



## Anti-NMDA receptor encephalitis: A review of the data and an approach to testing

# Agenda

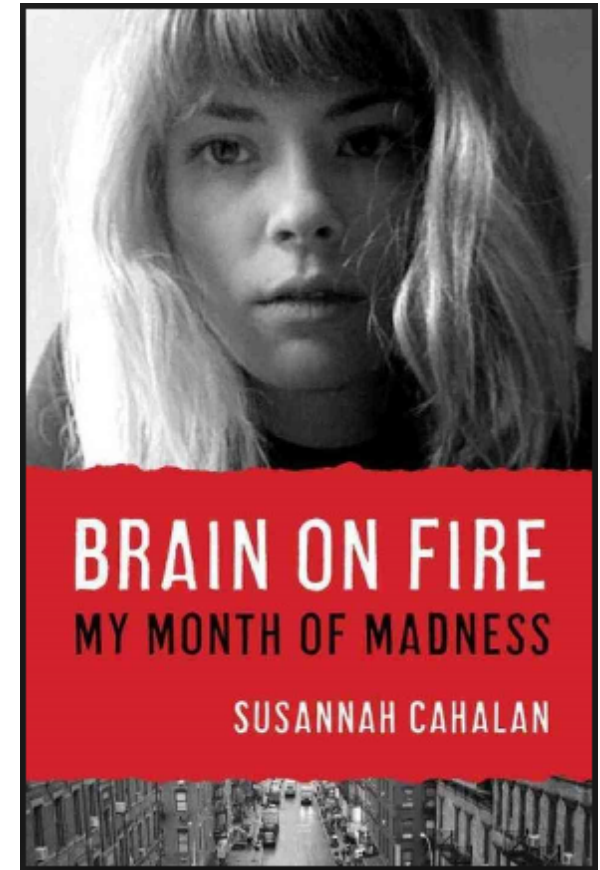
- Case
- Background and Rationale
- Research Question
- Methods
- Results
- Take Home Points

**26 F** is brought into the ER by her boyfriend following a **?seizure** where she was “*shaking for 2 minutes*”

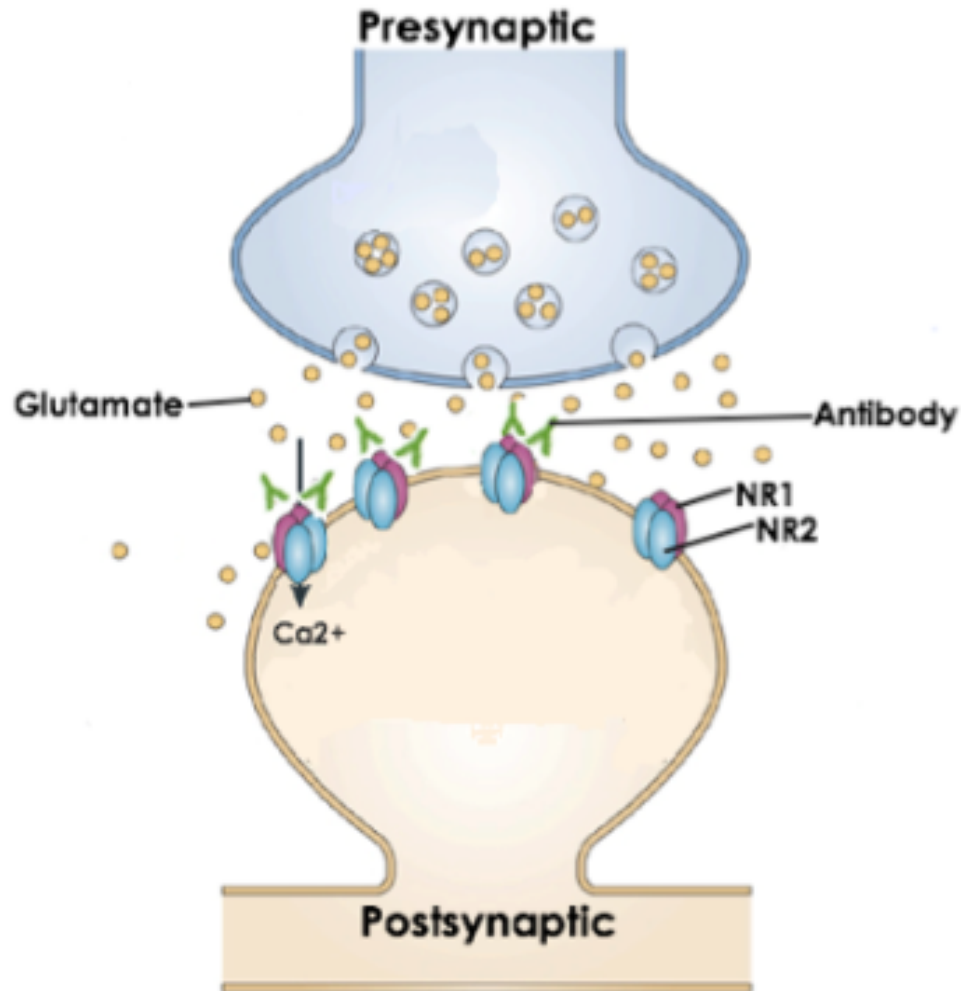
- She is now stable with a temp of 37.6
- She appears to be post-ictal...
  
