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MEDICINE &
BIOLOGICAL
SCIENCES

83 yo Woman With Elevated Anti-Thyroid Antibodies and AMS

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Endorama Sept 2018

Dr. Casimiro does not have any relevant
financial relationships with any
commercial interests.

Objectives

- Discuss the role of anti-thyroid antibodies in thyroid disease & non-thyroidal illness
- Understand the pathophysiology and treatment of encephalopathy associated with autoimmune thyroiditis

HPI

- 8/5/17: Admitted at OSH for AMS/confusion (baseline normal cognition)
- 2-3 wks Hx of progressive disorientation, agitation, paranoia, & echolalia (repeatedly saying “seven”)
- Sodium found to be 119 on admission improved to 125 prior to transfer
- Was on broad spectrum Abx for WBC 20.1 (concern for PNA vs meningitis)
- 8/7/17: normal LP, normal MRI brain
- 8/8/17: Abx d/c'd, Na and WBC improved; EEG: right PLEDs (periodic lateralized epileptiform discharges) -> transferred to Neuro ICU
- 8/12/17 new hyperintensity along the cortex of the R posterior inferior temporal lobe, inferior lateral frontal & parietal lobes, R insula & R posterior thalamus along w R hippocampus, no evidence of metastatic or meningeal dz
- Transferred to U of C on 8/16/17 for further work up
- Abnormal thyroid function tests on admission, Endo consulted

PMH

- Adenocarcinoma of the breast s/p mastectomy (2017), chemo
- IBS
- CAD
- HTN
- Depression, anxiety
- HLD
- Hashimoto's thyroiditis (?)
- Gout

FH

- Son: Bipolar dz
- Sister: breast cancer

SH

- Pt lives with son. She worked for the post office before retirement in 1997.
- No EtOH or IVDU

Meds*

*Meds started this hospitalization

- Acyclovir 600mg Q8hr
- Famotidine 20mg Qd
- Heparin 5000 UQ8hr
- Novolog SSI 2-10 U Q6hr prn
- Levetiracetam/Keppra 1000mg Q12h
- Lorazepam/Ativan 1mg Q15 min prn
- Phenytoin/Dilantin 100mg Q8hr

PTA Meds:

- Amlodipine
- ASA
- Letrozole
- Lisinopril
- Simvastatin
- Clonazepam
- Escitalopram

Physical Exam on U of C Admission

- General: Patient is non-responsive, but in no acute distress
- HEENT: NC/AT, conjunctiva pink, sclera white, oropharynx pink and moist
- CV: RRR, no murmurs
- LUNGS: CTA bilaterally
- ABD: BS+, mildly distended, no apparent pain to palpation
- EXT: no C/C/E, extremities warm
- SKIN: no rashes or bruising or ulcers
- Neuro: **Motor:** No spontaneous movements; Increased tone in all extremities; No rhythmic or myoclonic movements are evident

Reflexes: Hypertonic, reflexes hard to obtain

	Right	Left
Biceps	-	-
Triceps	-	-
BR	-	-
Patella	-	-
Ankles	-	-
Plantar response	down	down
Hoffmans	neg	neg
Ankle clonus	neg	neg

Vitals: BP: 124/58, HR: 67, T 36.8, RR: 24, Wt 59.2kg 130 lb

Labs

139	104	14	104
4.1	22	0.5	

Calcium: 8.3

Phos: 2.9

Mag: 1.6

Protein: 5.3

Albumin 2.7

Tbili: 0.3

Alk phos: 47

AST: 41

ALT: 25

CK: 642

9.4	10.7	226
31.8		

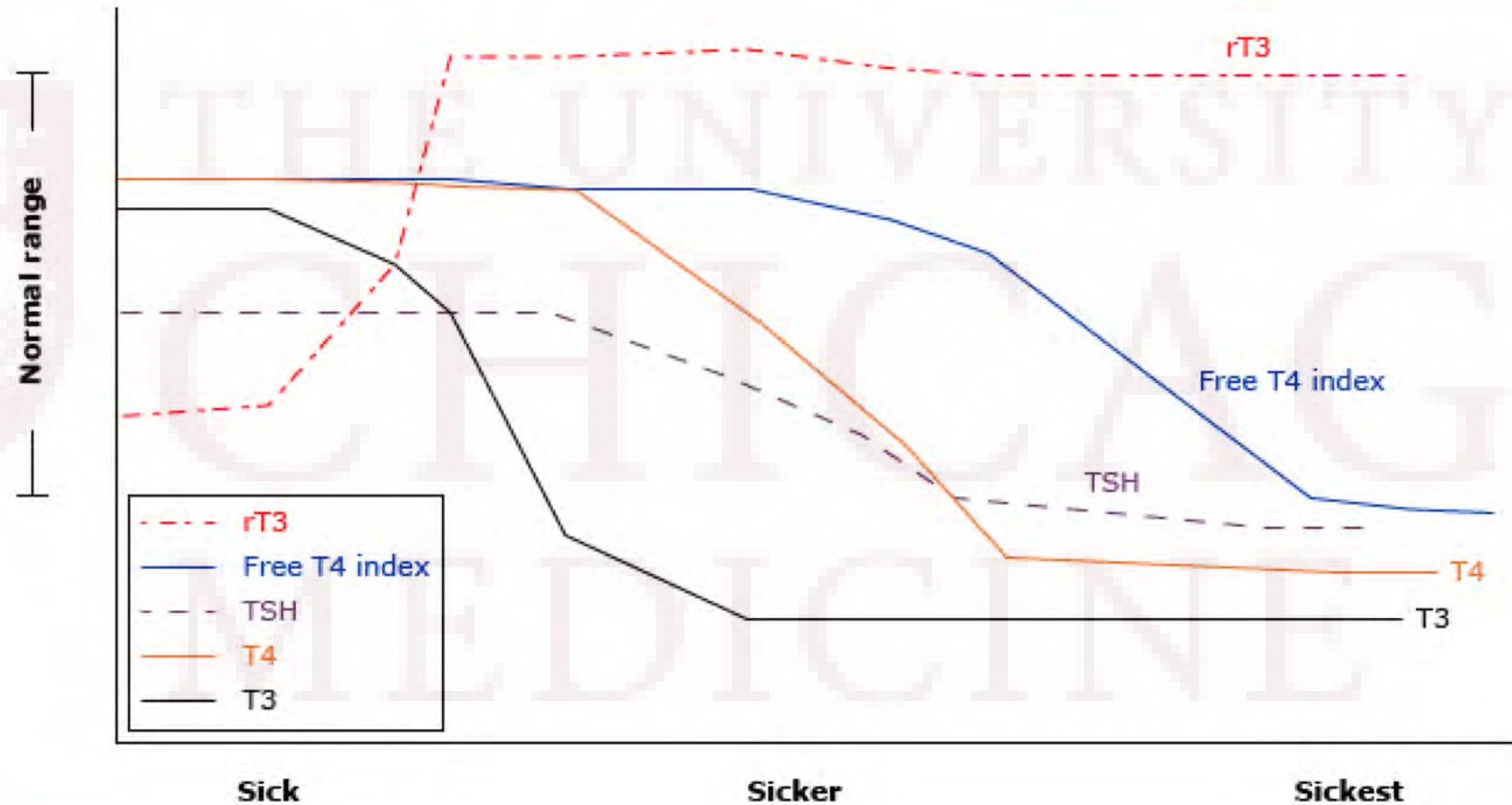
TSH: 4.47 (0.3 -4)

FT4: 0.94 (0.9 -1.7)

T3: 64 (80 -195)

Cortisol (03:16am) 10.7

Thyroid function tests in nonthyroidal illness



Schematic representation of the changes in thyroid function tests in patients with nonthyroidal illness of increasing severity.

