Cerebellar Ataxia in patients with Anti-GAD antibody

Dr. Hemang Shah

Patient Profile

LR is a 56 year old AAF, Right handed

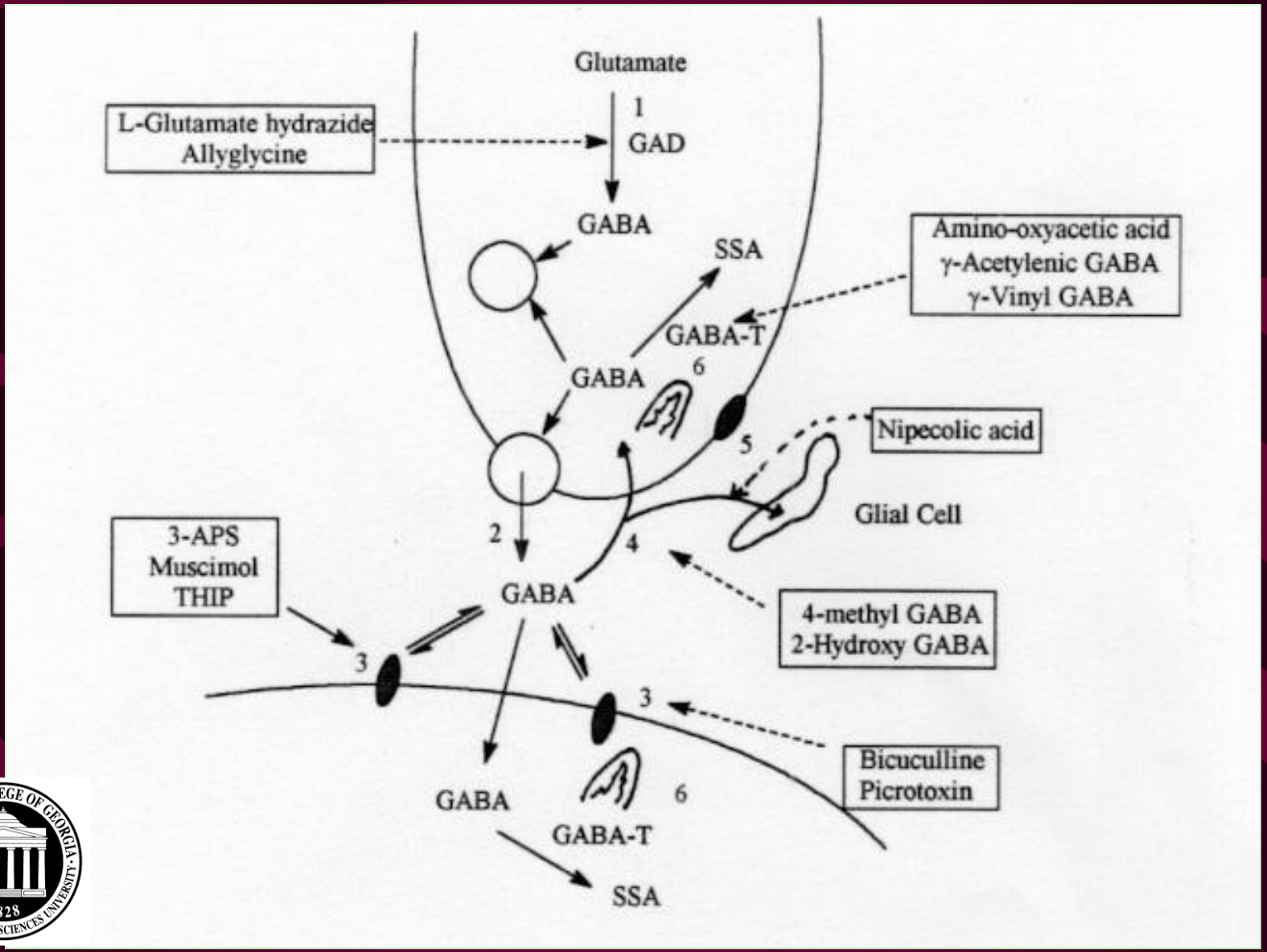
•Diabetic ketoacidosis in 6/2002 – type I - DM, she started using cane around 2003

•She was admitted 7/7/2007 for inability to walk for 1 week (acute on chronic deterioration of balance, also found to have dysmetria Rt > Lt, dysarthria, gait apraxia).

•CT and MRI showed – significant cerebellar atrophy and cortical atrophy left > right.

•Patient was found to have high titers of anti GAD antibody in serum (206 nmol/L, Ref: =< 0.02) CSF (3.84 nmol/L, Ref: =<0.02), para neoplastic panel in CSF was negative and limited work up to look for systemic primary malignancy is negative.

