

Department of Neurology

Neurology
Neuroradiology
X-ray conference

22 May 2020

Resident waroth pipatpratarnporn

- ผู้ป่วยชายไทยคู่อายุ 52 ปี อาชีพ นักประดาน้ำ
- ภูมิลำเนาจังหวัด สมุทรปราการ
- รับไว้ในโรงพยาบาลจุฬาลงกรณ์ ครั้งที่ 1 วันที่ 28/8/2557
- ประวัติได้จากผู้ป่วย ญาติ และเวชระเบียนเชื่อถือได้

- **Chief complaint** : ปวดศีรษะข้างขวา 5 วันก่อนมาโรงพยาบาล

Previous status : แข็งแรงดี ทำงานดำน้ำได้ ใช้ชีวิตประจำวันได้ปกติ ไม่มีอาการปวดศีรษะเรื้อรังในอดีต

Present illness

5 วันก่อนมาโรงพยาบาล ช่วงเช้าสังเกตเห็นมีอาการปวดเมื่อยตามตัว ไอแห้งๆ ไม่มีน้ำมูก ไม่มีไข้ ต่อมาช่วงกลางวันรู้สึกปวดศีรษะบริเวณค่อนไปด้านขวา หลังร้าวไปถึงบริเวณท้ายทอยด้านขวา ลักษณะปวดตื้อๆตลอดเวลา PS 4/10 ไม่มีปวดร้าวขึ้นกลางยอดศีรษะหรือร้าวไปกระบอกตา ไม่สัมพันธ์กับการไอเบ่งตามหรือเปลี่ยนท่าทาง ร่วมกับมีอาการคลื่นไส้อาเจียนร่วม 10 ครั้ง ไม่มีอาการสะอึก การมองเห็นเป็นปกติดี ไม่มีแขนขาอ่อนแรงหรือชา ไม่มีเดินเซ กินอาหารได้น้อยลงแต่ไม่มีสลักอาหาร ไม่มีอาการซึมลง

อาการปวดศีรษะเป็นรุนแรงมากขึ้นเรื่อยๆ ได้ไปตรวจที่ clinic วินิจฉัยเป็นไข้หวัดได้ยาพาราและยาฉีดแก้ปวดไม่ทราบชนิด

4 วันก่อนมาโรงพยาบาล อาการปวดปวดศีรษะด้านขวาบ่อย ๆ รุนแรงมากขึ้นเรื่อย ๆ PS 10/10 เวลาลุกเดินจะมีเวียนศีรษะเดินเซไปทางขวา ต้องนอนพักบนเตียงเกือบตลอดเวลา และเริ่มมีไข้วัดได้ 38 องศาเซลเซียส ญาติพาไปตรวจที่ clinic ได้เจาะเลือดและนัดมาฟังผลเลือดอีก 3 วัน ยังไม่ได้ยามาเชื้อ

3 วันก่อนมาโรงพยาบาล มีอาการชาใบหน้าซีกขวาเวลาล้างหน้า ไม่รู้สึกชาตัวหรือแขนขา

วันที่มาโรงพยาบาล ยังคงมีอาการไข้ ปวดศีรษะด้านขวามาก คลื่นไส้ อาเจียนชาใบหน้าซีกขวา ลุกขึ้นนั่งไม่ไหว กลืนอาหารแล้วสำลัก มีน้ำรั่วมุมปากซ้าย พูดเสียงปกติดี อาการไม่ดีขึ้นญาติจึงพามาโรงพยาบาล

Past history

- no known underlying disease
- no previous history of traumatic head
- no previous history of CNS infection

Personal history – Social history

- no smoking
- no history of alcohol drinking, illicit drug abuse
- no history of TB contact

Medications prior to admission

- none

Physical examination

- **Vital Signs**

- BP 160/96 mmHg

- PR 96 bpm

- SpO2 RA 96%

- RR 22 /min

- BT 38.5° C

- GA : A Thai male, **looked fatigued**

- HEENT

- Head : normal shape, no evidence of head trauma

- Eye : not pale conjunctiva, anicteric sclerae, no thyroid enlargement

- Ear : no redness ear canal, no discharge, TM intact
no auricular vesicle eruptions

- Nose : no rhinorrhea, paranasal sinus not tender

- Throat : no lips, buccal ulcer

Physical examination

- Skin and appendages : No rash, no petechia, no purpura, no ecchymosis.
- Chest : good air entry, equal breath sound, no adventitious sound.
- CVS : regular and full pulse, no carotid bruit, normal s1s2, no murmur.
- Abdomen :
no distention, normoactive BS, soft, not tender, no guarding, liver and spleen can't be palpated
- Extremities : no pitting edema, no arthritis
- LN : no superficial lymphadenopathy

Neurological examination

- **Mental status** : **drowsiness**, orientation to TPP, well co-operative
- **Speech** : no dysarthria, no aphasia
- **Cranial nerves**
 - CN I : no anosmia
 - CN II : no VF defect on confrontation test, pupil 2 mm RTLBE, RAPD negative
Eye ground : sharp disc, no papilledema, spontaneous venous pulsatile in both eyes
 - CN III,IV,VI : no ptosis, midline resting eye position, **limit Lt lateral conjugate gaze**
 - CN V : **decreased PPS at Rt face, absent Rt corneal reflex**, no weakness of temporalis and masseter muscle power
 - CN VII : **Lt facial weakness LMN type**
 - CN VIII : not evaluated
 - CN IX,X,XI : **absence of the gag reflex**, uvula in midline
 - CN XII : no tongue deviation

Neurological examination

- **Motor** : motor power : gr.V all extremities, **pronator drift positive Rt side**
- **DTR** : Biceps and Triceps 2+ both sides, Quadriceps and Ankle 1+ both sides
- **BBK** : neutral
- **Sensation** : **decreased PPS at Rt sided of body**, intact proprioception, Rhomberg negative
- **Cerebellar sign** : **finger to nose – swaying Rt side, dysdiadokokinesia Rt side, overshoot Rt side**
- **Stiff neck** : negative

Problem List

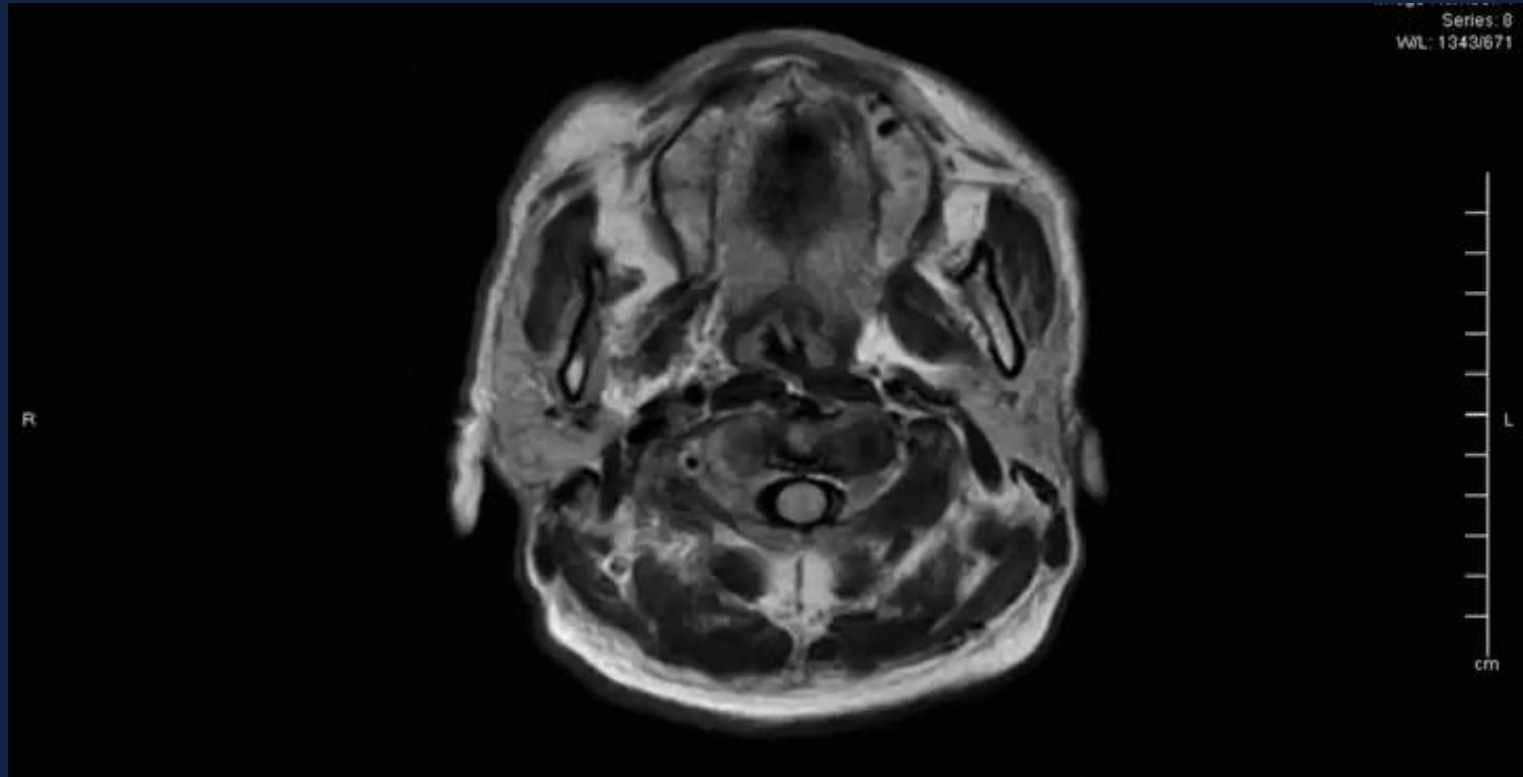
1. Acute fever with progressive dull-aching headache at right occipital region 5 days
2. Acute progressive right cerebellar ataxia with right hemihypoesthesia, Left facial weakness LMN 4 days
3. right pronator drift positive, left lateral conjugate gaze palsy, and gag reflex negative

CT brain non - contrast

CT brain with contrast

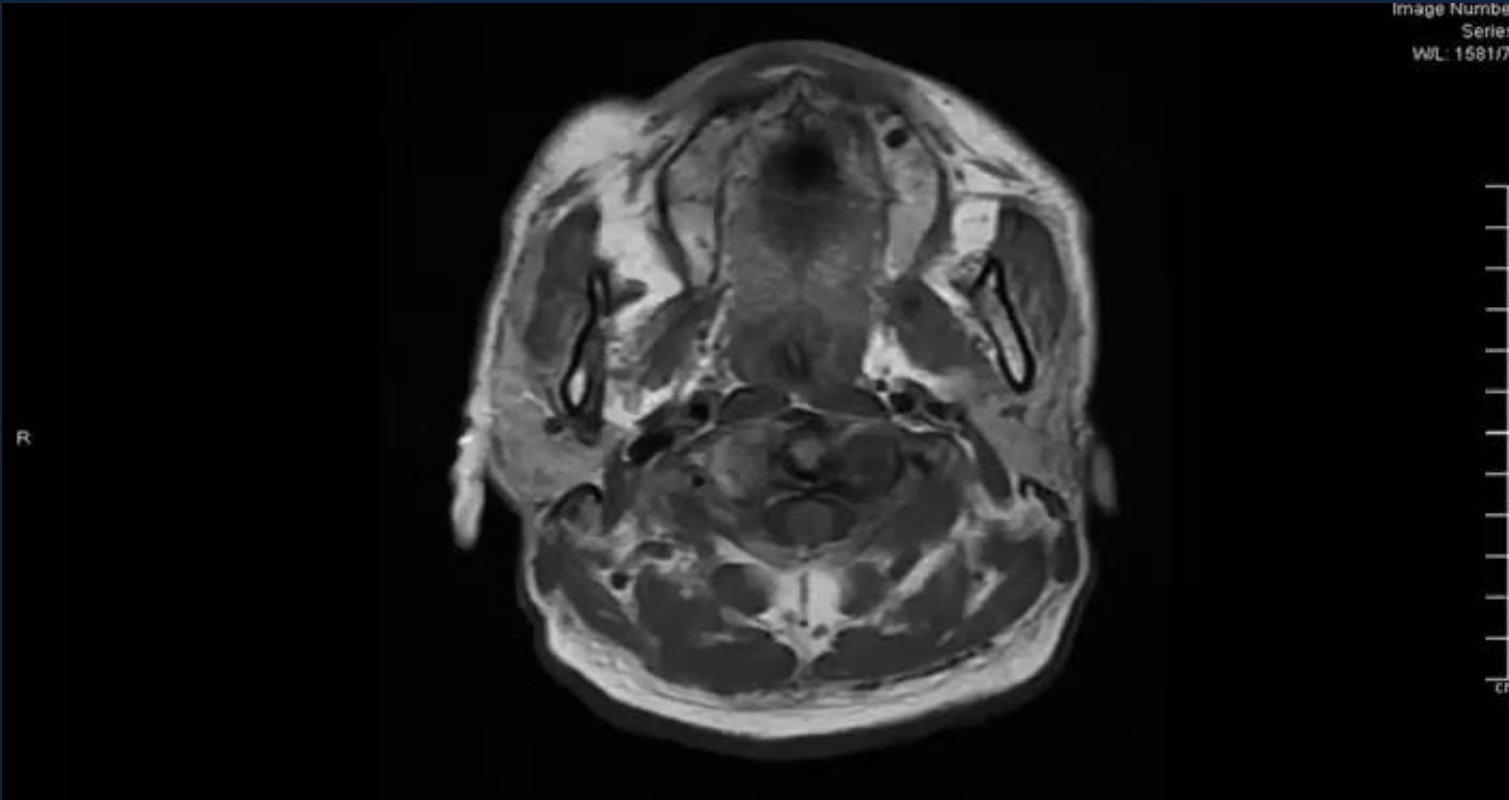
MRI brain

T2 FLAIR

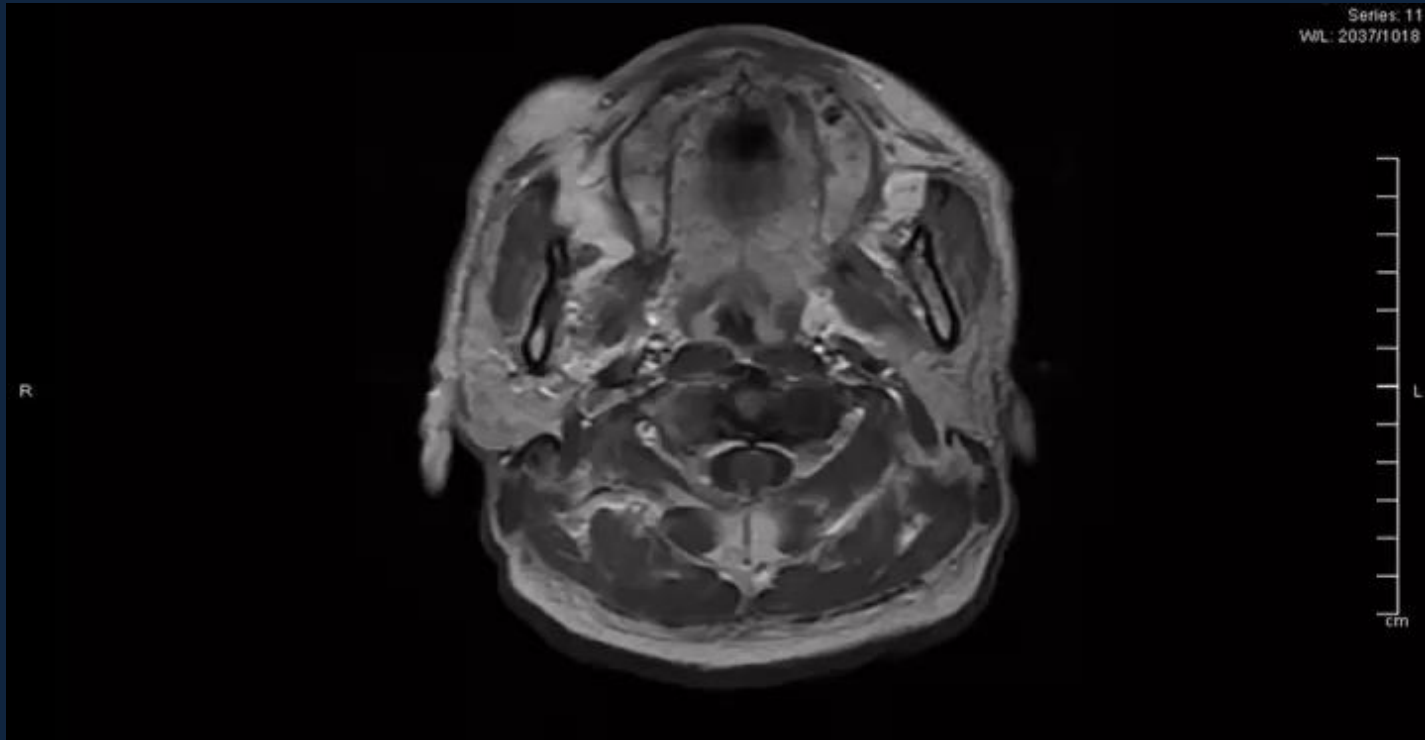


T1W

Image Number:
Series:
W/L: 1581/7



T1 with Gd



Laboratory Investigation

- Lumbar puncture (non traumatic)
 - Appearance : Clear colorless CSF
 - Open pressure 8 cmH₂O, Close pressure 7 cmH₂O
 - WBC 582 cells/cu.mm. : PMN 2 Mono 98
 - RBC 400 cells/cu.mm.
 - Total protein 184 glucose 66/152 (43%)
 - Culture for bacteria : negative
 - PCR for MTB, wright stain : negative
 - PCR for HSV DNA : negative

