GFAP (Glial Fibrillary Acidic Protein) meningoencephalomyelitis : clinical and MRI features

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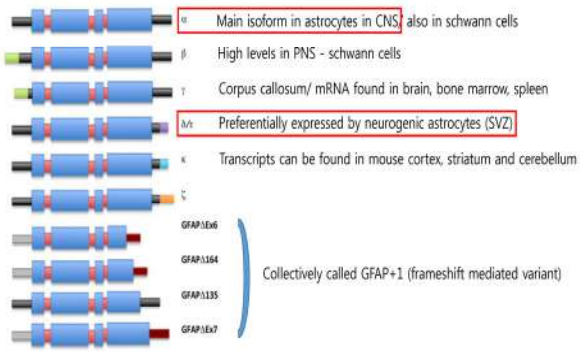
Glial fibrillary acidic protein (GFAP)

Cytosolic intermediate filament protein



Autoimmune GFAP Astrocytopathy

- A **episodic**, **relapsing**, **immunotherapy responsive** meningoencephalomyelitis
  - (m/c) *Subacute onset* of memory loss, confusion (with or without psychiatric symptoms), and 1 or more of meningeal symptoms (headache, photophobia, neck stiffness) and myelopathic symptoms (weakness or numbness in extremities)
  - outright paralysis (a frequent NMO accompaniment) is rare
- Unified by GFAP-IgG positivity
  - Surrogate marker for pathogenic GFAP peptide-specific cytotoxic $CD8^+$ T cells
  - CSF: more sensitive and specific

Presentations

- Median age, 44 (8-103); M=F (54%)
- Meningitis, encephalitis, myelitis (mild reversible)

TABLE 3. Detailed Clinical and Treatment Characteristics of 38 Mayo Clinic GFAP-IgG–Positive Cases

Clinical Features	Patients, No. (%)*
Subacute onset, <8 weeks	27 (71)
CNS disorder	33 (87)
Encephalopathy	21 of 37 (57)
Tremor	15 of 37 (41)
Headache	14 of 36 (39)
Myelopathic symptoms/signs	9 of 37 (24)
Other meningeal symptoms/signs	12 of 37 (32)
Optic disk edema[b]	12 of 37 (32)
Ataxia	10 of 35 (29)
Psychiatric symptoms[c]	10 of 35 (29)
Autonomic dysfunction[d]	8 of 34 (24)
Seizures	7 of 37 (19)
Eye movement disorder	6 of 37 (16)
Vomiting	6 of 37 (16)
Coexisting autoimmune disorder	8 of 37 (22)

Depression (6), anxiety (2), insomnia (2), vivid dreams (1), catatonia (1)

Orthostasis (5), gastrointestinal motility disorder (3), bladder dysfunction (2), erectile dysfunction (1)

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Laboratory findings

TABLE 2. Laboratory and Serologic Findings of 102 GFAP-IgG–Positive Cases

	Patients (%)	Median [range]
Demographics		
Age at onset, yr		44 [8–103]
Female sex	55 (54)	
CSF findings		
Elevated white cell count, >5/μl*	45 of 51 (88)	78.5 [13–950]
Elevated protein, >35mg/dl	30 of 36 (83)	80 [44–205]
Hypoglycorrhachia, <40mg/dl	4 of 22 (18)	37 [36–38]
CSF-exclusive oligoclonal bands, ≥4	13 of 24 (54)	
Serological data		
GFAP IFA positivity	102 (100)	
Serum IFA positive, titer, end-dilution	56 of 83 (67)	1:7,680 [1:120–491,520]
CSF IFA positive, titer	64 of 66 (96)	1:128 [1:4–8,192]
GFAPα CBA positive	102 (100)	
GFAPβ CBA positive	76 of 94 (81)	
GFAPγ CBA positive	51 of 94 (54)	

*Lymphocyte predominant, 94%; monocytic, 6%.
CBA = cell-based assay; CSF = cerebrospinal fluid; GFAP = glial fibrillary acidic protein; IFA = immunofluorescence assay.

