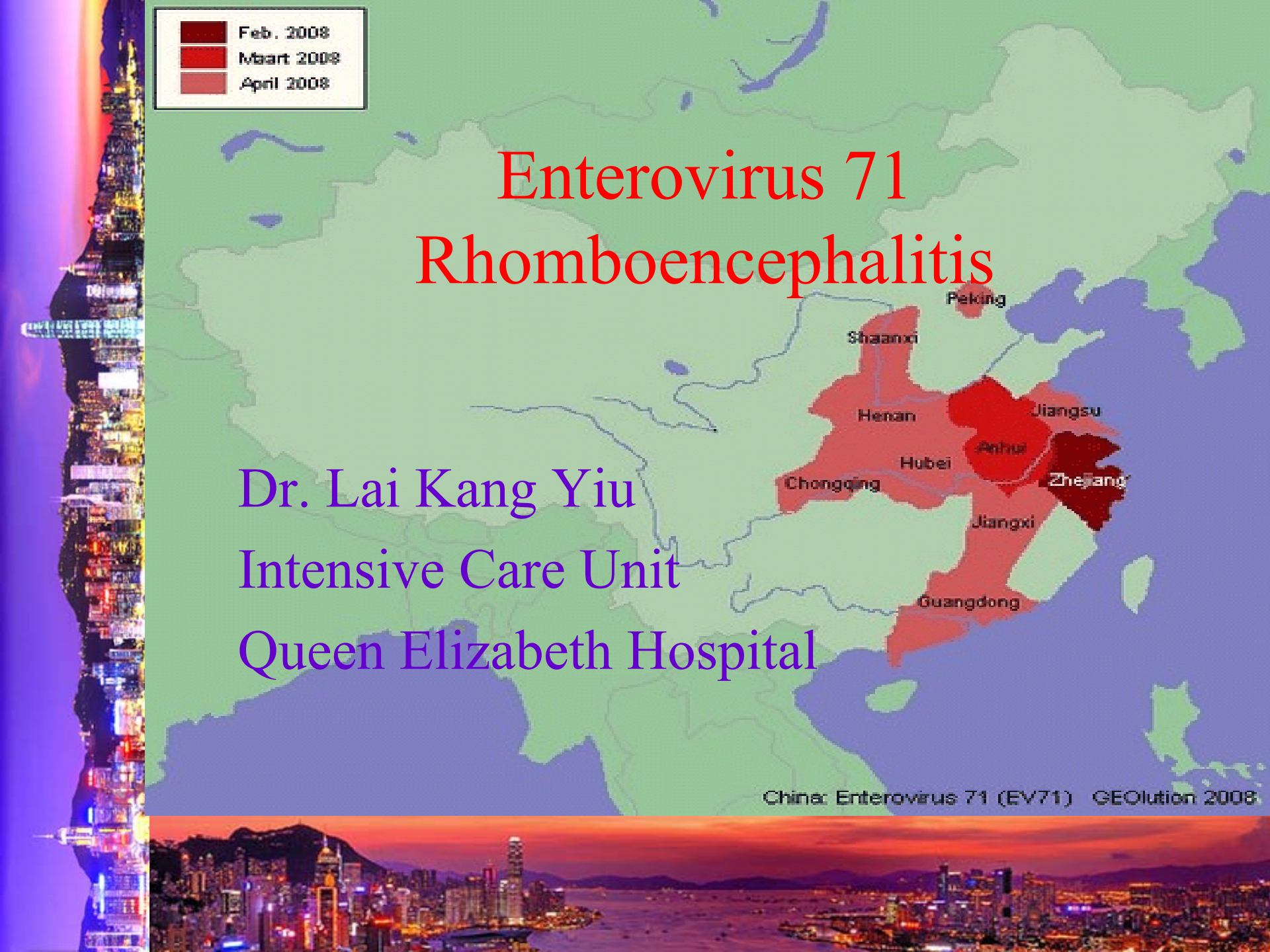
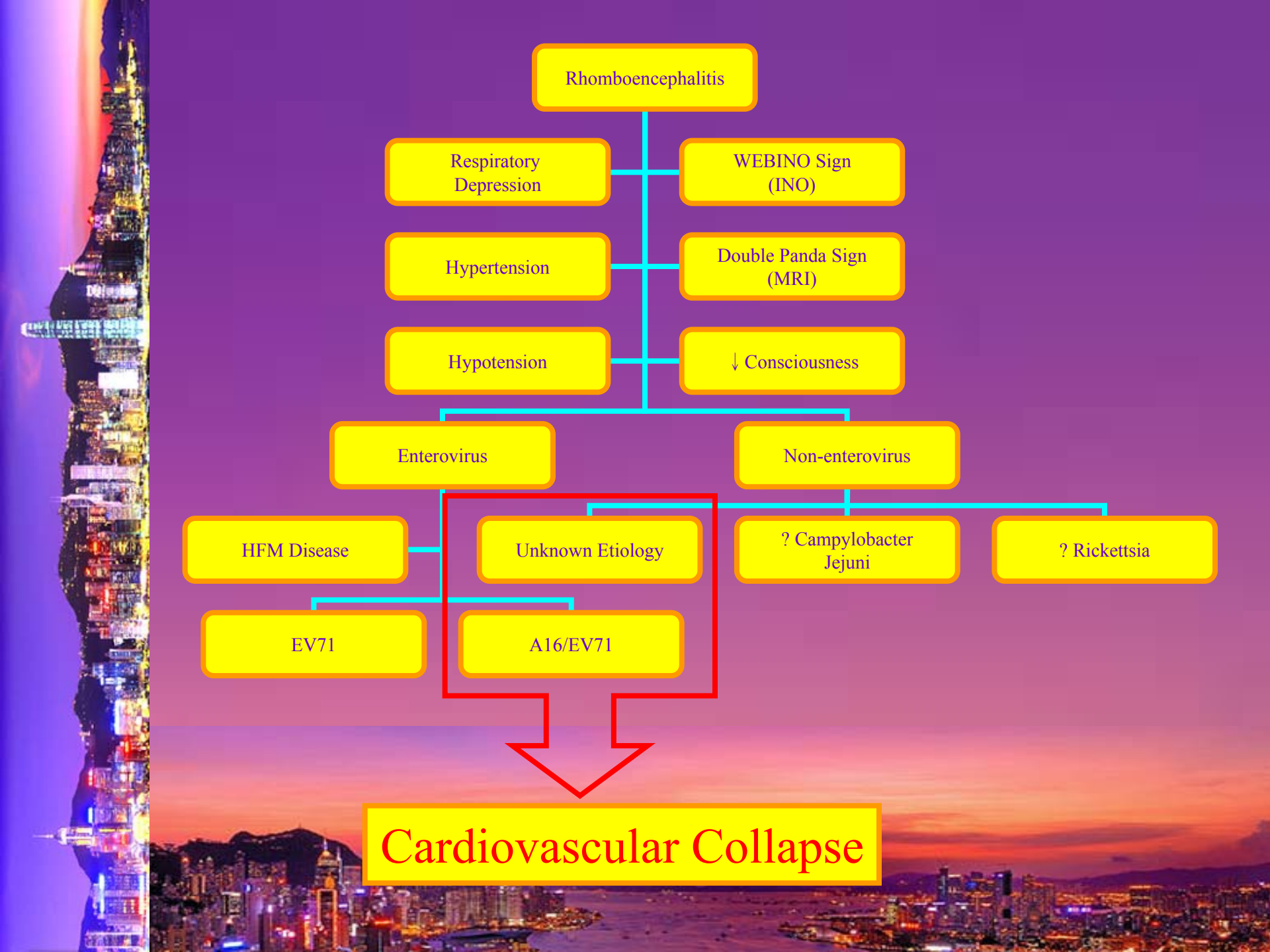
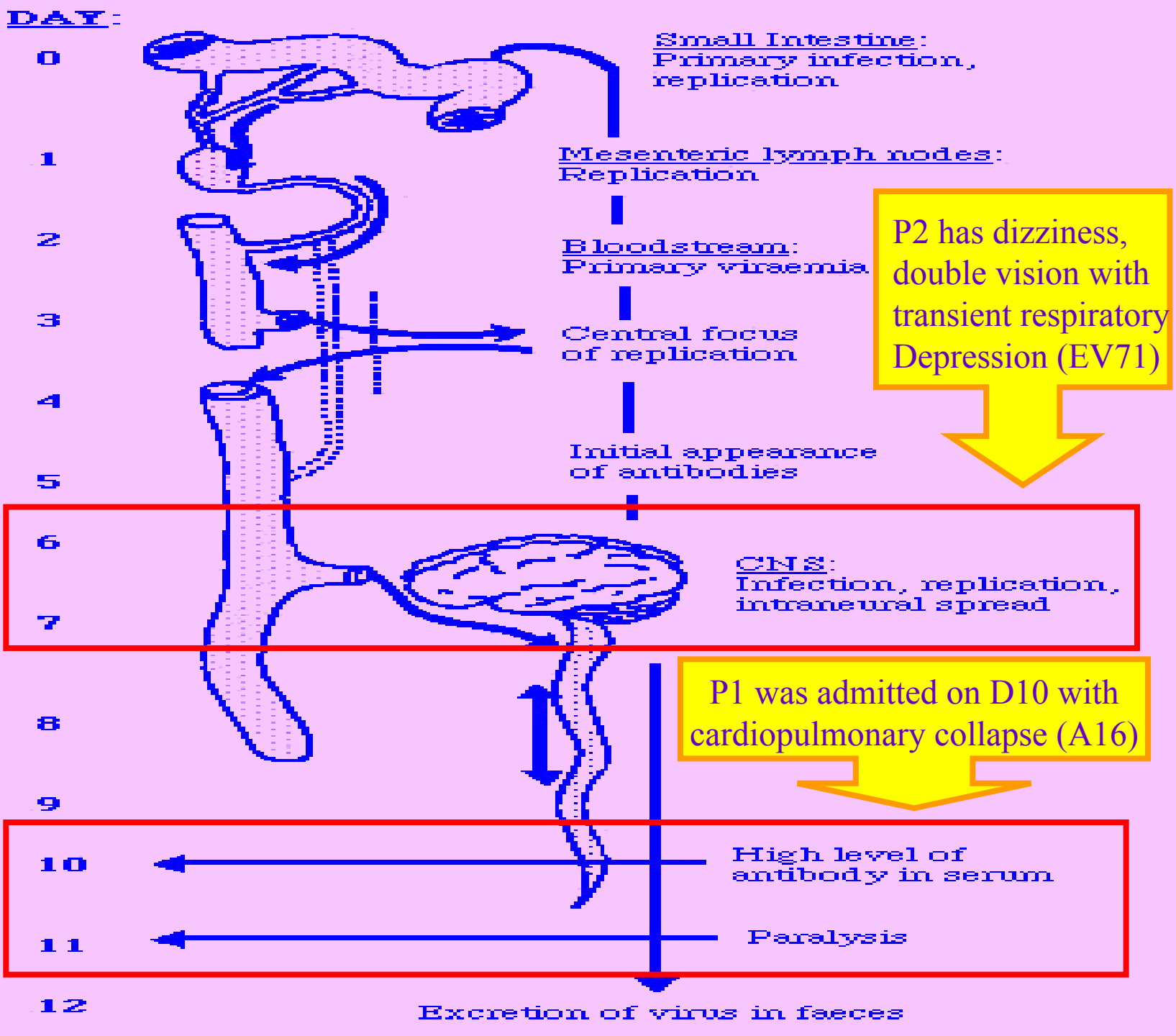


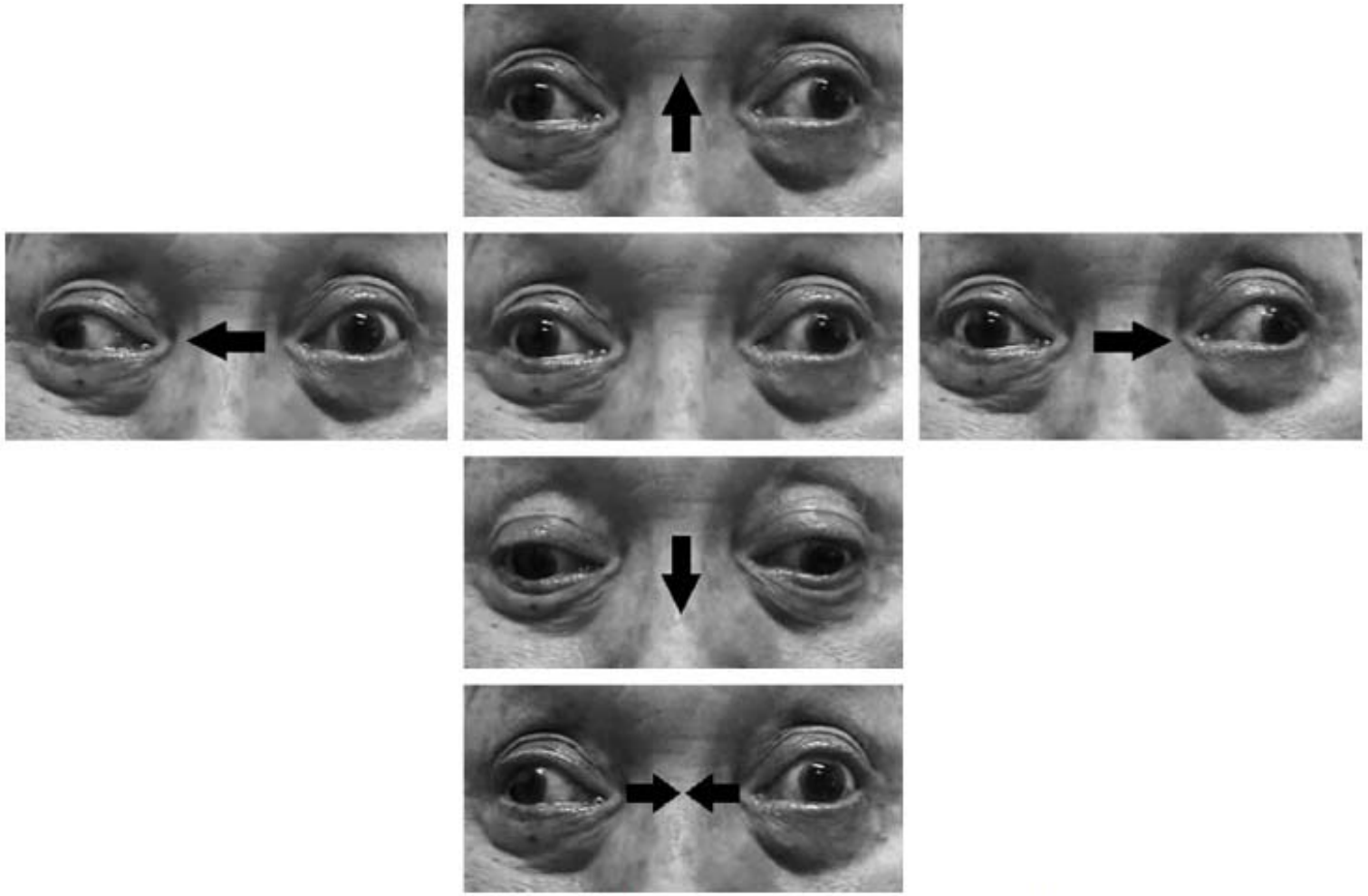
Enterovirus 71 Rhomboencephalitis

Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital


Rhomboencephalitis
Respiratory Depression
WEBINO Sign (INO)
Hypertension
Double Panda Sign (MRI)
Hypotension
↓ Consciousness
Enterovirus
Non-enterovirus
HFM Disease
Unknown Etiology
? Campylobacter Jejuni
? Rickettsia
EV71
A16/EV71
Cardiovascular Collapse

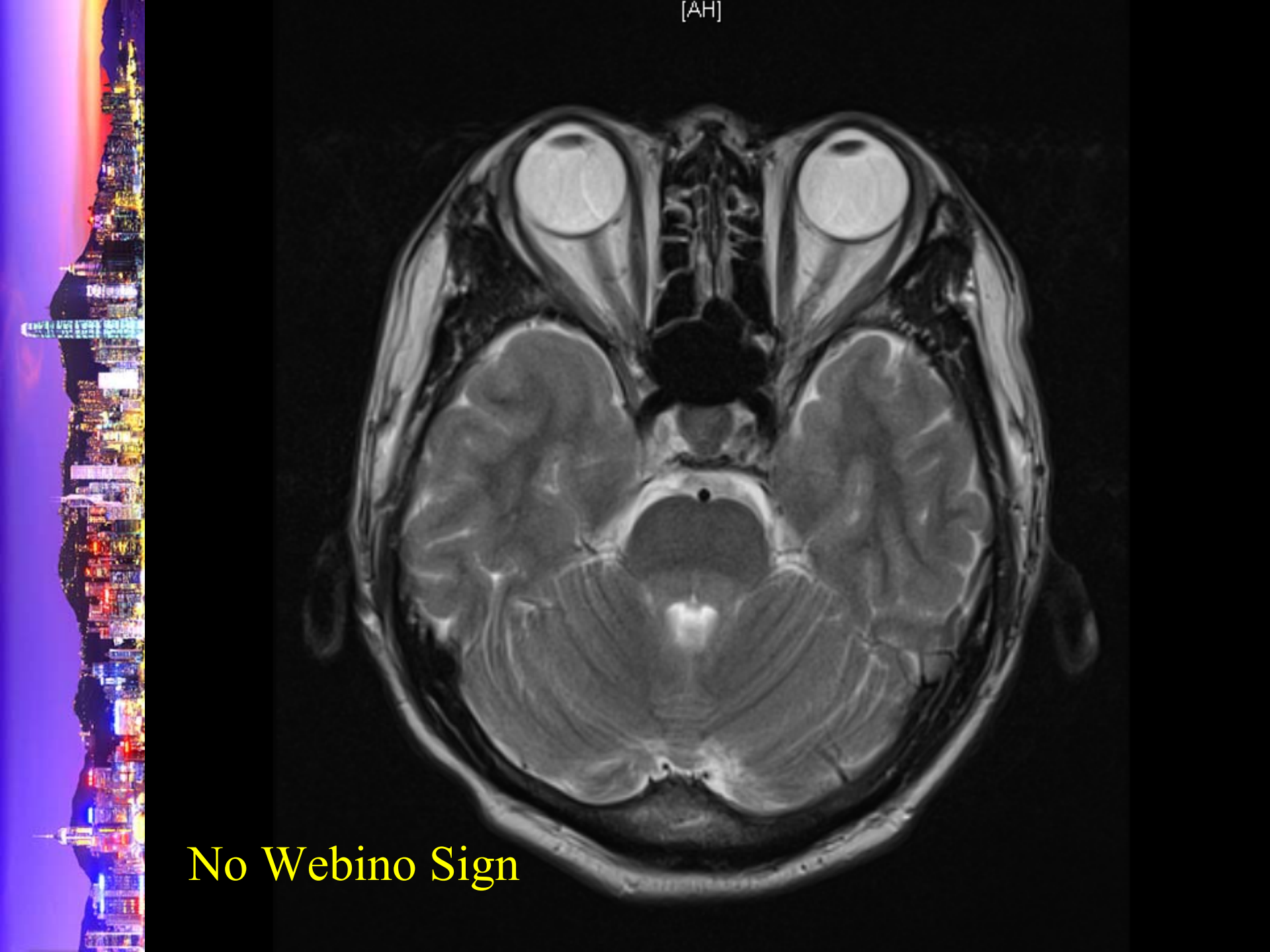
	P1	P2	P3	P4	P5
	F/35	M/43	M/58	F/31	F/27
CSF					
◎P	1.14g	0.69	0.18	3.71	0.13
◎G mmol/L	3.2	3.0	4.0	5.2	5.6
◎RBC	15	300	1	168	145
◎WBC	2	56	1	1	6
◎ PMN		46			
◎Lymphocyte		54			
◎Culture	-ve	-ve	-ve	-ve	-ve
◎CSF	-ve	-ve	-ve	-ve	-ve
TA/TS	EV+ EV71 -	EV71 +	EV - EV71 -	EV - EV71 -	EV - EV71 -
Stool	EV+ EV71 -	EV71+	EV - EV71 -	EV - EV71 -	EV - EV71 -
C3 (0.90-1.80)	1.18	1.42	0.66	1.37	0.76
C4 (0.10-0.40)	0.57	0.39	0.13	0.36	0.10
OX2	1:20	1:80	>1:1280	1:40	1:40
OX19	<1:20	<1:20	1:80	1:20	< 1:20
OXK	1:20	1:40	1:40	1:40	1:40
Liver problem			Alcoholic		HBsAg +


DAY:
0
1
2
3
4
5
6
7
8
9
10
11
12
Small Intestine:
Primary infection,
replication
Mesenteric lymph nodes:
Replication
Bloodstream:
Primary viraemia
Central focus
of replication
Initial appearance
of antibodies
CNS:
Infection, replication,
intraneural spread
High level of
antibody in serum
Paralysis
Excretion of virus in faeces
P2 has dizziness, double vision with transient respiratory Depression (EV71)
P1 was admitted on D10 with cardiopulmonary collapse (A16)

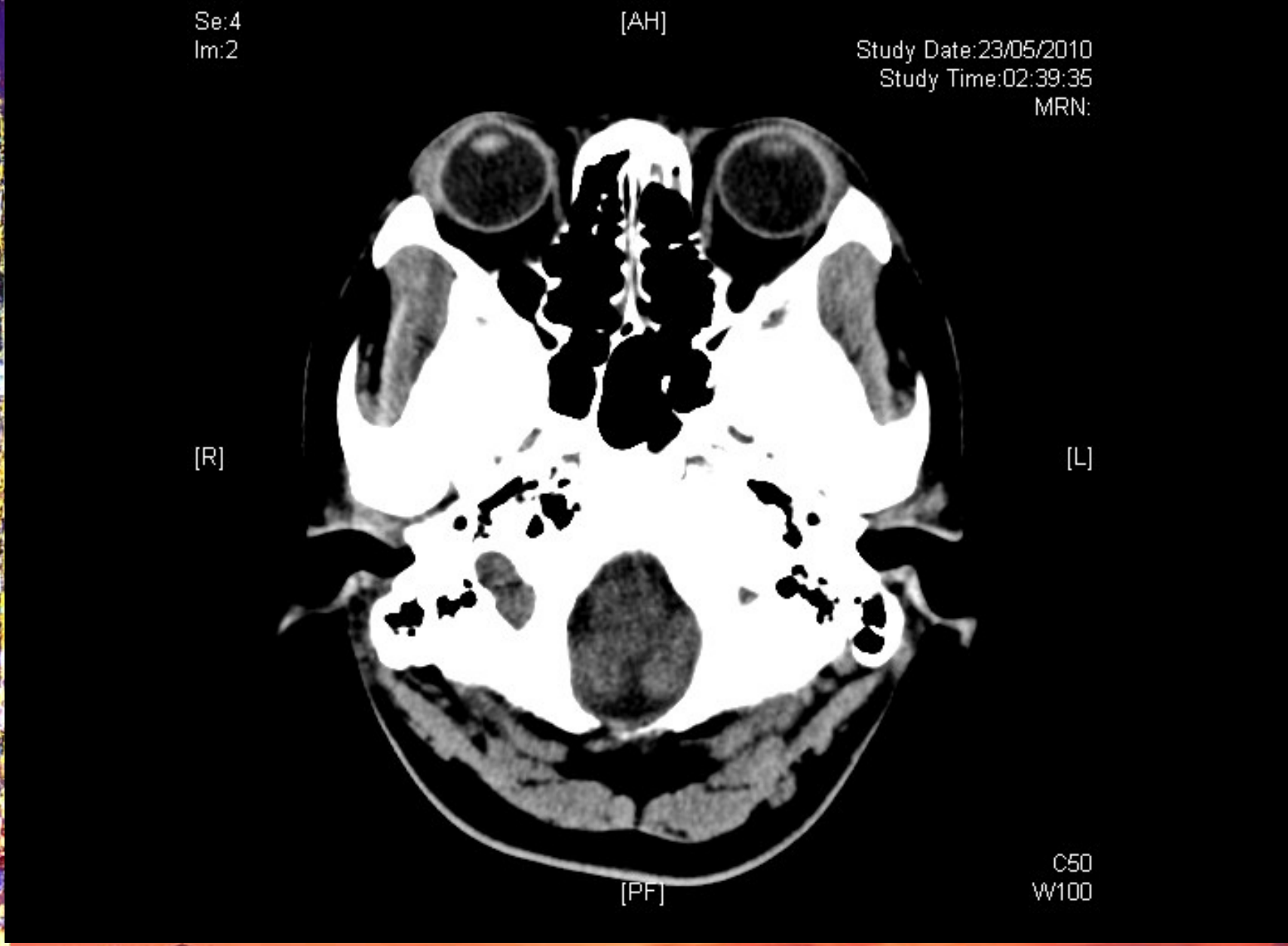


Cardinal gaze positions: primary position, lateral (←, →), upward (↑), downward (↓), and convergence (→ ←). Exotropia is evident in the primary position. Adduction deficits are evident on lateral gaze bilaterally. Upward and downward eye movements are severely reduced. Convergence is absent.

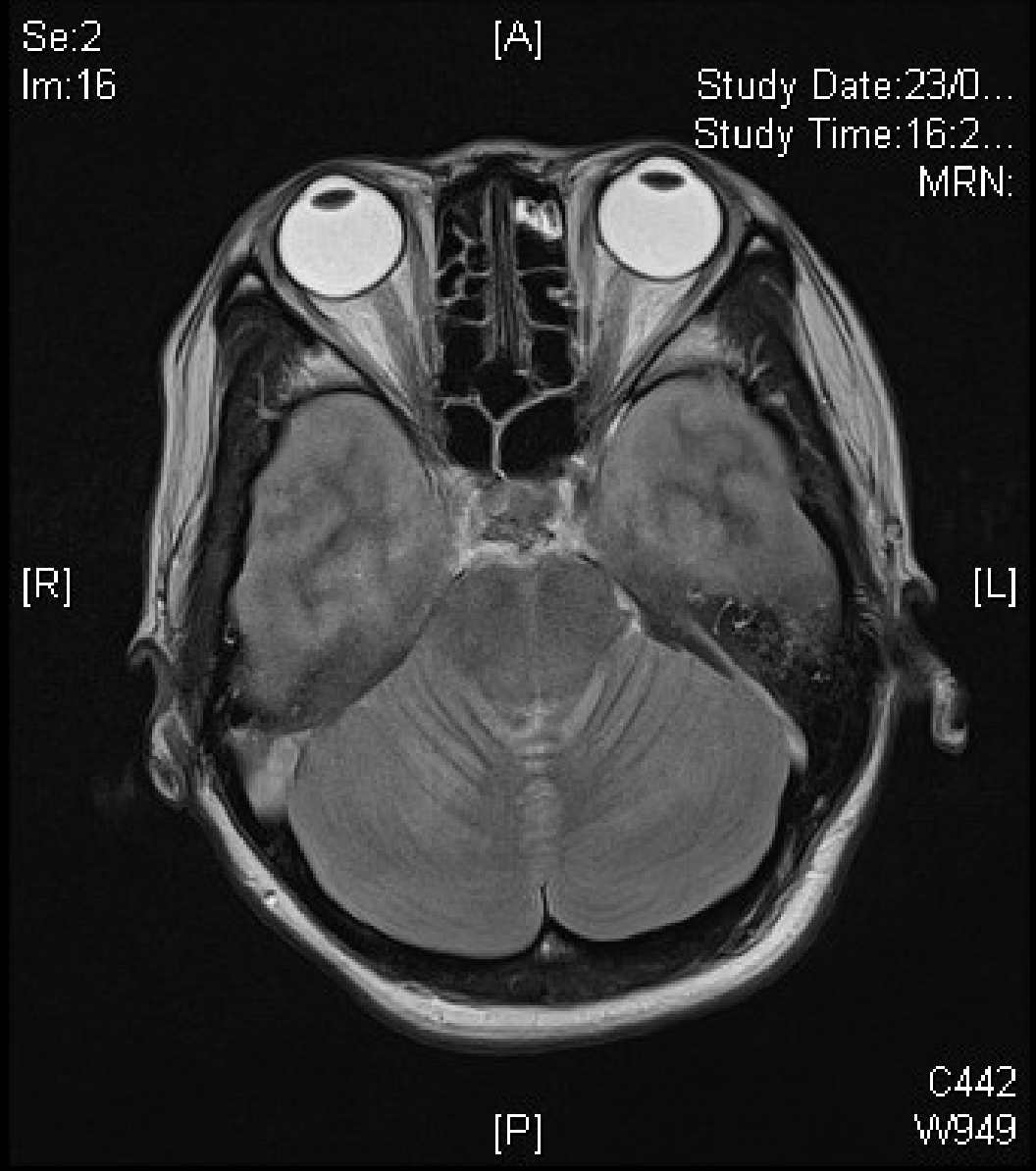
Wall-Eyed Bilateral Internuclear Ophthalmoplegia



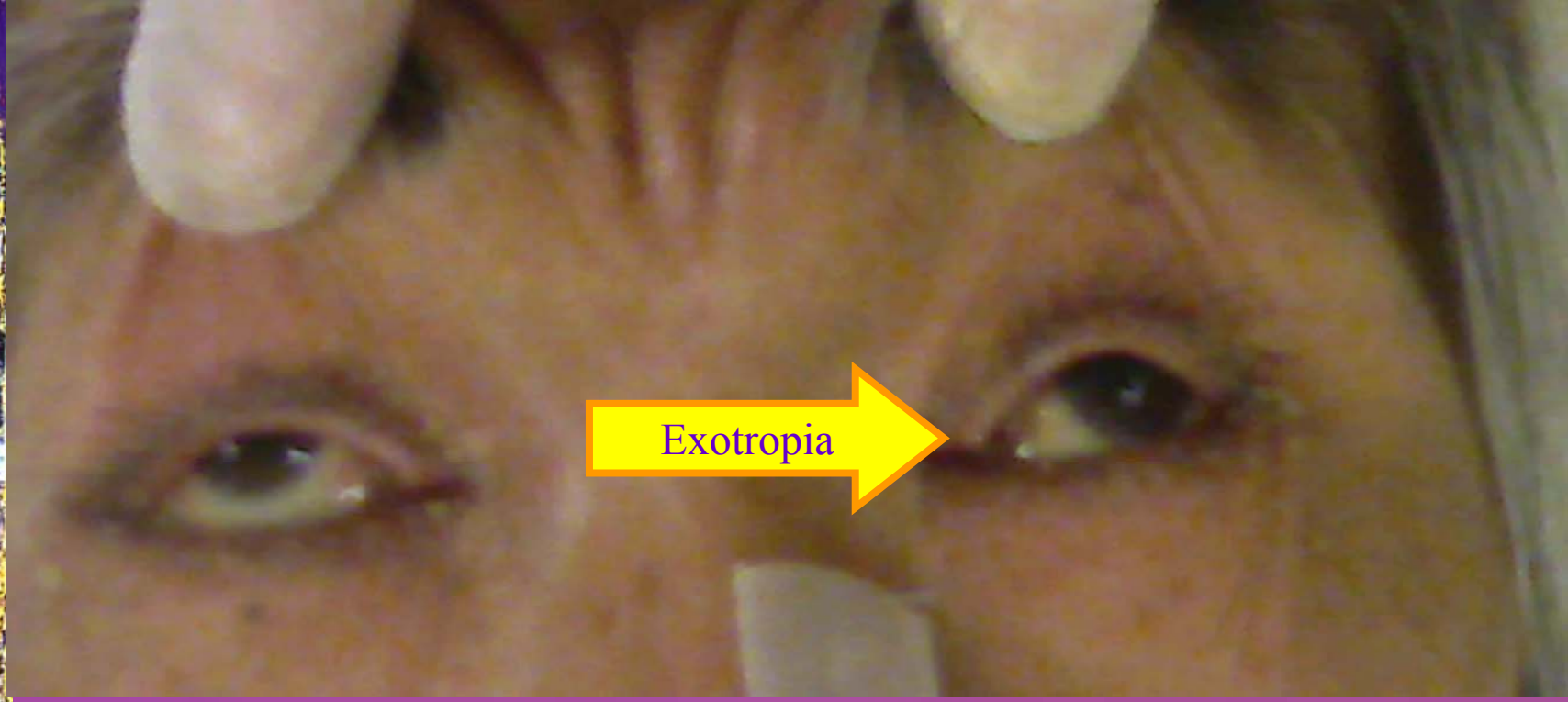
No Webino Sign



WEBINO Sign (P1)

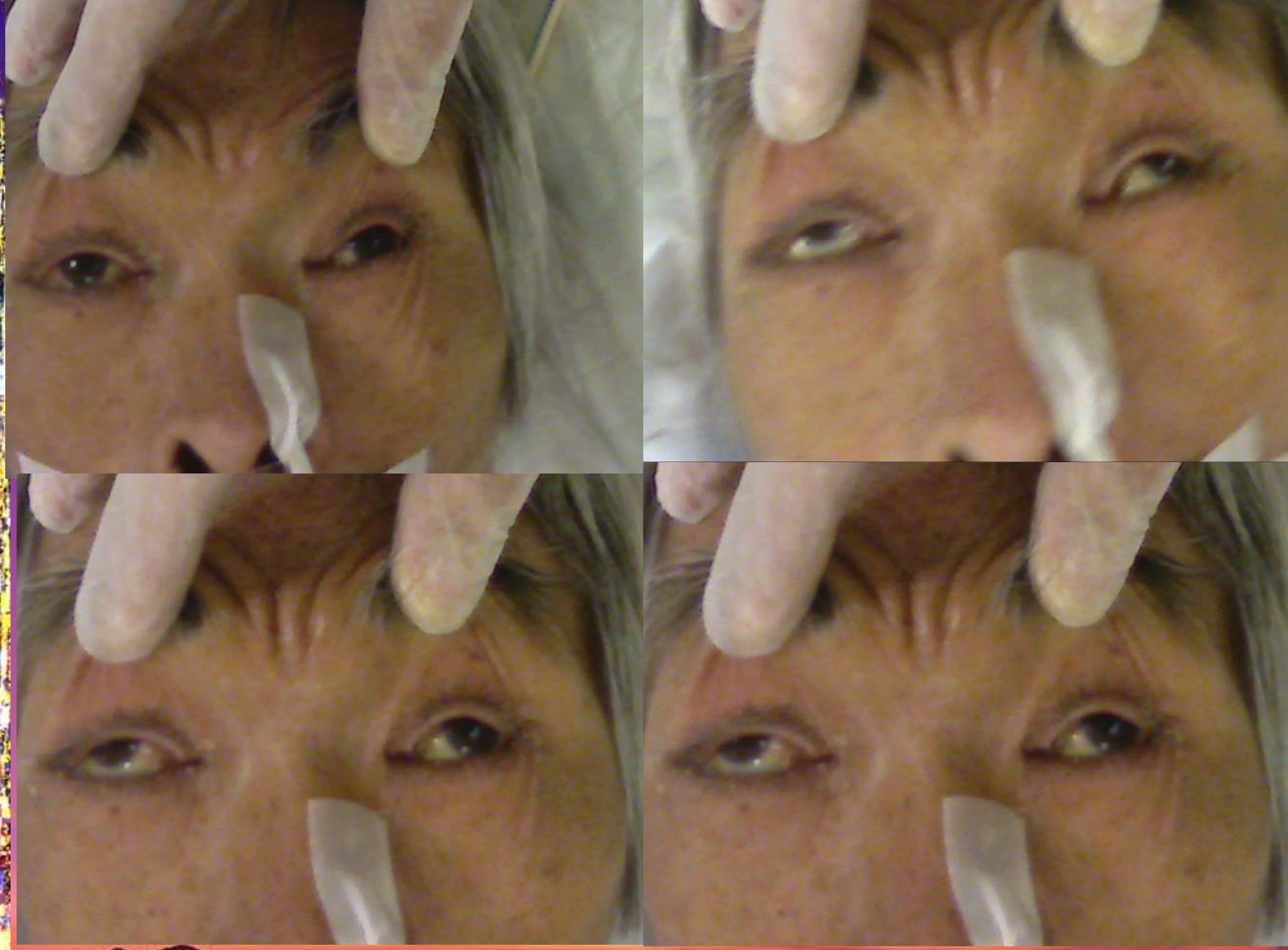


WEBINO Sign (P1)



Dysconjugate gaze is generally found among patients with stroke of the brainstem. A small infarction of the rostral pons or caudal midbrain may produce an internuclear opthalmoplegia. A rostral lesion within the midbrain may affect the convergence center thus causing bilateral divergence of the eyes which is known as the WEBINO syndrome (Wall Eyed Bilateral INO) as each eye looks at the opposite "wall".

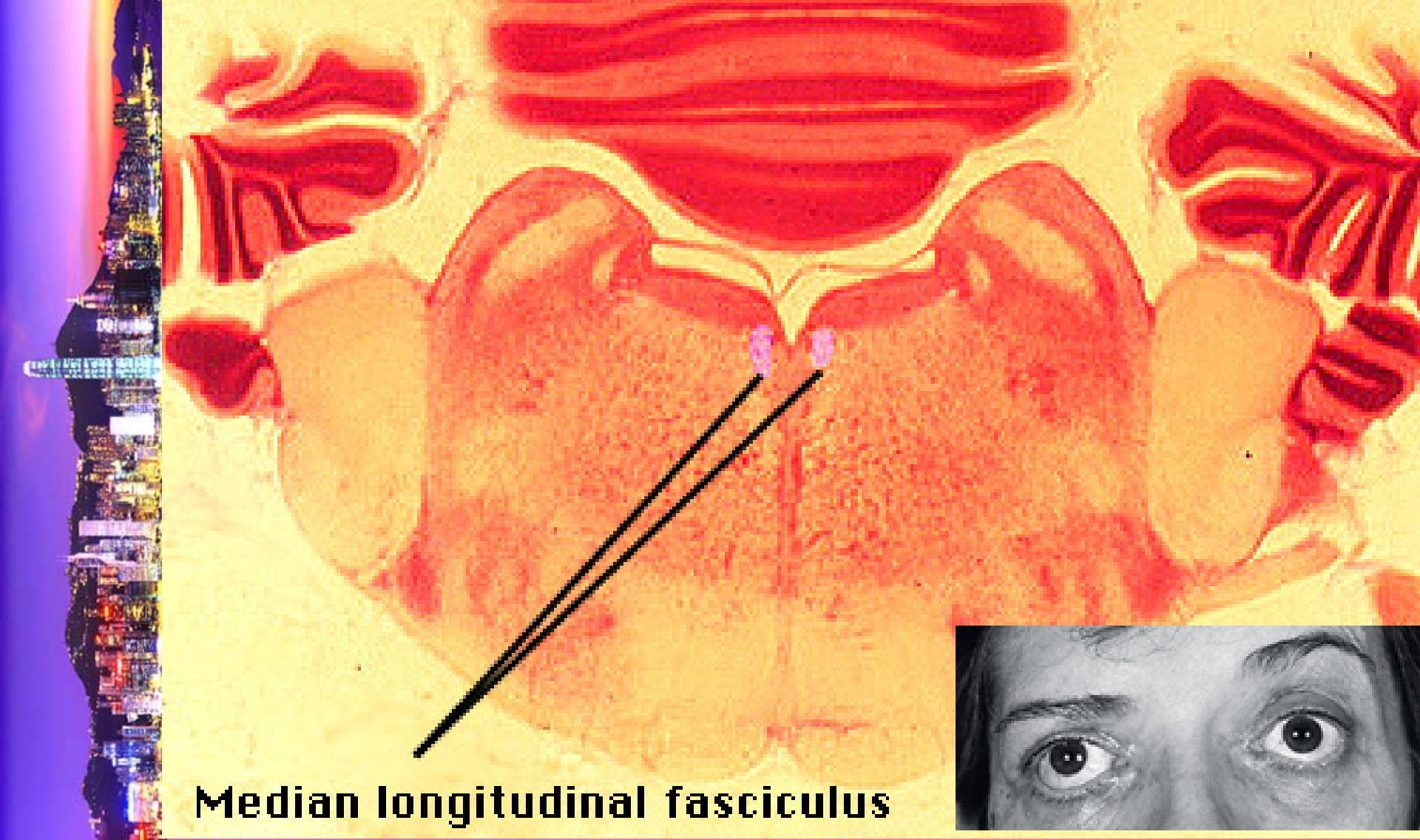
Neurological Finding in ICU (P3)



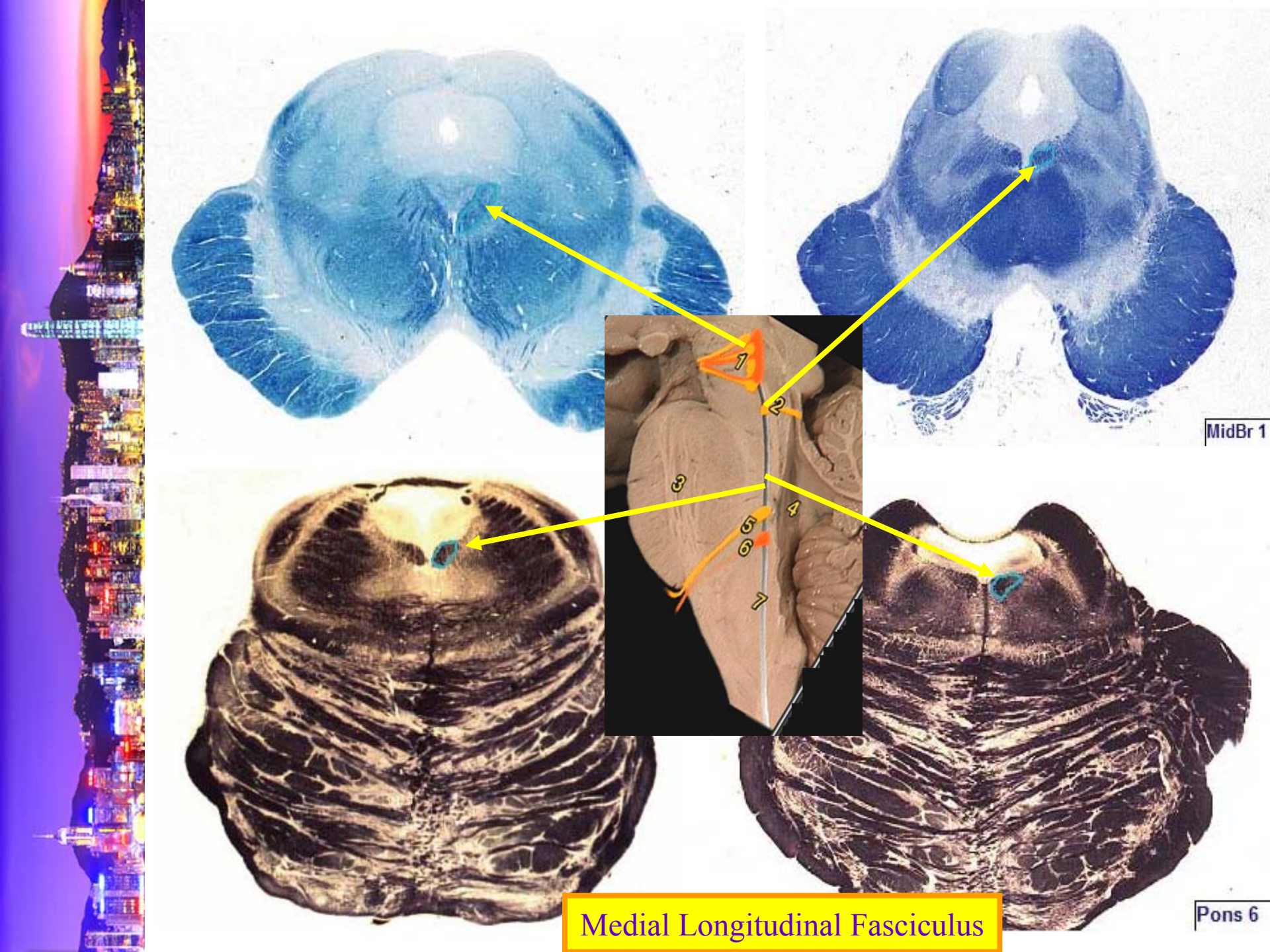
Neurological Finding in ICU: Skew deviation with bilateral exotropia (the left eye more affected than right eye). WEBINO syndrome (P3)

WEBINO Sign (P5)

