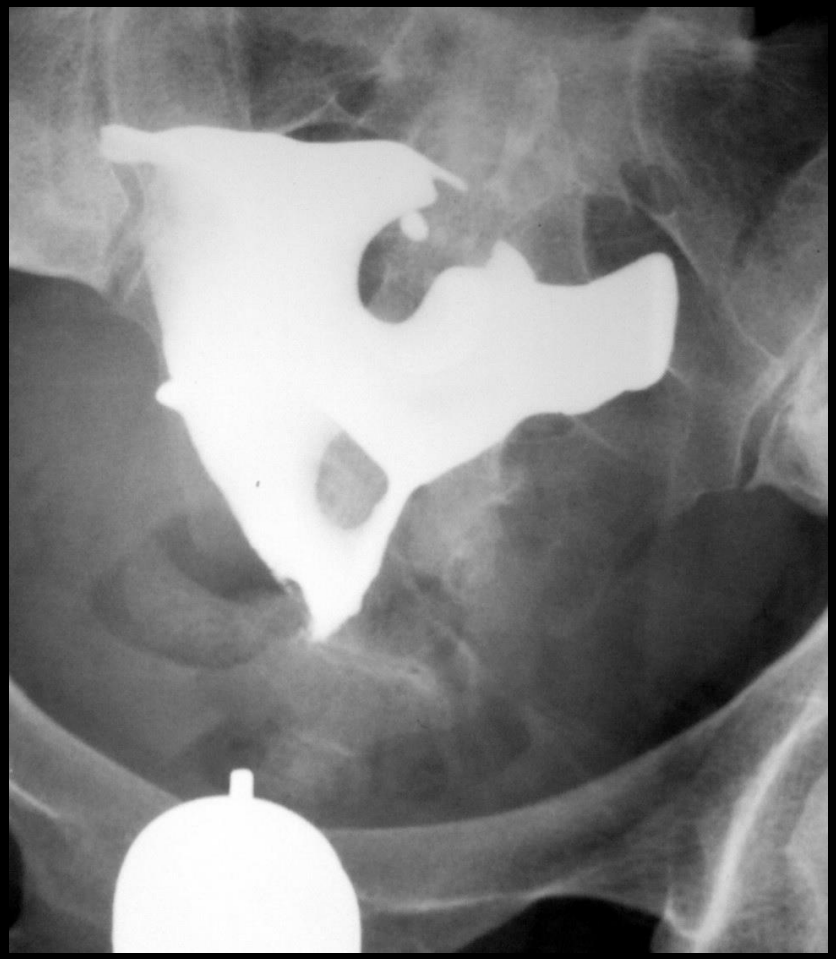
MY COLD CASE

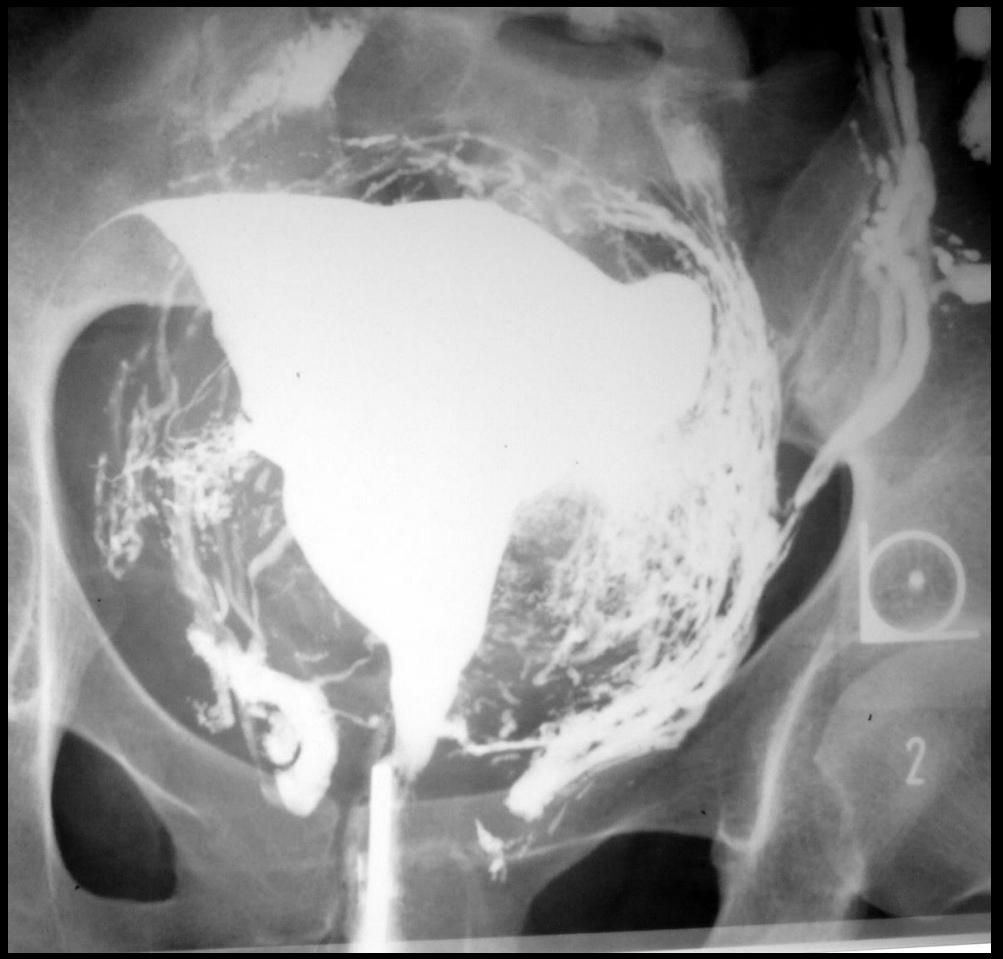
相模原中央病院
菅　信一

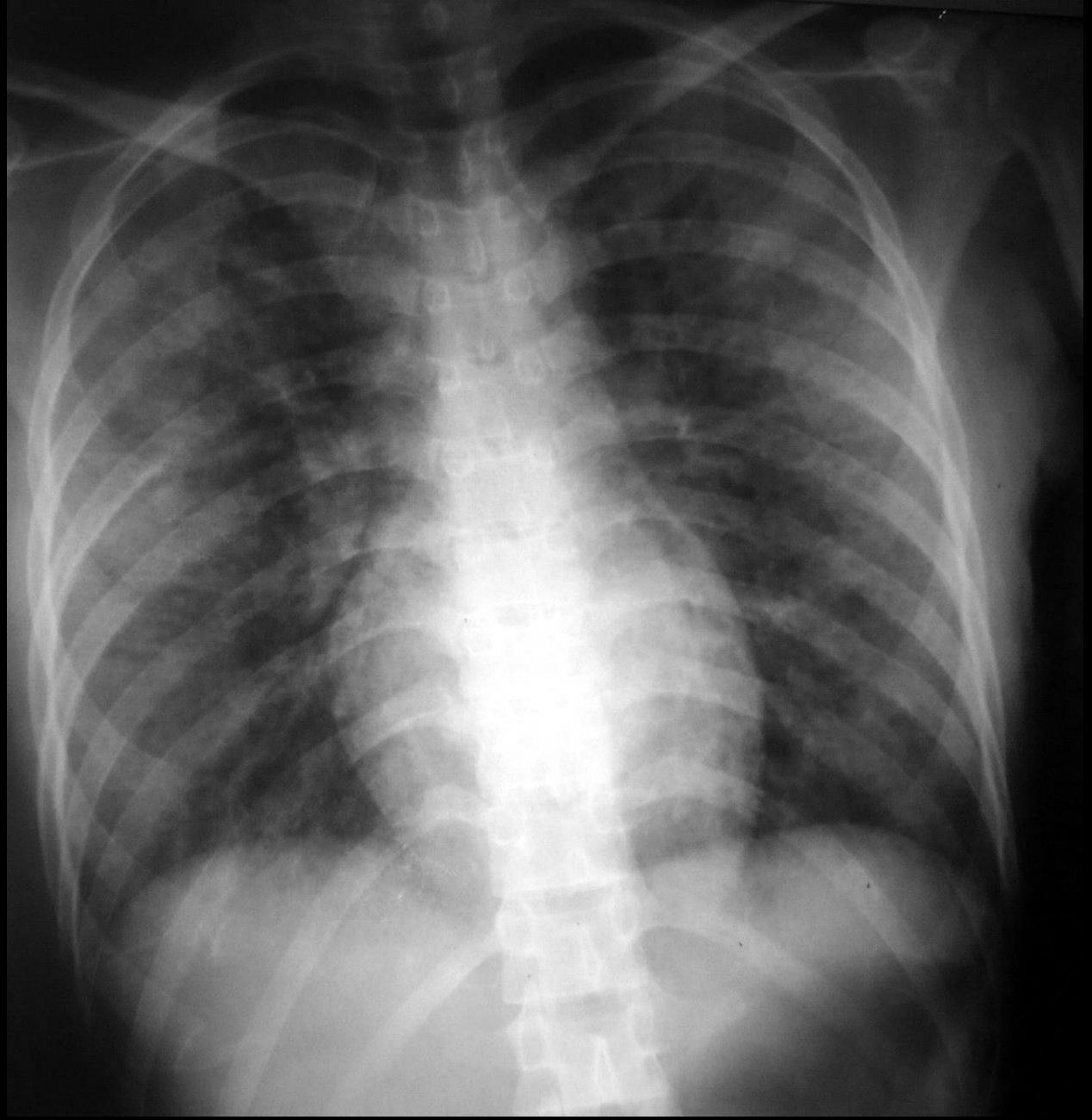
時効制度のないアメリカで、時の流れに置き去りにされてきた未解決の凶悪事件、通称コールドケースに、敏腕女性刑事リリー・ラッシュが挑む。最新科学と時空を超えた洞察力で、封印された事件の謎に新たな突破口を見出す。事件解決と共に浮き彫りになる、各時代のアメリカが抱える社会問題と普遍の人間性。事件当時の大ヒット曲が時に切なく、時に残酷な悲しいストーリーを盛り立て、郷愁と余情を誘う珠玉のクライム・サスペンス。