- **PMHx:** previous miscarriage
- **FHx:** NO history of epilepsy
- **SHx:** NO history of substance use
  
- **HPI:** boyfriend states she has “*not been herself*” for the last week – irritable, forgetful, twitching – thought it was stress related to an upcoming exam; also notes she had a viral illness 2 weeks ago but “*seemed to get over it*”

# Background

- first described by Dr. Dalmau in 2007
- “auto-immune” encephalitis
  - Anti-bodies attack NMDA receptors
- More common in 30 and under
- Women (80%) > Men (20%)
- Often paraneoplastic
  - i.e. teratoma
  - more common in women

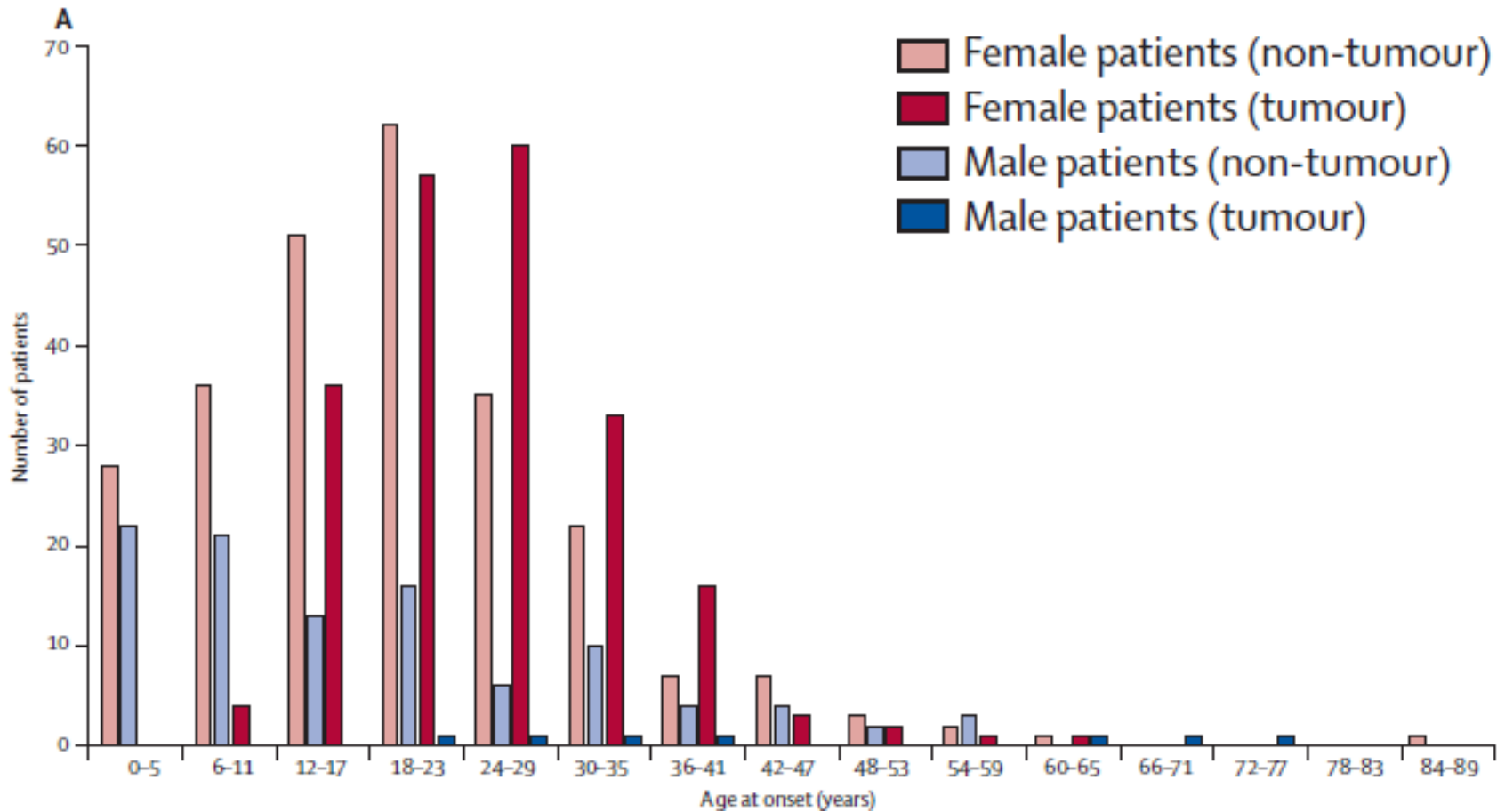


# Pathophysiology



Dalmau et al. (Lancet 2008)

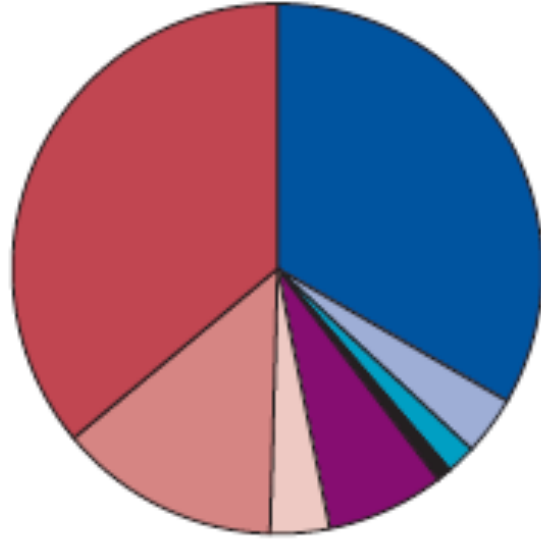
# Patient Demographics



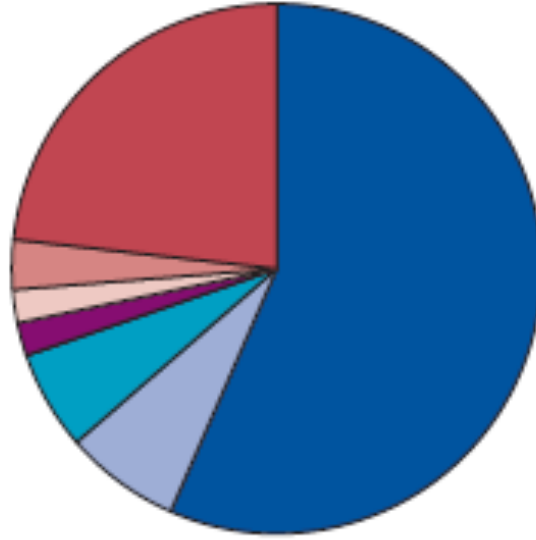
Titulaer et al. (Lancet 2013)