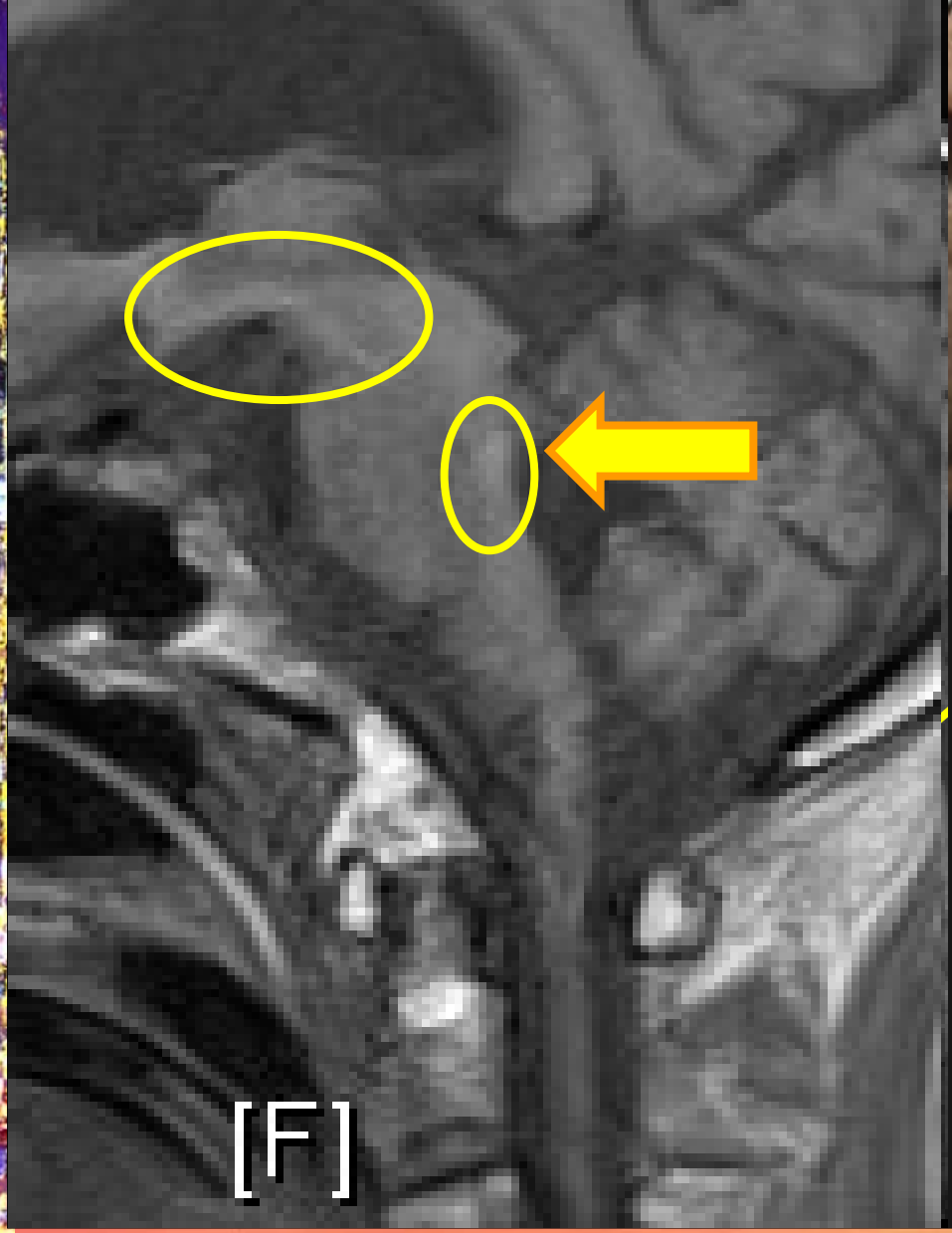
WEBINO Sign (P5)



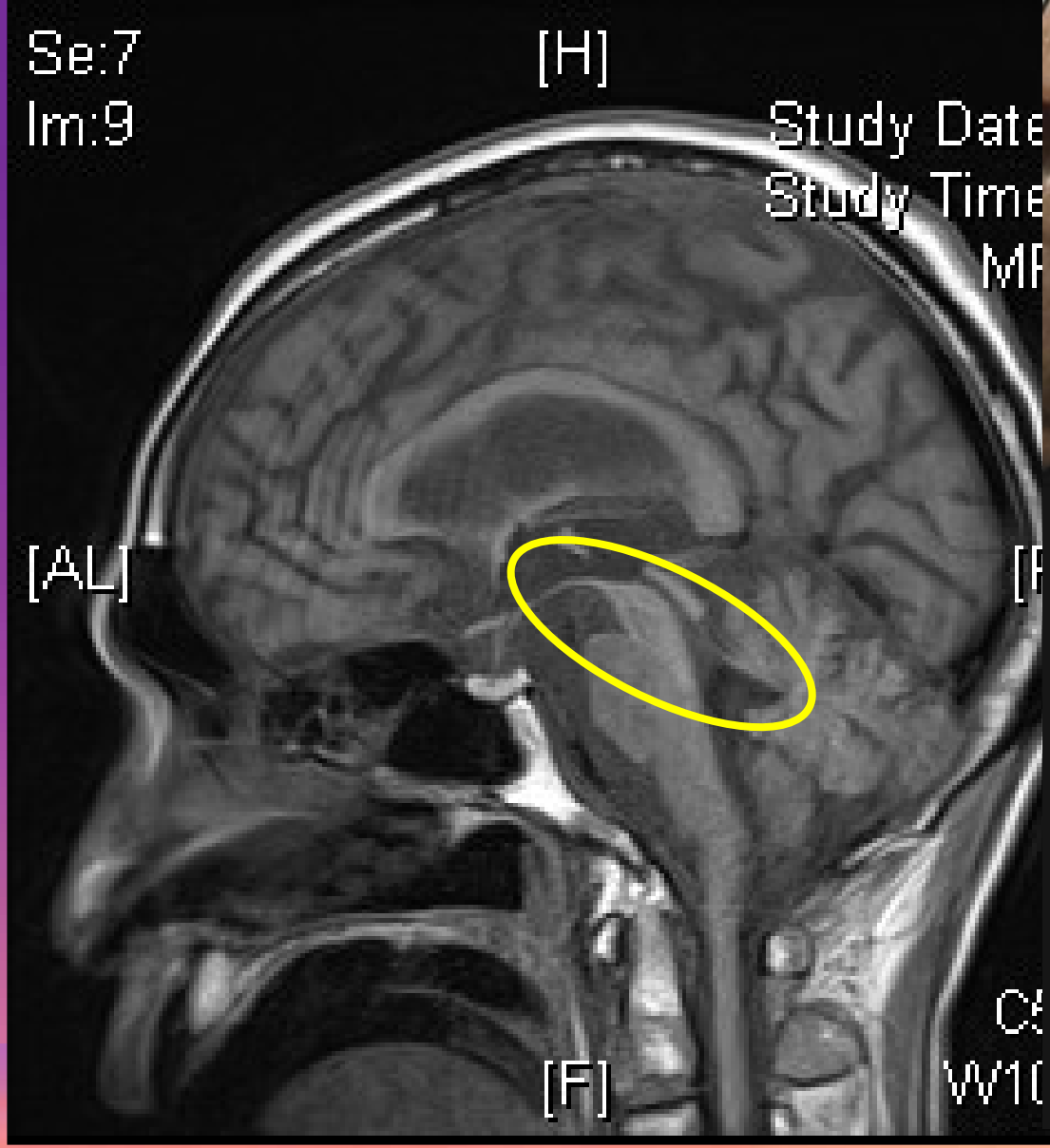
Skew Deviation



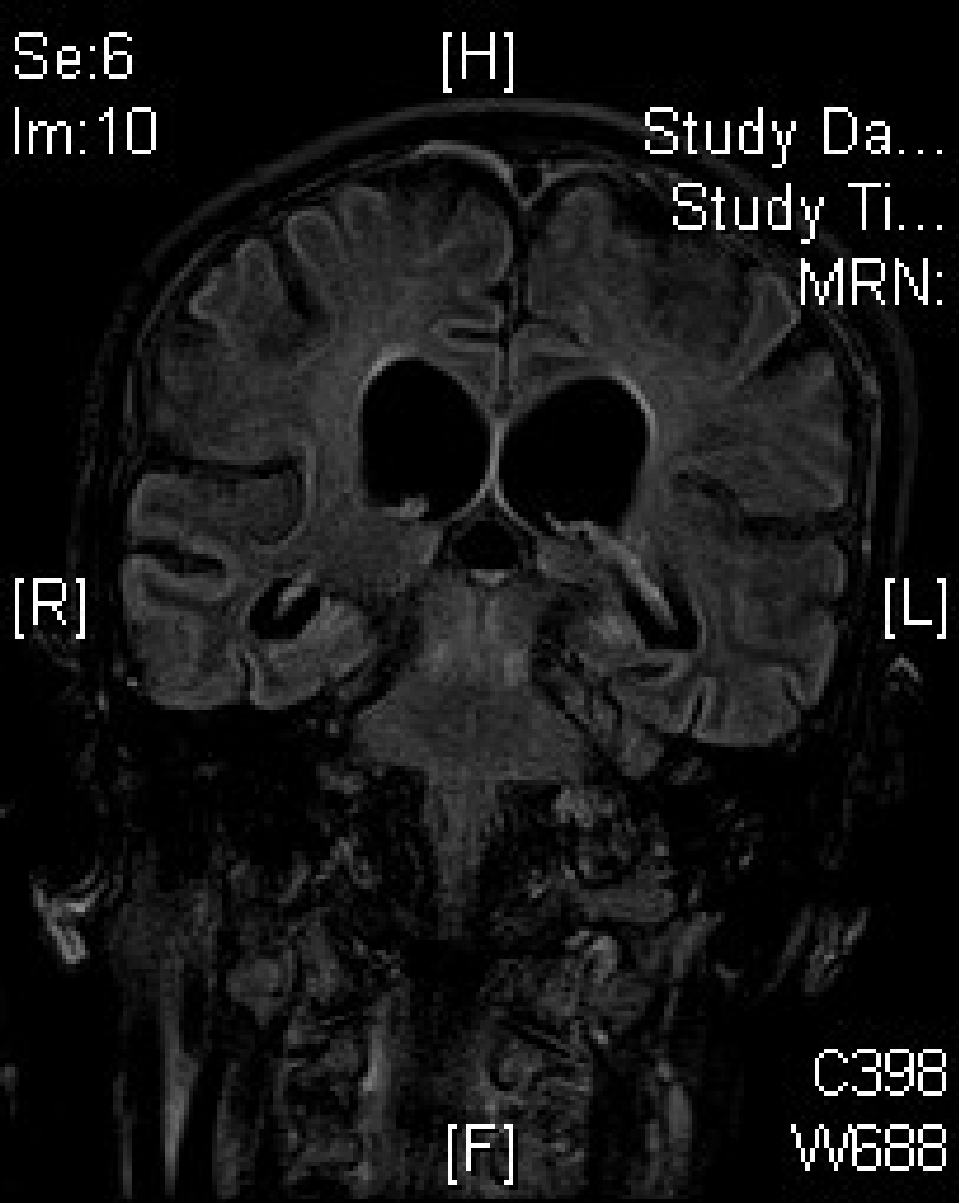
Medial Longitudinal Fasciculus



1 = Oculomotor N nuclei; 2 = Trochlear nerve; 3 = pons; 4= 4th ventricle;
5= abducen nuclei; 6 = vestibular nuclei; 7 = medial longitudinal fasciculus; (P3)



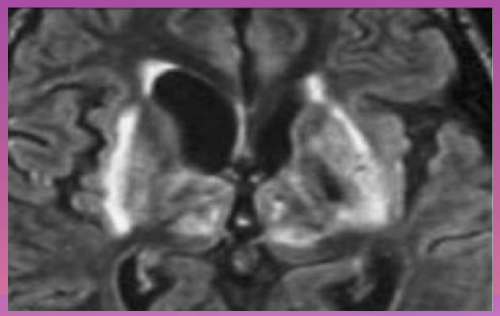
MRI Finding with Anatomical Correlation (P3)



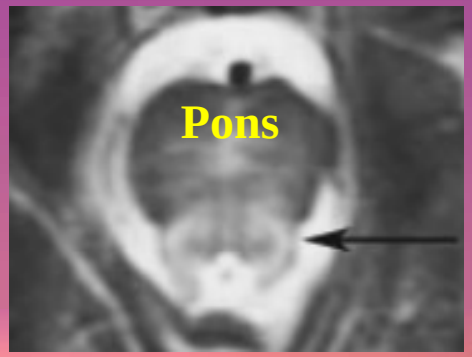
Medial Longitudinal Fasciculus: Etiology of Skew Deviation (P3)

Special MRI Finding in Wilson's Disease

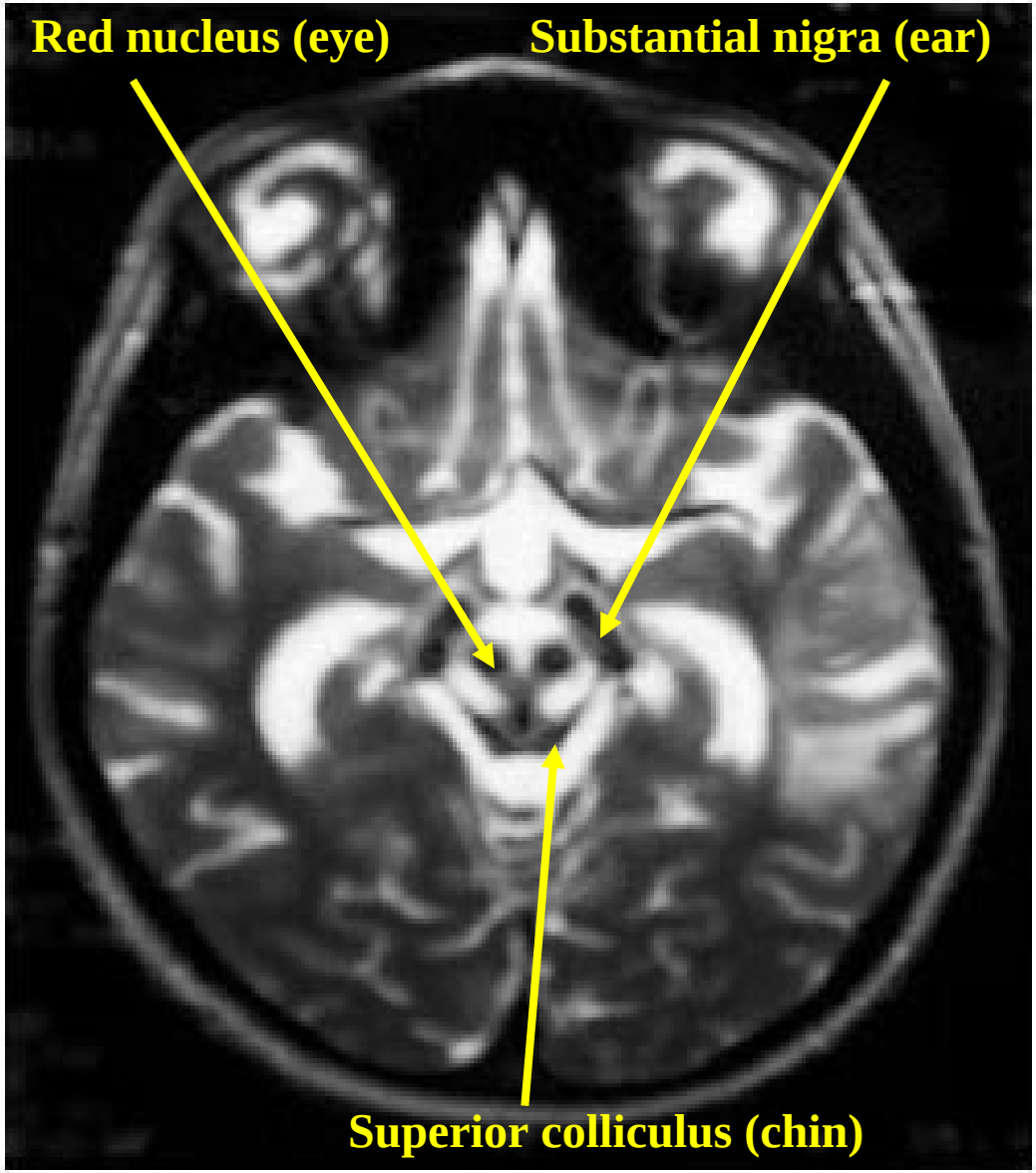
- **Flair Sequence**
  - **The Bright Claustrum**
- **T2-Weighted**
  - **Face of the Giant panda**
  - **Face of the Miniature panda**



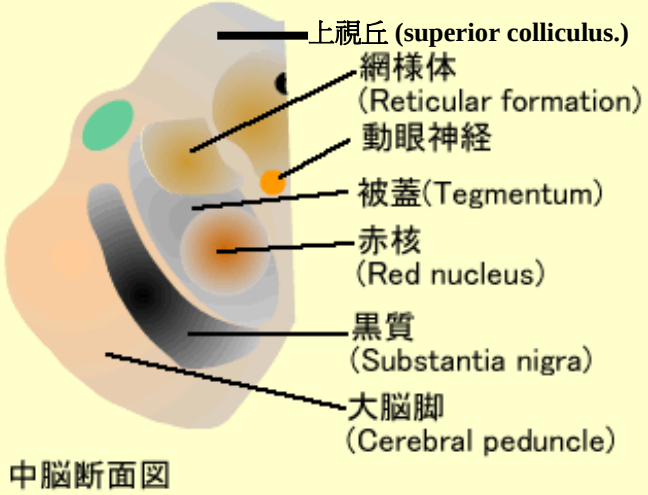
Claustrum outside Putamen and pallidum



"Face of the panda cub"



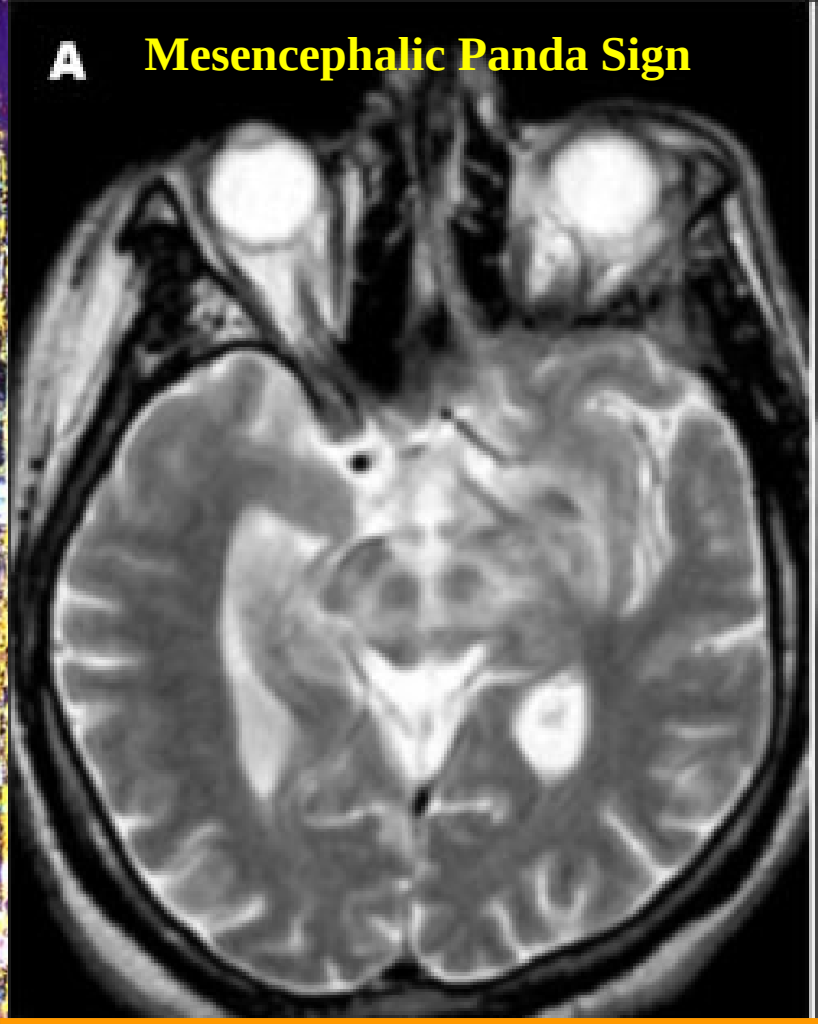
The giant panda sign is due to the preservation of normal signal intensity in the red nuclei and lateral portion of the pars reticulata of the substantia nigra, high signal in the tegmentum, and hypointensity of the superior colliculus.



中脳断面図

The typical 'face of the giant panda' seen in the midbrain on T2-weighted MRI of the brain.

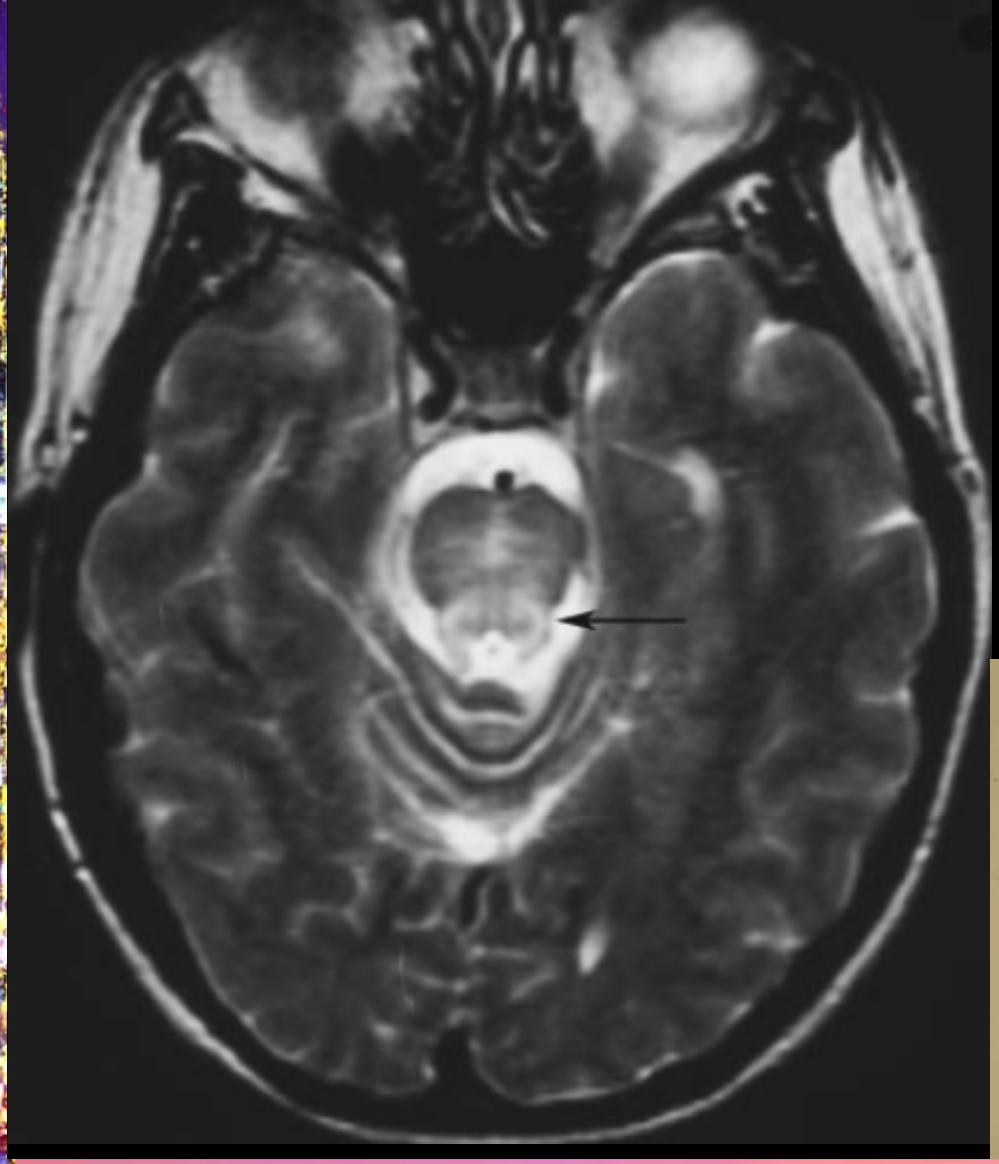
Wilson's disease: an update Shyamal K Das and Kunal Ray *Nature Clinical Practice Neurology* (2006) 2, 482-493



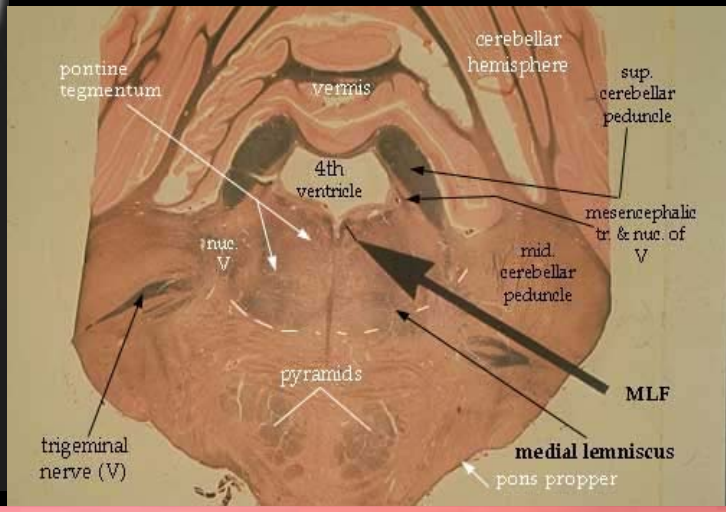
Neuropareidolia: diagnostic clues apropos of visual illusions Arq. Neuro-Psiquiatr. vol.67 no.4 São Paulo dic. 2009

T2 weighted MRI of midbrain of Wilson's disease

Normal signal at the red nuclei (eyes) and the lateral aspect of the substantial nigra pars reticulata (ears), high signal at the tegmentum and hypointense supercoliculi.

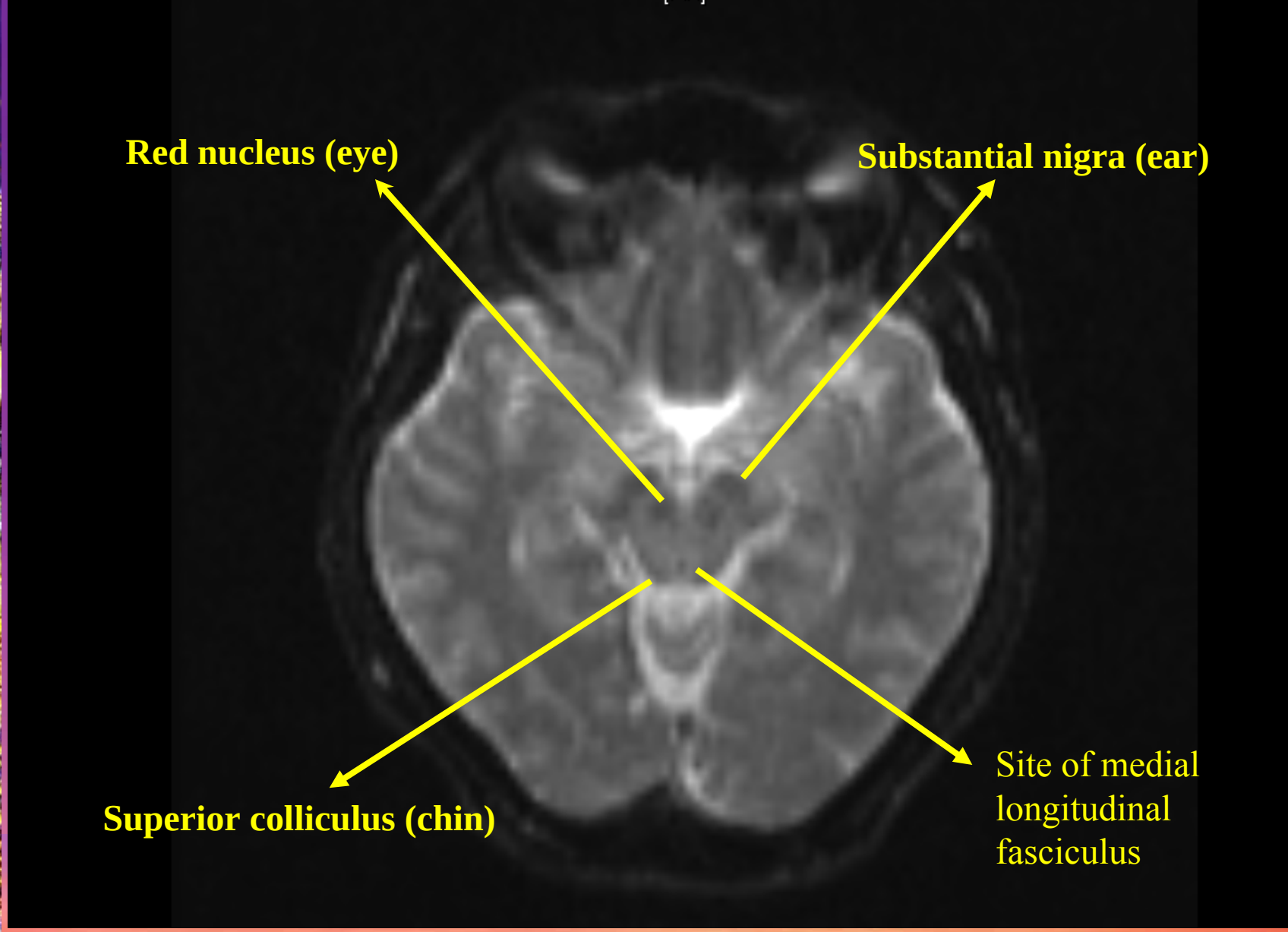


The "face of the miniature panda" is delineated by the relative hypointensity of the medial longitudinal fasciculi and central tegmental tracts ("eyes of the panda") in contrast with the hyperintensity of the aqueduct opening into the fourth ventricle ("nose and mouth of the panda") bounded inferiorly by the superior medullary velum . The superior cerebellar peduncles form the panda's "cheeks."

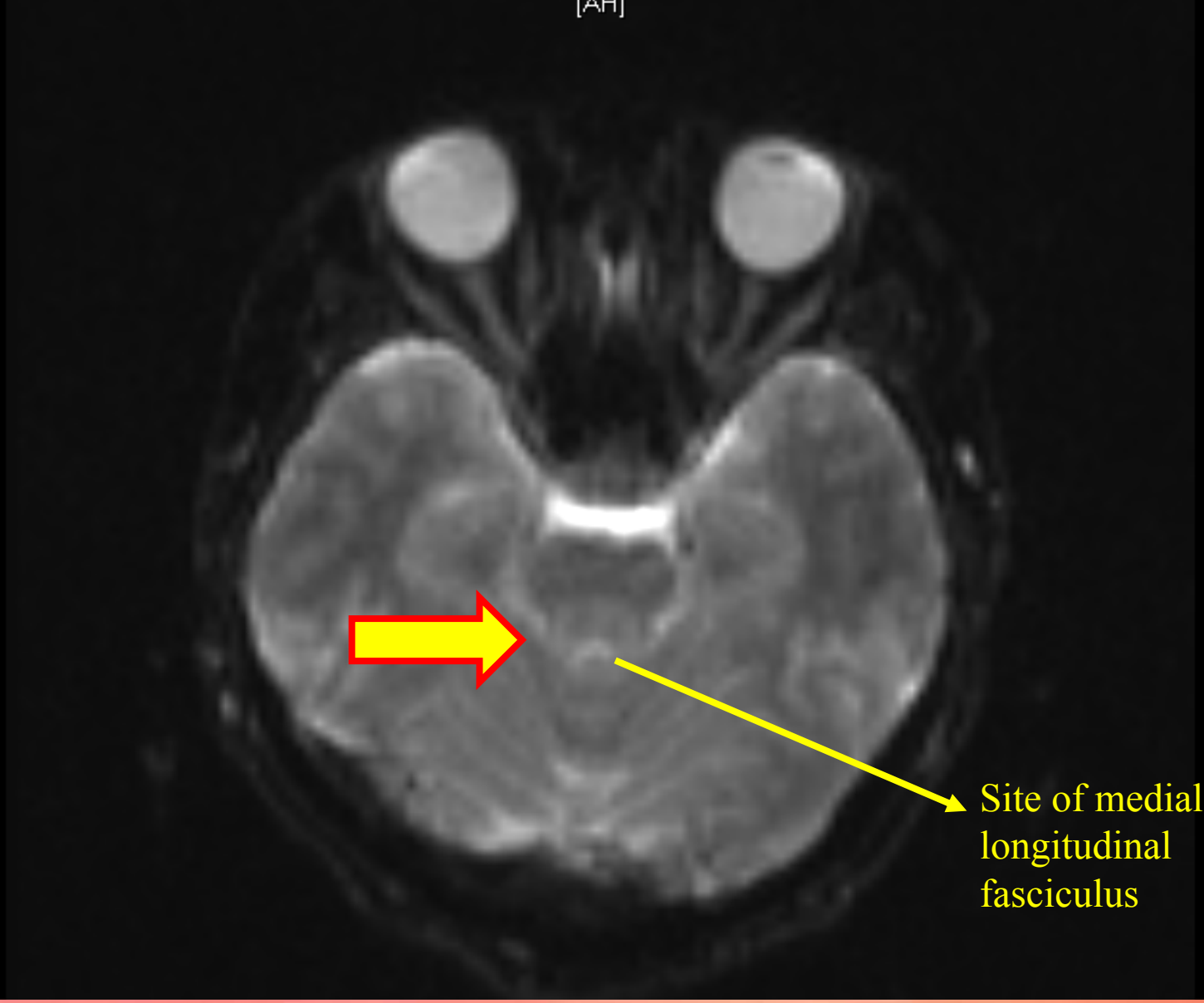


T2-weighted axial MRI reveals the "face of the miniature panda" in the pontine tegmentum (arrow)

Wilson's disease: an update Shyamal K Das and Kunal Ray *Nature Clinical Practice Neurology* (2006) 2, 482-493

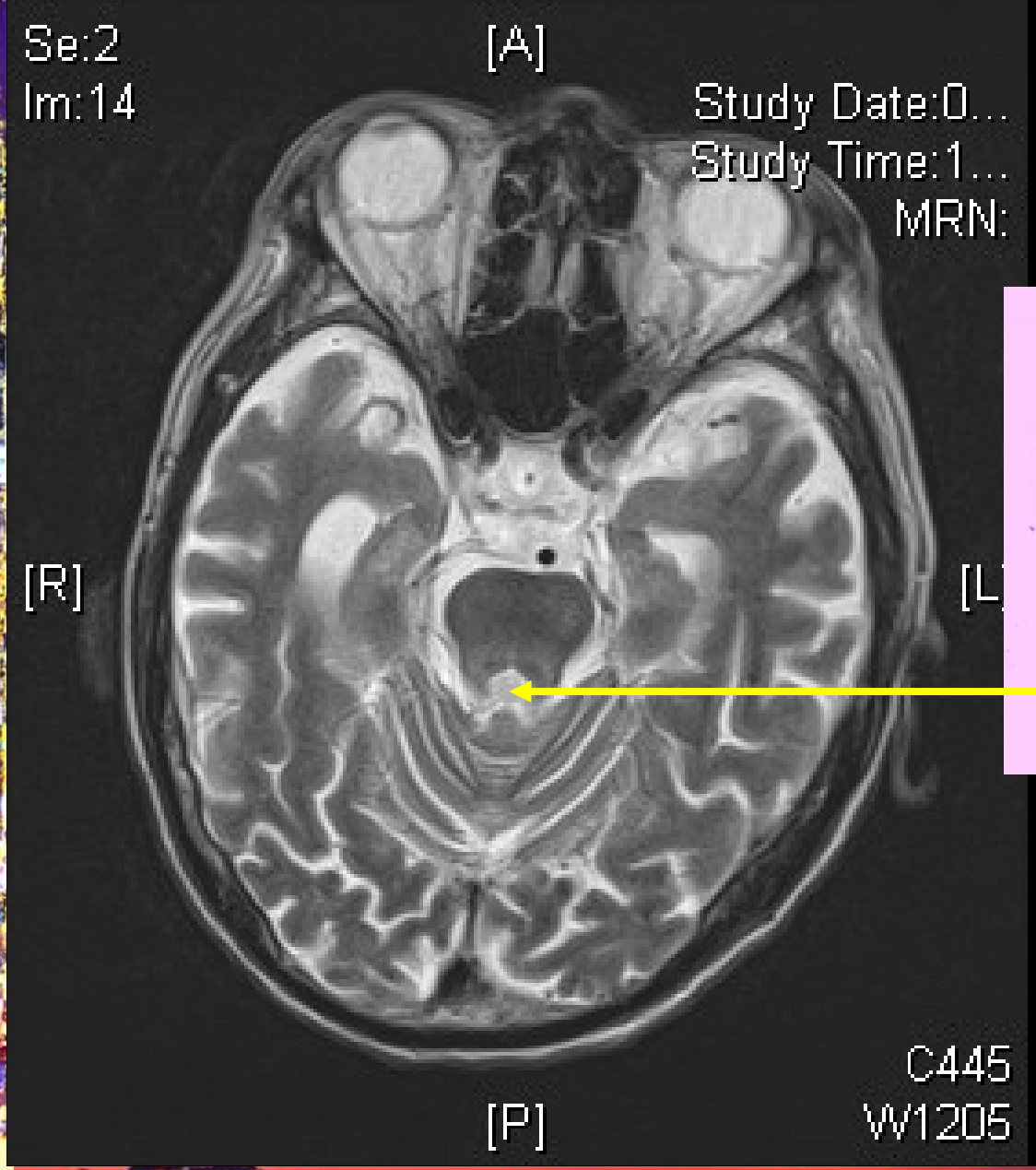


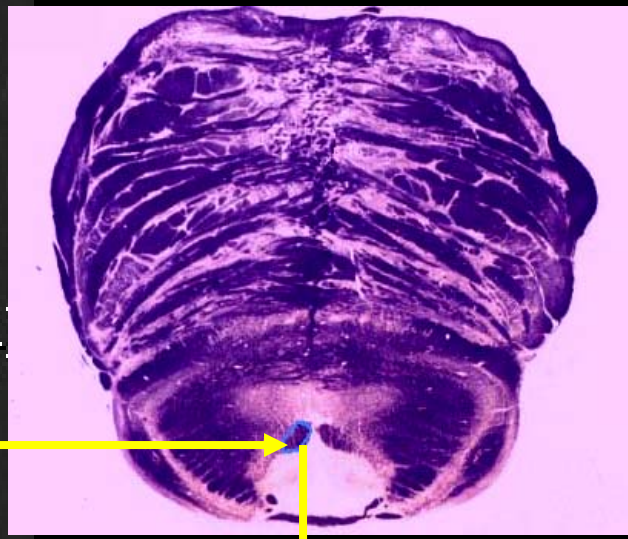
‘Face of the giant panda' seen in the midbrain on MRI of the brain. (P2)



"Face of the miniature panda" in the pontine tegmentum (P2)

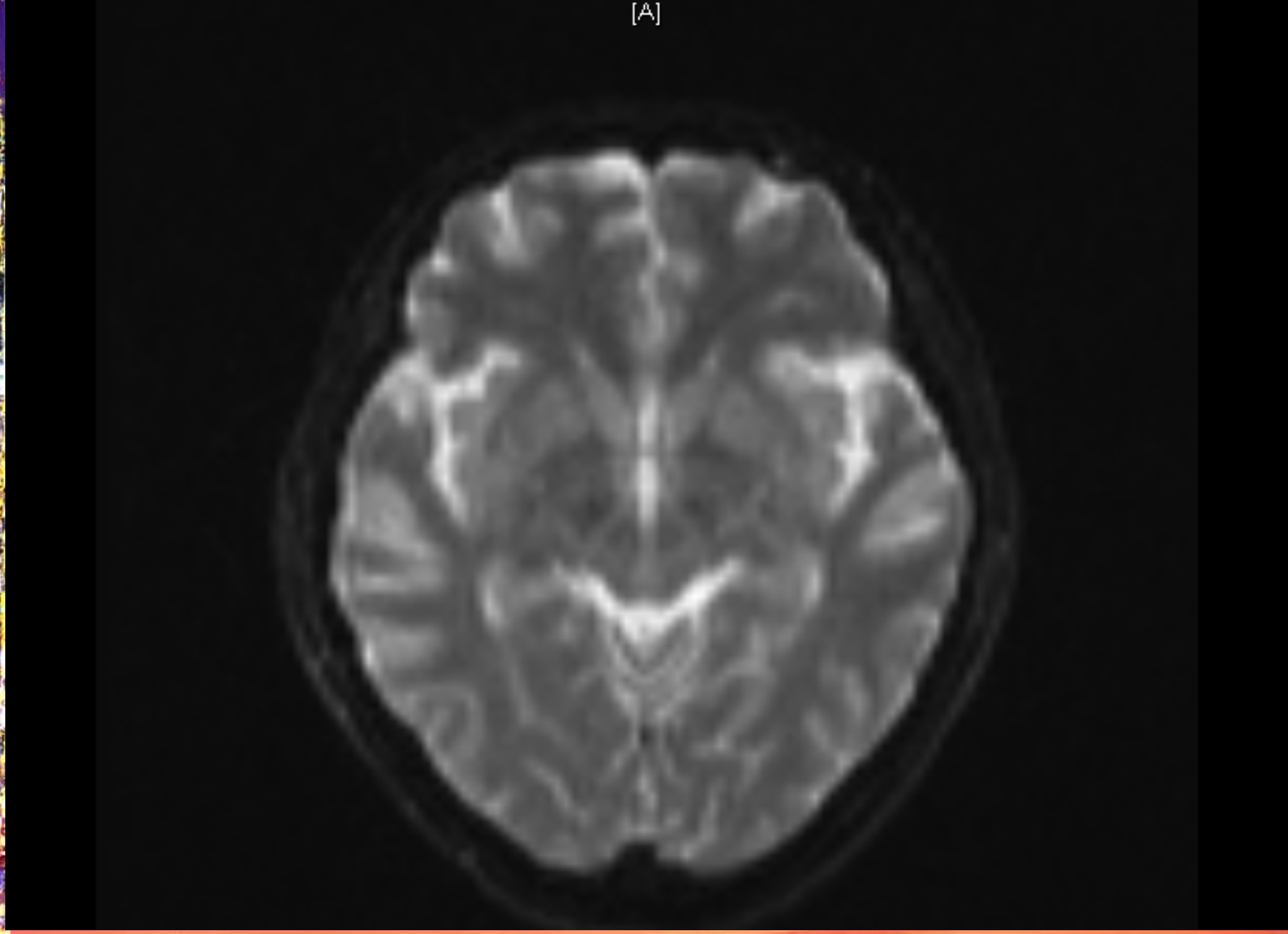
Anatomy of Pons



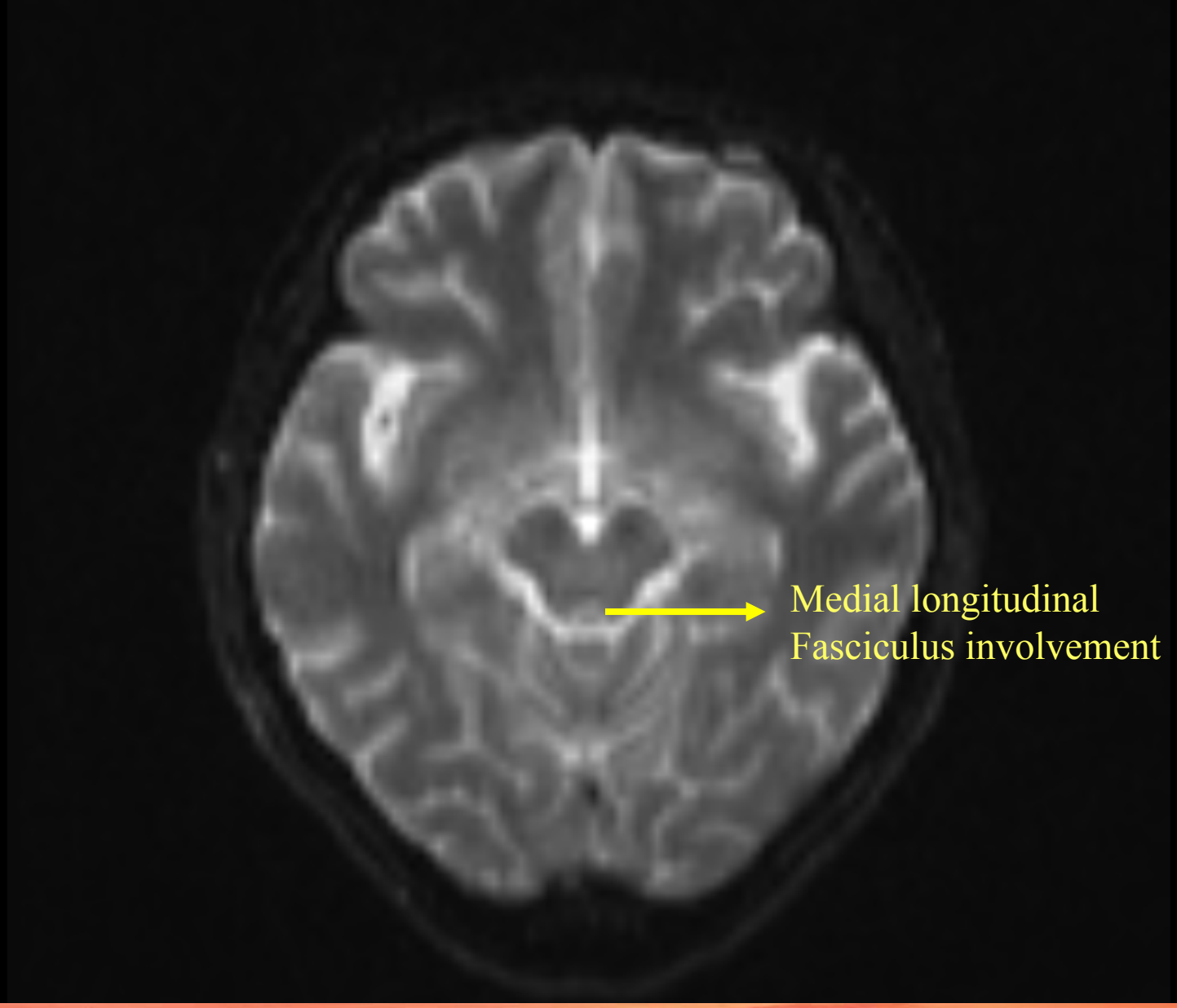


Medial longitudinal fasciculus

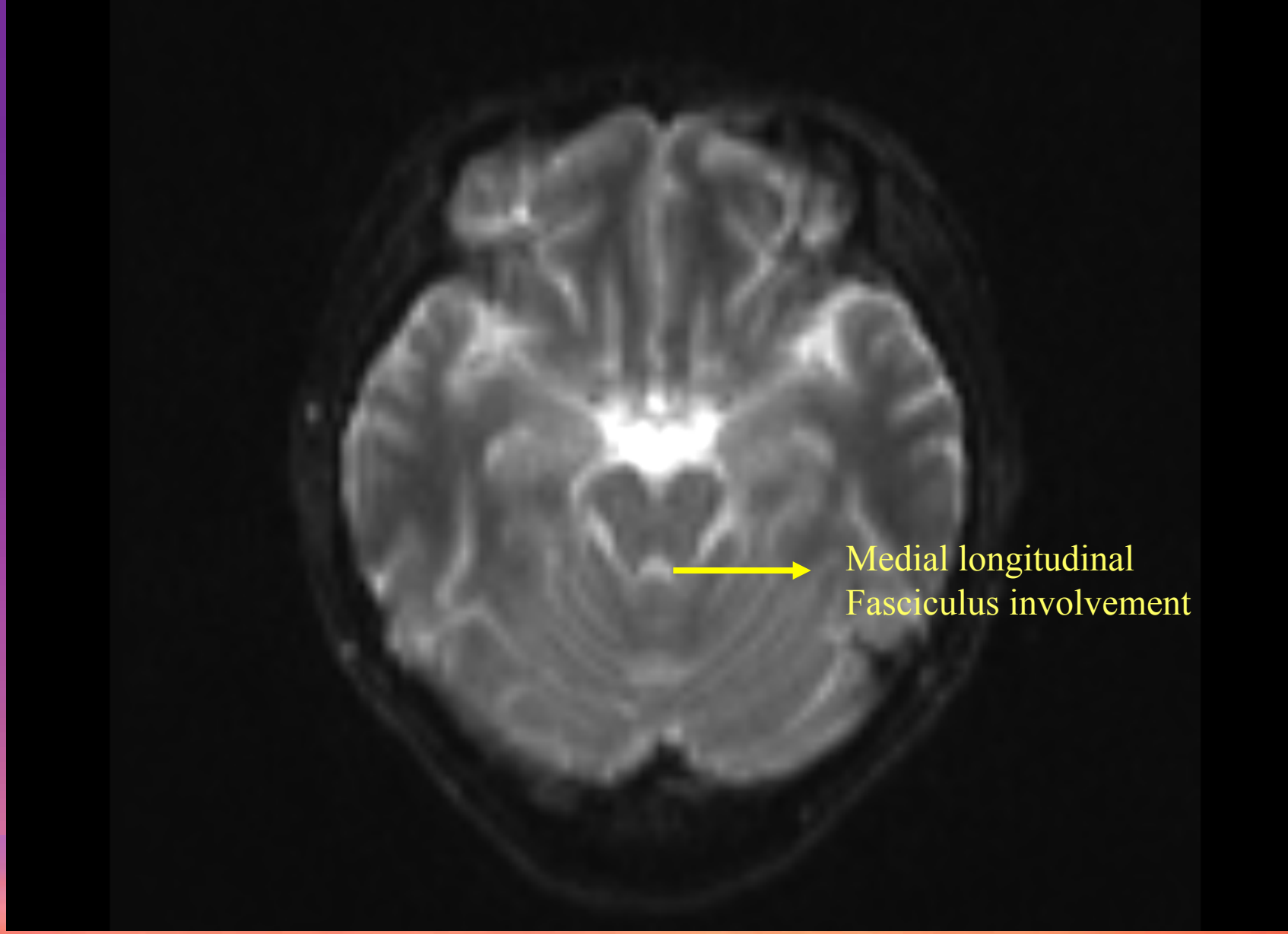
Clinical and Anatomical Correlation of Exotropia of Patient (P3)



