Rapidly Progress Dementia

MCI Project

٢٠١٨

Rapidly Progress Dementia

- The time frame of an RPD: the author typically uses the term to refer to conditions that progress from onset of first symptom to dementia in less than ١ to ٢ years, although most occur over weeks to months.
- decline in more than one cognitive domain with functional impairment.

Rapidly Progress Dementia

- If clinical history and examination of a patient with cognitive decline do not conform to the stereotyped picture of Alzheimer's disease, the clinician's level of suspicion should be great that the diagnosis lies elsewhere.

Rapidly Progress Dementia

- Perhaps the prototypical RPDs are prion diseases, such as Jakob-Creutzfeldt disease.

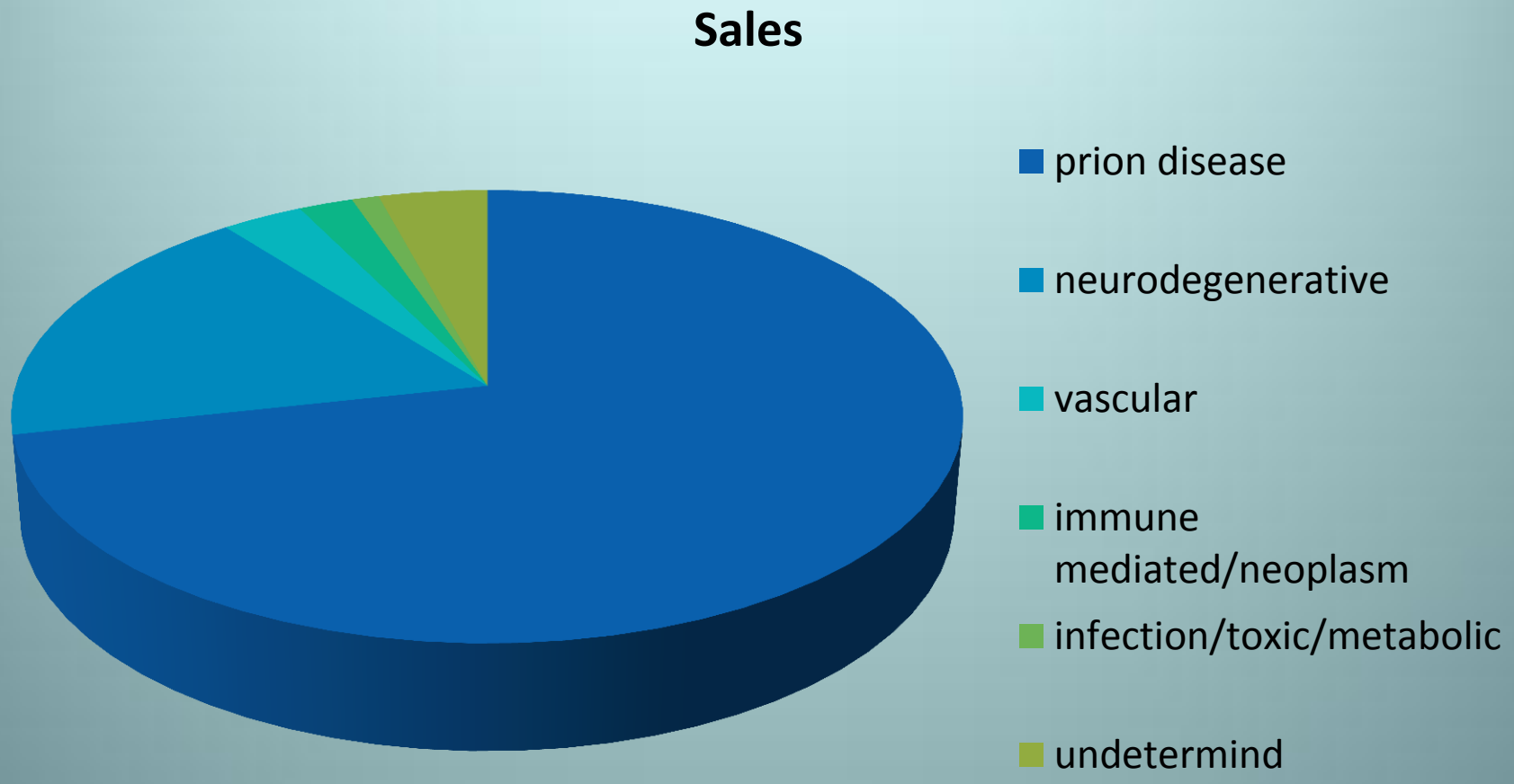
Rapidly Progress Dementia

- Nonprion causes
- Prion disease

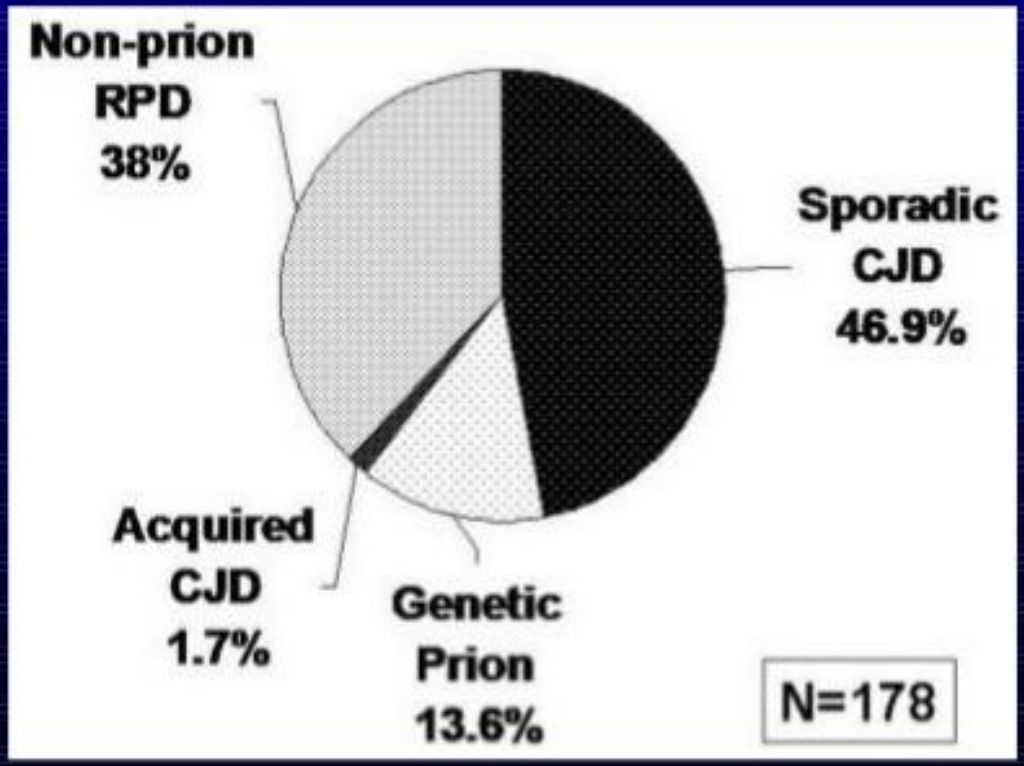
Rapidly Progress Dementia

- Major diagnostic categories of patients with rapidly progressive dementia (RPD) referred to, versus evaluated at, the University of California, San Francisco (UCSF) rapidly progressive dementia program over ١٣ years.

At the US National Prion Disease Pathology Surveillance Center, of the ١,١٠٦ patients autopsied



UCSF (RPD/CJD Referrals)



Geschwind MD, *Ann Neurol* 2008

Non-Prion RPD's

Diagnosis	Percentage
Neurodegenerative	39%
Autoimmune	22%
Unknown	12%
Infectious	6%
Psychiatric	6%
Malignancy	6%

Geschwind MD, *Ann Neurol* 2008

Rapidly Progress Dementia

- ۶۸% were diagnosed with prion diseases.
- ۱۷% with neurodegenerative conditions.
- ۳% vascular.
- ۲% each immune-mediated and neoplasm.
- ۱% each infection and toxic-metabolic.
- ۴% undetermined (insufficient tissue).