Laboratory Investigation

- Hemoculture : *Listeria monocytogenes* x 1 specimen

Laboratory Investigation

- CBC : Hb 13.6 Hct 38.2 WBC 9,210 (N63), Plt 305,000 INR 1.1
- Electrolyte : Na 138 K 4.1 Cl 102 HCO₃ 21 BUN/Cr 13/0.9
- LFT : tb/db 0.83/0.29 ast/alt/alp 31/42/60 alb/glb 4.1/3.2
- UA : wbc 1-2

Diagnosis

- **Listeria rhombencephalitis with microabscesses**

Rhombencephalitis

OUTLINE

- Introduction
- Etiology
- Overview clinical manifestation
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Rhombencephalitis

- Infectious rhombencephalitis
- Autoimmune rhombencephalitis
- Paraneoplastic rhombencephalitis

CLIPPERS

Bickerstaff brainstem encephalitis

Multiple sclerosis

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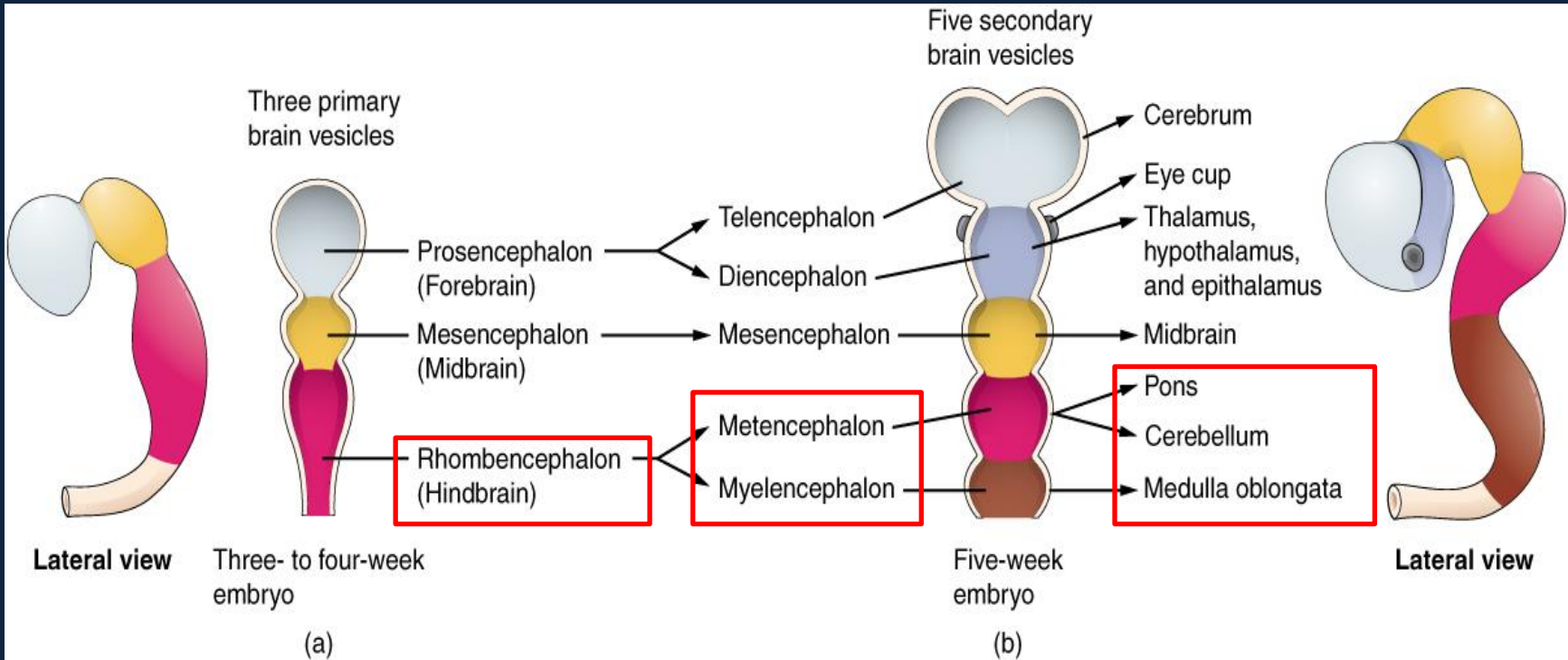
Introduction

Brainstem encephalitis

- Rhombencephalitis : Hindbrain
- CLIPPERS : Pons, cerebellum
- Bickerstaff encephalitis : Upper brainstem

Introduction

- Rhombencephalitis (RE) is inflammatory disease of the rhombencephalon (medulla oblongata , pons, cerebellum,)
- Term “brainstem encephalitis” often used interchangeably eventhough anatomically slightly different.
- RE has a wide variety of etiologies, some of them potentially severe and life threatening without roper early treatment.



Introduction

- Diagnosis
 - brainstem dysfunction (cranial nerve, long tract signs)
 - and/or cerebellar dysfunction demonstrated clinically or by neuroimaging
 - pleocytosis (>4 cells/mm³) in CSF.

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Etiology

- Infection
- Autoimmune disease
- Paraneoplastic syndromes (PNS)

Etiology	Frequency ^a
Infectious	
<i>Listeria</i>	Common
Enteroviruses	
Enterovirus 71	Common
Bulbar poliomyelitis	Now very rare
Coxsackievirus A16	Very rare
Echovirus	Very rare
Flaviviruses	
Japanese encephalitis	Common
St. Louis encephalitis	Very rare
West Nile virus	Rare
Herpes viruses	
HSV	Uncommon
EBV	Rare
HH6	Rare
CMV	Very rare
VZV	Very rare

Common : 100 cases

Uncommon : dozen to several dozen cases

Rare : less than to around a dozen

Very rare : isolated cases (1-5 or 6 cases)

Other infections

Bacterial RE

TB	Rare
Pneumococcus	Very rare
<i>Brucella</i>	Very rare
<i>Borrelia</i> (Lyme disease)	Very rare
<i>Salmonella</i>	Very rare
<i>Legionella</i>	Very rare
<i>Mycoplasma</i>	Rare

Viral RE

Rabies virus	Very rare
Eastern equine encephalitis	Very rare
Adenovirus	Very rare
Influenza A	Very rare

Other

Melioidosis	Rare
<i>Aspergillus</i>	Very rare
Mucormycosis	Very rare
<i>Nocardia</i>	Very rare
Cysticercosis	Very rare
Toxoplasmosis	Very rare

Autoimmune

Behcet disease	Common
SLE	Very rare
Relapsing polychondritis	Very rare
Sjogren's syndrome	Very rare
Sarcoidosis	Very rare
Vogt-Koyanagi-Harada	Very rare

Paraneoplastic

Uncommon

Other

Lymphoma	Very rare
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Paraneoplastic antibodies*, syndromes, and associated cancers

Antibody	Syndrome	Associated cancers
Well-characterized paraneoplastic antibodies ¶		
Anti-Hu (ANNA-1)	Encephalomyelitis including cortical, limbic, and brainstem encephalitis; cerebellar degeneration; myelitis; sensory neuronopathy; and/or autonomic dysfunction	SCLC, other
Anti-Yo (PCA-1)	Cerebellar degeneration	Gynecologic, breast
Anti-Ri (ANNA-2)	Cerebellar degeneration, brainstem encephalitis, opsoclonus-myoclonus	Breast, gynecologic, SCLC
Anti-Tr (DNER)	Cerebellar degeneration	Hodgkin lymphoma
Anti-CV2/CRMP5	Encephalomyelitis, cerebellar degeneration, chorea, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma proteins ^Δ (Ma1, Ma2)	Limbic, hypothalamic, brainstem encephalomyelitis (infrequently cerebellar degeneration)	Testicular germ cell tumors, lung cancer, other solid tumors
Anti-VGCC [◇]	Cerebellar degeneration	SCLC
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis	Breast, lung cancer
Anti-PCA-2 (MAP1B)	Peripheral neuropathy, cerebellar ataxia, encephalopathy	SCLC
Antirecoverin [§]	Cancer-associated retinopathy	SCLC
Antibipolar cells of the retina [¥]	Melanoma-associated retinopathy	Melanoma
Partially characterized paraneoplastic antibodies ¶		
Anti-Zic 4	Cerebellar degeneration	SCLC
Anti-ANNA-3	Sensory neuronopathy, encephalomyelitis	No tumor or Hodgkin lymphoma

ANNA: antineuronal nuclear antibody; SCLC: small cell lung cancer; PCA: Purkinje cell antibody; DNER: Delta/Notch-like epidermal growth factor-related receptor; CRMP5: collapsin-responsive mediator protein 5; VGCC: voltage-gated calcium channel.

* Antibodies that are almost exclusively found in patients with cancer and neurologic symptoms.

¶ Well-characterized antibodies are those directed against antigens whose molecular identity is known, or that have been identified by several investigators.^[1]

Δ Antibodies to Ma2: younger than 45 years, usually men with testicular germ cell tumors; older than 45, men or women with lung cancer and less frequently other tumors. Ma1 antibodies: often associated with tumors other than germ cell neoplasms and confer a worse prognosis, with more prominent brainstem and cerebellar dysfunction.

◇ The identification of these antibodies in a patient with cerebellar dysfunction indicates paraneoplasia, almost always associated with an SCLC. These antibodies are also found in patients with Lambert-Eaton myasthenic syndrome, in which only approximately 50% of patients have cancer.

§ Other antibodies reported in a few or isolated cases include antibodies to tubby-like protein and the photoreceptor-specific nuclear receptor.

¥ Target antigens include transducin-b, rhodopsin, and arrestin, among others.

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CLIPPERS

Bickerstaff brainstem encephalitis

Multiple sclerosis

Clinical presentation

- Cranial nerve paresis (nuclei) : all types : 75%
- Cerebellar ataxia
: common in infection and PNS, uncommon in BD
- Long tract signs (corticospinal, spinothalamic, posterior column)
: majority with BD, minority of infectious except Listeria, infrequent with PNS
- Alteration of consciousness
: infection, uncommon with other etiologies.
- Fever : common in infection and BD, infrequent in PNS
- Meningismus : majority in infectious

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Multiple sclerosis

Rhombencephalitis

A Series of 97 Patients

Mireia Moragas, MD, Sergio Martínez-Yélamos, MD, Carles Majós, MD, Pedro Fernández-Viladrich, MD, Francisco Rubio, MD, and Txomin Arbizu, MD

TABLE 1. Etiologic Spectrum of Rhombencephalitis in 97 Patients

Etiology	Patients
Unknown cause	31
Multiple sclerosis	28
Behçet disease	10
<i>Listeria monocytogenes</i>	9
Paraneoplastic syndrome	6
Anti-Yo antibodies	3
Anti-Tr antibodies	3
Epstein-Barr virus	4
Tuberculosis	2
Pneumococcal infection	2
Systemic lupus erythematosus	1
Lymphoma	1
<i>Brucella</i>	1
JC virus	1
Relapsing polychondritis	1
Total	97

TABLE 2. Clinical Characteristics of 97 Patients With RE

Etiology (No.)	Age, yr, Median (Range)	Sex M/F	Cranial Nerve Involvement (%)	Ataxia (%)	Long Tract Abnormality (%)	Low Level of Consciousness (%)	Fever (%)	Meningeal Sign (%)	MRS
Unknown cause (31)	40 (15–79)	19/12	74	77	55	16	45	10	1
MS (28)	25 (15–55)*	14/14	86	64	71	0†	0†	0†	1
Behçet disease (10)	30 (19–52)	3/7	70	10†	70	0	50	20	0
<i>Listeria</i> (9)	59 (46–74)*	5/4	78	78	44	78†	89†	62†	2
PNP syndrome (6)	51 (14–77)	4/2	67	100	17	17	33	0	4†
Anti-Yo (3)	59 (42–63)*								
Anti-Tr (3)	43 (14–77)								
EBV (4)	20 (19–44)	0/4	75	100	0†	50	75	25	0.5
Other (9)	25 (16–73)	3/6	67	78	67	22	67	22	1
Total (97)	32 (14–79)	48/49	76	69	56	17	39	13	1

Abbreviations: MRS = modified Rankin Scale, PNP = paraneoplastic.

*Student t test, statistically significant.

†Chi-square or Fisher exact test, as appropriate, statistically significant.

TABLE 3. CSF and MRI Findings in 97 Patients With RE

Etiology (No.)	CSF Findings, Mean (Range)				MRI Findings			Prior Known Disease (No.)
	Cells (Cells/mm ³)	Lymphocyte Count (%)	Protein (g/L)	Glucose (mmol/L)	Infratentorial Damage (%)	Supratentorial Damage (%)	Normal (%)	
Unknown cause (31)	23 (5–6762)	86	0.54 (0.20–2.32)	3.25 (0–5.10)	47	33	43*	—
MS (28)	10 (5–30)	100	0.39 (0.20–4.10)	3.20 (2.40–5.50)	89	100	0	—
Behçet disease(10)	126 (10–1000)	43	0.65 (0.32–3.06)	2.85 (1.90–3.70)	100*	50	0	4
<i>Listeria</i> (9)	237 (20–3300)	50	1.24 (0.53–2.37)	2.15 (0.10–3.50)	100	0	0	0
PNP syndrome (6)	45 (13–109)	67	0.52 (0.25–0.85)	3.7 (3.1–4.2)	0	0	100*	0
EBV (4)	24 (8–55)	100	0.74 (0.54–1.72)	3.00 (2.70–3.40)	50	50	25	0
Other (9)	184 (18–439)	71	1.26 (0.24–3.44)	2.84 (0.3–4.9)	78	56	0	3†
Total (97)	189 (5–6762)	72	0.76 (0.2–4.1)	3.11 (0.0–5.5)	63	51	17	7

Abbreviations: See previous tables.

*Chi-square or Fisher exact test, as appropriate, statistically significant.

†One case systemic lupus erythematosus, 1 pneumococcal infection, 1 relapsing polychondritis.

Cerebrospinal fluid characteristics

- **Pleocytosis**
 - : **Listeria** – average wbc 240 cells/mm³ (range 20-3,300) with 50% lymphocytes
 - : Others viral infections - average wbc 150 cells (range 5-500) with 50% lymphocytes
 - : **Behcet disease** - average 126 cells (range 10-1,000) with 43% lymphocytes
 - : **Paraneoplastic syndromes** – average 45 cells (range 13-109) with 67% lymphocytes
- **Protein**
 - : most etiologies is elevated but may be normal in PNS.
- **Glucose**
 - : low CSF glucose is primarily found in bacterial infection.

Neuroimaging

- MRI brain
 - **typical finding** : T2W and FLAIR - increased signal intensity in the pons, medulla, upper cervical cord, cerebellum more frequently than midbrain.
 - **Listeria cases** : 100% abnormal MRI brain (100% infratentorial, 50% infratentorial), **ring enhancement**
 - **Viral cases**
 - : Enterovirus 71 : 70-75% abnormal MRI
 - : West Nile : 50% abnormal MRI
 - : HSV, EBV, CMV, VZV, human herpesvirus 6 : 2/3 abnormal
 - **Behcet disease** : 100% abnormal MRI
 - **PNS cases** : 100% normal MRI brain

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Listeria monocytogenes rhombencephalitis

- Considered as one of the most dangerous human and ruminant infection, also the most severe bacterial foodborne infection.
- **Epidemiology**
 - CNS listeriosis is rare, 7.4 – 16 cases in 1 million individuals, RE is about 9% of all CNS listeriosis.
 - Age of patients range from 14-79 (mean 48)
 - male = female.
 - 1-5% of the general population are asymptomatic carrier
 - Listeria rhombencephalitis occurs primarily in immunocompetent.

Listeria monocytogenes rhombencephalitis

- **Pathogenesis**

- - gram-positive, facultative intracellular rod.

- 2 major routes of infection

- : oral route (rhombencephalitis)

- retrograde neural route via oral epithelium

- immunocompetent host

- : hematogenous route (meningoencephalitis)

- GI tract → lymphatic system → hematogenous.