Giant Panda Sign (P4)

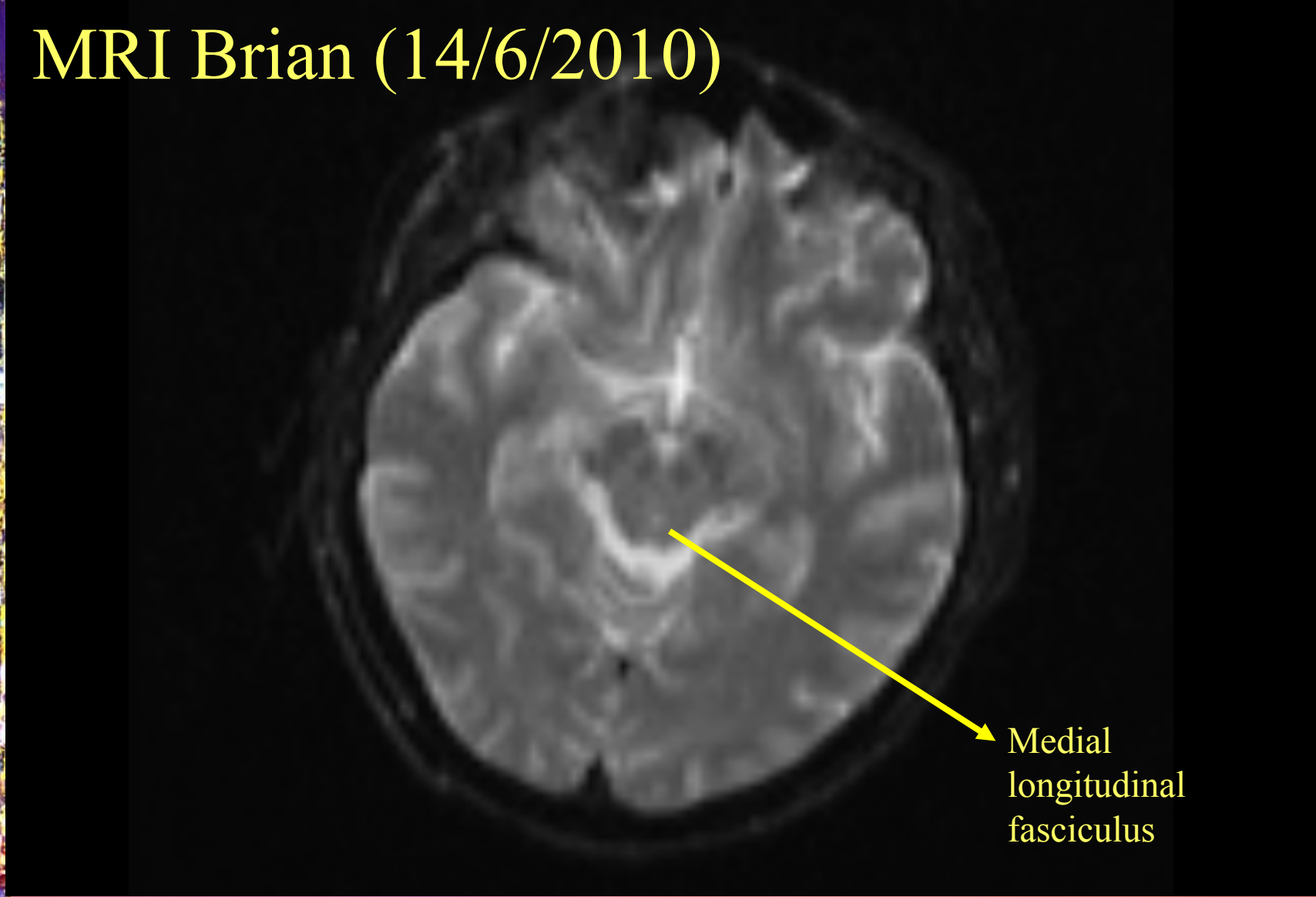


"Face of the miniature panda" (P4)

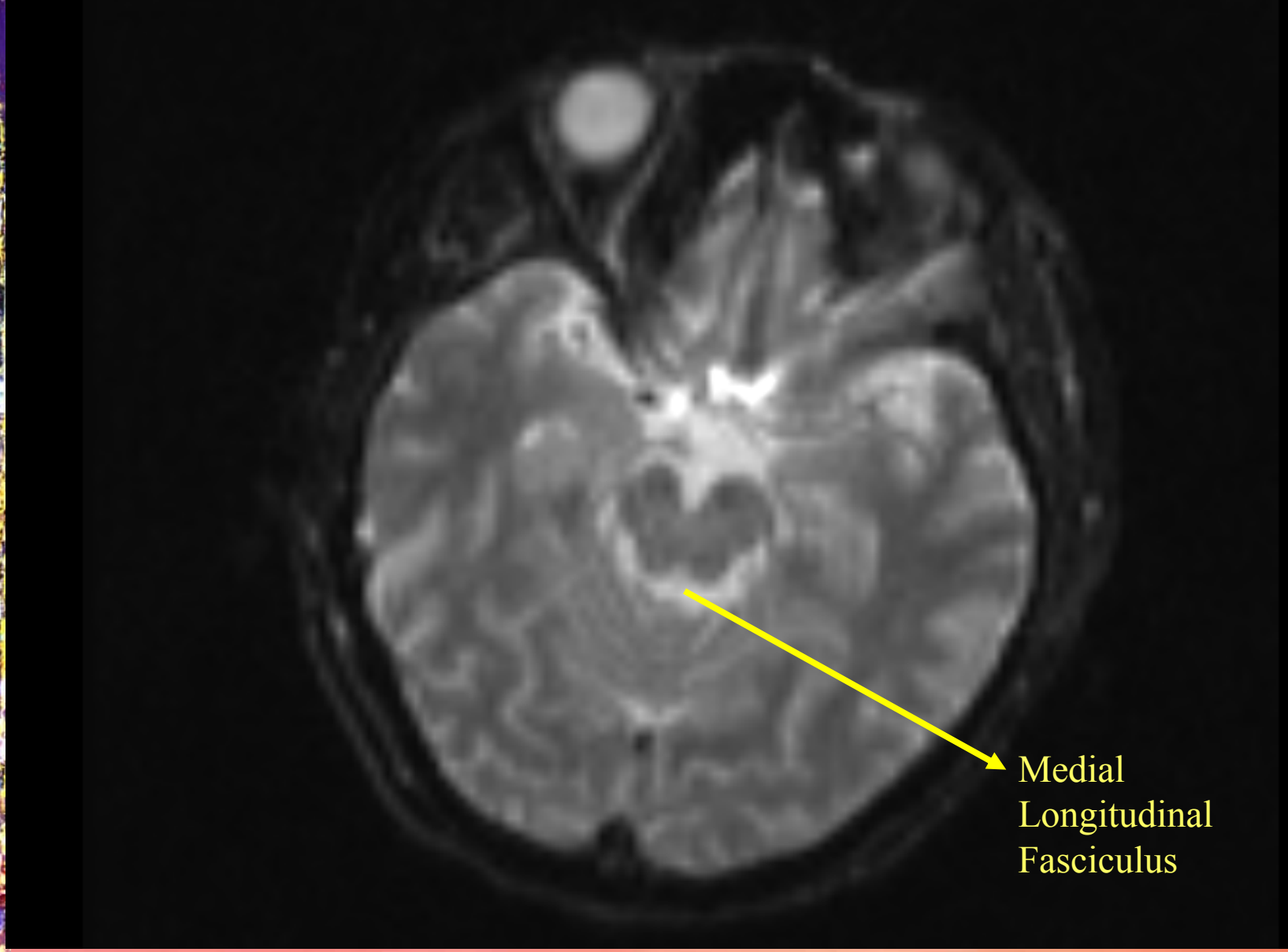


"Face of the miniature panda" (P4)

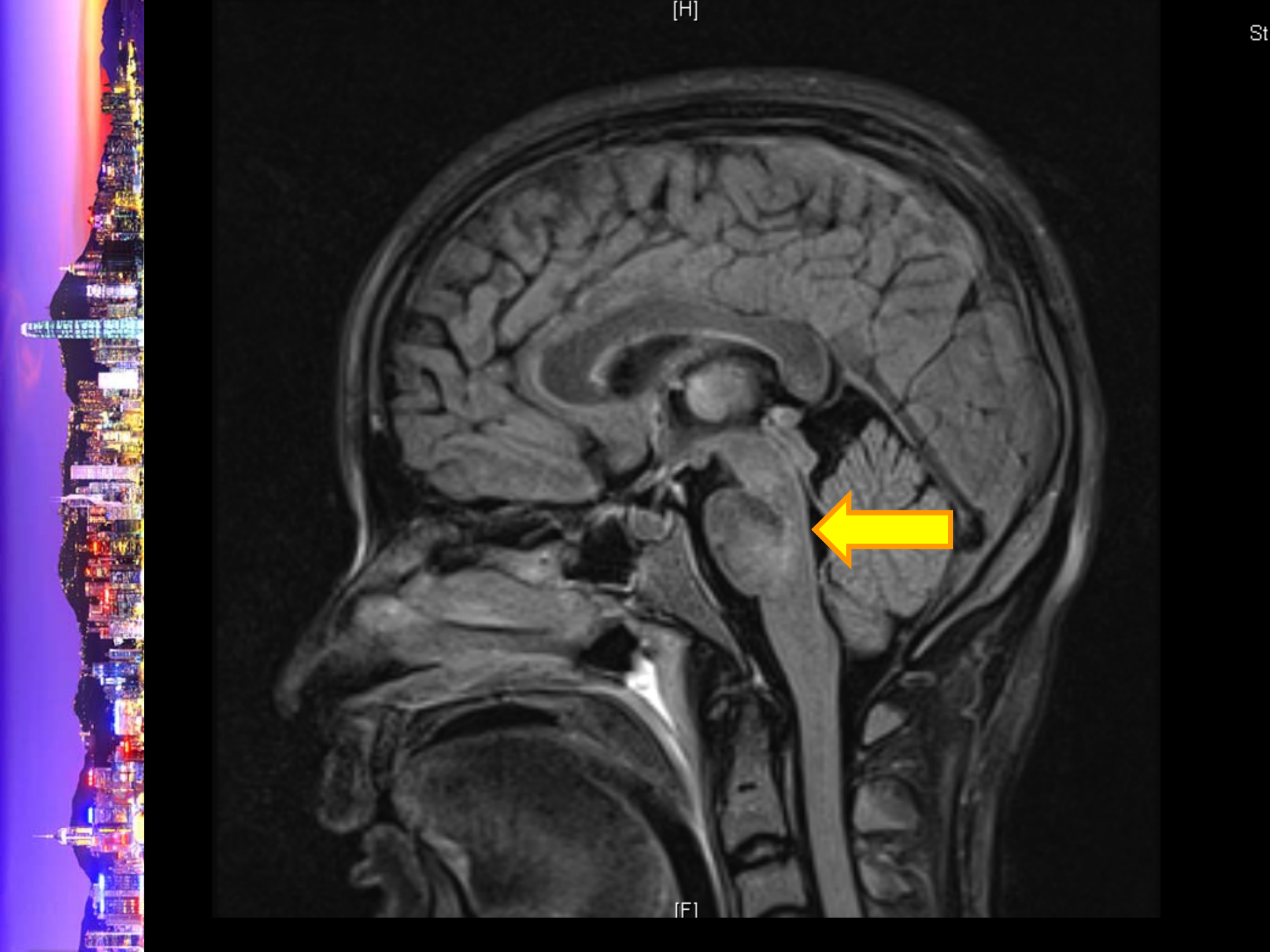
MRI Brian (14/6/2010)

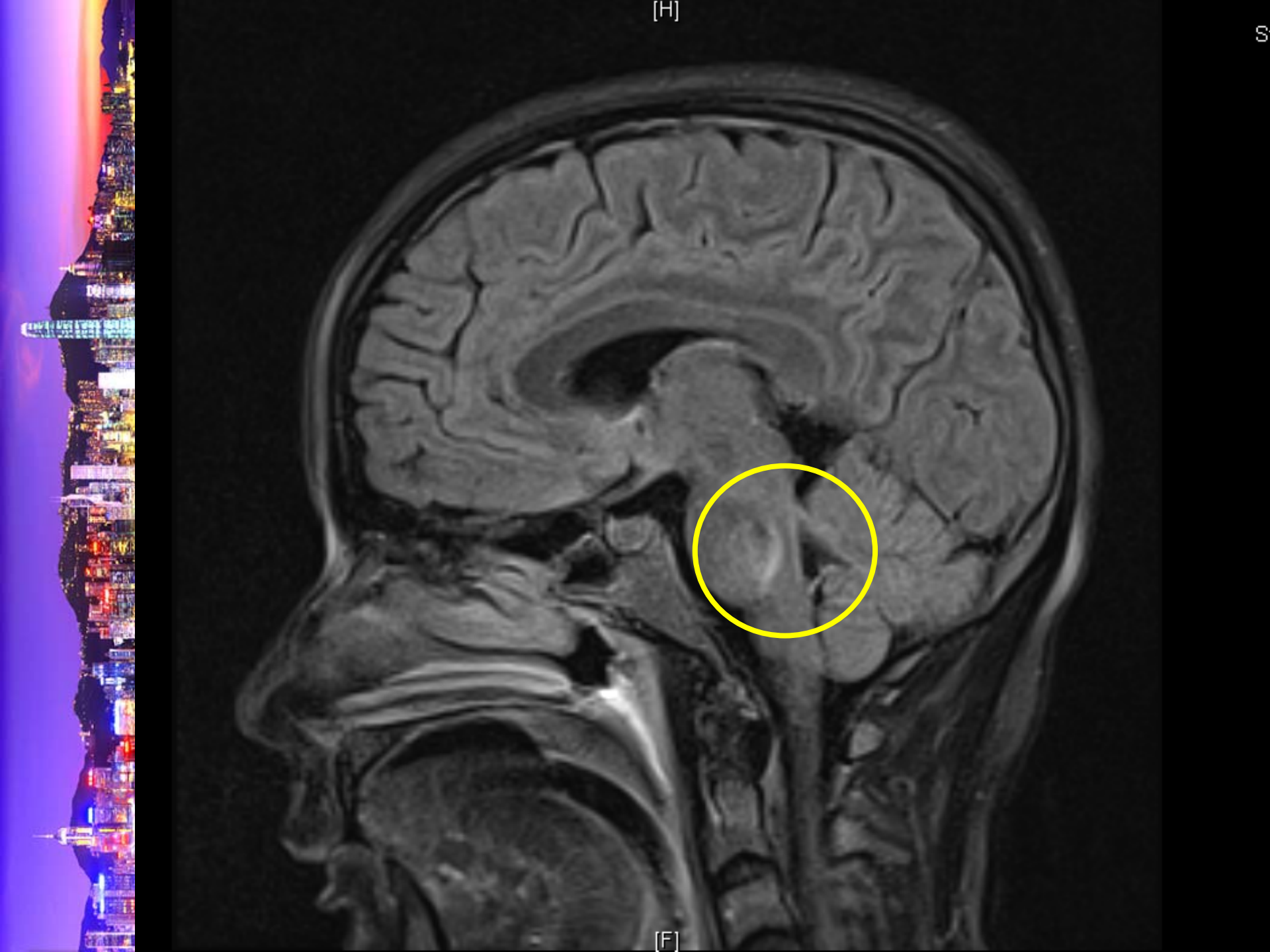


Giant Panda Sign (P5)

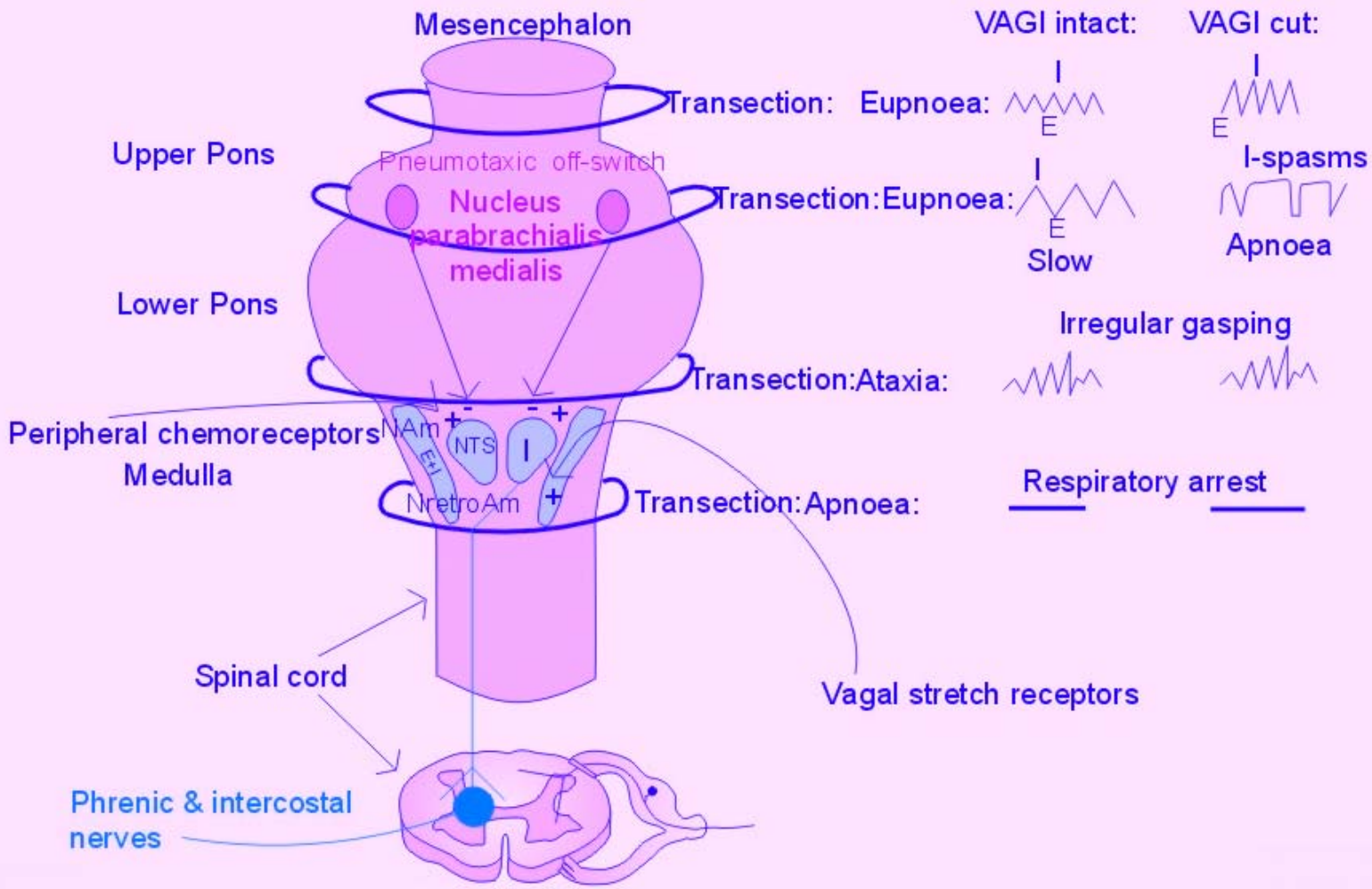


Minature Panda Sign (P5)


[H]
St
[F]


[H]
[F]

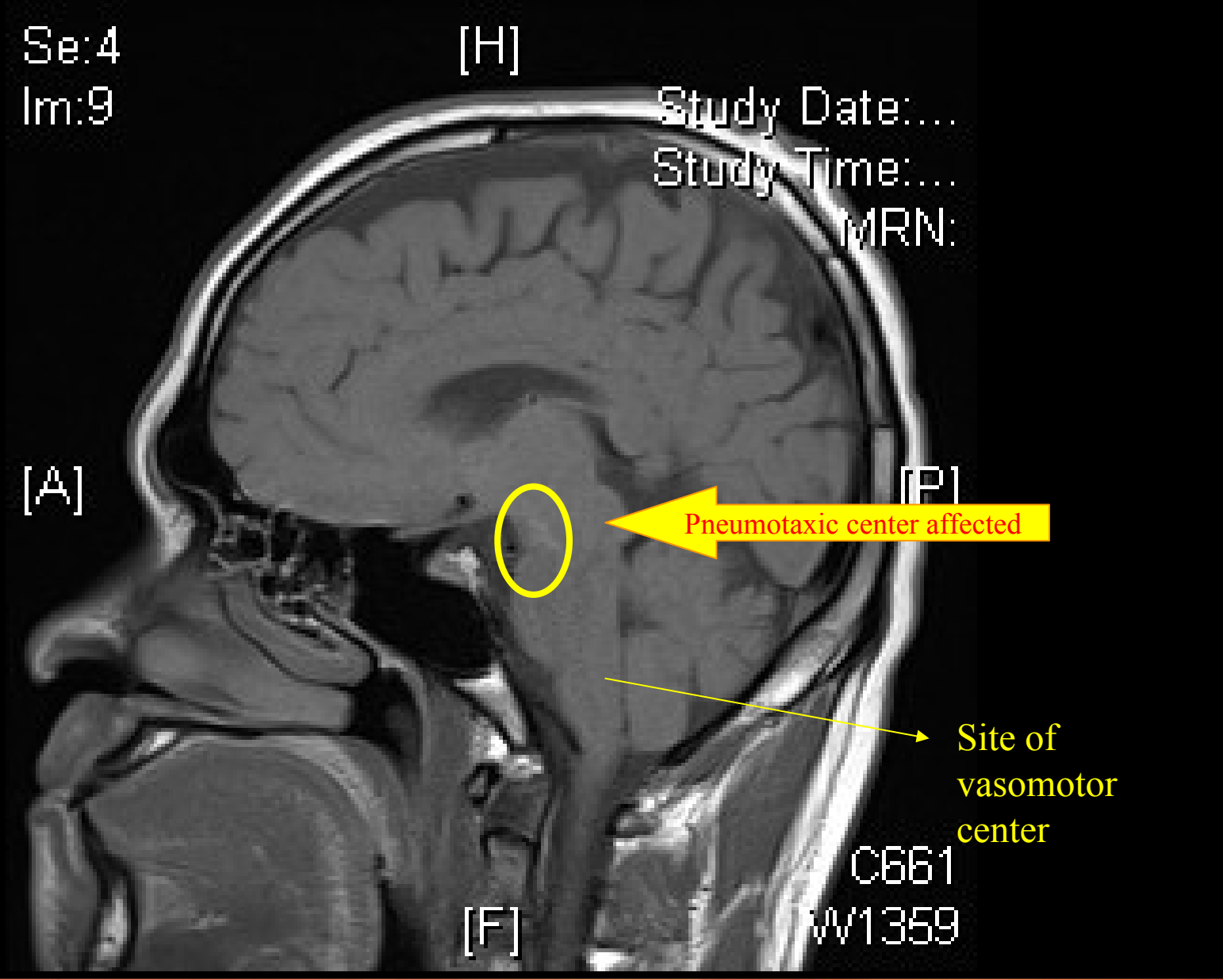
The Respiratory Rhythm Generator



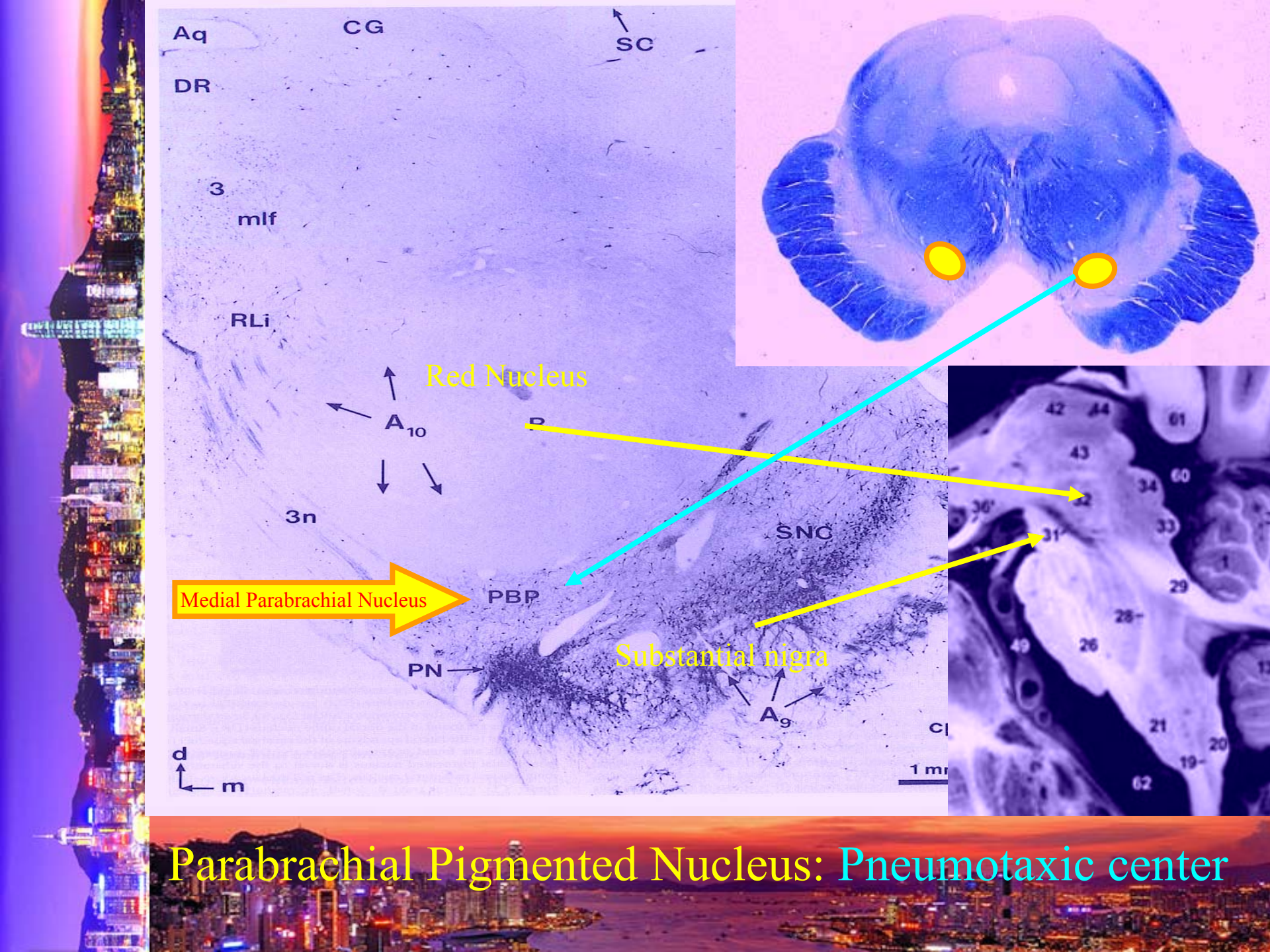
The respiratory rhythm generator with results of brain stem transection. NTS = nucleus tractus solitarius, NAm = nucleus ambigualis, NretroAm= nucleus retroambigualis.

Progress

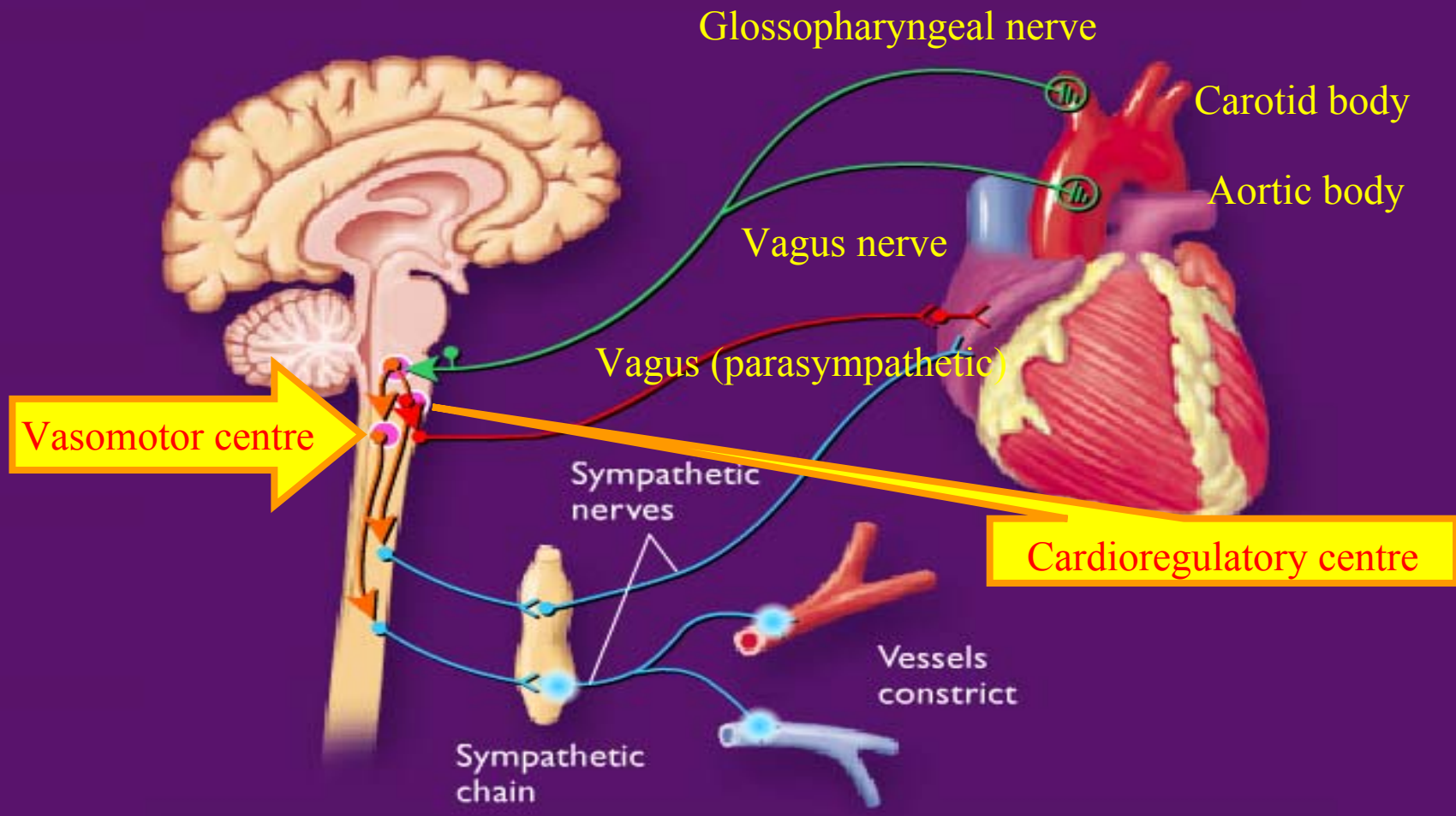
- Patient has transient compensated CO_2 retention but no intubation or mechanical ventilation required
- 28/05/10
  - pH 7.44 $PaCO_2$ 5.6 kPa PaO_2 17.3 kPa HCO_3 28 mmol/L BE 3.3 mmol/L K 4.1 mmol/L (18:40)
  - pH 7.40 $PaCO_2$ 6.4 kPa PaO_2 12.1 kPa HCO_3 29 mmol/L BE 3.5 mmol/L K 3.8 mmol/L (23:31)
- 29/05/10
  - pH 7.39 $PaCO_2$ 6.4 kPa PaO_2 13.8 kPa HCO_3 29 mmol/L BE 2.8 mmol/L K 4.0 mmol/L (02:28)
  - pH 7.43 $PaCO_2$ 5.5 kPa PaO_2 12.9 kPa HCO_3 27 mmol/L BE 2.1 mmol/L K 3.9 mmol/L (06:46)
  - pH 7.44 $PaCO_2$ 5.4 kPa PaO_2 13.9 kPa HCO_3 25 mmol/L BE 2.5 mmol/L (12:45)
- 30/5/10
  - pH 7.43 $PaCO_2$ 5.1 kPa PaO_2 13.6 kPa HCO_3 25 mmol/L BE 0.3 mmol/L K 3.9 mmol/L (30/05/10)
- Diplopia and cerebellar sign improved after IVIG therapy.
- Patient discharged to general ward on 31/5/2010
- Patient discharged from hospital on 4/6/2010



This explains why this patient has no vasomotor disturbance but only has diplopia and cerebellar sign with CO_2 retention



Parabrachial Pigmented Nucleus: Pneumotaxic center



Vasomotor Centre

Vasomotor Center

Cardiac Accelerator Center

Cardiac Inhibitory Center

Vasodilator Center

Vasoconstrictor Centre

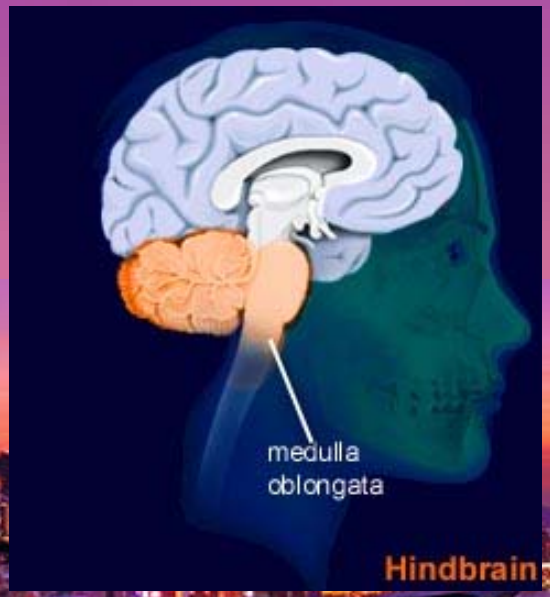
Dorsal motor nucleus Of vagus nerve Below hypothalamus

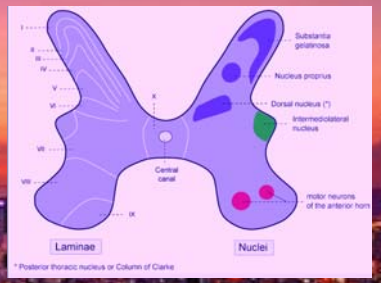
Caudal Ventrolateral Medulla

Rostral Ventrolateral Medulla

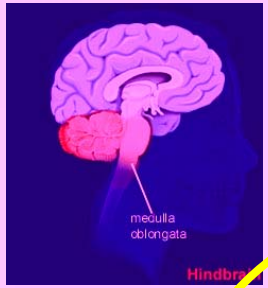
Reticulospinal tract To sympathetic Preganglionic neurons

Inhibitory GABAergic input





EV 71 Rhombencephalitis

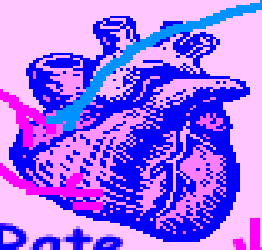


Hypertension

CARDIAC ACCELERATOR CENTER

CARDIAC INHIBITORY CENTER

VASO-CONSTRICTOR CENTER



↓ Heart Rate

↓ Heart Rate
↓ Contractility

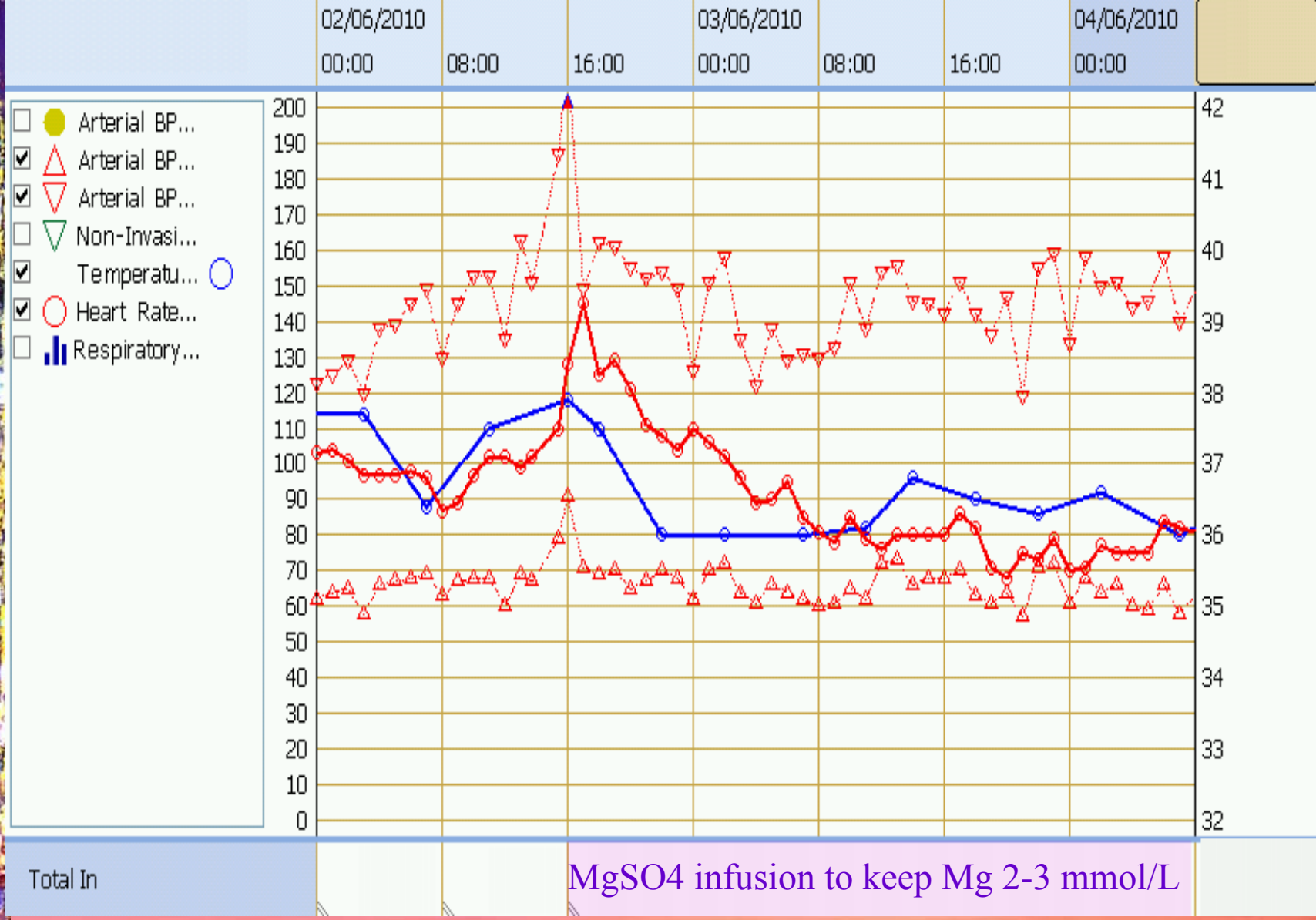
↓ Cardiac Output
↓ Peripheral Vascular Resistance