Diagnostic Approach

- Clinical assessment Making the correct diagnosis of an RPD is often difficult, but is the key to appropriate treatment.
- RPD diagnosis usually requires a systematic and thorough approach.

Diagnostic Approach

- A detailed medical history, including emphasis on elucidating first symptoms, documenting all prescribed and nonprescribed medications and any relevant family history, is imperative.

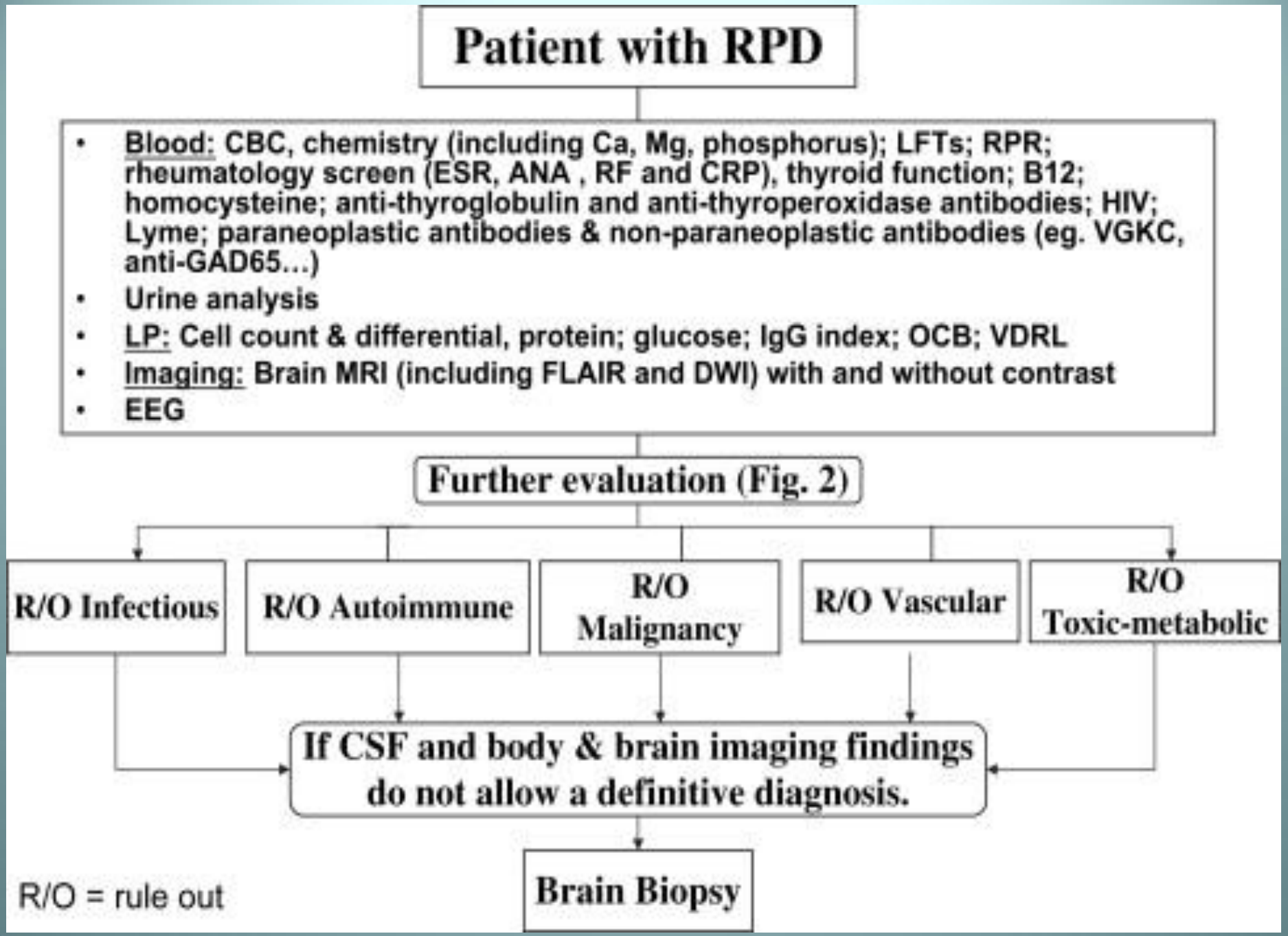
Diagnostic Approach

- Examination should establish if any other neurologic features are present and determine whether other organ systems are involved, so physical and neurologic examination must be thought.
- Cognitive assessment can be done with a brief test, such as the MoCA, but a more detailed assessment might further refine the localization of cognitive deficits.

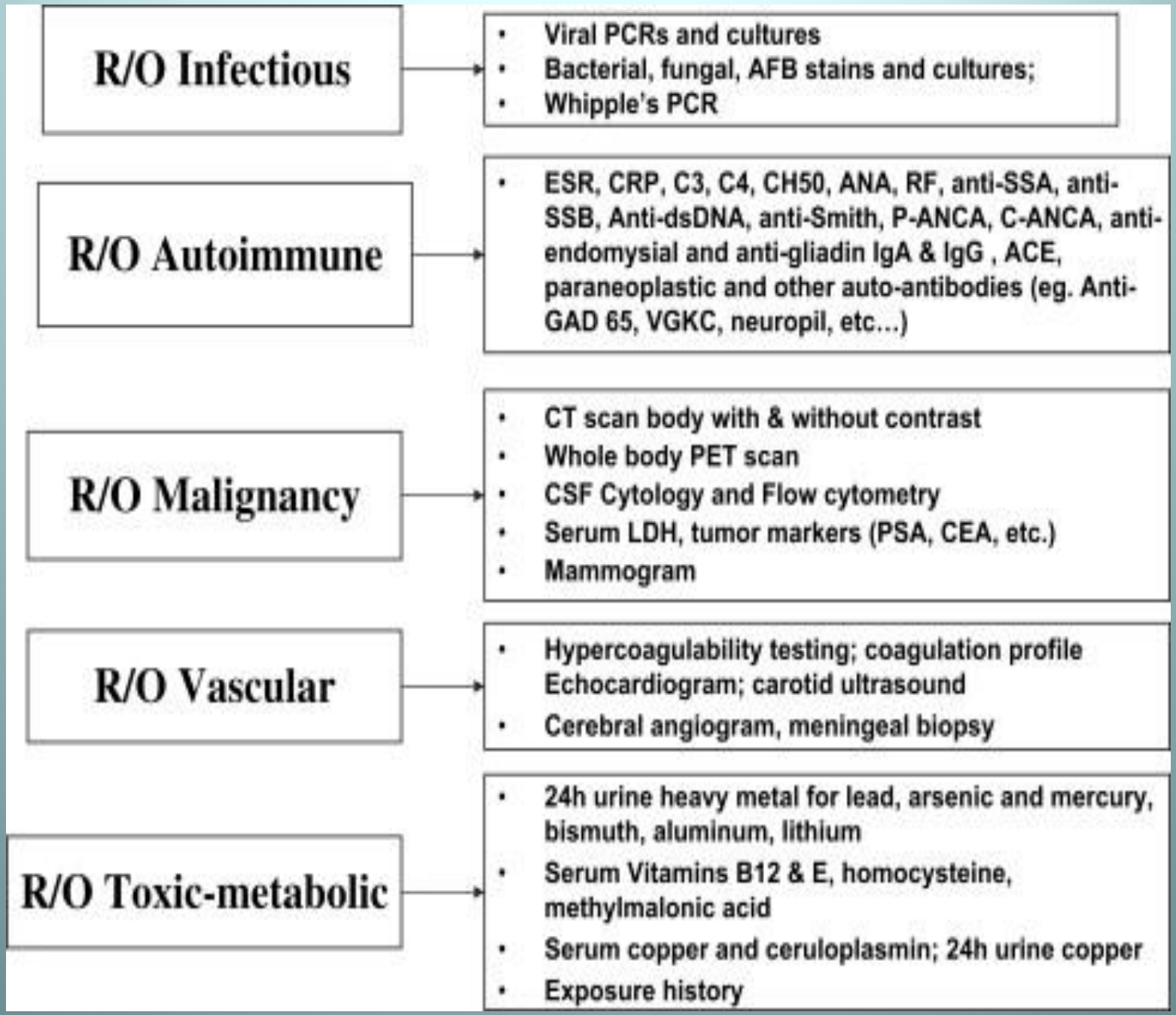
Diagnostic Approach

- Use of the mnemonic VITAMINS is a useful way to review potential etiologies for RPDs:

vascular, infectious, toxic-metabolic, autoimmune, metastases/neoplasm, iatrogenic/inborn error of metabolism, neurodegenerative, or systemic/seizures.