- immunocompromise host

Summary of Trigeminal Sensory innervation of the mouth:

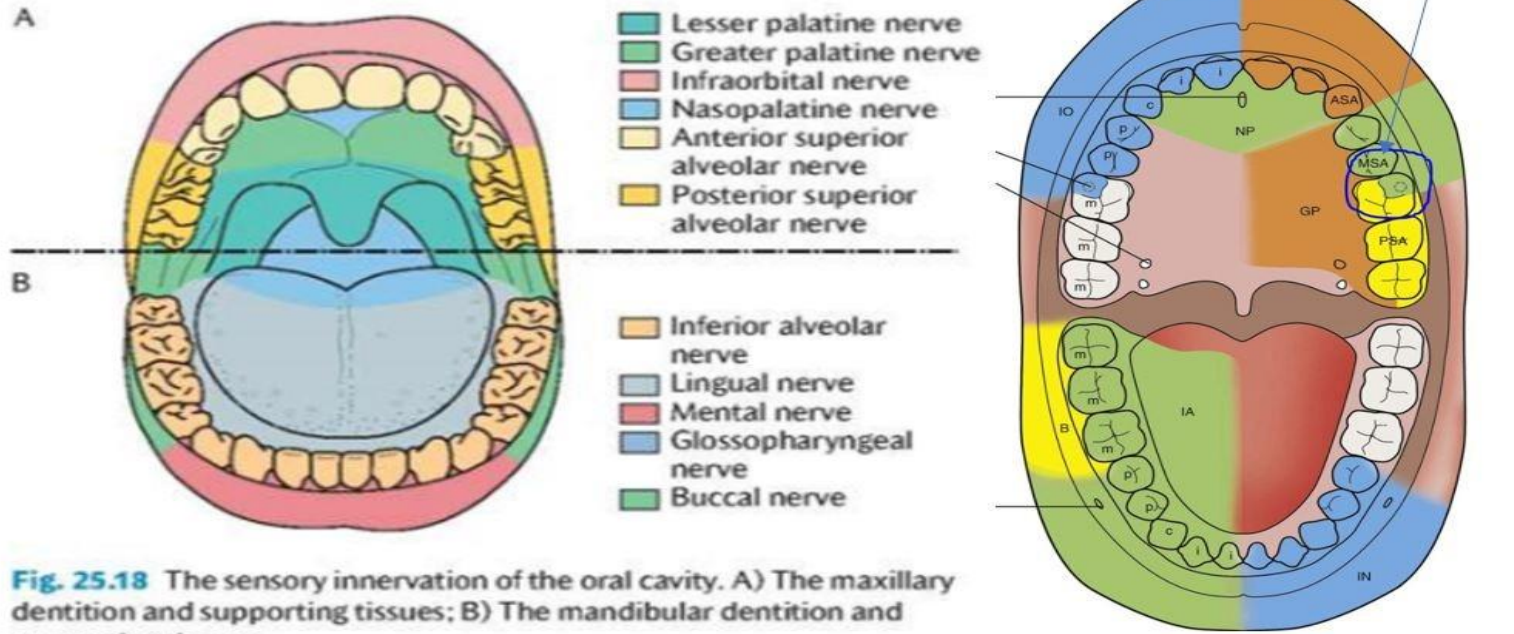


Fig. 25.18 The sensory innervation of the oral cavity. A) The maxillary dentition and supporting tissues; B) The mandibular dentition and supporting tissues.



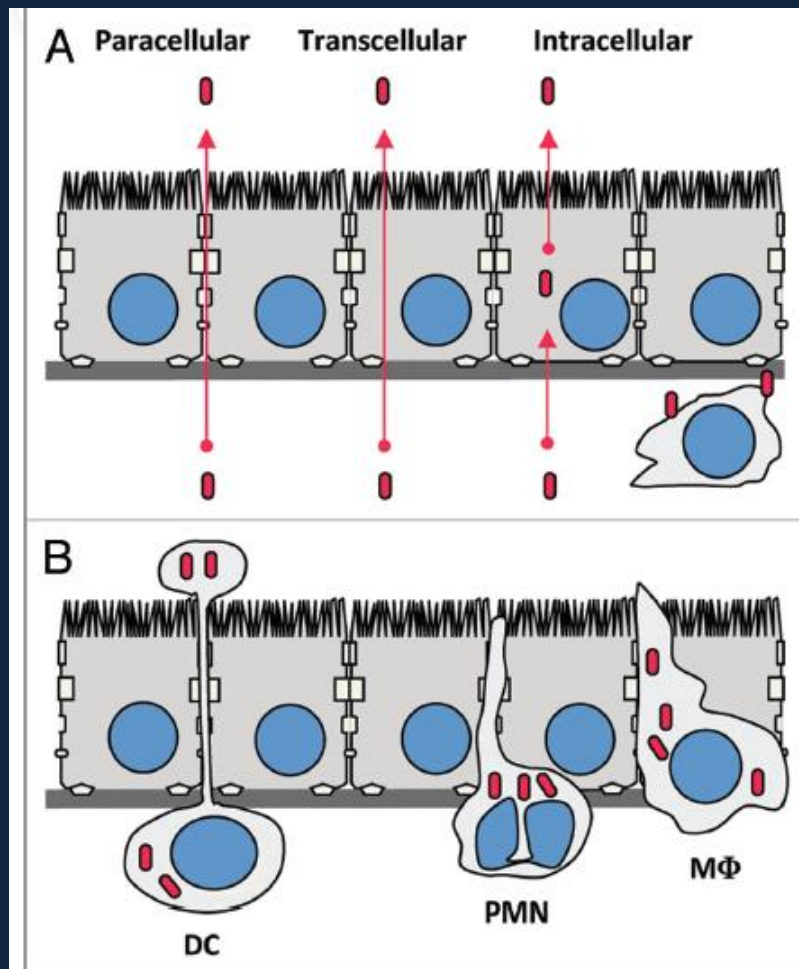


Figure 3. Potential mechanisms by which *Lm* could cross the blood-brain barrier. (A) Extracellular *Lm*, either free in the blood and/or associated to circulating cells, may recognize receptors at the surface of the barriers (as InlA, InlB or Vip) and cross them. (B) Trojan horse mechanism: Circulating leucocytes infected by *Lm*, such as monocytes, dendritic cells or polymorphonuclear cells, may cross the BBB hence targeting the bacteria in the CNS. DC, dendritic cell; PMN, polymorphonuclear leukocyte; MΦ, monocyte/macrophage.

Listeria monocytogenes rhombencephalitis

- Clinical manifestation
- - bacteremia, CNS involvement (meningitis, meningoencephalitis, rhombencephalitis)
 - Biphasic time course
 - : Flu-like prodrome 1-15 days : fever, headache, nausea, vomiting, malaise
 - : Brainstem dysfunction : usually asymmetric, 2/3 localized to the pons and medulla

Table 2 Signs and symptoms of *Listeria rhombencephalitis*

Unilateral cranial nerve deficits (100%)

VII (78%)

VI (74%)

IX (58%)

X (56%)

V (47%)

<20%: XII, VIII, IV, III, XI

Ipsilateral corticospinal tract deficits (81%)

Cerebellar deficits (53%): hemiataxia, vertigo, cerebellar dysarthria

Respiratory failure (41%)

Triad of headache, fever, meningismus (46%)

Rare: peduncular hallucinosis, Weber syndrome

(Data from Armstrong and Fund [1].)

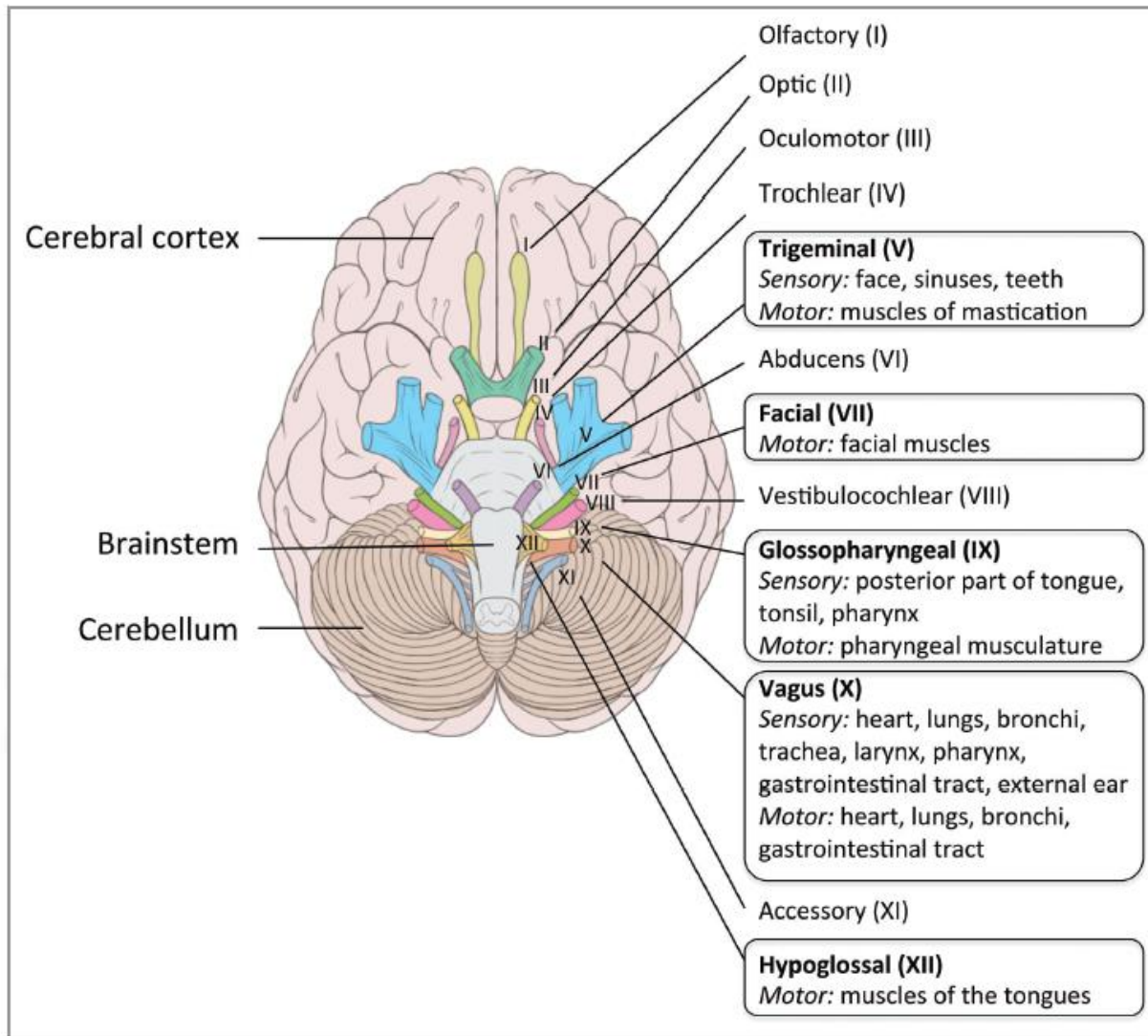


Figure 2. Cranial nerves in human. A frame surrounds the nerves that emerge from the regions most frequently infected by *Lm* in the brainstem. Adapted from Patrick Lynch; Creative Commons Attribution 2.5 License 2006; www.patricklynch.net.

Evaluation and diagnosis

- **CSF**

- : ¾ have pleocytosis (mono = pmn, mono>pmn, pmn>mono)
- : culture positive : mean wbc 263 cell/mm³
- : culture negative : mean wbc 154 cell/mm³
- : 85% protein is elevated

- **MRI**

- : Moragas et al case series 97 cases : 9 cases of Listeria RE were 100% abnormal infratentorially, no supratentorial lesions.
- : increase signal intensities on T2W and FLAIR in brainstem, cerebellum, upper cervical cord
- : unlike other etiologies, ring-enhancing abscesses may be seen in same locations.

- **CSF and blood cultures are most specific for diagnosis.**

- : yield for positive : CSF culture 33%, Blood culture 46% => repeat cultures increased the rate of positive results.

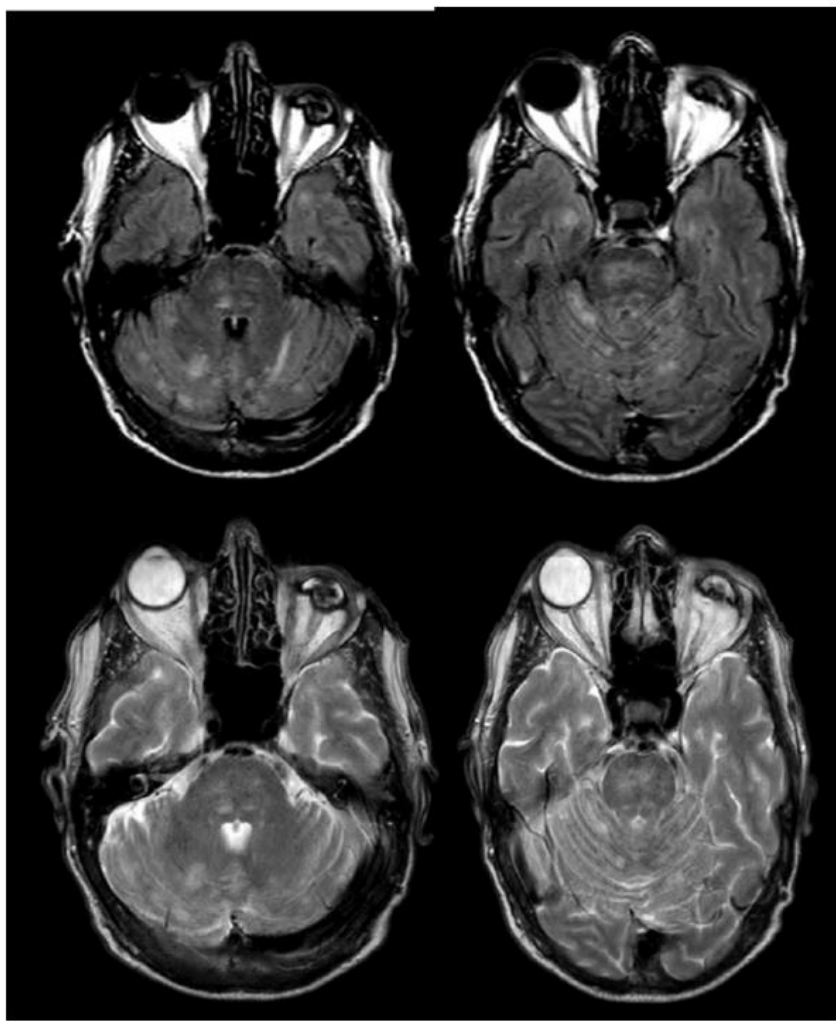


Fig. 4: Listeria. MRI reveals patchy ill-defined T2 hyperintense lesions with peripheral contrast-enhancement and with hyperintensity on DWI sequences.

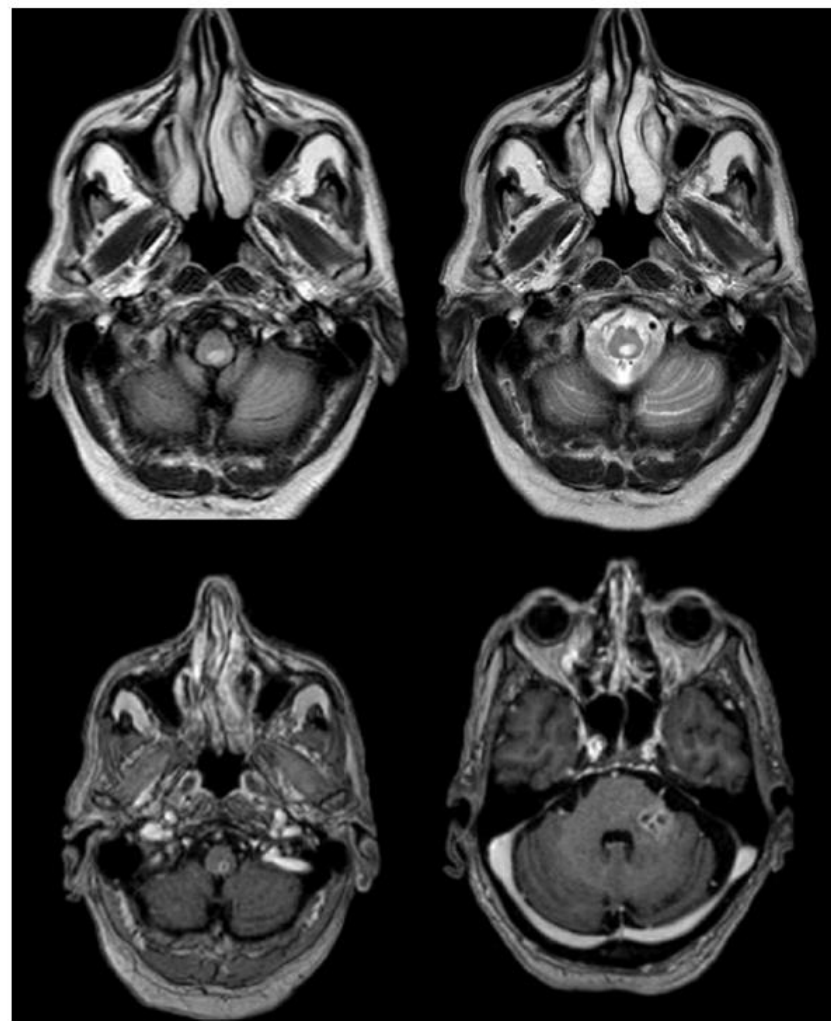


Fig. 5: Listeria. Multiple ring enhancement lesions in the left pons, medulla oblongata and cerebellum.

Treatment

- Antibiotics

- Ampicillin 2 gm iv q 4 hrs (adult), 100-300 mg/kg/day divide in 4-6 times (children)
- Gentamicin iv (synergistic effects with ampicillin)
- Penicillin G (alternative to ampicillin) 24 mU/day

Prognosis

- mortality rate in treated vs untreated is 20-30% : 66%
- 55% of survivors will have neurologic sequelae.

Enterovirus 71 rhombencephalitis (EV 71 RE)

- EV71 has been recognized as causing outbreaks of hand-foot-mouth disease (HFMD), URI, AGE.
- Neurologic involvement may occur in up to 25% of patients
- children and teenagers primarily affected

Enterovirus 71 rhombencephalitis (EV 71 RE)

- **Investigation**

- MRI : increased signal intensities in T2W and FLAIR at brainstem and cerebellum
- CSF : mean wbc 194 cells/mm³ (range, 5–379)
- virus isolation : throat, feces, or vesicles

- **Management**

- No specific treatment

Herpes virus rhombencephalitis

- uncommon cause but available specific treatment
- **Herpes simplex virus**
 - mean age 41 years (range 18-71), male = female
 - HSV1 > HSV2 > EBV/HH6 > CMV/VZV
 - 54% encephalitis was limited to the rhombencephalon. temporal lobe (42%) and frontal lobe (33%) were involved.