Vasodilation

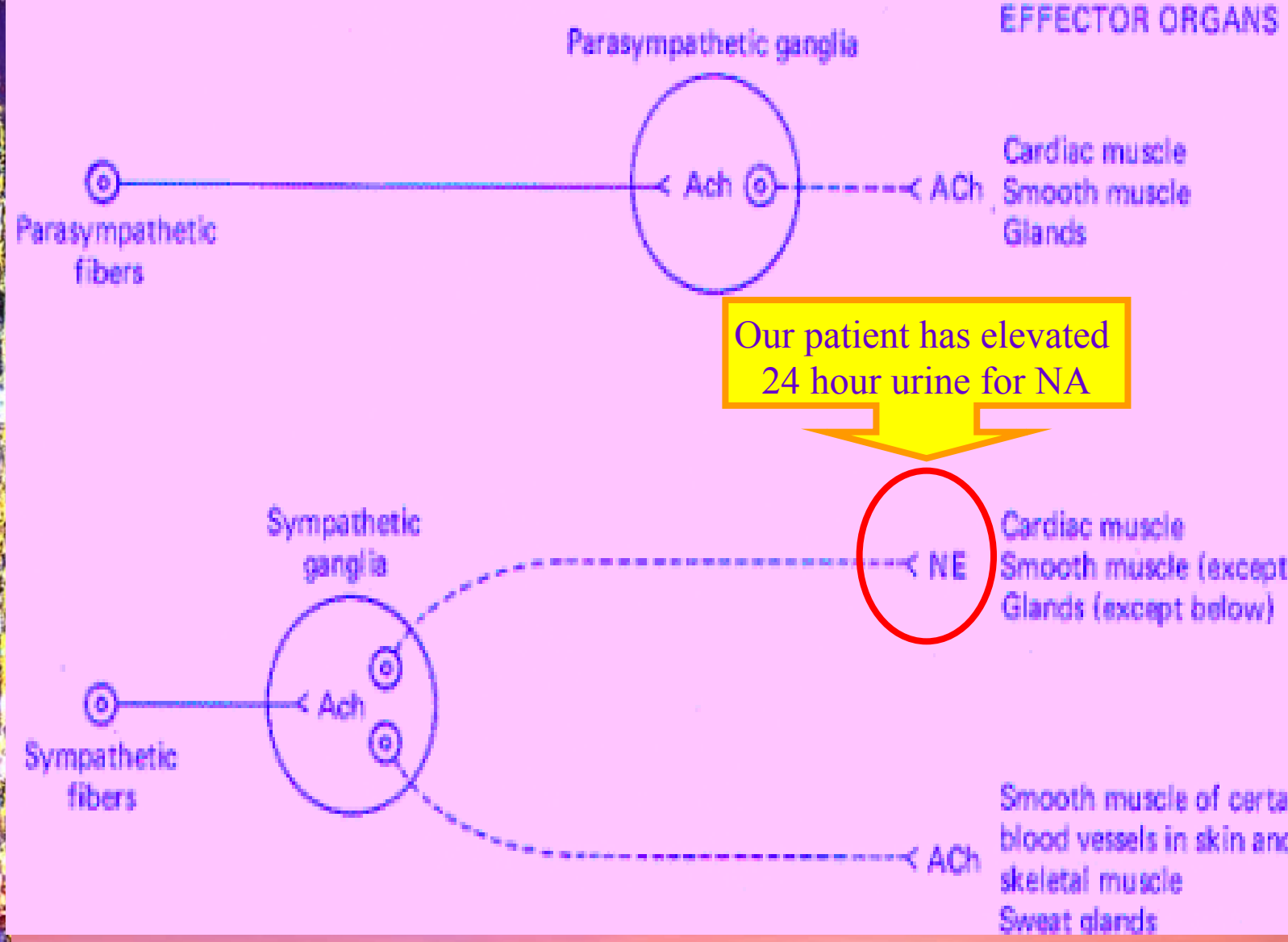
Rostral Ventrolateral Medulla Stimulation ➔ Tachycardia and Hypertension

P3 Hypertension and tachycardia

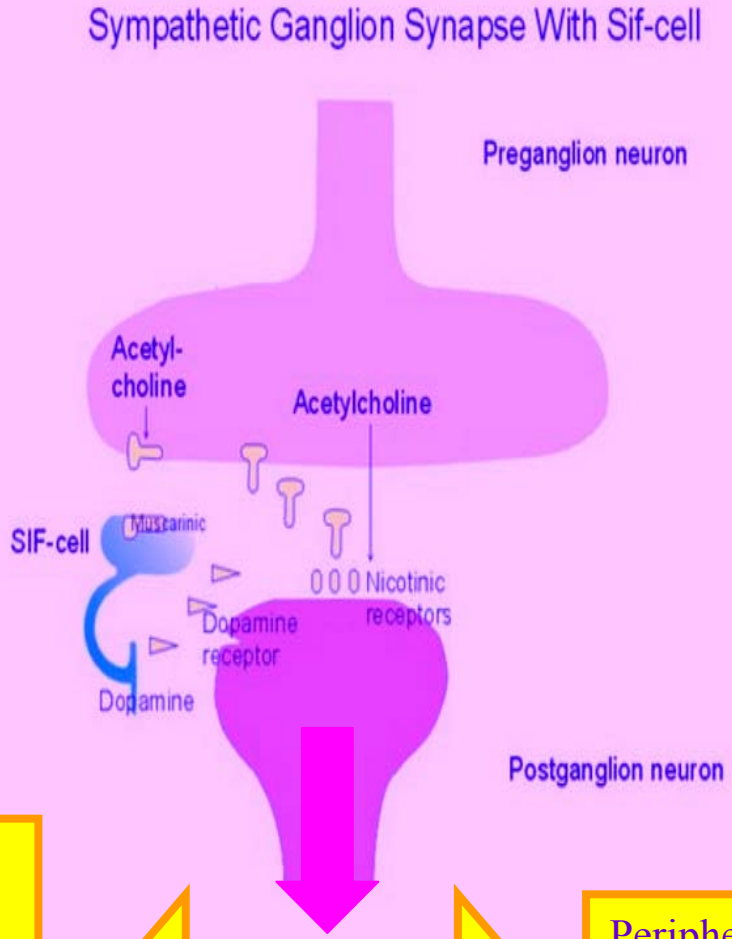
- Patient has hypertension and tachycardia after ICU admission
- Put on MgSO4 infusion on 2/6/2010 - 8/6/2010 to keep Mg level 2-3 mmol/L
- BP and tachycardia well controlled in the absence of anti-hypertensive medication after MgSO4 infusion
- Mg SO4 infusion was weand off after several days when BP become more stable
- 24 hour urine showed elevated noradrenaline during hypertension
- Ur. Volume,24h
  - (a) Adrenaline 27(04/06/10) 51(06/06/10) 54(07/06/10) (19 - 113) nmol/d
  - (b) Noradrenaline 283 (04/06/10) 536 (06/06/10) 525 (07/06/10) (63 - 416) nmol/d
  - (c) VMA 7.6 (06/06/10) 7.1 (07/06/10) (N< 41.0) umol/d



MgSO4 infusion to control hypertensive storm from vasomotor centre (P3)



Adrenal tumour has been excluded because patient has CT scan of abdomen on 28/5/2010



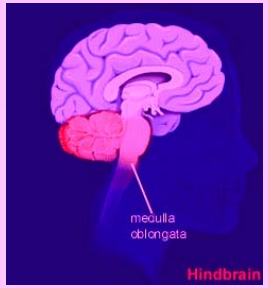
β 1-receptors stimulation lead to tachycardia and increased myocardial contractility

Noradrenaline

Peripheral sympathetic vasoconstriction
➔ Constriction of both
(a) arterioles and arterial vessel
(b) veins and venules.

Sympathetic Stimulation

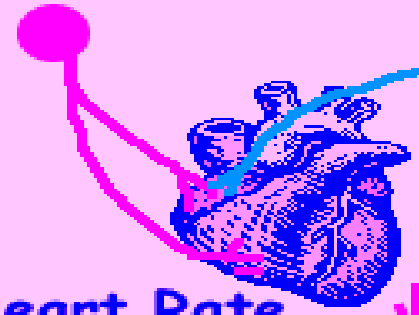
EV 71 Rhombencephalitis



CARDIAC ACCELERATOR CENTER

CARDIAC INHIBITORY CENTER

VASO-CONSTRICTOR CENTER



↓ Heart Rate

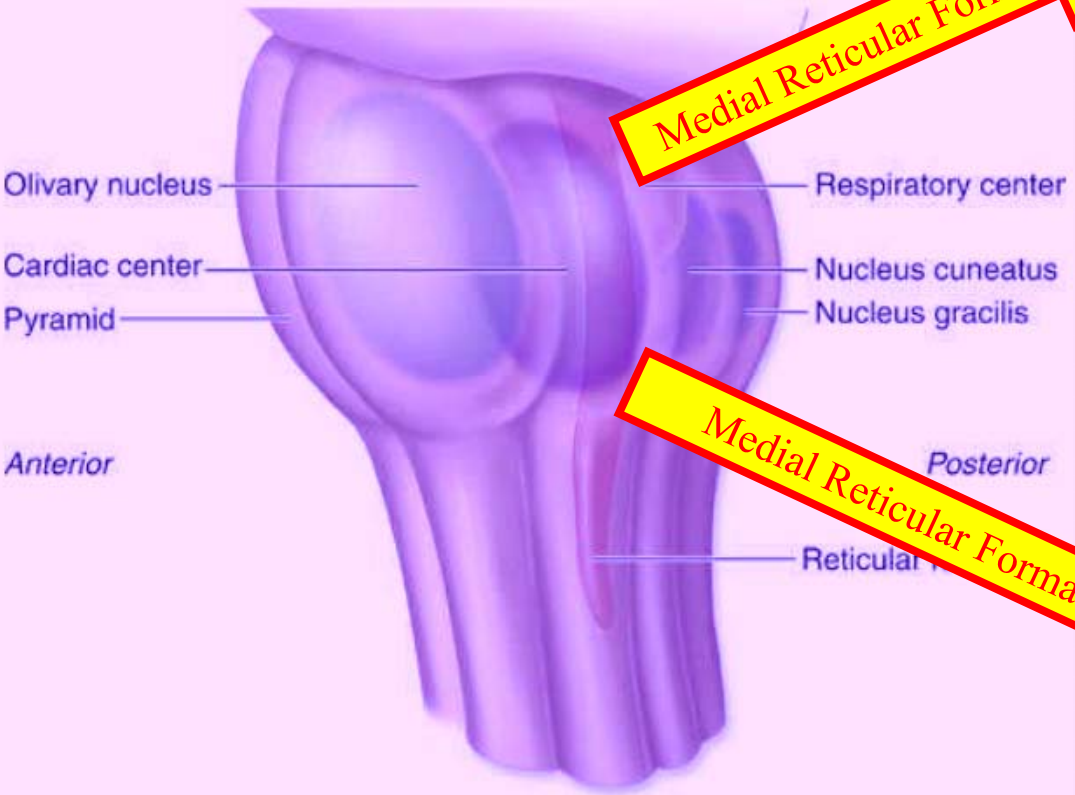
↓ Heart Rate
↓ Contractility

↓ Cardiac Output
↓ Peripheral Vascular Resistance

Vasodilation

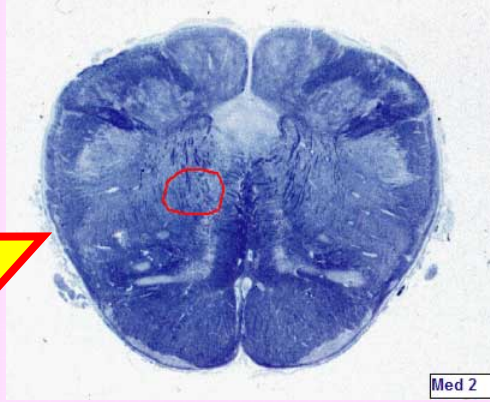
Shock and Cardiovascular Collapse

Pathogenesis of Shock in Vasomotor collapse

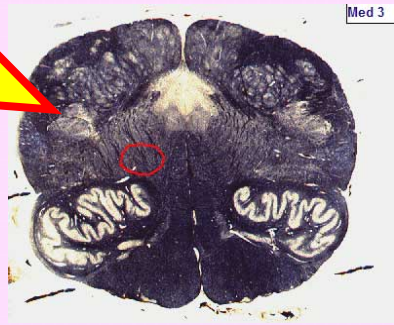


Medulla oblongata, lateral view

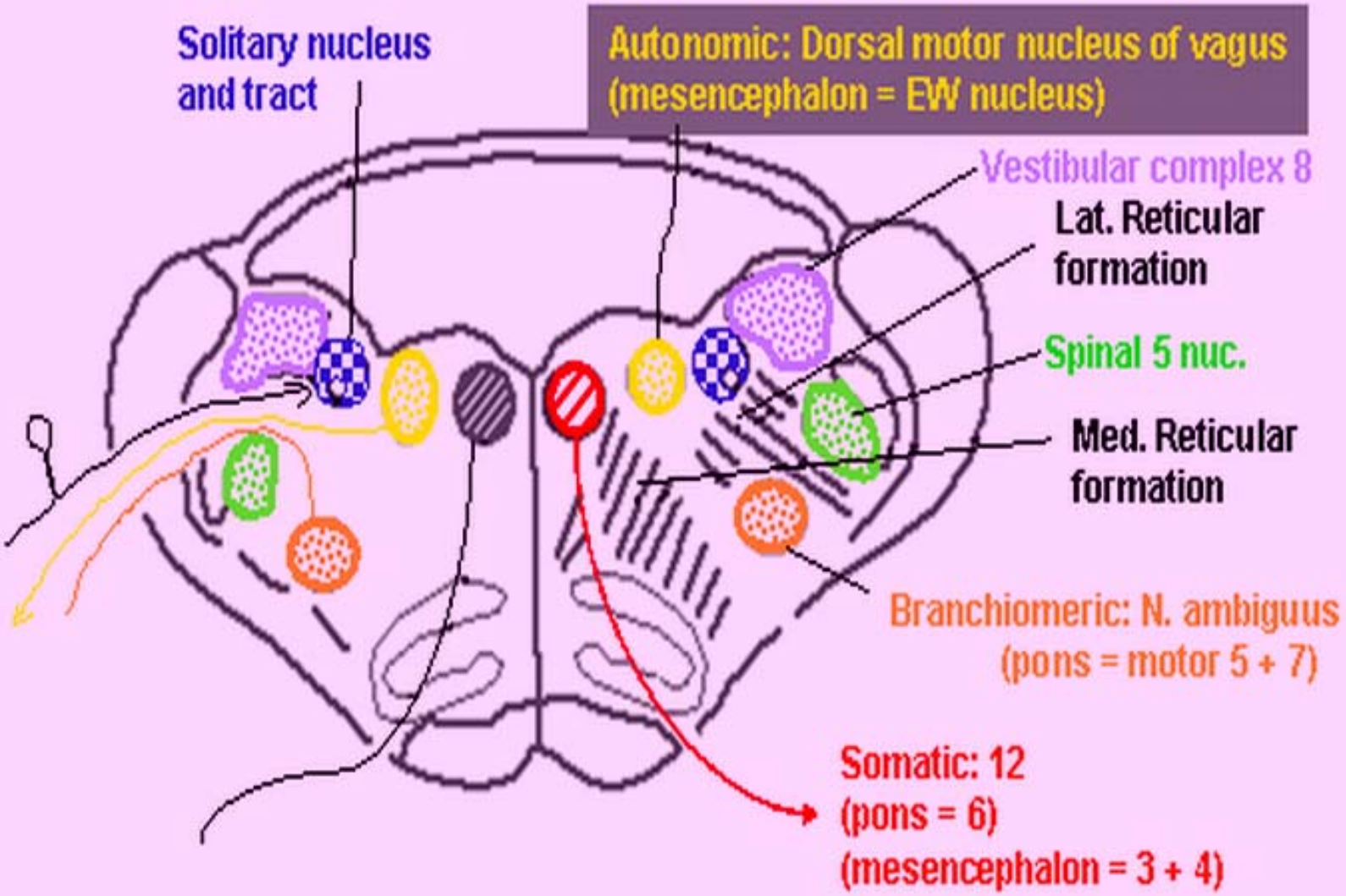
Medial Reticular Formation



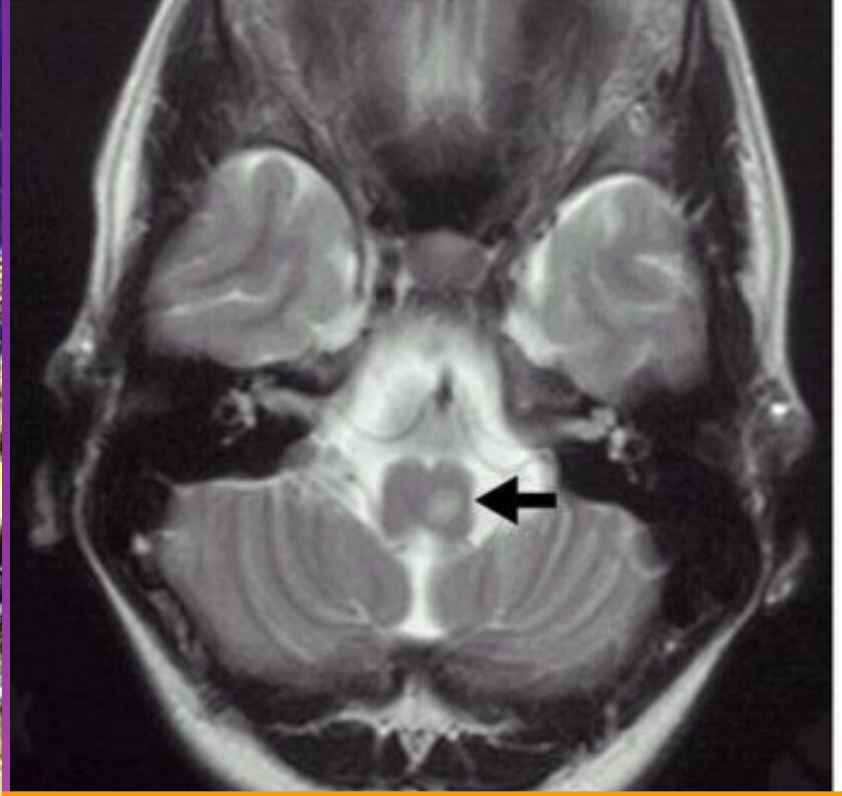
Medial Reticular Formation

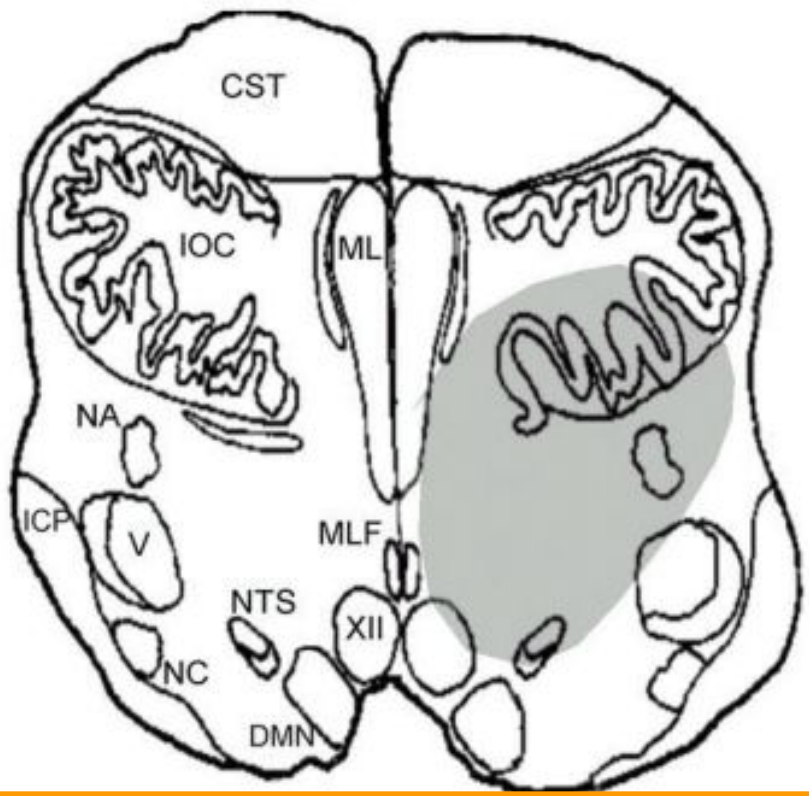


Vasomotor Centre is at the Medulla Oblongata



Medial reticular formation is part of the vasomotor center

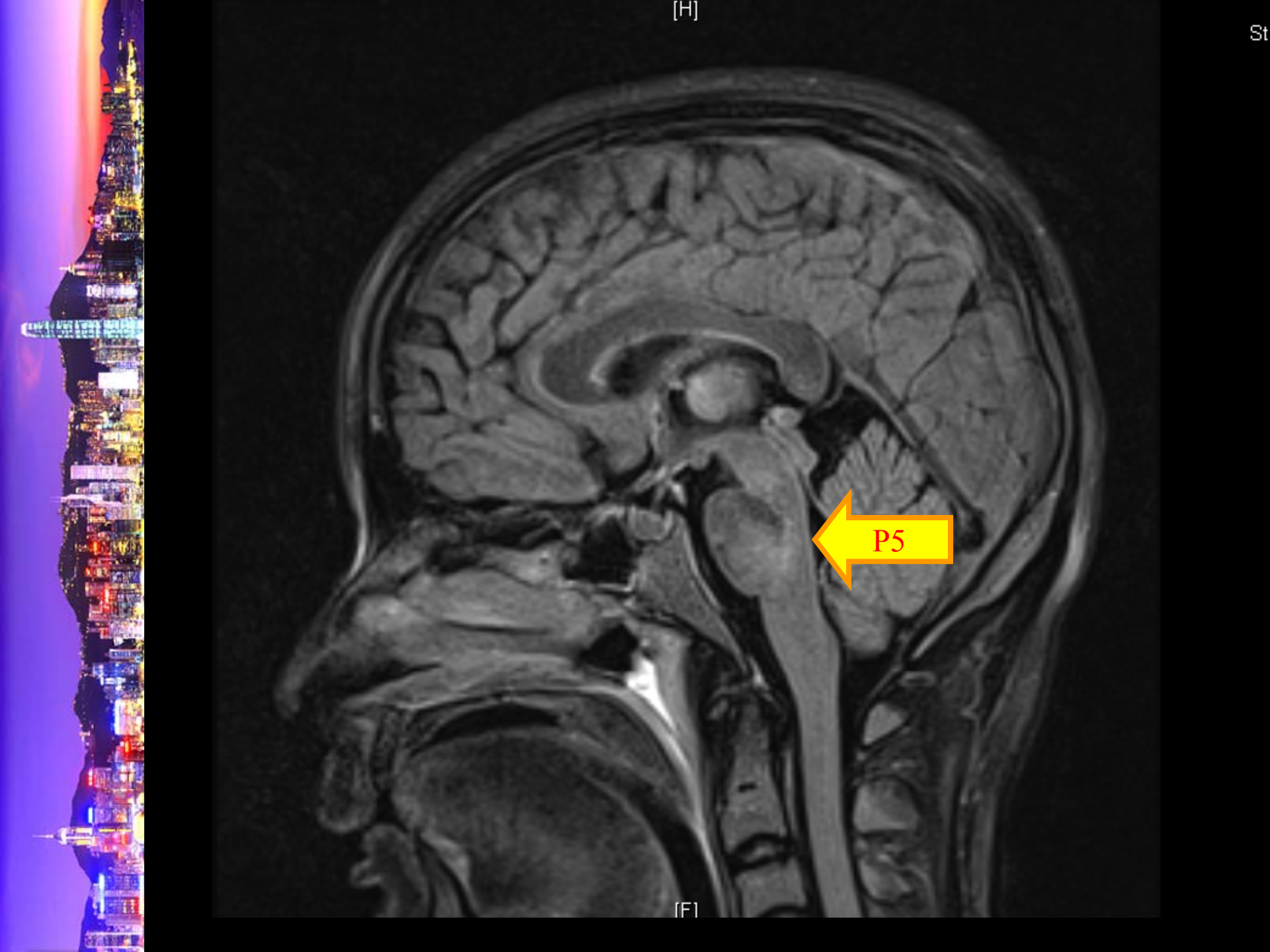


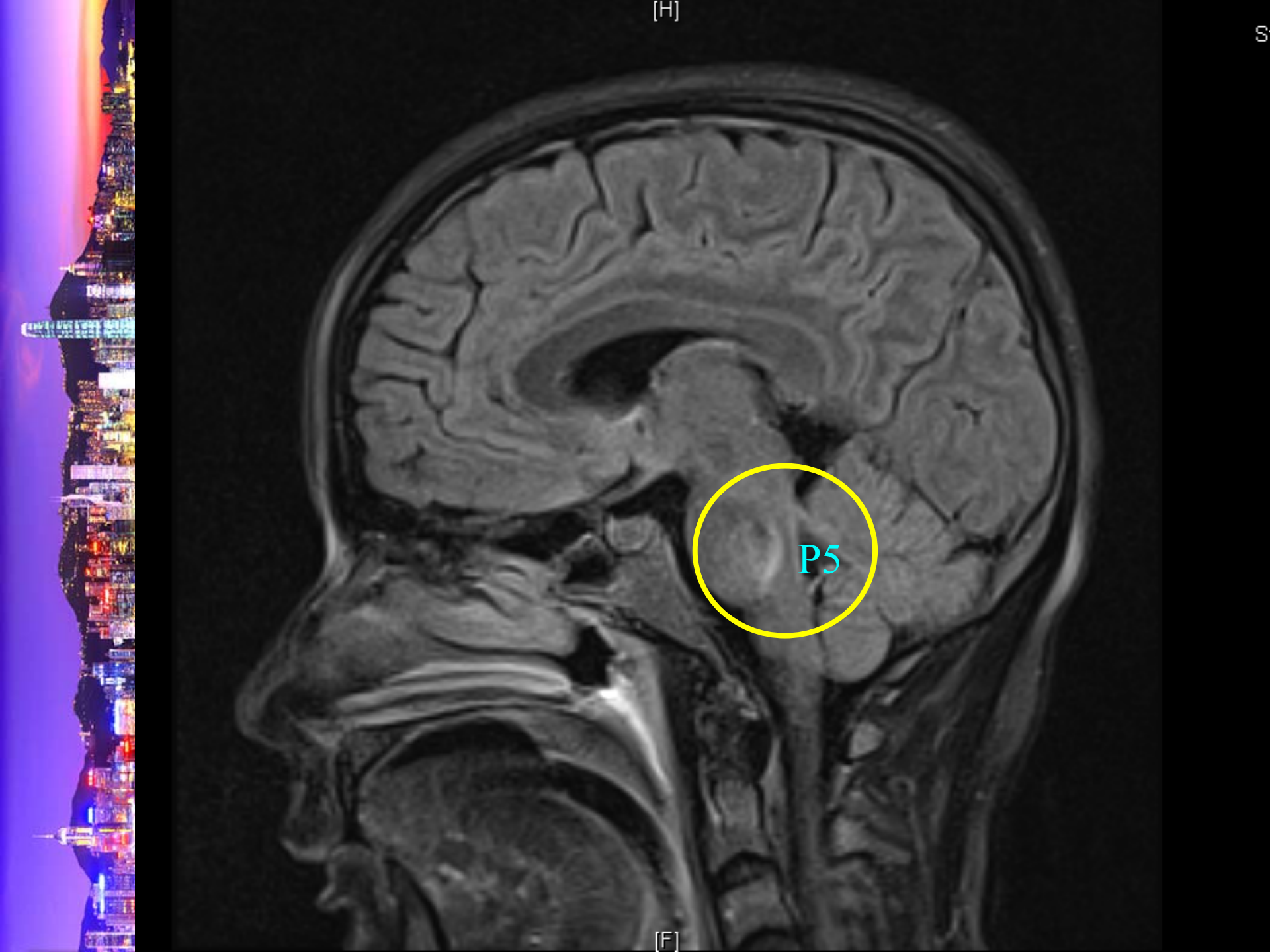


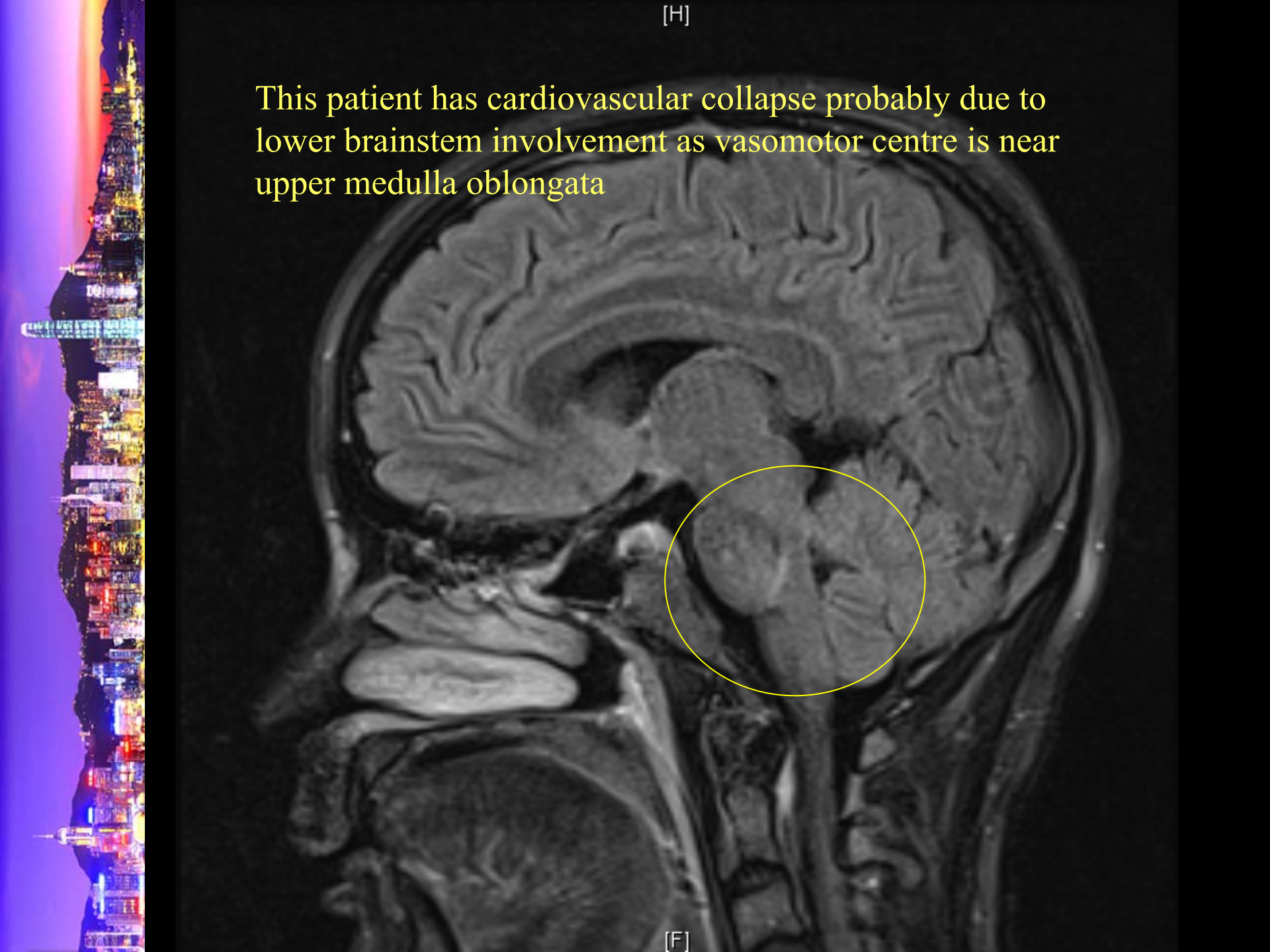
An example of pulmonary edema secondary to involvement of medial reticular formation in a patient with multiple sclerosis. Cerebral damage can lead to sympathetic stimulation, resulting in systemic and pulmonary hypertension and cardiac dysfunction with secondary neurogenic pulmonary oedema or even vasomotor collapse. The caudal part of the nucleus tractus solitarius, the dorsal motor nucleus of the vagal nerve, and the medial reticular formation are believed to have a role in the pathogenesis of neurogenic acute pulmonary edema

A woman with multiple sclerosis and pink saliva Martha T van de Beek, Walter Taal, Rolf F Veldkamp, Dr Charles J Vecht The Lancet Neurology, Volume 2, Issue 4, Pages 254 - 255, April 2003

Pathogenesis of Neurogenic Acute Pulmonary Edema


[H]
St
P5
[F]


[H]
P5
[F]

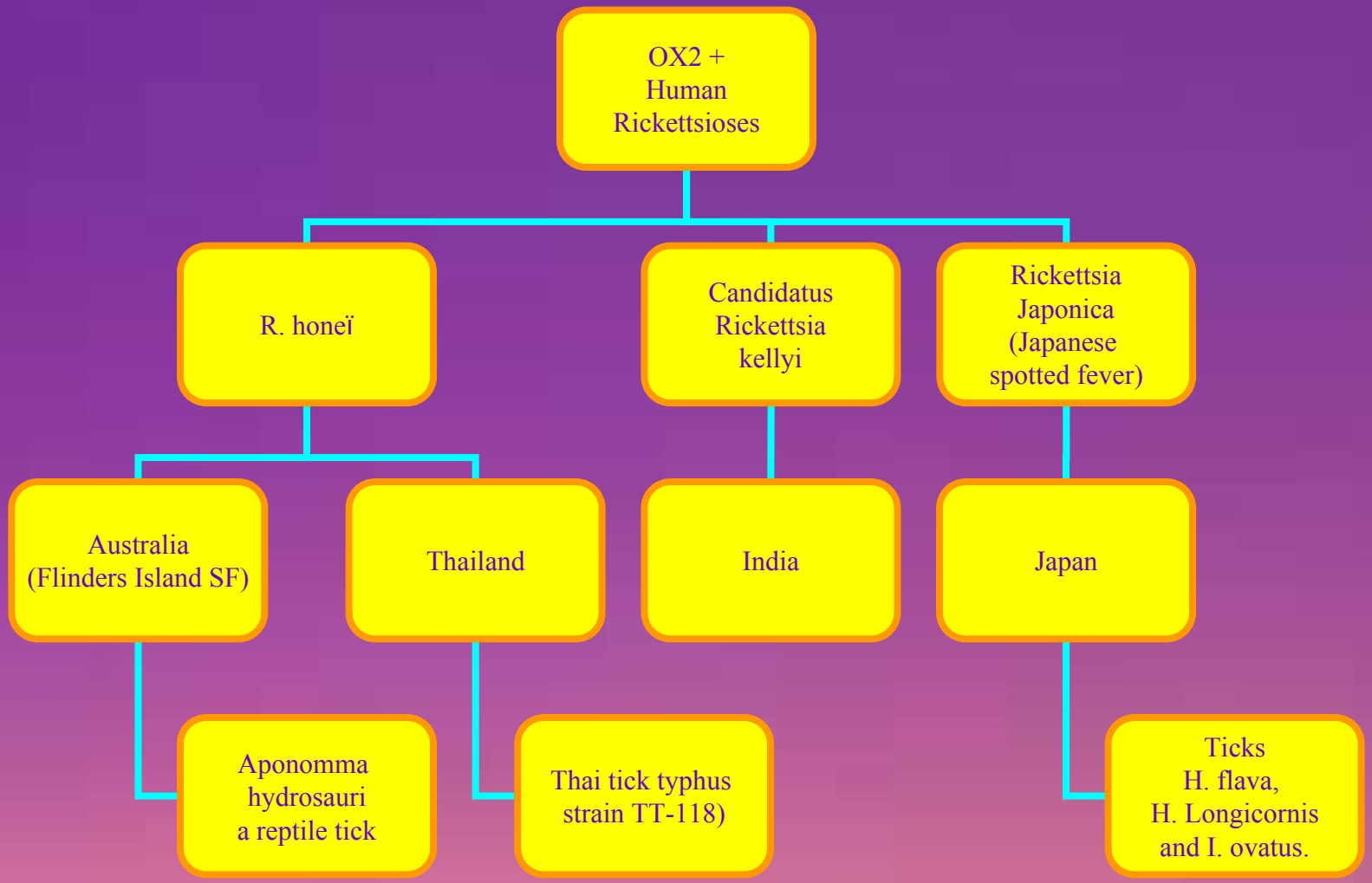

[H]
This patient has cardiovascular collapse probably due to lower brainstem involvement as vasomotor centre is near upper medulla oblongata
[F]

Patient 3
(? Unidentified Rickettsia infection)

- Weil Felix Test:
- OX2: 1:80 (2/6/2010) 1:640 (14/06/10) > 1:1280 (28/06/10)
- OX19: 1:20 (2/6/2010) 1:20 (14/06/10) 1:80 (28/06/10)
- OXK: <1:20 (2/6/2010) <1:20 (14/06/10) 1:40 (28/06/10)

- Spotted fever group rickettsia < 1:128 (2/6/10) < 1:128 (18/6/10)
- Typhus group rickettsia < 1:128 (2/6/10) < 1:128 (18/6/10)
- Orientia Tsutsugamushi < 1:128 (2/6/10) < 1:128 (18/6/10)
- Rickettsia Japonica <1:128

Infection	Vector	PROGEN antigen suspension		
		OX19	OX2	OXK
Epidemic typhus	Louse	+++	+	-
Murine typhus	Flea	+++	+	-
Endemic typhus	Flea	+++	+	-
Rocky Mountain Spotted Fever	Tick	+++	+	-
Tsutsugamushi Fever	Mite	-	-	+++
Scrub typhus Mite	Mite	-	-	+++
Boutonneuse fever	Tick	+	+	+
South African tick-bit fever	Tick	+	+	+
Brills, disease Louse	Louse.	Usually neg.	Usually neg.	-/±
Trench fever Louse	Louse	-	-	-
Q Fever	Tick	-	-	-

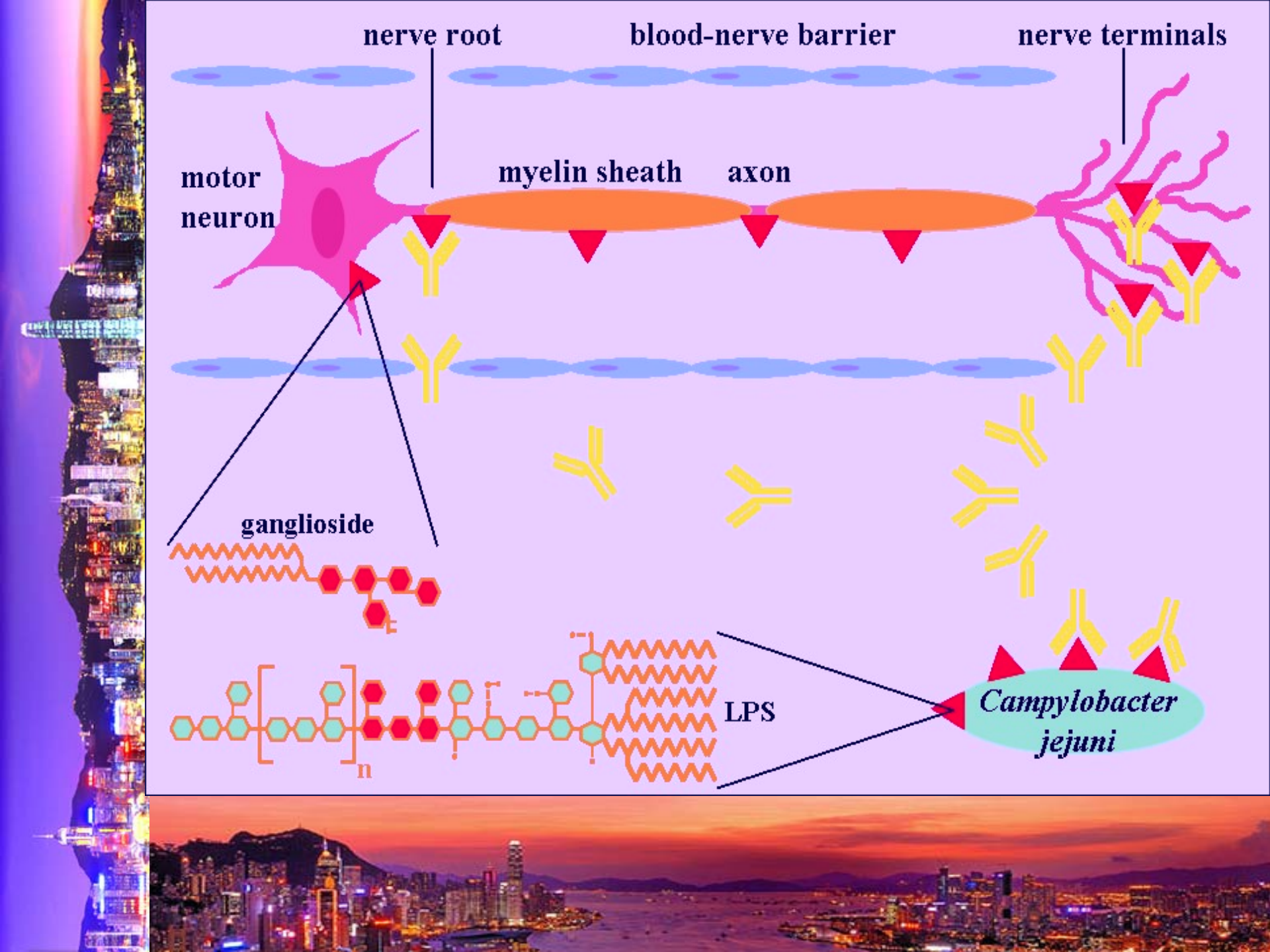


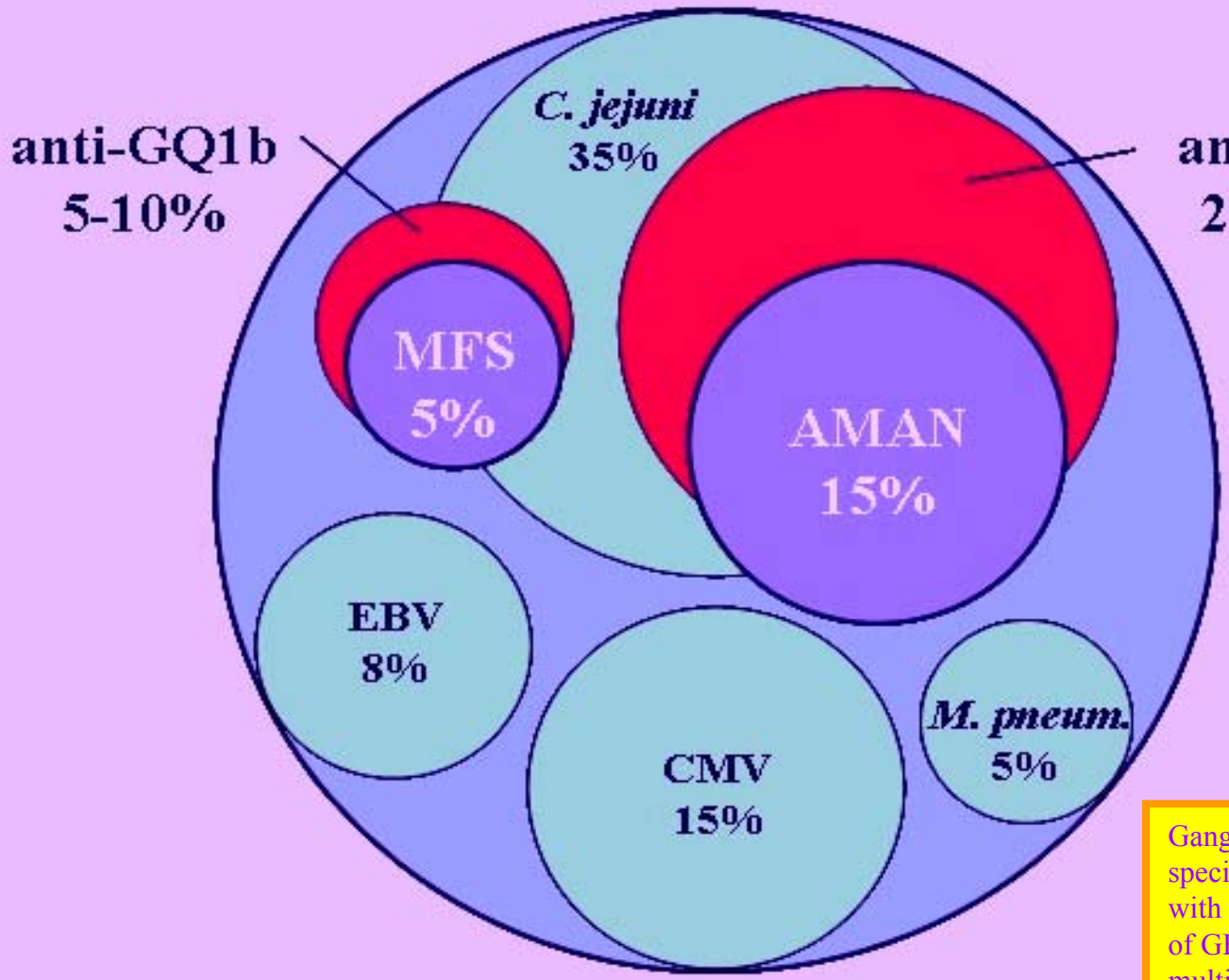
Japanese spotted fever: report of 31 cases and review of the literature Mahara F Emerg Infect Dis. 1997 Apr-Jun;3(2):105-11.

