ recruitment
  - ADCC amplification of astrocyte toxicity
  - Inflammation & secondary demyelination
Pathogenesis of NMO/SD: 3

- **Sero– Pathogenesis:**
  - Likely initial loss of immune tolerance
  - MOG (myelin Ag) & other Ag candidates
  - If Ab-mediated, similar to NMO-IgG path:
    - Direct C’ astrocyte toxicity
    - Inflammatory cell recruitment
    - Primary de-myelination
  - If not Ab-mediated, other mechanism(s)
Pathogenesis of NMO/SD: 4

• Prototypic Histology:
  - IgG & IgM perivascular accumulation
  - Complement activation & deposition
  - Neutrophil, eosinophil, Mϕ trafficking
  - Major loss of immunoreactive AQP-4
  - Less extensive loss of myelin antigens
  - Non-necrotic, reversible astrocytopathy
  - Non-focal, diffuse astrocyte activation
Pathogenesis of NMO/SD: 5
Clinical Laboratory Results

- **Prototypic Findings:**
  - 70-80% of patients sero+ for NMO-IgG
  - Co-morbid auto-antibodies are common
  - CSF distinct from infectious disease:
    - Typically normal glucose
    - Modest rise in total protein
  - Imaging: ON, LETM; ± brain lesions
  - In context of altered vision and/or CNS
Module 2: Summary

- Astrocytes & AQP4 Protein
- NMO/SD Etiologic Theories
- Loss of Immune Tolerance
- Pathogenesis of NMO/SD
- Clinical Laboratory Results
Module 2: References


NMO/SD Resources

- 2015 IPND Diagnostic Card / Toolkit
- **NMOtion** Patient & Advocate Gateway
- Searchable NMO/SD Biomedical Library
- **The NMO Story** Video & NMO TV
- **NMO Resources** Downloadable App
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Authorship Team:

Brian Weinshenker, M.D.
Jacinta Behne, M.A.
Terry Smith, M.D.
Michael Yeaman, Ph.D.
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