Clinical manifestation

- 80% neuro-ophthalmology abnormalities (EOM, nystagmus, anisocoria, ptosis, oscillopsia)
- 70% other cranial nerve deficits
- 70% fever, 50% headache, 45% pyramidal tract findings, 38% ataxia, 30% dysphagia

Herpes virus rhombencephalitis

- **Investigation**

- MRI : increased signal intensities in T2W and FLAIR at brainstem and upper cervical cord.
- CSF : mean wbc 93 cells/mm³ (range 0-465), neutrophilic = lymphocytic predominance.

- **Treatment**

- intravenous acyclovir
- mortality rate in treated group is 22% compared to 75% in untreated group.

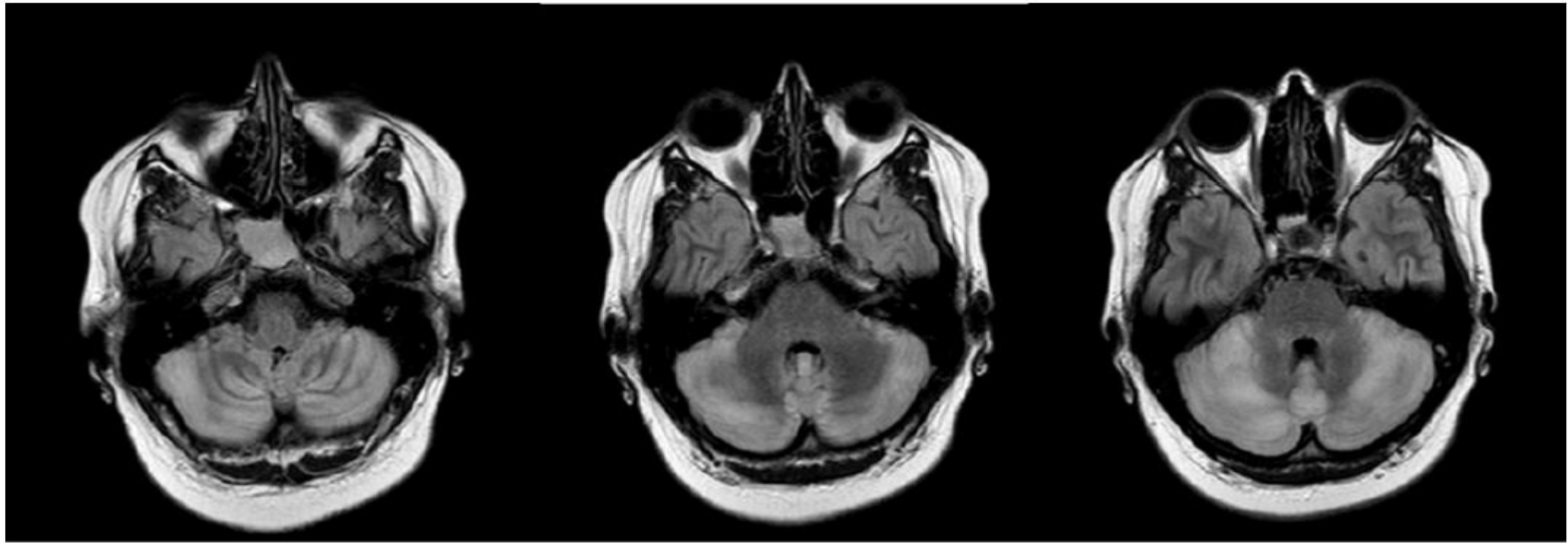


Fig. 6: Herpes virus. Hyperintense FLAIR lesions on cerebellum, involving white and gray matter, without restriction diffusion and without enhancement post administration of contrast medium.

Epstein-Barr virus (EBV)

- mean age 20 years (range 19-44), female >> male
- clinical manifestation
 - fever (75%)
 - ataxia (100%)
 - AOC (50%)
 - no long tract signs.
- Investigation
 - MRI : $\frac{3}{4}$ abnormal, 50% supratentorial ad 50% infratentorial.
 - CSF : mean wbc 24 cells/mm³ (range 8-55),
lymphocytic predominated

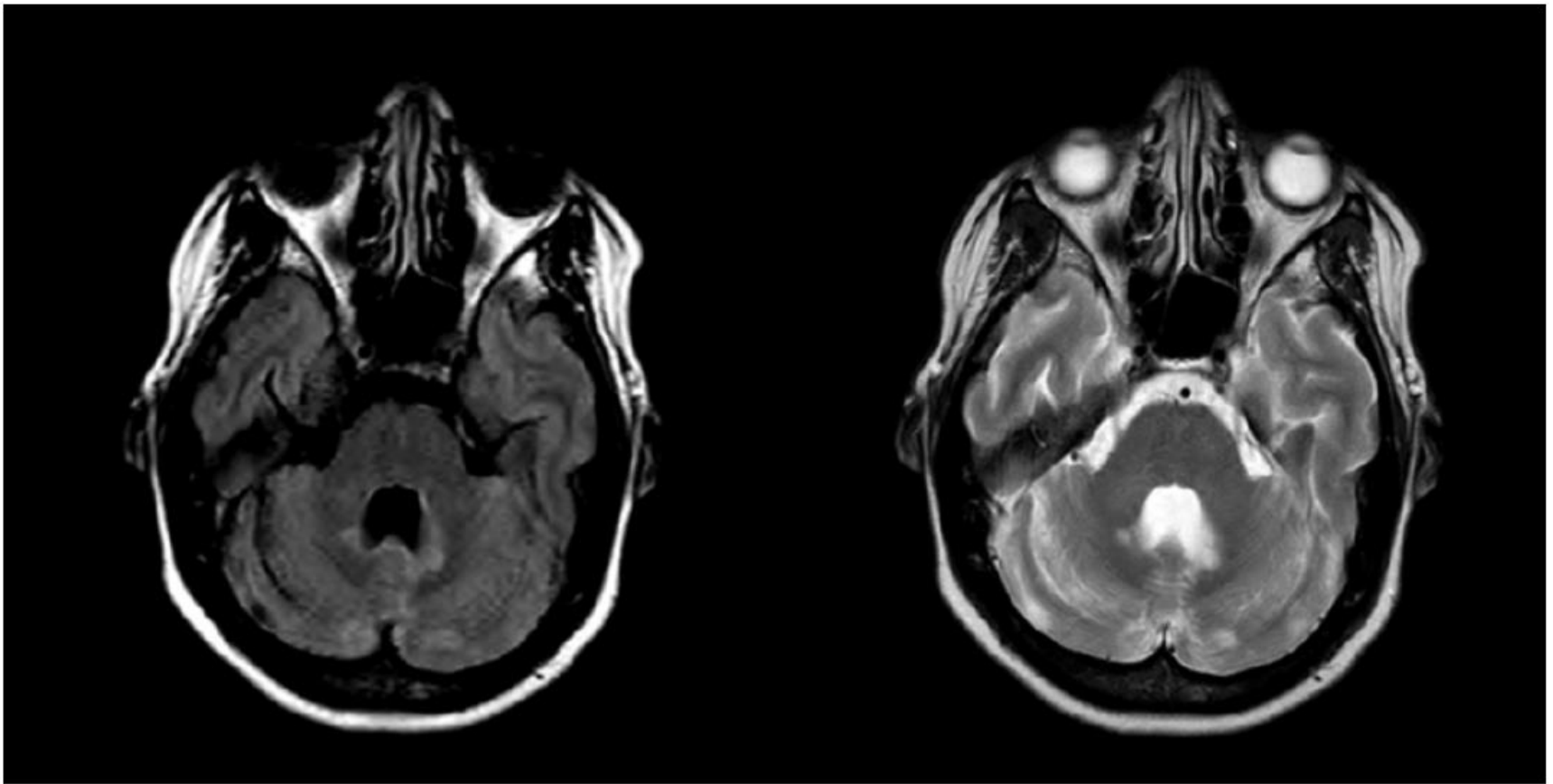


Fig. 7: Combined EBV, CMV and HSV. T2 and Flair axial images show patchy asymmetric regions of high signal intensity bilaterally affecting the pons and cerebellar peduncles without significant mass effect and without enhancement.

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Rhombencephalitis

- Infectious rhombencephalitis
- **Autoimmune rhombencephalitis**
- Paraneoplastic rhombencephalitis

CLIPPERS

Bickerstaff brainstem encephalitis

Multiple sclerosis

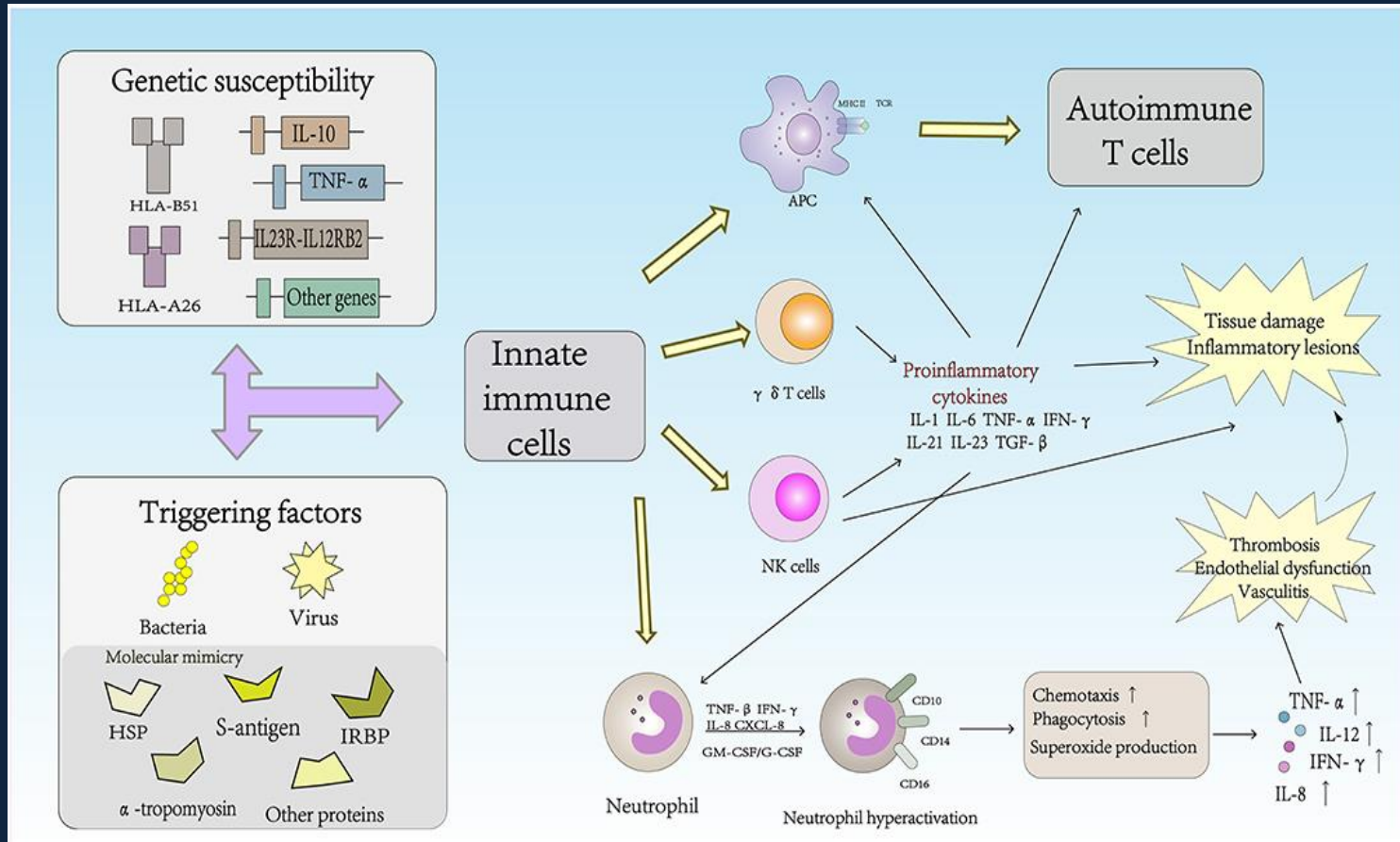
Autoimmune rhombencephalitis

- **Behcet disease**

- Multisystem relapsing inflammatory disorder of unknown cause.
- As with autoimmune disease, the disorder may represent aberrant immune activity triggered by exposure to agent, perhaps infectious, in patients with a genetic predisposition.
- Neurological Behcet's disease (NBD) is rare but one of the most serious cause of long-term morbidity and mortality, commonly mentioned in the ddx of demyelinating CNS disease.

Autoimmune rhombencephalitis

- **Behcet disease**
 - Various clinical and epidemiological features : parenchymal vs non-parenchymal
 - Male : Female 2.8 : 1
 - Age of onset of NBD : usually 20-40 years. if above 50 ; exclude more common neurological disorders (stroke, non-specific white matter change.
 - commonly develop NBD 3-6 years after the onset of the other systemic features of BD, some studies
- reported that NBD presentation precede systemic features (about 6%)



	Frequency	Comments
Oral ulcers	97–99%	..
Genital ulcers	~85%	..
Genital scar	~50%	More common in men
Papulopustular lesions	~85%	..
Erythema nodosum	~50%	..
Pathergy reaction	~60%	Predominantly in Mediterranean countries and Japan
Uveitis	~50%	..
Arthritis	30–50%	..
Subcutaneous thrombophlebitis	25%	..
Deep vein thrombosis	~5%	..
Arterial occlusion (aneurysm)	~4%	..
Epididymitis	~5%	..
Gastrointestinal lesions	1–30%	More common in Japan

*Adapted from Yazici et al,⁴ with permission from Nature Publishing Group.

Table 1: Clinical manifestations of Behçet's disease*

Panel 1: International Behçet's Disease Study Group criteria for the diagnosis of Behçet's disease⁵

For diagnosis, patient must have had the following symptoms:

Recurrent oral ulceration—minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred at least three times in one 12-month period

Plus two of the following:

Recurrent genital ulceration—aphthous or scarring, observed by physician or patient

Eye lesions—anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist

Skin lesions—erythema nodosum observed by physician or patient, pseudofolliculitis, papulopustular lesions; or acneiform nodules observed by physician in post-adolescent patients not on corticosteroids

Positive pathergy test—read by physician at 24–48 h

Findings applicable only in the absence of other clinical explanations.

Panel 2: Classification of neuro-Behçet's disease

CNS

Parenchymal

- Brainstem
- Diffuse ("brainstem plus")
- Spinal cord
- Cerebral
- Asymptomatic ("silent")

Non-parenchymal

- Cerebral venous thrombosis: intracranial hypertension
- Intracranial aneurysm
- Extracranial aneurysm/dissection

Peripheral nervous system (relation to Behçet's disease uncertain)

- Peripheral neuropathy and mononeuritis multiplex
- Myopathy and myositis

Other uncommon but recognised syndromes

- Acute meningeal syndrome
- Tumour-like neuro-Behçet's disease
- Psychiatric symptoms
- Optic neuropathy

Diagnosis (Behcet's disease)

- no validated criteria for definite diagnosis, based on clinical (clinical syndrome of systemic BD, pathergy, the presence of inflammatory brainstem lesion)

: blood : ESR associated with disease activity, HLA type B51 (6 times increased risk of BD and more severe), HLA-B27

: CSF

- 70-80% abnormal in parenchymal NBD
- increased CSF protein (modestly raised in most case, may over 1 g/dL), oligoclonal bands are usually absent.
- prominent pleocytosis (>50/ uL) – range 0-400 cells/mm³ (med 40), usually neutrophilia in early stages, replaced later by lymphocytosis

Diagnosis (Behcet's disease)

- MRI

- parenchymal NBD : upper brainstem, extends to thalamus and basal ganglia on one side, bilateral lesions are less common.
- increase signal intensities in T2W with enhancement and often edema.
- diminish in size after treatment.
- patient with a more diffuse meningoencephalitis show hyperSI T2 lesions within the subcortical white matter of the temporal, frontal and hypothalamic regions, but MRI can be normal.

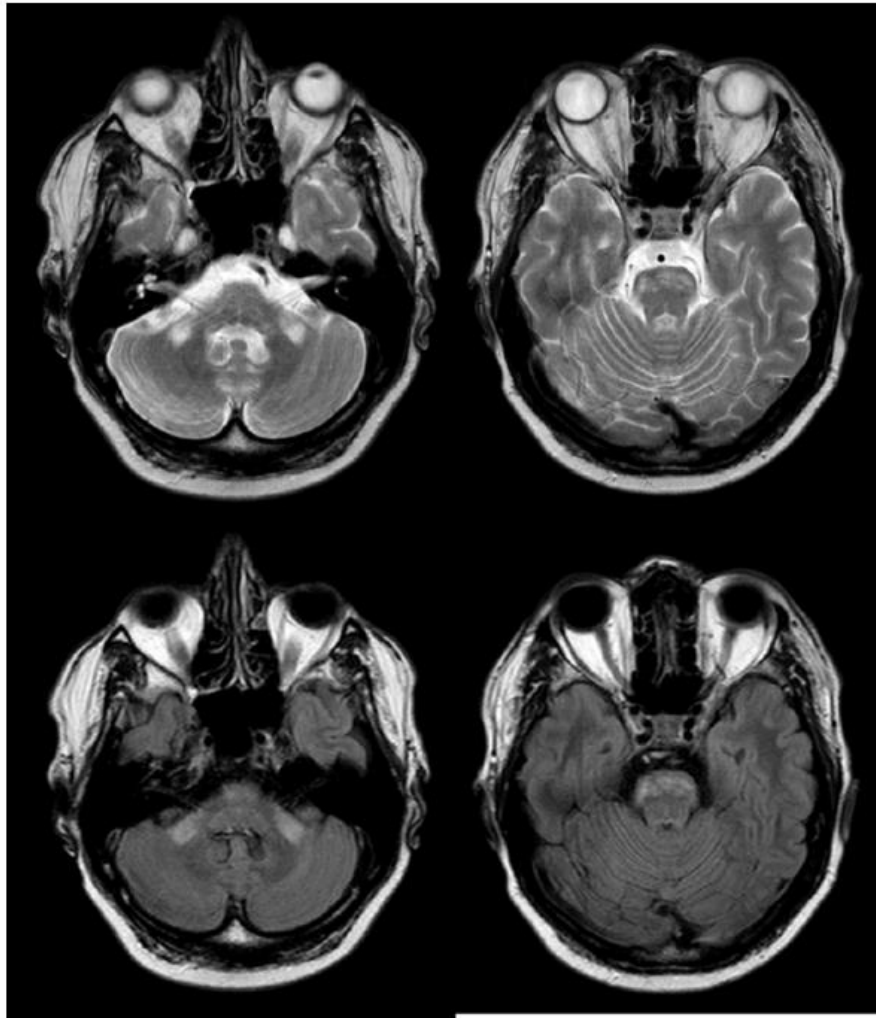


Fig. 9: Neuro-Behçet. T2 and Flair axial images: at the level of the crus cerebri shows heterogeneous bilateral mesodiencephalic junction lesion with extensive edema, sparing the red nucleus. There is extension of perilesional edema caudally to the superior cerebellar peduncle and pontine tegmentum, and upward to the white matter of the temporal lobe, external capsule, and thalamus.