Labs

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Phos: 2.9

Mag: 1.6

Anti-Tg:>30 (200x: 1860)

Anti-TPO>20 (440)

TG by MS: 565

Protein: 5.3

Albumin 2.7

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Mag: 1.6

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Consult Question:
Does Pt have Hashimoto's
encephalitis?

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ALT: 25

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31.8

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Hashimoto's Encephalopathy (HE)



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Hashimoto's Encephalopathy (HE)

- Originally described in 1966, it remains a somewhat controversial disorder; ~ 100 cases described worldwide
- AKA Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) or nonvasculitic autoimmune meningoencephalitis
- Characterized by subacute onset of confusion with altered level of consciousness, seizures, and myoclonus
 - Diagnostic criteria proposed by Peschen-Rosin 1999: seizures, psychiatric dz, focal neuro deficits with elevated thyroid Abs & excellent response to steroids
- Believed to be an immune-mediated disorder rather than representing the direct effect of an altered thyroid state on the CNS

Anti-thyroid Antibodies

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Estimated prevalence of antithyroid antibodies (in percent)

Group	Anti-TSHR Ab	Anti-Tg Ab	Anti-TPO Ab
General population	0	5 to 20	8 to 27
Graves' disease	80 to 95	50 to 70	50 to 80
Autoimmune thyroiditis /Hashimoto's thyroiditis	10 to 20	80 to 90	90 to 100

Anti-thyroid Antibodies

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Relatives of patients with autoimmune thyroiditis	0	30 to 50	30 to 50

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Relatives of patients with autoimmune thyroiditis	0	30 to 50	30 to 50
Type 1 diabetes	0	30 to 40	30 to 40

Anti-thyroid Antibodies

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Relatives of patients with autoimmune thyroiditis	0	30 to 50	30 to 50
Type 1 diabetes	0	30 to 40	30 to 40
Pregnant women	0	about 14	about 14

Anti-thyroid Antibodies

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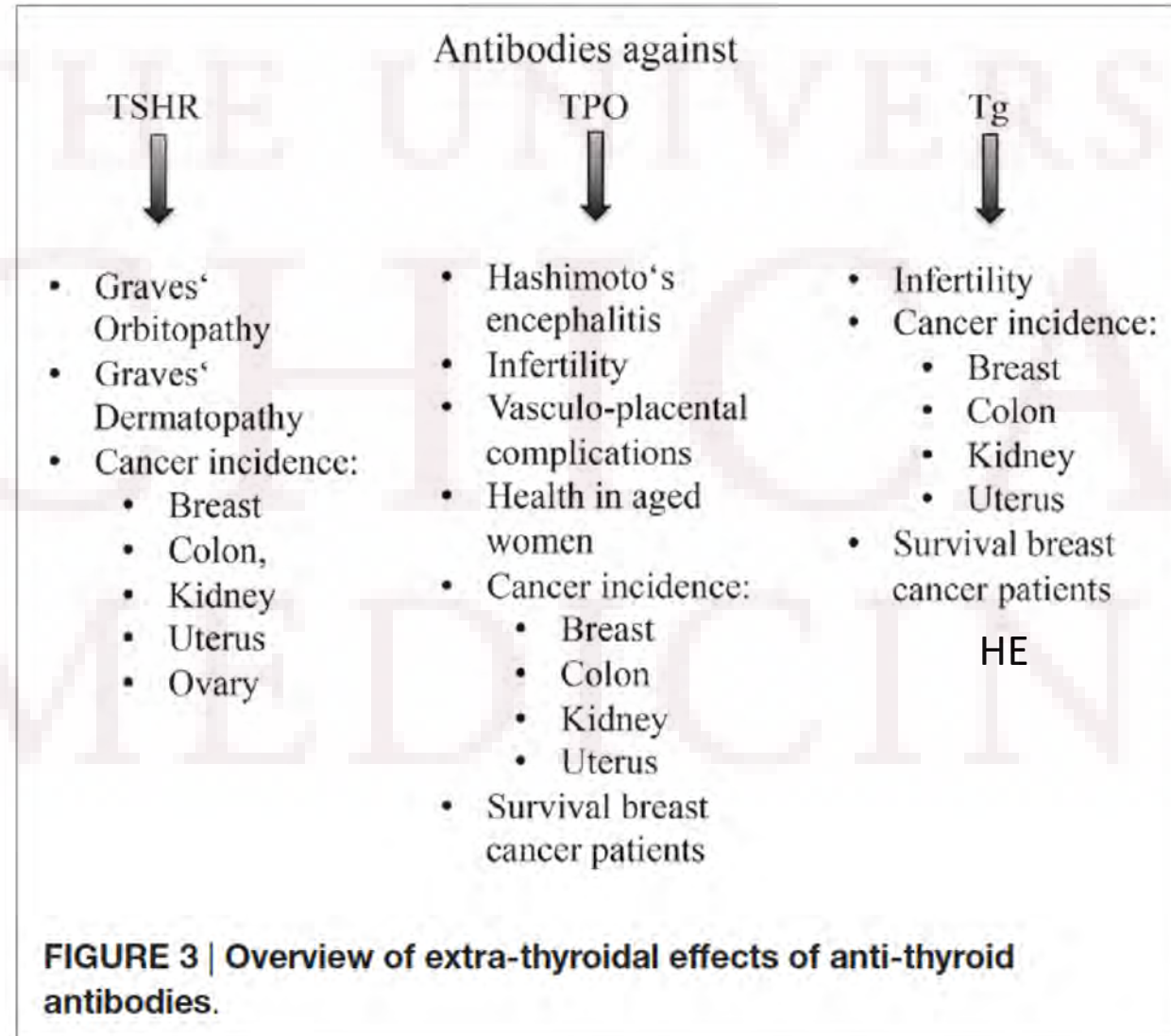
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Pregnant women	0	about 14	about 14

Anti-TSHR Ab: anti-thyroid-stimulating hormone receptor antibodies; anti-Tg Ab: anti-thyroglobulin antibodies; anti-TPO Ab: anti-thyroid peroxidase antibodies.