Lympho-dominant : median, 93% range, 75-97%

Isoforms - not associated with frequency of meningoencephalitis, cancer detection

Also positive for GFAPε

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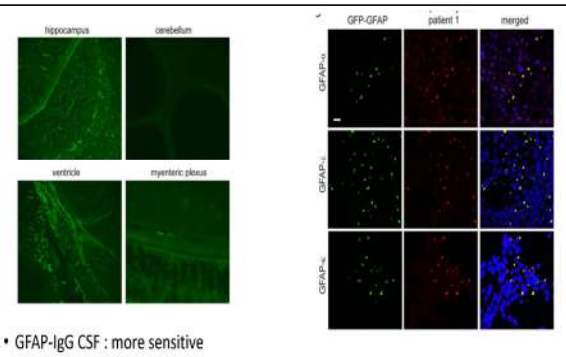

- GFAP-IgG CSF : more sensitive
  - *Among 49 patients both serum and CSF: positivity - 92% (CSF) vs. 45% (serum)*
  - Especially among those with meningoencephalitis?
- Meningoencephalomyelitis diagnosis is independent of IFA GFAP titer

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- 22 patients with GFAP autoantibodies Iorio R, et al. JNNP 2018;89:138–146
  - Median age, 52 (6-80), Γ (59%)
  - Subacute (8), acute (11) onset and 3 with chronic epilepsy
  - (m/c) meningoencephalitis with or without myelitis (10, 45%)
    - Movement disorders (3), AED-resistant epilepsy (3), cerebellar ataxia (3), myelitis (2), ON (1)
  - CBA (serum)
    - Bound to GFAPα isoform in all (100%)
    - Bound to both GFAPα and GFAPδ isoforms (14/22, 64%)
    - Bound only to GFAPδ isoform (0%)
  - CSF of 12 patients: positive in 8 patients (67%)

MRI findings: Brain

- T2 hyperintensities in 18/32 (56%)
- Gd enhancement in 21/32 (66%)
  - Linear (punctate) perivascular Gd-enhancement (17, 56%): radial to ventricles
  - Leptomeningeal (7, 22%), serpentine (6, 19%), ependymal (3, 9%)
  - Vs. CNS vasculitis (suspected in 12/38, 32%) – MRA (n=12) & DSA (n=6): WNL
- Normal DWI
- Normal brain MRI in 7/32 (18%)

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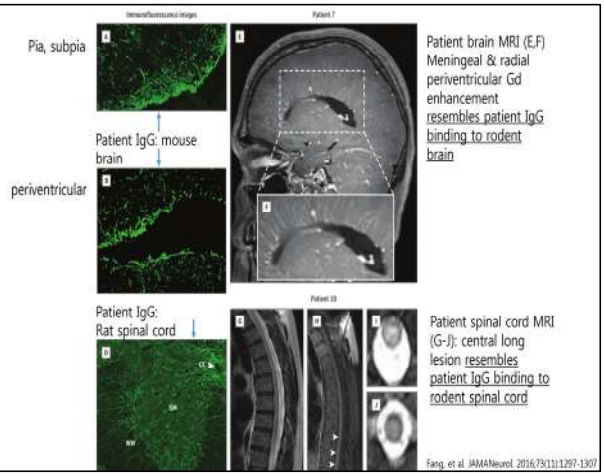
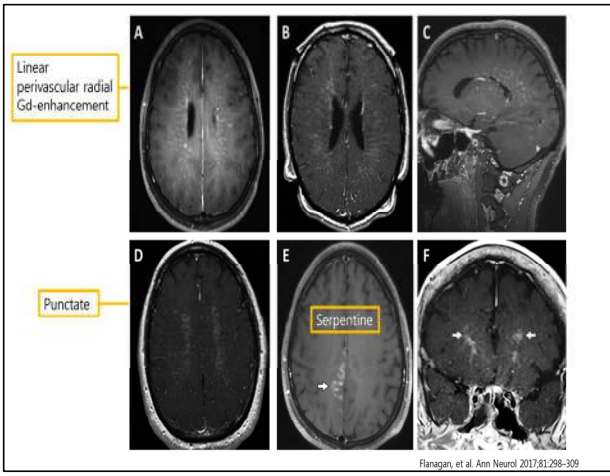


Fang, et al. JAMA Neurol. 2016;73(11):1297-1307



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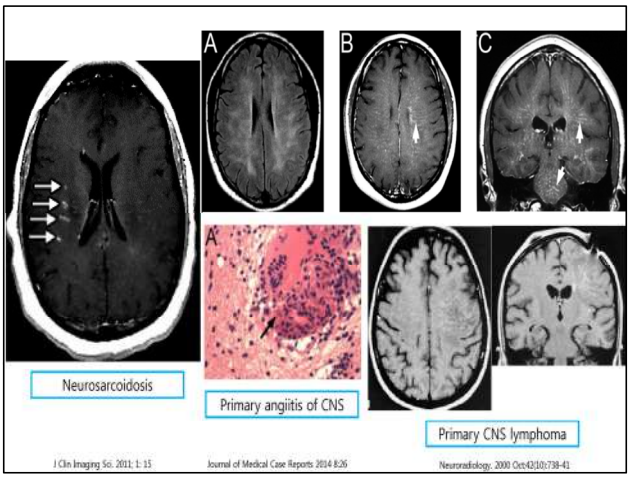