# Clinical Presentation

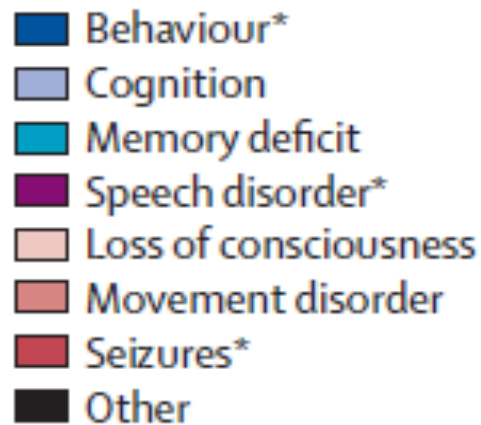
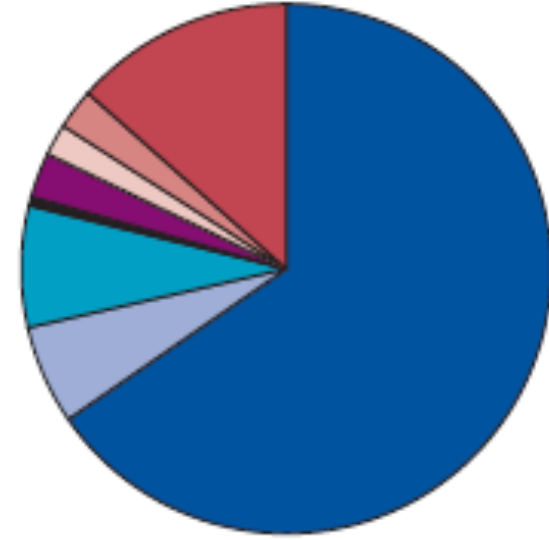
B Age <12 years (n=111)



C Age 12-17 years (n=99)

