INTERESTING CASE

Management in CNS Inflammation Related Epilepsy

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CASE A 15-YEAR-OLD GIRL

- **CHIEF COMPLAINT:**

  ซึมลง 1 สัปดาห์ก่อนมาโรงพยาบาล

Present illness

- 17 วัน PTA-> มีอาการชักเกร็งกระตุกทั้งตัว เรียกไม่รู้สึกตัว เป็นอยู่นานประมาณ 2 นาที ไปโรงพยาบาล มีอาการชักเกร็งกระตุกทั้งตัวอีกครั้ง ได้ Diazepam IV 1 dose แล้วหยุดชัก
- Rx: Phenytoin IV loading dose ที่วอร์ด หลังได้ยาไป 2-3นาที มีอาการผื่นคันเป็นปื้นใหญ่ขึ้นตามตัวและแขนขา แพทย์วินิจฉัยแพ้ยา จึงเปลี่ยนจาก PHT เป็น VPA หลังจากนั้นไม่มีอาการชักเกร็งกระตุกอีก-> D/C
- หลังกลับบ้านไปไม่มีอาการชักเกร็งอีก แต่มีอาการพูดน้อยลง ทำตามคำสั่งได้บ้างบางครั้ง ยังเดินได้แต่ช้าลง น้าสาวที่เป็นพยาบาลคิดว่าอาจเป็นผลข้างเคียงจาก VPA จึงพาไปตรวจซ้ำ

Present illness

- ขณะรอตรวจมีอาการชักเกร็งกระตุกอีกครั้ง ได้ Diazepam IV 1 dose จึงหยุดชัก และ admit ICU
- เปลี่ยนยา VPA เป็น LEV IV หลังจากนั้นไม่มีอาการชักอีก
- Investigations:
  - EEG: normal
  - CT brain: normal
  - Serum paraneoplastic screening: negative
- Dx: epilepsy
- Treatment: LEV 1000 mg/day
- หลังจากนั้นมีอาการแปลก ๆ ไม่พูด ถามไม่ตอบ ทำตามคำสั่งได้น้อยมาก ดูง่วงซึมตลอดเวลา แพทย์ที่พิษณุโลกจึงแนะนำให้มารักษาที่รพ.พระมงกุฎเกล้า

Past history

- ปฏิเสธโรคประจำตัว สุขภาพแข็งแรงดี
- Term , normal labor AGA, หลังคลอดมีปัญหาหายใจเร็ว on oxygen box 1 วัน ไม่ได้ใส่ท่อช่วยหายใจ กลับบ้านพร้อมมารดา
- ได้รับวัคซีนครบตามเกณฑ์
- พัฒนาการสมวัย
- Family history: ปฏิเสธประวัติโรคลมชักในครอบครัว

Physical Examination

- Heart : pulse full and regular all extremities, capillary refill < 2 sec, normal S1 and S2, no murmur
- Lungs : normal breath sound , no adventitious sound
- Abdomen : no distension, normoactive bowel sound, soft, not tender , liver and spleen could not be palpated
- Extremities : no edema
- Skin : no rash

Physical Examination

- Vital signs : BT 37˚C, PR 92 bpm, RR 20/min, BP 112/68 mmHg
- Measurement : BW 45 kg (P 25- P50), Ht 155cm(P 25- P50)
- General appearance : A Thai teenage girl, drowsiness, not well co operative
- HEENT : not pale conjunctivae, anicteric sclera, pharynx and tonsils were not injected, no oral ulcer, no alopecia, no rash
- Lymph node : could not be palpated

Neurological Examination

- Mental status: Drowsiness, diminished speech, follow command sometimes
- Cranial nerves: pupils 3 mm RTLBE, EOM full, gag reflex positive, no facial palsy, no nystagmus, no papilledema
- Motor: normal tone, motor power- grade IV+ all at least
- Sensory: could not evaluate
- Cerebella sign: intact
- Reflex: DTR 2+ all
- Babinski sign : plantar response
- Clonus negative both sides
- Meningeal sign: negative

Video orolingual dyskinesia

with permission

Summary

- A previously healthy 15-year-old girl
- Subacute onset of behavioral change, decreased level of consciousness
- History of recurrence seizure
- Speech reduction
- Orolingual dyskinesia/ hand dyskinesia
- Negative initial investigations (CT brain, EEG, serum paraneoplastic screening)

ANY COMMENTS?

MANAGEMENT?