Let's talk about GAD 65



Neurological disorders associated with anti – GAD antibody

1) Stiff person syndrome (SPS)
2) SPS-plus (SPS, cerebellar ataxia, cognitive dysfunction)
3) Idiopathic cerebellar ataxia
4) Focal epilepsy/myoclonus
5) Batten's disease (juvenile neuronal ceroid lipofuscinosis of autosomal recessive inheritance due to deletions in the CLN3 gene)
6) Paraneoplastic association with thymoma, breast and lung carcinoma

Symptomatology of stiff-person syndrome

- Fluctuating muscle rigidity of truncal and proximal limb muscles with superimposed spasms.
- Continuous contraction of agonist and antagonist muscles caused by the involuntary motor unit firing at rest, are the hallmark clinical and electrophysiological signs of the disease.
- Autoimmune pathogenesis

a) The presence of antibodies against glutamic acid decarboxylase (GAD 65)

b) Antibodies are produced intrathecally

c) Association with other autoimmune disorder

The role of IVIg in the treatment of patients with stiff person syndrome and other neurological diseases associated with anti-GAD antibodies

Prof. **Marinos C.Dalakas**

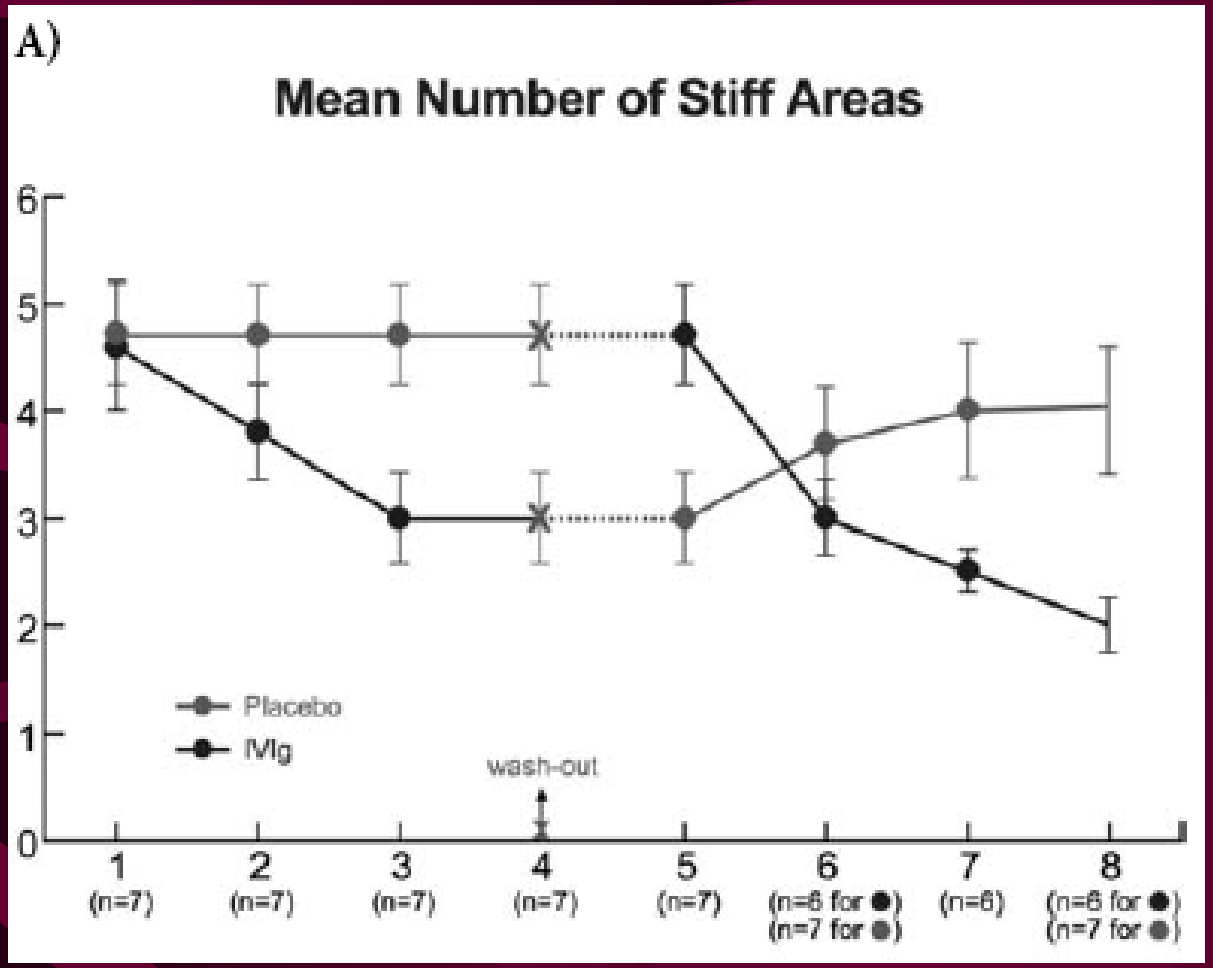
Chief, Neuromuscular disease section, NINDS