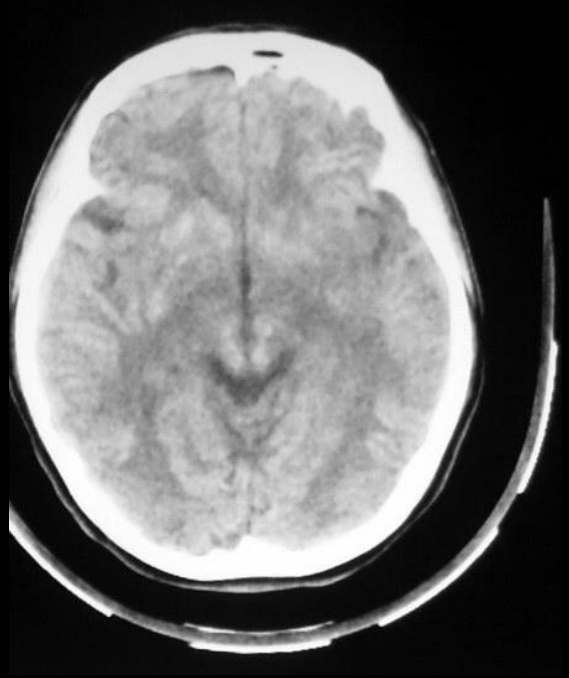
エピソード　1

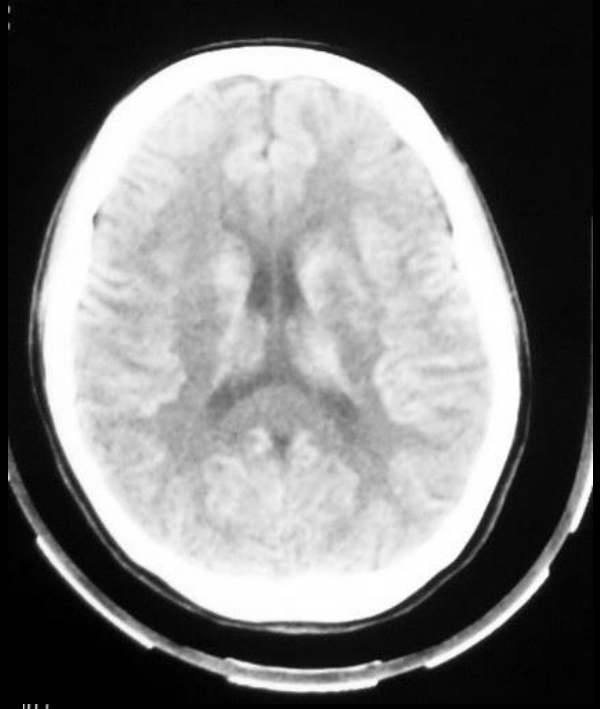
Unwanted thing

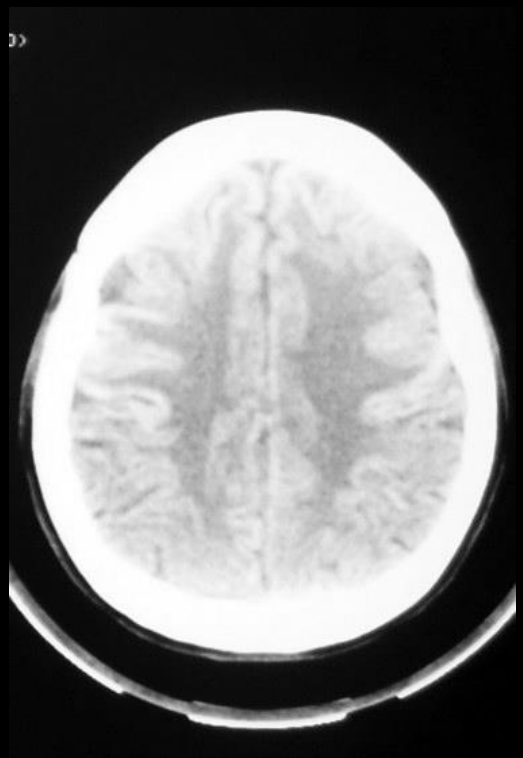


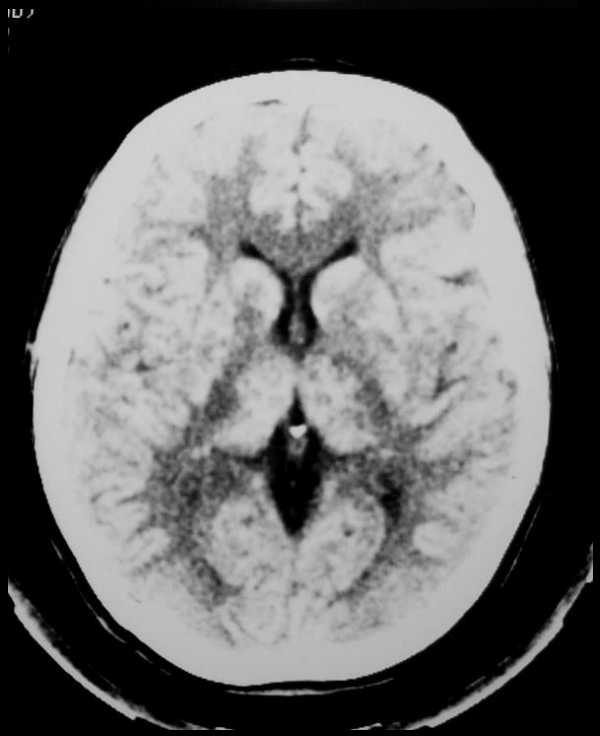

2











素朴な疑問

注入された異物は、血流の多い皮質
脂肪塞栓症の所見は、白質優位だが

４７歳　女性

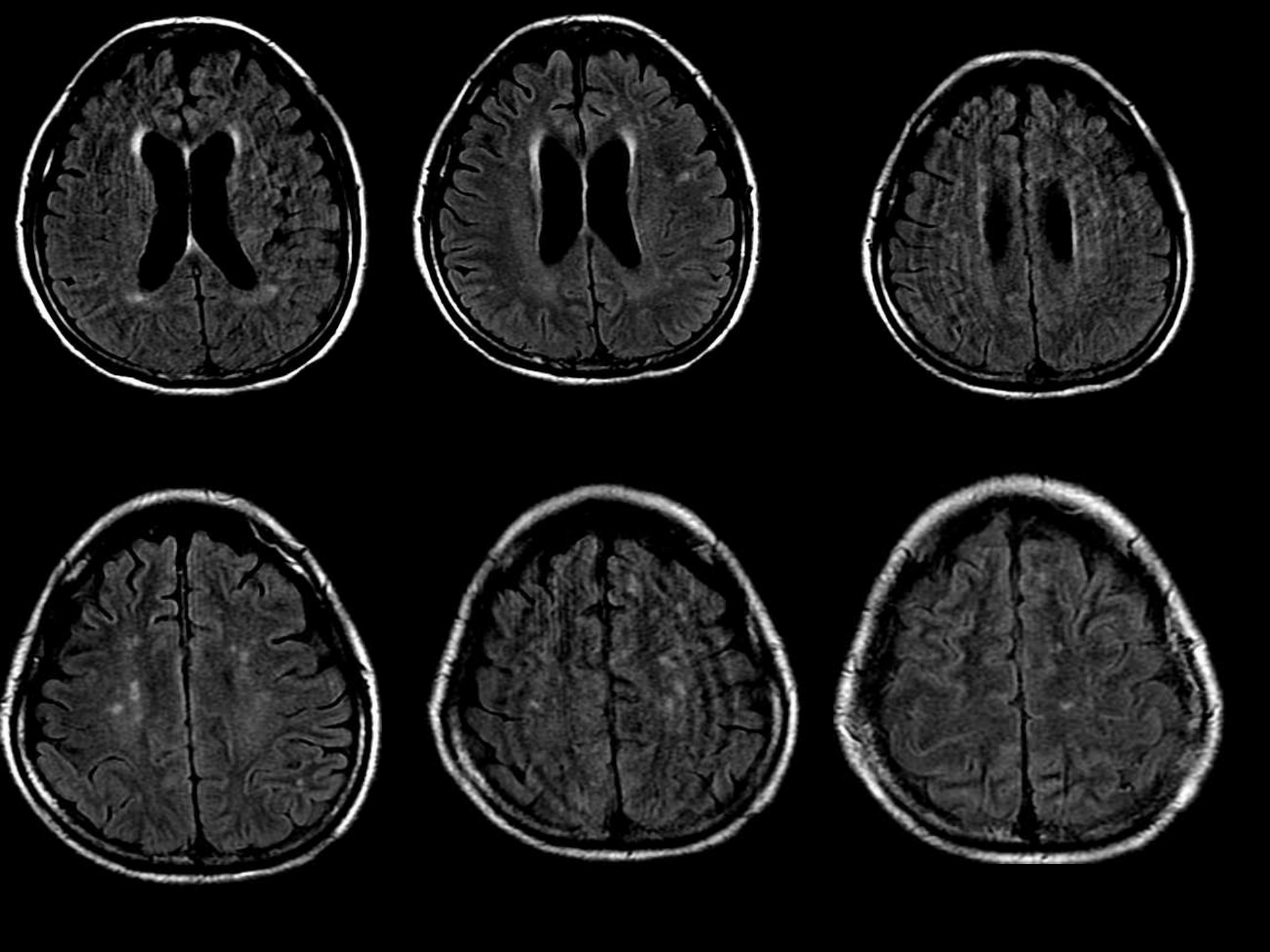
転落外傷

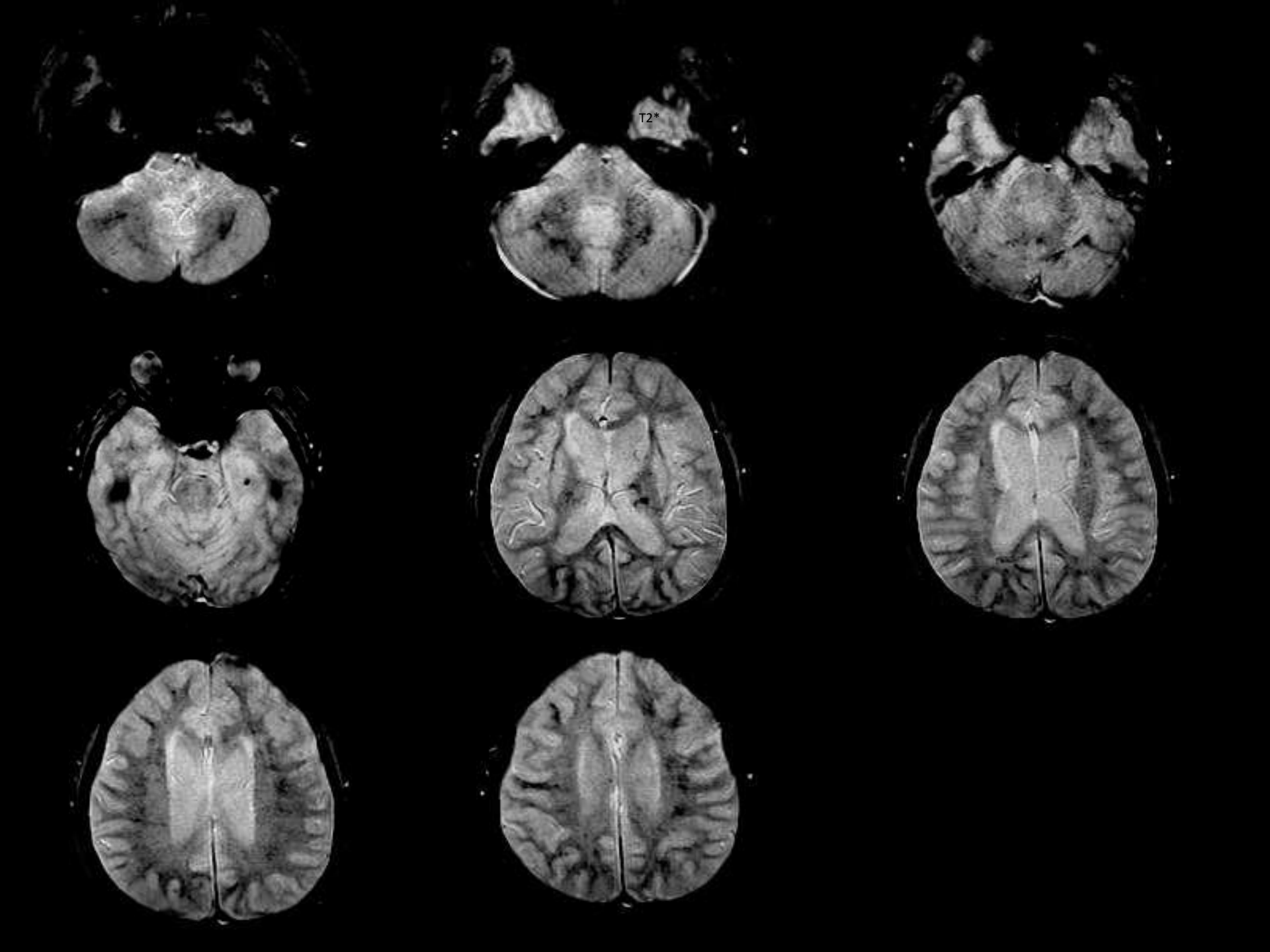
骨盤骨折、下腿開放骨折

それぞれ手術し、抜管後開眼するが

発語がない

外傷より7W後に　MRI




T2*

FES

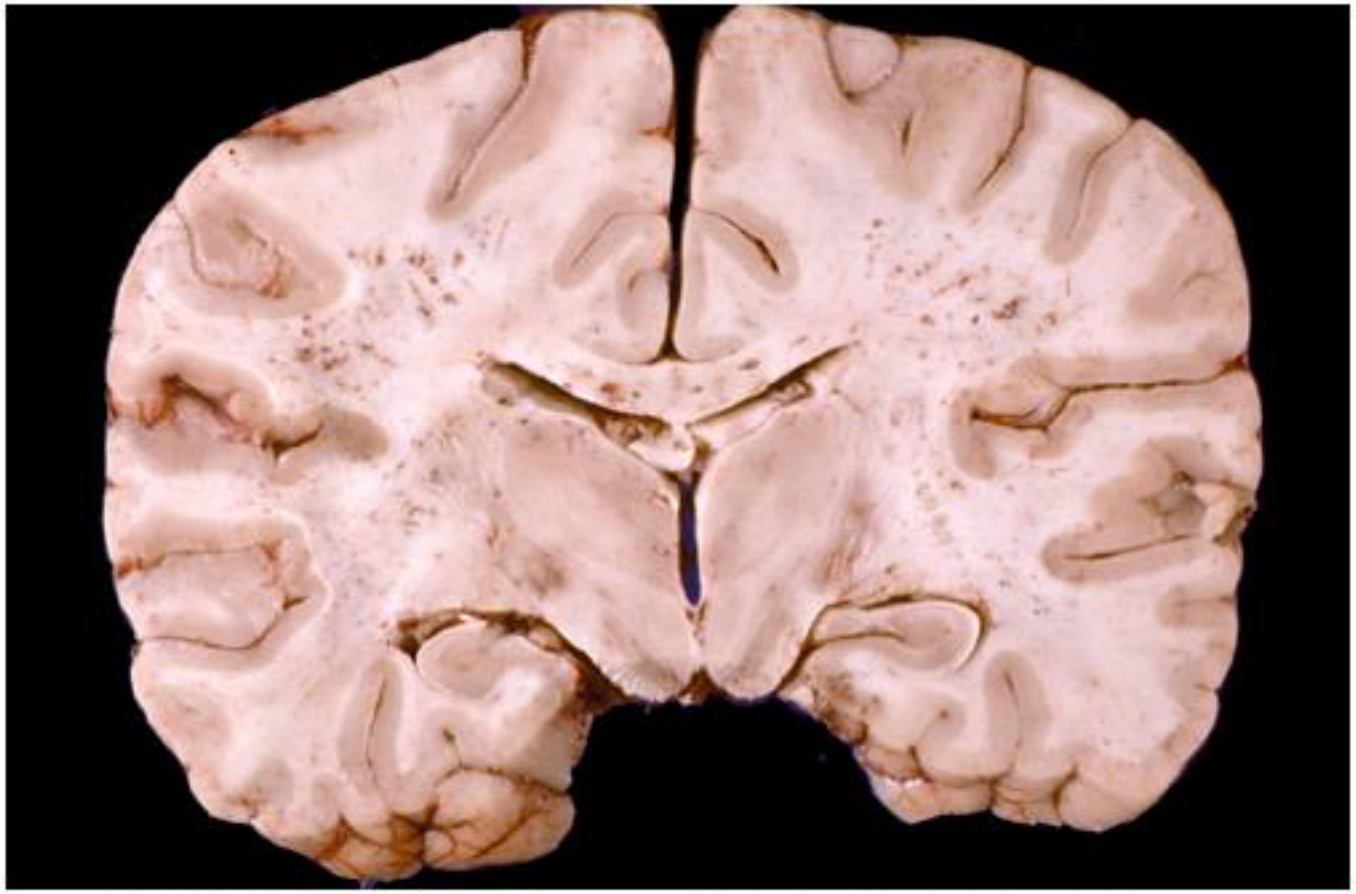
several organ system dysfunction

lung, brain and skin

Direct deposit of fat globules into the blood stream or the production of toxic intermediaries of plasma-derived fat.

Multiple cerebral petechiae associated with intravasular globules of fat that are localized primarily within the white matter are distinctive lesions that secure the pathologic diagnosis of cerebral fat embolism.

Combination of mechanical and biochemical effect



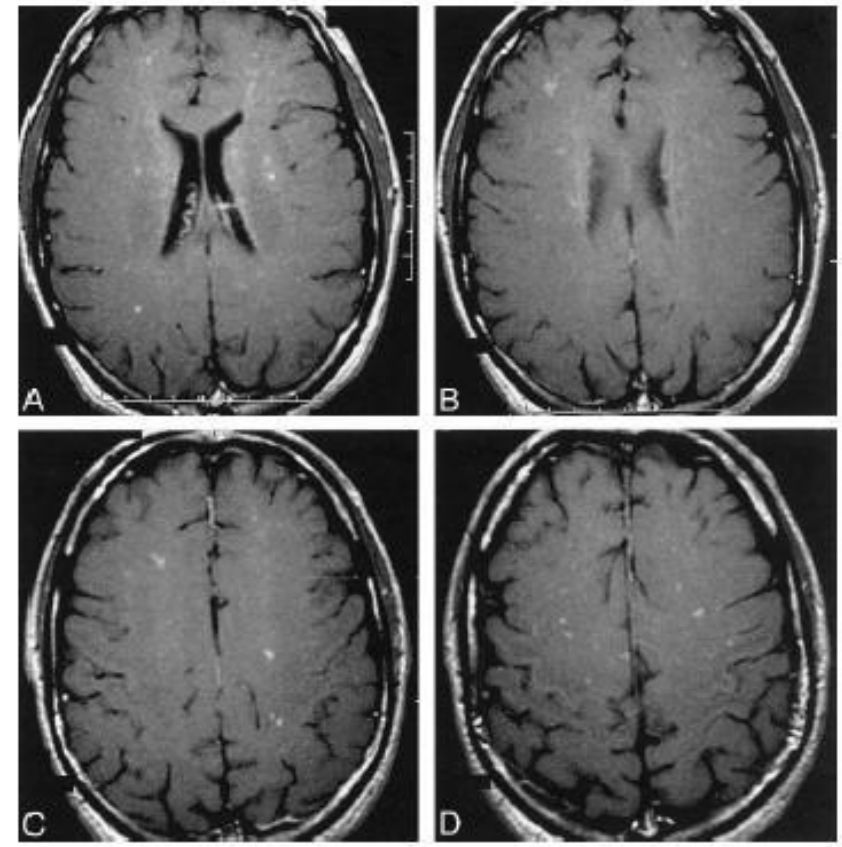
From several days to a week following the event initiating fat embolism syndrome, there may be loss of consciousness from lesions evidenced by the "brain purpura" as shown here. Numerous **petechial hemorrhages** are produced by fat emboli to the brain, particularly in the white matter. Subsequent to this there can be brain edema with herniation.