Behcet's disease

- Treatment
 - HD intravenous corticosteroid followed by oral maintenance.
 - immunosuppressive drugs : azathioprine, MMF, MTX
- Prognosis
 - about 25% complete recovery, 75% have residual impairment

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Bickerstaff brainstem encephalitis

Multiple sclerosis

Paraneoplastic rhombencephalitis

- Paraneoplastic syndromes (PNS) are the result of onco-neural cross-reactivity; the cancer stimulates the production of antibodies which cross react with neural tissue.
- Rare and possibly under reported because the specific Ab cannot always be detected.
- May antedate the onset of cancer and therefore allows for early detection in 50-80% of patients.

	Classic	Non-classic
Brain, cranial nerves, and retina	Cerebellar degeneration Limbic encephalitis Encephalomyelitis Opsoclonus-myoclonus	Brainstem encephalitis Optic neuritis Cancer-associated retinopathy Melanoma-associated retinopathy
Spinal cord		Stiff-person syndrome Myelitis Necrotising myelopathy Motor-neuron syndromes
Neuromuscular junction*	Lambert-Eaton myasthenic syndrome	Myasthenia gravis
Peripheral nerves or muscle*	Sensory neuronopathy Intestinal pseudo-obstruction Dermatomyositis	Sensorimotor neuropathy Neuropathy and paraproteinaemia Neuropathy with vasculitis Acquired neuromyotonia Autonomic neuropathies Polymyositis Acute necrotising myopathy

*Disorder reviewed elsewhere.³⁻⁵

Table 1: Paraneoplastic syndromes of the nervous system by location

	Syndrome	Associated cancers
Well characterised paraneoplastic antibodies*		
Anti-Hu (ANNA-1)	PEM including cortical, limbic, brainstem encephalitis, PCD, myelitis, PSN, autonomic dysfunction	SCLC, other
Anti-Yo (PCA-1)	PCD	Gynaecological, breast
Anti-Ri (ANNA-2)	PCD, brainstem encephalitis, opsoclonus-myoclonus	Breast, gynaecological, SCLC
Anti-CV2/CRMP5	PEM, PCD, chorea, uveitis, optic neuritis, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma protein [†]	Limbic, hypothalamic, brainstem encephalitis (infrequently PCD)	Germ-cell tumours of testis, non-SCLC, other solid tumors
Anti-amphiphysin	Stiff-person syndrome, PEM, limbic encephalitis, myelopathy	SCLC, breast
Partly characterised paraneoplastic antibodies*		
Anti-Tr	PCD	Hodgkin's lymphoma
Anti-Zic 4	PCD	SCLC
mGluR1 [‡]	PCD	Hodgkin's lymphoma
ANNA3	Various PND of the CNS	SCLC
PCA2	Various PND of the CNS	SCLC
Antibodies that occur with and without cancer association		
Anti-NR1/NR2 of NMDA receptor [‡]	Characteristic encephalitis [§]	Teratoma (usually in the ovary)
Anti-VGKC [‡]	Limbic encephalitis, PNH (neuromyotonia), other	Thymoma, SCLC, other
Anti-VGCC [‡]	LEMS, PCD	SCLC
Anti-AChR [‡]	MG	Thymoma
Anti-nAChR [‡]	Subacute pandysautonomia	SCLC, others
Anti-GAD	Stiff-person syndrome, cerebellar ataxia, limbic encephalitis, other	Thymoma, other

Table 2: Antibodies, paraneoplastic syndromes, and associated cancers

Paraneoplastic antibodies*, syndromes, and associated cancers

Antibody	Syndrome	Associated cancers
Well-characterized paraneoplastic antibodies ¶		
Anti-Hu (ANNA-1)	Encephalomyelitis including cortical, limbic, and brainstem encephalitis; cerebellar degeneration; myelitis; sensory neuronopathy; and/or autonomic dysfunction	SCLC, other
Anti-Yo (PCA-1)	Cerebellar degeneration	Gynecologic, breast
Anti-Ri (ANNA-2)	Cerebellar degeneration; brainstem encephalitis; opsoclonus-myoclonus	Breast, gynecologic, SCLC
Anti-Tr (DNER)	Cerebellar degeneration	Hodgkin lymphoma
Anti-CV2/CRMP5	Encephalomyelitis, cerebellar degeneration, chorea, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma proteins ^Δ (Ma1, Ma2)	Limbic, hypothalamic, brainstem encephalomyelitis (infrequently cerebellar degeneration)	Testicular germ cell tumors, lung cancer, other solid tumors
Anti-VGCC [◇]	Cerebellar degeneration	SCLC
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis	Breast, lung cancer
Anti-PCA-2 (MAP1B)	Peripheral neuropathy, cerebellar ataxia, encephalopathy	SCLC
Antirecoverin [§]	Cancer-associated retinopathy	SCLC
Antibipolar cells of the retina [¥]	Melanoma-associated retinopathy	Melanoma
Partially characterized paraneoplastic antibodies ¶		
Anti-Zic 4	Cerebellar degeneration	SCLC
Anti-ANNA-3	Sensory neuronopathy, encephalomyelitis	No tumor or Hodgkin lymphoma

ANNA: antineuronal nuclear antibody; SCLC: small cell lung cancer; PCA: Purkinje cell antibody; DNER: Delta/Notch-like epidermal growth factor-related receptor; CRMP5: collapsin-responsive mediator protein 5; VGCC: voltage-gated calcium channel.

* Antibodies that are almost exclusively found in patients with cancer and neurologic symptoms.

¶ Well-characterized antibodies are those directed against antigens whose molecular identity is known, or that have been identified by several investigators.^[1]

Δ Antibodies to Ma2: younger than 45 years, usually men with testicular germ cell tumors; older than 45, men or women with lung cancer and less frequently other tumors. Ma1 antibodies: often associated with tumors other than germ cell neoplasms and confer a worse prognosis, with more prominent brainstem and cerebellar dysfunction.

◇ The identification of these antibodies in a patient with cerebellar dysfunction indicates paraneoplasia, almost always associated with an SCLC. These antibodies are also found in patients with Lambert-Eaton myasthenic syndrome, in which only approximately 50% of patients have cancer.

§ Other antibodies reported in a few or isolated cases include antibodies to tubby-like protein and the photoreceptor-specific nuclear receptor.

¥ Target antigens include transducin-b, rhodopsin, and arrestin, among others.

Panel: Diagnostic criteria of PND of the CNS³⁸

Definite PND

- 1 Classic syndrome with cancer diagnosed within 5 years of neurological symptom development
- 2 Non-classic syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission
- 3 Non-classic syndrome with cancer diagnosed within 5 years of neurological symptom development and positive neuronal antibodies
- 4 Neurological syndrome (classic or not) without cancer and with well characterised antineuronal antibodies (Hu, Yo, CV2/CRMP5, Ri, Ma2, or amphiphysin)

Possible PND

- 1 Classic syndrome with high risk of cancer, without antineuronal antibodies
- 2 Neurological syndrome (classic or not) without cancer and with partly characterised antineuronal antibodies
- 3 Non-classic syndrome with cancer diagnosed within 2 years of neurological symptom development, without neuronal antibodies

Paraneoplastic rhombencephalitis

- Neurologic symptoms may be antedated by non-specific dizziness, nausea which raising the suspicion of peripheral vestibular dysfunction.
However, followed soon by progressive rapidly ataxia, diplopia, dysarthria, dysphagia.
- Symptoms may stabilize for weeks to months, but may be severely affected by then.

Paraneoplastic rhombencephalitis

Investigation

- MRI
 - usually normal in early, but later may show cerebellar atrophy.
- CSF
 - may increase in protein, but cell count is usually increased.

Treatment

- corticosteroid, IVIg, Rituximab.

Prognosis

- poor prognosis.

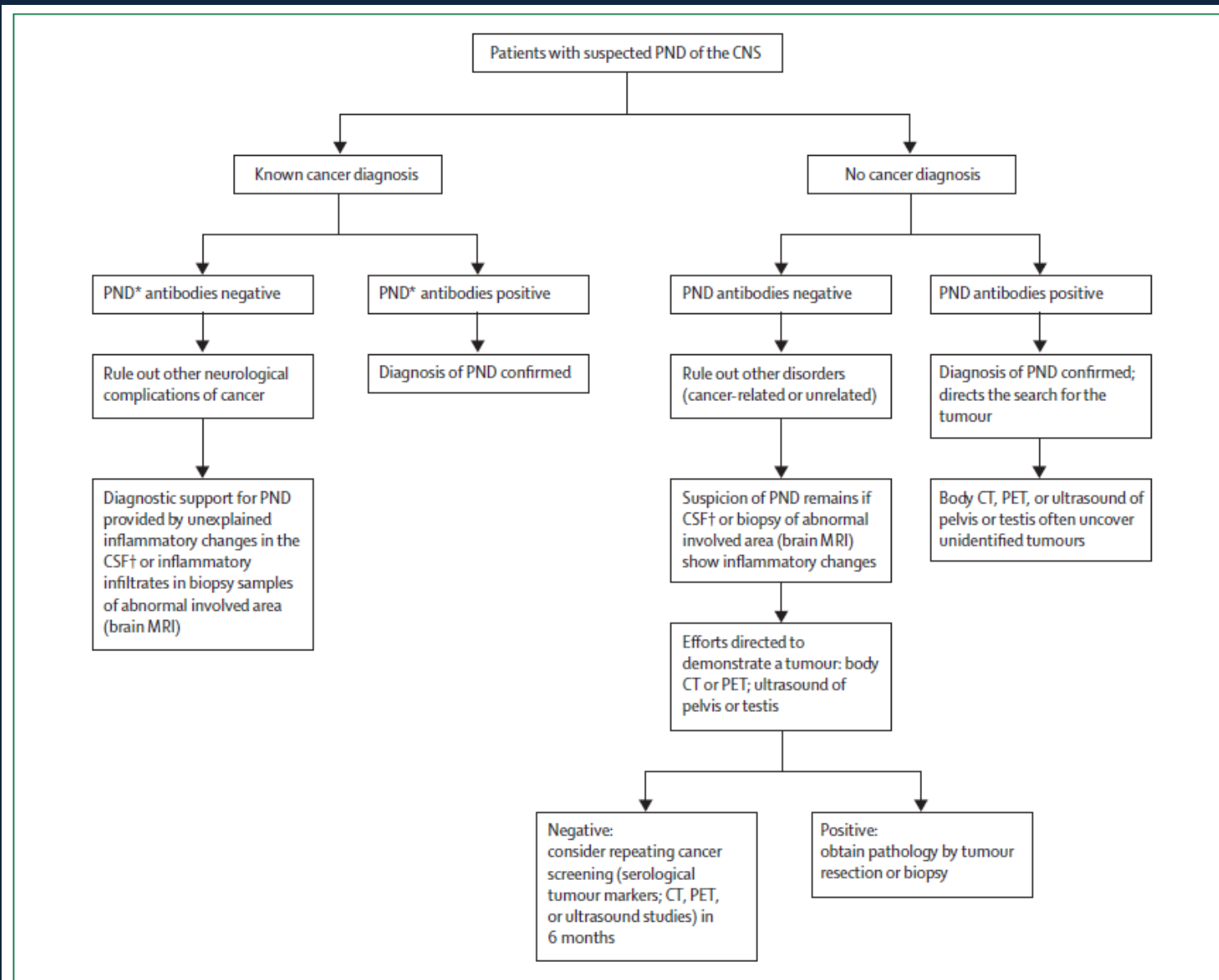


Figure 1: Initial diagnostic approach to PND of the CNS

*Well characterised onconeural antibodies. †Lymphocytic pleocytosis, high IgG index, and oligoclonal bands with or without high protein concentration.

Conclusion

- MRI is the preferred imaging method to help establish a diagnosis of rhombencephalitis but finding in most case **not conclusive for a final diagnosis**.
- Certain clinical, cerebrospinal fluid, and imaging **characteristics** that are commonly seen in some of these etiologies can guide us in the first approach to the etiologic diagnosis of rhombencephalitis.
- CSF analysis results may be key to diagnosing **infectious rhomboencephalitis**.

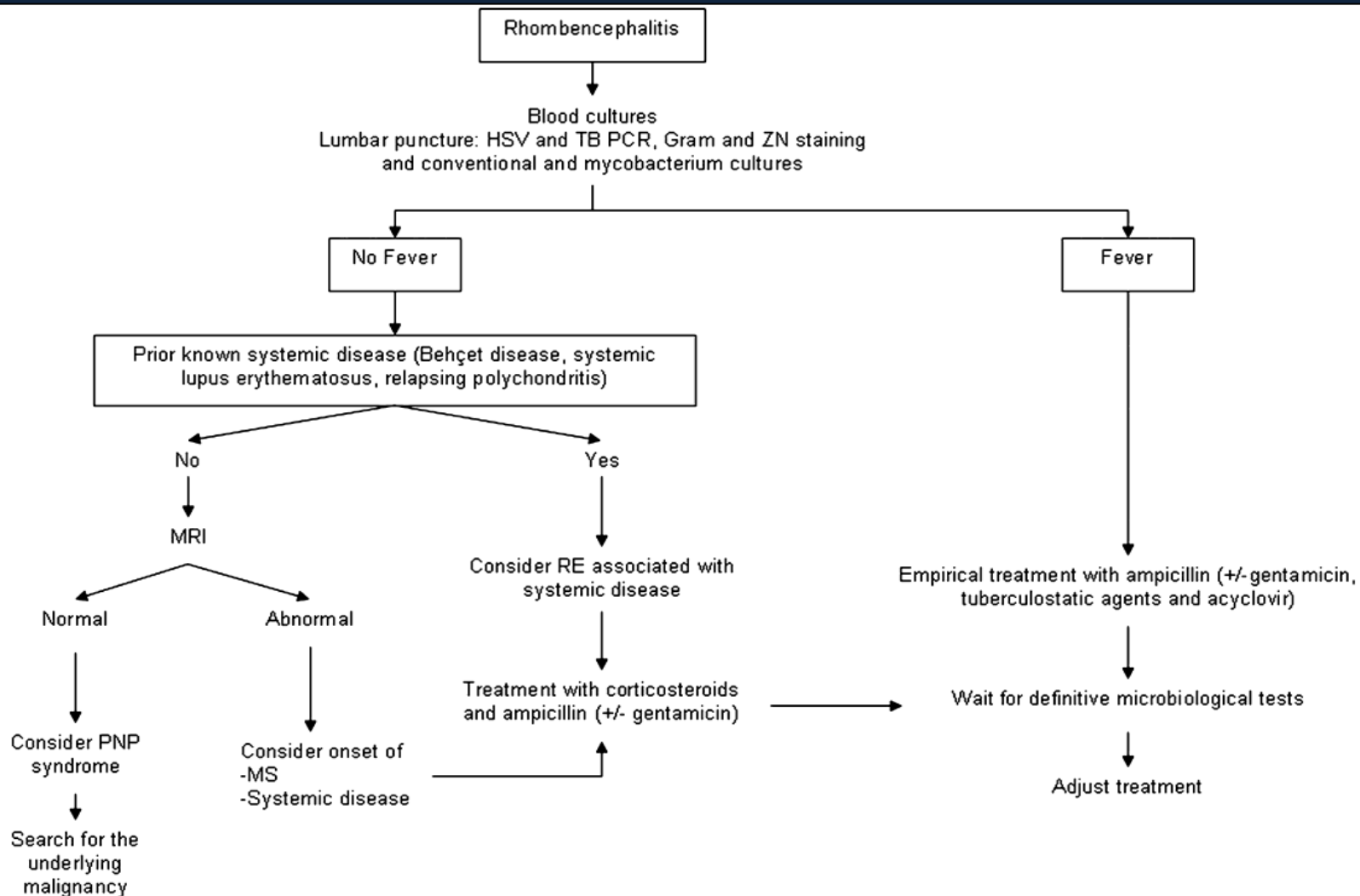


FIGURE 2. Diagnostic algorithm for RE. Abbreviations: HSV = herpes simplex virus, PNP = paraneoplastic, TB = tuberculosis, ZN = Ziehl-Neelsen.