- A randomised double-blind, placebo controlled, crossover clinical trial – supported by NIH – study design
- www.clinicaltrials.gov NCT00001550
- Study design

Baseline characteristics for randomization

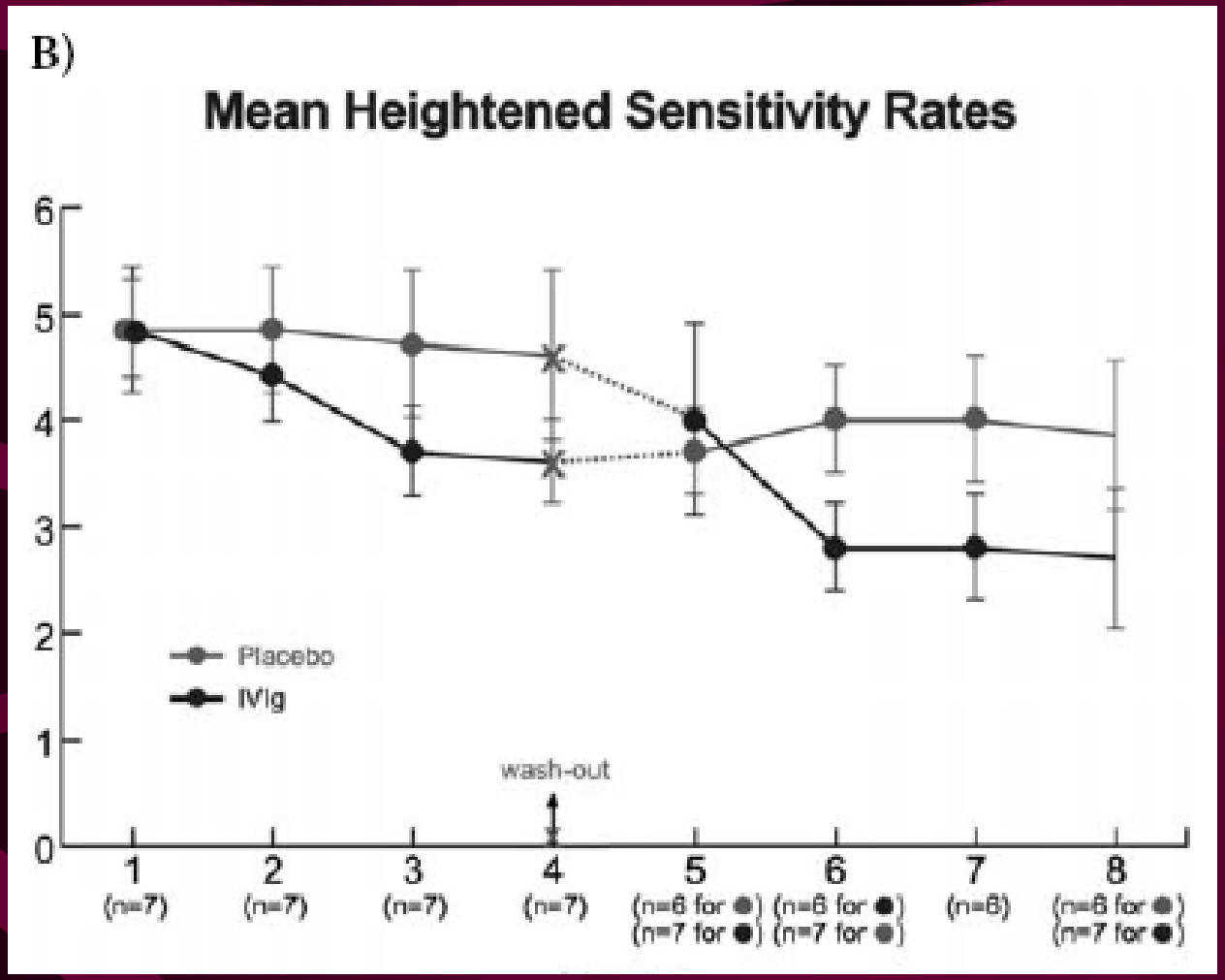
Patient Characteristics	Group A (8)	Group B (8)
Age of onset	35–47 (mean 41 yrs)	27–54 (mean 39 yrs)
Sex	4 M; 4 W	3 M; 5 W
Disease duration	5–22 yrs (mean 11 yrs)	3–23 years (mean 12 yrs)
Disease severity:		
Mean heightened sensitivity scores	4.85 ± 1.7 (SD)**	4.85 ± 1.4 (SD)**
Mean distribution of stiff areas	4.71 ± 1.3 (SD)	4.57 ± 1.6 (SD)
Co-existing autoimmune diseases:		
Diabetes*	4	3
Polymyositis	1	0
Pernicious anaemia	1	0
Thyroiditis	1	3
Vitiligo	0	1
Seizures	1	1
Medications on enrolment:		
Benzodiazepines	10	6
Baclofen	1	5
Gabapentin	1	2
Valproic acid	0	1