Video

Differential diagnosis

Infectious Encephalitis
- HSV

Non-infectious Encephalitis
- Autoimmune
  - Anti-NMDAR encephalitis
  - Paraneoplastic limbic encephalitis
  - Hashimoto's encephalitis
- Post infectious encephalitis
  - Acute disseminated encephalomyelitis (ADEM)

Other
- Systemic: SLE
- Subclinical seizures
- Metabolic:Toxin/drug

Non-infectious encephalitis

- Autoimmune
  - Anti-NMDAR encephalitis
  - Paraneoplastic limbic encephalitis
  - Hashimoto's encephalitis
- Post infectious encephalitis
  - Acute disseminated encephalomyelitis (ADEM)
- Metabolic encephalopathy
  - Toxin/drug

Panel 4: Diagnostic criteria for anti-NMDA receptor encephalitis

Probable anti-NMDA receptor encephalitis*

Diagnosis can be made when all three of the following criteria have been met:

√ 1 Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:
- Abnormal (psychiatric) behaviour or cognitive dysfunction √
- Speech dysfunction (pressured speech, verbal reduction, mutism) √
- Seizures √
- Movement disorder, dyskinesias, or rigidity/abnormal postures √
- Decreased level of consciousness √
- Autonomic dysfunction or central hypoventilation

2 At least one of the following laboratory study results:
- Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
- CSF with pleocytosis or oligoclonal bands

3 Reasonable exclusion of other disorders (appendix)

Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

Definite anti-NMDA receptor encephalitis*

Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies,† after reasonable exclusion of other disorders (appendix)

*Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurological symptoms (post-herpes simplex virus encephalitis). †Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to cell-based assay).

CSF	10/1/60
Appearance	clear
Xanthochromia	-
RBC	193 cell/mm3
WBC	-
PMN	-
Mononuclear	-
Protein	54 mg/dl
Sugar	82 mg/dl (DTX 80 mg/dl)

Lab	10/1/60
Hemoculture	
CSF culture	NG
CSF PCR for enterovirus	Negative
CSF PCR for HSV-1 and HSV-2	Negative
CSF for anti-NMDA	Positive

Serum (7/1/60) : negative for ANNA, PCA, GAD, Amphiphysin, CRMP-5,NMDA, AMPA, GABA, VGKC

Lancet Neurol. 2014 February ; 13(2): 167–177. doi:10.1016/S1474-4422(13)70282-5.

Diagnosis and significance of antibody titers in anti-NMDA receptor encephalitis, a retrospective study

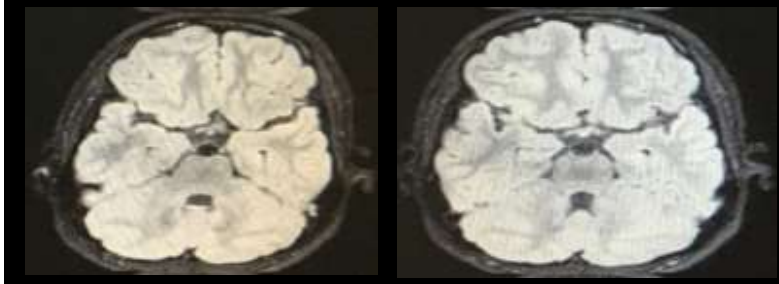
Nuria Gresa-Arribas, PhD[1,*], Maarten J. Titulaer, MD[1,2,*], Abiguei Torrents, BS[3], Esther Aguilar[1], Lindsey McCracken, MPH[4], Frank Leypoldt, MD[1], Amy J. Gleichman, PhD[5,8], Rita Balice-Gordon, PhD[6], Myrna R. Rosenfeld, MD[1,7], David Lynch, MD[7,8], Francesc Graus, MD[1], and Josep Dalmau, MD[1,9]

Sensitivity and specificity of testing for NMDAR antibodies

Sensitivity	CSF		Serum	
Number of patients	250		250	
Both tests positive	250	100.0%	214	85.6%
95% CI		(98.5 – 100.0%		(80.7 – 89.4%)

Lancet Neurol. 2014

MRI brain (27/1/60): normal



EEG : generalized intermittent slow

Immunology	4/1/60	10/1/60	13/1/60
ANA	Negative	Cytoplasm 1:80 Centrioles 1:80	
Anticytoplasmic Ab	Negative		
Anti ds-DNA	Negative		
Anti-Smith Ab	Negative		
Antiphospholipid Ab	Negative		

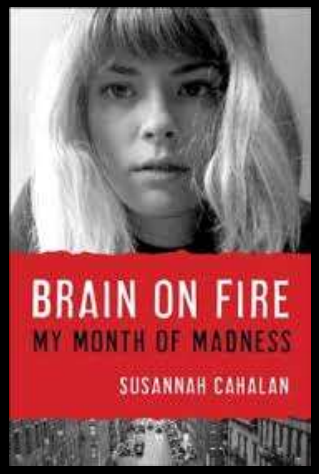
Thyroid function test	4/1/60	10/1/60
FT3	3.94	2.84
FT4	1.87	1.9
TSH	1.06	1.0
Anti TPO Ab (IU/mL)		11.17 (<35)