"*Candidatus Rickettsia kellyi,*" India Jean-Marc Rolain,* Elizabeth Mathai,† Hubert Lepidi,* Hosaagrahara R. Somashekar,† Leni G. Mathew,† John A.J. Prakash,† and Didier Raoult Emerg Infect Dis. 2006 Mar;12(3):483-5.

Patient 4
(?Campylobacter Jejuni Infection)

- NCT
  - Mild decrease CMAP of bil median and ulnar nerve, with normal veloocity and F wave
  - LL F waves are all absent
  - Also completely absence sensory response
  - Findings are compatible with Miller-Fisher Variant of GBS
- Ganglioside GQ1b autoantibodies 57 (N<20) (12/6/2010)

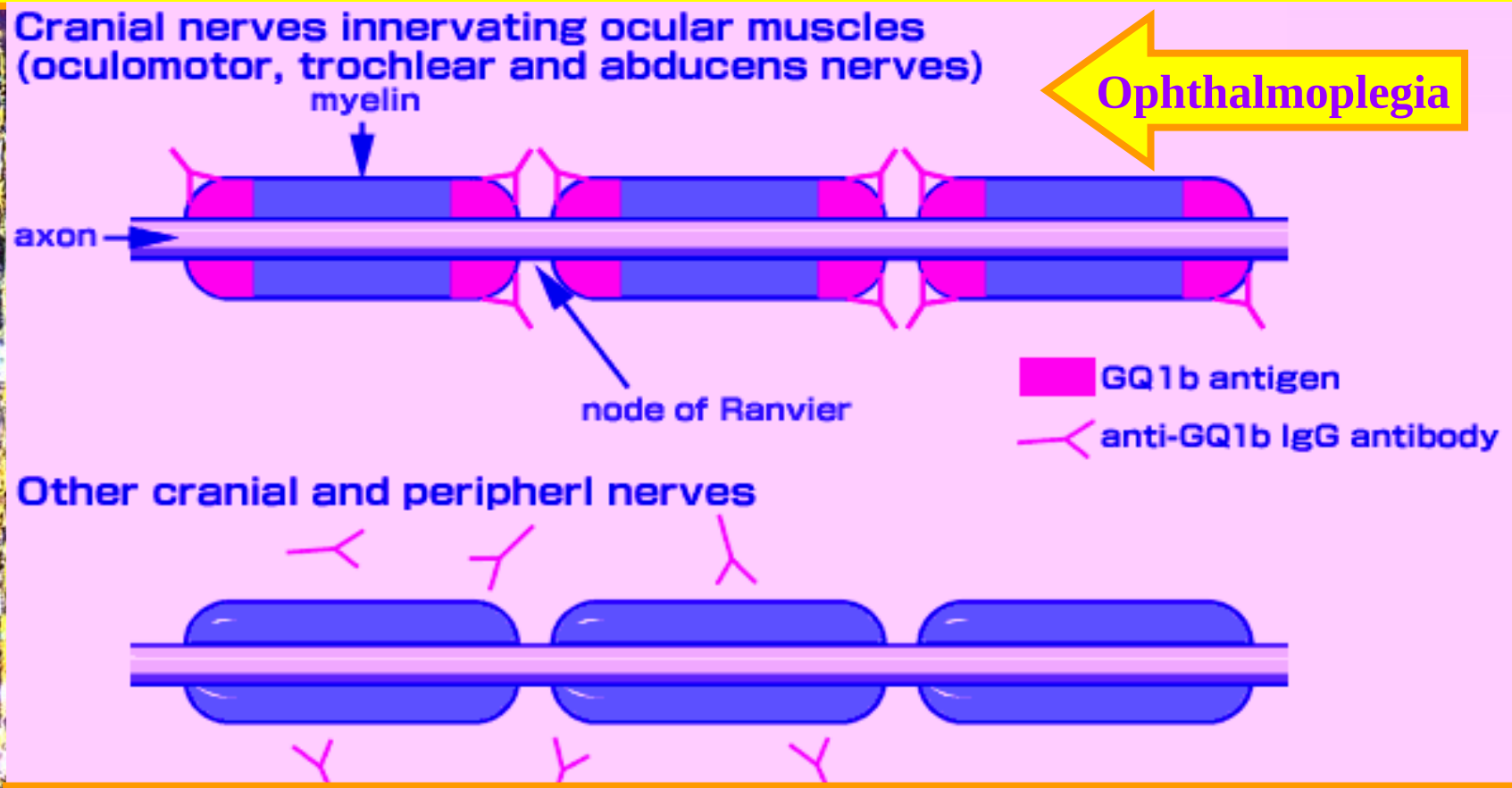

nerve root
blood-nerve barrier
nerve terminals
motor neuron
myelin sheath
axon
ganglioside
LPS
n
Campylobacter jejuni



Ganglioside GM1 is specifically associated with a pure motor type of GBS (IgG) and with multifocal motor neuropathy (IgM).

Significance of autoimmune reactions against nervous system antigens in neurological diseases

Anti-GQ1b and GD1b Antibodies



Chiba, A, Kusunoki, S, Obata, H, et al.: Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: Clinical and immunohistochemical studies. Neurology 43: 1911-1917, 1993.

Ganglioside GD1b present in dorsal root ganglia, cerebellar granular layer or spinocerebellar Ia fibers. . Anti GD1b Ab are specifically associated with sensory disturbances including paresthesia or dysesthesia and cerebellar ataxic neuropathy

Kusunoki, S, Shimizu, J, Chiba, A, et al.: Experimental sensory neuropathy induced by sensitization with ganglioside GD1b. Ann Neurol 39: 424-431, 1996

Features required for diagnosis

Miller Fisher syndrome:
- Progressive, relatively symmetric ophthalmoplegia and ataxia by 4 weeks
- Hyporeflexia or areflexia
- Limb strength with 5 or 4 on the Medical Research Council scale

Bickerstaff's brain stem encephalitis:
- Progressive, relatively symmetric ophthalmoplegia and ataxia by 4 weeks
- Either consciousness disturbance (coma, semicoma, or stupor) or pyramidal signs (hyperreflexia or pathological reflexes)
- Limb strength with 5 or 4 on the Medical Research Council scale

Acute ophthalmoparesis:
- Progressive, relatively symmetric ophthalmoplegia by 4 weeks
- Neither ataxia nor limb weakness

Features strongly supportive of the diagnosis for each condition

A history of infectious symptoms within 4 weeks before the onset of neurological symptoms

CSF albuminocytological dissociation

Presence of anti-GQ1b IgG antibody

Features that rule out the diagnosis

Wernicke's encephalopathy, vascular disease involving the brain stem, multiple sclerosis, neuro-Behçet's disease, botulism, myasthenia gravis, brain stem tumour, pituitary apoplexy, vasculitis, and lymphoma

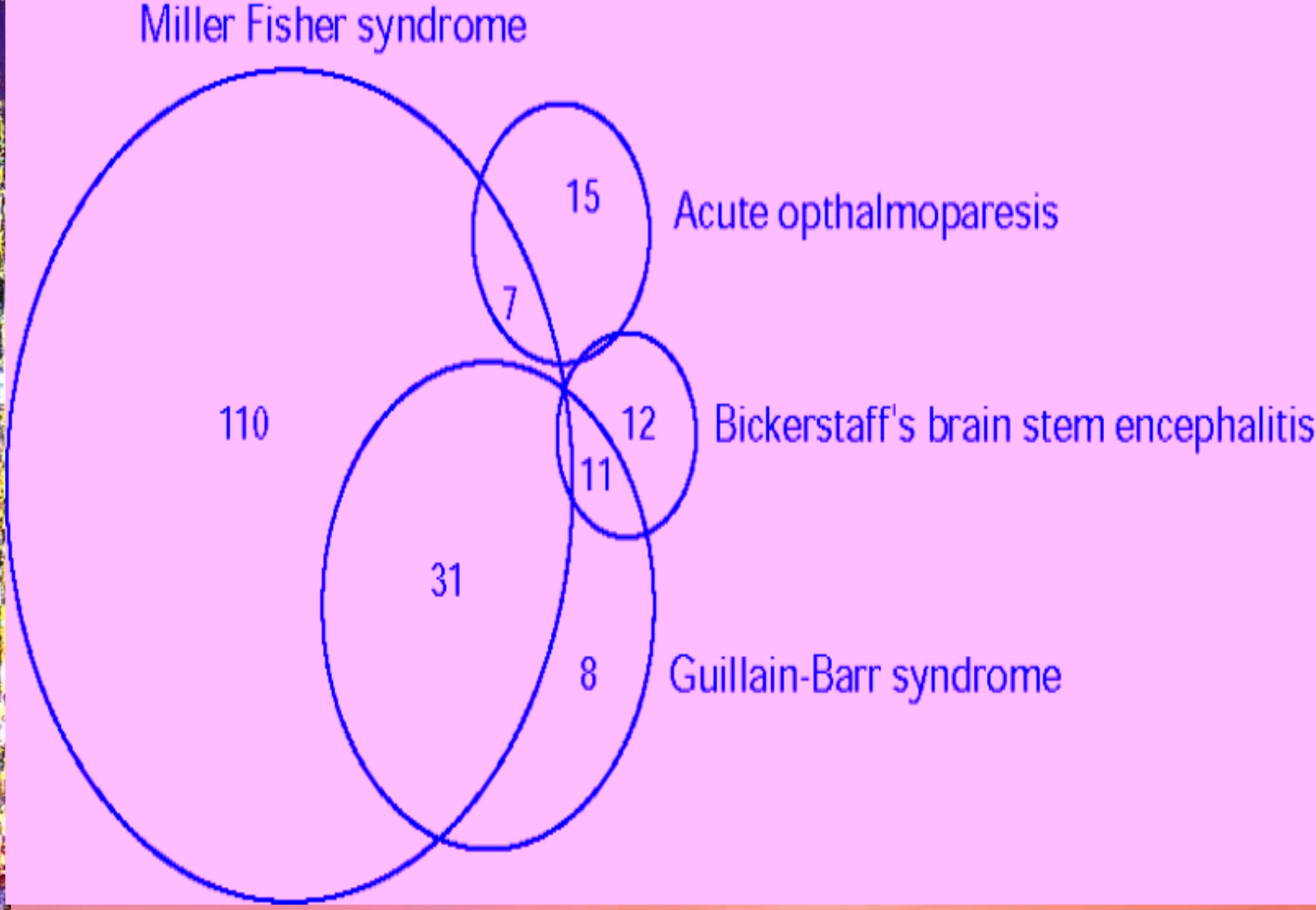
Appendix

Patients showing limb weakness (3 or less on the Medical Research Council scale), in addition to ophthalmoplegia and ataxia, were diagnosed as having overlapping Miller Fisher syndrome and Guillain-Barré syndrome.

Patients showing limb weakness (≤3 on the Medical Research Council scale), in addition to consciousness disturbance (coma, semicoma, or stupor) or pyramidal signs as well as ophthalmoplegia, were diagnosed as having overlapping Bickerstaff's brain stem encephalitis and Guillain-Barré syndrome.

Anti-GQ1b IgG antibody syndrome: clinical and immunological range

[Odaka: J Neurol Neurosurg Psychiatry, Volume 70(1).January 1, 2001.50-55]



Nosological relations between Miller Fisher syndrome, acute ophthalmoparesis, Bickerstaff's brain stem encephalitis, and Guillain-Barré syndrome
[Odaka: J Neurol Neurosurg Psychiatry, Volume 70(1).January 1, 2001.50-55]

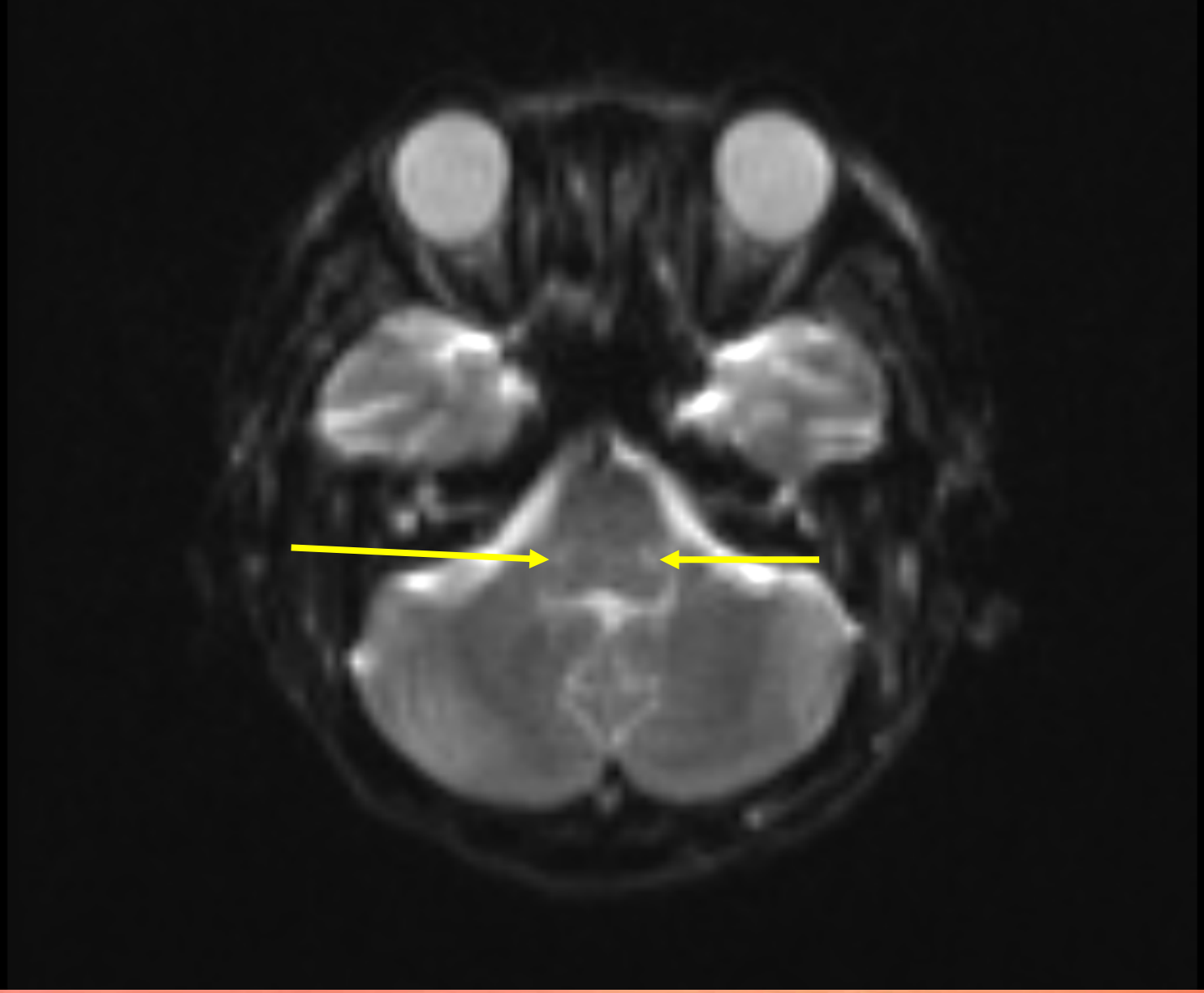
Proposed and tested set: one of the following abnormalities in at least two nerves should be demonstrated.

1. DML > 150% of ULN
2. m-NCV < 70% of LLN
3. F wave latency > 150% of ULN
4. Abnormal CMAP amplitude decay > ULN
5. Abnormal distal temporal dispersion: distal CMAP duration > 300% ULN
6. Abnormal temporal dispersion: distal to proximal CMAP duration ratio > 150% of ULN

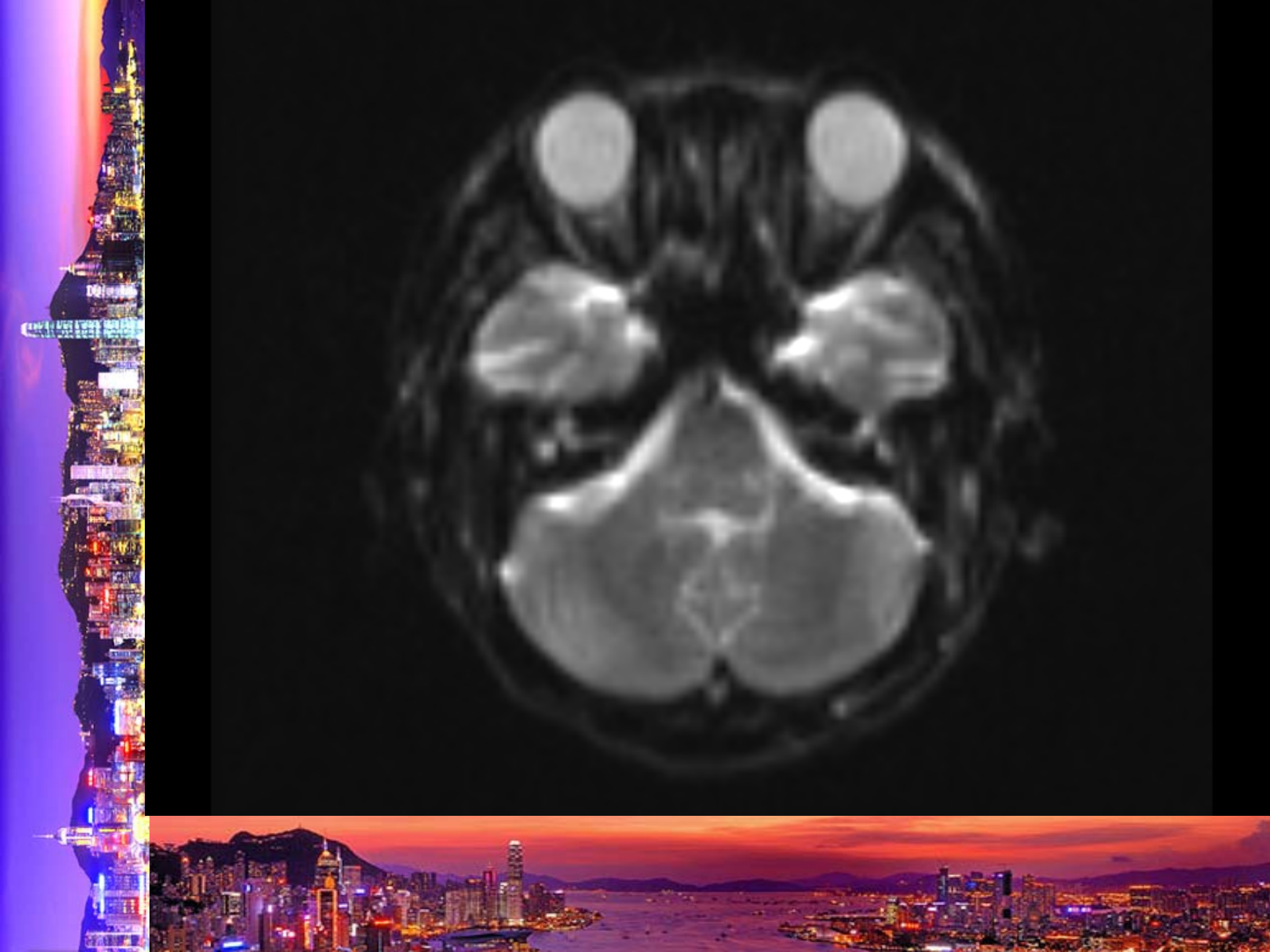
? Most early finding

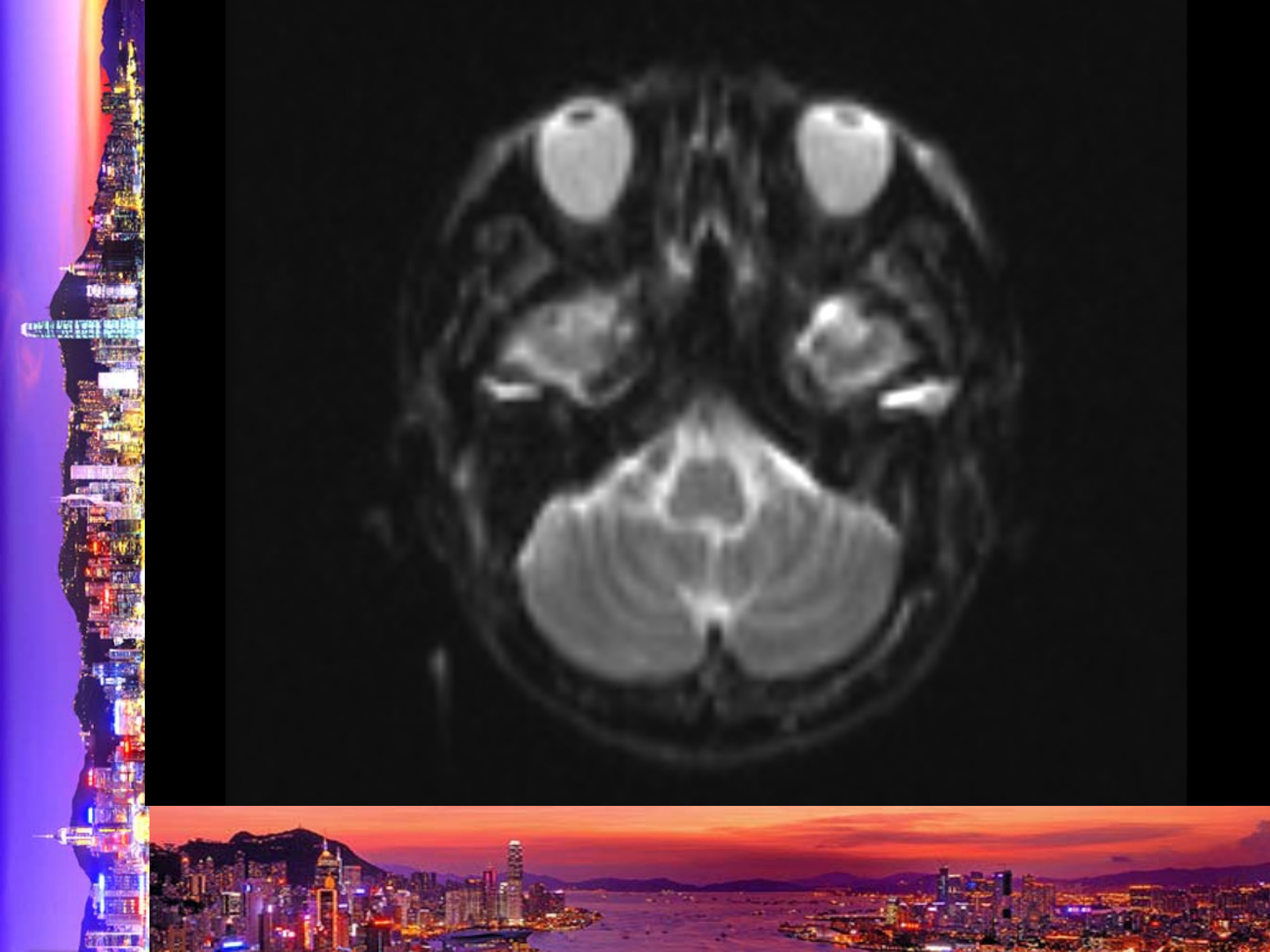
DML = distal motor latency; ULN = upper limit of normal; m-NCV = motor nerve conduction velocity; LLN = laboratory limits of normal; s-NCV = sensory nerve potential; CMAP = compound muscle action potential; CSNAP = compound sensory nerve action potential; SP = single pattern.


Isolated absence of F wave
Physiological conduction failure (**Ranvier node**) and impaired excitability
↓ CMAP
Axonal degeneration
↓ Conduction velocity
Demyelination
Early reversible and selective involvement of the nerve roots
Progress AMAN
Progress to AIDP
Good Prognosis



Medulla Oblongata Involvement





Campylobacter jejuni Gastroenteritis

Between 30-50% of all GBS cases are linked to *C. jejuni* infection, usually appearing 1-3 weeks after bacterial infection with F:M ratio 3.5:1 (c.f 1.5:1)

Contaminated milk

Improper handling Or consumption

Untreated water

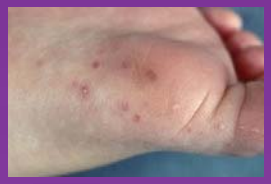
Raw livestock

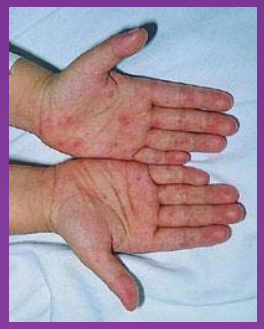
Raw poultry

Around 1:1000 will developed GBS. In a Swedish cohort of 29,567 individuals with laboratory-confirmed *C. jejuni* infection. The authors noted that of 6,293 persons below age 20 years, no cases of GBS were found. Among 20,856 adults aged 20–59 years, the rate of GBS was 14 per 100,000, while in the set of 2,417 people over age 59 years, the rate was 248 per 100,000

Thank you for your attention

EV 71 Virus



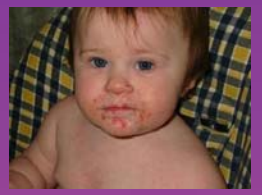


Aseptic meningitis

Hand Foot & Mouth Disease

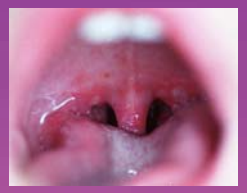
Rhomboencephalitis

Herpangina



Acute flaccid paralysis (Radiculomyelitis)

Acute pulmonary edema



EV 71 A

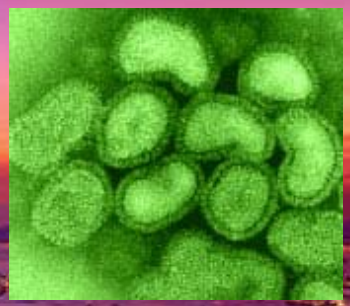
EV 71 B (65 strains)

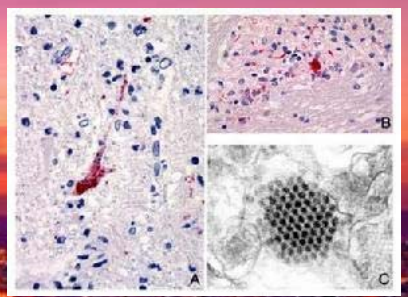
EV 71 C (47 strains)

B1-B5

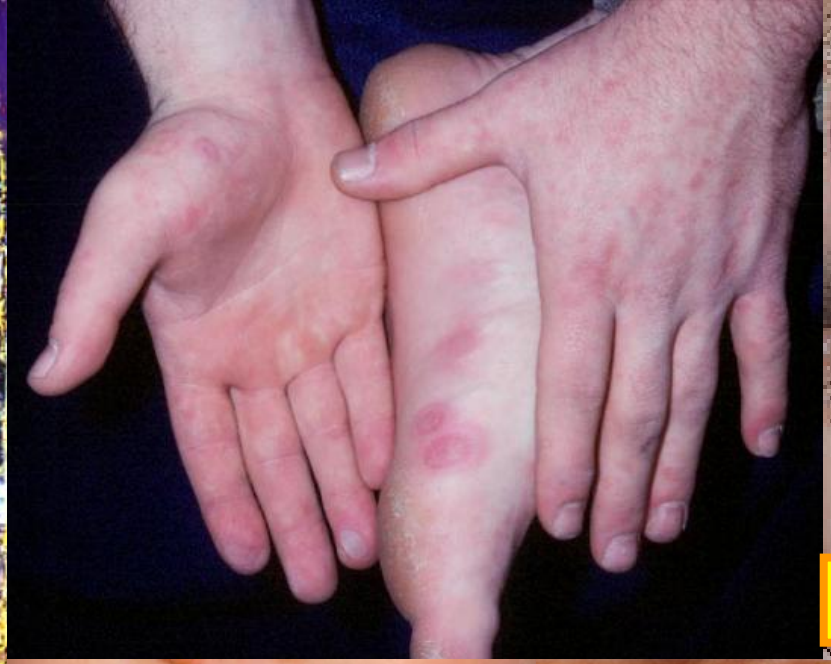
C1-C5 (C4 China)

EV71 radiculomyelitis tends to be unilateral and to specifically involve both the anterior horn cells of the cord and the ventral roots. MR imaging allows early detection of spinal cord and root lesions.

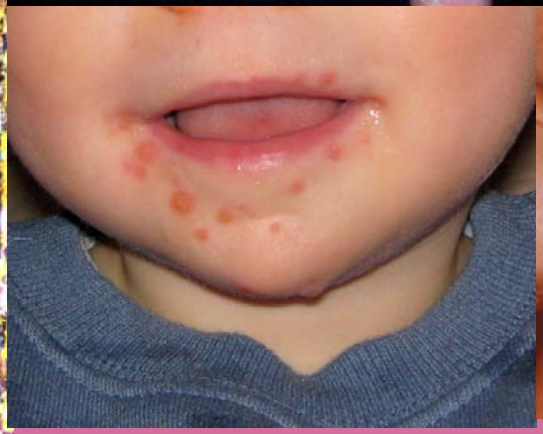


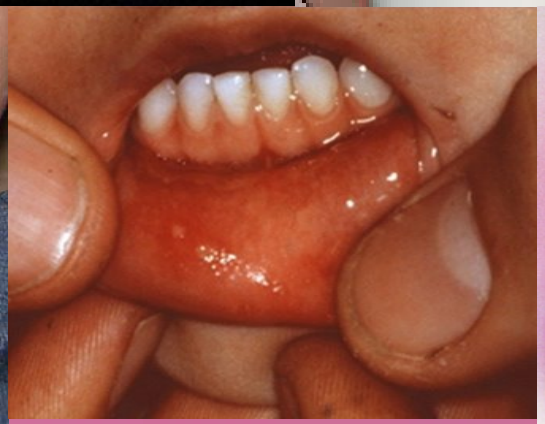


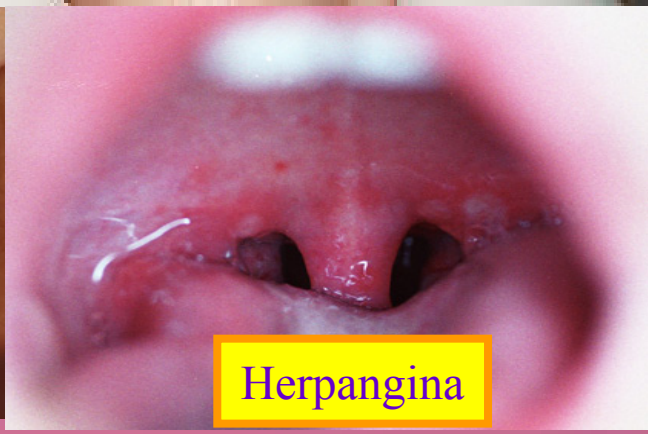
HFM disease usually begins with a fever, poor appetite, malaise (feeling vaguely unwell), and often with a sore throat.



Acute Haemorrhagic Conjuncitivitis





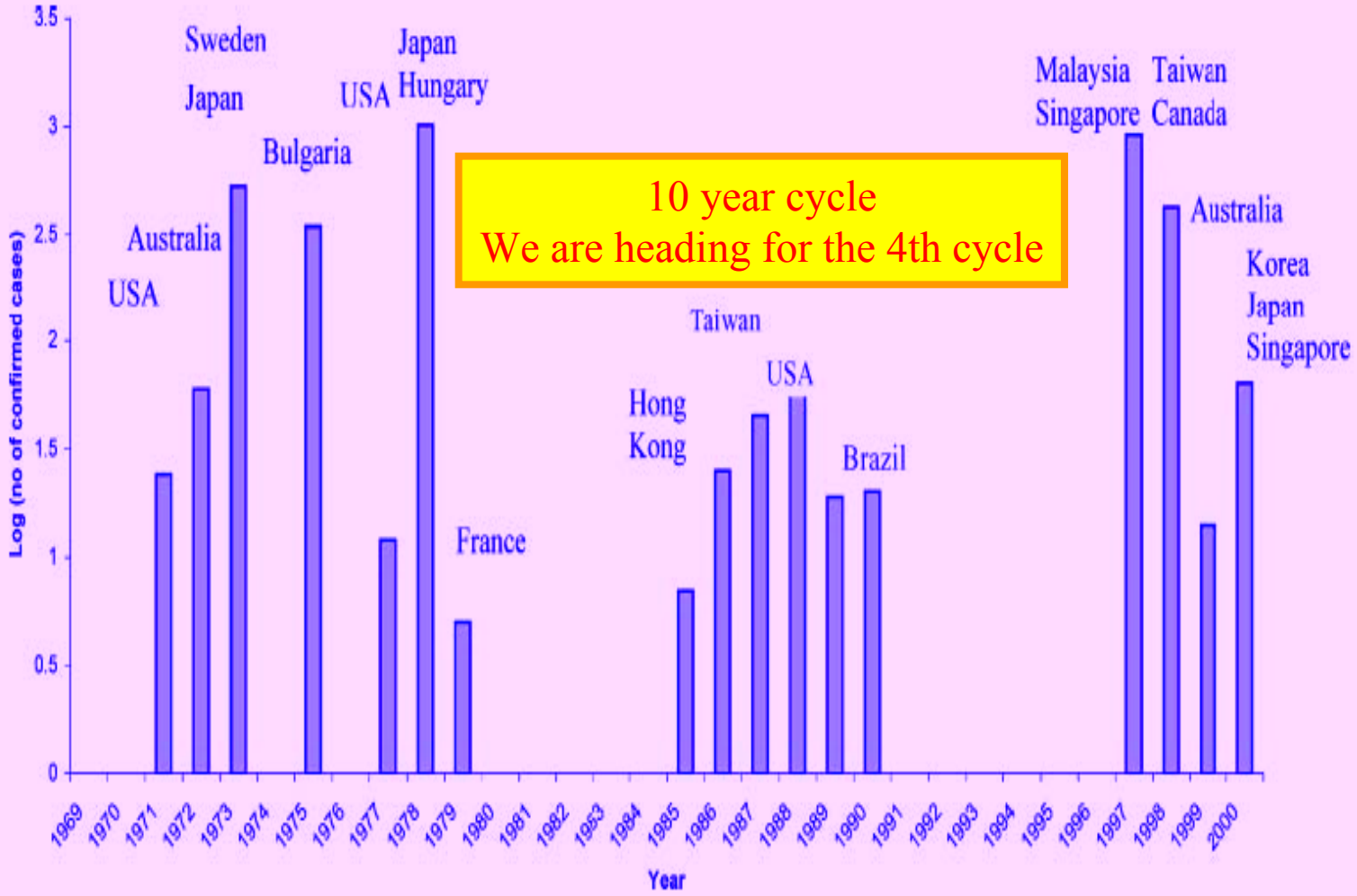


Herpangina

Hand Foot and Mouth Disease

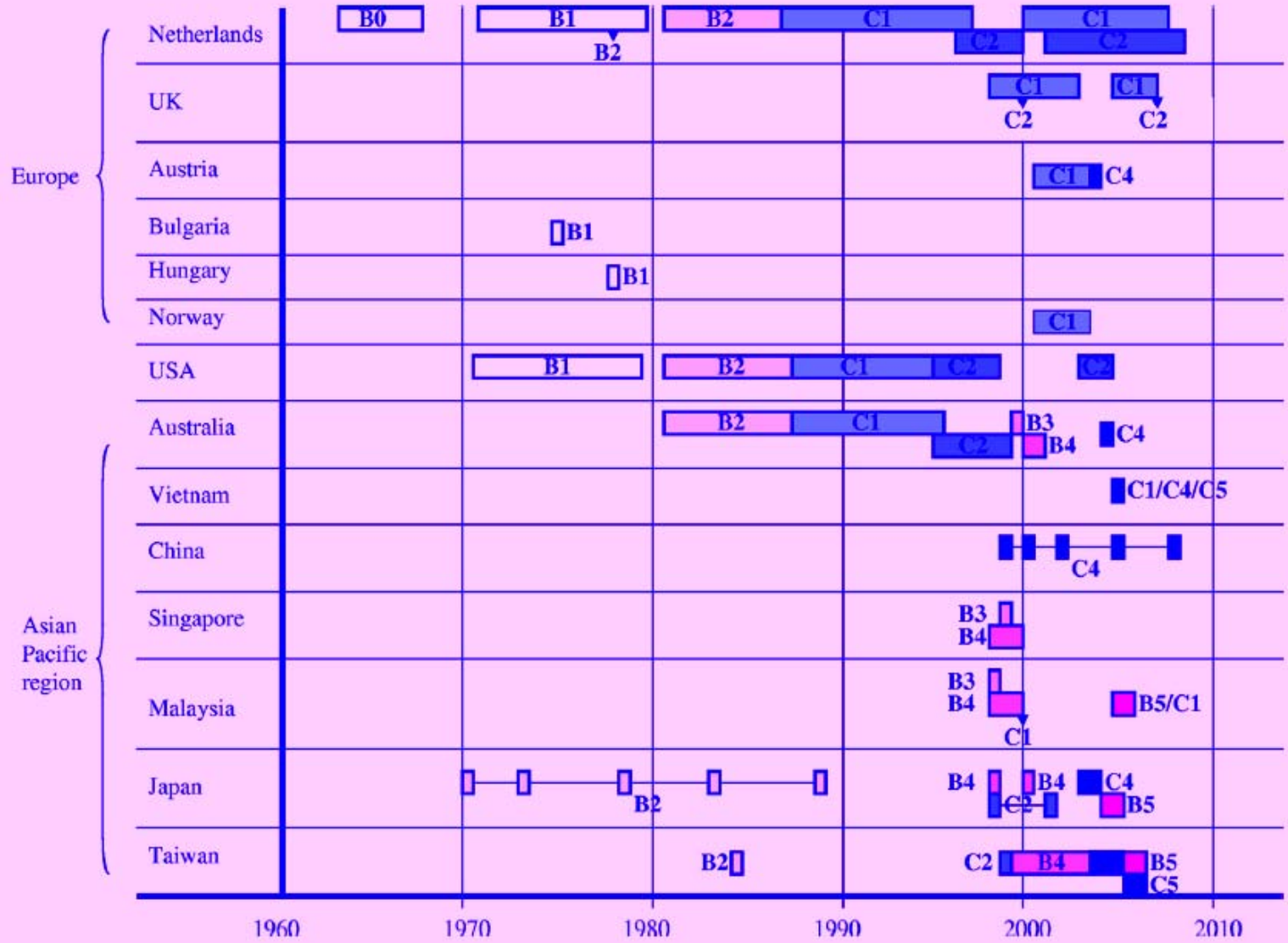
The Evolution of EV71 to Our First Patient The ICU Nurse Who Died

Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital

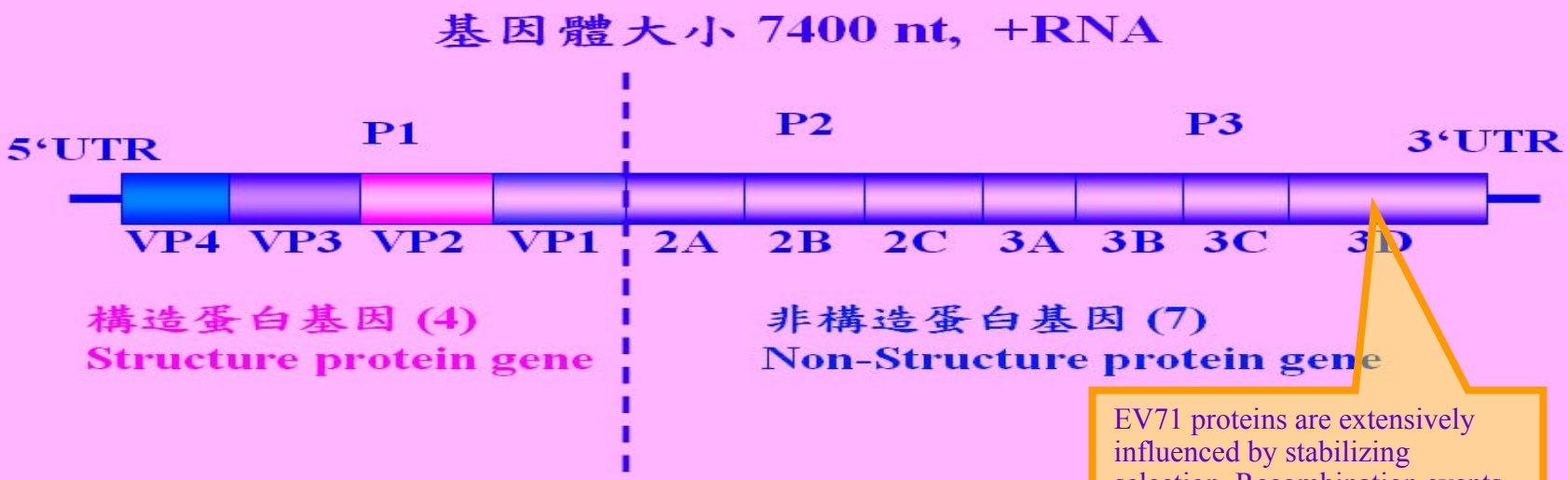


Charts showing global reports of EV71 infection since 1970. Only laboratory-confirmed cases were included in the count. The chart suggests that there were three separate waves of EV71 activities in the world, one in each decade, between 1970 to 2000

Genetic evolution of enterovirus 71: epidemiological and pathological implications. Bible JM. Pantelidis P. Chan PK. Tong CY. Reviews in Medical Virology. 17(6):371-9, 2007 Nov-Dec.



Epidemiology of enterovirus 71 in the Netherlands, 1963 to 2008. van der Sanden S. Koopmans M. Uslu G. van der Avoort H. Dutch Working Group for Clinical Virology. Journal of Clinical Microbiology. 47(9):2826-33, 2009 Sep.



UTR: untranslation region 非轉譯區
指沒有轉譯出蛋白質的核酸區域

EV71 proteins are extensively influenced by stabilizing selection. Recombination events were found to be distributed nonrandomly with the highest frequency at the 3D (viral polymerase) region.

Due to the absence of proofreading activity, the misinsertion rate by the 3D polymerase is high, and mutations accumulate during replication. intratypic recombination recombination play an important role in the formation of genetic diversity in enterovirus. Intratypic and intertypic recombination of EV71 nonstructural genes during natural infection and circulation lead to production of new EV71 variants. Co-infection is common in China. Recombination frequently occurs among EV71 circulating in China, and might bring a novel biologic characteristic, such as immune escape or improved virulence.

Analysis of recombination and natural selection in human enterovirus 71. Chen X. Zhang Q. Li J. Cao W. Zhang JX. Zhang L. Zhang W. Shao ZJ. Yan Y. Virology. 398(2):251-61, 2010 Mar 15.
Appearance of intratypic recombination of enterovirus 71 in Taiwan from 2002 to 2005. Huang SC. Hsu YW. Wang HC. Huang SW. Kiang D. Tsai HP. Wang SM. Liu CC. Lin KH. Su IJ. Wang JR. Virus Research. 131(2):250-9, 2008 Feb.
Appearance of mosaic enterovirus 71 in the 2008 outbreak of China. Ding NZ. Wang XM. Sun SW. Song Q. Li SN. He CQ. Virus Research. 145(1):157-61, 2009 Oct.

In the past, many outbreaks of EV71 were not associated with hand foot and mouth disease or herpangina until the outbreak in Japan 1973 and 1978.

Coxsackie A16 is characterized by its dermatotropic clinical features and EV71 is characterized by its neurotropic clinical features.