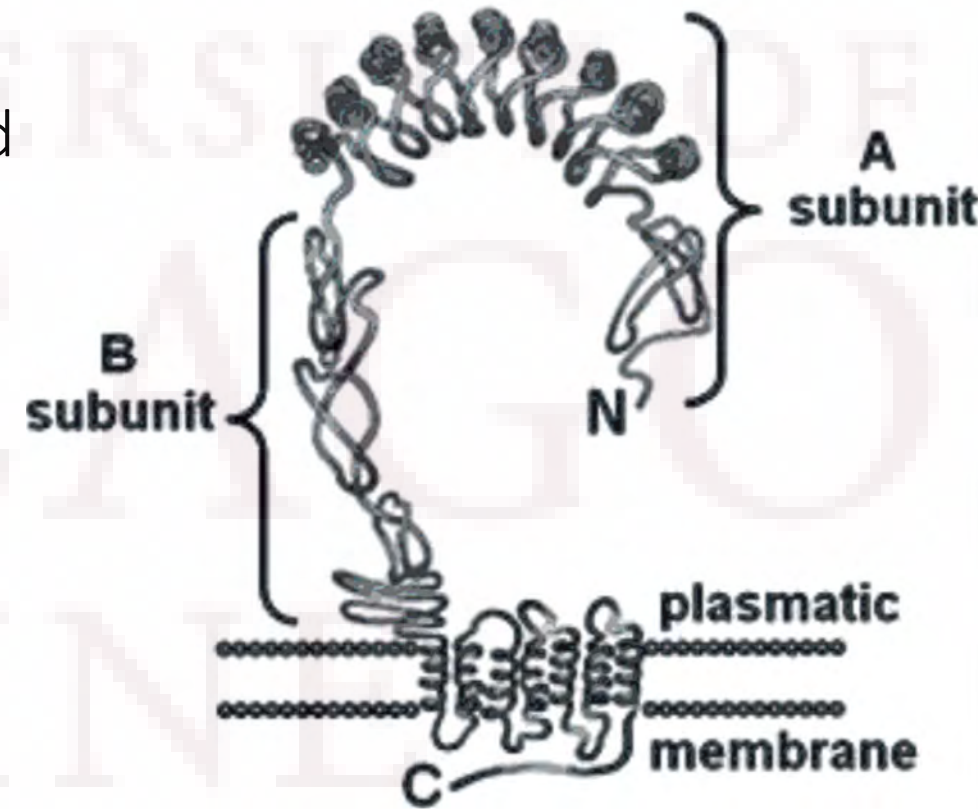
Healthy people: 11% anti-TG, 13% anti-TPO

Anti-thyroid Antibodies in Non-thyroidal Illness



History of TSH Receptor Ab: TRAb

- TSHR autoantibodies were discovered in 1956 by Adams & Purves and were called long-acting thyroid stimulator (LATS)
 - The presence of these antibodies were detected in patients with Graves' disease
 - 20 years later, the exact binding site for the TSHR antibodies was described; the leucine rich domain of the A subunit of TSHR (same binding site for TSH)
 - Stimulation of TSH by GD-TRAb's leads to activation of adenylate cyclase leading to cAMP generation, which eventually lead to T4 and T3 release
- The A subunit is shed which is thought to be important in the generation of autoimmunity in GD



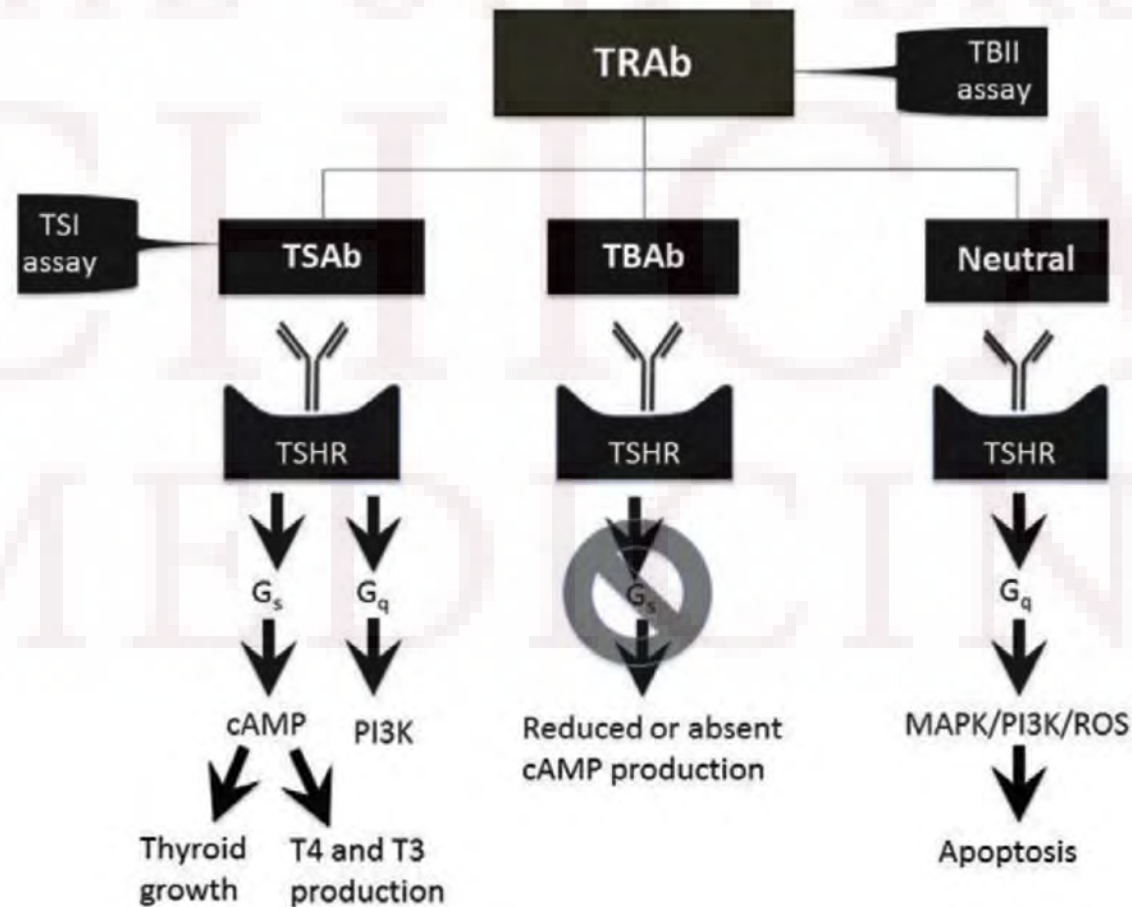
TSH Receptor (Olga et al., JBM 2017)

Graves Disease

- Syndrome of hyperthyroidism caused by autoimmunity; extrathyroidal manifestations can include eye disease (Graves ophthalmopathy), dermopathy (pretibial myxedema/Graves dermopathy), and/or goiter
- Symptoms of hyperthyroidism: weight loss, weakness, dyspnea, palpitations, increased hunger/thirst, hyperdefecation, sweating, sensitivity to heat, tremor, irritability, menstrual irregularity
- Activating autoantibodies to TRAb stimulate thyroid hormone synthesis and secretion as well as sometimes thyroid growth (goiter)
- In the assessment of TSH receptor autoimmunity three types of TSH receptor antibodies (TRAbs) can be measured:
 - TSAbs: stimulating TRAbs (Graves dz)
 - TBAbs: blocking TRAbs (extrathyroidal GD manifestations, also seen in hypothyroidism)
 - Neutral Abs: unknown clinical significance