Patient with RPD
Blood: CBC, chemistry (including Ca, Mg, phosphorus); LFTs; RPR; rheumatology screen (ESR, ANA , RF and CRP), thyroid function; B12; homocysteine; anti-thyroglobulin and anti-thyroperoxidase antibodies; HIV; Lyme; paraneoplastic antibodies & non-paraneoplastic antibodies (eg. VGKC, anti-GAD65…)
Urine analysis
LP: Cell count & differential, protein; glucose; IgG index; OCB; VDRL
Imaging: Brain MRI (including FLAIR and DWI) with and without contrast
EEG
Further evaluation (Fig. 2)
R/O Infectious
R/O Autoimmune
R/O Malignancy
R/O Vascular
R/O Toxic-metabolic
If CSF and body & brain imaging findings do not allow a definitive diagnosis.
Brain Biopsy
R/O = rule out

Blood tests	CSF	Imaging	Urine/Other
Basic panel of tests			
- Complete blood count - Basic metabolic panel (+Ca,P,Mg) - Liver function tests (including ammonia) - Renal function tests - Thyroid function tests - Anti-TG and Anti-TP antibodies - Vitamin B12/MMA/homocysteine - Rheumatologic screen (ANA, ESR, CRP, RF, ANCAs, SSA, SSB) - Rapid plasma reagin (RPR) - HIV serology - Paraneoplastic/autoimmune antibodies	- Cell count and differential - Protein - Glucose - IgG index - Oligoclonal bands - VDRL - 14-3-3/NSE/total tau	- Brain MRI (including FLAIR, DWI and ADC sequences), at least one scan with and without contrast	- Urine analysis (and culture if indicated) - EEG
Tests to consider in selected cases			
- Lyme disease (in endemic areas) - Cancer screen - Blood smear - Coagulation profile - Hypercoagulability testing - Copper and ceruloplasmin - Additional rheumatologic tests (complement, dsDNA, anti-Sm, anti-RNP, anticardiolipin, anti-SCL 70, Anti-Jo, anti-centromere antibodies)	- Bacterial, fungal, acid-fast bacilli stains and cultures - Cytology - Flow cytometry - Whipple PCR - Cryptococcal antigen - Viral PCRs and cultures	- Cancer screen (CT chest, abdomen, and pelvis with and without contrast; mammogram; body PET scan) - MR angiography or brain angiogram - MR spectroscopy - Carotid ultrasound - Echocardiogram	- Heavy metal screen (24h urine) - Copper (24h urine) - Porphobilinogen (PBG)/delta-aminolevulinic acid (ALA) in urine (24h) - EMG/nerve conduction study - Brain biopsy


R/O Infectious
Viral PCRs and cultures
Bacterial, fungal, AFB stains and cultures;
Whipple's PCR
R/O Autoimmune
ESR, CRP, C3, C4, CH50, ANA, RF, anti-SSA, anti-SSB, Anti-dsDNA, anti-Smith, P-ANCA, C-ANCA, anti-endomysial and anti-gliadin IgA & IgG , ACE, paraneoplastic and other auto-antibodies (eg. Anti-GAD 65, VGKC, neuropil, etc…)
R/O Malignancy
CT scan body with & without contrast
Whole body PET scan
CSF Cytology and Flow cytometry
Serum LDH, tumor markers (PSA, CEA, etc.)
Mammogram
R/O Vascular
Hypercoagulability testing; coagulation profile Echocardiogram; carotid ultrasound
Cerebral angiogram, meningeal biopsy
R/O Toxic-metabolic
24h urine heavy metal for lead, arsenic and mercury, bismuth, aluminum, lithium
Serum Vitamins B12 & E, homocysteine, methylmalonic acid
Serum copper and ceruloplasmin; 24h urine copper
Exposure history

Limbic Encephalitis

- It was recognized in the ١٩٦٠s that systemic cancer can present with neurobehavioral symptoms.
- Degenerative and inflammatory pathology as neuronal loss, astrocytic proliferation with gliosis and perivascular infiltration was seen.