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CLIPPERS

Bickerstaff brainstem encephalitis

Multiple sclerosis

CLIPPERS

- **Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)** represents a rare central nervous system (CNS) inflammatory disorder involving predominantly the pons.
- first described in 2010 as a distinct form of **brainstem encephalitis centred on the pons** which is characterized by a predominant T cell pathology, and **responsive to immunosuppression with glucocorticosteroids (GCS)**

Pathogenesis

- still unknown
- clinico-radiological response to GCS-based immunosuppressive therapies suggest an immune-mediated /inflammatory process
- may be microstructures localized preferentially in the pons and peripontine regions, which are not characterized to date
- potential predispositions or triggering events are unclear
- Elevated serum immunoglobulin (Ig)E levels in several cases without hypereosinophilia, skin rash, hx of allergy/asthma
- an allergic trigger factor may contribute to the evolution of the perivascular inflammation process
- perivascular and T cell predominant inflammatory cell infiltrates in affected CNS lesions

Diagnosis

- no validated diagnostic criteria
- based on core features
 - 1) clinical
 - 2) radiological
 - 3) GCS response
 - 4) histopathological
- laboratory and CSF investigation for exclude alternative condition

I. Clinical

- Subacute progressive ataxia and diplopia
- A range of other clinical features referable to brainstem pathology plus cognitive and spinal features occur in some patients

II. Radiological

- Numerous punctate or nodular enhancing lesions bilaterally within at least two of the three following anatomical locations: pons, brachium pontis, cerebellum
- Individual radiological lesions are small but may coalesce to form larger lesions (mass effect may suggest an alternative diagnosis)
- Lesions may occur in the spinal cord, basal ganglia or cerebral white matter but should be decreasing density with increasing distance from the pons/hindbrain
- Absence of the following radiological features:
 - Restricted diffusion on diffusion weighted imaging
 - Marked hyperintensity on T2-weighted images
 - Abnormal cerebral angiography

III. Glucocorticosteroid responsiveness

- Prompt and significant clinical and radiological response to glucocorticosteroids

IV. Histopathological

- White matter perivascular lymphohistiocytic infiltrate with or without parenchymal extension
- Infiltrate contains predominantly CD3 and CD4 lymphocytes
- Absence of the following histopathological characteristics:
 - Monoclonal or atypical lymphocyte population
 - Necrotizing granulomas or giant cells
 - Histological features of vasculitis

Differential diagnoses should be excluded

e.g. neurosarcoidosis, Sjögren's syndrome, neuro-Behçet's disease, MS, ADEM, NMO, Bickerstaff encephalitis, other autoimmune encephalitides, CNS vasculitis, CNS infections, histiocytosis, lymphoma, glioma, paraneoplastic syndromes

Clinical manifestation

- male = female
- age 13 to 86 years (mean 52.4, 43.4 years from 2 large series)
- subacutely over several weeks
- varying symptomatology related to brainstem, cranial nerve and/or cerebellar dysfunction
- Possible additional features such as long tract affections and/or a spinal cord syndrome
- Meningism, alterations of quantitative consciousness, systemic symptoms, symptoms related to connective tissue diseases, rheumatic disorders or Behçet are generally not a feature of CLIPPERS patients.

Neuroimaging

MRI

- faint on T2W, FLAIR : multiple 'punctate' and/or 'curvilinear' with gadolinium enhancement (salt-and-pepper appearance) the pons with/without spread into the cerebellar peduncles and the cerebellum
- may extend
 - caudally : medulla, cervicothoracic spinal cord
 - rostrally : midbrain, supratentorial (thalamus, internal capsule, basal ganglia, corpus callosum, cerebral white matter)
- Lesions are typically less numerous and smaller as distance from the pons increases
- usually cause no mass effect and minimal or no vasogenic edema
- normal angiography, no changes seen in vasculitis disorders

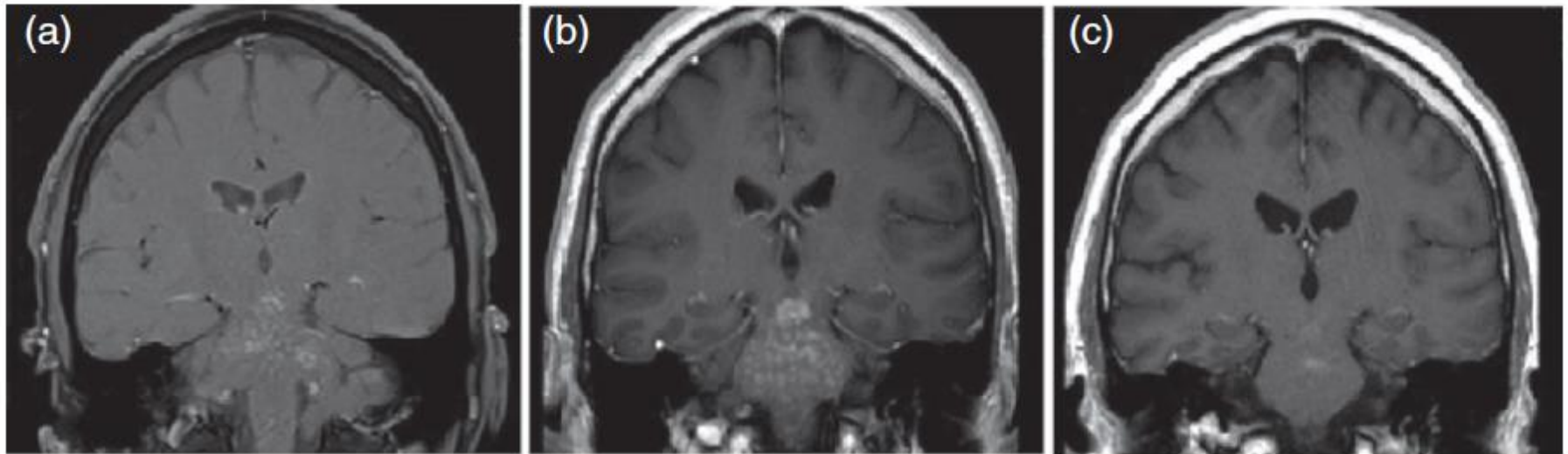
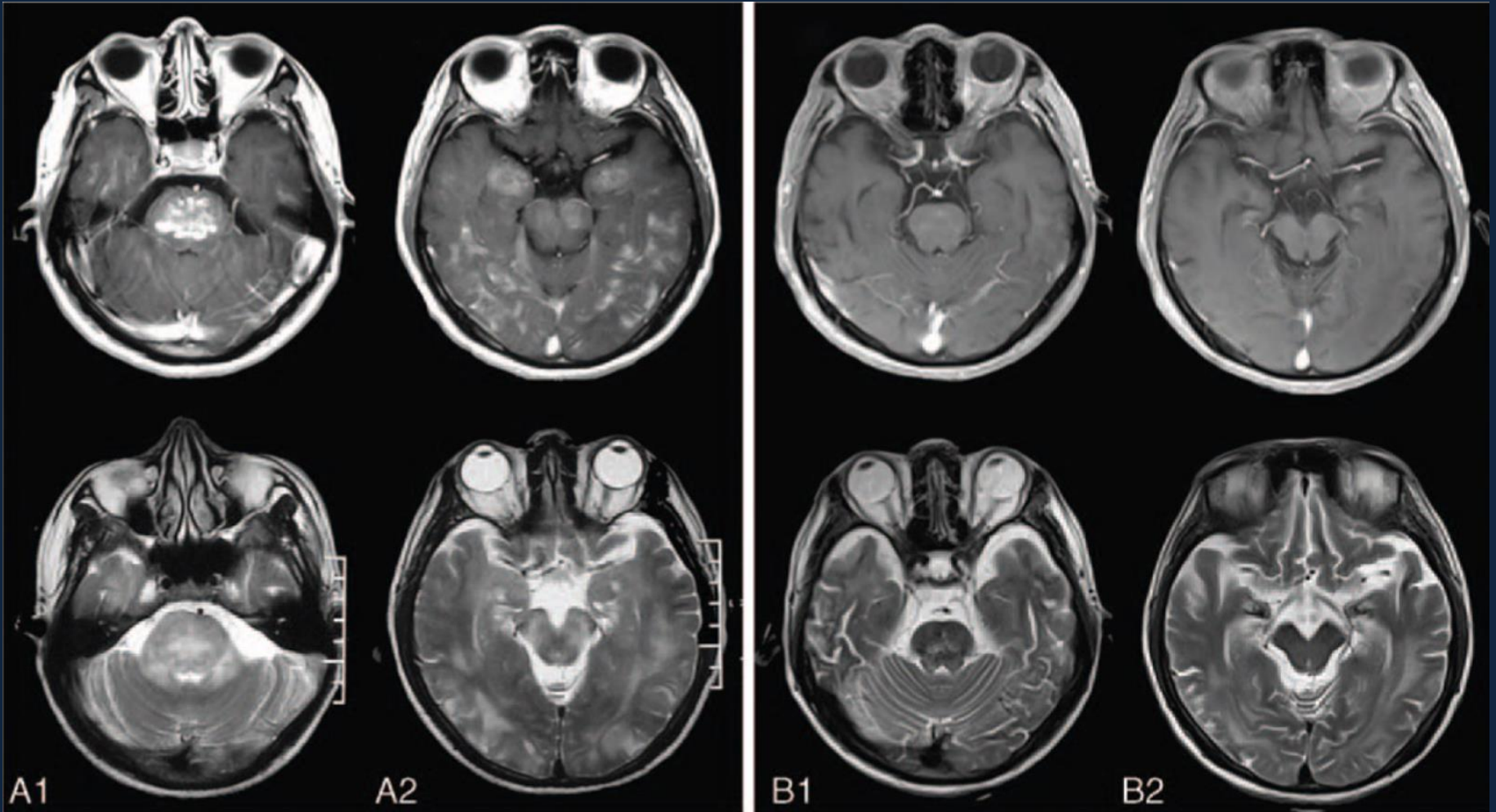


Fig. 1. Brain magnetic resonance imaging (MRI) of a patient with CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) (coronar post-contrast T1-weighted images). (a) Initial MRI shows foci of gadolinium enhancement with a punctate and curvilinear pattern predominantly in the pons, the cerebellar peduncles and the mesencephalon. (b) Progression of gadolinium-enhancing lesions 6 weeks later. (c) Following oral glucocorticosteroids (GCS) and additive methotrexate therapy, a follow-up MRI performed 5 months later shows marked reduction in the extent of gadolinium enhancing lesions. Figures reproduced from [25], with kind permission of Springer Science + Business Media.



Neuroradiological images on admission and 3 weeks after steroid therapy and pathological findings from brain biopsy. Representative T1-weighted imaging with gadolinium enhancement (top row) and corresponding T2-weighted imaging (bottom row) on cervical MRI demonstrate changes of MRI features after steroid therapy. The images performed on admission show punctate and nodular enhancing lesions in the bilateral pons, the basal ganglia, the midbrain, the pontine brachium, and extensively in cerebral white matter, with a perivascular enhancement pattern (A1, A2). A decrease in the number and extent of pathology is observed on a cervical MRI scan after steroid treatment (B1, B2). In pathology findings from the parietal lobe specimen, hematoxylin and eosin staining showed lymphocytic inflammatory infiltration with perivascular and parenchymal cells (C; $\times 100$). The lymphocytic infiltrates were mainly composed of CD3⁺ T lymphocytes (D; $\times 100$). Proliferation rate, detected by Ki67 antigen immunohistochemistry, was about 10% (E; $\times 100$). MRI = magnetic resonance imaging.

CSF analyses and CNS histopathology

CSF analyses

- **cell count** : normal / mild pleocytosis (5-50 : lymphocytic pattern)
- **protein** : normal / mild to moderately elevated

CNS neuropathology

- **perivascular, CD4-dominated T cell or lymphohistiocytic infiltrate**
- basically the white matter, but also the grey matter and scantily leptomeningeal tissue.
- The perivascular distribution affects both **small arteries and veins**
- histological features of **vasculitis not be found** (fibrinoid necrosis, fibrin thrombi)

Table 2. Clinical features of CLIPPERS*.

Symptoms/signs referable to brainstem-, cranial nerve- and/or cerebellar dysfunctions

- *Ataxia* (gait ataxia, stance ataxia, truncal ataxia, limb ataxia)
- *Dysarthria*
- *Dysphagia*
- *Dysgeusia*
- *Diplopia/oculomotor abnormalities* (oculomotor palsies, gaze palsy, internuclear ophthalmoplegia, one-and-a-half syndrome, disturbances of saccadic eye and slow eye pursuit)
- *Nystagmus* (spontaneous, gaze evoked, upbeat, downbeat, rotational nystagmus)
- *Altered sensation or tingling of the face* (facial tingling, par-/dysaesthesias, hypaesthesia), altered sensation of the scalp, palate or tongue
- *Facial nerve palsy*
- *Vertigo*, hyperacusis, hearing impairment, tinnitus
- Hoarse voice
- Tongue weakness
- Hiccup
- Nausea

Symptoms/signs referable to long tract affections and/or spinal cord syndrome

- *Paraparesis*, tetraparesis, hemiparesis, paresis of a single extremity
- *Spasticity, long tract motor signs* (extensor plantar response, hyperreflexia)
- *Altered sensation/sensory loss of extremities* (bilateral, unilateral; hemi-hypaesthesia, tetra-hypaesthesia, hypoaesthesia in single limbs)
- Decreased vibration sense
- Neurogenic bladder (urine retention/incontinence)

Cognitive dysfunction

- *Cognitive deficits, dysexecutive syndrome, psychomotor slowing*
- Frontal disinhibition reflexes

Possible additional features

- *Pseudobulbar affect* (pathological/involuntary crying or laughter, labile affect)
- Tremor (action, intention, Holmes tremor)
- Headaches
- Abnormal fatigue

Generally absent symptoms/signs

- Quantitative consciousness
- Fever, night sweating, weight loss
- Lymphadenopathy
- Arthritis
- Uveitis
- Oral and/or genital ulcers; pathergia
- Sicca syndrome (keratoconjunctivitis sicca, xerophthalmia),
- Meningism
- Altered symptoms of hypothalamic dysfunction (polydipsia/polyuria)

Management and prognosis

- pulse methylprednisolone 1 gm iv for 5 days follow by oral GCS
- GCS sparing immunosuppressants : monotherapy or combined with oral GCS but many monotherapy not capable for maintaining remission
- IVIg is not effective
- use of GCS, usually show early and marked clinical improvement within days, in many cases the restitution remain incomplete
- The clinical course without specific treatment seems to be relapsing–remitting in nature
- Progressive clinical worsening is seen during relapses, which may leave residual neurological sequelae

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CLIPPERS

Bickerstaff brainstem encephalitis

Multiple sclerosis

Bickerstaff brainstem encephalitis

- **Fisher-Bickerstaff syndrome** is a rare immune-mediated condition believed to be one of a number of conditions sharing a similar immunological mechanism, and collectively termed **anti-GQ1b IgG antibody syndrome**.
- Associated with antecedent illness caused by URI was present in 60% to 80% of the patients

Epidemiology

- Incidence of GBS in Western countries ranges from 0.89 to 1.89 cases per 100 000 person-years.
- In comparison with GBS, both BBE and FS are relatively rare.
- There are no epidemiology data specifically looking at the prevalence and incidence of FS or BBE. Any available data have been extracted from existing GBS population studies.
- Western countries, FS incidence 1%–5% of GBS cases.
- Asian countries, FS incidence such as Taiwan (19%) and Japan (25%).
- There have been no epidemiology studies of BBE with accurate incidence figures to date but suggests that BBE is less frequent.

Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. *Neuroepidemiology* 2011;36:123–33.

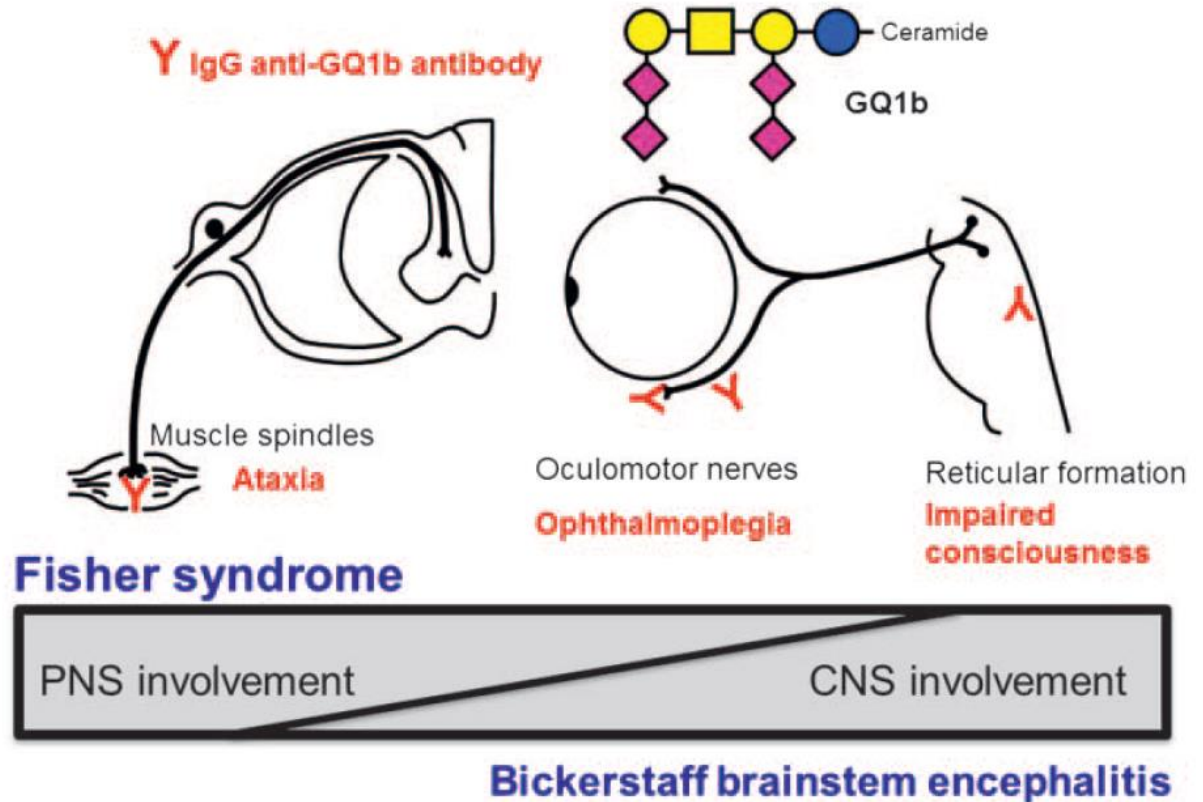
Guillain-Barré Syndrome: F.A. Davis. FA Davis, Philadelphia, 1991.