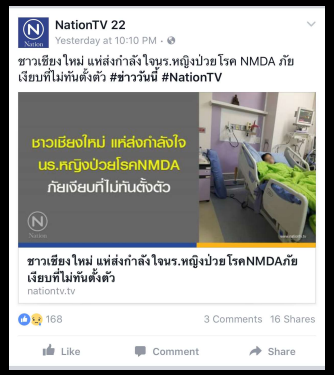
Clinical presentations of anti-NMDAR encephalitis

- **Psychiatric symptoms ****
  - **Change of personality and behavior, irritability, anxiety, aggressive behavior, delusional thoughts, paranoid, catatonia**
- **Movement disorder (dyskinesia)**
- **Seizures Partial or generalized seizures**
- **Autonomic instability (hypoventilation, tachycardia, hypertension)**
- **Short-term memory loss**

Dalmau et al. Nat Clin Pract Neurol. 2007

ANTI-NMDAR ENCEPHALITIS





Varied Clinical finding between children and adult

- **More seizure and movement disorder in children < 12 years**
- **Atypical symptoms (ataxia, hemiparesis) predominated in children**
- **More behavioral problem, memory deficit, central hypoventilation in adult**

" More neurological in children, more psychiatric in adults"

Titulaer et al. Lancet Neurol 2013

Clinical presentations of anti-NMDAR encephalitis

In Children and Adolescents < 18 years
- Behavioral or personality change associated with seizures, sleep dysfunction (87.5%)
- Dyskinesias or dystonia (9.5%)
- Speech reduction (3%)

On admission
- Severe speech deficits (53%)

After admission
- Seizure (77%)
- Stereotyped movements (84%)
- Autonomic instability (86%)
- Hypoventilation (23%)

Florence et al. Ann Neurol. 2009

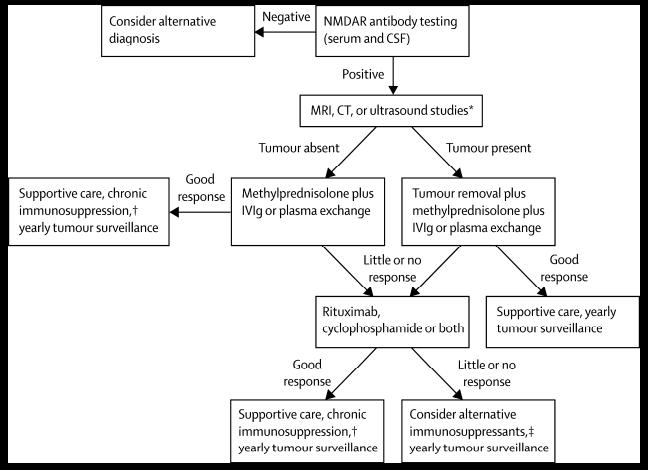
Treatment

- Tumor removal
- Which drugs?
  - First-line immunotherapy
    - Steroids, IVIG, plasmapheresis
  - Second-line immunotherapy
    - Rituximab
    - Cyclophosphamide
- Monotherapy or Combination?
- How long should we treat?

Investigation

- CSF and/or serum NMDA Ab → Gold standard
- CSF: mild pleocytosis, oligoclonal bands → 79% abnormal
- MRI: unremarkable, T2/FLAIR signal hyperintensity at non-specific region → 30-50% abnormal
- EEG: slow background, non-specific → 90% abnormal

Proposed algorithm for the treatment of anti-NMDAR encephalitis



Dalmau et al. Lancet Neurol 2011

Treatment

- No clinical trials evaluating efficacy in either adults or children
- Specific immunotherapy regimens and their long-term outcomes have not been well defined
- Combination at least 2 therapy shows higher efficacy (recovery faster within 1 year)

Wang. Frontiers in Bioscience, Landmark 2016

Table 1: The Modified Rankin Scale (mRS)