MRI findings: Spine

- Among 8 patients with myelitis and MRI spine images
  - longitudinally extensive myelitic abnormalities (3 vertebral segments long): 6 (75%)
    - With AQP4 Ab in 2
  - Short myelitis: 1, normal: 1
  - Linear-appearing central canal enhancement in 21%
  - Punctate or patchy enhancement

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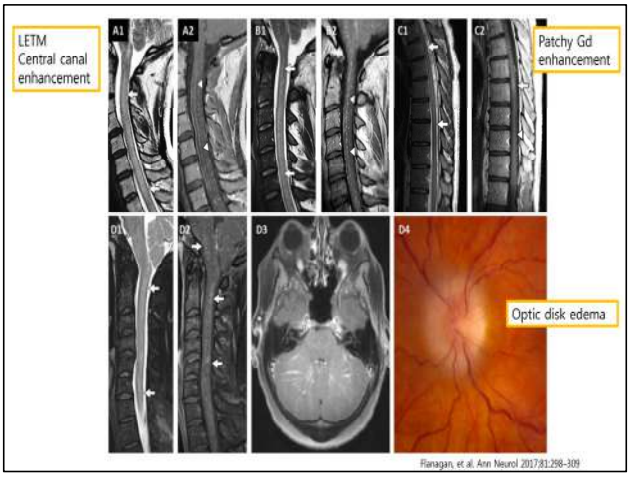

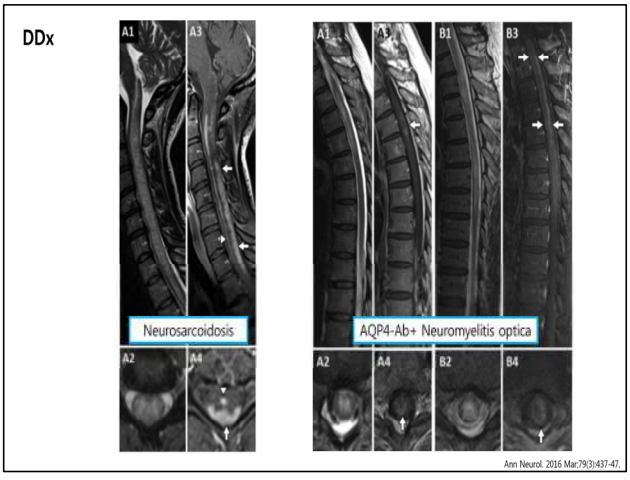

Oncologic findings

- 35 patients /102 (**34%**) had neoplasia
  - 66%: tumors were detected within 2 years of symptom onset
- 24 newly detected neoplasms in 22 (median = 0.5 months, range = 0–60)
  - **Ovarian teratoma (15, mature:13)**, adenocarcinoma (3, endometrium, esophagus, kidney), *glioma* (2), *head and neck squamous cell carcinoma, multiple myeloma*, pleomorphic parotid adenoma, carcinoid
- 18 historical neoplasms in 14
  - Prostate adenocarcinoma (3), Hodgkin lymphoma (2), lung carcinoma (2), colon adenocarcinoma (2), melanoma (2), **ovarian teratoma**, ovarian adenocarcinoma, nasopharyngeal carcinoma, chronic lymphocytic leukemia, renal cell carcinoma, breast ductal carcinoma, urothelial bladder carcinoma

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Infectious and immunodeficiency accompaniments

- Prodromal influenza-like symptoms in 11/38 (29%)
  - Infections in 5: URI (2), pneumonia (1), UTI (1), prostatitis (1)
- HIV/AIDS in one patient
- Treated with ipilimumab (monoclonal antibody antagonist of cytotoxic T-lymphocyte–associated protein 4) in one patient with melanoma

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Coexisting neural autoantibodies

- 41/102 (40%) patients had ≥1 other autoantibodies in serum or CSF
  - **NMDA-R IgG** (m/c) in CSF (22/102, **22%**)
  - **AQP4-IgG** in 10 (10%), serum or CSF

NMDA-R IgG and AQP4-IgG (n=7)	NMDA-R IgG alone (n=15)	AQP4-IgG alone (n=3)
• **Encephalitis (100%)** • **Teratoma (71%)**	• encephalitis (n=13) • encephalomyelitis (n=1) • meningoencephalomyelitis (n=1) • Teratoma (53%)	• encephalomyelitis (n=2) • neuromyelitis optica (n=1) • Teratoma (66%) No CSF available for NMDA-R IgG

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Coexisting neural autoantibodies

- Glutamic acid decarboxylase 65 (GAD 65) in 7
- Striated muscle antigens in 5
- Ganglionic acetylcholine receptor in 4
- P/Q-type calcium channel in 3
- voltage-gated potassium channel complex in 2