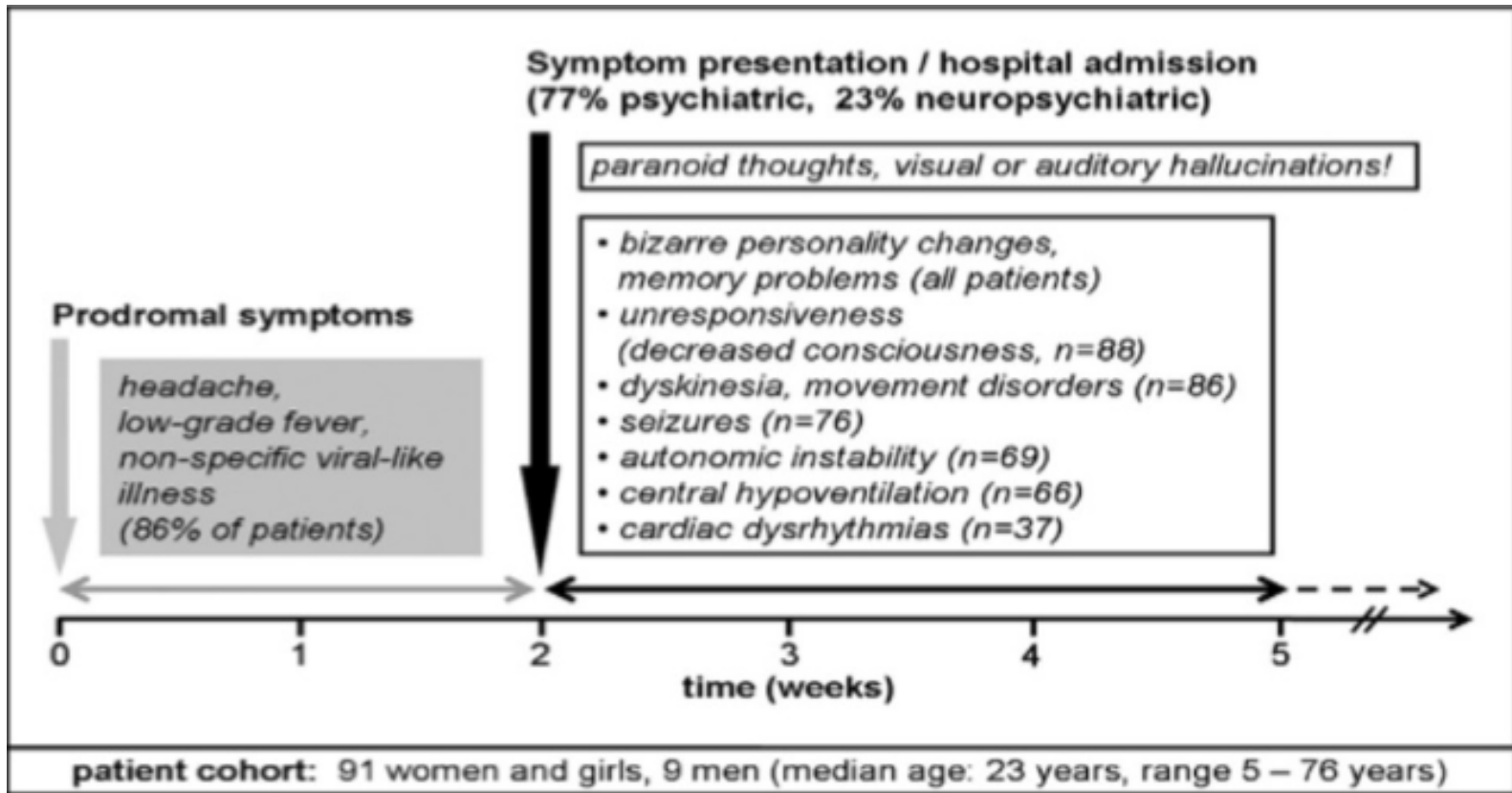


D Age ≥18 years (n=364)



Titulaer et al. (Lancet 2013)

# ...depends on stage of the disease



Dalmou et al. (Lancet 2008)



# Diagnostic Work-up

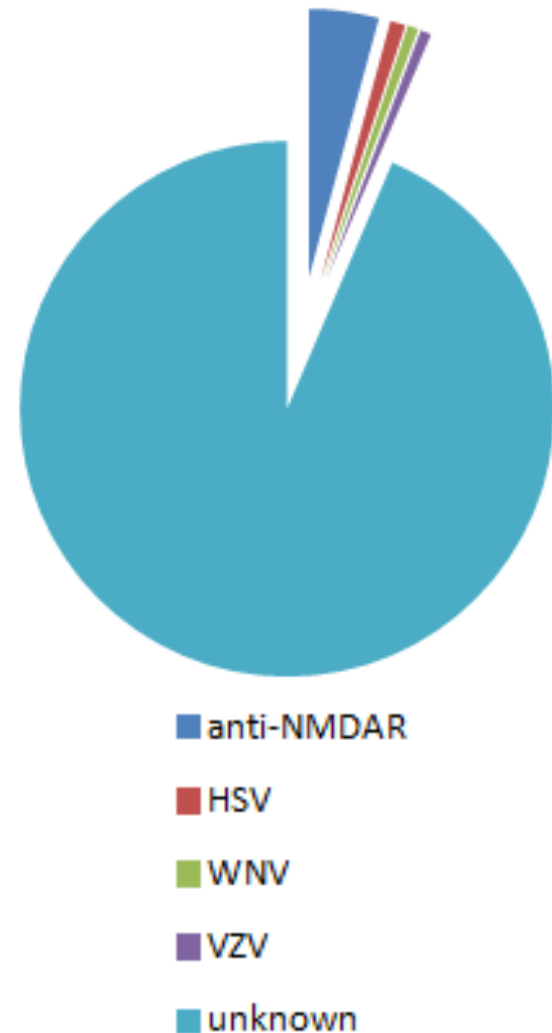
- Lumbar Puncture
  - Lymphocytic pleocytosis (90%)
  - Oligoclonal bands (60%)
  - NMDA (NR1) receptor anti-bodies
- MRI
  - Non-specific abnormalities
  - 60% are normal
- EEG
  - Generalized or focal slow activity
  - Sometimes super-imposed epileptic activity

# Treatment

- 1<sup>st</sup> line: steroids, IVIG, plasmaphoresis +/- tumor removal
- 2<sup>nd</sup> line: rituximab, cyclophosphamide

# Rationale: Why do we care?

- Not as rare as you might think...
  - most common identified viral encephalitis in CEP database in *30 and under age group*
  - More than 500 cases, exact prevalence unknown