AJNR Am J Neuroradiol 24:97–101, January 2003

Case Report

Contrast-Enhanced MR Imaging of Cerebral Fat Embolism: Case Report and Review of the Literature

Andrew D. Simon, John L. Ulmer, and James M. Strottmann



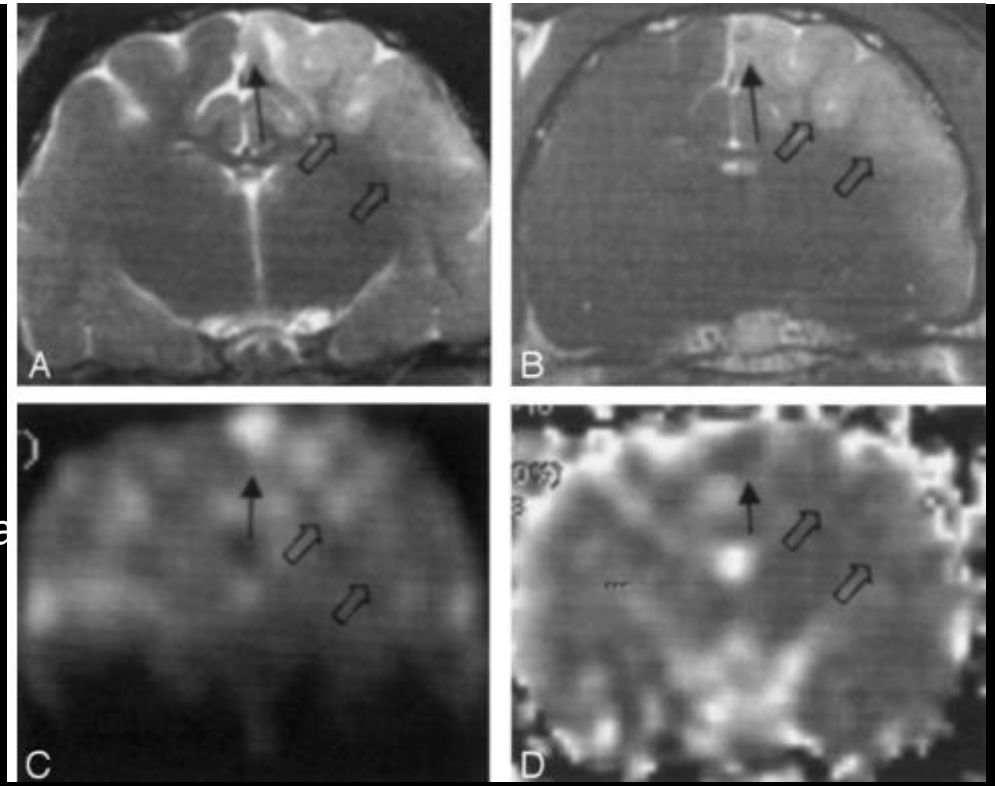
AJNR Am J Neuroradiol 23:1516–1523, October 2002

Experimental Cerebral Fat Embolism: Embolic Effects of Triolein and Oleic Acid Depicted by MR Imaging and Electron Microscopy

Hak Jin Kim, Jong Hwa Lee, Chang Hun Lee, Suk Hong Lee, Tae Yong Moon, Byung Mann Cho, Hae Kyu Kim, Byung Rae Park, and Kee Hyun Chang

Type I solid arrow
Type 2 open arrow

A: T2強調像
B : 造影T1強調像
C : DWI
D: ADC
Type 1 vasogenic and cyototoxic edema
Type 2 vasogenic edema



Cerebral Fat Embolism: A Neuropathological Study of a Microembolic State

ELIZABETH KAMENAR, M.D., AND PETER C. BURGER, M.D.

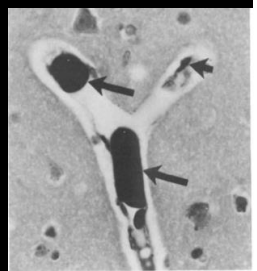
SUMMARY Multiple cerebral petechiae associated with intravascular globules of neutral fat and localized primarily within the white matter are distinctive lesions which secure the pathologic diagnosis of cerebral fat embolism. The abundance of these lesions in an unknown, but presumably small, percentage of cases of fat embolism, along with the even more widespread distribution of embolic fat droplets throughout both white and gray matter, suggest that these lesions and emboli must have a profound effect on neurologic function. Nevertheless, respiratory insufficiency is by far a more common clinical manifestation of the fat embolism syndrome and the neurologic involvement of such patients is often attributed to the secondary effects of generalized hypoxia. The following patient with overt respiratory and neurologic symptoms re-emphasizes the direct primary effect of fat emboli within the central nervous system as a cause of white matter hemorrhages and neurologic deterioration. Explanations for the selectivity of the lesions for the cerebral white matter are explored.

Stroke, Vol 11, No 5, 1980

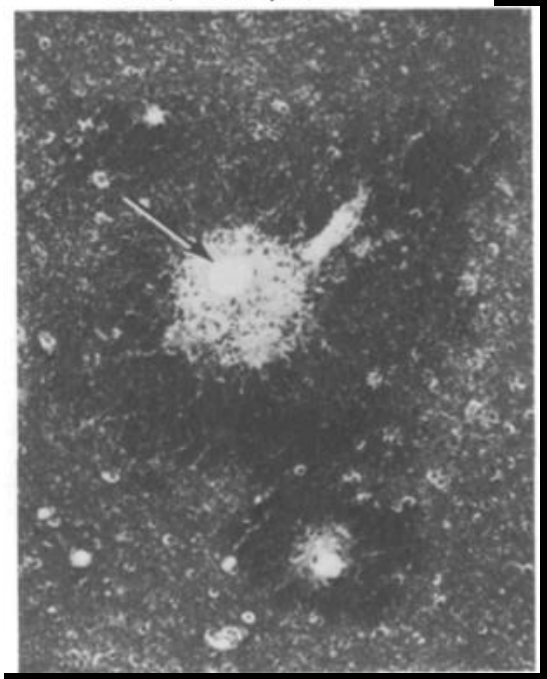
TABLE *Number of Cerebral Fat Emboli/20 mm²*

	Cortex	White Matter
Right Frontal	109	26
Left Frontal	126	44
Right Parietal	122	31
Left Parietal	81	18
Right Occipital	125	15
Left Occipital	78	25
Right Temporal	19	9
Left Temporal	38	16
Total	698	184

$\frac{\text{Cortex}}{\text{White Matter}} = 3.8$



脂肪塞栓そのものは
皮質に多い



出血巣
中央に
脂肪滴

推定される白質優位となる機序

protection may have an upper limit.[56] Although this consideration of the anatomy of the vascular bed would offer the simplest explanation for the white matter predominance of the petechiae, it has also been suggested that the white matter lesions are produced indirectly by cortical emboli through venous sludging and white matter edema.[57]

Journal of the Neurological Sciences 320 (2012) 141–144

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

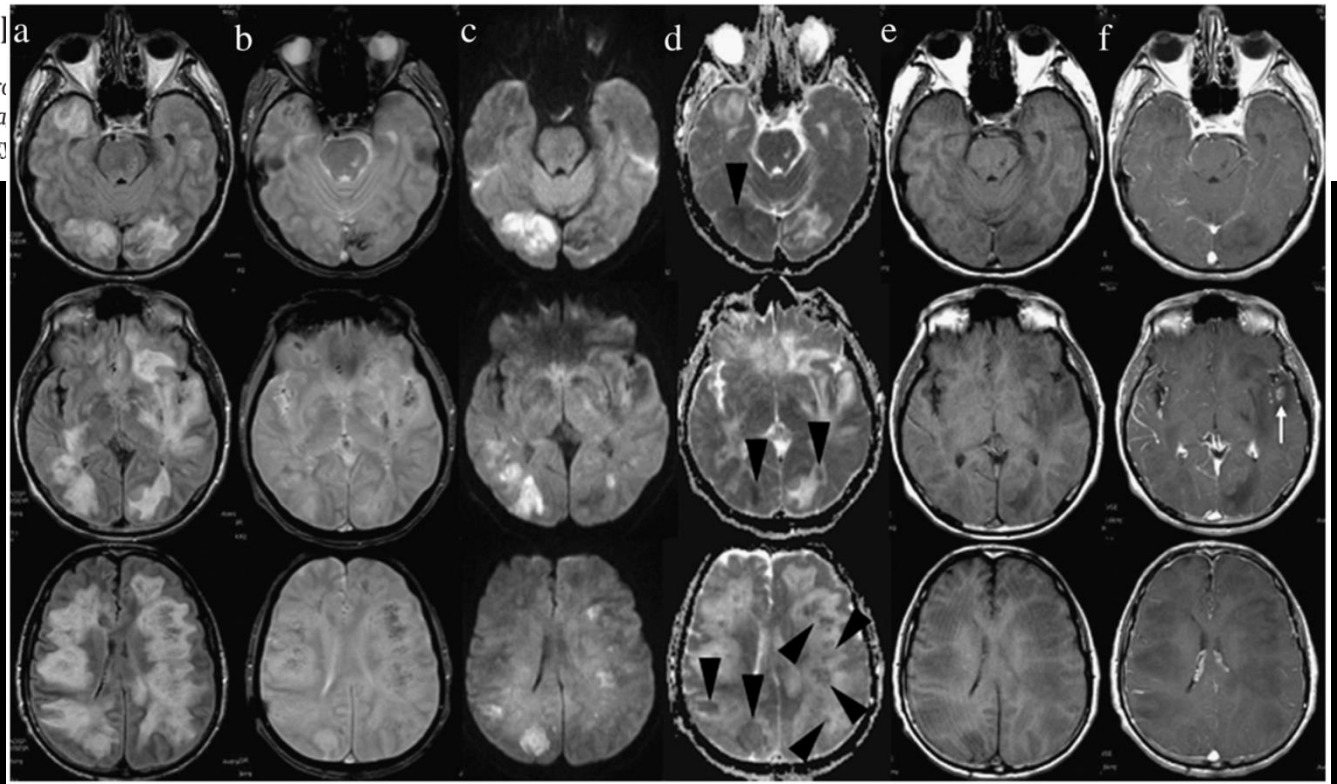
journal homepage: www.elsevier.com/locate/jns

Short communication

Fulminant intravascular lymphomatosis mimicking acute haemorrhagic leukoencephalopathy