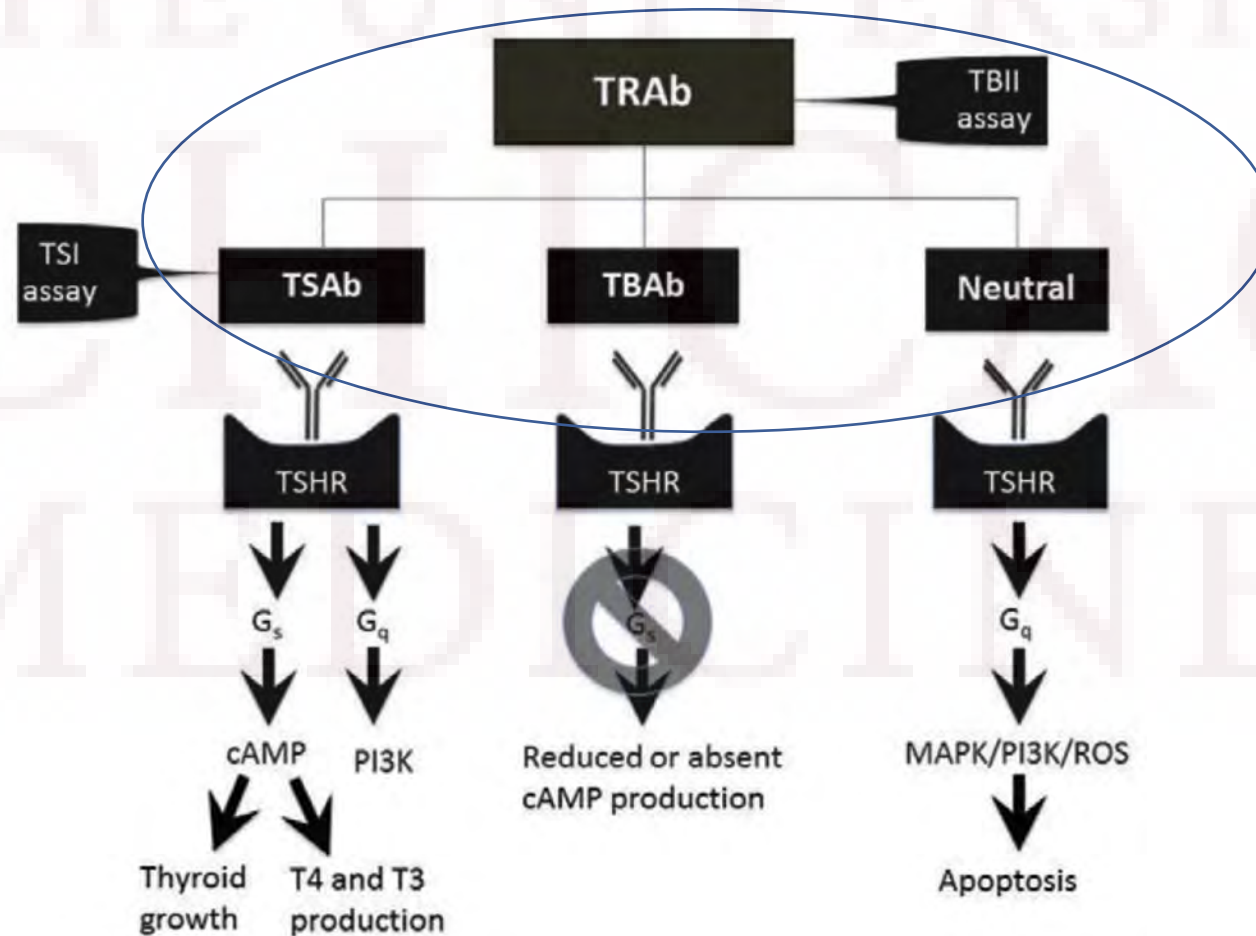
TRAb Assays

Ophthal Plast Reconstr Surg, Vol. 34, No. 4S, 2018



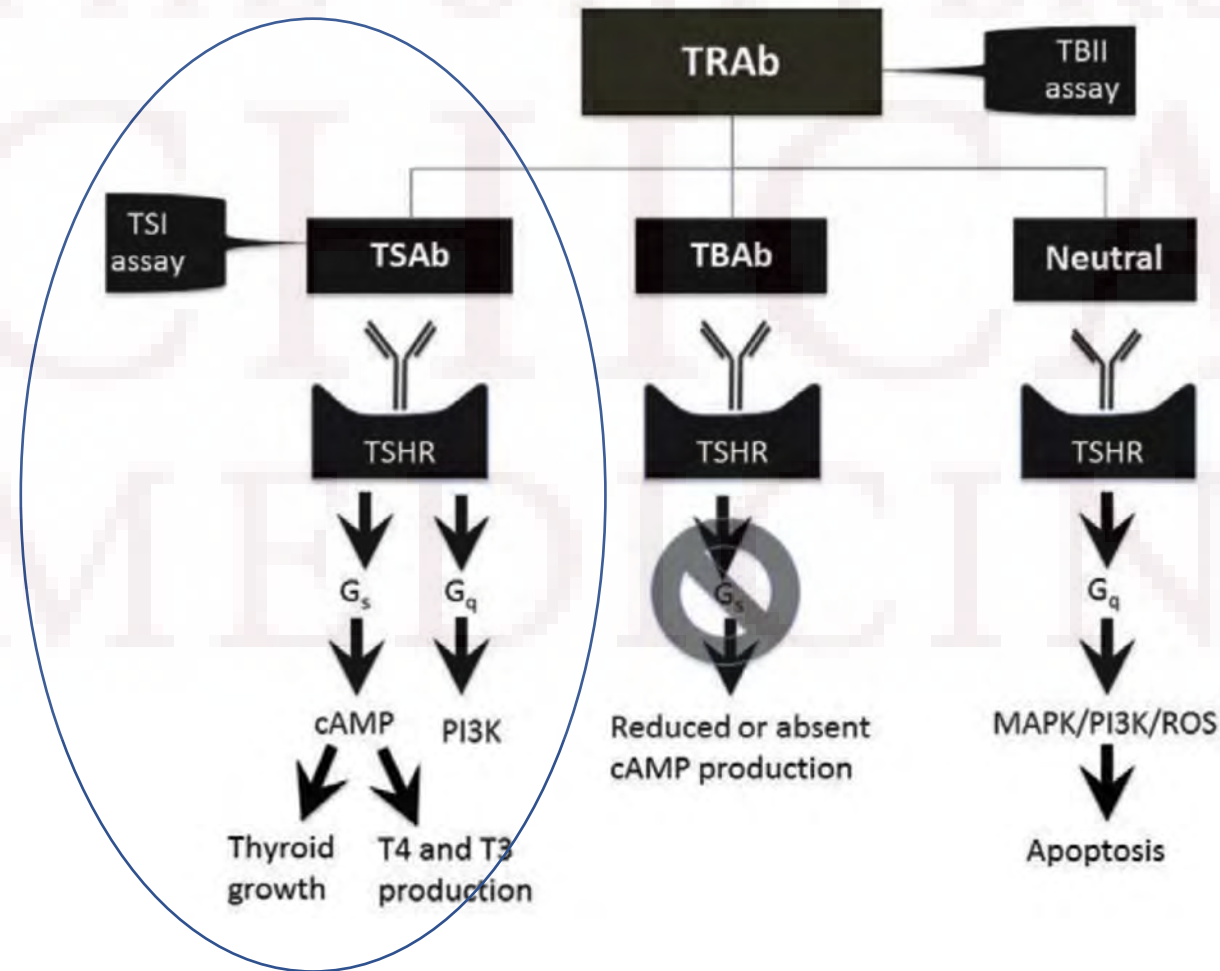
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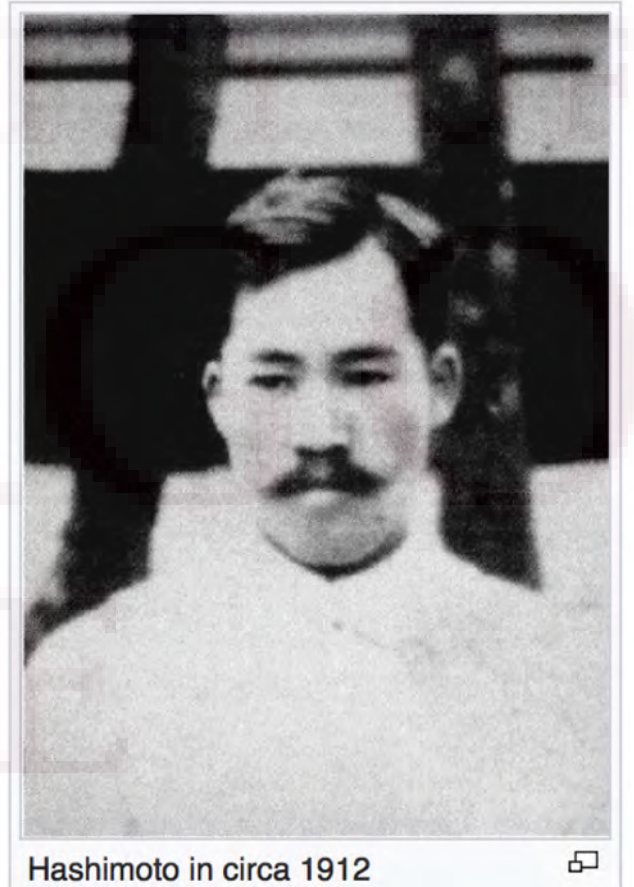
TRAb Assays