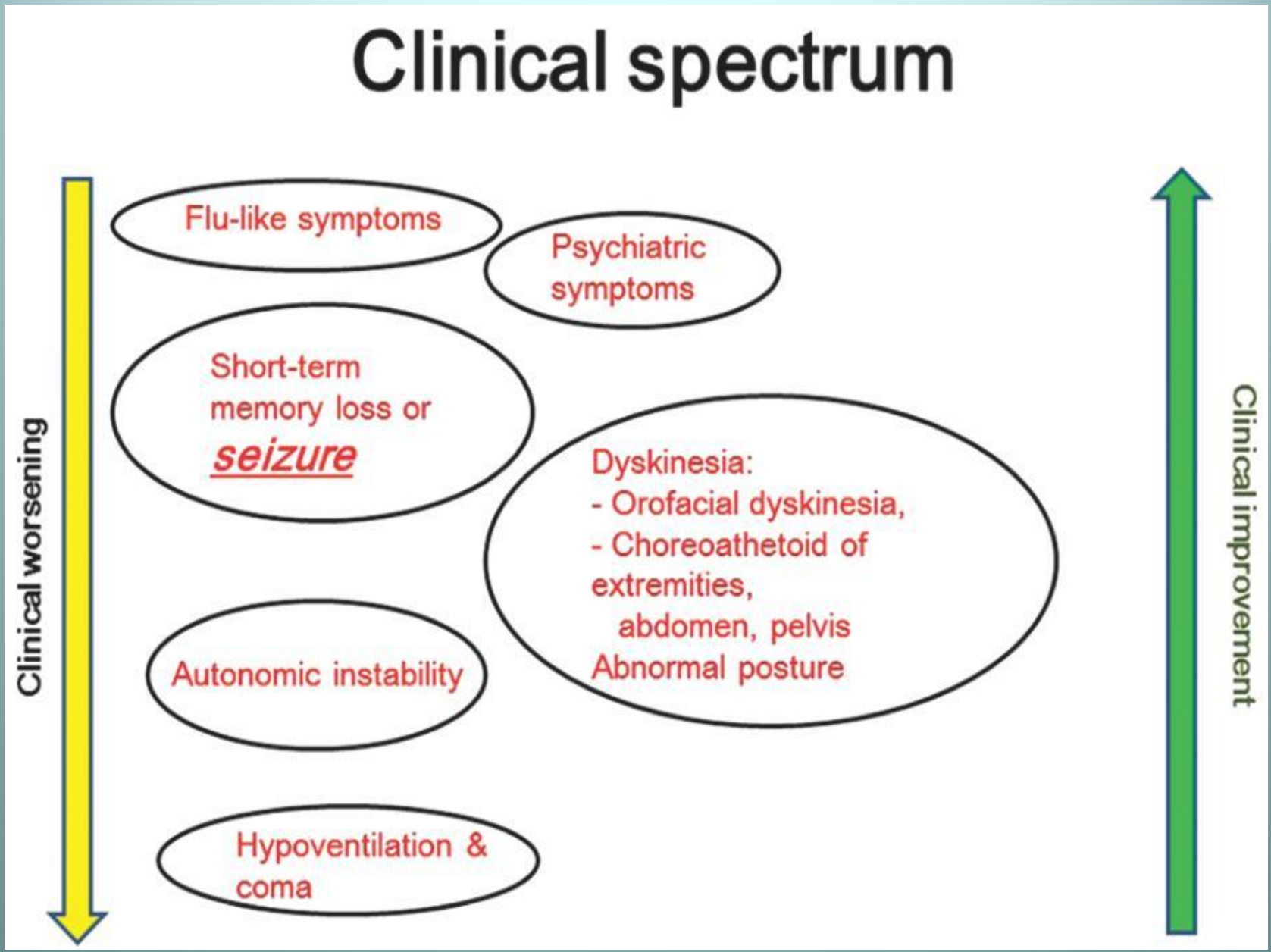
Limbic Encephalitis

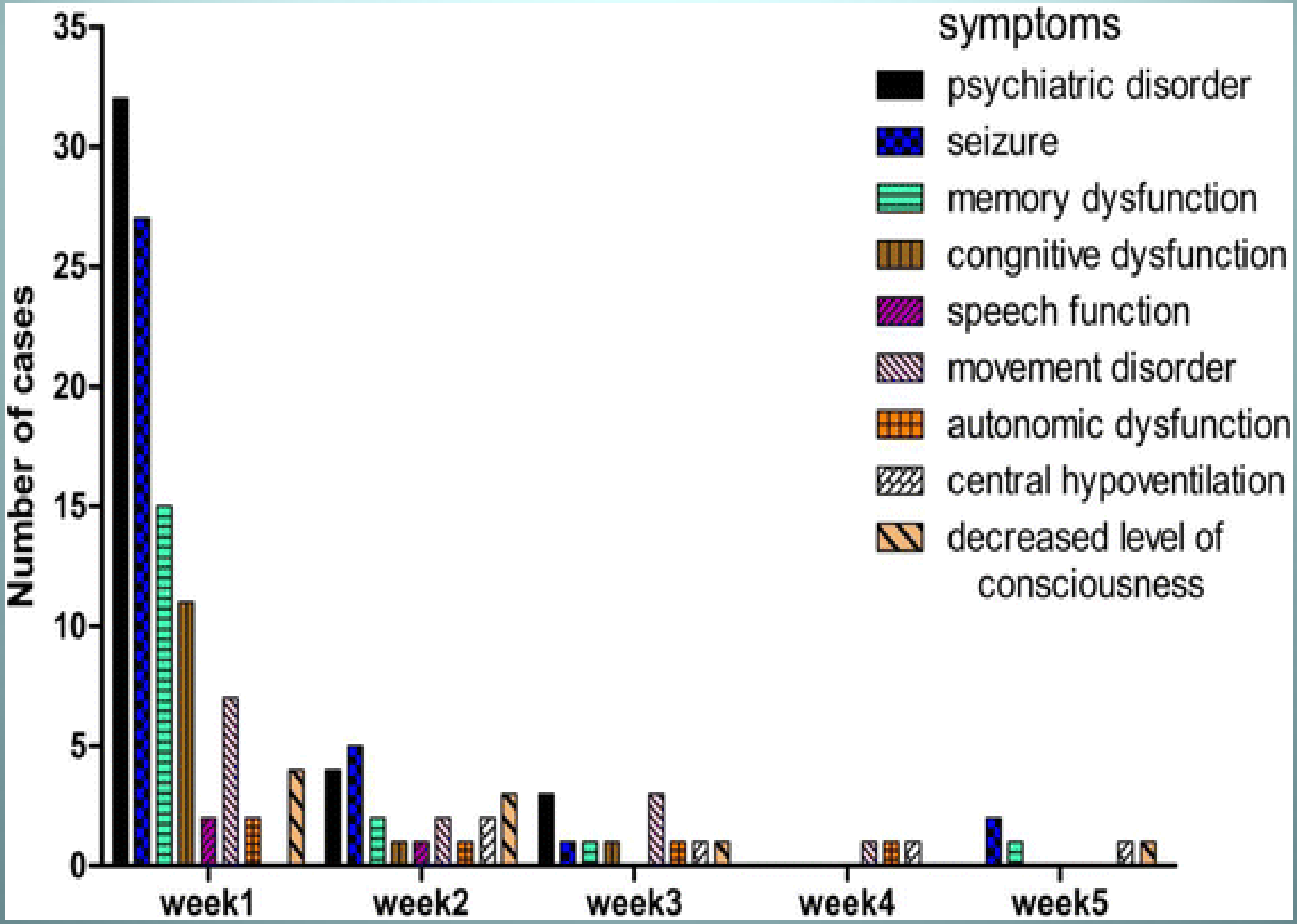
- Limbic structures particularly in the medial temporal regions—amygdala, hippocampus, and parahippocampal gyrus—but also in the cingulate gyrus and hypothalamus were involved.

Limbic Encephalitis

- Limbic encephalitis may predate the symptoms of cancer by as much as ۴ years.

Clinical spectrum




Number of cases
35
30
25
20
15
10
5
0
week1
week2
week3
week4
week5
symptoms
psychiatric disorder
seizure
memory dysfunction
congnitive dysfunction
speech function
movement disorder
autonomic dysfunction
central hypoventilation
decreased level of consciousness

LE may be categorized as follows:

- LE associated with antibodies from an identified tumor
- LE in which tumor is found but no antibodies are detected
- LE in which there are antibodies but no tumor (i.e., not a paraneoplastic phenomenon)
- LE (after a full diagnostic evaluation is otherwise negative) in which there is neither antibody identified nor a tumor detected, but the patient responds well to immunotherapy