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

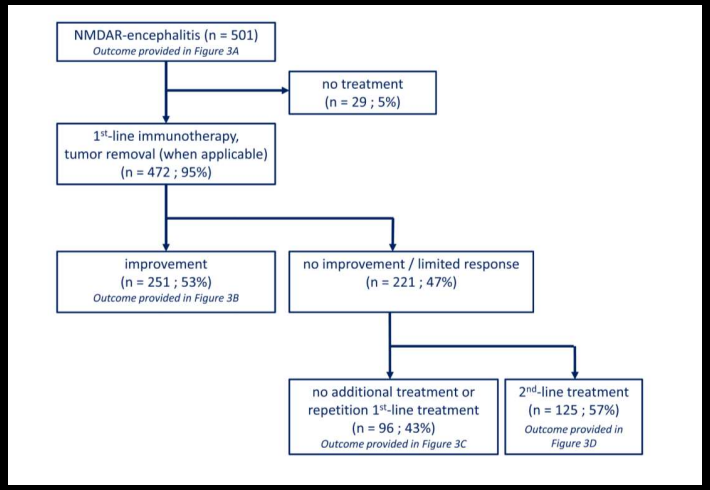
Adapted from van Swieten, *et al*, 1988

Lancet Neurol. 2013 February ; 12(2): 157–165. doi:10.1016/S1474-4422(12)70310-1.

Treatment and prognostic factors for long-term outcome in patients with anti-*N*-Methyl-D-Aspartate (NMDA) receptor encephalitis: a cohort study

Maarten J. Titulaer, MD[1,2], Lindsey McCracken, BS[1], Iñigo Gabilondo, MD[2], Thaís Armangué, MD[2], Carol Glaser, MD[3], Takahiro Iizuka, MD[4], Lawrence S. Honig, MD[5], Susanne M. Benseler, MD[6], Izumi Kawachi, MD[7], Eugenia Martinez-Hernandez, MD[1,8], Esther Aguilar, BS[2], Núria Gresa-Arribas, PhD[2], Nicole Ryan-Florance, MD[9], Abiguei Torrents, BS[10], Albert Saiz, MD[2], Myrna R. Rosenfeld, MD[1,2], Rita Balice-Gordon, PhD[1], Francesc Graus, MD[2], and Josep Dalmau, MD[1,2,11]

Results—577 patients (1-85 years, median 21) were studied, 212 were children (<18 years). Treatment effects and outcome were assessable in 501 (median follow-up 24 months): 472 (94%) underwent first-line immunotherapy or tumor removal, resulting in improvement within four weeks in 251 (53%). Of 221 patients who failed first-line therapy, 125 (57%) received second-line immunotherapy resulting in better outcome than those who did not (OR 2·69, CI 1·24-5·80, p=0·012). During the first 24 months, 394/501 reached good outcome (mRS 0-2; median 6 months), and 30 died. At 24 month follow-up 204/252 (81%) had good outcome. Outcomes continued to improve for up to 18 months after symptom onset. Predictors of good outcome were early treatment (OR 0·62, CI 0·50-0·76, p<0·0001) and lack of ICU admission (OR 0.12, CI 0·06-0·22,p<0·0001). 45 patients had one or multiple relapses (representing a 12% risk within 2 years); 46/69 (67%) relapses were milder than previous episodes (p<0·0001). In 177 children, predictors of good outcome and the magnitude of effect of second-line immunotherapy were comparable to those of the entire cohort.



Titulaer et al. Lancet Neurol 2013

Good outcome

- Outcome after first-line therapy; steroid (87%), IVIG (73%), plasmapheresis (26%) in non-tumor group
- The combination of first-line immunotherapy (steroids and IVIG (202 pts,44%)
- Improved 53% within 4 weeks of treatment (251/472)
- Reach mRS 0-2 at 3 months (median)
- At 24 months (115), 97% good outcome (same as at 18-month follow up)

Titulaer et al. Lancet Neurol 2013

Back to our patient

- Pulse methylprednisolone plus IVIG -> prednisolone
- Controlled seizure with LEV
- Consult gyne for pelvic ultrasonography -> no tumor
- Follow up for 6 months -> mRS 0

Poor outcome

- Failure 47% (221/472) with in 4 week (mRS >3)
- 125 cases received second-line Rx (Rituximab, cyclophosphamide)
  - At 24 months, 67% reach mRS 0-2

Titulaer et al. Lancet Neurol 2013

Frequency of tumor screening

- If the tumor is not found, the screening should take into the patient's age and gender
- Female > 12 years old -> screening MRI of the abdomen and pelvis is every 6 months for 4 years
- In young children and males the need for repeat screening is unclear

Titulaer et al. Lancet Neurol 2013

Before treatment

- video

After treatment

- video

Summary

- Anti-NMDAR encephalitis is common
- Characterized by subacute onset of psychiatric symptoms, seizures, movement disorder, decrease in consciousness and dysautonomia
- Confirmed diagnosis with CSF and Serum NMDA receptor Ab
- Prompt initiation of immunotherapy and tumor removal predict good outcome
- Serial tumor surveilance
- Treatable disease with favorable long term outcome

Predictors of good outcome

- Lower severity of symptoms as no need for ICU support
- Prompt initiation of immunotherapy and tumor removal

Titulaer et al. Lancet Neurol 2013

Thank you for your attention