Mean number of stiff Areas



- Distribution of stiffness index – a validated score

Mean Heightened Sensitivity Rates



- Heightened sensitivity score – validated score

Statistical analysis and Results

- Primary end point: change in the scores of distribution of stiffness index and heightened sensitivity from baseline.
- Unbiased estimates of

a) baseline sequence group difference;

b) direct treatment effect;

c) first order carry-over effect;

d) second order carry-over effect – least square techniques. Significance testing – permutation techniques.

- Patient's own assessment of response to therapy

Negative points about the study

- Sample size – 16
- Inflation of result interpretation
- Unanswered basic science question of *in vitro* evidence
- SPS is a functional disorder rather than structural disorder – my patient has developed structural lesion – how likely is the improvement

References

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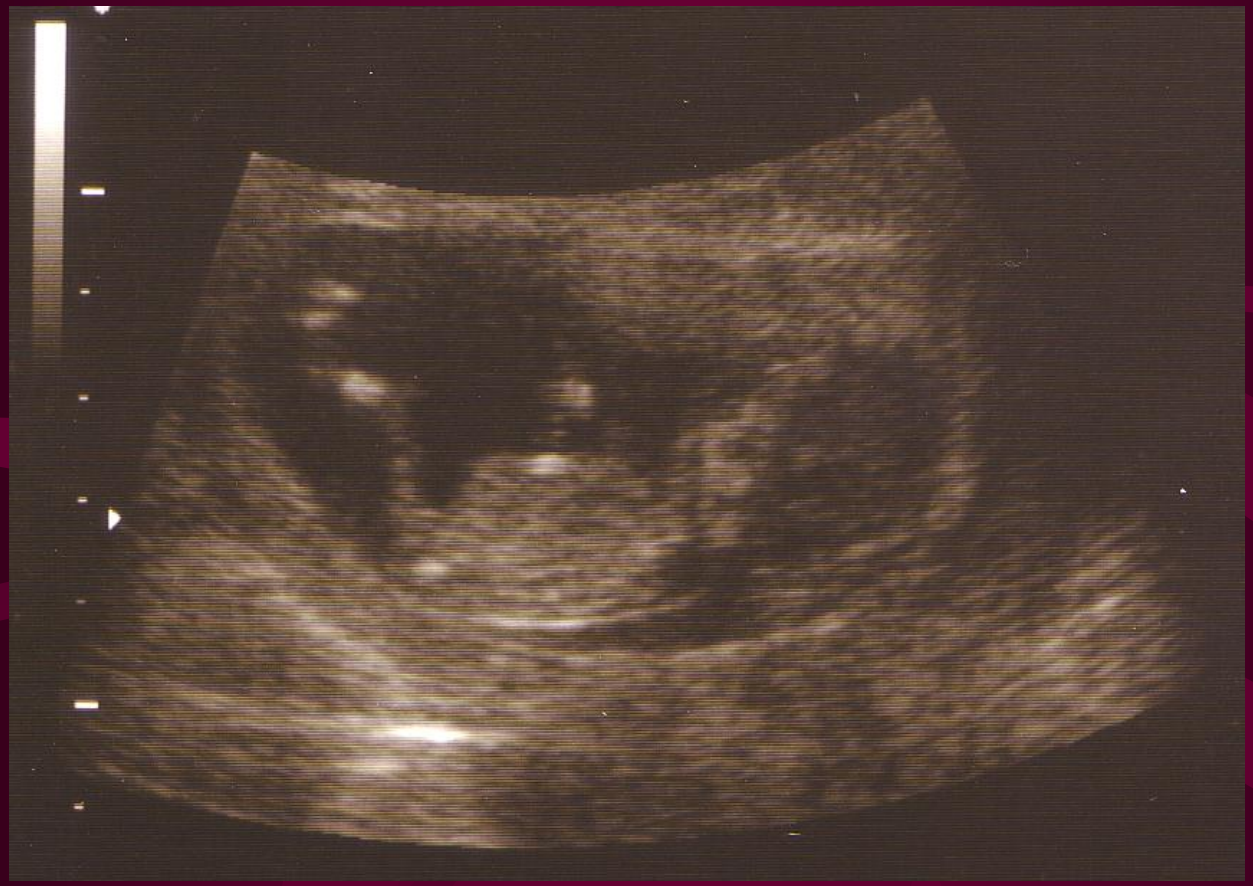
Coming soon…



Ria Shah

Thanks