Antineuronal Antibody–Associated Paraneoplastic Disorders*

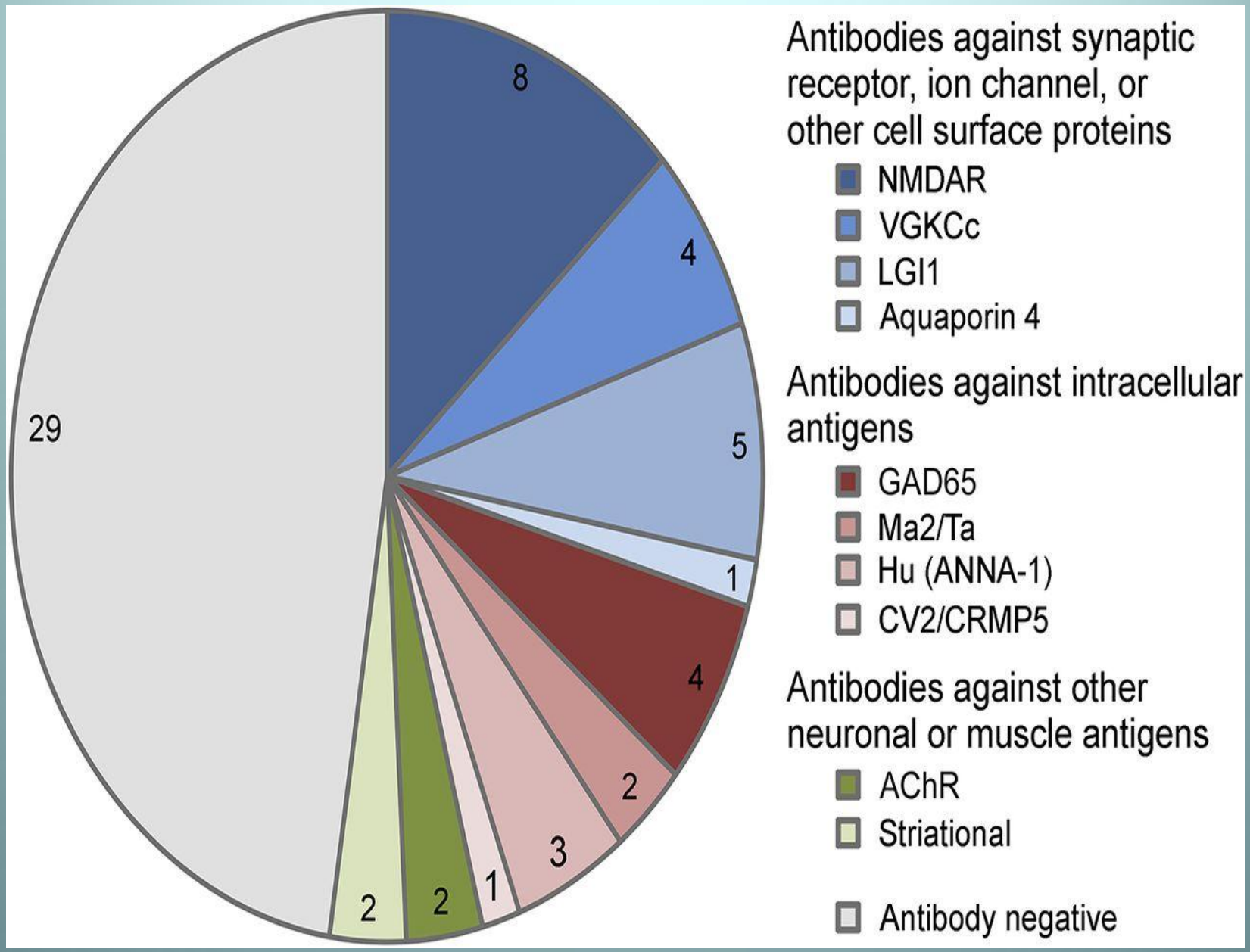
Antibody	Associated Cancer	Syndrome	Antigen	Onconeuronal Antigen
Anti-Hu	SCLC and neuroblastoma	Encephalomyelitis, sensory neuronopathy	All neuronal nuclei, 35-40 kd	HuD, HuC, and Hel-N1
Anti-Yo	Gynecologic and breast	Cerebellar degeneration	Cytoplasm Purkinje cells, 34 and 62 kd	CDR34, CDR62-1, and CDR62-2
Anti-Ri	Breast, gynecologic, and SCLC	Cerebellar ataxia, opsoclonus	Neuronal nuclei CNS, 55 and 80 kd	NOVA1 and NOVA2
Antiamphiphysin	Breast	Stiff-man, encephalomyelitis	Synaptic vesicles, 128 kd	Amphiphysin
Anti-VGCC	SCLC	Lambert-Eaton myasthenic syndrome	Presynaptic VGCC	α_1-Subunit
Anti-MysB	SCLC	Lambert-Eaton myasthenic syndrome	Presynaptic VGCC	β-Subunit VGCC
Anti-Ma	Multiple	Cerebellar, brainstem dysfunction	Neuronal nuclei and cytoplasm, 37 and 40 kd	Ma1 and Ma2
Anti-Ta	Testicular	Limbic encephalitis, brainstem dysfunction	Neuronal nuclei and cytoplasm, 40 kd	Ma2
Anti-Tr	Hodgkin lymphoma	Cerebellar degeneration	Cytoplasm neurons, Purkinje cells, and spiny dendrites	In progress
Anti-CAR	SCLC and others	Photoreceptor degeneration	Retinal photoreceptor, 23 kd	Recoverin
Anti-CV2	SCLC and others	Encephalomyelitis, cerebellar degeneration	Glia (subset), 66 kd	POP66

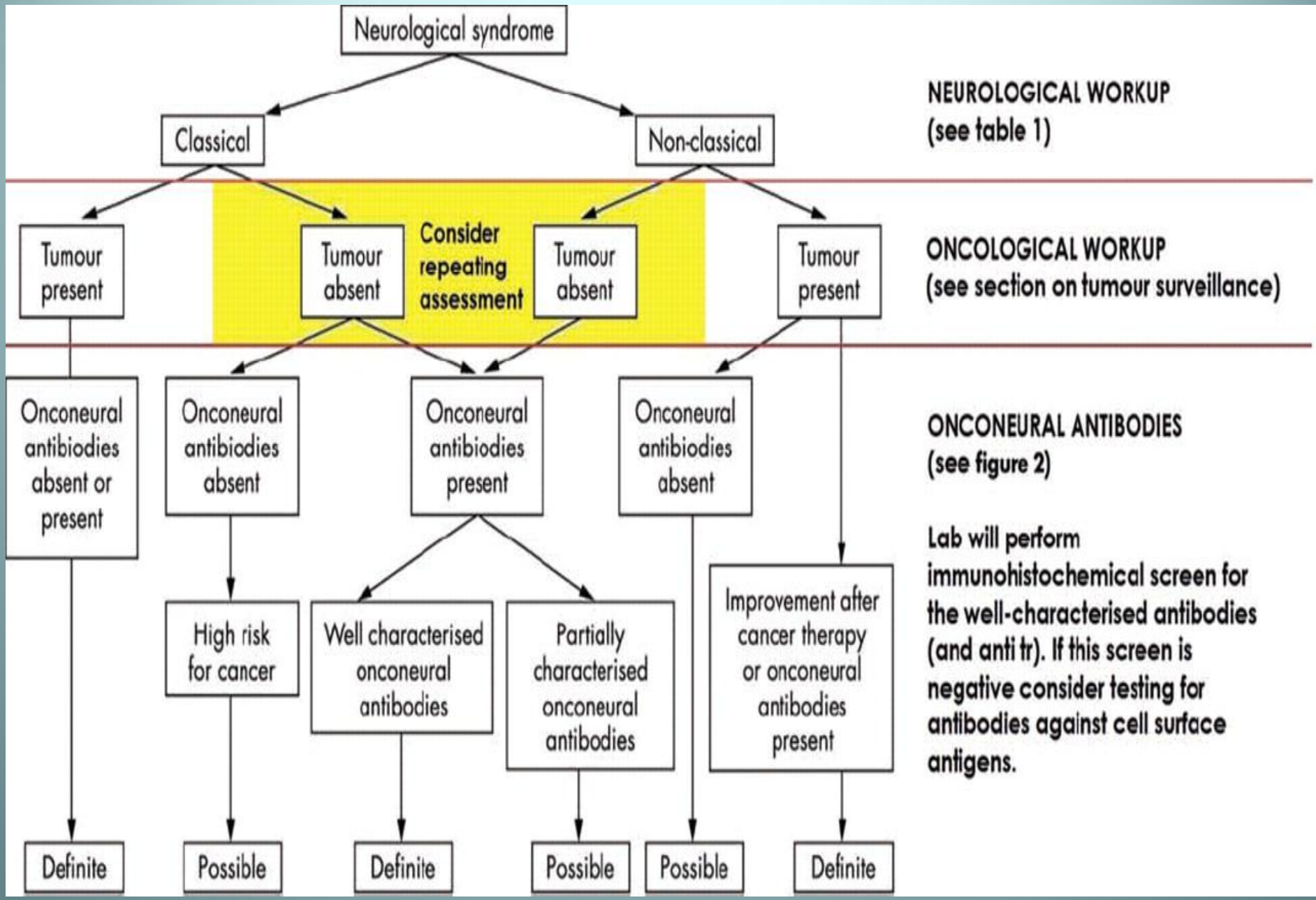
**Data modified from Dalmau and Posner.[1] SCLC indicates small cell lung cancer; CNS, central nervous system; VGCC, voltage-gated calcium channels; and CAR, carcinoma-associated retinopathy.*

Table 1: Neuronal surface autoantibodies, associated tumors and clinical syndromes

Antigen	Tumor	Clinical symptoms	Clinical clues
NMDAR	Ovarian teratoma (58%) < 18 years old	Memory impairment, psychosis (mainly in women), seizures (mainly in men), central hypoventilation	Orobuccal dyskinesia; dysautonomia
LGI1	Thymoma (< 10%)	LE	Hyponatremia; faciobrachial dystonic seizures
CASPR2	Thymoma (38%)	Encephalitis/Morvansynd/ neuromyotonia	Peripheral nerve hyperexcitability; neuropathic pain
AMPAR	SCLC, breast, thymoma (60-70%)	LE, psychosis	
GABA(B) R	SCLC (50%)	LE, ataxia	Refractory seizures
GABA(A) R	-	Status epilepticus, seizures, LE	Refractory seizures
mGluR1	Hodgkin and non Hodgkin lymphoma (e.g. cutaneus lymphoma); prostate adenocarcinoma[3]	Cerebell arataxia	
mGluR5	M. Hodgkin	Ophelia syndrome	Memory impairment
DPPX (Kv4.1)	Follicular B cell, lymphoma, CLL	Hallucinations, agitation, myoclonus, tremor, SPS	Diarrhea
IgLON5	-	Brain stem dysfunction, LE	Non-REM and REM-sleep disorder
GlyR	Thymoma	SPS, progressive encephalitis	
Dopamine 2R	-	Basal ganglia encephalitis, Sydenham Chorea	