D. Marino [a], I

[a] Department of Neuro
[b] Unit NINT Neuroima
[c] Institute of Patholog



エピソード 2

How complex is complex

41　歳　男性

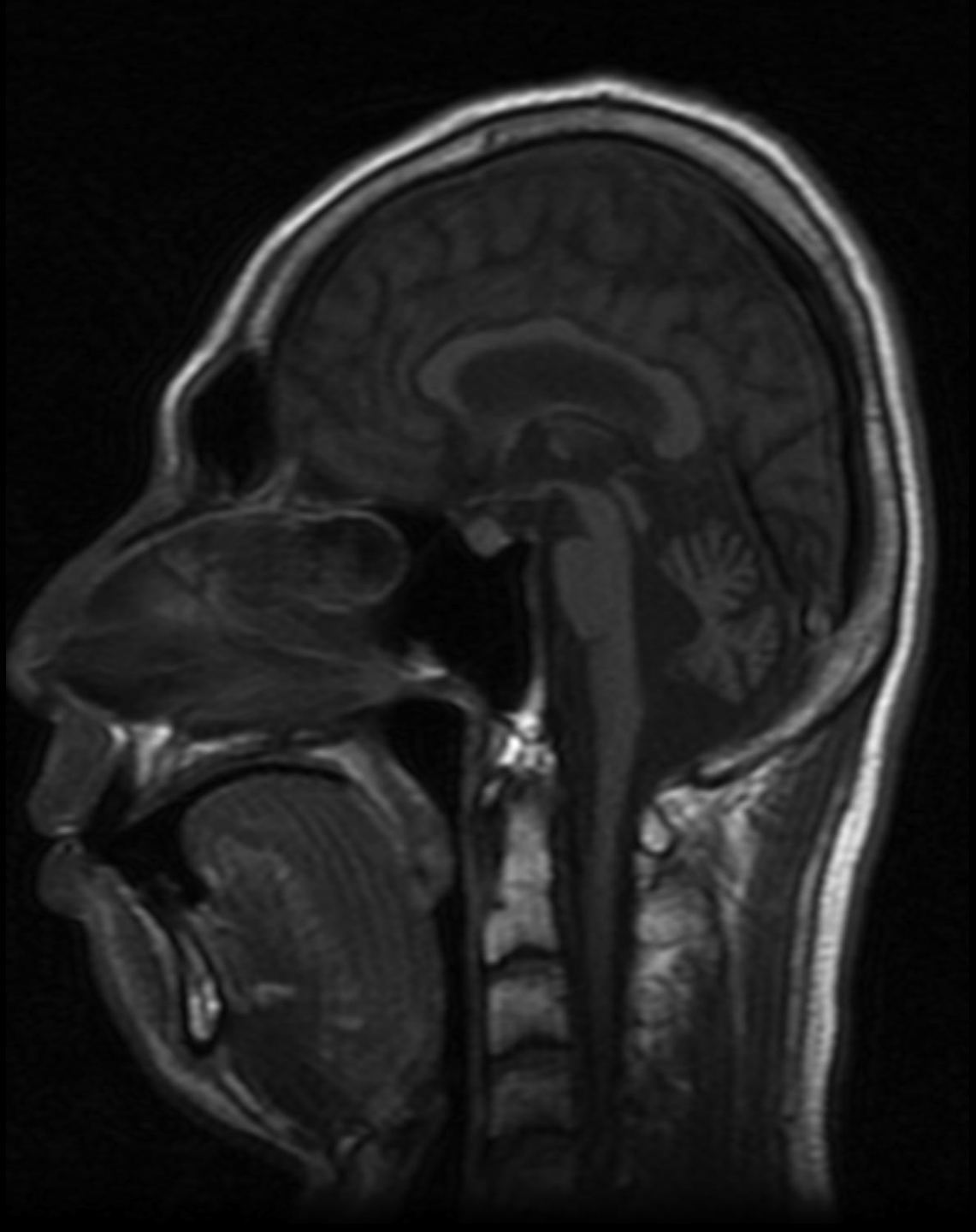
主訴:　ふらつき

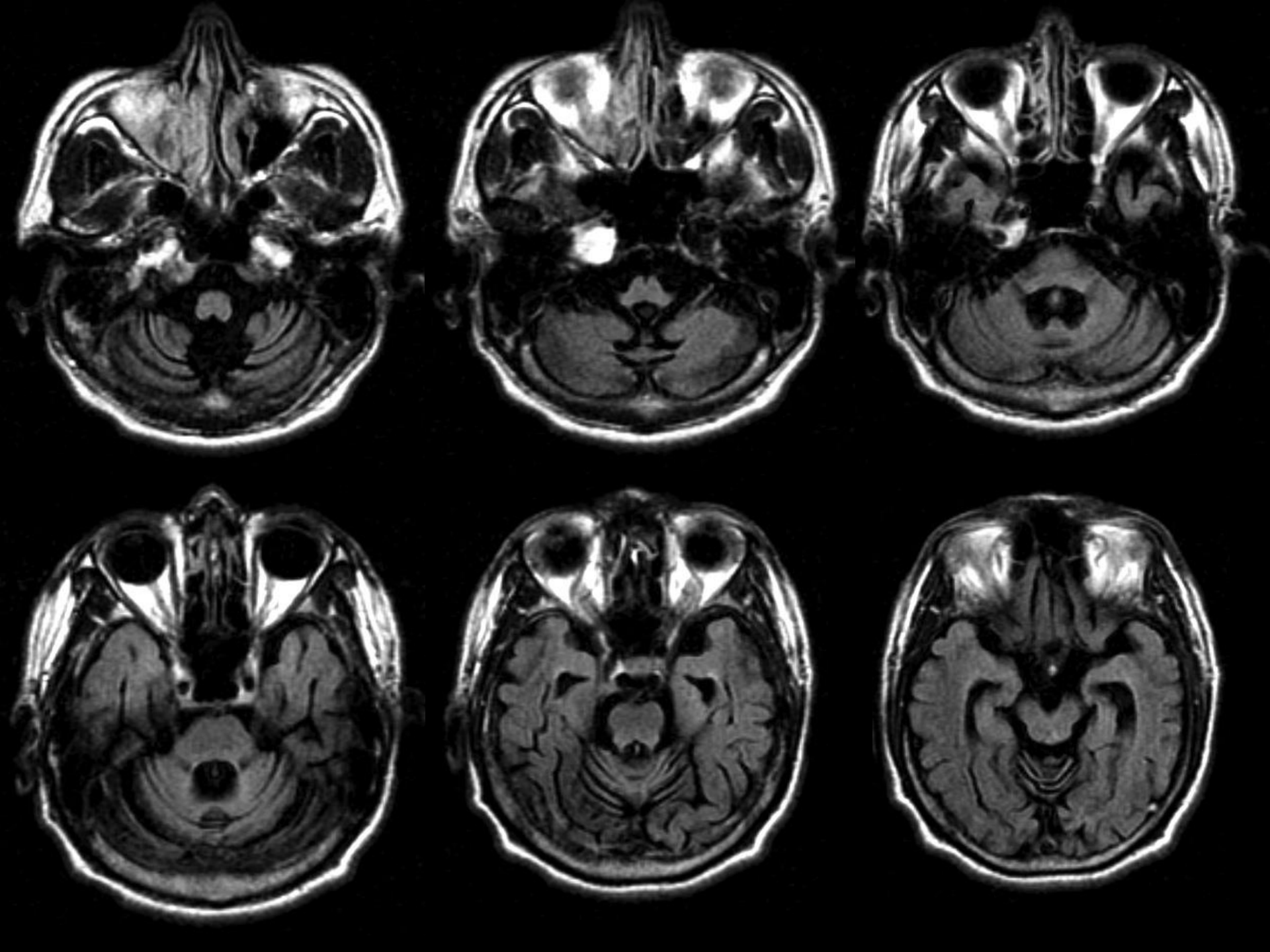
５歳時にネフローゼ症候群を呈し，徐々に悪化

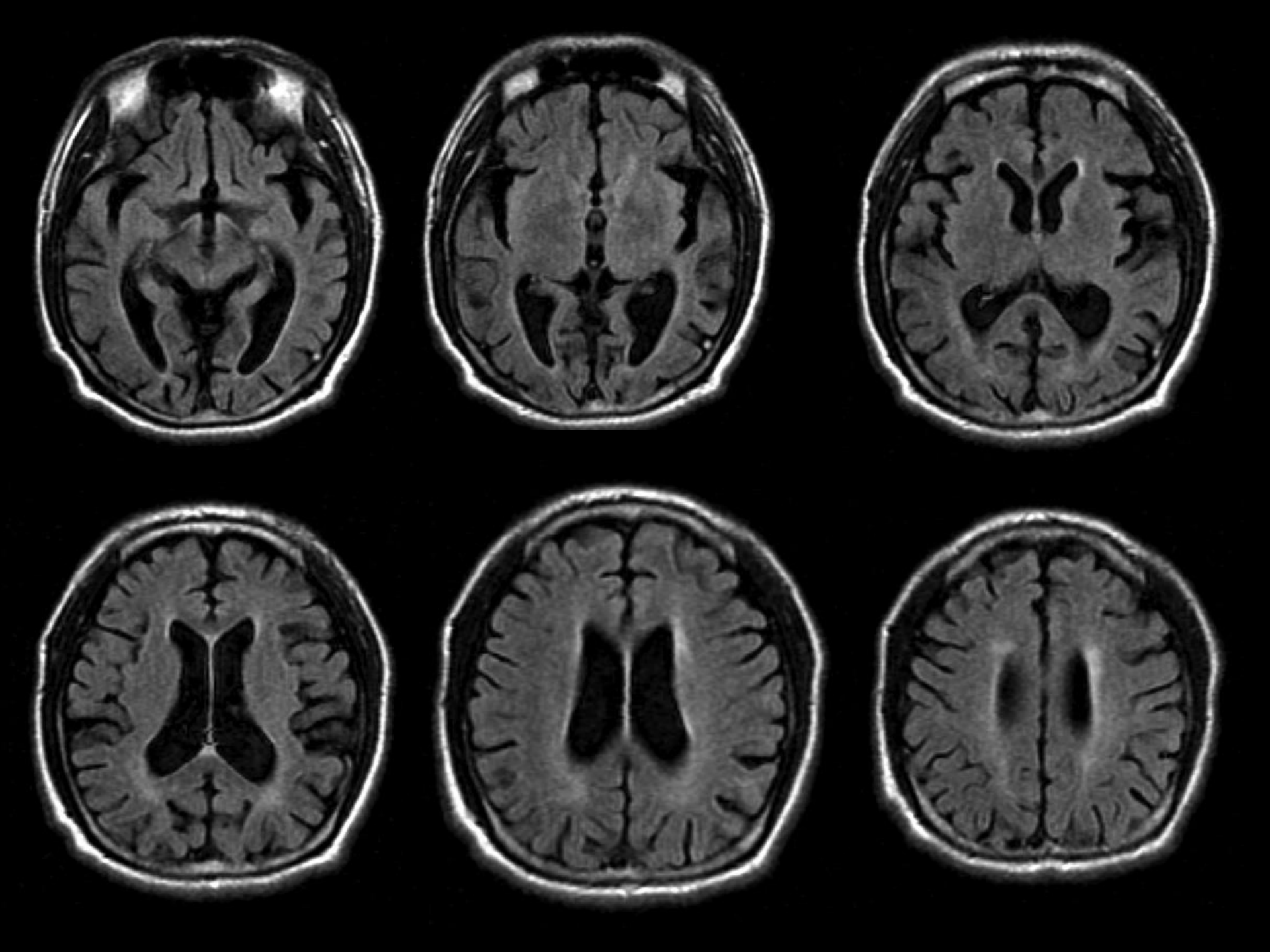
12年前より透析

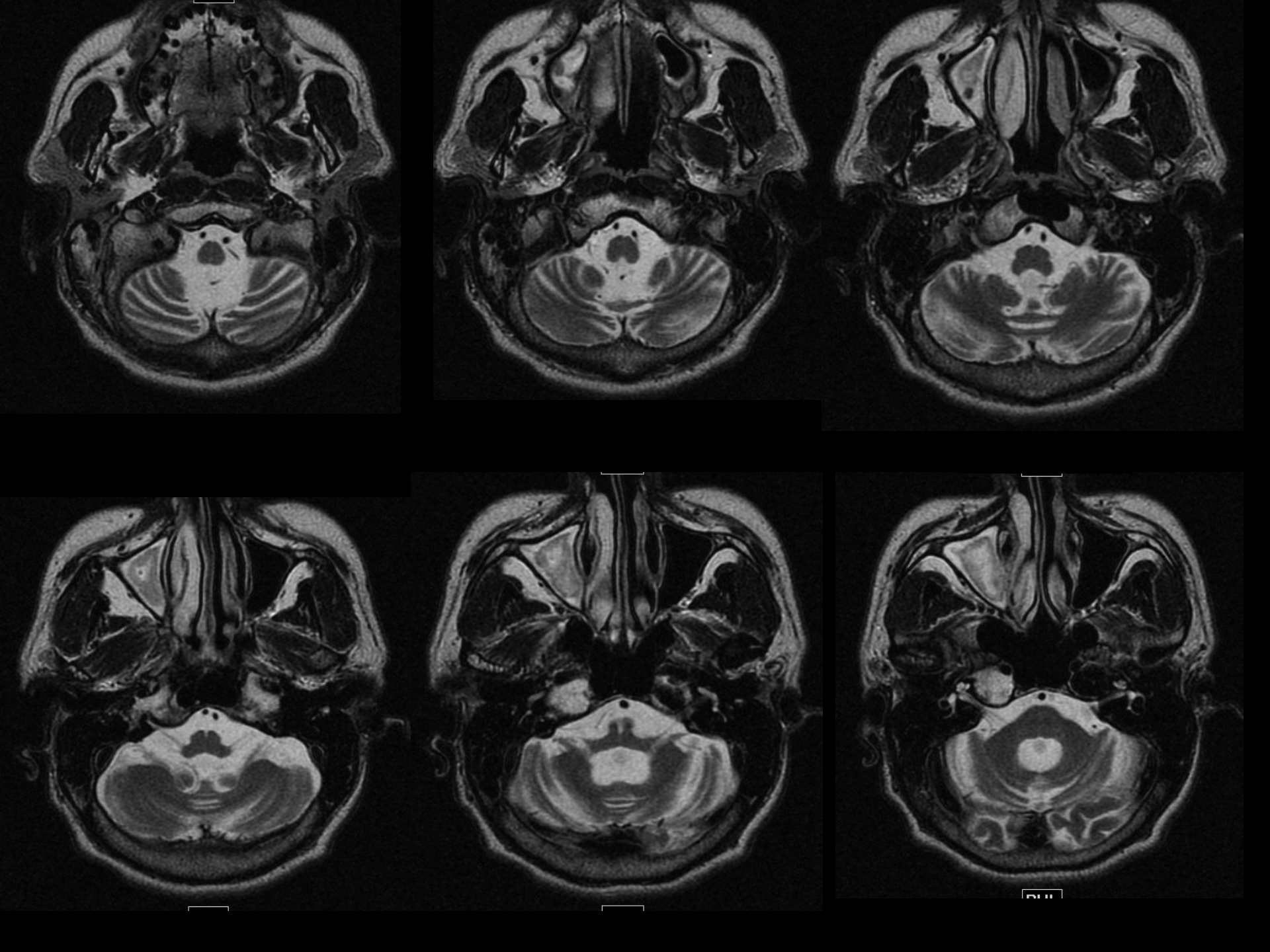
頭が小さいことに気づき，聖マリアンナ医大で頭部MRI施行したところ小脳萎縮が指摘された。

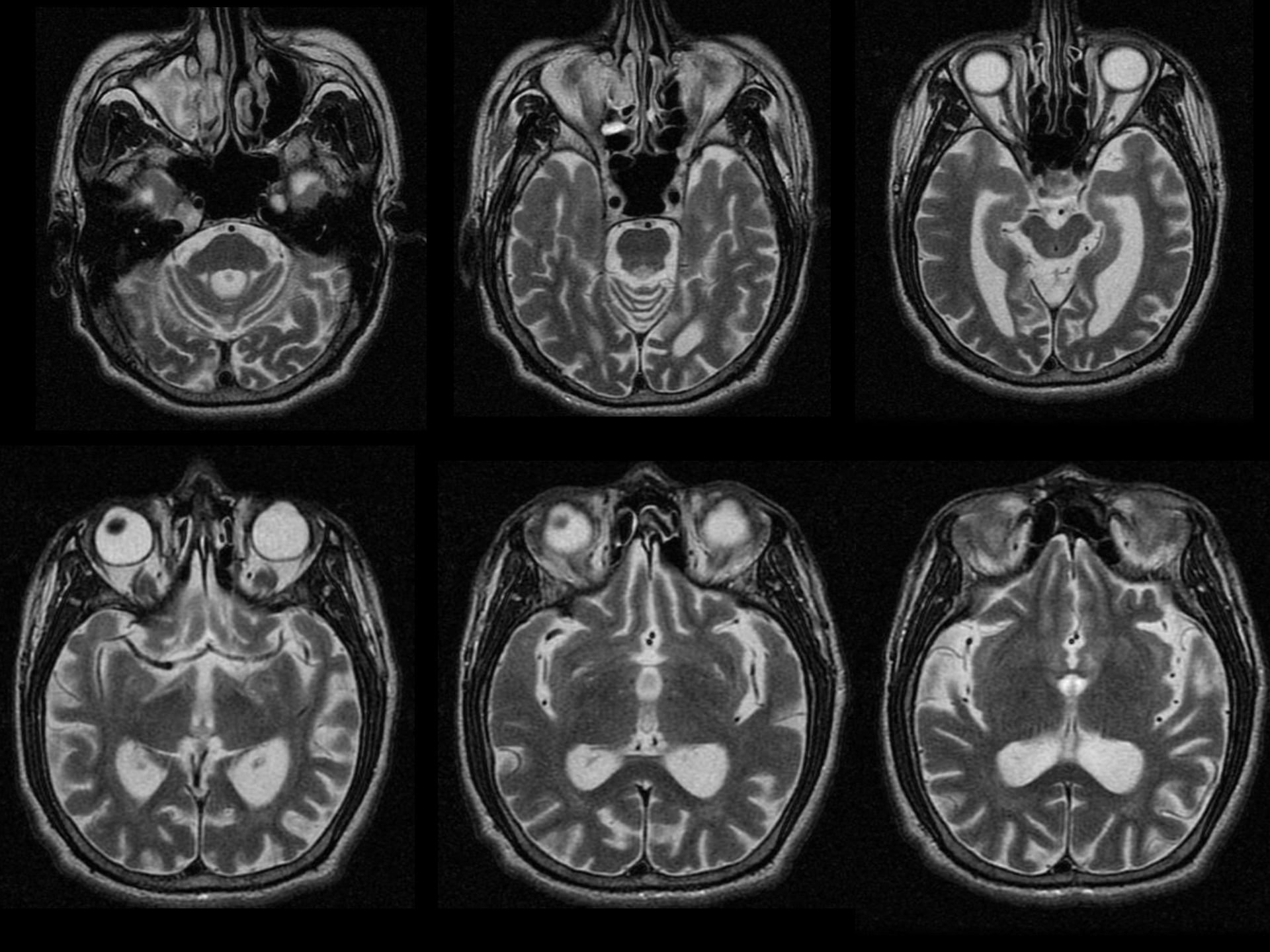
29歳頃、透析を受けるようになってから視力の低下に気づく（網膜色素変性症）、3年前頃より聴力低下、2ヶ月前よりふらつきを認めるようになった。











小脳失調,小脳萎縮,網膜色素変性症、感音性難聴

Kearns-Sayre

Marinesco-Sjogren

SCA 7

mtDNA　異常

08993T>G

Leigh脳症と診断された。

- Mitochondrial genetics does explain some important features of mtDNA-related diseases. For example, different degrees of heteroplasmy (70% vs 90%) readily explain how the same mutation (m. 8993T . G) in ATPase 6 can cause 2 different syndromes, often in members of the same family: a relatively benign and late-onset disorder with neuropathy, ataxia, and retinitis pigmentosa (NARP) or a devastating neurodegenerative disease of infancy or childhood with the neuroradiologic and neuropathologic features of Leigh syndrome (MILS).