1. Schmidt NJ, Lennett EH, Ho HH. An apparently new enterovirus isolated from patients with disease of the central nervous system. J Infect Dis. 1974;129:304 –309.
2. Chumakov M, Voroshilova M, Shindarov L, et al. Enterovirus 71 isolated from cases of epidemic poliomyelitis-like disease in Bulgaria. Arch Virol. 1979;60:329 –340.
3. Deibel R, Gross LL, Collins DN. Isolation of a new enterovirus. Proc Soc Exp Biol Med. 1975;148:203–207.
4. Blomberg J, Lycke E, Ahlfors K, et al. New enerovirus type associated with epidemic of aseptic meningitis and/or hand, foot, and mouth disease. Lancet. 1974;2:112.
5. Shindarov LM, Chumakov MP, Voroshilova MK, et al. Epidemiological, clinical, and pathomorphological characteristics of epidemic poliomyelitislike disease caused by enterovirus 71. J Hyg Epidemiol Microbiol Immunol.1979;23:284 –295.
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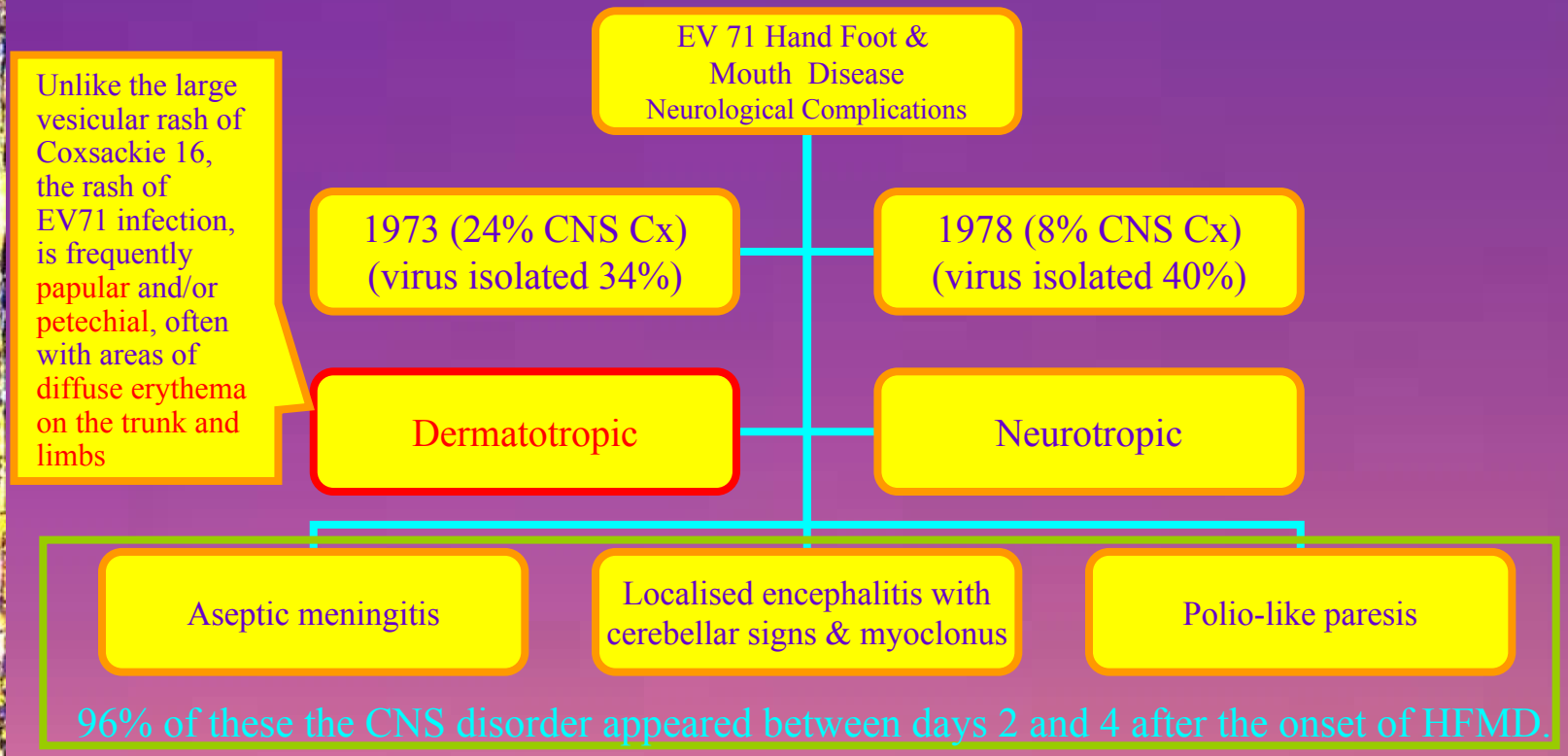
Enterovirus 71

- First isolated in 1969 in stool from an infant suffering from encephalitis in California
- Bulgaria in 1975 (44/705 death due to bulbar encephalitis)
  - 77.3% aseptic meningitis
  - 21.1% acute flaccid paralysis
  - No evidence of hand foot and mouth disease
- Hungary in 1978 (826 patients with 47 deaths)
  - 87.7% aseptic meningitis
  - 4 had hand foot and mouth disease
- Japan 1973 and 1978

A large-scale epidemic of hand, foot and mouth disease associated with enterovirus 71 infection in Japan in 1978. Tagaya I, Takayama R, Hagiwara A Jpn J Med Sci Biol. 1981 Jun;34(3):191-6.

Japan 1973 and 1978 ~ 36,000 Cases
Brain stem encephalitis and paralysis

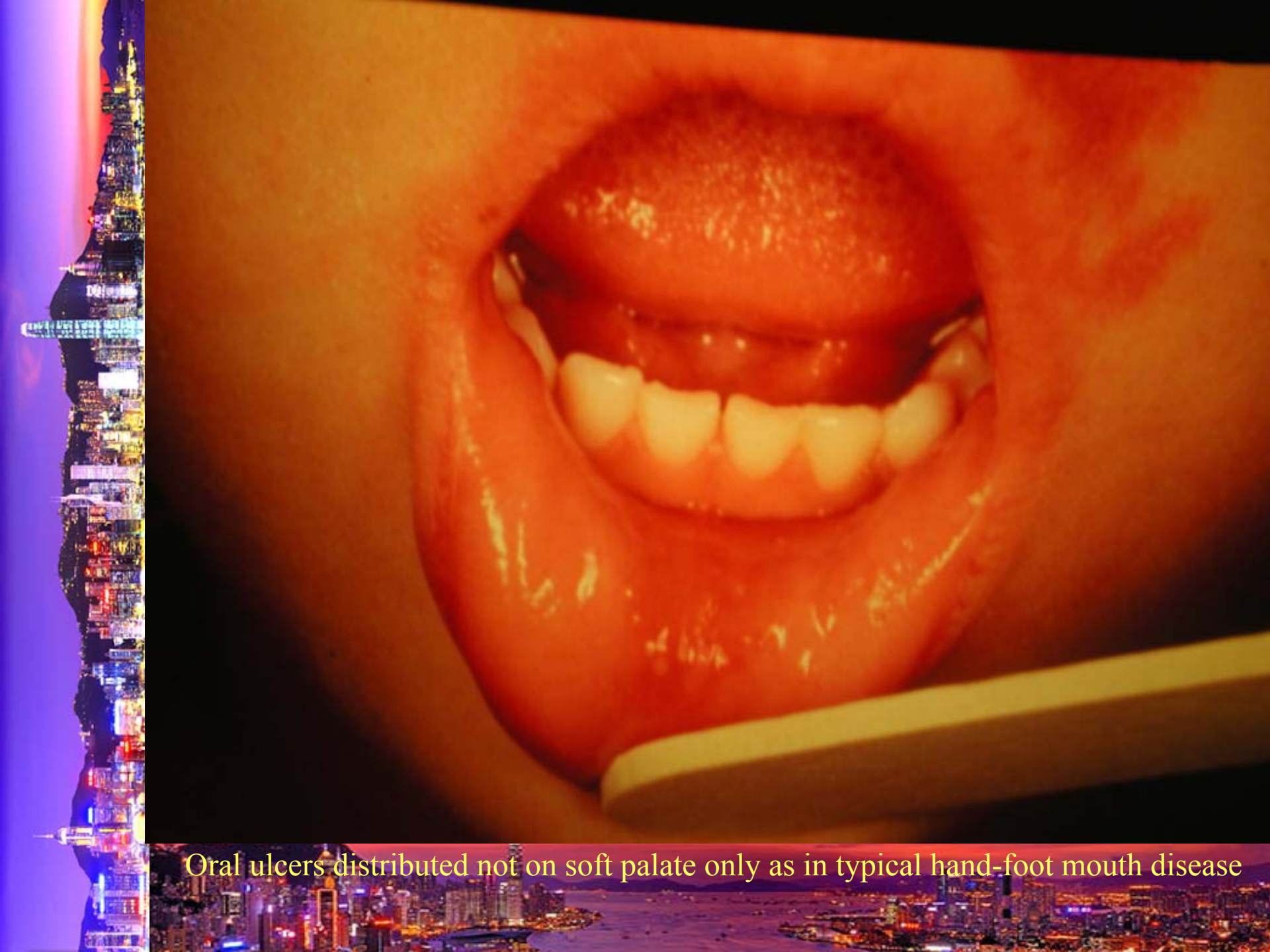


I. Tagaya and K. Tachibana, Epidemic of hand, foot and mouth disease in Japan, 1972–1973: difference in epidemiologic and virologic features from the previous one, Japanese Journal of Medical Science and Biology 28 (August (4)) (1975), pp. 231–234.

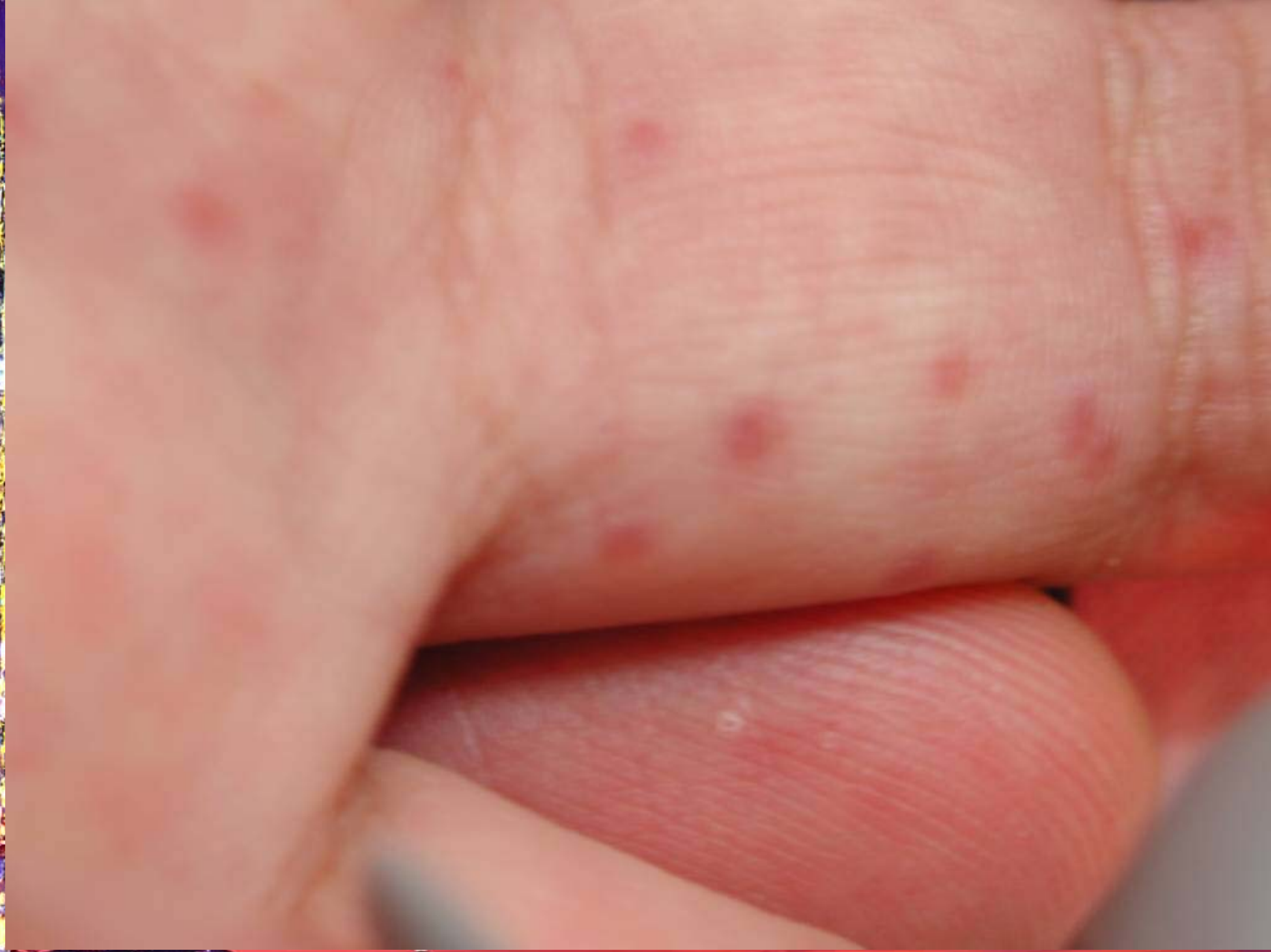
II. A. Hagiwara, I. Tagaya and T. Yoneyama, Epidemic of hand, foot and mouth disease associated with enterovirus 71 infection, Intervirology 9 (1) (1978), pp. 60–63.

III. Outbreaks of hand, foot, and mouth disease by enterovirus 71. High incidence of complication disorders of central nervous system. Y Ishimaru, S Nakano, K Yamaoka, and S Takami Arch Dis Child. 1980 August; 55(8): 583–588.

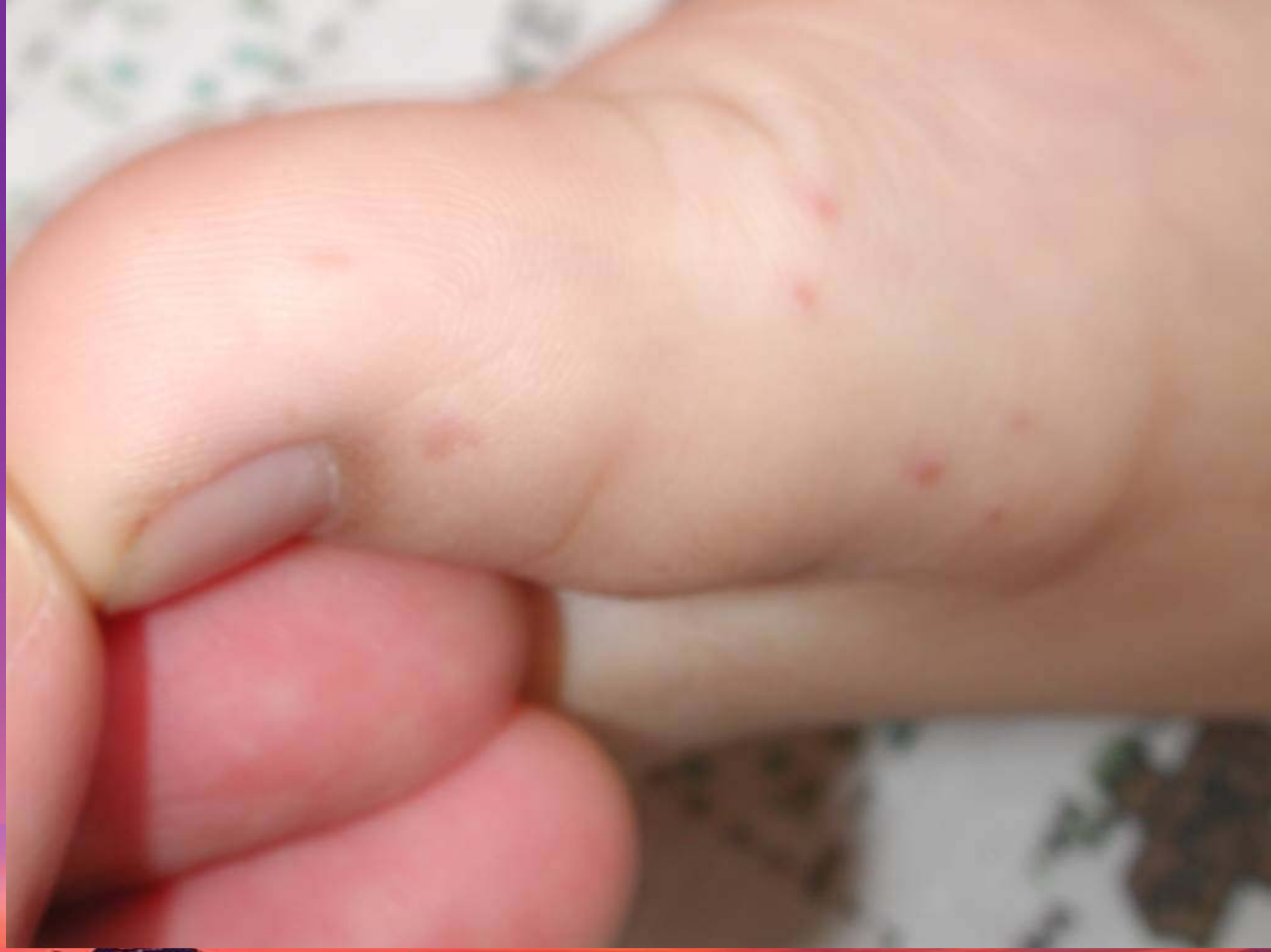
IV. A large-scale epidemic of hand, foot and mouth disease associated with enterovirus 71 infection in Japan in 1978. Tagaya I. Takayama R. Hagiwara A. Japanese Journal of Medical Science & Biology. 34(3):191-6, 1981 Jun.



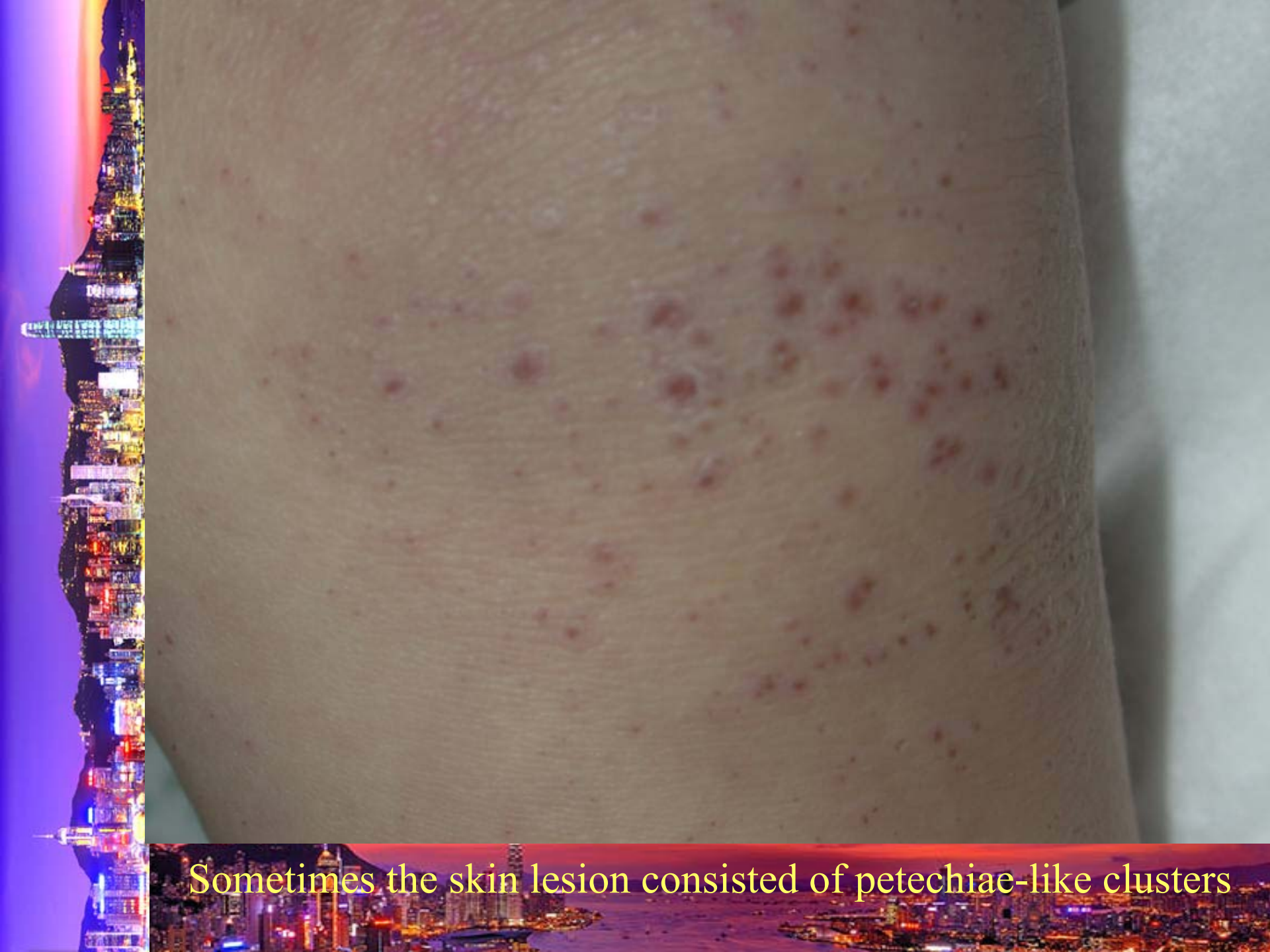
Oral ulcers distributed not on soft palate only as in typical hand-foot mouth disease



Vesicles on hand and foot were smaller (pin-point) than typical HFM disease



Vesicles on hand and foot were smaller (pin-point) than typical HFM disease



Sometimes the skin lesion consisted of petechiae-like clusters

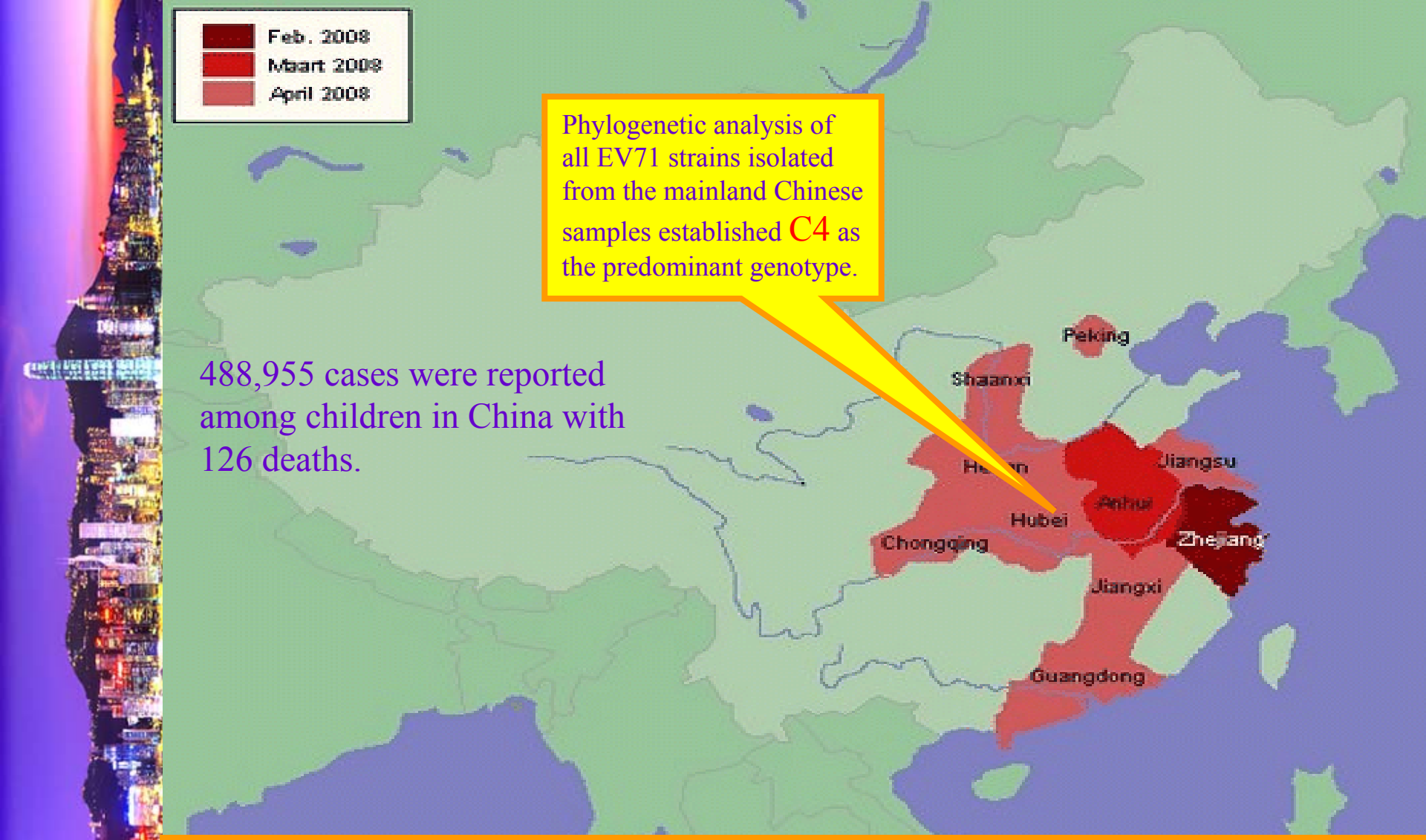
Enterovirus 71

- **Hong Kong**
  - **1985: 5 children with acute flaccid monoplegia; 3 had hand foot and mouth disease, 1 has oral lesion and 1 has diffuse erythema in limbs.**
  - **1999: 8 death**
- **Malaysia in 1997 (at least 31 deaths)**
- **Taiwan in 1980, 1986, 1998**
  - **1980: 20 children poliomyelitis-like flaccid paresis associated with hand-foot-and-mouth disease or herpangina**
  - **1986 in Kaohsiung**
  - **1998 large outbreak (78 deaths)**
- **Singapore**
  - **2007: April 15–21: 688 cases reported**
  - **2008 Late March –mid April: 2,600 cases reported, no serious cases**

Enterovirus 71 in Taiwan Chang LY. Pediatrics & Neonatology. 49(4):103-12, 2008 Aug.
Monoplegia caused by Enterovirus 71: an outbreak in Hong Kong.
Samuda GM, Chang WK, Yeung CY, Tang PS. Pediatr Infect Dis J. 1987 Feb;6(2):206-8.

China 1999-2010

- Shenzhen
  - 1999-2004: EV71 (C4) and CA16 co-circulation
    - In patients with HFMD, EV71 (12.93%) and CA16 (27.89%). The etiological viral pathogens were not identified in approximately 60% of HFMD cases. The cause of low rate of viral isolation is unclear
- 2002: Shanghai
  - CA16: EV71 = 6.4:1
  - 2/9 belong to a new lineage (C4) within genogroup C
  - One patient with EV71-associated HFMD had a complication of encephalitis with convulsion, shock, coma and dyspnea.
- 2007: Beijing
  - Cox A16 and 2 strains of EV71 of C4 subtype



F. Yang, L. Ren, Z. Xiong, J. Li, Y. Xiao and R. Zhao et al., Enterovirus 71 outbreak in the People's Republic of China in 2008, Journal of clinical Microbiology 47 (July (7)) (2009), pp. 2351–2352.
http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohbgt/s3582/200902/39079.htm

Major Outbreak of EV71 in China in 2008

EV71 spreading from Zhejiang 浙江 to Anhui 安徽 then to rest of China

Etiologies for Increasing Incidence of EV71 in China since 2008

- Ever-increasing travel and migration spreads the disease further by moving infected people between population centers.
- In May 2008, China added HFMD to its category C of notifiable diseases, meaning that all diagnosed cases must be reported. The recent apparent ncrease in EV71 infection might be due to higher reporting rates rather than an increase in disease prevalence.
- The genetic changes in the circulating EV71 strain. Before 2004, the predominant strain was called C4b; since then, a different strain, C4a, has been most common. C4a also caused the epidemic in 2008

An emerging recombinant human enterovirus 71 responsible for the 2008 outbreak of Hand Foot and Mouth Disease in Fuyang city of China

Yan Zhang†1, Zhen Zhu†1, Weizhong Yang†2, Jun Ren†3, Xiaojuan Tan†1, Yu Wang2, Naiying Mao1, Songtao Xu1, Shuangli Zhu1, Aili Cui1, Yong Zhang1, Dongmei Yan1, Qun Li4, Xiaoping Dong1, Jing Zhang4, Yueping Zhao3, Junfeng Wan5, Zijian Feng4, Junling Sun4, Shiwen Wang1, Dexin Li*1 and Wenbo Xu*1,2

Abstract

Hand, foot and mouth disease (HFMD), a common contagious disease that usually affects children, is normally mild but can have life-threatening manifestations. It can be caused by enteroviruses, particularly Coxsackieviruses and human enterovirus 71 (HEV71) with highly variable clinical manifestations. In the spring of 2008, a large, unprecedented HFMD outbreak in Fuyang city of Anhui province in the central part of southeastern China resulted in a high aggregation of fatal cases. In this study, epidemiologic and clinical investigations, laboratory testing, and genetic analyses were performed to identify the causal pathogen of the outbreak. Of the 6,049 cases reported between 1 March and 9 May of 2008, 3023 (50%) were hospitalized, 353 (5.8%) were severe and 22 (0.36%) were fatal. HEV71 was confirmed as the etiological pathogen of the outbreak. Phylogenetic analyses of entire VP1 capsid protein sequence of 45 Fuyang HEV71 isolates showed that they belong to C4a cluster of the C4 subgenotype. In addition, genetic recombinations were found in the 3D region (RNA-dependent RNA polymerase, a major component of the viral replication complex of the genome) between the Fuyang HEV71 strain and Coxsackievirus A16 (CV-A16), resulting in a recombination virus. In conclusion, an emerging recombinant HEV71 was responsible for the HFMD outbreak in Fuyang City of China, 2008.

Zhang et al. Virology Journal 2010, 7:94 http://www.virologyj.com/content/7/1/94

Clinical symptoms of fatal HFMD cases in Fuyang hospital (n = 15).

Clinical symptom	Number of cases	Proportion (%)
Fever	15	100
Tachypnea	14	93.3
Oral cyanosis	12	80
Pink foaming at the mouth	9	60
Coughing	7	46.7
Vomiting	8	53.3
Myoclonic twitching	5	33.3
Tiny pink rash on palm, sole	2	13.3
Nasal discharge	2	13.3
Stiff neck	2	13.3

An emerging recombinant human enterovirus 71 responsible for the 2008 outbreak of Hand Foot and Mouth Disease in Fuyang city of China Yan Zhang ***Virol J.*** **2010; 7: 94. Published online 2010 May 12. doi: 10.1186/1743-422X-7-94.PMCID: PMC2885340**

Case classification and HEV71 positive number (rate) by RT-PCR or virus isolation.

Case Classification	No. of Cases	HEV71		Other Enterovirus	
		direct RT-PCR	virus Isolation	direct RT-PCR for CV-A16	virus Isolation
Fatal cases	13	6(46%)	6(46%)	0	0
Severe cases	99	36(36%)	26(26%)	0	1(E9),1(CV-A4)
Mild outpatients	39	17(44%)	13(33%)	0	1(E9),1(CV-B3), 1(CV-A9)
Total	151	59(39%)	45(30%)	0	5

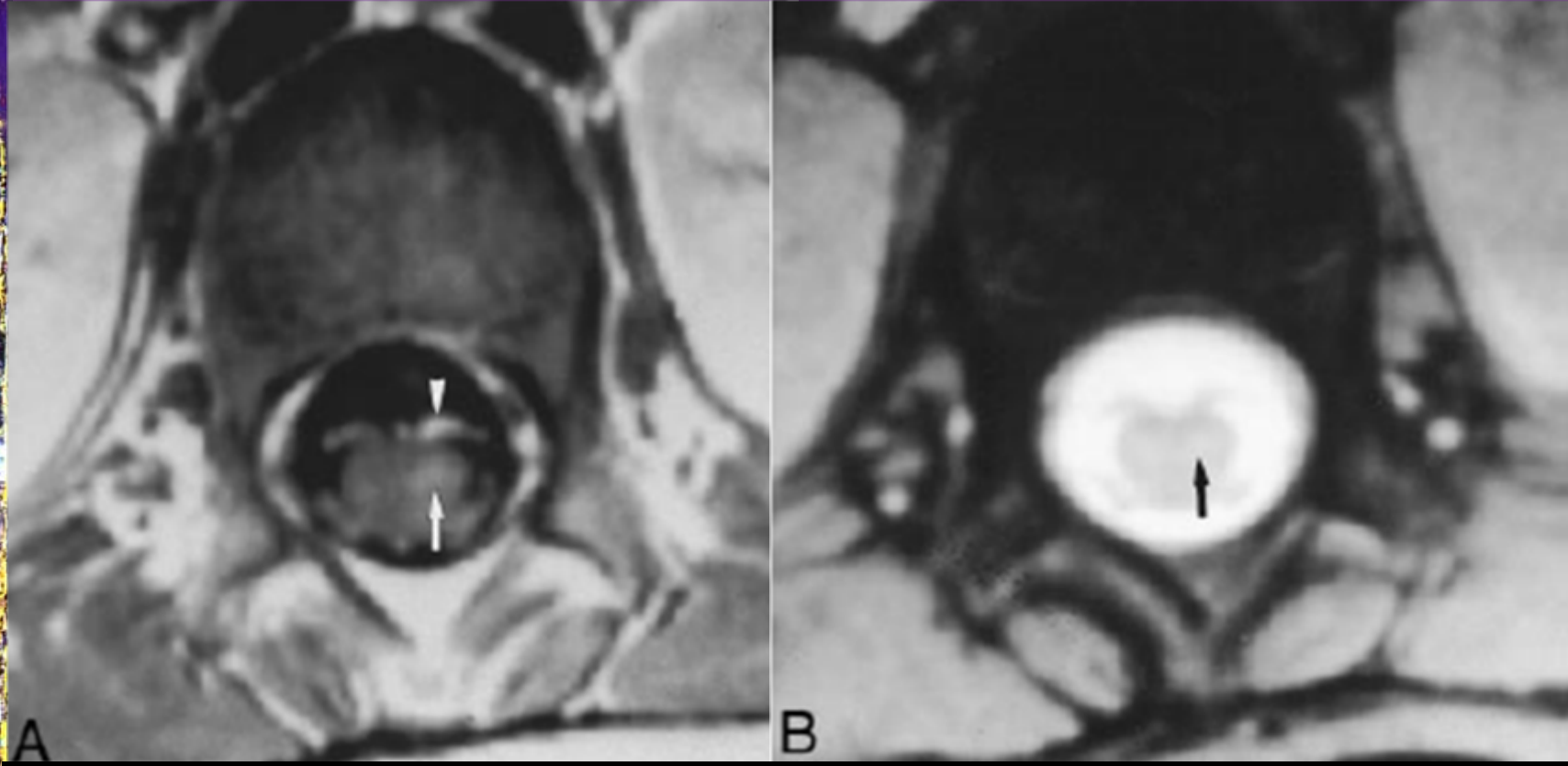
Note: E9: Echovirus 9; CV-A4: Coxackievirus A4; CV-B3: Coxackievirus B3; CV-A9:Coxackievirus A9. All the positive PCR fragments and isolates were confirmed by sequencing.

An emerging recombinant human enterovirus 71 responsible for the 2008 outbreak of Hand Foot and Mouth Disease in Fuyang city of China Yan Zhang *Virol J.* 2010; 7: 94. Published online 2010 May 12. doi: 10.1186/1743-422X-7-94.PMCID: PMC2885340


From January to April 11 2010, Guangxi reported a total of 17,345 cases of hand, foot and mouth disease (mainly caused by EV71 virus disease) resulting in 27 deaths. The disease quickly spread from Quanzhou county (全州縣) in Guilin (桂林) to Liuzhou(柳州) and to the rest of Guangxi Zhuang Autonomous Region. Many children were admitted in shock state with pulmonary edema and pulmonary hemorrhage.
Patient 1 in Hong Kong
China - Alarming Outbreak of "Mutated" Virulent form of Hand, Foot, and Mouth Disease in Guangxi 2010

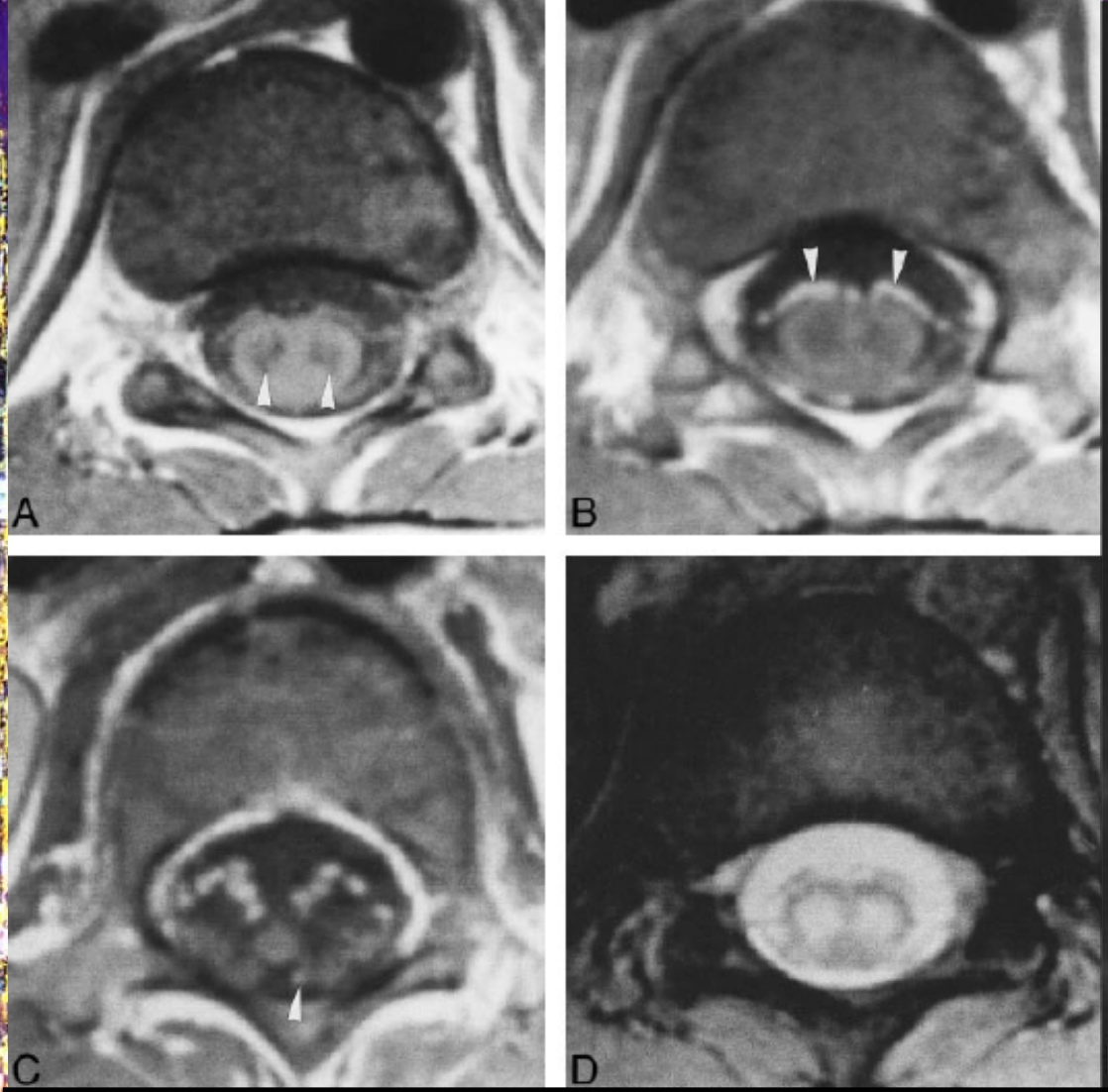
EV 71 Radiculomyelitis

Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital

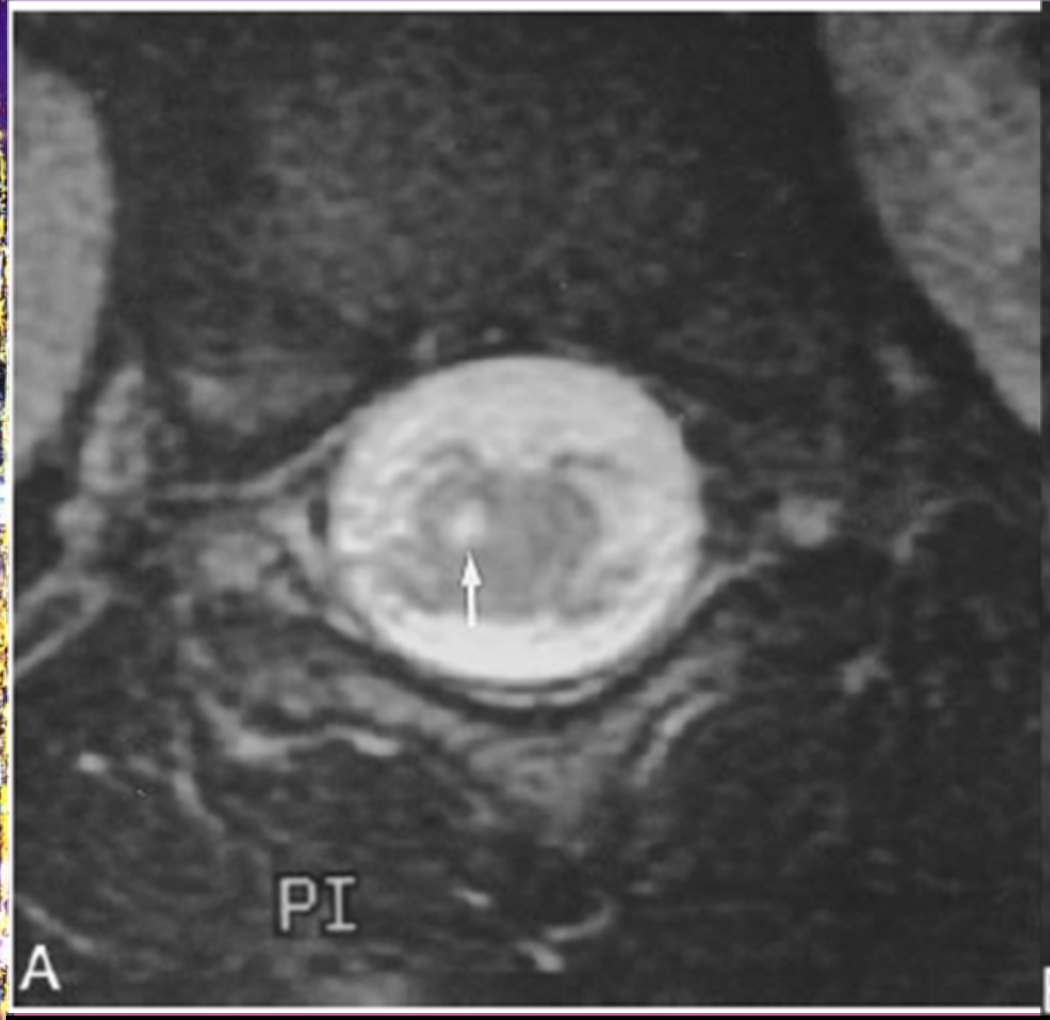


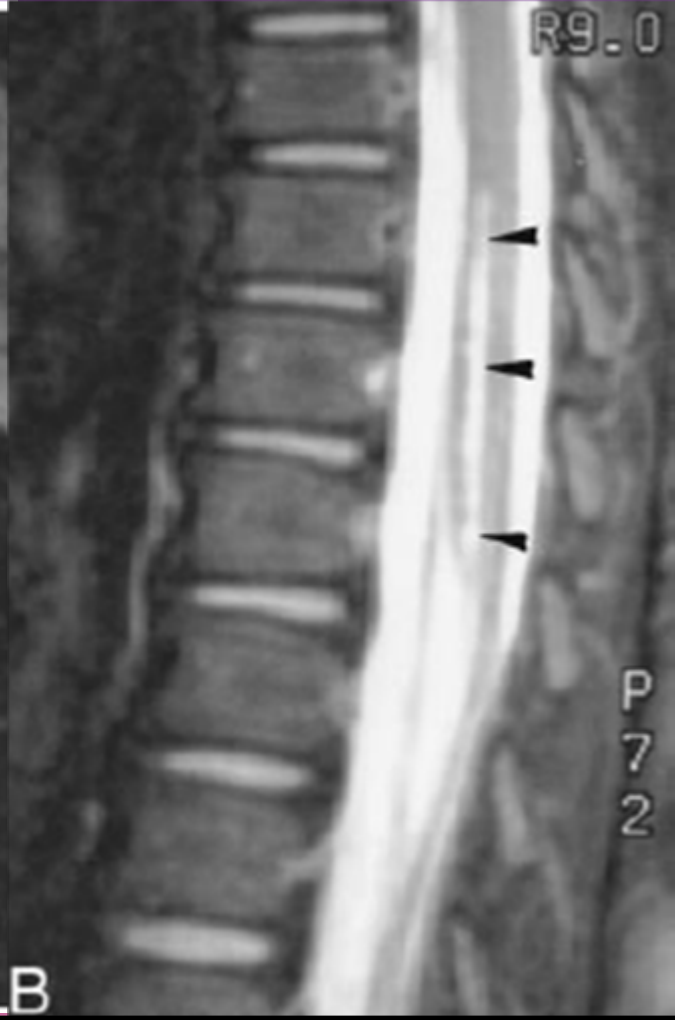
Unilateral AFP and transient urinary retention in 18-month-old girl with lumbosacral radiculomyelitis.
A, Contrast-enhanced axial T1-weighted image (752/15/1) at L1 level shows strong enhancement of the left ventral root (arrowhead)
and mild enhancement of the left anterior horn cells (arrow) of the sacral cord.
B, Left anterior horn lesion (arrow) is inconspicuous on gradient-echo T2-weighted image.