NMDAR: N-methyl-d-aspartate receptor; LGI1: leucine-rich glioma-inactivated 1; CASPR2:contactin-associated protein-like 2; AMPAR: amino-3-hydroxy-5-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GABA A/B R: gamma-aminobutyric acid A/B receptor; mGluR1/5: metabotropic glutamate receptor type 1/5; DPPX: dipeptidyl-peptidase-like protein-6; GlyR: Glycine receptor; CLL: chronic lymphatic leukemia; SCLC: small cell lung cancer; LE: limbic encephalitis; SPS: stiff-person syndrome; IgLON5: IgLON family member 5


8
4
5
1
4
2
3
1
2
2
29
Antibodies against synaptic receptor, ion channel, or other cell surface proteins
NMDAR
VGKCc
LGI1
Aquaporin 4
Antibodies against intracellular antigens
GAD65
Ma2/Ta
Hu (ANNA-1)
CV2/CRMP5
Antibodies against other neuronal or muscle antigens
AChR
Striational
Antibody negative

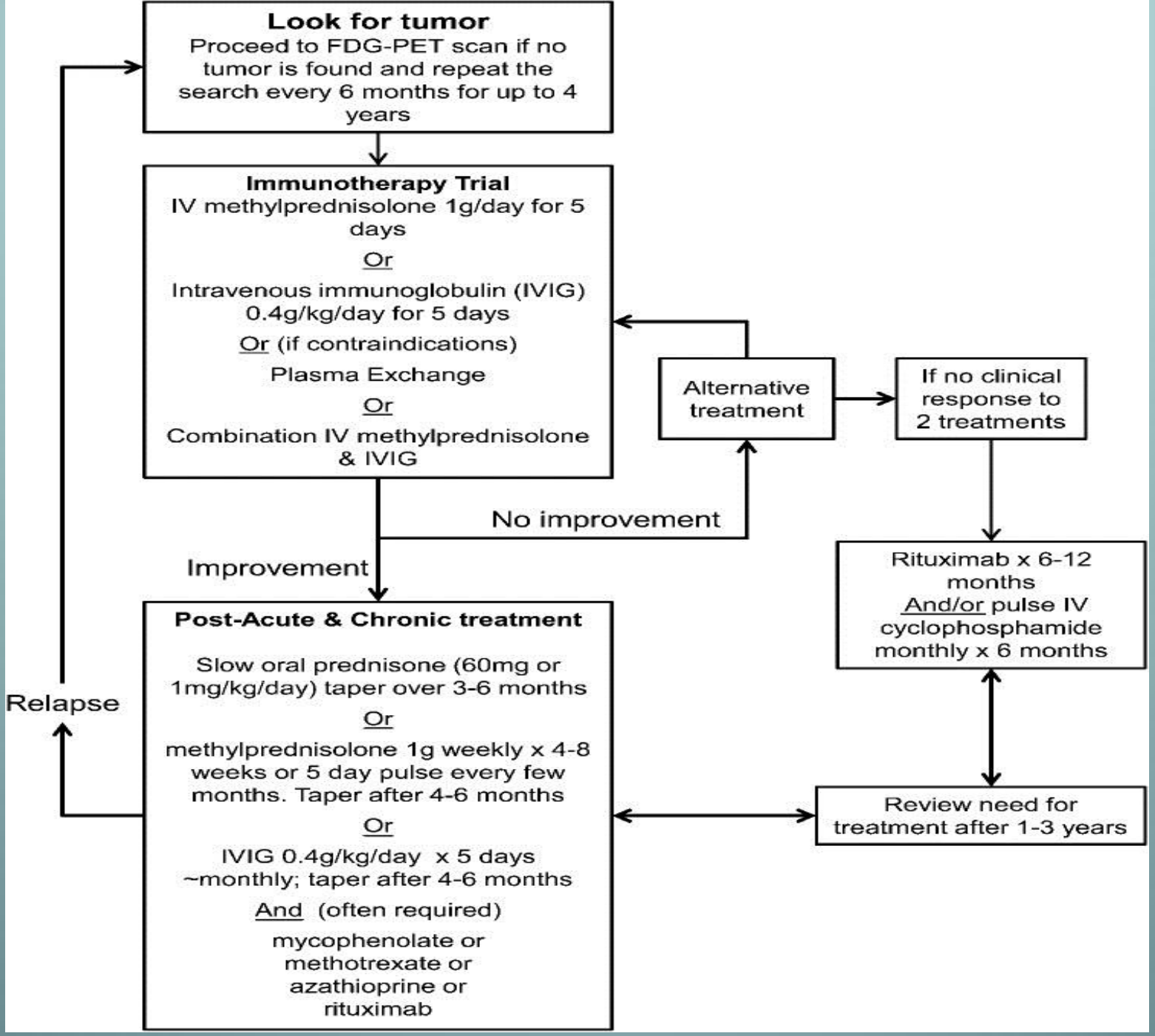

Neurological syndrome
Classical
Non-classical
NEUROLOGICAL WORKUP
(see table 1)
Tumour present
Tumour absent
Consider repeating assessment
Tumour absent
Tumour present
ONCOLOGICAL WORKUP
(see section on tumour surveillance)
Onconeural antibodies absent or present
Onconeural antibodies absent
Onconeural antibodies present
Onconeural antibodies absent
ONCONEURAL ANTIBODIES
(see figure 2)
Lab will perform immunohistochemical screen for the well-characterised antibodies (and anti tr). If this screen is negative consider testing for antibodies against cell surface antigens.
High risk for cancer
Well characterised onconeural antibodies
Partially characterised onconeural antibodies
Improvement after cancer therapy or onconeural antibodies present
Definite
Possible
Definite
Possible
Possible
Definite

Treatments for Autoimmune Encephalitis

- The cornerstone of treatment is immunomodulatory therapy
  - Steroids
  - Plasmapheresis
  - IV immunoglobulin (IVIG)
  - Oral immunosuppressants including Cellcept or azathioprine
  - Rituximab
  - Cyclophosphomide (Cytoxan)
- Removal of tumors – for example, ovarian teratoma in anti-NMDAR encephalitis
- Management of symptoms while waiting for immunomodulatory therapy to work (e.g., for seizures, agitation)

International Autoimmune Encephalitis Society

http://www.autoimmuneencephalitis.net/


Look for tumor
Proceed to FDG-PET scan if no tumor is found and repeat the search every 6 months for up to 4 years
Immunotherapy Trial
IV methylprednisolone 1g/day for 5 days
Or
Intravenous immunoglobulin (IVIG) 0.4g/kg/day for 5 days
Or (if contraindications)
Plasma Exchange
Or
Combination IV methylprednisolone & IVIG
Alternative treatment
If no clinical response to 2 treatments
No improvement
Improvement
Rituximab x 6-12 months
And/or pulse IV cyclophosphamide monthly x 6 months
Post-Acute & Chronic treatment
Slow oral prednisone (60mg or 1mg/kg/day) taper over 3-6 months
Or
methylprednisolone 1g weekly x 4-8 weeks or 5 day pulse every few months. Taper after 4-6 months
Or
IVIG 0.4g/kg/day x 5 days ~monthly; taper after 4-6 months
And (often required)
mycophenolate or methotrexate or azathioprine or rituximab
Relapse
Review need for treatment after 1-3 years

Hashimoto Encephalopathy

- An acute or subacute cognitive and psychiatric syndrome occurs in the setting of antibodies directed against the thyroid gland (thyroglobulin, thyroid peroxidase) not necessarily associated at the same time with the symptoms or metabolic markers of thryotoxicosis or hypothyroidism