- GABAAR-IgG, Yo-IgG

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Treatment Response and Outcome (Mayo Clinic 38 Patients)

- Median follow-up duration: 20 months (range 0 – 174)
- Among 26 patients with meningoencephalomyelitis, or limited forms
  - 50%: relapsing course
  - 27%: monophasic course
  - 23%: progressive despite treatment

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- Among 9 patients with long-term (≥24 months) treatment details
  - 3 pts with coexisting NMDA-R IgG: IV steroid in 3, oral Pd in 2, PE in 1, MMF in 1, AZT in 1 → successful steroid tapering without relapse
  - 6 pts without other autoantibodies: encephalitis with/without meningeal or myelitic findings
    - IV steroid in 6, oral Pd in 6, MMF in 5, AZT in 2
    - Relapse
      - 50% (n=3): not taking a steroid-sparing drug (Pd <20mg/day)
      - 50% (n=3): when steroid-sparing immunotherapy was discontinued
      - frequently accompanied by recurrent gadolinium enhancement on MRI and elevated CSF white cell counts
    - All in remission at last follow-up; 5 had discontinued Pd

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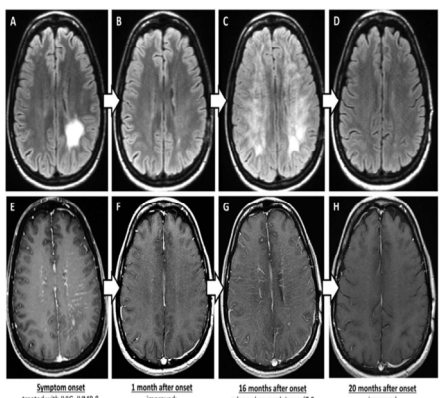
MRI abnormalities after steroid Tx



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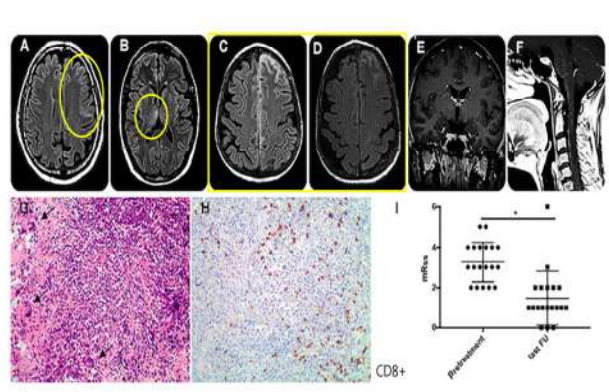

Leptomeningeal biopsy
- necrosis(+), lymphocytes intermixed with macrophages, histiocytes and some multinucleated giant cells

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Summary (autoimmune GFAP astrocytopathy)

- Episodic, relapsing, immunotherapy-responsive meningitis, encephalitis, or myelitis
- **Manifestations**
  - Headache; subacute encephalopathy; optic papillitis (normal intracranial pressure); inflammatory myelitis; postural tremor; cerebellar ataxia; seizure; dysautonomia
- **CSF**: leukocytosis; lymphocyte-predominant (up to 550/mL)
- **MRI**
  - ***Brain***: periventricular white matter T2 abnormality; predominant linear perivascular enhancement (radial to ventricle); leptomeningeal enhancement
  - ***Spine***: central long T2 lesion, more subtle to NMO

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- Differential diagnosis
  - Infectious, granulomatous, inflammatory demyelinating disorders; vasculitis; CNS lymphoma & carcinoma
- Co-existing neural antibodies
  - **40%** (**NMDAR-IgG > AQP4-IgG** > GAD65 > VGCC-P/Q, PCA-1/Yo, ANNA-1/Hu,GABAA-R)
  - When NMDAR-IgG or AQP4-IgG co-exist (minority or cases) → teratoma (predicted); meningoencephalomyelitis (predominant)
- Co-existing autoimmune disorders
  - type 1 diabetes, Graves, cerebellar ataxia, rheumatoid arthritis, ulcerative colitis
- **Long-term immunosuppressive treatment to prevent relapse**

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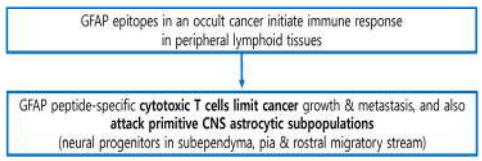
- **Cancer association**
  - ~1/4 cases (ovarian teratoma; carcinomas: ovary, breast, prostate, esophagus, stomach) melanoma, myeloma, carcinoid, parotid adenoma
- Hypothesis for GFAP autoimmunity origins



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