Guillain-Barré syndrome in Taiwan: a clinical study of 167 patients. *J Neurol Neurosurg Psychiatry* 1997;63:494–500.

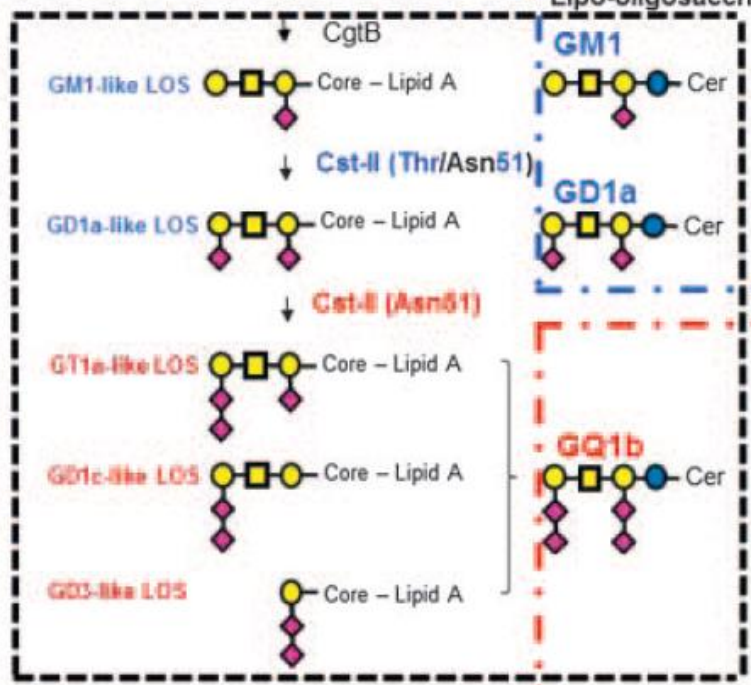
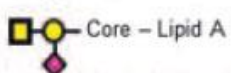
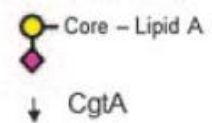
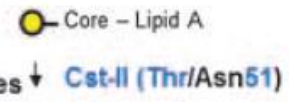
Clinical features and prognosis of Miller Fisher syndrome. *Neurology* 2001;56:1104–6.

Pathophysiology

Figure 1 Fisher–Bickerstaff syndrome. The GQ1b antigen is highly expressed in the oculomotor, trochlear and abducens nerves, muscle spindles in the limbs, and probably reticular formation in the brainstem. Infection by microorganisms bearing the GQ1b epitope may induce production of immunoglobulin G (IgG) anti-GQ1b antibodies in susceptible patients. The binding of anti-GQ1b antibodies to GQ1b antigens expressed on the relevant cranial nerves and muscle spindles induces Fisher syndrome. In some cases, the anti-GQ1b antibodies may also enter the brainstem and bind to GQ1b, inducing Bickerstaff brainstem encephalitis. A continuous spectrum exists between these conditions presenting with variable central and peripheral nervous system (CNS and PNS) involvement. Modified from reference⁶ with permission.

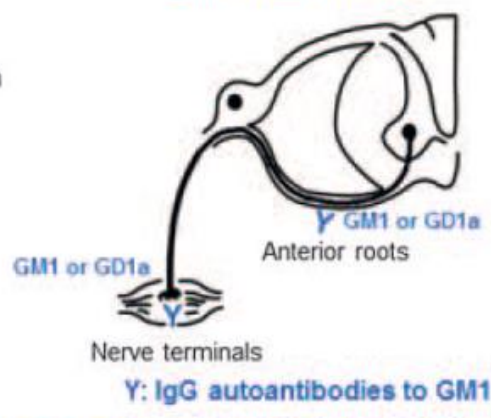


Biosynthesis of
Ganglioside-like
Lipo-oligosaccharides



Guillain-Barré syndrome

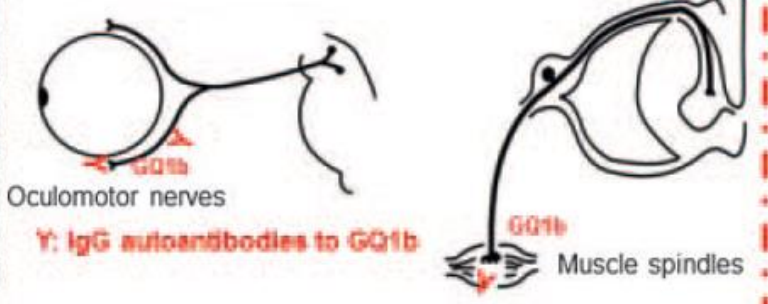
LIMB WEAKNESS



Molecular Mimicry between
Gangliosides and
Lipo-oligosaccharides

OPHTHALMOPLÉGIA

ATAXIA



Fisher syndrome

● Galactose ■ N-Acetylgalactosamine ◆ N-Acetylneuraminic acid ● Glucose Cer Ceramide

Bickerstaff brainstem encephalitis

Clinical manifestation of anti-GQ1b IgG antibody syndrome.

PNS [Miller Fisher syndrome triad]

- **Ophthalmoparesis** : CN3, 4, 6
- **Ataxia** : muscle spindle
- **Areflexia** : muscle spindle

CNS [Bickerstaff brainstem encephalitis]

- **Alteration of consciousness** : brainstem (reticular formation)
- **Hyperreflexia** : brainstem

Table 1 Anti-GQ1b antibody syndrome

Subtypes	Signs required for diagnosis								
	External ophthalmoplegia	Ptosis	Mydriasis	Oropharyngeal palsy	Ataxia	Impaired consciousness or hyperreflexia	Areflexia or hyporeflexia	Arm weakness	Leg weakness
Fisher–Bickerstaff syndrome									
Fisher syndrome	✓				✓		✓		
Incomplete forms									
Acute ophthalmoparesis (without ataxia)	✓								
Acute ptosis		✓							
Acute mydriasis			✓						
Acute oropharyngeal palsy				✓					
Acute ataxic neuropathy (without ophthalmoplegia)					✓				
Ataxic Guillain–Barré syndrome					✓				
Acute sensory ataxic neuropathy					✓				
Bickerstaff brainstem encephalitis	✓				✓	✓			
Pharyngeal-cervical-brachial weakness				✓				✓	
Overlap									
Fisher–Bickerstaff syndrome overlapped by pharyngeal-cervical-brachial weakness				✓				✓	
Fisher–Bickerstaff syndrome overlapped by Guillain–Barré syndrome				✓				✓	✓

Diagnostic approach

- **Diagnosis** of FS/BBE lies in the recognition of unique set of clinical features.
 - antecedent illness associated with the anti-GQ1b syndrome.
- **Exclude** of possible differential diagnosis which include brainstem.
 - stroke, others etiology of rhombencephalitis.

Investigations

- Brain imaging : MRI brain
 - : transiently high T2 signal with little if any enhancement involves the brainstem and basal ganglia.
 - : Typically some minor restricted diffusion.
- Electrophysiological examinations (axonopathy)
- CSF albuminocytological dissociation
 - : first week - 37% of FS, 25% of BBE
- CSF pleocytosis
 - : first week - 4% of FS, 32% of BBE

Fig 1: Initial MRI of the Brain (FLAIR SCAN)

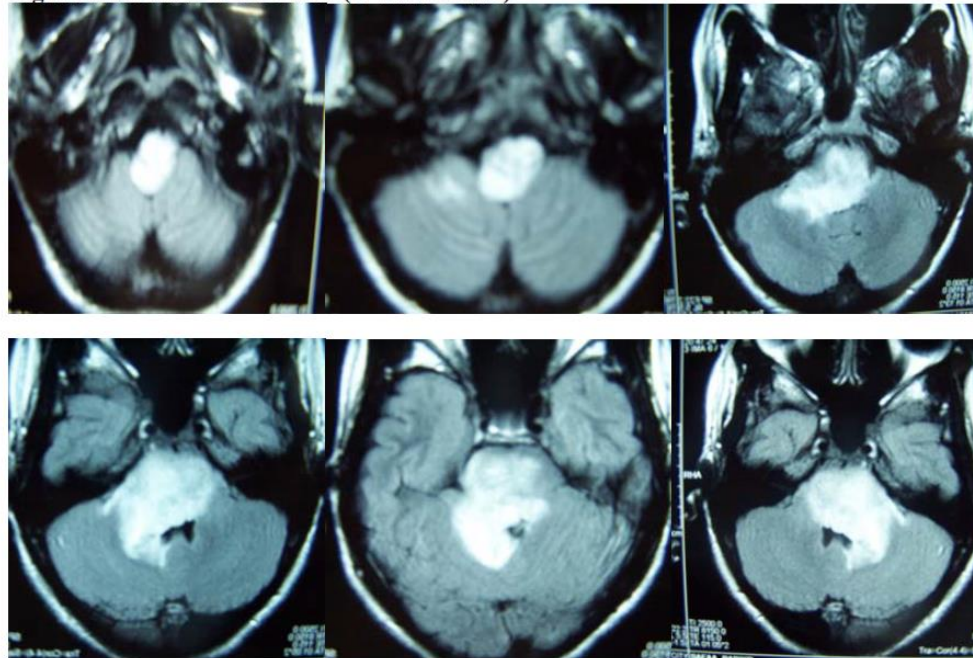
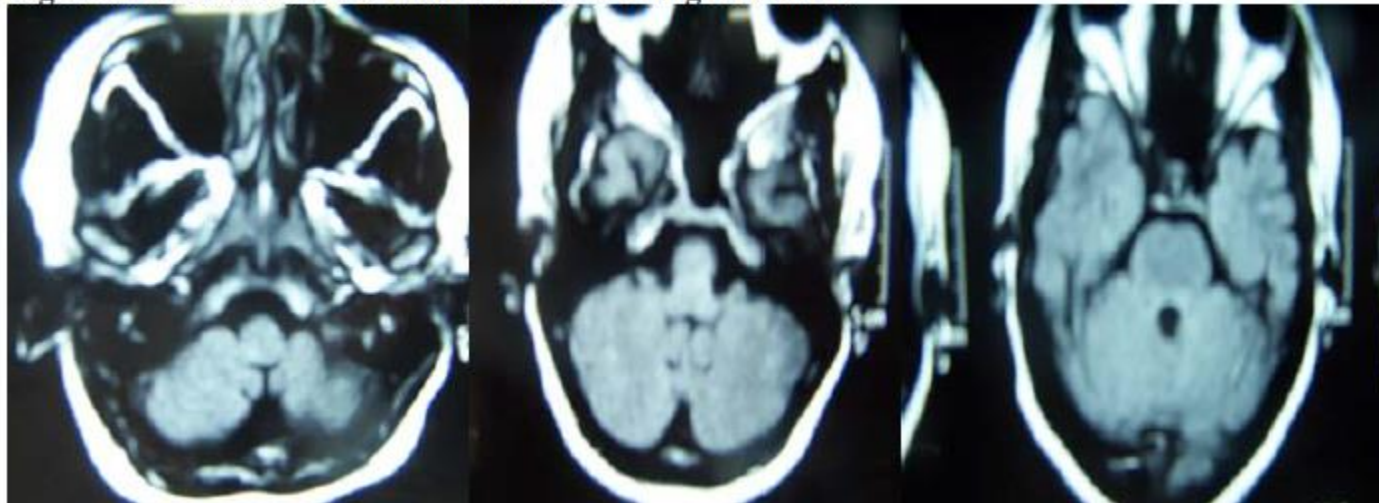


Fig 2: MRI of the Brain 5 months after starting treatment



Management and prognosis

- Although symptoms are severe, the condition is usually self-limiting with a good prognosis, complete remission by 6 months.
- IVIg or PLEX was slight hastening in recovery although the final outcome remained unchanged.
- Current recommendation would be not to treat.
- Indication to treat : more extensive end of the anti-GQ1b spectrum, overlap with PCB or GBS, both (IVIg, PLEX) have been established as efficacious in improving outcome based on RCT in GBS.
- Typically monophasic, recurrent episode are rare and the time between relapses varies. Each episode may be similar in its clinical characteristics.

OUTLINE

- Introduction
- Etiology
- Overview clinical manifestation
- Overview Investigation
 - CSF analysis
 - Neuroimaging

Rhombencephalitis

- Infectious rhombencephalitis
- Autoimmune rhombencephalitis
- Paraneoplastic rhombencephalitis

CLIPPERS

Bickerstaff brainstem encephalitis

Multiple sclerosis

Multiple sclerosis

- Multiple sclerosis (MS) is autoimmune-mediated demyelination in which environmental factors act upon genetically susceptible individuals
- Estimated 2.5 million people in world have MS
- Most common disabling CNS disease of young adults
1:1000 in Western world
- age 20-40, peak onset 30
- Male : Female = 1:2

ตารางที่ 3 เกณฑ์การวินิจฉัยโรค MS (ดัดแปลงจาก 2017 McDonald criteria)⁽⁵⁾

น้ำหนักคำแนะนำ	การประเมิน	ผลการประเมิน วันที่.....
		ใช่
++	1. หลักฐานการมีพยาธิสภาพ 2 ตำแหน่งมี 2 ใน 4 ข้อ (เกณฑ์กำหนดการกระจายของโรค) dissemination in space ○ รอยโรคที่สมองบริเวณรอบช่องโพรงสมอง (periventricular) อย่างน้อย 1 รอย [†] ○ รอยโรคที่สมองบริเวณ juxtacortical อย่างน้อย 1 รอย ○ รอยโรคที่สมองบริเวณ infratentorial อย่างน้อย 1 รอย ○ รอยโรคที่ไขสันหลัง ในภาพ T2W อย่างน้อย 1 รอย	<input type="checkbox"/>
++	2. หลักฐานการมีพยาธิสภาพ 2 ครั้งขึ้นไป มี 1 ใน 2 ข้อ (เกณฑ์กำหนดการกระจายของโรค) dissemination in time ○ ภาพ MRI ครั้งแรก พบรอยโรค T2W และ/หรือชนิด Gd+ ที่ตำแหน่งต่างจากตำแหน่งที่เกิดอาการ ○ ภาพ MRI ที่ตรวจติดตาม (follow up) โดยไม่จำกัดช่วงห่างของการตรวจ แล้วพบรอยโรคใหม่ชนิด T2W หรือชนิด Gd+ ○ หรือตรวจพบ oligoclonal bands	<input type="checkbox"/>
++	ตรวจไม่พบ AQP4-IgG ด้วยวิธี cell-based assay	<input type="checkbox"/>
++	ไม่พบสาเหตุอื่นที่อธิบายอาการได้ เช่น SLE, Behcet's disease, antiphospholipid syndrome, lymphoma	<input type="checkbox"/>
สรุปการวินิจฉัย: เข้าได้กับ Multiple sclerosis (ต้องตอบ 'ใช่' ทุกข้อ)		<input type="checkbox"/>

[†]กรณีผู้ป่วยอายุมากกว่า 50 ปีหรือมีปัจจัยเสี่ยงโรคหลอดเลือดสมองรวมถึงโรคไมเกรน แนะนำให้พิจารณาคำแนะนำ periventricular area มากกว่า 1 รอย

Neuroimaging

MRI

- **morphology** : linear, round, or ovoid
- **best diagnostic clue** : multiple **perpendicular calloseseptal T2 hyperintensities** "Dawson fingers"
- **Location**
 - bilateral, asymmetric linear/ovoid FLAIR hyperintensities**
 - : > 85% periventricular/perivenular
 - : 50-90% calloseseptal interface
 - : also commonly involve subcortical U-fiber, brachium pontis, **brainstem**, spinal cord
- **transient enhancement during active demyelination** (>90% disappear within 6 months)
 - nodular (68%) ring (23%)

THE MS LESION CHECKLIST

Description of Lesion Types	Present = yes Absent = no (Circle)	Note Number of Lesions
<p>Nerve root entry zone. The lesions that track along nerve roots, especially the trigeminal nerve root, favor an inflammatory over vascular etiology. In an active MS lesion, enhancement may extend from parenchyma into nerve proper.¹⁶</p>	Yes No	
<p>Middle cerebellar peduncle. Middle cerebellar peduncle (MCP) involvement in MS is seen frequently, but less than in the body of the pons.^{17,18}</p>	Yes No	
<p>Medial longitudinal fasciculus. This tract is commonly affected in MS both clinically (internuclear ophthalmoplegia [INO]) and on MRI, however, vascular etiology is more common. Bilateral internuclear ophthalmoplegia may be somewhat more common in MS compared to stroke but is seen in many conditions.¹⁹</p>	Yes No	
<p>Other brainstem lesions adjacent to cerebrospinal fluid border. "With remarkable regularity the brainstem lesions [are] contiguous with the inner and outer cerebrospinal fluid (CSF) borders."⁴</p>	Yes No	
<p>Cerebellar hemisphere. Demyelinating cerebellar lesions are not contiguous with the CSF border, but appear within the deep cerebellar white matter. The cerebellum is often spared in vascular disease, but is commonly affected in MS, especially when the brainstem is involved.^{4,16}</p>	Yes No	
<p>Inferior temporal lobe. Another area of white matter that is preferentially affected in MS compared to vascular disease.²</p>	Yes No	
<p>Lesions adjacent to lateral ventricle—Dawson's fingers. "Wedge-shaped areas with broad base to the [lateral] ventricle, and extensions into adjoining tissue in the form of finger-like processes or ampullae, in each of which a central vessel could usually be found."²³ Frontal caps and bands along ventricular surface are normal signs of aging and should not be confused with periventricular demyelinating lesions.¹⁰</p>	Yes No	
<p>Corpus callosum. Demyelination at the callosal-septal interface may take the form of discrete lesions or more diffuse lumpy-bumpy appearance (ie, dot-dash sign), which is seen on multiple sagittal FLAIR images, in contrast to the smooth appearance of the subcallosal vein that is usually only seen on a single sagittal image.^{20,21}</p>	Yes No	
<p>U-fibers (arcuate fibers). U-fiber lesions that track along arcuate fibers are particularly characteristic of demyelination and are not seen in normal aging or vascular disease.²²</p>	Yes No	
<p>Other cortical/juxtacortical lesions. Plaques in cortex and at junction of cortex and white matter are very common in MS. A recent study recommended combining cortical and juxtacortical lesions for purposes of MS diagnosis.²³ Cortical lesions may be better appreciated on double inversion recovery (DIR) sequence, which is not routinely available.</p>	Yes No	



Figure 1. Nerve root entry zone lesion. Arrow: Lesion along left trigeminal root; the trigeminal nerves are seen in the prepontine cisterns.