Ophthal Plast Reconstr Surg, Vol. 34, No. 4S, 2018



Hashimoto's Thyroiditis (HT)

- MCC of hypothyroidism in iodine sufficient areas of the world
- Dr. Hashimoto first described *struma lymphomatosa*, an intense infiltration of lymphocytes within the thyroid
- Characterized by gradual thyroid failure due to autoimmune mediated destruction of the thyroid gland
- Symptoms: fatigue, weight gain, increased sensitivity to cold, difficulty concentrating, dry skin/nails/hair, constipation, drowsiness, muscle soreness, increased menstrual flow)
 - More likely to develop in Pts with another autoimmune disease
- High concentrations of Abs against one or more thyroid antigens; diffuse lymphocytic infiltration of the thyroid (thyroid specific B & T cells) & follicular destruction (hallmark of thyroiditis)
- HT may lead to hypothyroidism or subclinical hypothyroidism (inc TSH and normal TH levels)
- Autoantibodies: blocking TSHR Abs, TG Abs, TPO Abs



Hashimoto in circa 1912

Hashimoto's Encephalitis (HE) & Thyroid Disease

- Does not appear to be directly related to hypo or hyperthyroidism
 - 23-35% pts had subclinical hypothyroidism, 17-20% hypothyroidism, 7% hyperthyroid, remainder were euthyroid (Ferracci & Carnivale 2006)
- The relationship between Hashimoto's thyroiditis and HE is unclear
- Elevated anti-thyroid Abs (TPO-Ab, TG-Ab) are seen, but also seen in healthy populations
 - There is no relationship between Ab concentration & severity of neurologic symptoms
- Ab levels usually decrease following treatment & clinical improvement (but not always)

Table 1 Symptoms recorded in 121 patients with of HE

Symptoms	Frequency
Seizures	63 (52%)
Confusion	52 (43%)
Myoclonus	45 (37%)
Cognitive impairment	44 (36%)
Altered consciousness	44 (36%)
Ataxia	40 (33%)
Focal deficits	37 (31%)
Psychiatric disorders	36 (30%)
Tremor	34 (28%)
Hallucinations	31 (26%)
Pyramidal signs	25 (21%)
Headache	16 (13%)
Extrapyramidal symptoms	13 (11%)
Cerebellar symptoms	6 (5%)
Vertigo	4 (3%)
Myelopathy	3 (2%)
Fatigue	2 (2%)

Pathophysiology of HE

- Autoimmune vasculitis or other inflammatory process, perhaps associated with immune complex deposition, and possibly disrupting the cerebral microvasculature
- Antibodies thought to cross BBB and react with brain antigens causing encephalopathy, bind to cerebellar astrocytes, anti-thyroid antibodies found in CSF (not in all patients)
- Autopsy studies have shown peri-venular and peri-arteriolar lymphocytic infiltrates within leptomeninges & parenchyma, but this has not been consistent

Treatment of HE

- High dose corticosteroids: Prednisone doses 50—150mg daily have been used
 - High dose IV Methylpred has also been used, but benefit to oral prednisone has not been shown
- Alternative treatments: IVIG, methotrexate, mycophenolate/cellcept, azathioprine, rituximab, cyclophosphamide (case reports); as alternative treatment, or in patients refractory to steroids or with relapses

Back to Our Patient

- Endo recs:
 - “[HE] is a diagnosis of exclusion and other etiologies of altered mental status should be ruled out prior to making this diagnosis (toxic metabolic encephalopathies, infection, CJD, psychiatric disease, malignancy, paraneoplastic syndrome, dementia, vasculitis, etc)
 - If other etiologies are ruled out, can consider treatment for Hashimoto's encephalopathy with corticosteroids - Prednisone 60mg daily (1mg/kg) ”

Can HE be diagnosed accurately?

- Most published case reports of HE comprise a very small sample, and there is no comprehensive statistical analysis of the clinical features associated with HE
- HE remains problematic regarding its pathophysiology, diagnosis, and treatment
- HE is a diagnosis of exclusion, but important to recognize as it's prognosis is generally good with steroid treatment

A case control study to analyze HE characteristics

OPEN ACCESS Freely available online



Cognitive Impairments in Hashimoto's Encephalopathy: A Case-Control Study

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Abstract

Background/Aims: Hashimoto's encephalopathy is considered as a treatable dementia, but it is often misdiagnosed. We investigated cognitive impairment and the MRI pathology of Hashimoto's encephalopathy patients.

Methods: The study comprised eight patients with Hashimoto's encephalopathy, 16 patients with mild Alzheimer's disease and 24 healthy subjects. A neuropsychological battery included assessments of memory, language, attention, executive function and visuospatial ability. Cranial MRI was obtained from all Hashimoto's encephalopathy patients.

Table 1. General information for the three groups (means $\pm$ SD).

Index	HE group(n = 8)	Normal group(n = 24)	mild AD group(n = 16)	F(χ^2) value	P value
Age	38.88 $\pm$ 11.57	60.25 $\pm$ 6.64* *	60.44 $\pm$ 5.76	28.204	<0.001
Years of Education	12.50 $\pm$ 2.45	13.38 $\pm$ 2.39	11.38 $\pm$ 3.20	2.642	0.082
Gender(M:F)a	5:3	5:11	15:9	4.087	0.130
MMSE Total score	21.63 $\pm$ 1.51	28.75 $\pm$ 1.19* *	23.31 $\pm$ 2.94	56.586	<0.001
CESD	7.58 $\pm$ 3.47	9.16 $\pm$ 7.99	9.00 $\pm$ 5.07	0.197	0.898

CES-D = Center for Epidemiologic Studies Depression Scale.

a = χ^2 analysis.

** = $P < 0.01$, normal group vs. HE group.

doi:10.1371/journal.pone.0055758.t001

Table 2. Clinical and laboratory findings for the HE group.