Acute flaccid paralysis (Radiculomyelitis)



Radiculomyelitis causing bilateral AFP and urinary retention.
A, Unenhanced axial T1-weighted image (752/15) shows hypointense lesions (arrowheads) in the anterior horn cells of spinal cord bilaterally at T11 level.
B, Contrast-enhanced T1-weighted image at the same level as in A shows predominant enhancement of the ventral roots (arrowheads). The anterior horn cell lesions do not enhance.
C, Contrast-enhanced T1-weighted image at the conus level clearly shows the predominant ventral root enhancement. The slightly hyperintense dot at the left dorsal root region (arrowhead) is probably due to enhancement of the radicular vein.
D, The anterior horn cell lesions are hyperintense and more conspicuous on gradient-echo T2-weighted image (808/15/20) as compared with T1-weighted image (A).
E, Sagittal fast spin-echo T2-weighted image (2300/103/2) shows the extent of the anterior horn cell lesions (arrowheads) from midthoracic to conus levels.





Persistent weakness of right lower limb 2 months after EV71 infection in a 16-month-old infant.

A, Axial fast spin-echo T2-weighted image (4000/80/3) at lumbosacral cord 2 months after acute paralysis shows a hyperintense lesion in the right anterior horn region (arrow).

B, Sagittal fast spin-echo T2-weighted image shows a long-segment hyperintense lesion (arrowheads) extending from the lower thoracic to the lumbosacral levels.

Acute Pulmonary Edema with Rhombencephalitis Complicating EV 71

Dr. Lai Kang Yiu
Intensive Care Unit
Queen Elizabeth Hospital

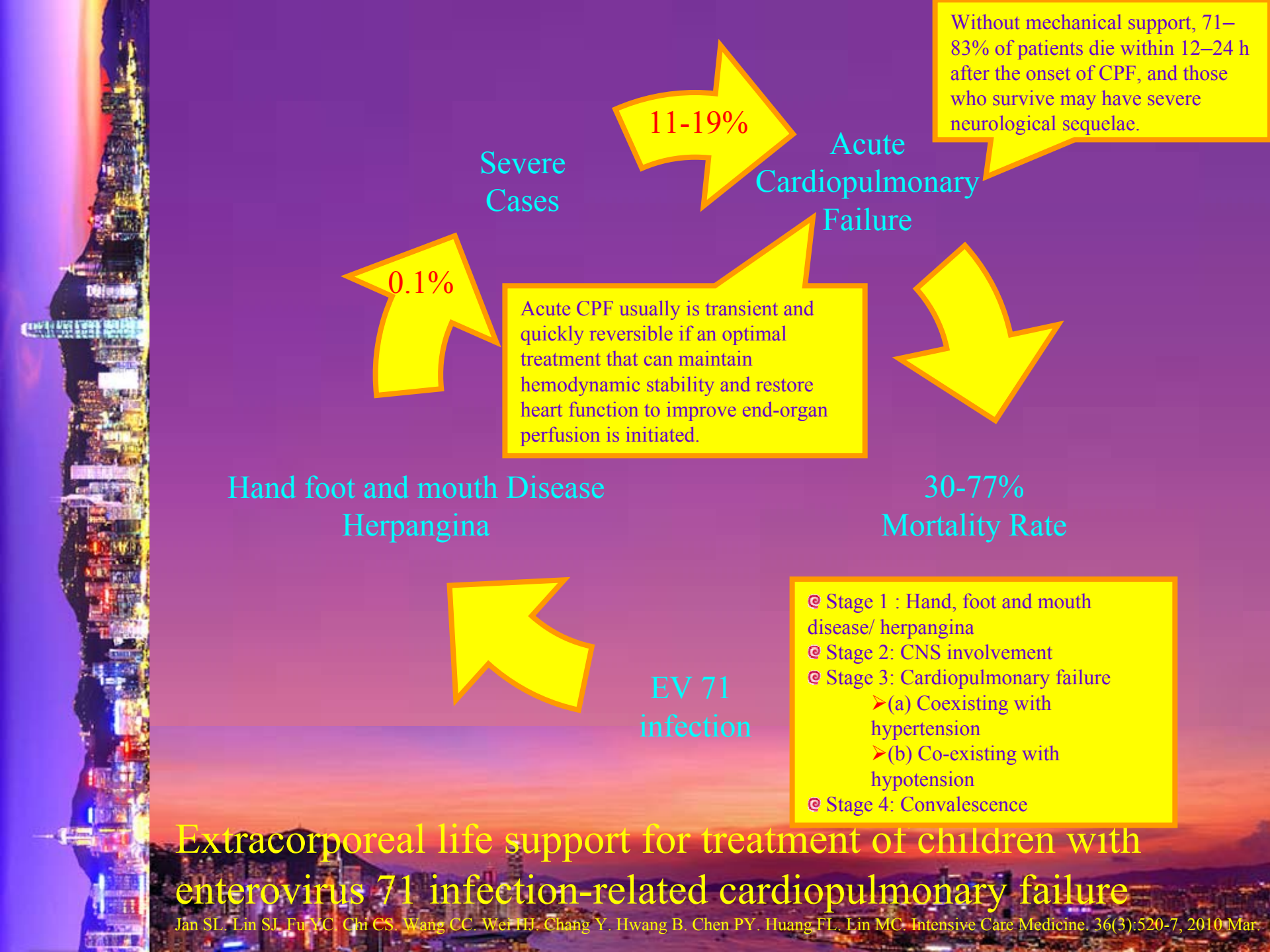
10 such patients from a series of 150 patients with bulbar poliomyelitis developed pulmonary edema

The pulmonary edema was described as sudden in its onset, resisted all forms of treatment, and resulted in death.

All had involvement of the dorsal nuclei of the vagus and the vasomotor (medial reticular) nuclei in the medulla oblongata.

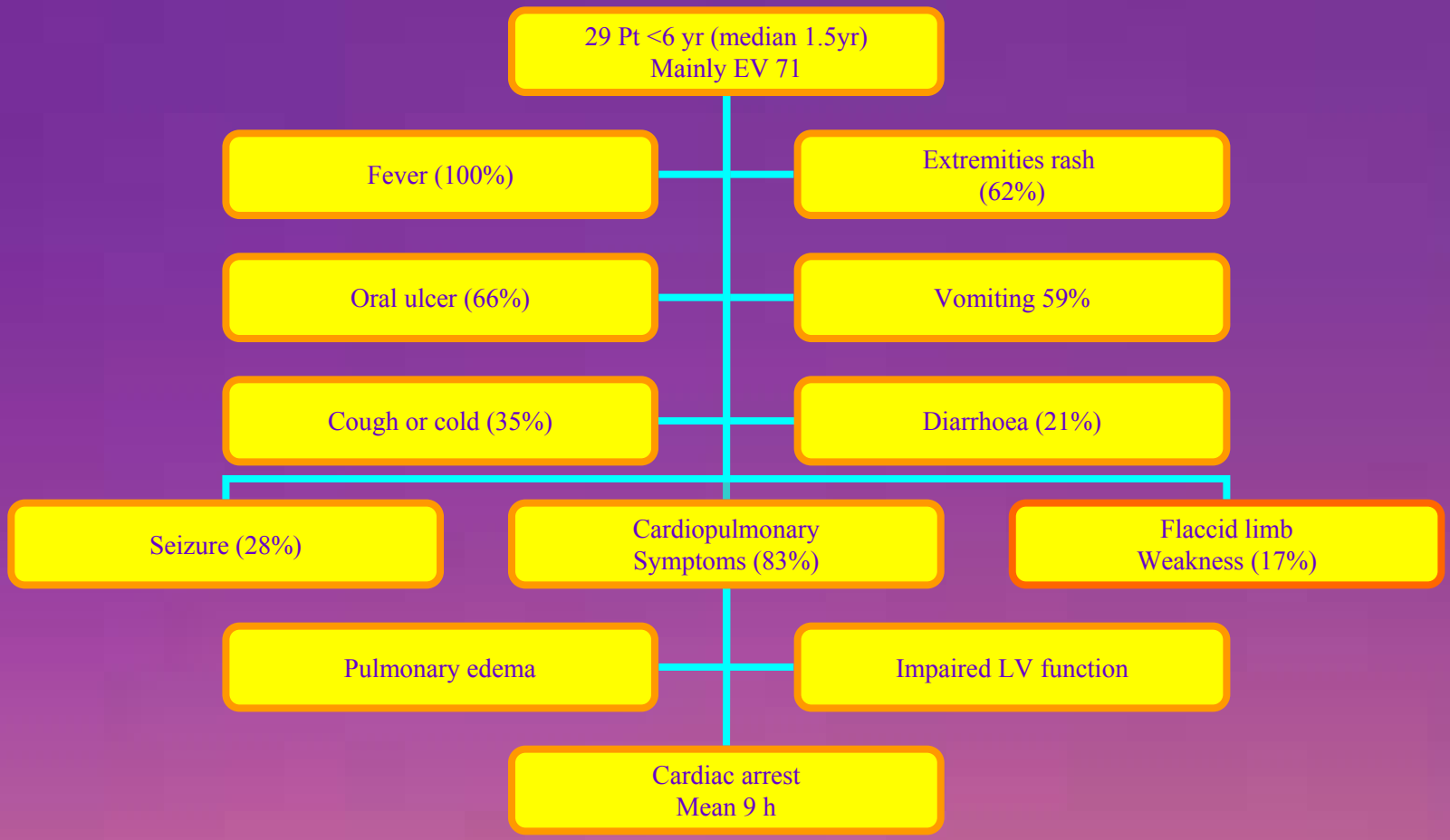
Poliomyelitis: a study of pulmonary edema.

Baker A.B. Neurology 1957;7:743-51.



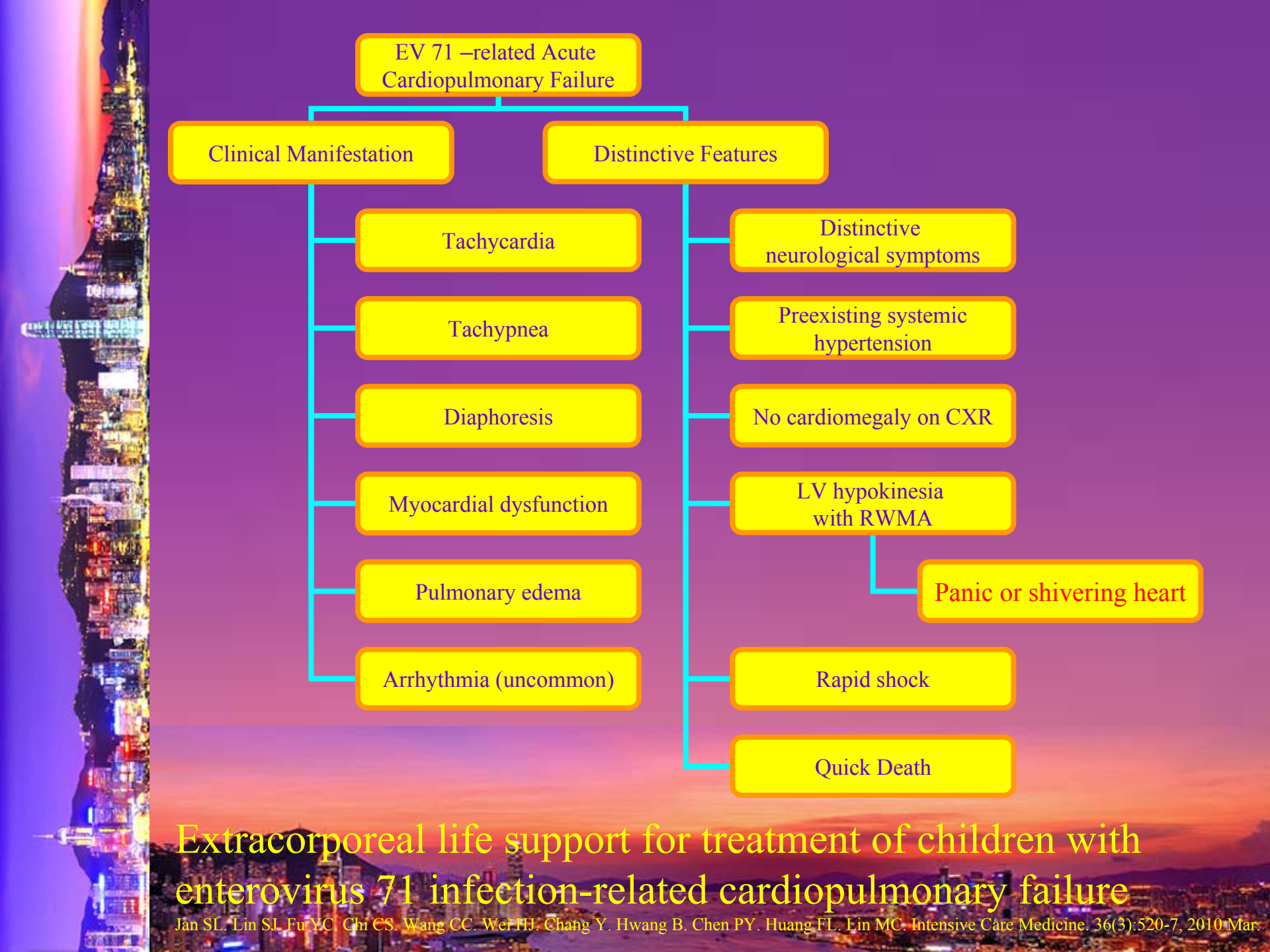
Extracorporeal life support for treatment of children with enterovirus 71 infection-related cardiopulmonary failure

Jan SL. Lin SJ. Fu YC. Chi CS. Wang CC. Wei HJ. Chang Y. Hwang B. Chen PY. Huang FL. Lin MC. Intensive Care Medicine. 36(3):520-7, 2010 Mar.



PM: Normal myocardium with no evidence of inflammation or myocyte necrosis or degeneration. CNS tissue showed congestion, edema, and perivascular and meningeal lymphocytic infiltration. Brain-stem tissue, showed extensive neuronal degeneration and necrosis associated with an inflammatory reaction resembling microabscesses and positive staining for anti-EV71 monoclonal antibody.

L.G. Chan, U.D. Parashar, M.S. Lye, F.G. Ong, S.R. Zaki and J.P. Alexander et al., Deaths of children during an outbreak of hand, foot, and mouth disease in sarawak, Malaysia: clinical and pathological characteristics of the disease, Clinical Infections and Disorders 31 (September (3)) (2000), pp. 678–683.



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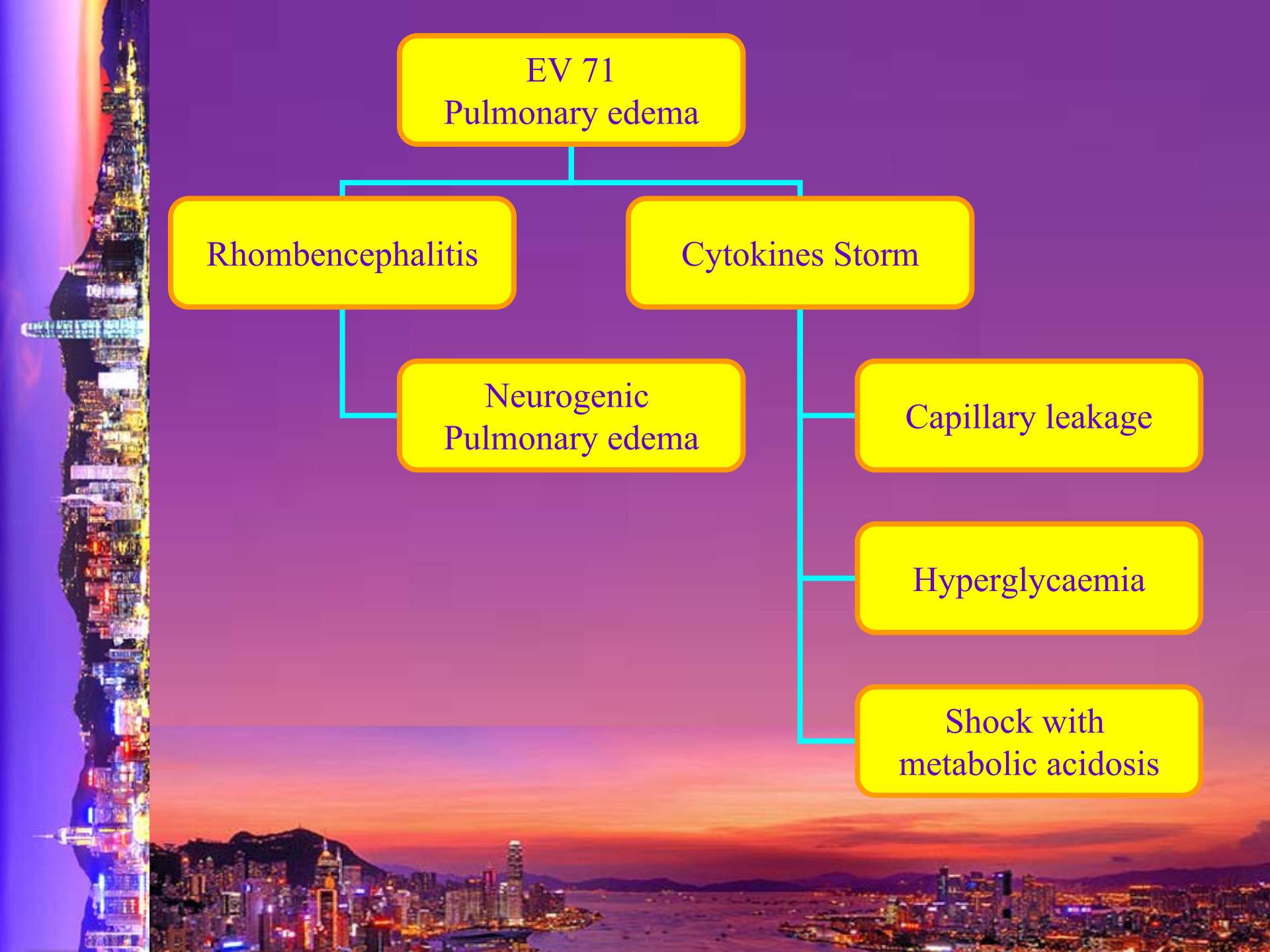
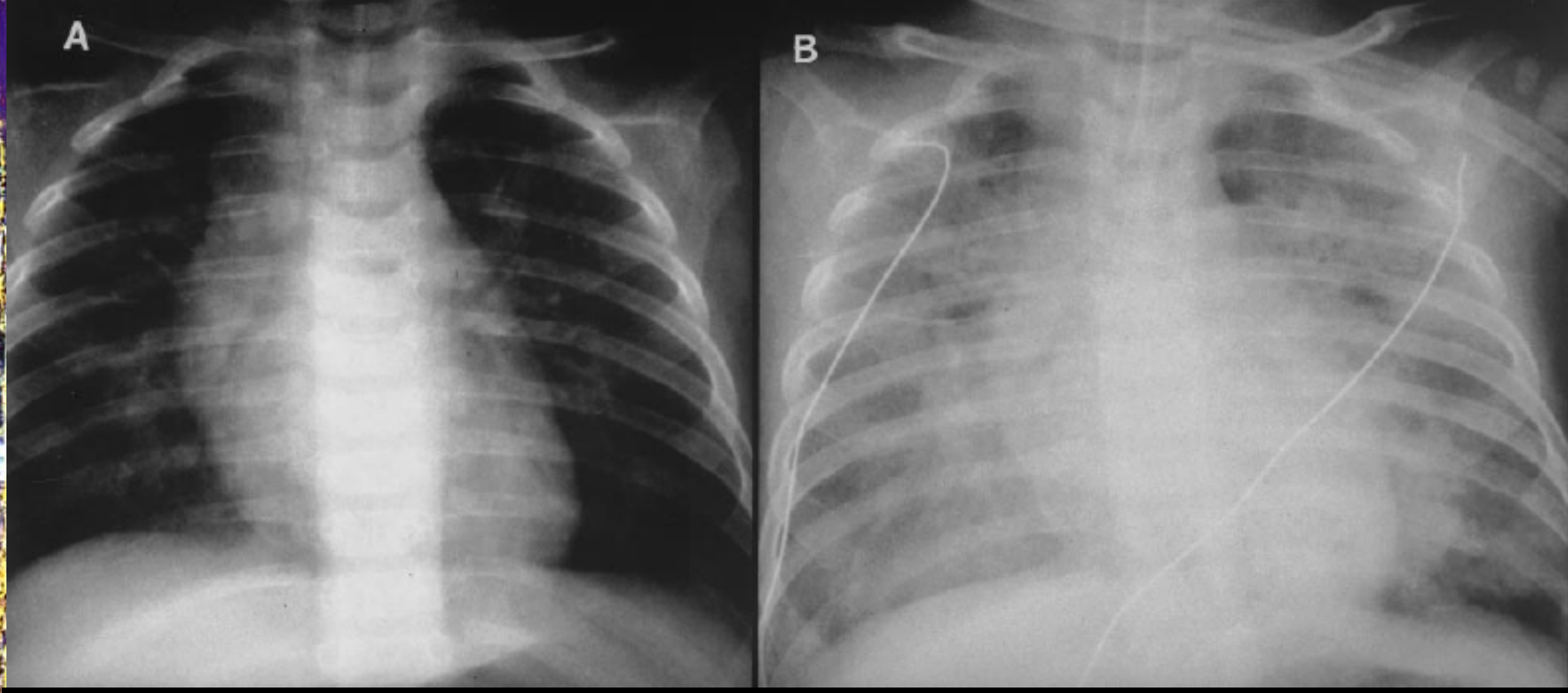

EV 71
Pulmonary edema
Rhombencephalitis
Cytokines Storm
Neurogenic
Pulmonary edema
Capillary leakage
Hyperglycaemia
Shock with
metabolic acidosis

Risk factors	Pulmonary oedema (n=11)	CNS involvement without pulmonary oedema (n=38)	Odds ratio (95% CI)	p
Hyperglycaemia*	9 (82%)	4 (11%)	38 (6–211)	0·001‡
Leucocytosis†	9 (82%)	12 (32%)	9·7 (2·9–33·6)	0·003
Upper limb weakness	4 (36%)	4 (11%)	4·9 (2·6–9·2)	0·04§
Lower limb weakness	7 (64%)	11 (29%)	4·3 (2·0–9·2)	0·04

*Blood glucose >8·3 mmol/L on admission. †White-blood-cell count >17 500/μL on admission. ‡p=0·001 by Fisher's exact test. §p=0·06 by Fisher's exact test.

Factors significantly associated with pulmonary oedema

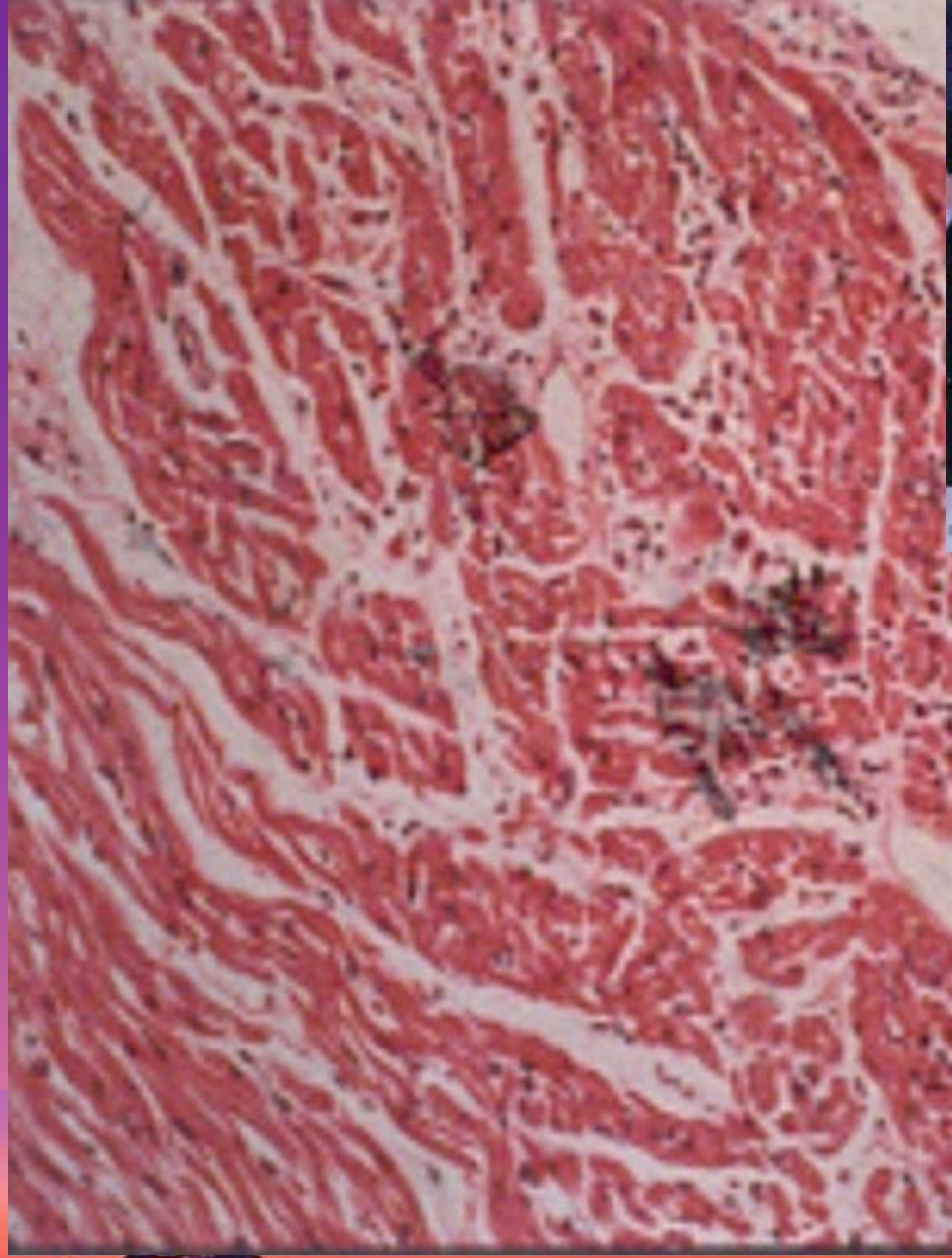


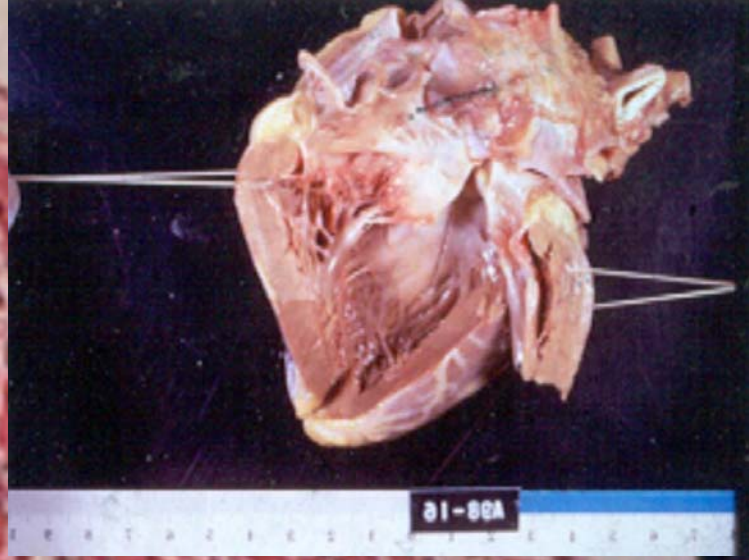
A, Chest radiographs of patient 2 were initially normal. B, Increased alveolar density without obvious cardiomegaly after PE.

Initial Hemodynamic Measurement in Patients With EV71

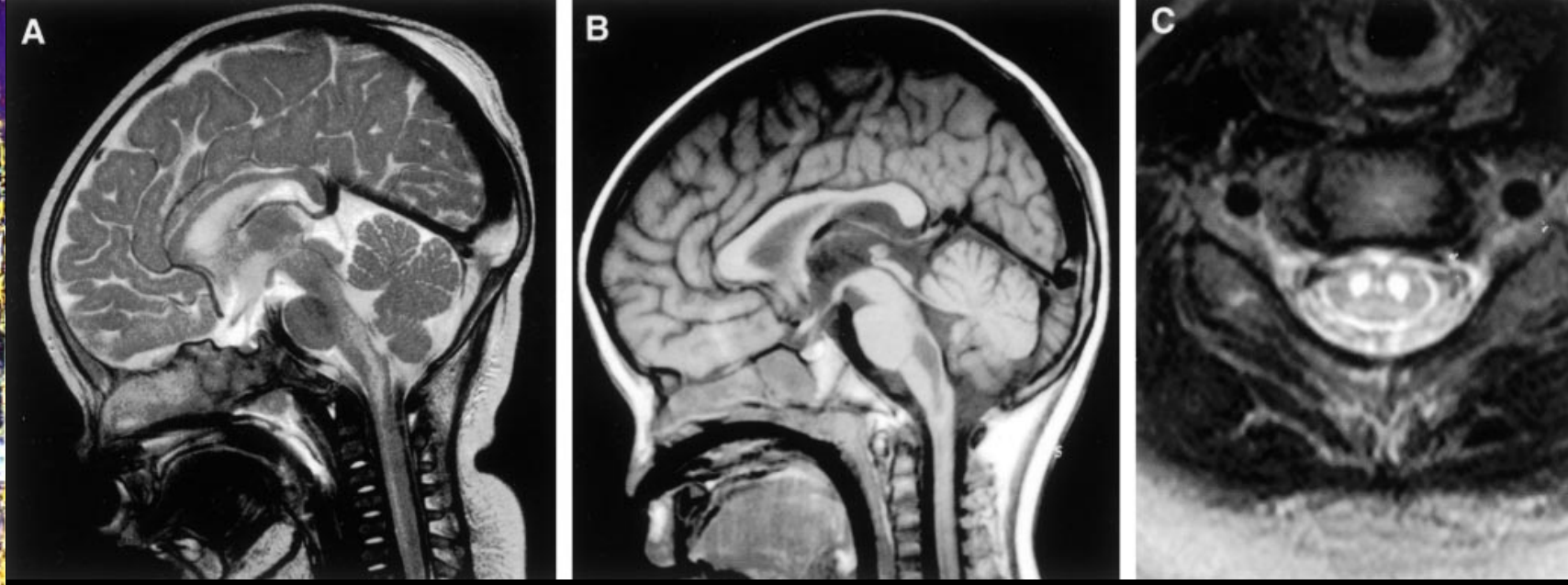
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
CT°C	41.6	41.5	38.4	38.9	39.7
HR bpm	202	217	167	152	195
BP (S/D/M) mm Hg	101/40/60	65/34/44	107/73/81	141/66/91	95/63/73
PAP (S/D/M) mm Hg	29/24/26	26/19/21	29/21/23	31/23/25	27/14/20
CVP mm Hg	22	10	15	12	12
PAOP mm Hg	14	13	16	15	15
CI L/min/m²	3.93	4.53	6.01	2.32	3.97
SI mL/m²	19.5	20.9	35.7	15.3	20.4
SVRI dyne/s/cm⁵/m²	779	600	826	2720	1228
PVRI dyne/s/cm⁵/m²	244	141	133	344	101
LVSWI gm/m/m²	12.2	8.8	31.5	15.8	16.1
RVSWI gm/m/m²	1.06	3.12	3.88	2.70	2.22

CT indicates core temperature; HR, heart rate; BP, blood pressure; S/D/M, systolic/diastolic/mean; CVP, central venous pressure; SI, stroke index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; LVSWI, left ventricular stroke work index; RVSWI, right ventricular stroke work index.





Heart is grossly hypertrophic and there is no inflammatory change on microscopy



(A) T2-weighted sagittal section through the posterior fossa in Patient 1, 4 days after onset of pulmonary edema (PE). Note the hyperintense signal abnormality in the posterior pons and medulla, which extends into the region of the anterior horns of the cervical spine, typical of the MRI changes in the acute phase of the disease. (B) T1-weighted sagittal section through the posterior fossa in Patient 5, 28 days after disease onset. Note the hypointense signal abnormality consistent with encephalomalacia in the posterior pons and medulla, concordant with persistent central respiratory failure and severe bulbar palsy. (C) T2-weighted axial section at the level of C3 in the cervical spine in Patient 4, 56 days after disease onset. Note the persistent hyperintense signal abnormality in the regions of the anterior horns bilaterally, consistent with persistent injury of anterior horn cells of the phrenic nerves and concordant with the observation of unstimulatable phrenic nerves.

Survival after pulmonary edema due to enterovirus 71 encephalitis

M. A. Nolan, M. E. Craig, M. M. Lahra, W. D. Rawlinson, P. C. Prager, G. D

***Neurology* 2003;60;1651-1656**

Fulminant EV71 infection may lead to severe neurologic complications and acute PE. Magnetic resonance imaging revealed that all 5 infants had brainstem lesions.

The acute PE and cardiopulmonary decompensation in EV71 infection are not directly caused by viral myocarditis. The mechanism of PE may be related to increased pulmonary vascular permeability caused by brainstem lesions and/or systemic inflammatory response instead of increased pulmonary capillary hydrostatic pressure.

Cardiopulmonary function usually returns to nearly normal within days, but the neurologic sequelae are severe and usually permanent.

All patients had tachycardia and hyperthermia. Transient systolic hypertension was noted in 1 patient, and 1 presented with hypotension. Pulmonary artery pressure in all 5 infants was normal or mildly elevated (26-31 mm Hg), and central venous pressure ranged from 10 to 22 mm Hg. Pulmonary artery occlusion pressures were normal or slightly elevated (13-16 mm Hg). Systemic and pulmonary vascular resistances were transiently increased in only 1 patient. The stroke volume index decreased to 15.3 to 35.7 mL/M2 (normal: 30-60 mL/M2), but because of the elevated heart rate, the cardiac index did not decrease.

Cardiopulmonary manifestations of fulminant enterovirus 71 infection

Wu JM, Wang JN, Tsai YC, Liu CC, Huang CC, Chen YJ, Yeh TF. Pediatrics. 2002 Feb;109(2):E26-.

	Past cohort (1998–2000) ($n = 10$)	Present cohort (2000–2008) ($n = 13$)	P value	Present cohort EV71-stage 3a ($n = 8$)	Present cohort EV71-stage 3b ($n = 5$)	P value
Management	Conventional	ECLS		ECMO (5)/ECLVS (3)	ECMO (5)	
Age (months)	18 ± 14 (13)	16 ± 10 (16)	0.901	16 ± 12 (13)	16 ± 7 (18)	0.883
Gender	5M/5F	9M/4F	0.349	5M/3F	4M/1F	0.506
BW (kg)	10 ± 3 (10)	10 ± 3 (10)	0.901	10 ± 3 (10)	11 ± 3 (11)	0.604
Onset to admission (day)	4 ± 1 (4)	3 ± 1 (3)	0.139	3 ± 1 (3)	3 ± 1 (3)	0.503
MaxHR (bpm)	204 ± 37 (209)	213 ± 22 (205)	0.756	202 ± 15 (200)	230 ± 20 (220)	0.012*
MaxSBP (mmHg)	117 ± 15 (118)	106 ± 40 (126)	0.509	132 ± 11 (31)	56 ± 22 (59)	0.006*
CTR in CxR	0.50 ± 0.06 (0.51)	0.51 ± 0.04 (0.51)	0.876	0.52 ± 0.03 (0.52)	0.49 ± 0.05 (0.49)	0.295
LVEDD, Z score	0.9 ± 1.9 (1.0)	1.2 ± 2.4 (0.2)	0.804	0.91 ± 2.1 (0.1)	1.6 ± 3.0 (2.6)	0.660
Initial EF%	38 ± 14 (36)	33 ± 9 (34)	0.576	33 ± 7 (33)	32 ± 11 (39)	0.941
CK (IU/l)	344 ± 445 (183)	333 ± 162 (369)	0.222	316 ± 168 (357)	368 ± 167 (416)	0.552
CK-MB (IU/l)	13.7 ± 11.9 (11)	19.8 ± 10 (20)	0.364	19.5 ± 7.4 (20.9)	20.3 ± 21.9 (15.1)	0.831
Glucose (mg/dl)	251 ± 137 (232)	323 ± 308 (181)	0.776	236 ± 203 (125)	444 ± 408 (237)	0.465
Pulmonary edema	9 (90%)	11 (85%)	0.709	6 (75%)	5 (100%)	0.224
Good neurological outcome	0 (0%)	6 (46%)	0.005*	6 (75%)	0 (0%)	0.002*
Survival rate (>7 days)	30%	77%	0.024*	100%	40%	0.012*
	7 Early deaths 3 Late deaths	3 Early deaths 1 Late death		All survived	3 Early deaths 1 Late death	

Data are presented as mean ± standard deviation (median) or case numbers (%). Good neurological outcome is defined survival to discharge with PCPC of 1, 2 or 3 at hospital discharge or no change from pre-ECLS PCPC. *P* value is assessed by comparisons of data between past and present, stage 3a and 3b cohorts

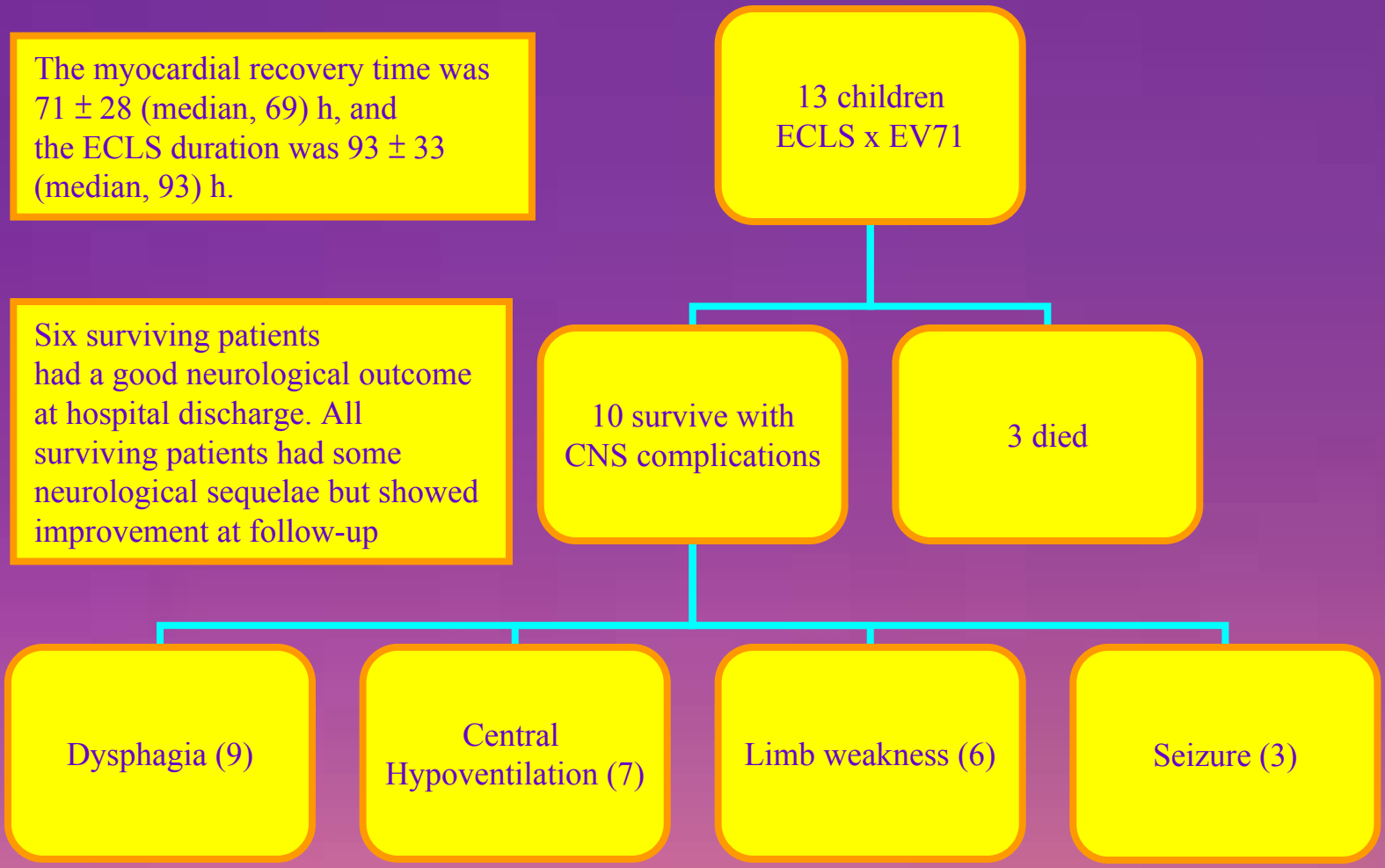
BW body weight, *CK* creatine kinase, *CK-MB* muscle-brain fraction of creatine kinase, *CTR* cardiothoracic ratio, *CXR* chest X-ray, *ECMO* extracorporeal membrane oxygenation, *ECLVS* extracorporeal left ventricular support, *EF* ejection fraction of the left ventricle, *EV* enterovirus, *MaxHR* maximum heart rate, *LVEDD* left ventricular end-diastolic dimension, *MaxSBP* maximum systolic blood pressure

* $P < 0.05$

Extracorporeal life support for treatment of children with enterovirus 71 infection-related cardiopulmonary failure

Jan SL. Lin SJ. Fu YC. Chi CS. Wang CC. Wei HJ. Chang Y. Hwang B. Chen PY. Huang FL. Lin MC. Intensive Care Medicine. 36(3):520-7, 2010 Mar.

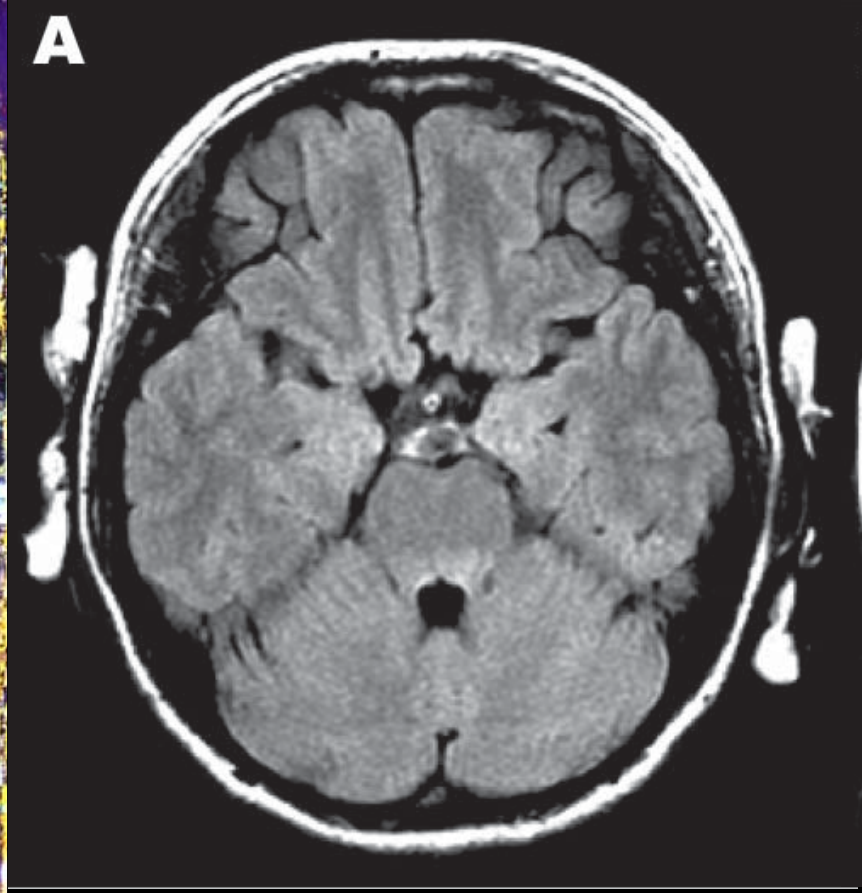
The myocardial recovery time was 71 ± 28 (median, 69) h, and the ECLS duration was 93 ± 33 (median, 93) h.