Maternally inherited Leigh syndrome

mtDNA　異常

08993T>G

一般的には、 Leigh脳症とされてるが,

おそらく NARP と

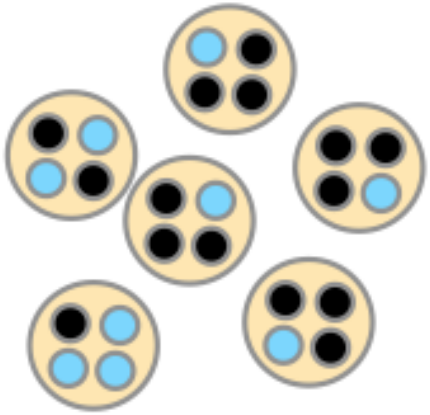
neuropathy, ataxia, retinitis pigmentosa

ホモプラスミーとヘテロプラスミー

● 変化あり
● 変化なし

ホモプラスミー

細胞中のミトコンドリアDNAが
すべて同じ（異常または正常）



ヘテロプラスミー

細胞中に正常なミトコンドリアDNAと
異常なミトコンドリアDNAが混在している

細胞や組織によって割合が異なる〈細胞／組織特異性〉

異常DNAの割合が一定以上になると機能が障害される
〈閾値（しきいち／いきち）効果〉

異常DNAの割合は細胞分裂のときに変化する

ミトコンドリア病パンフレット

厚生労働科学研究費
小児疾患臨床研究事業

小児期発症のミトコンドリア脳筋症に対するＬ－アルギニンおよびジクロロ酢酸療法の効果判定と分子病態を踏まえた新しい治療法開発に関する臨床研究（H14－小児－006）

主任研究者：久留米大学医学部小児科　古賀　靖敏

平成17年３月作成

Leigh脳症の責任遺伝子

ミトコンドリアDNAの異常

ATP6のT8993G、T8993C、T9176C、T9176G

ND3のサブユニット3 T10158C, サブユニット5 13730,サブユニット6 G14459A

複合体のサブユニット　3 G9379A

tRNA-Leu遺伝子　A3243G, tRNA-Val遺伝子　C１６２４T、tRNA-Lys遺伝子 A8344G

t RNA-Try遺伝子　5537

核DNAの異常

複合体のサブユニット

NDU FV1, NDU FS3, NDUFS7,NDUFS8

SDHA, BCS1L,COX10およびCOX15

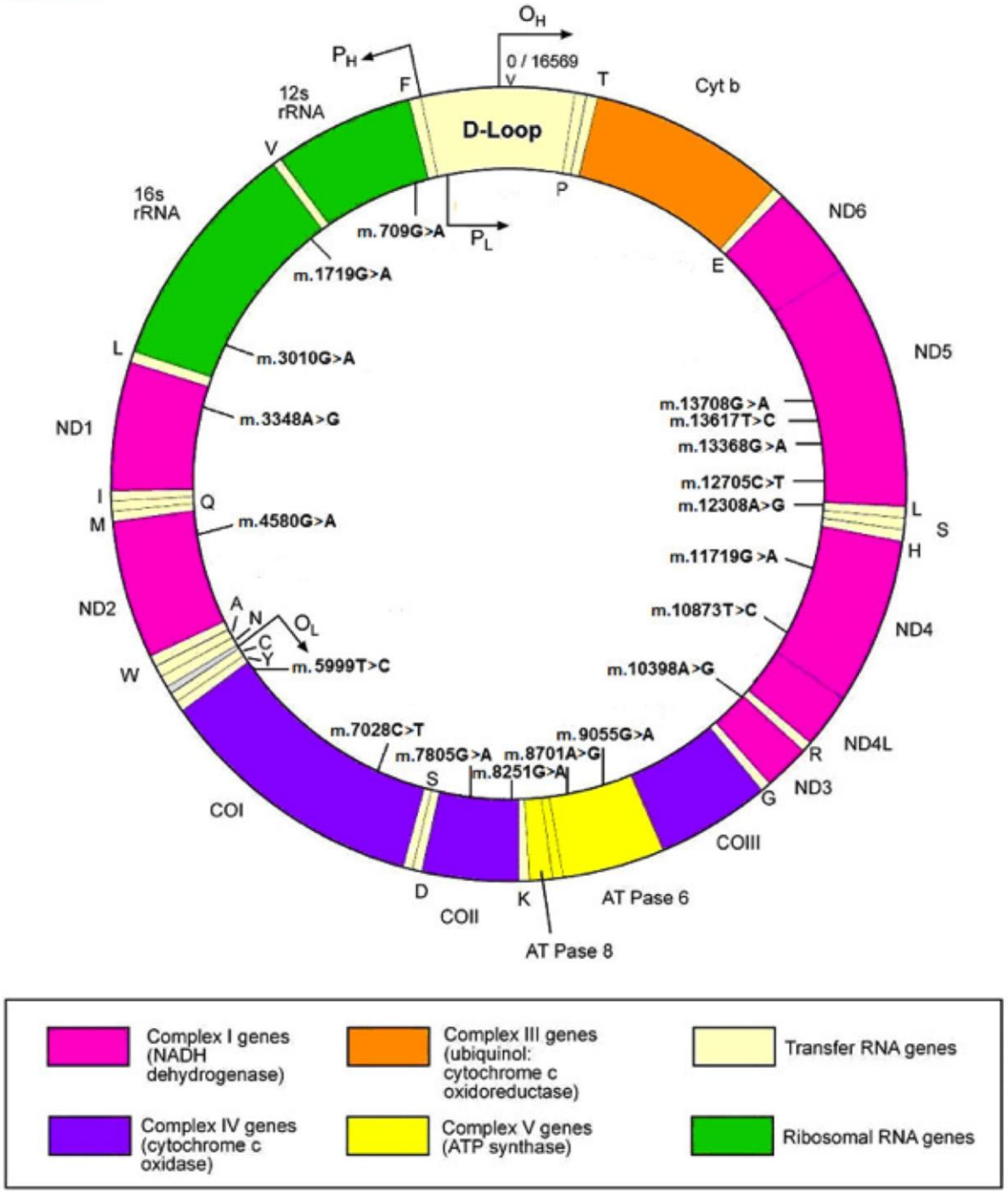
アッセンブリー遺伝子

SURF1

ピルビン酸脱水素酵素　PDHA1

ピルビン酸カルボキシラーゼ

Figure 1.


O_H
0 / 16569
P_H
F
12s rRNA
V
16s rRNA
L
ND1
I
Q
M
ND2
W
A
N
C
Y
O_L
COI
S
D
COII
K
AT Pase 8
AT Pase 6
COIII
G
ND3
R
ND4L
ND4
H
S
L
ND5
E
ND6
T
Cyt b
P
D-Loop
P_L
m.709G>A
m.1719G>A
m.3010G>A
m.3348A>G
m.4580G>A
m.5999T>C
m.7028C>T
m.7805G>A
m.8251G>A
m.8701A>G
m.9055G>A
m.10398A>G
m.10873T>C
m.11719G>A
m.12308A>G
m.12705C>T
m.13368G>A
m.13617T>C
m.13708G>A
Complex I genes (NADH dehydrogenase)
Complex III genes (ubiquinol: cytochrome c oxidoreductase)
Transfer RNA genes
Complex IV genes (cytochrome c oxidase)
Complex V genes (ATP synthase)
Ribosomal RNA genes

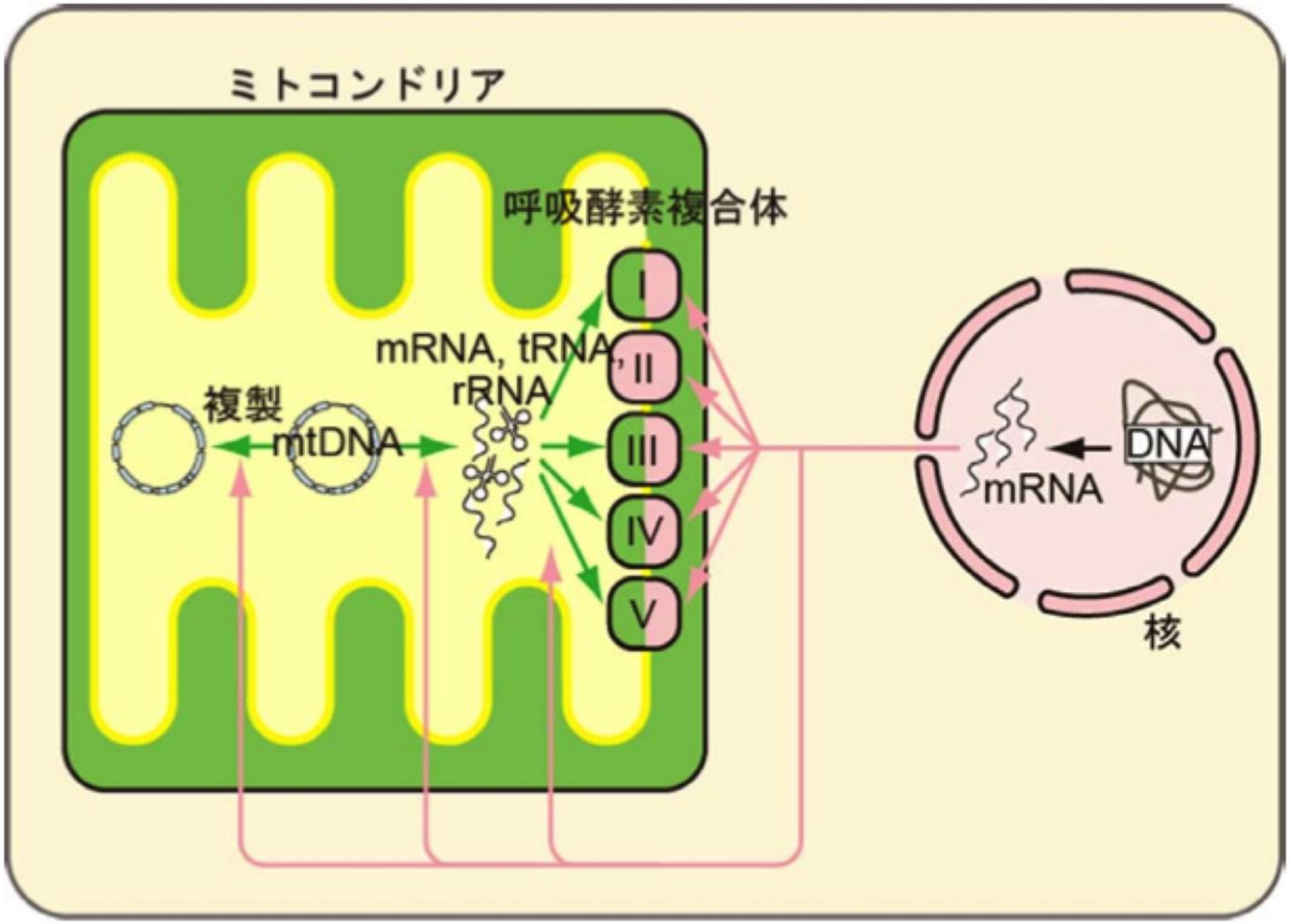
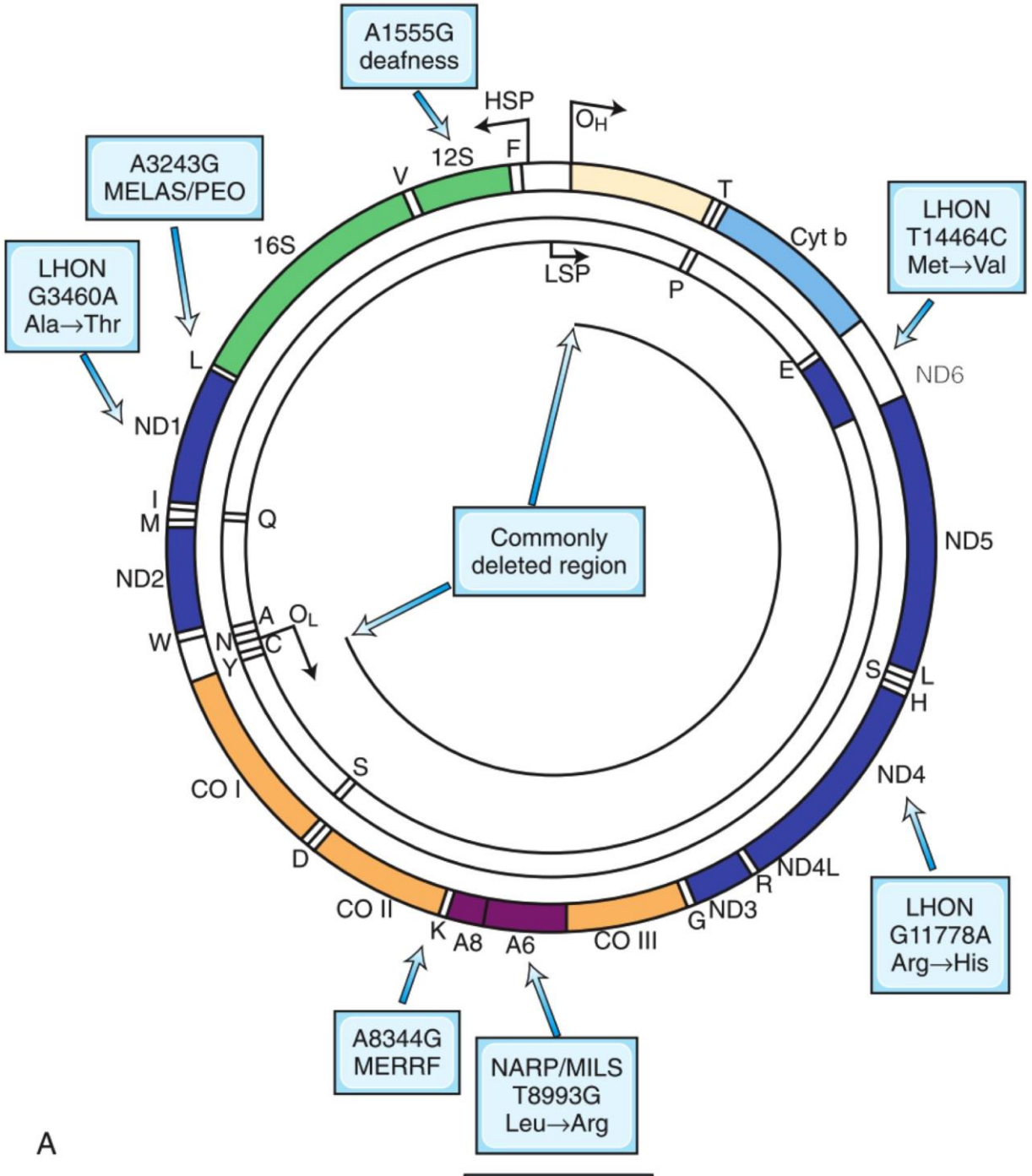