Case	Age (yrs)	Sex	Clinical presentation	Special examinations	Treatment	Evolution
1	58	F	Partial complex seizures, cognitive impairment	Hippocampus swelling and N angio, EEG diffuse slowing, sharp waves>left	A, S	Occasional relapses, then stable
2	47	F	Partial complex and generalized seizures, cognitive impairment	MRI bilateral medial temporal and hippocampus FLAIR hypersignal, EEG diffuse slowing, sharp waves>right	A, S	Improvement after ttt
3	41	F	Cognitive impairment, apathy	MRI white matter alterations, N EEG	S	Improvement after ttt, persistent mild cognitive impairment
4	24	F	Focal and generalized seizures, cognitive impairment	MRI left medial temporal and amygdala FLAIR hypersignal, N EEG	A,S	Improvement after ttt, seizure free
5	38	M	Cognitive impairment, anxiety	Hippocampus mild swelling, EEG delta slowing	S,T4	Slight improvement after ttt
6	46	M	Generalized seizures, cognitive impairment	Hippocampus mild swelling, EEG slowing	S	Improvement after ttt, no seizure relapse
7	31	F	cognitive impairment, occasional stupor	MRI white matter alteration, EEG diffuse slowing,	S	Significant improvement after ttt, relapses
8	26	M	cognitive impairment	Hippocampus well-stacked, N EEG	S	Improvement after ttt

N, normal; angio, cerebral angiography; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; S, steroid; A, anticonvulsant; t, treatment; T4, levothyroxin.

doi:10.1371/journal.pone.0055758.t002

Results From This Study

- Scores from HE group were worse than those of normal control group in most tests
- There was no significant difference in performance between HE and AD group except HE patients showed preserved long term semantic memory (naming ability)
- Pts cognitive function improved with steroid treatment (MMSE scored improved to 28-30/30 from mean of 21.6)
- MRI pathology revealed no involvement of the temporal cortex (which plays a role in naming ability)
- MRI revealed two types of HE manifestation:
 - Leukoencephalopathy type
 - Limbic encephalitis-like type

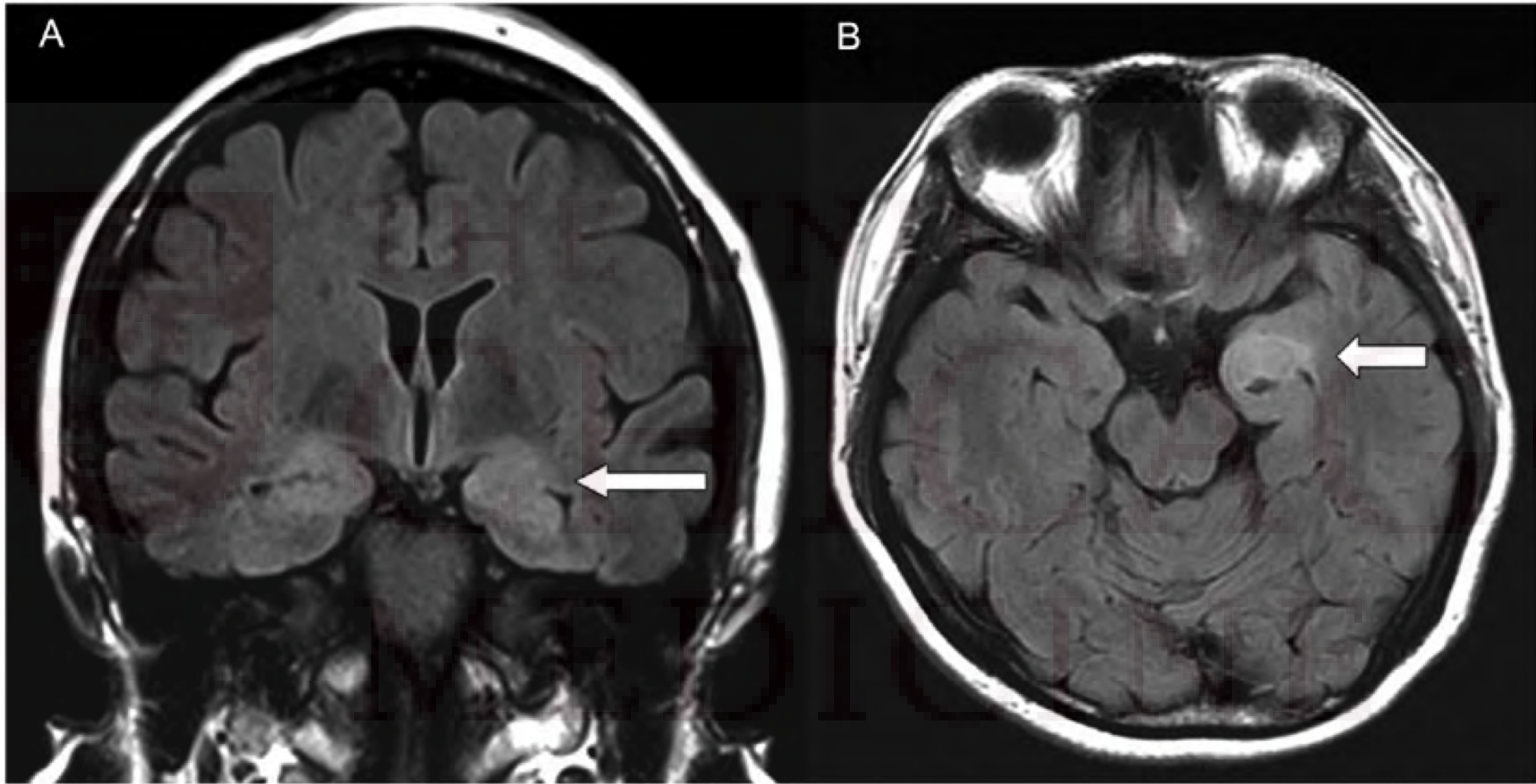


Figure 2. Limbic encephalitis-like manifestations on MRI images. (A) Coronal MRI image shows bilateral medial temporal and hippocampus hypersignal on FLAIR. (B) Axial MRI image shows left medial temporal and amygdala hypersignal on FLAIR.