Gable et al. (CID 2012)

# Rationale: Why do we care?

- **Morbidity & Mortality**

- 6% mortality during first 24-months
- ONLY 15% get better within 1-month
- 81% had a “good outcome” by 3 months
- Relapse present in 12% (tend to be less severe)

**\*EARLY recognition and initiation of immunotherapy or tumor removal was predictor of good outcome**

Titulaer et al. (Lancet 2013)

# Research Questions:

1. How often are we sending cerebrospinal fluid to test for herpes simplex virus in the 30 and under age group?
  - b) How often are we sending the anti-NMDAR antibody test in this population?
2. How many times have we sent the anti-NMDAR antibody test since 2013?
3. What are the logistical issues and costs associated with ordering the test?

# Methods

HGH/ JCC/ SJH/ MUMC

HSV PCR sent between  
January 2013 - August 2015  
\*Age 30 and under

(n = 171 )

## Exclusion

Non-CSF samples:  
i.e. corneal, amniotic, blood

Infants <1 year

Outpatient clinic

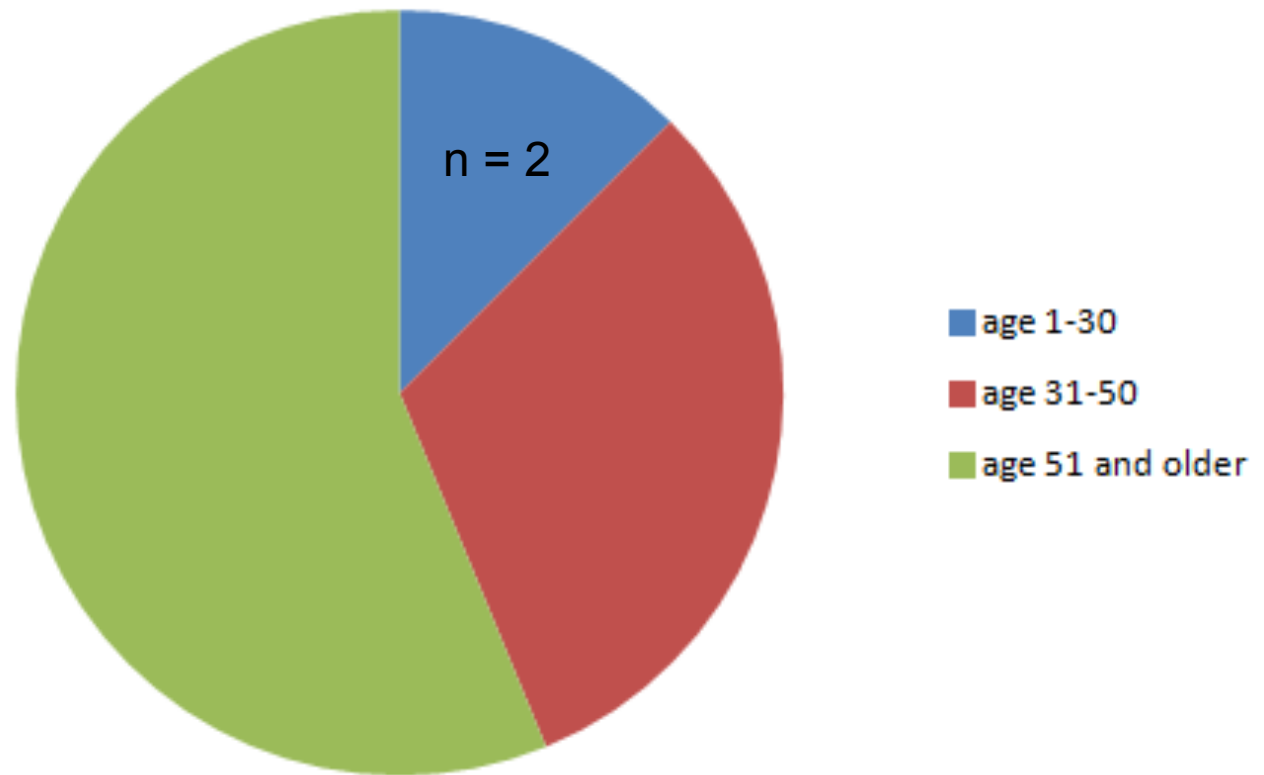
ER or inpatient who had HSV  
sent from "CSF" or "LP"