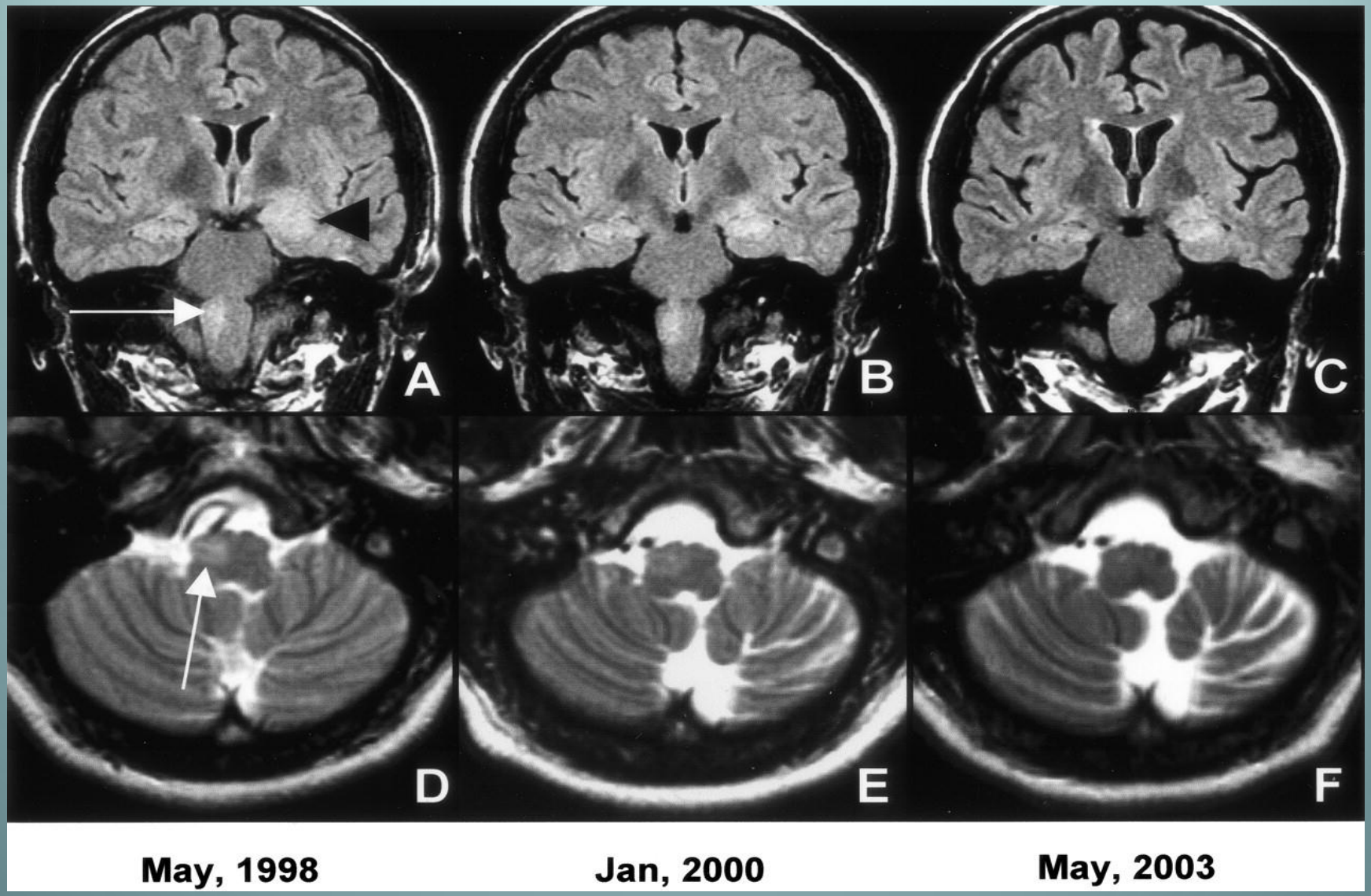
Hashimoto encephalopathy

- acute to subacute
- evidence of cognitive impairment
- variable psychiatric symptoms, alteration in consciousness, hallucinations
- Involuntary movements, seizures, myoclonus, opsoclonus, chorea, ataxia, stroke like episodes, and myelopathy.
- Adolescent females are mostly affected.

Hashimoto's Encephalitis

- CSF protein elevated 75%
- CSF pleocytosis 25%
- EEG changes nonspecific (slowing)
- MRI typically normal (occasional T2-weighted abnormalities)

MRI Finding



A ٥٠-year-old right-handed man with a history of alcoholism (current), hypertension, hypercholesterolemia, and hepatitis C developed nausea, vomiting, and diarrhea for ٣ days.

He reduced his alcohol consumption and increased his water intake for hydration.

One week later, he had two episodes of seizures and was treated for encephalopathy and hyponatremia at a local intensive care unit.

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- he had behavioral symptoms (emotional blunting, violent outbursts, delusions, and hallucinations), impaired episodic memory, speech disturbance (slurred, halting), executive problems, gait imbalance, and myoclonus of the hands and trunk

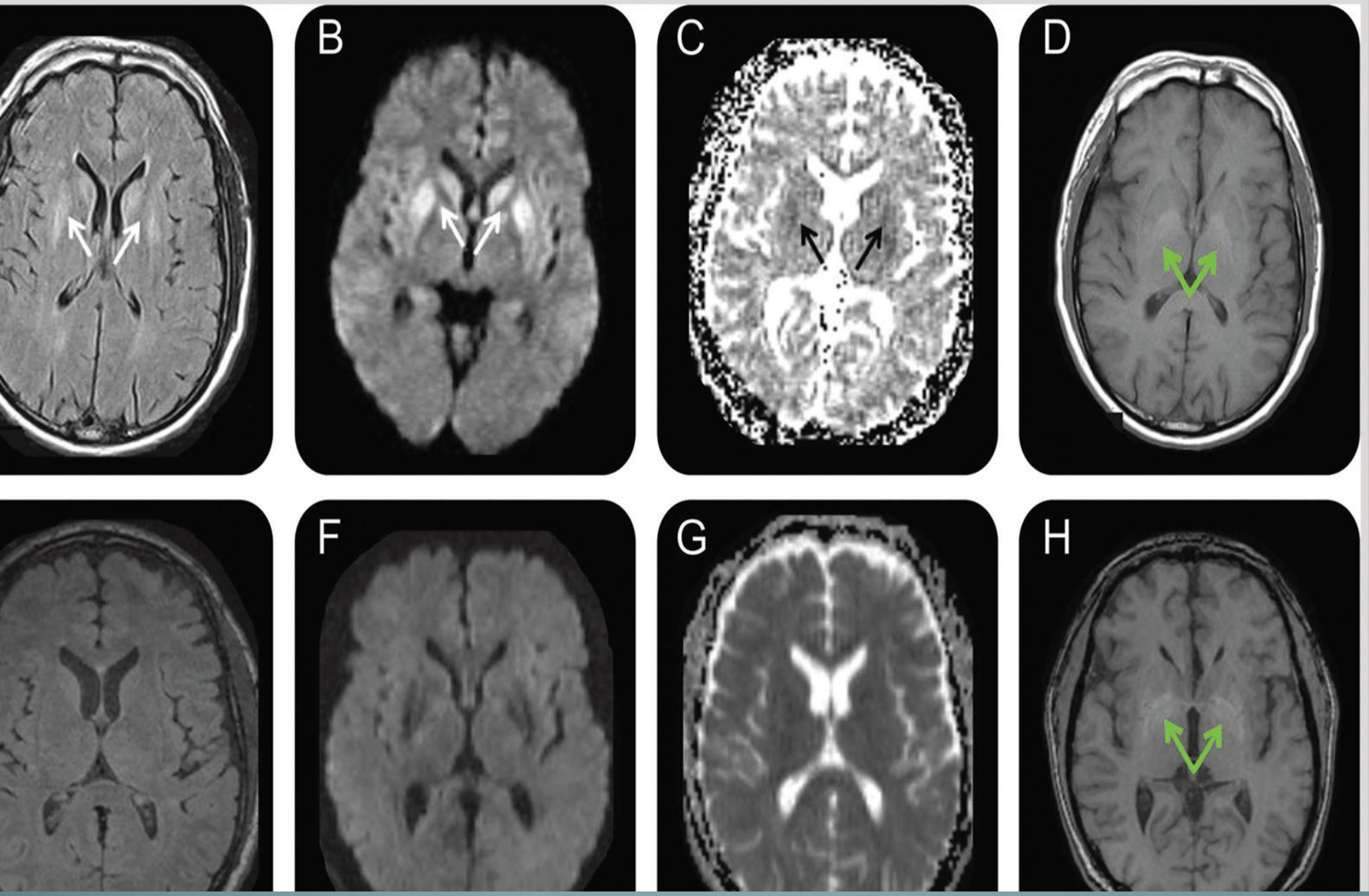
His first brain MRI at approximately ۲ months after the onset of symptoms showed restricted diffusion with hyperintensities on T۲, FLAIR, and DWI in the bilateral striata with corresponding hypointensity on ADC map, and T۱ hyperintensities in bilateral globus pallidi .