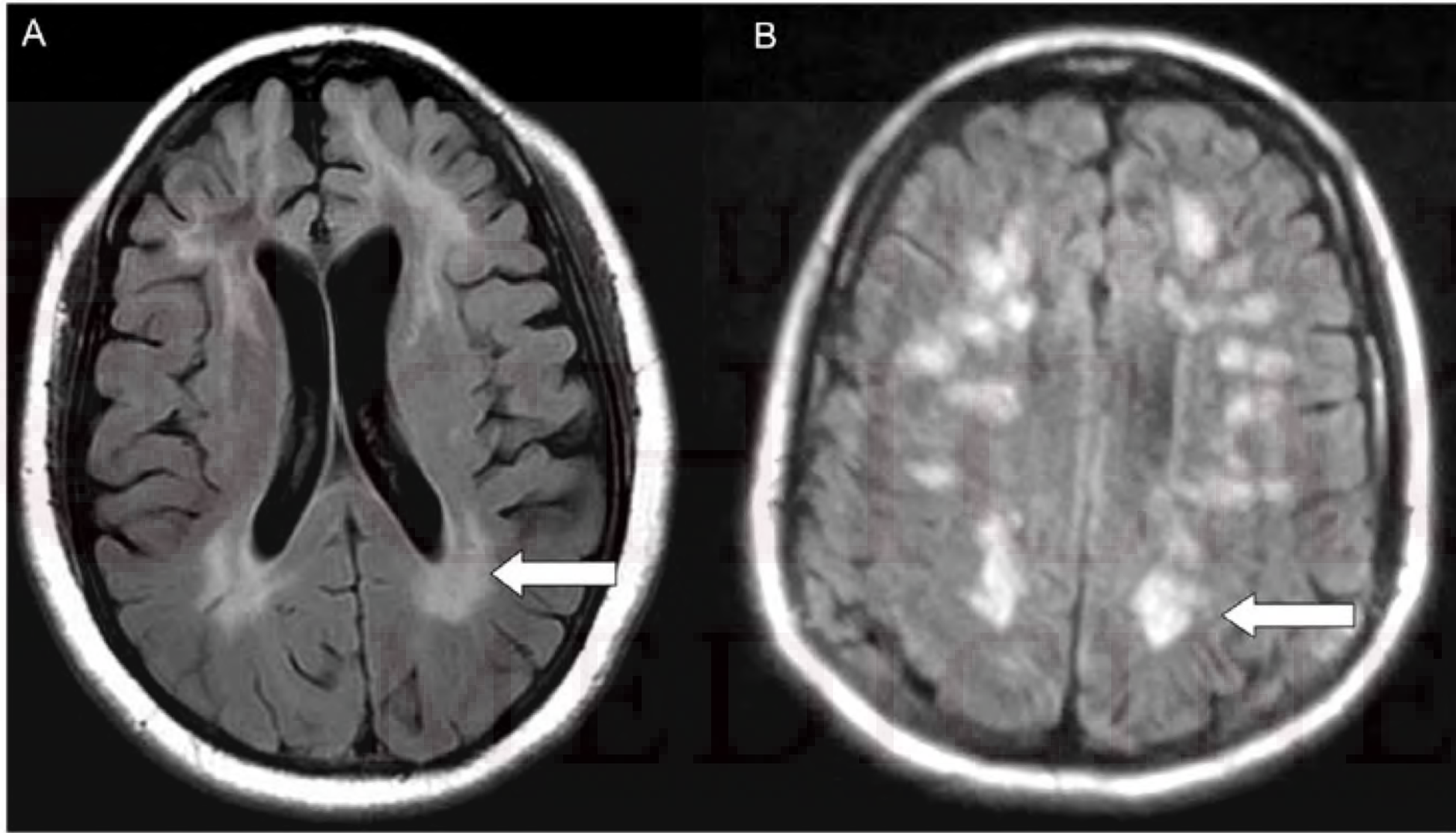
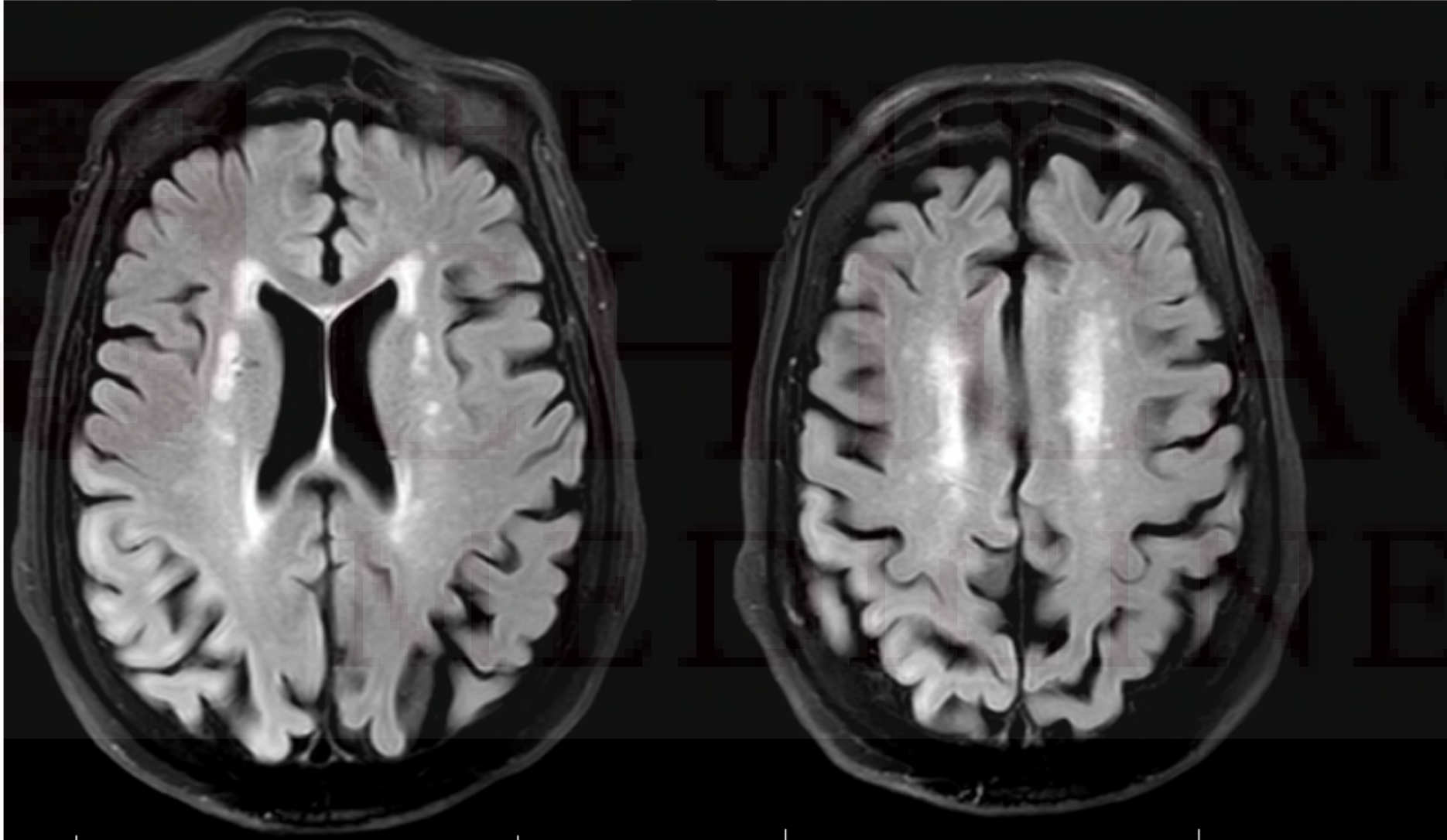


Figure 1. Leukoencephalopathy-like manifestations on MRI images. (A, B) Axial MRI images demonstrate widespread periventricular hyperintense signals in the cerebral white matter.