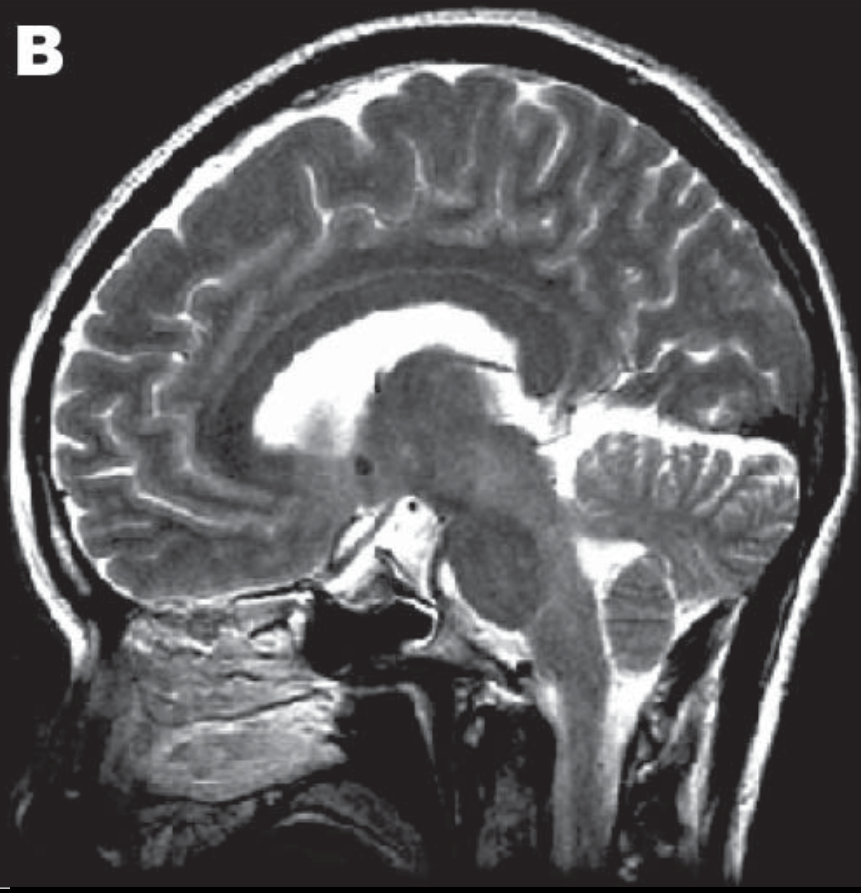


Six surviving patients had a good neurological outcome at hospital discharge. All surviving patients had some neurological sequelae but showed improvement at follow-up

The present cohort had better neurological outcomes (46 vs. 0%, P = 0.005) and a higher survival rate (77 vs. 30%, P = 0.024) than the past cohort.

Extracorporeal life support for treatment of children with enterovirus 71 infection-related cardiopulmonary failure. Jan SL. Lin SJ. Fu YC. Chi CS. Wang CC. Wei HJ. Chang Y. Hwang B. Chen PY. Huang FL. Lin MC. Intensive Care Medicine. 36(3):520-7, 2010 Mar.





Hyperintense lesions in the tegmentum of the pons in the axial section of the fl uid-attenuated inversion recovery image.

In the sagittal section of the T2-weighted image, hyperintense lesions are present in the tegmentum of the midbrain, pons, and medulla oblongata.

- The 07-Ishikawa strain shows a close genetic relationship to recent subgenogroup **C4** strains in mainland **China** (97.4% nt identity to the SHZH04–38 strain) and those in Japan (97.0% nt identity to the 2779-Yamagata strain)

Acute encephalitis caused by intrafamilial transmission of enterovirus 71 in adult. Hamaguchi T. Fujisawa H. Sakai K. Okino S. Kurosaki N. Nishimura Y. Shimizu H. Yamada M. Emerging Infectious Diseases. 14(5):828-30, 2008 May.

Thank you for your attention

Treatment of EV71 Rhomboencephalitis

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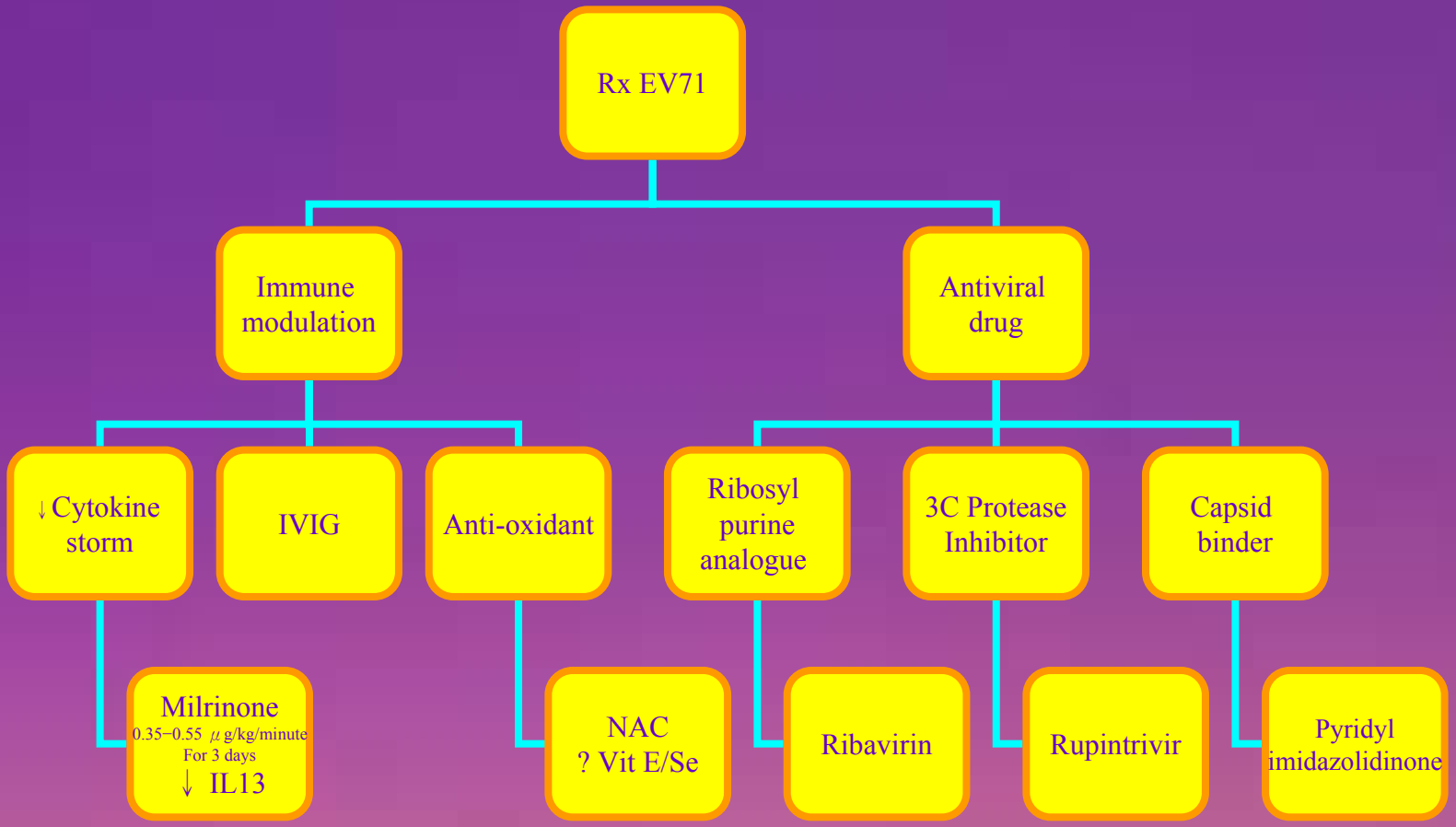
Clinical staging and management of enterovirus 71 infection

Stage	Clinical manifestations	Management
1	HFMD/herpangina	Symptomatic treatment only
2	CNS involvement	Fluid restriction, osmotic diuretics for increased intracranial pressure, and furosemide for fluid overload (CVP >8 cmH_2O), intravenous immunoglobulin for encephalitis and/or polio-like syndrome and close monitoring of heart rate, blood pressure, oxygenation, coma scale and blood glucose
3	Cardiopulmonary failure	
3A	Hypertension/ pulmonary edema	Phosphodiesterase inhibitor, milrinone, to increase cardiac output, early intubation with positive pressure mechanical ventilation with increased positive end expiratory pressure for pulmonary edema, and high frequency oscillatory ventilation if pulmonary edema/hemorrhage persists or severe hypoxemia develops
3B	Hypotension	Add inotropic agents such as dopamine and epinephrine
4	Convalescence	Rehabilitation for limb weakness, dysphagia, apnea or central hypoventilation, and sufficient chest care to avoid recurrent pneumonia

HFMD = hand, foot, and mouth disease; CNS = central nervous system; CVP = central venous pressure.

Enterovirus 71 in Taiwan. Chang LY. Pediatrics & Neonatology. 49(4):103-12, 2008 Aug.



Diseases caused by enterovirus 71 infection. Lee TC. Guo HR. Su HJ. Yang YC. Chang HL. Chen KT. Pediatric Infectious Disease Journal. 28(10):904-10, 2009 Oct.

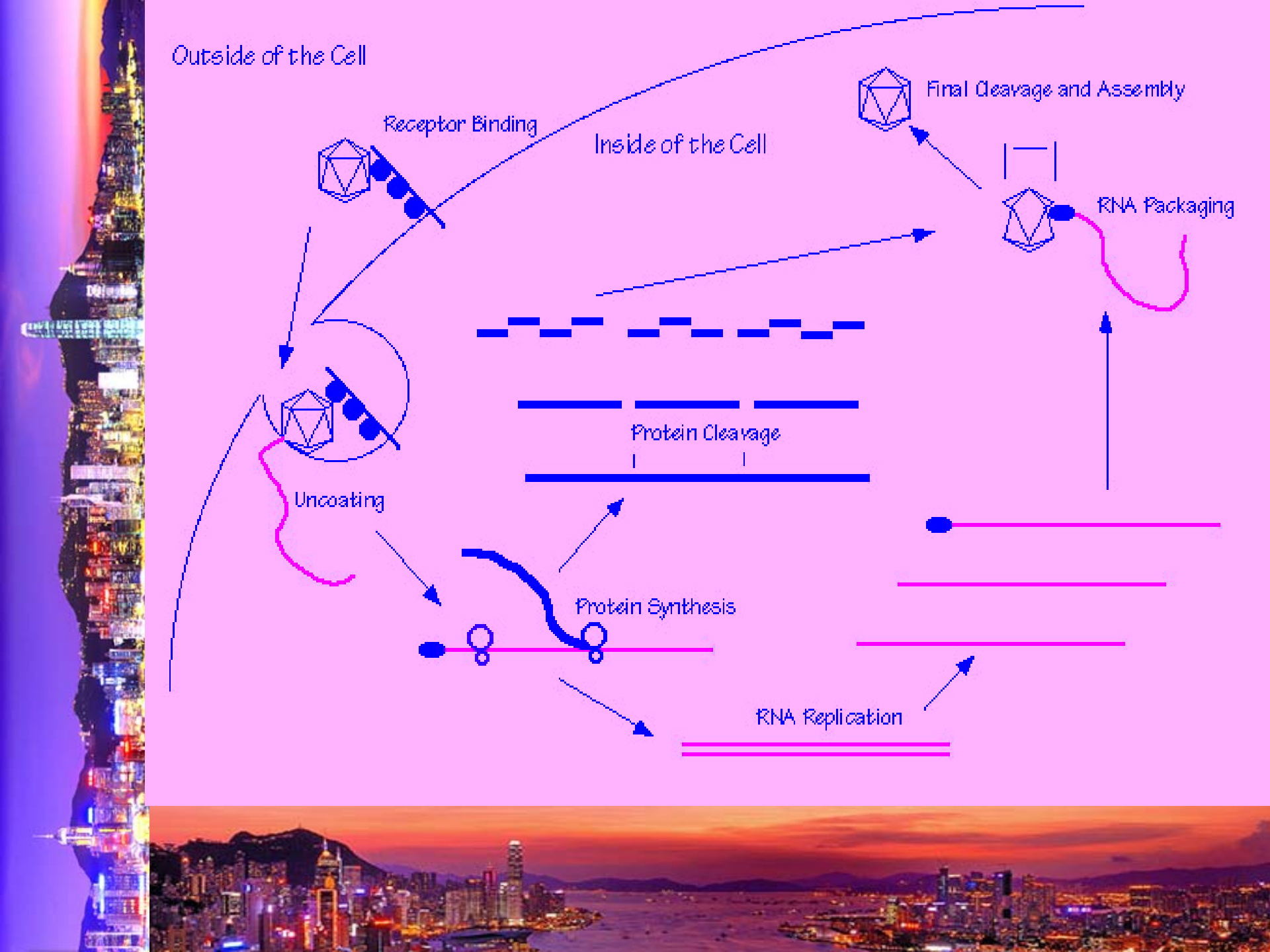
Rupintrivir is a promising candidate for treating severe cases of Enterovirus-71 infection. Zhang XN. Song ZG. Jiang T. Shi BS. Hu YW. Yuan ZH. World Journal of Gastroenterology. 16(2):201-9, 2010 Jan 14.

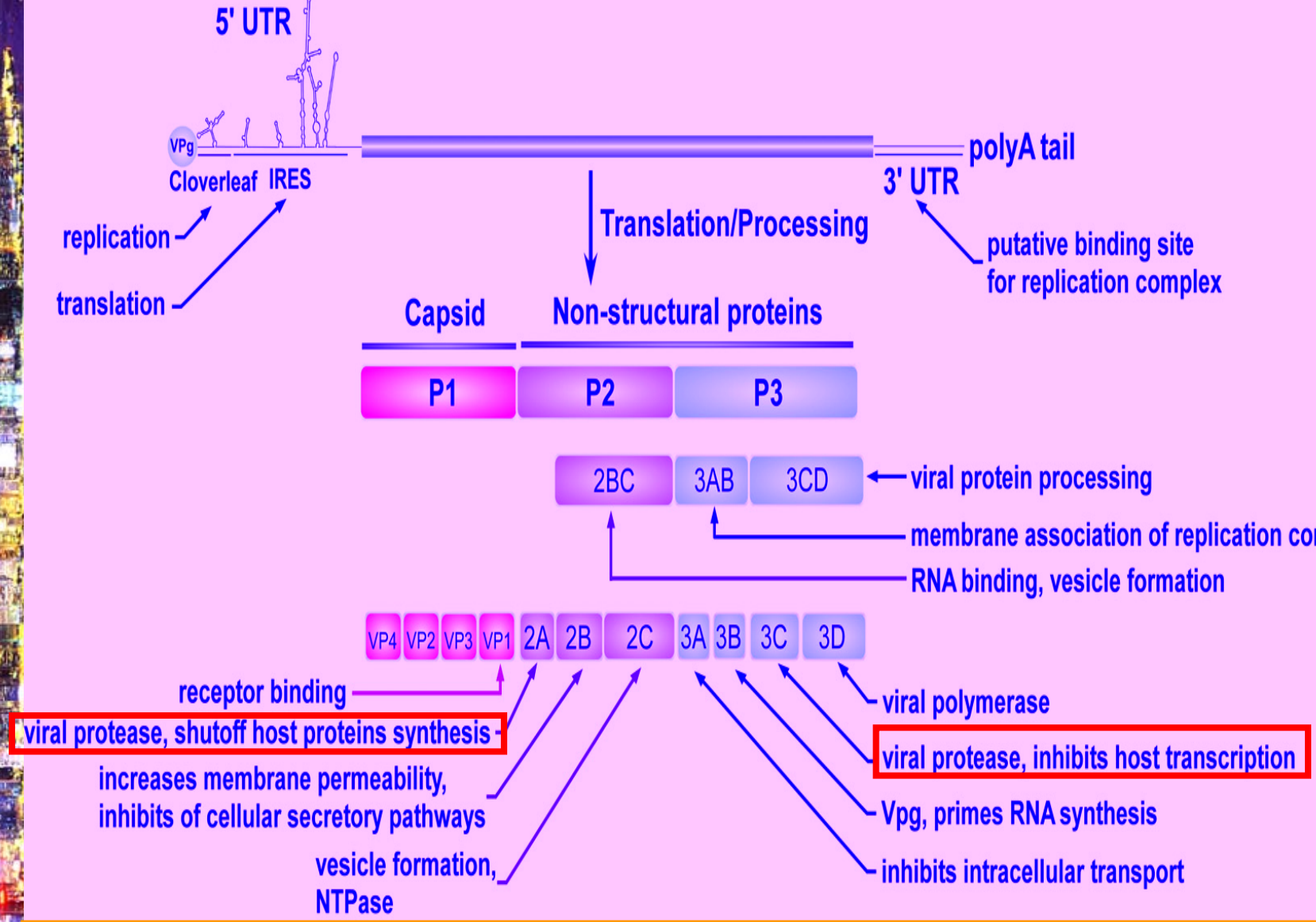
Enterovirus 71: epidemiology, pathogenesis and management. Wang SM. Liu CC. Expert Review of Antiinfective Therapy. 7(6):735-42, 2009 Aug.

Wang SM, Lei HY, Huang MC, et al. Modulation of cytokine production by intravenous immunoglobulin in patients with enterovirus 71-associated brainstem encephalitis. J Clin Virol 2006;37:47−52.

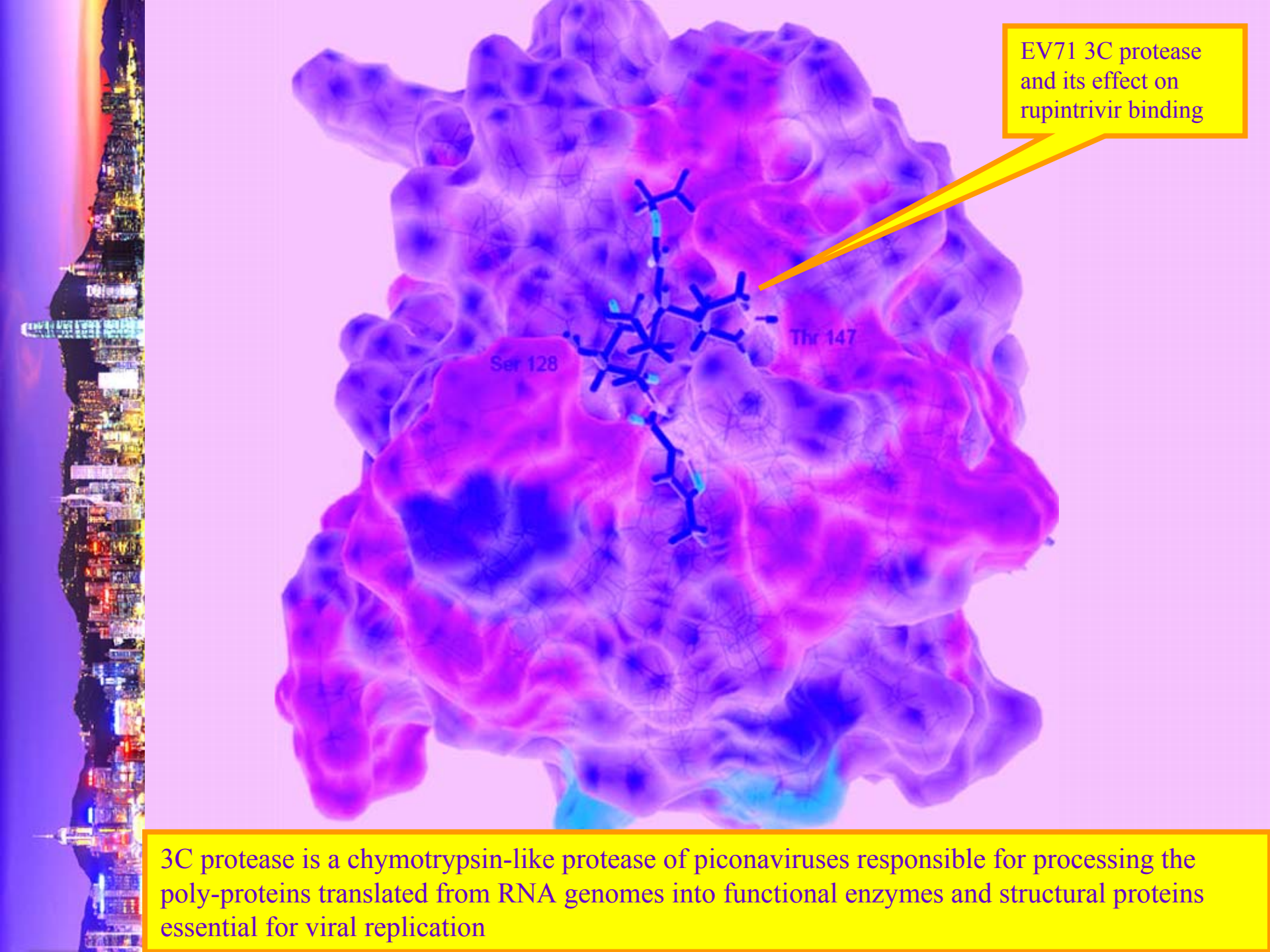
Therapeutic efficacy of milrinone in the management of enterovirus 71-induced pulmonary edema. Wang SM. Lei HY. Huang MC. Wu JM. Chen CT. Wang JN. Wang JR. Liu CC. Pediatric Pulmonology. 39(3):219-23, 2005 Mar.

Glucose-6-phosphate dehydrogenase deficiency enhances enterovirus 71 infection Hung-Yao Ho1,, Mei-Ling Cheng,, Shiue-Fen Weng1, Lo Chang, Tsun-Tsun Yeh1, Shin-Ru Shih1,and Daniel Tsun-Yee Chiu1,J Gen Virol 89 (2008), 2080-2089


Outside of the Cell
Receptor Binding
Inside of the Cell
Final Cleavage and Assembly
RNA Packaging
Protein Cleavage
Uncoating
Protein Synthesis
RNA Replication



Schematic of the enterovirus genome, the polyprotein products and their major functions.
A diagrammatic representation of the enterovirus genome is shown. The 11 mature polypeptides are shown, together with the three main cleavage intermediates. The main biological functions are included for each polypeptide. UTR, untranslated region; IRES, internal ribosome entry site; VPg, viral protein genome-linked. http://www.jbiomedsci.com/content/16/1/103



3C protease is a chymotrypsin-like protease of piconaviruses responsible for processing the poly-proteins translated from RNA genomes into functional enzymes and structural proteins essential for viral replication

Rupintrivir is a Novel Inhibitor of Human Rhinovirus 3C Protease

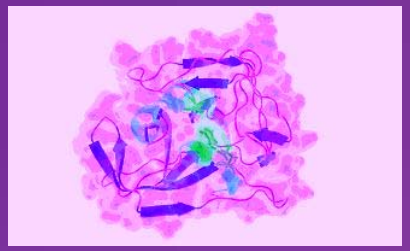
Rupintrivir had favorable binding affinity with 3C protease of China 2008 EV71 virus isolated in Shanghai

Rupintrivir is a promising candidate for treating severe cases of Enterovirus-71 infection. Zhang XN. Song ZG. Jiang T. Shi BS. Hu YW. Yuan ZH. World Journal of Gastroenterology. 16(2):201-9, 2010 Jan 14.

Glucose-6-phosphate dehydrogenase deficiency enhances enterovirus 71 infection

Cellular redox status affects infectivity as well as the outcome of enterovirus 71 (EV71) infection. Treatment with N-acetylcysteine offered resistance to EV71 propagation and a cytoprotective effect on the infected cells.

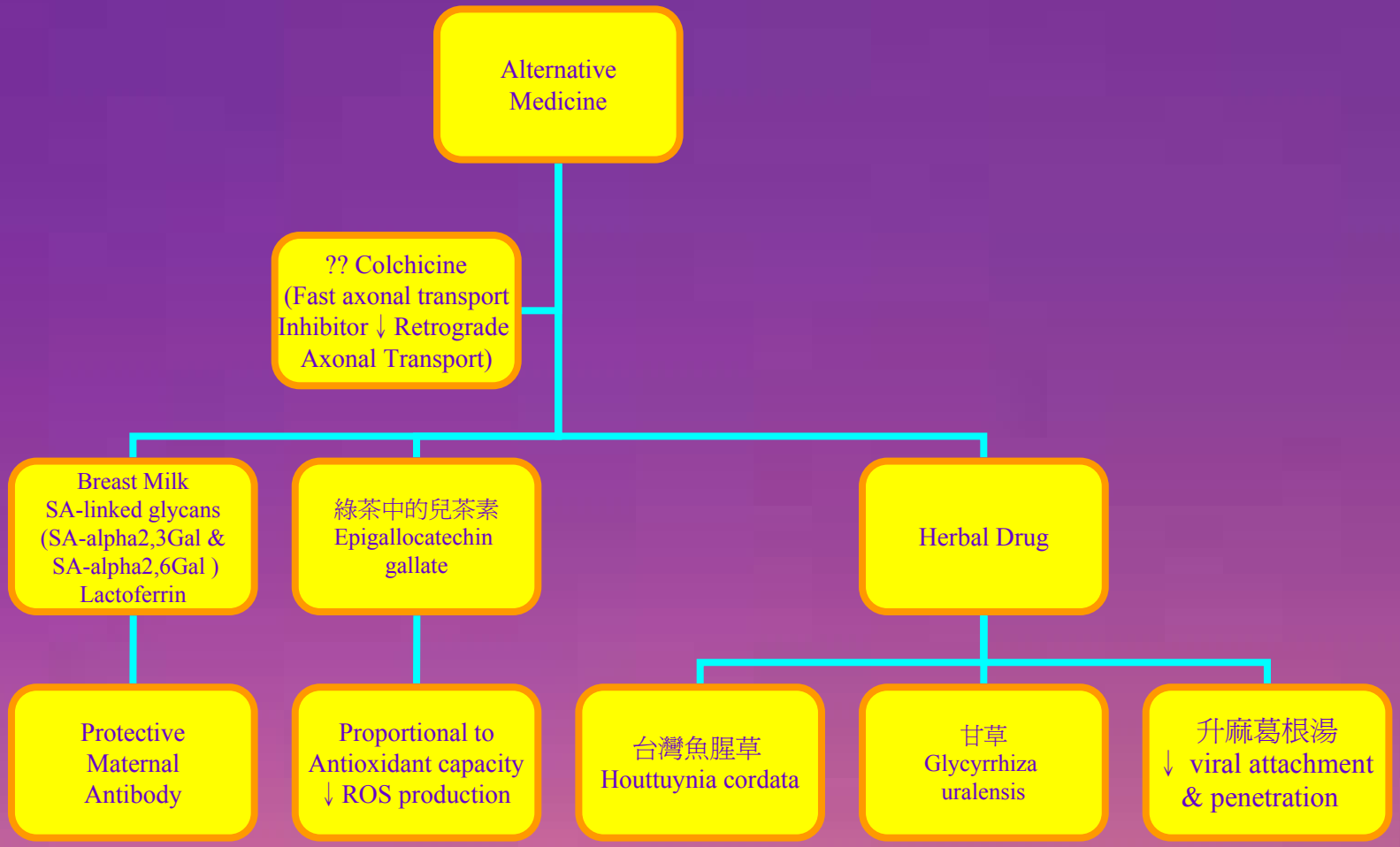
Glucose-6-phosphate dehydrogenase deficiency enhances enterovirus 71 infection.
Ho HY. Cheng ML. Weng SF. Chang L. Yeh TT. Shih SR. Chiu DT.



The 3C Protein of Enterovirus 71 Inhibits RIG-I Mediated IRF3 Activation and Type I Interferon Responses Xiaobo Lei, Xinlei Liu, Yijie Ma, Zhenmin Sun, Yaowu Yang, Qi Jin*, Bin He*, and Jianwei Wang J. Virol. doi:10.1128/JVI.02491-09

Infection with enterovirus 71 or expression of its 2A protease induces apoptotic cell death.
Kuo RL, Kung SH, Hsu YY, Liu WT. J Gen Virol. 2002 Jun;83(Pt 6):1367-76.

The 3C protease activity of enterovirus 71 induces human neural cell apoptosis. Li ML, Hsu TA, Chen TC, Chang SC, Lee JC, Chen CC, Stollar V, Shih SR. Virology. 2002 Feb 15;293(2):386-95.



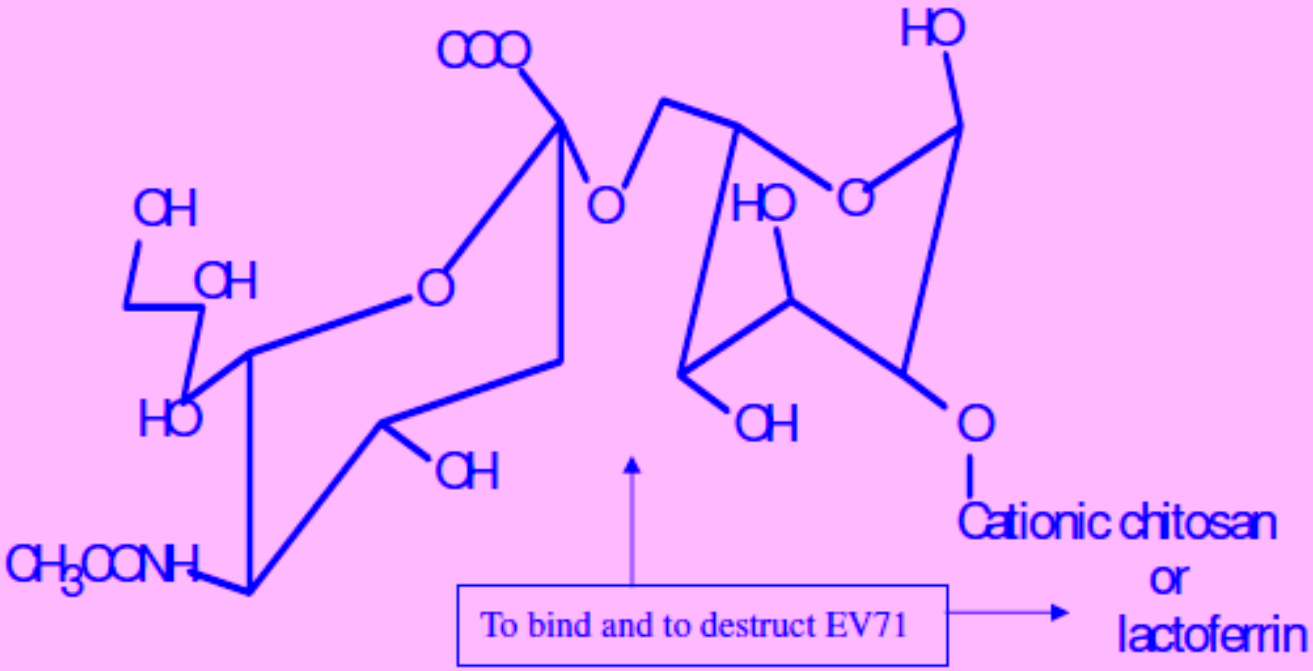
Water extract of Glycyrrhiza uralensis inhibited enterovirus 71 in a human foreskin fibroblast cell line. Kuo KK. Chang JS. Wang KC. Chiang LC. American Journal of Chinese Medicine. 37(2):383-94, 2009.

Sialylated glycans as receptor and inhibitor of enterovirus 71 infection to DLD-1 intestinal cells. Yang B. Chuang H. Yang KD. Virology Journal. 6:141, 2009.

Antiviral effect of epigallocatechin gallate on enterovirus 71. Ho HY. Cheng ML. Weng SF. Leu YL. Chiu DT. Journal of Agricultural & Food Chemistry. 57(14):6140-7, 2009 Jul 22.

Enterovirus 71 maternal antibodies in infants, Taiwan. Luo ST. Chiang PS. Chao AS. Liou GY. Lin R. Lin TY. Lee MS. Emerging Infectious Diseases. 15(4):581-4, 2009 Apr.

Sheng-Ma-Ge-Gen-Tang inhibited Enterovirus 71 infection in human foreskin fibroblast cell line. Chang JS. Wang KC. Chiang LC. Journal of Ethnopharmacology. 119(1):104-8, 2008 Sep 2.



A proposed SA-based "double-edge sword" on blocking and destructioing of EV71 infections. SA (α2,6)-linked galactose can block EV71 infection by competition of sugar receptor, and the galactose can be linked with cationic compounds such as lactoferrin or chitosan for destruction of EV71.

Sialylated glycans as receptor and inhibitor of enterovirus 71 infection to DLD-1 intestinal cells. Yang B. Chuang H. Yang KD. Virology Journal. 6:141, 2009.

Thank you for your attention

Vaccination for EV71 ?

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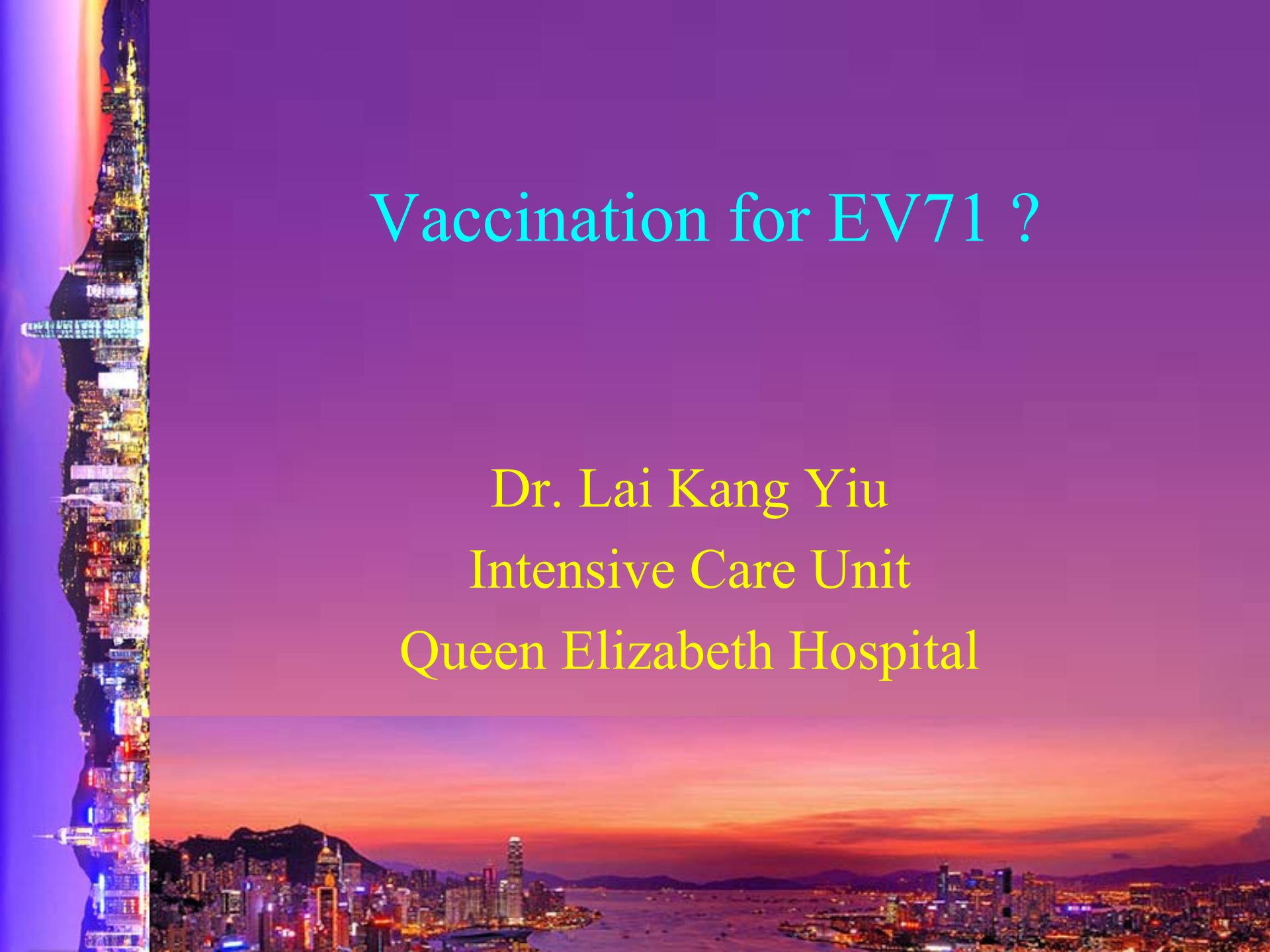
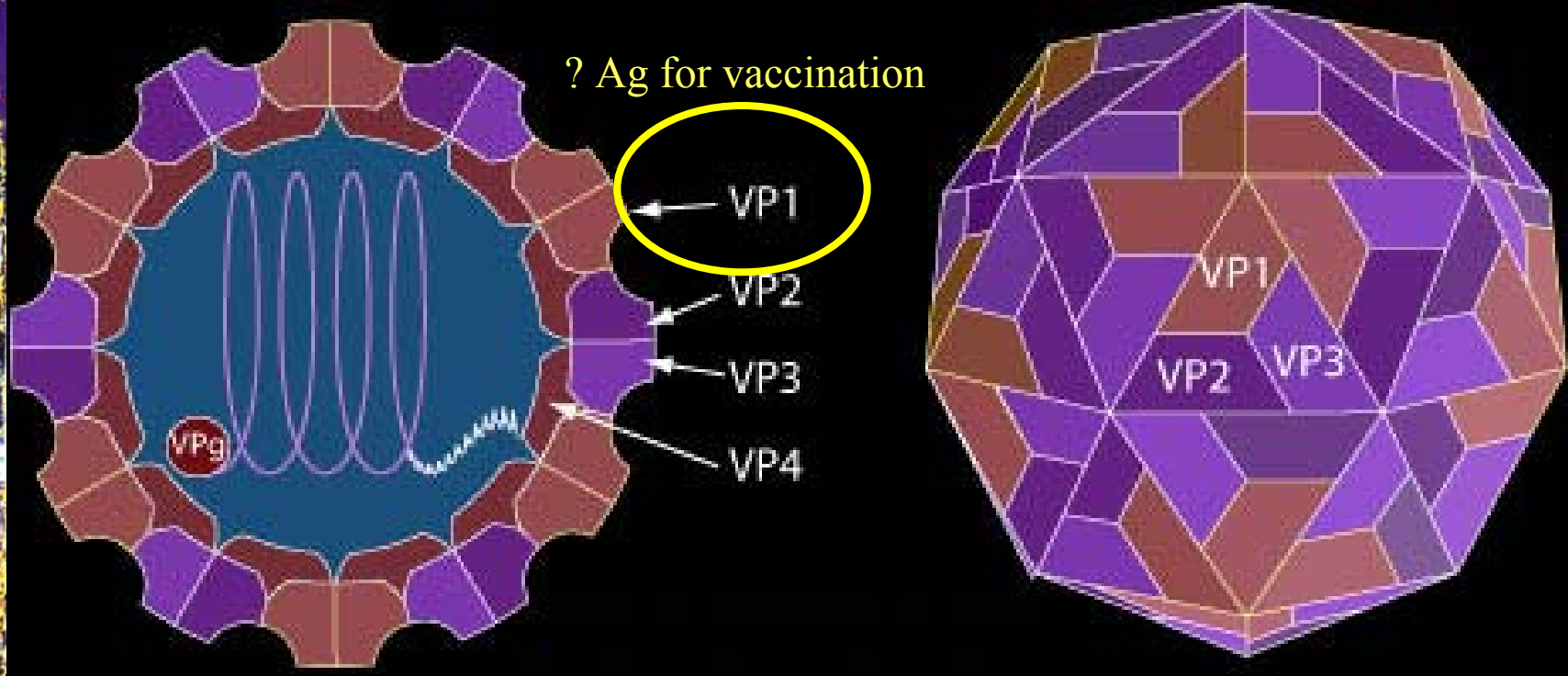




Non-enveloped, spherical, about 30 nm in diameter, composed of a protein shell surrounding the naked RNA genome. The capsid consists of a densely-packed icosahedral arrangement of 60 protomers, each consisting of 4 polypeptides, VP1, VP2, VP3 and VP4. VP4 is located on the internal side of the capsid.

VP1 protein, responsible for adsorption and the uncoating process of the virus can bind three human proteins, i.e. ornithine decarboxylase (ODC1), gene trap ankyrin repeat (GTAR), and KIAA0697 expressed in brain tissue, and their interactions may interfere the proteins' function in brain leading to neurological complications such as acute flaccid paralysis and encephalitis.

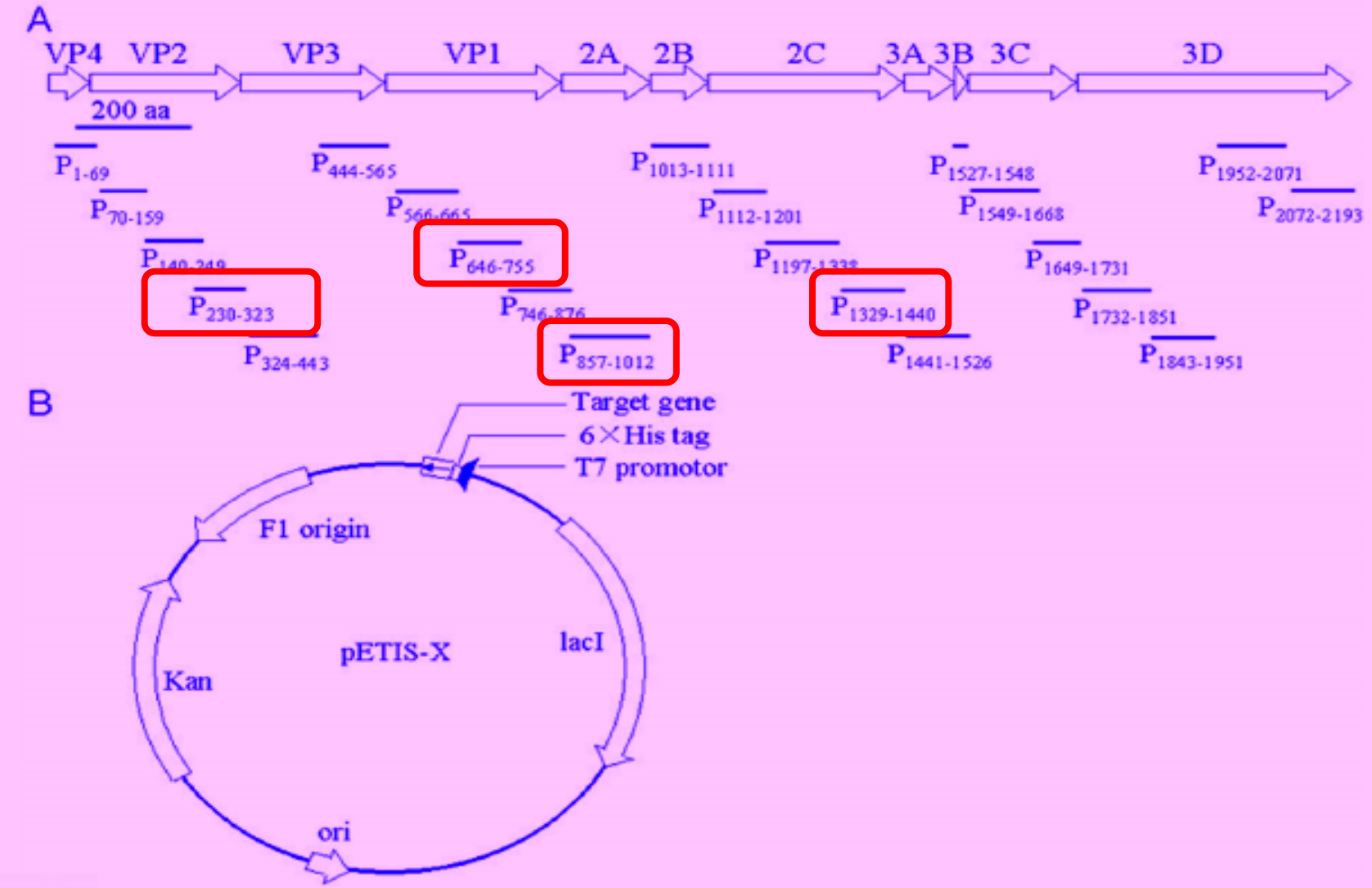
EV71: an emerging infectious disease vaccine target in the Far East?. Xu J. Qian Y. Wang S. Serrano JM. Li W. Huang Z. Lu S. Vaccine. 28(20):3516-21, 2010 Apr 30.

EV71 induced IgG could enter BBB and cross-reacted with brain tissue in EV71 infected neonatal mice, and then the peptides of EV71 that could induce cross-reactivity with brain tissue were identified, which should be avoided in future vaccine designing.

- All of the tested EV71 infected patients' sera were presence of IgG to cross-react with health human brain tissues
- Identification of EV71 fragments inducing cross-reactivity to human brain tissue
  - Peptides of P230-323, P646-755, P857-1012 and P1329-1440 could induce strong IgG cross-reactivity to human brain tissue. The significant of cross reactivity was not relevant to the specific IgG titer induced by individual peptides, which indicated the cross reactivity was a specific IgG behavior rather than an antibody dose dependent artifact.
- EV71 infection increased BBB permeability and IgG transport and enhance both the naïve IgG and EV71 induced IgG entry.

The cross-reactivity of the enterovirus 71 to human brain tissue and identification of the cross-reactivity related fragments.

Jia CS. Liu JN. Li WB. Ma CM. Lin SZ. Hao Y. Gao XZ. Liu XL. Xu YF. Zhang LF. Qin C. Virology Journal. 7:47, 2010.



Diagrams of divided 22 peptides from EV71 and expression construction. The position and length of 22 peptides divided from EV71 (a) and expression constructs for 22 peptides (b) were diagramed.

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