Because of his clinical symptoms and MRI findings, he was diagnosed with sporadic Jakob-Creutzfeldt disease and referred to our center.

At our center, ٣ months after the onset, we noted that although he had deficits (mild cognitive and motor deficits), he had improved profoundly.

A repeat brain MRI showed resolution of the diffusion and T٢ striatal abnormalities .

- Extensive laboratory workup for rapidly progressive dementia was negative, but a careful review of his outside medical records determined that at his initial hospitalization his first sodium level was ١٠٦ mEq/L, which decreased to ١٠٢ mEq/L within ٣,٥ hours and then was corrected to ١٣٠ mEq/L in less than ٣٦ hours. Given the MRI findings and the history of rapidly corrected hyponatremia, he was diagnosed with extrapontine myelinolysis.


B
C
D
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G
H

An Approach to Differential Diagnosis by Category and Disease

Trauma

- Diffuse axonal injury, hemorrhage
- Chronic subdural hematoma
- Postconcussion syndrome
- Chronic traumatic encephalopathy

An Approach to Differential Diagnosis by Category and Disease

Inflammation/Infection

- Herpes simplex encephalitis
- HIV and infectious complications
- Focal cerebritis/abscess
- Subacute bacterial endocarditis
- Prion disease—CJD, variant
- Progressive multifocal leukoencephalopathy
- Lyme encephalopathy (with or without meningitis)
- Subacute or chronic meningitis (tuberculosis, cryptococcus, cysticercosis, Listeria)
- Neurosyphilis (general paresis, gumma, meningovascular)
- Cerebral sarcoidosis
- Subacute sclerosing panencephalitis
- Whipple's disease of the brain

An Approach to Differential Diagnosis by Category and Disease

Neoplastic

- Tumor—benign (frontal meningioma, clivus chordoma invading medial temporal structures)
- Tumor—malignant; presentation depends on location
- Intravascular lymphoma
- Paraneoplastic limbic encephalitis
- Radiation necrosis
- Postchemotherapy cognitive impairment (chemobrain)

An Approach to Differential Diagnosis by Category and Disease

Metabolic/Hormonal

- Renal—uremic encephalopathy (acute or chronic) and dialysis dementia
- Hepatic encephalopathy (acute or chronic)
- Hypercapnea/hyperviscosity/hypoxemia (acute or chronic)
- Vitamin B_1 (thiamine) deficiency (Wernicke-Korsakoff)
- Vitamin B_3 deficiency (nicotinic acid/niacin—Pellagra; dermatitis, diarrhea, dementia)
- Vitamin B_{12} deficiency (+/- pernicious anemia)
- Hypothroidism (myxedema madness)
- Vitamin E deficiency (neuropathy, ataxia, encephalopathy in Celiac disease)
- Acute intermittent porphyria

An Approach to Differential Diagnosis by Category and Disease

Vascular

- Focal vascular syndromes (thalamus, inferotemporal, anterior cingulate, bifrontal, triple border-zone watershed infarction, cerebellar posterior lobe)
- Multi-infarct dementia
- Binswanger progressive subcortical ischemic leukoencephalopathy
- Cerebral amyloid angiopathy +/– amyloid vasculitis
- Diffuse hypoxic/ischemic injury
- PRES (posterior reversible encephalopathy syndrome)
- Thrombotic thrombocytopenic purpura
- CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts, leukoencephalopathy, migraine)
- MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes)

An Approach to Differential Diagnosis by Category and Disease

Autoimmune

- Nonparaneoplastic limbic encephalitis
- Hashimoto encephalopathy (steroid-responsive encephalopathy syndrome [SREAT])
- Systemic lupus erythematosus
- Isolated angiitis of the nervous system
- Temporal arteritis
- Wegener's granulomatosis
- Polyarteritis nodosa
- Susac syndrome

An Approach to Differential Diagnosis by Category and Disease

Iatrogenic/Drugs/Toxins

- Medications: beta blockers, neuroleptics, antidepressants, anticonvulsants, histamine/dopamine blockade, methotrexate
- Alcohol (Wernicke-Korsakoff, Marchiafava-Bignami)
- Heroin: “chasing the dragon” leukoencephalopathy
- Mescaline, phencyclidine, cocaine
- Marijuana psychosis
- Toxic exposure: carbon monoxide, toluene, lead, mercury
- Poisoning: arsenic, cyanide

An Approach to Differential Diagnosis by Category and Disease

Demyelinating

- ❑ Acquired
  - Multiple sclerosis, Schilder's, Balo's sclerosis
  - ADEM (acute disseminated encephalomyelitis)
  - Toxins
  - Delayed posthypoxic leukoencephalopathy
  - Electricity-induced demyelination
  - Decompression sickness demyelination
- ❑ Genetic
  - Adult-onset leukodystrophy with neuroaxonal spheroids
  - X-linked adrenoleukodystrophy
  - Metachromatic leukodystrophy
  - Globoid cell leukodystrophy
  - Vanishing white matter disease

An Approach to Differential Diagnosis by Category and Disease

Obstructive/Mechanical

- Obstructive hydrocephalus
- Normal pressure hydrocephalus
- Sagging brain syndrome—mimics frontotemporal dementia

An Approach to Differential Diagnosis by Category and Disease

Late-Life Degenerative Disorders

- Alzheimer's disease
- Frontotemporal dementia/Pick's disease
- Parkinson’s disease
- Progressive supranuclear palsy
- Corticobasal degeneration
- Lewy body disease
- Huntington’s disease
- ALS-dementia-Parkinson’s complex
- Primary progressive aphasia as manifestation of diseases of progranulin, tau, TDP-۴۳
- Posterior cortical atrophy as manifestation of Alzheimer’s disease
- Wilson’s disease
- Neurodegeneration with brain iron accumulation

An Approach to Differential Diagnosis by Category and Disease

Cerebellar Related

- Cerebellar cognitive affective syndrome in pure cerebellar disease—genetic or acquired
- Autosomal dominant spinocerebellar ataxias (SCAs)
- Recessively inherited ataxias and complex hereditary spastic paraplegias
- Fragile X tremor ataxia syndrome (FXTAS)
- Dentatorubropalidoluysian atrophy (DRPLA)
- Gordon Holmes syndrome
- Superficial siderosis
- Sagging brain syndrome
- Langerhans cell histiocytosis
- Cerebellar agenesis

An Approach to Differential Diagnosis by Category and Disease

Very Rare Pediatric Degenerative Disorders With Adult Presentations

- MERRF (mitochondrial encephalopathy with ragged red fibers)
- Niemann-Pick type C
- Gangliosidosis ٢ (GM٢/Adult Tay-Sachs)
- Alexander disease
- Lafora progressive myoclonus epilepsy
- Cerebrotendinous xanthomatosis
- PLO-SL (polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy)
- Neuronal intranuclear inclusion disease