図３　ミトコンドリア呼吸機能の二重支配

ミトコンドリアの呼吸機能は呼吸酵素複合体Ⅰ～Ⅴによって行われている。この呼吸酵素複合体Ⅰ，Ⅲ，Ⅳ，Ⅴはミトコンドリアゲノム由来のサブユニット（緑色）と核ゲノム由来のサブユニット（ピンク色）によって形成されている。このため、ミトコンドリアの呼吸機能は核とミトコンドリアの両方のゲノムによって制御されていることになる。


A1555G
deafness
HSP
O_H
12S
F
V
A3243G
MELAS/PEO
16S
LHON
G3460A
Ala→Thr
L
ND1
I
M
Q
ND2
W
A
O_L
N
C
Y
CO I
S
D
CO II
K
A8
A6
CO III
G
ND3
R
ND4L
ND4
S
L
H
ND5
E
ND6
P
LSP
T
Cyt b
LHON
T14464C
Met→Val
Commonly
deleted region
A8344G
MERRF
NARP/MILS
T8993G
Leu→Arg
LHON
G11778A
Arg→His

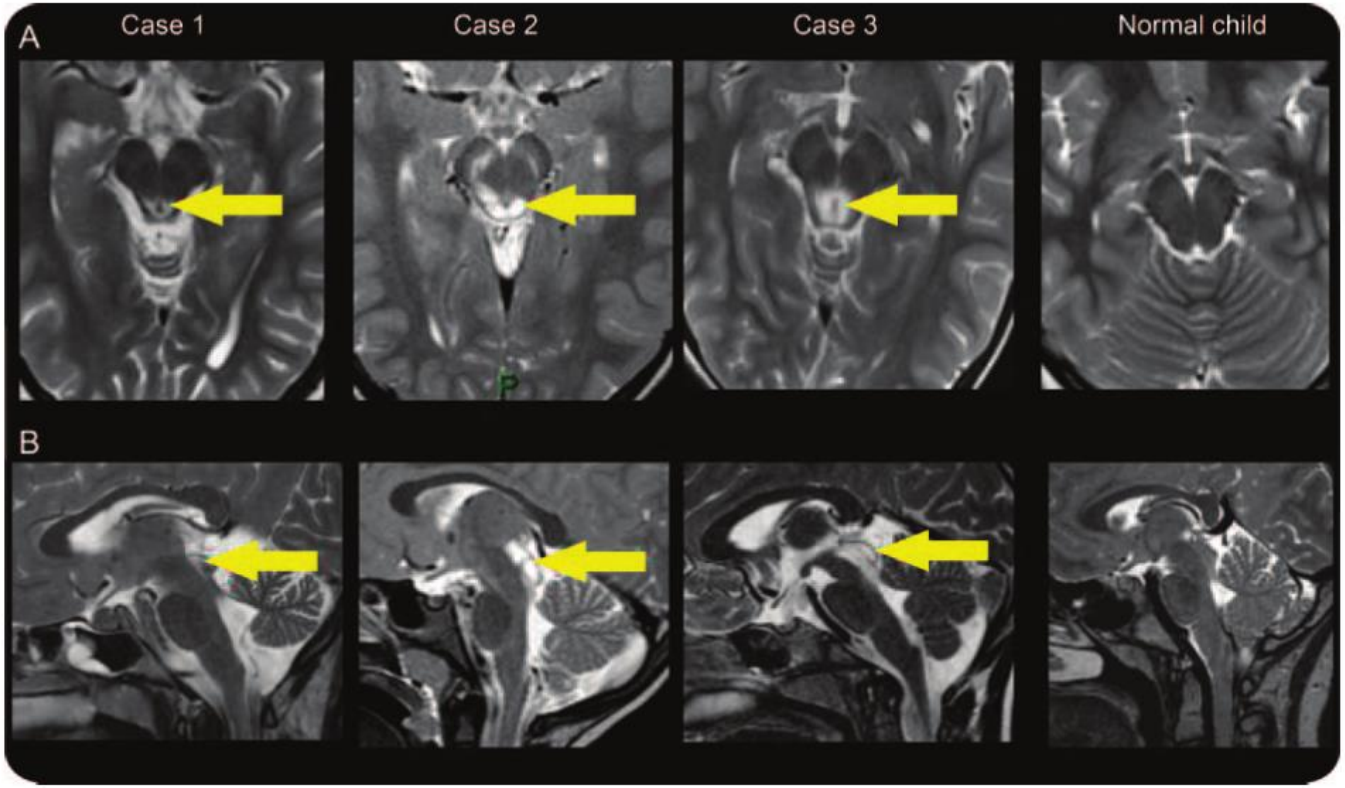
A

NEUROIMAGES

Mitochondrial ND5 mutations mimicking brainstem tectal glioma

2010 Neurology

Figure MRI showing a periaqueductal high T2 signal on axial T2 (A) and sagittal T2 (B) and an enlargement of the tectum that mimicked tectal glioma in all 3 children (case 1, 9 years; case 2, 6 years; case 3, 7 years)



We report MRI periaqueductal T2 hypersignal suggestive of tectal glioma in 3 unrelated children with reduced vision and normal mental development (figure). Increased CSF lactate and optic atrophy in the first case suggested mitochondrial dysfunction. Muscle biopsy revealed complex I deficiency. A heteroplasmic mt-ND5 mutation was found (m.13513G>A).[1] The second case presented with similar clinicoradiologic features, complex I deficiency, and the same heteroplasmic mutation. The third case had visual disturbance without optic atrophy, normal muscle enzyme activities, and a heteroplasmic mt-ND5 mutation (m.13514A>G).[2] Even in absence of optic atrophy, mental retardation, or multiorgan dysfunction, the combination of visual disturbance and periaqueductal T2 hypersignal should prompt the search for mitochondrial DNA mutation.

昨年のNRWS

24歳　男性

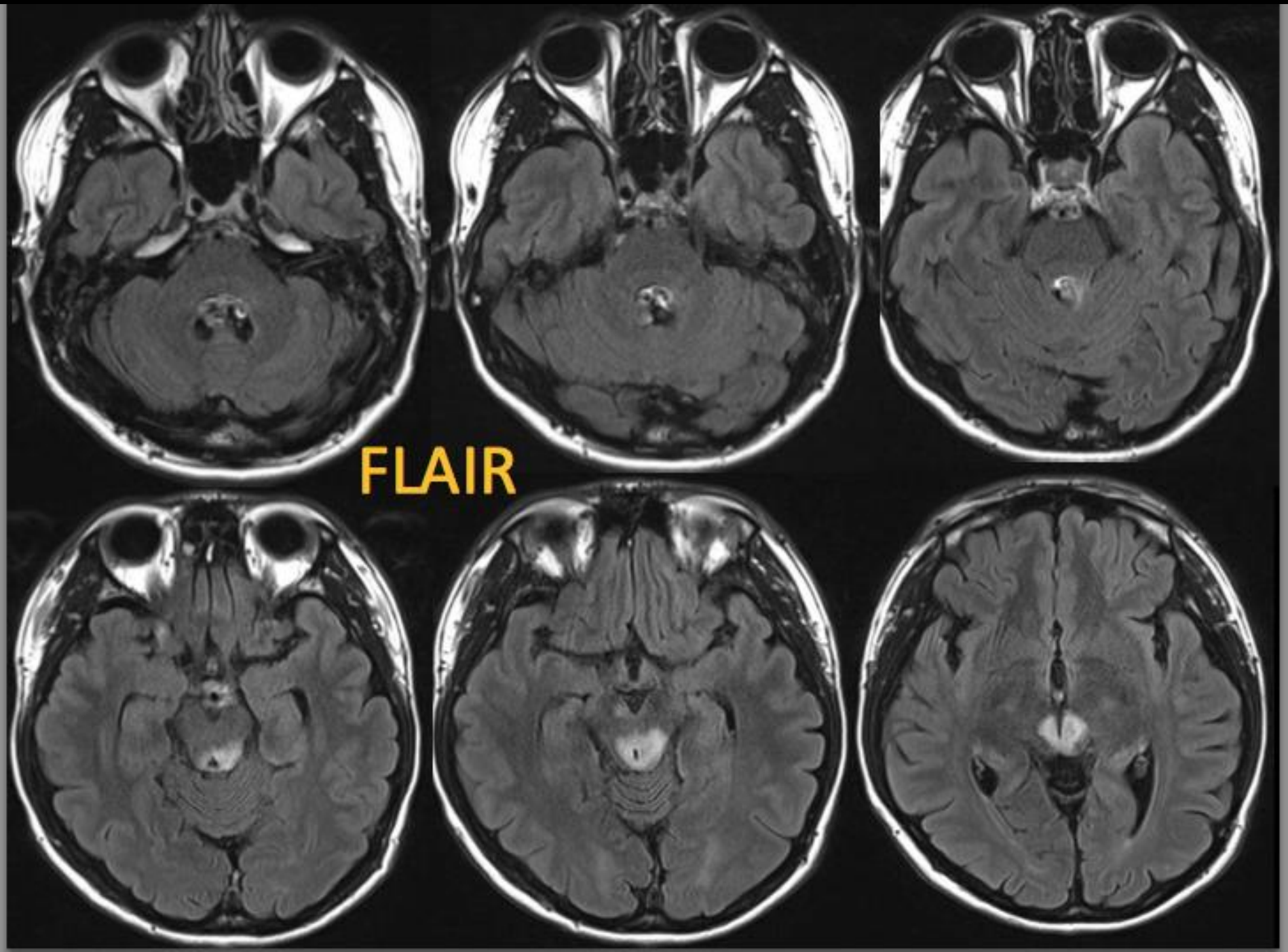
【主訴】複視・眼瞼下垂

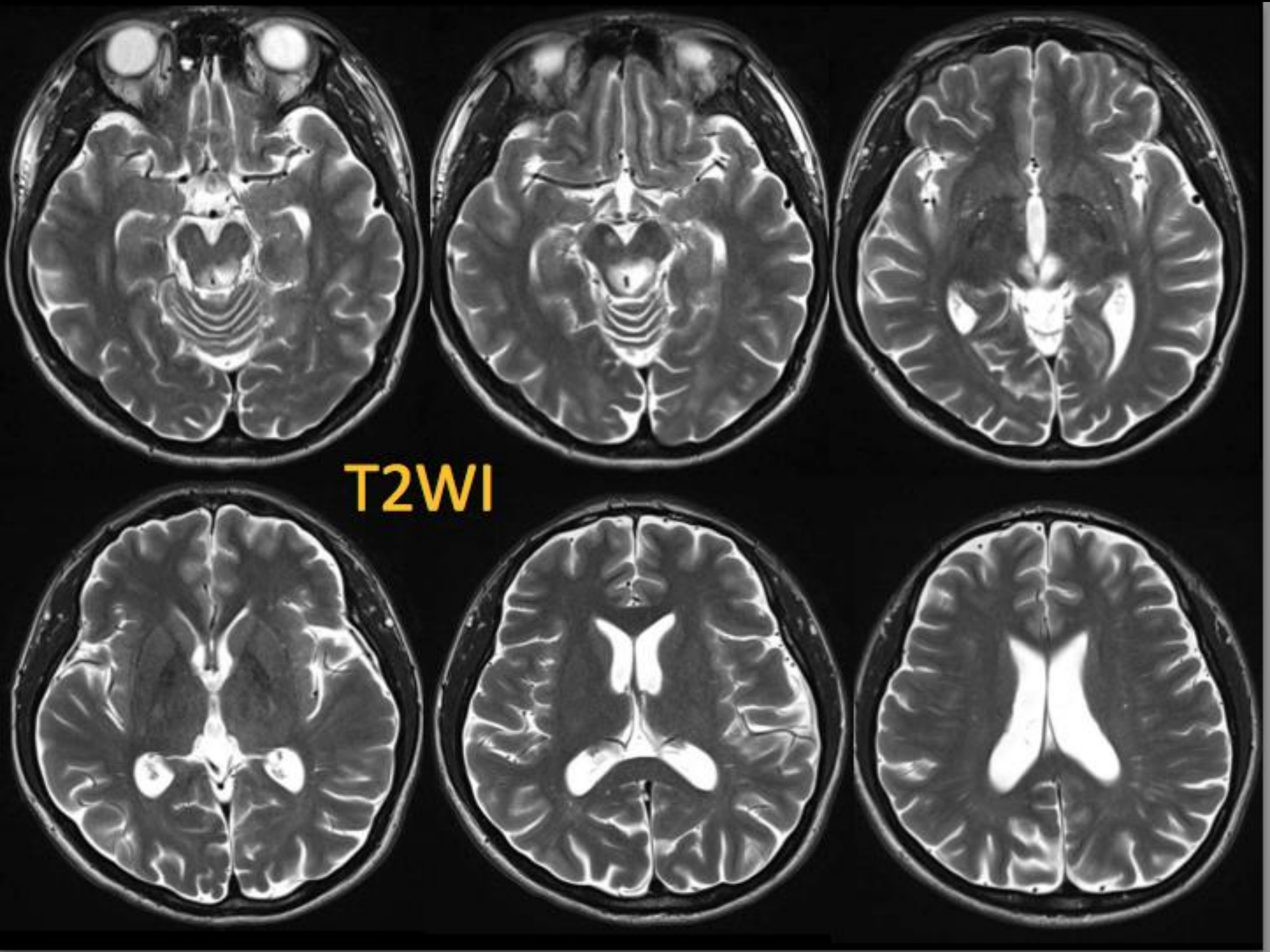
【現病歴】

1年前から複視が出現した。一旦改善を認めたが、半年前から症状が再燃し、眼瞼下垂と下腿浮腫も生じるようになったため精査目的に入院。入院後の採血で腎機能障害が指摘された。