Patient MRI



Looks like
leukocencephalopathy
like changes, but also
looks like chronic
ischemic vessel
disease

Patient MRI Formal Read

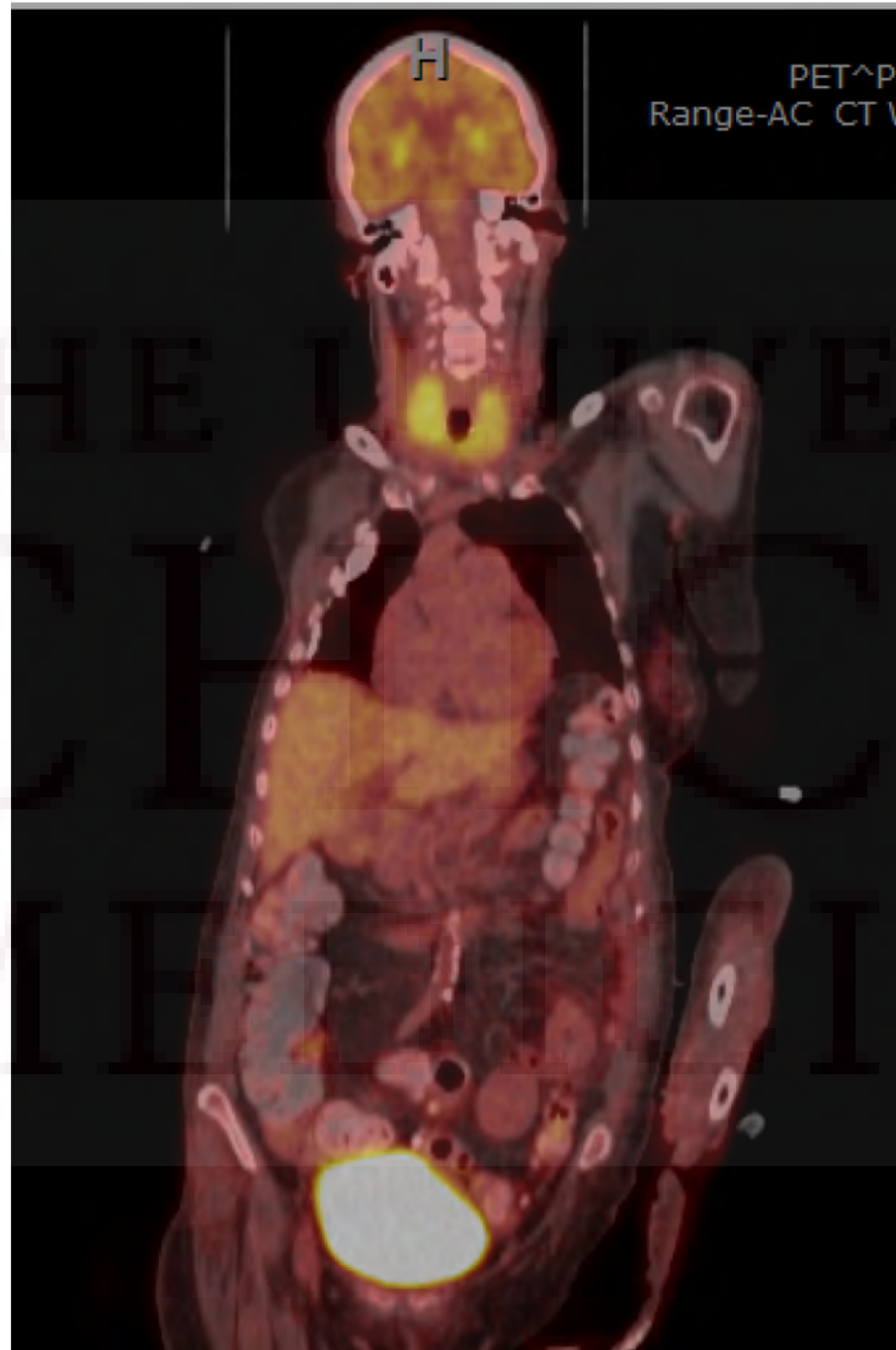


Impression: Abnormal signal intensity involving the right occipital, right temporal, and right parietal lobe gyri as well as the posterior right thalamus as detailed above. Findings raise the possibility of encephalitis, potentially infectious including viral etiologies, as well as Creutzfeldt-Jakob disease.

Back to Our Patient

- Encephalopathy autoimmune eval, CSF NEGATIVE
 - Abs for: NMDA-R, VGKC-complex, LGI1, CASPR2, GAD65, GABA-B-R, AMPA-R, ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, Amphiphysin, CRMP-5
- Paraneoplastic panel: NEGATIVE
- Infectious encephalitis panel: NEGATIVE
- Continued to have seizures, tongue sticking out w R gaze preference
- Diagnosed with encephalitis of undetermined etiology, steroids started (60mg prednisone + 1g methylpred Qd) and IVIG started on 8/24
- Course: able to speak own name -> catatonia -> following simple commands -> catatonia -> intermittently continued having seizures

PET Scan (Hx of breast cancer)



IMPRESSION:

1. No evidence of FDG avid tumor. The subpleural nodule in the right middle lobe is not FDG avid, which is most likely benign. However indolent tumor cannot be excluded. Suggest follow-up with CT.
2. Diffuse increased metabolic activity in the enlarged thyroid gland is most likely due to thyroiditis.
3. Inflammatory changes in the lower lungs/pleurae and bilateral gluteal regions.
4. Postprocedural changes in the left upper abdominal wall.

Continued Patient Course: Exam on 9/4/17

Constitutional: lying in bed, responds to voice

HEENT: does not open eyes on command

Neck: mild thyromegaly, no acanthosis nigricans

Cardiovascular: regular rate and rhythm, nml S1/S2

Pulmonary/Chest: clear to auscultation bilaterally

Abdomen: soft

Extremities: no edema

Neurological: not alert, stiff R arm, does not move extremities, unable to obtain reflexes

Skin: warm, dry

Other: GI tube with bloody output

Continued Patient Course

- Prednisone 40-60mg 8/24 – 8/27
- Methylprednisolone 1g IV 8/25- 9/3
- IVIG 8/24 – 8/28
- Ativan started for catatonia, Psych involved
- Solumedrol IV 30mg 9/4– close to discharge
- Discharged on 40mg prednisone on 9/15/17 (as well as seizure meds)
- Follow up chest CT showed stable lung nodule several months later
- TSH normalized a few months later

Clinic visit on 11/7/17

“Significantly improved. She still has occasional visual hallucinations, consisting of seeing her cat when the cat is not actually there. She possibly has auditory hallucinations at night and hears people talking. Catatonia significantly improved yet son describes that patient's arm "occasionally gets stuck in one position". Other complaint is depression, and patient "feels like crying in the morning upon waking up"

Clinic visit 07/17/18

“Patient has been doing well overall. She lives at home with her son and they have assistance Mon-Fri and additional resources if they need them. She is currently taking Ativan 0.5 mg TID, prednisone 30 mg daily, and Keppra 750 mg BID. Phenytoin has been tapered off. Son notes that that she is doing well, has intermittent mild hallucinations, although they have much improved. They obtained a pneumonia shot recently from their PCP in preparation of initiation of Cellcept.”

Conclusions

- HE is an autoimmune disorder that is associated with thyroid antibodies (anti-TPO and/or anti-TG), but not due to thyroid disease
- TRAbs include stimulating TSHR Abs (detected by TSI) and TSH blocking and neutral Abs (all 3 detected by TRAb assay)
- The presentation of HE is heterogeneous with a fulminant, subacute or more chronic course of declining mental status that is frequently accompanied by seizures, myoclonus and psychiatric symptoms
- The presence of elevated anti-thyroid Abs and exclusion of other causes of encephalopathy support its diagnosis
- MRI findings for HE are not specific or sensitive
- Prognosis of HE is generally good with steroid treatment. Other immunosuppressive therapies can be used in patients who are refractory to steroids or relapse
- Pt improved with steroid therapy (now 1+ year) to be transitioned to Cellcept

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Thyroid Hormone Synthesis