# Results

1. Over 32 months, CSF testing for HSV was **n = 109**, in the 30 and under age group
  - b) Only **n = 1** was sent for anti-NMDAR antibody

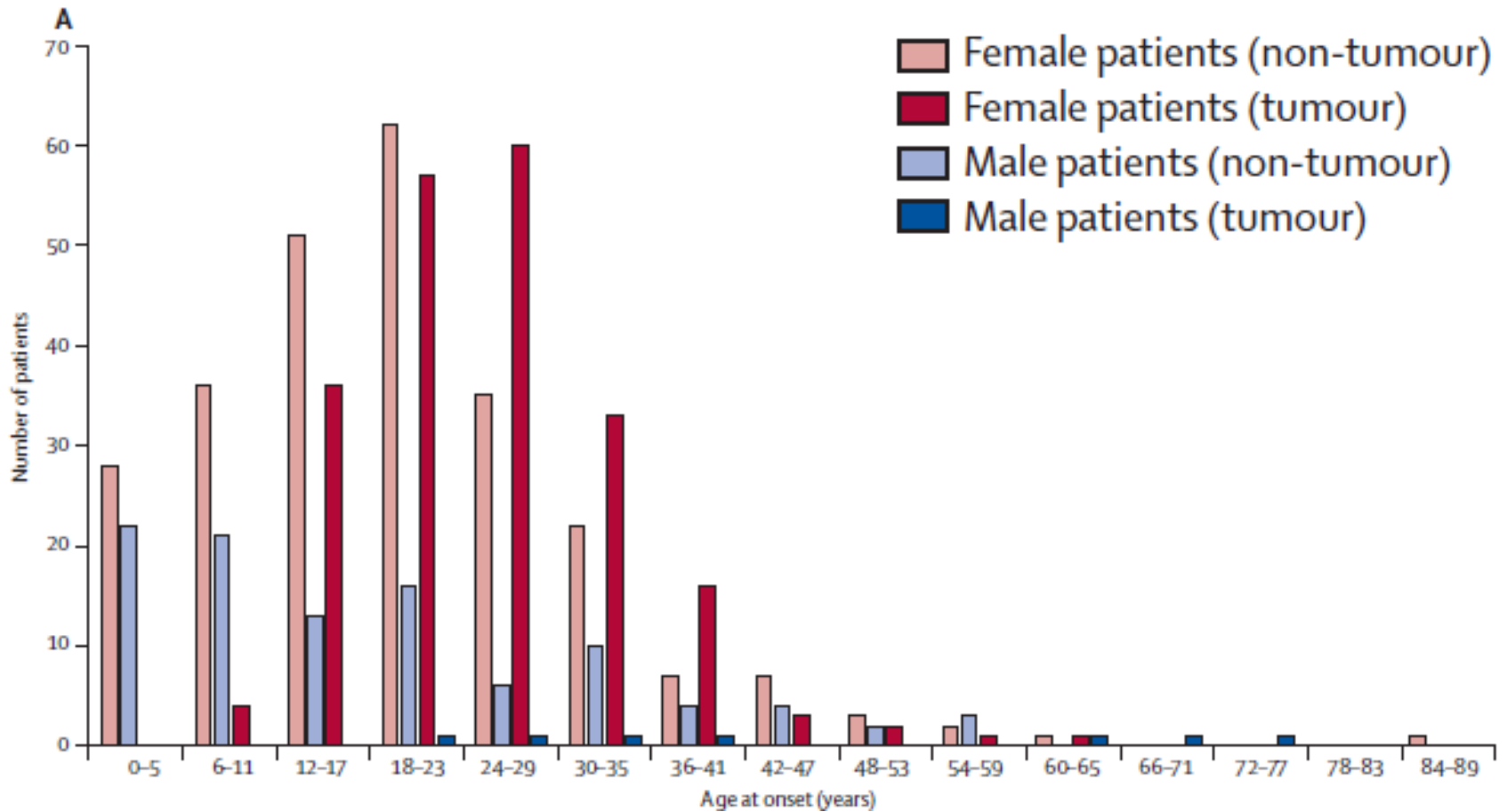
# Results

2. How many times has the test been sent in all age groups? **n = 16**





# Patient Demographics



Titulaer et al. (Lancet 2013)