【神経学的所見】眼球運動障害　眼瞼下垂

【家族歴】母：慢性腎不全で透析中


FLAIR


T2WI

その後の経過②

MRSでNAA/Cr比の低下、著明なLactate peakを認め、ミトコンドリア病が疑われた。

血清乳酸 24.5 mg/dl、ピルビン酸 1.97 mg/dl

髄液中乳酸　53.9 mg/dl、ピルビン酸 2.46 mg/dl

ミトコンドリア病を疑い筋生検を施行した。

m.13513 G>T 変異あり、ミトコンドリア病と診断。

診断

ミトコンドリア病

(臨床的にはCPEO？)

診断

ミトコンドリア病
(臨床的にはCPEO？)

Mitochondrial ND5 mutation

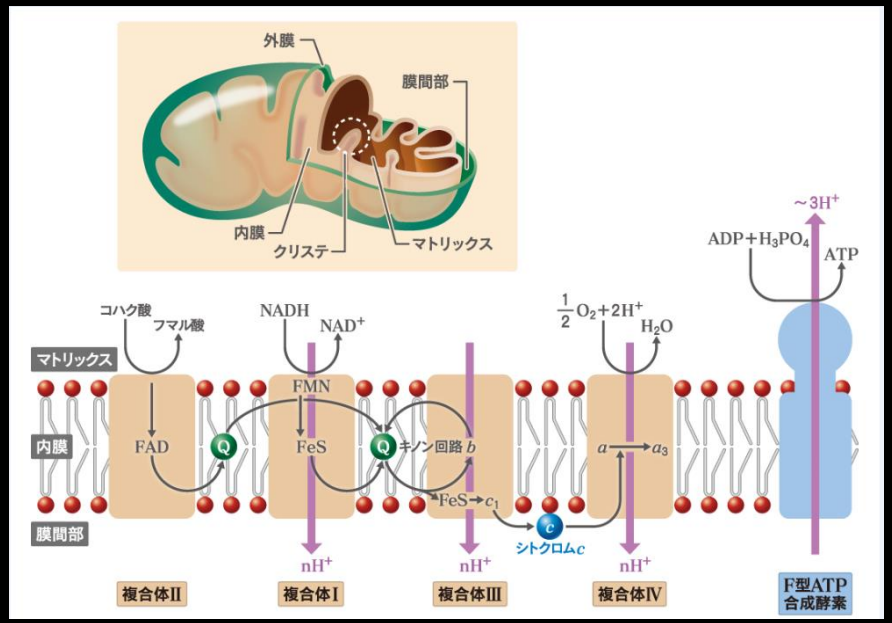
The G13513A Mutation in the *ND5* Gene of Mitochondrial DNA as a Common Cause of MELAS or Leigh Syndrome

Evidence From 12 Cases

Sara Shanske, PhD; Jorida Coku, BS; Jiesheng Lu, MD; Jaya Ganesh, MD; Sindu Krishna, PhD; Kurenai Tanji, MD; Eduardo Bonilla, MD; Ali B. Naini, PhD; Michio Hirano, MD; Salvatore DiMauro, MD

NADH nicoinamide adenine dinucleotide dehydrogenase 5 (ND5)

ミトコンドリアにおける酸化的リン酸化の“入り口酵素”である

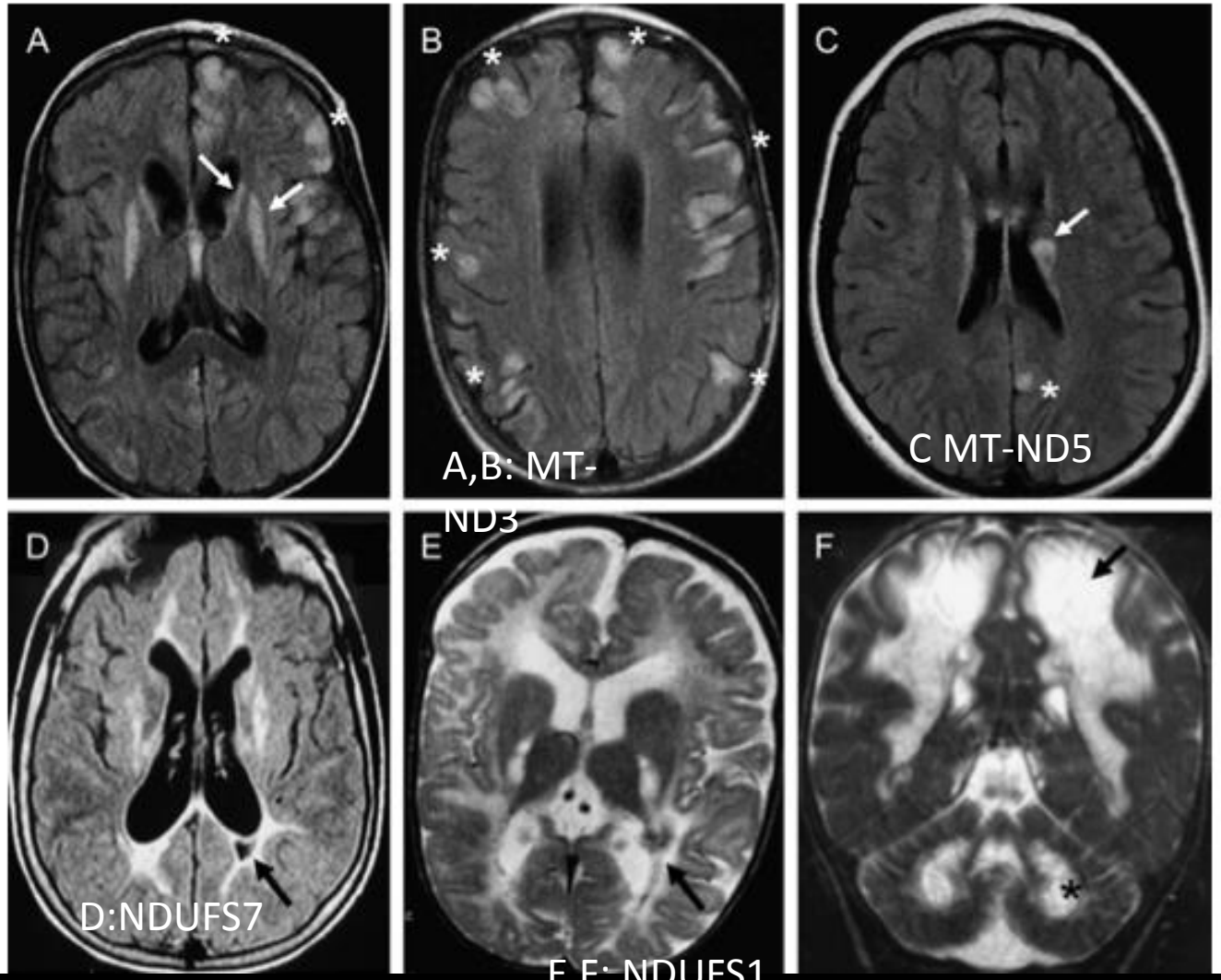


A common pattern of brain MRI imaging in mitochondrial diseases with complex I deficiency

A S Lebre,[1] M Rio,[1] L Faivre d'Arcier,[1] D Vernerey,[1] P Landrieu,[2] A Slama,[2] C Jardel,[3] P Laforêt,[3] D Rodriguez,[4] N Dorison,[4] D Galanaud,[3] B Chabrol,[5] V Paquis-Flucklinger,[6] D Grévent,[1] S Edvardson,[7] J Steffann,[1] B Funalot,[8] N Villeneuve,[5] V Valayannopoulos,[1] P de Lonlay,[1] I Desguerre,[1] F Brunelle,[1] J P Bonnefont,[1] A Rötig,[1] A Munnich,[1] N Boddaert[1]

J Med Genet 2011;**48**:16—23. doi:10.1136/jmg.2010.079624

Figure 2 Stroke-like and leucoencephalopathy images (axial FLAIR in A—D and T2 weighted images in E and F in absence of FLAIR images for patients 23—24). (A—C) Multiple stroke-like images (indicated with white stars) associated with basal ganglia hyperintensities (white arrows) in two cases (patient 2 with *MT-ND3* mutation in panels A and B; patient 14 with *MT-ND5* mutation in panel C). (D—F) Necrotising or cystic leucoencephalopathy images (patient 29 with *NDUFS7* mutations in panel D; patients 23 and 24 with *NDUFS1* mutations in panels E and F). Leucoencephalopathy is indicated with black arrows. White matter cerebellar hyperintensities are indicated with a white star.



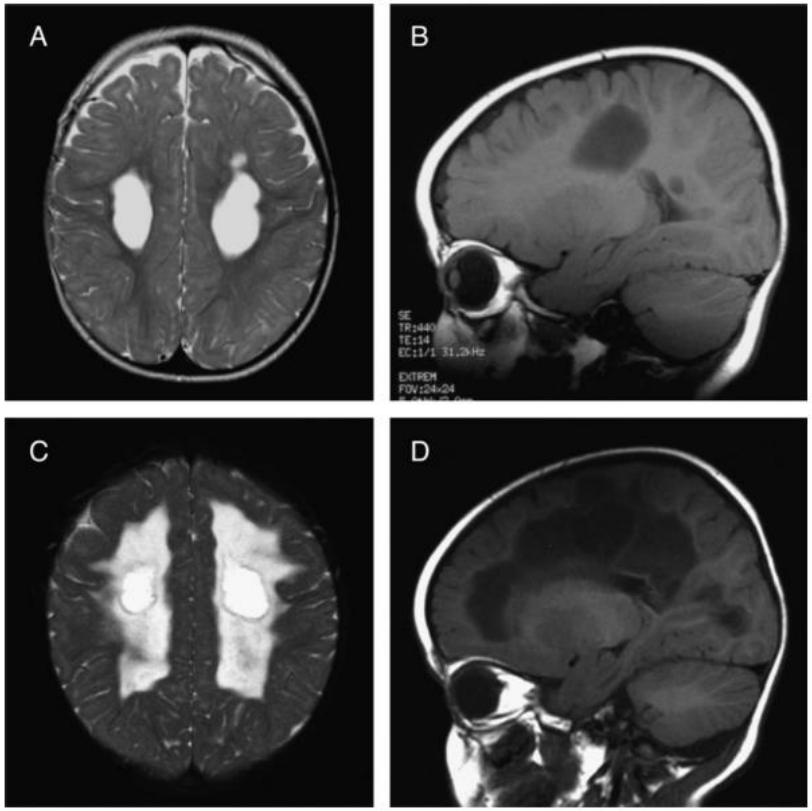
白質優位の病変

Teaching Neuro*Images*: Rapidly progressive leukoencephalopathy in mitochondrial complex I deficiency

2013

8ヶ月女児

Figure Brain imaging in *NDUFS1* mitochondrial complex I mutation



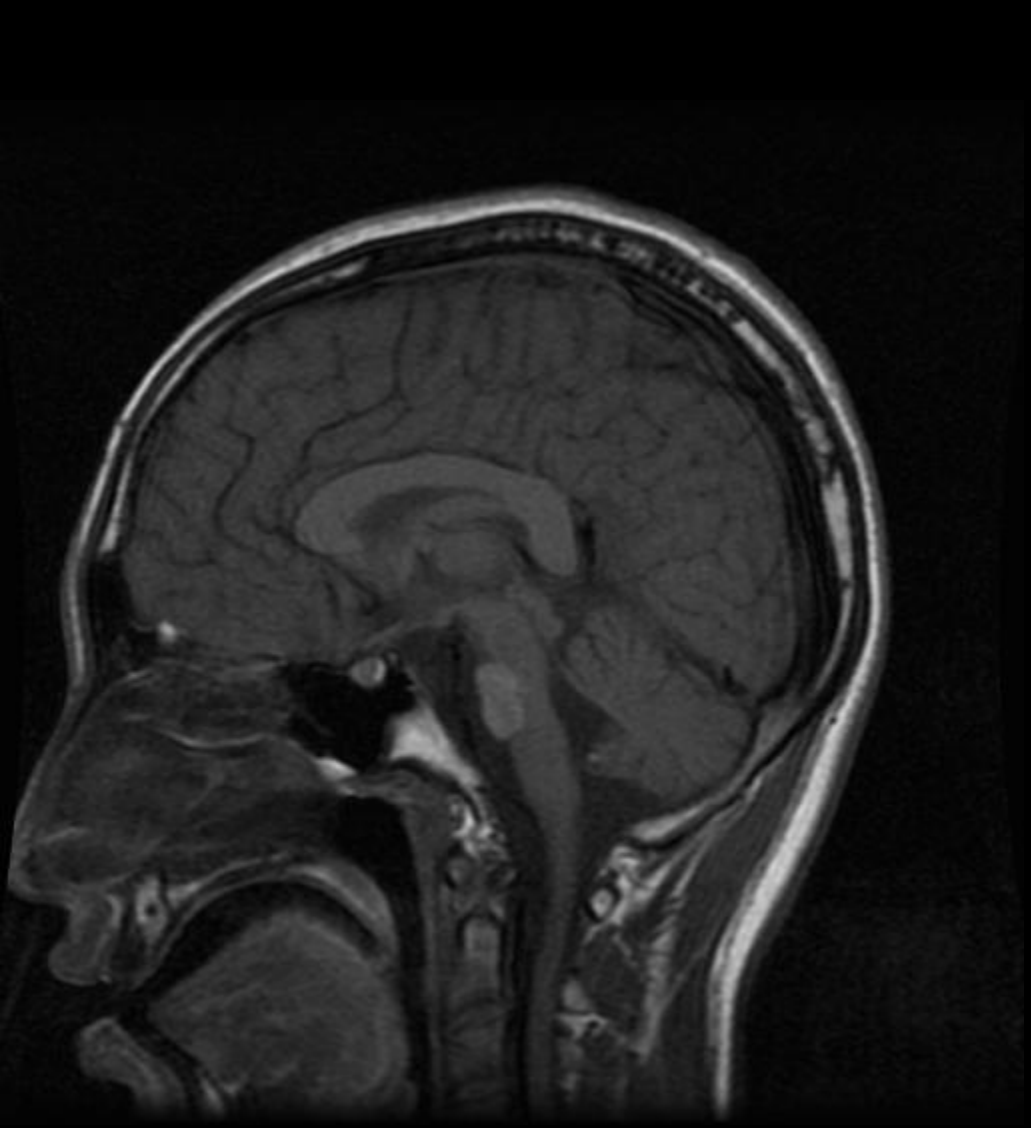
(A) Axial T2-weighted MRI of the brain demonstrates bilateral cystic white matter lesions in the centrum semiovale. (B) Corresponding sagittal T1-weighted MRI. (C, D) Follow-up MRI after 3 months reveals confluent demyelination of the entire supratentorial white matter.