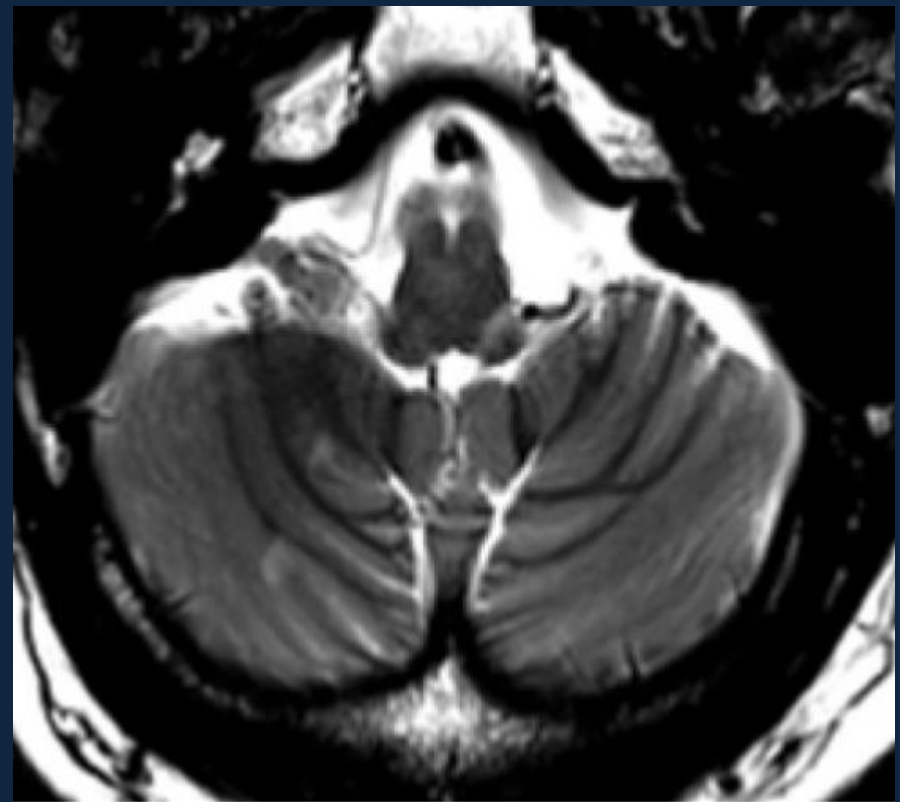


Figure 2. Cerebellar hemisphere lesions. Two small demyelinating lesions are seen in the right cerebellar hemisphere. Note there is also a typical peripheral brainstem lesion that appears to track along the left glossopharyngeal nerve root.

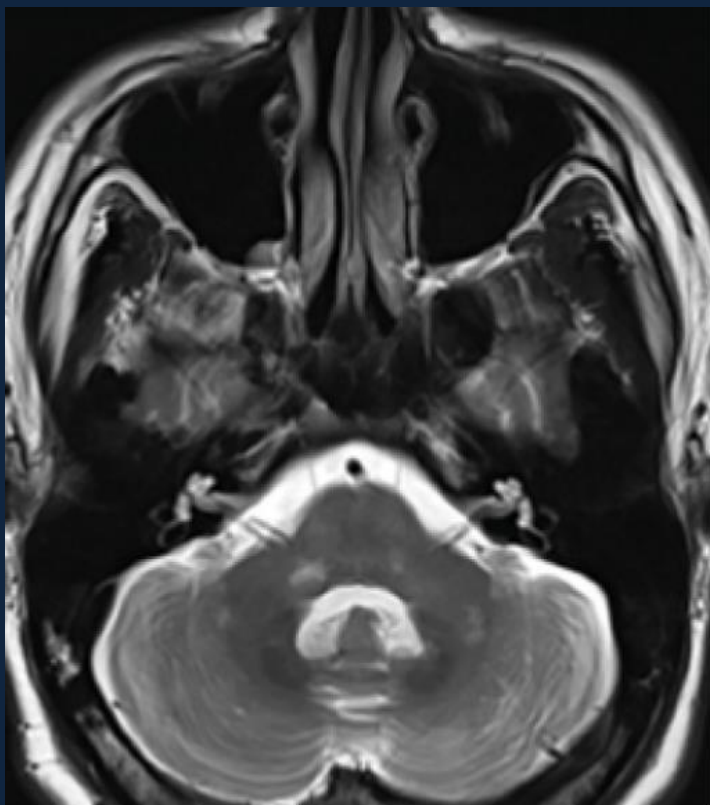


Figure 3. Middle cerebellar peduncle lesions. Bilateral middle cerebellar peduncle (MCP) lesions as well as lesions within basilar pons and cerebellar hemispheres.

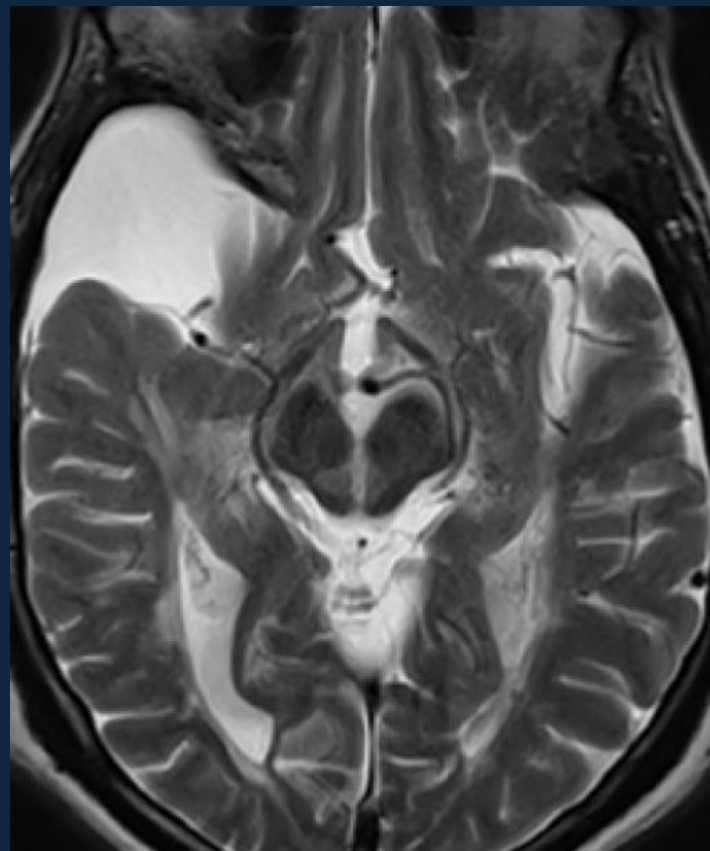


Figure 4. Medial longitudinal fasciculus lesion. A vertical lesion in the central midbrain involves the medial longitudinal fasciculus near the dorsal edge and spreads all the way to the ventral surface giving an appearance of a split midbrain. The right temporal lobe subarachnoid cyst is an incidental finding.

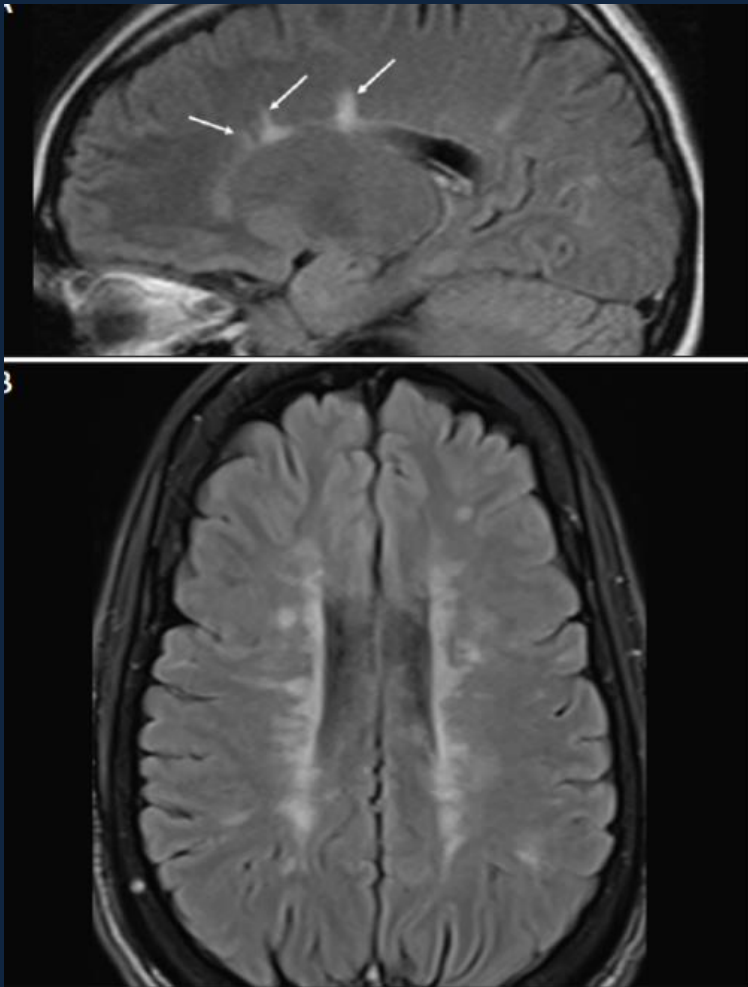


Figure 6. Lesions adjacent to lateral ventricle (Dawson's fingers). MRI from a patient with early MS shows a few Dawson's fingers on sagittal fluid-attenuated inversion recovery (FLAIR) image (A). MRI from a patient with more advanced MS shows numerous Dawson's fingers on axial FLAIR image (B).

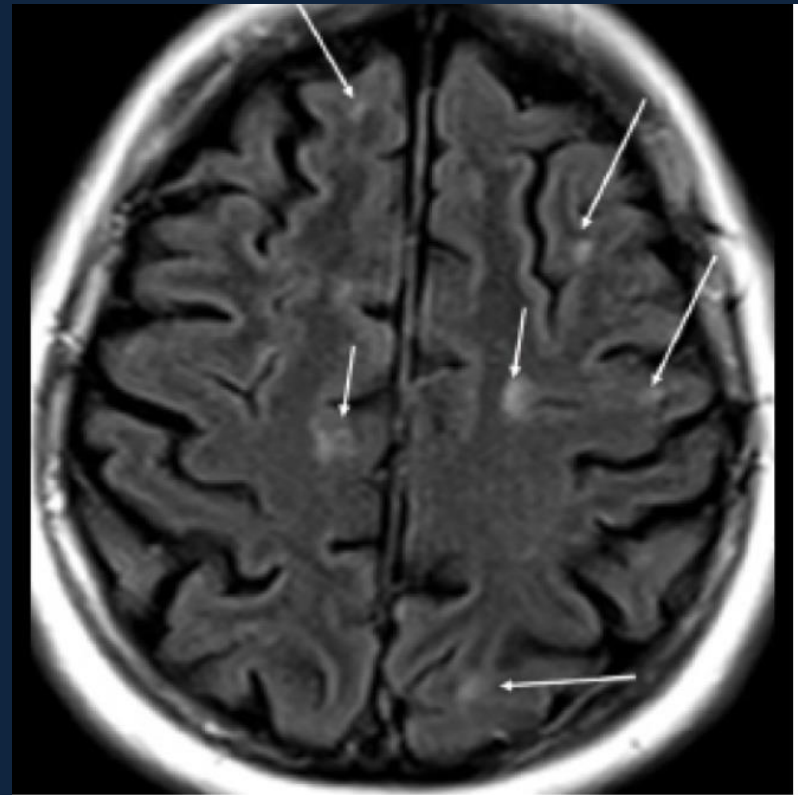
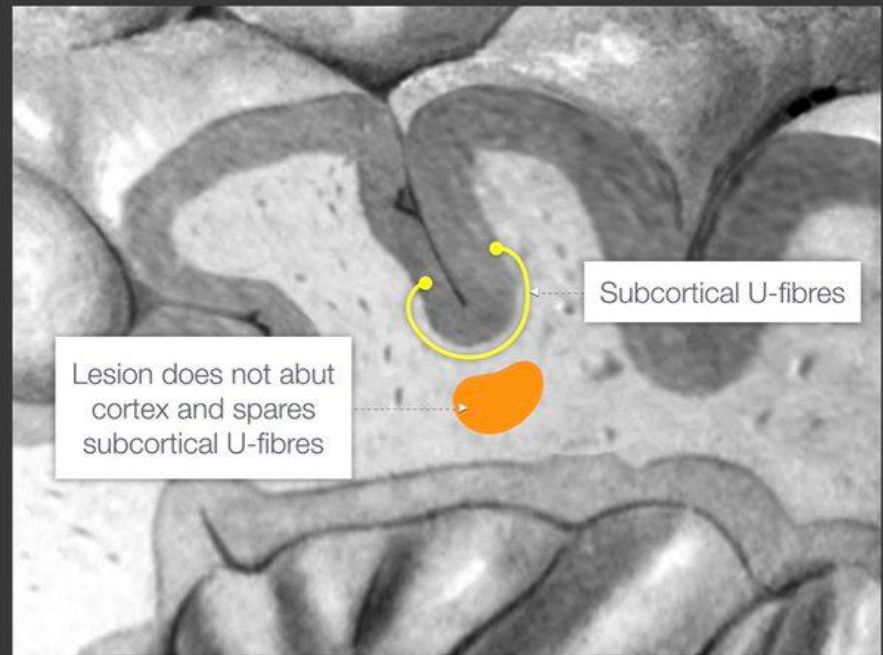
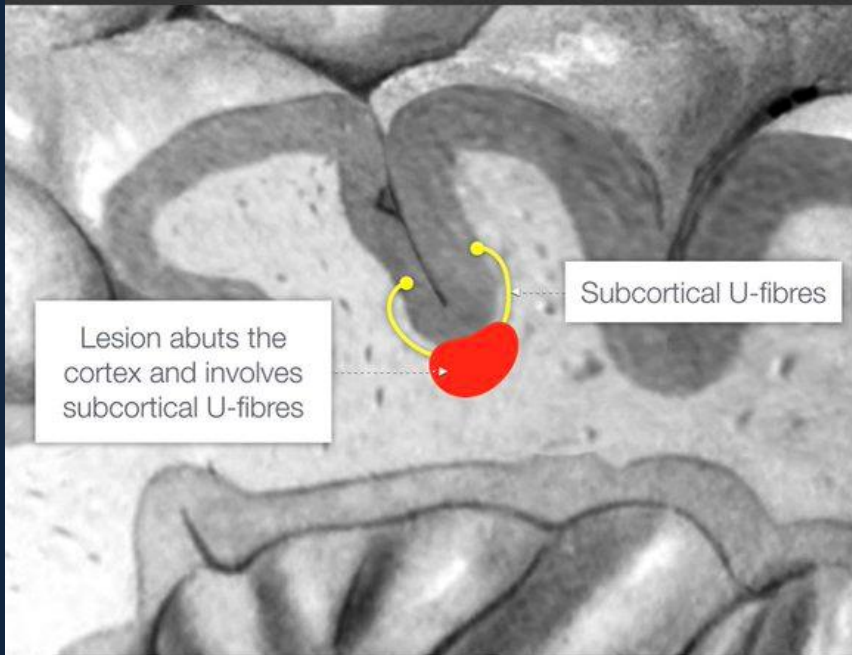


Figure 8. Cortical, juxtacortical lesions, and U-fiber lesions. Arrows: multiple small juxtacortical and cortical lesions throughout cerebral hemispheres. By definition, no white matter may interpose between a juxtacortical lesion and the cortex. Note U-fiber lesions along arcuate fibers in middle left frontal lobe, highly characteristic of demyelination and not seen in normal aging or vascular disease.

JUXACORTICAL vs SUBCORTICAL LESIONS



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Adapted from illustration from "Sobotta's Textbook and Atlas of Human Anatomy" 1908, now in the public domain.



"THANK YOU"