### 3. What are the logistical issues and costs associated with ordering the test?

- ONLY one lab in Canada
- Results in 5-7 business days *after sample received* by lab
- need approval of biochemist
  
- Cost: \$130
  - Compare to HSV test: \$22

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*Shaded area for lab use only*

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*Date rec'd:*

SSN:

### Autoantibody Test Requisition

Patient Information:		Referring Physician Information:	
*Name: (Surname, First)		*Dr. Name: (Surname, First)	
*PHN:		*Alpha Provider #	
*Health Region #:		Health Region #:	
*DOB: (dd/mm/yy)	*Gender:	Address:	
*Address:		*Phone:	
Postal Code:		*Email:	

Referring Lab Information:	Sample Information:
*Lab Name:	Date/Time collected: (dd/mm/yy: hr)
*Address:	*Diagnostic information pertinent to autoantibody test request:

\*Phone : \_\_\_\_\_

\*Fax # \_\_\_\_\_

\* = Required information.

**Medical Personnel:** Please mark ALL tests to be done

<input type="checkbox"/> ANA/ENA Screening Test. <i>(Indirect immunofluorescence screen)</i>	<input type="checkbox"/> A My MD PM A
<input type="checkbox"/> anti-ds-DNA (Chemiluminescence Assay ) <input type="checkbox"/> anti-Histone (Drug-Induced Lupus)	
<input type="checkbox"/> Systemic Lupus ENA Profile: anti-Sm , RNP, Ro52/TRIM21, SSA/Ro60, SSB/La, Jo-1, PCNA <input type="checkbox"/> Anti-C1q Antibody (SLE Nephritis )	<input type="checkbox"/> I - AS - AN
<input type="checkbox"/> Scleroderma Profile: CENP A + B, Topo- I/Sci-70, RNA polymerase, fibrillarin, Th/To, Ku, PDGFR, Ro52/TRIM21, PM/Sci-75, PM/Sci-100. <input type="checkbox"/> Anti-CCP Cyclic Citrullinated Peptide Antibodies	<input type="checkbox"/> D
<input type="checkbox"/> Autoimmune Liver Disease Profile: M2/M3, 3EBPO, LKM, SLA, SP100, gp210, PML, LC-1, Ro 52.	<input type="checkbox"/> I - AS - AN

- Encephalitis: NMDA (NR1) Receptor Antibodies
- VGKC antibodies (Voltage gated potassium channel – LGI1 & Caspr2)
- Anti-GAD 65 antibodies
- Anti-AMPA antibodies

<input type="checkbox"/> Anti-Phospholipase A2 receptor (Anti-PLA2R)	GQ1b
<input type="checkbox"/> Anti-DIF 70 (Dense Fine Speckles 70) <input type="checkbox"/> Phosohatidylserine/Prothrombin Complex -IgG, IgM ( PS/PT)	<input type="checkbox"/> Anti-p140/p155/TRIM28 (Research Use only) <input type="checkbox"/> Alveolar Proteinosis: anti- GM/CSF (Research Use only)
	<input type="checkbox"/> Anti-elastase (Research Use only)

## 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

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Titulaer et al. (Lancet 2016)

# Take home points

1. Anti-NMDAR encephalitis may be more common than HSV encephalitis in the 30 and under age group
2. More common in females and often related to ovarian teratoma... but not always
3. Clinical presentation may include: behavioural change, seizure, memory or cognitive impairment, abnormal movements, speech impairment

# Take home points

4. Consider anti-NMDAR encephalitis in the “bizarre” psych patient , OR in the patient you are working up for HSV encephalitis
5. If you are sending CSF for HSV testing or covering with acyclovir, consider testing for NMDAR antibodies
6. You don't know, what you don't know...

# References

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