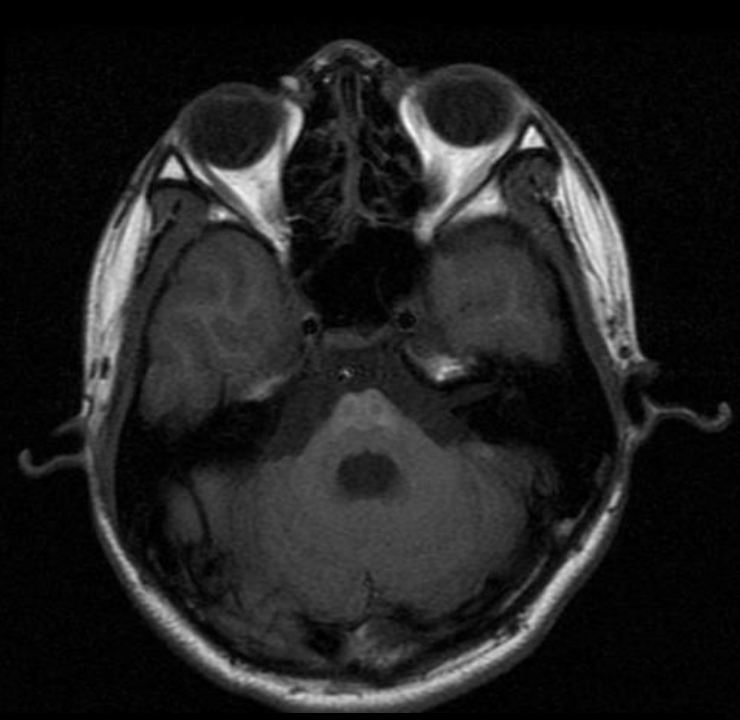
エピソード 3

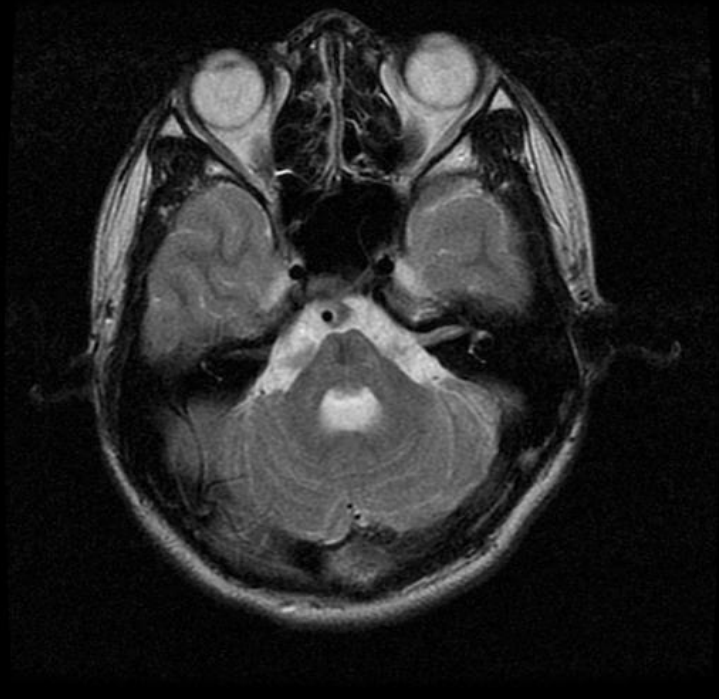
Ebony and ivory

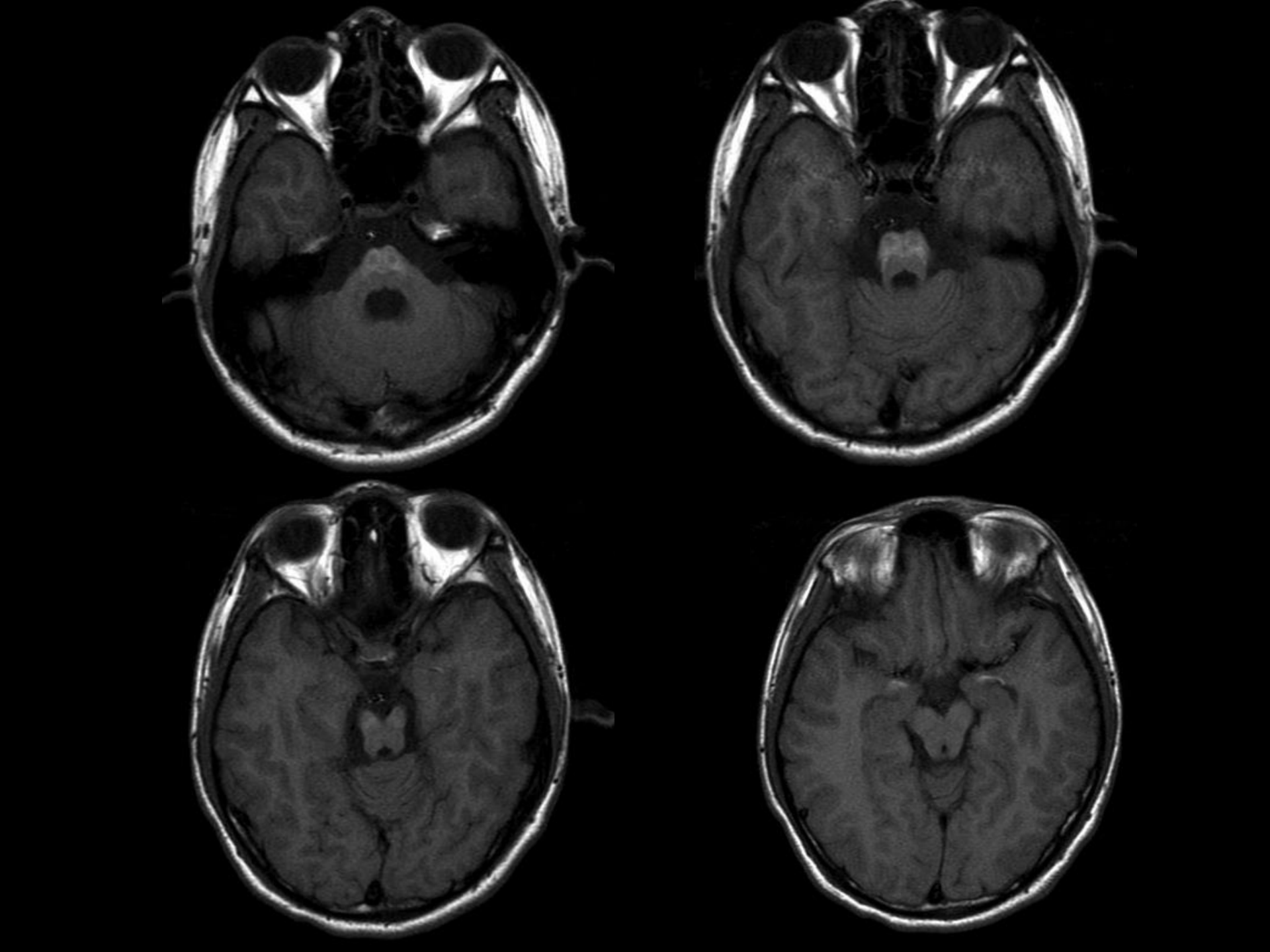
15歳　男性

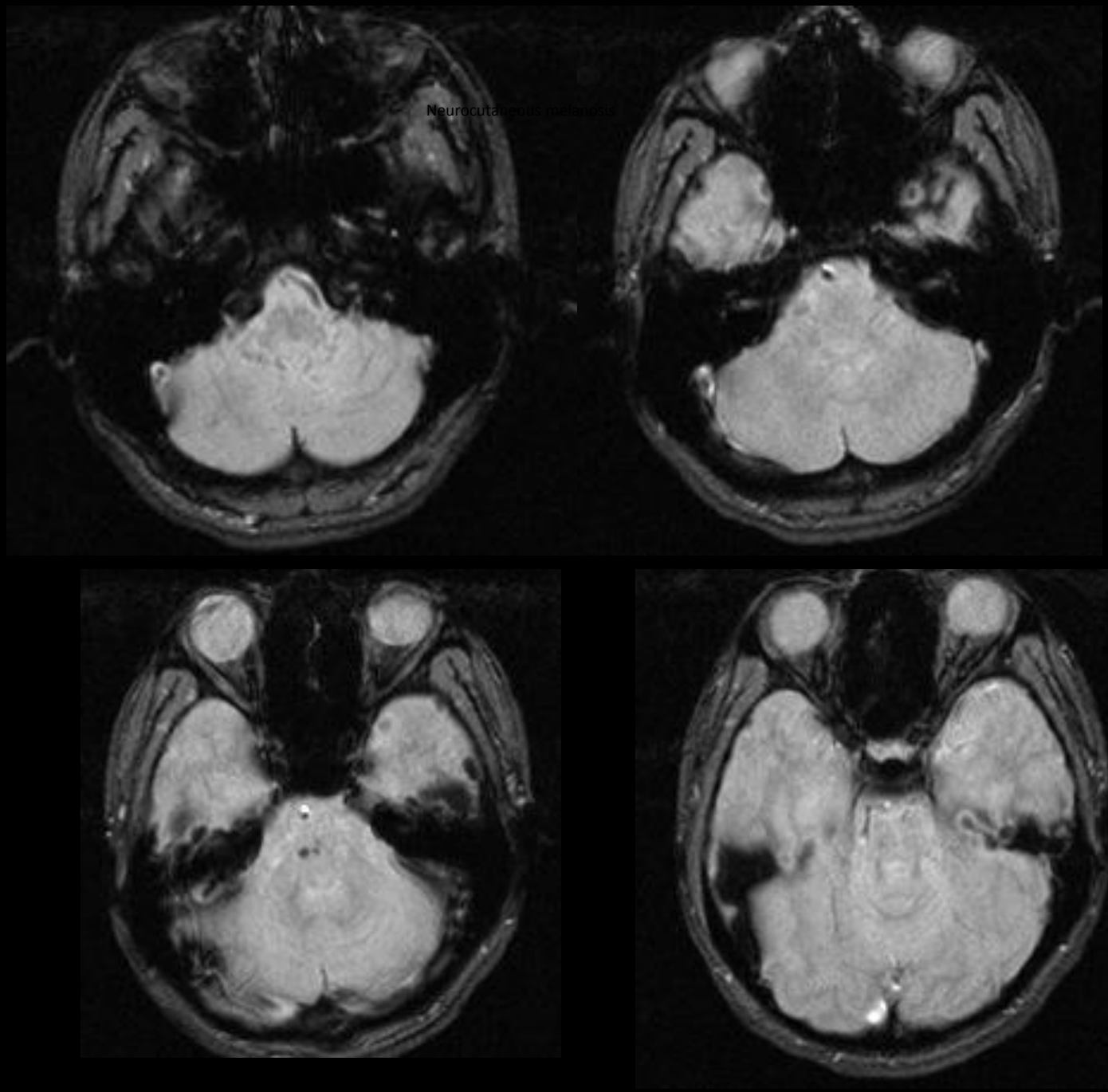
神経内科より依頼
症状は頭痛のみ
他院 MRIにて異常の指摘










Neurocutaneous melanosis

Brain & Development 32 (2010) 571–573

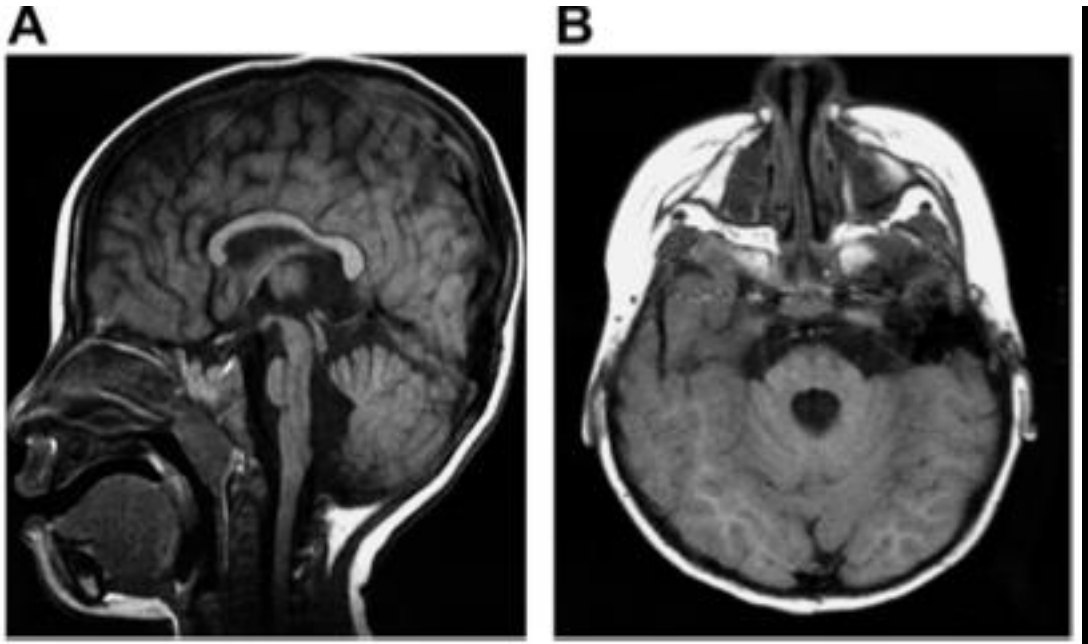
Offici
the Ja
of Chi

www.elsevier.co

Case report

Pontine hypoplasia in 5p-syndrome: A key MRI finding for a diagnosis

Takeshi Ninchoji, Jun-ichi Takanashi *



形成外科に受診歴あり

色素性母斑

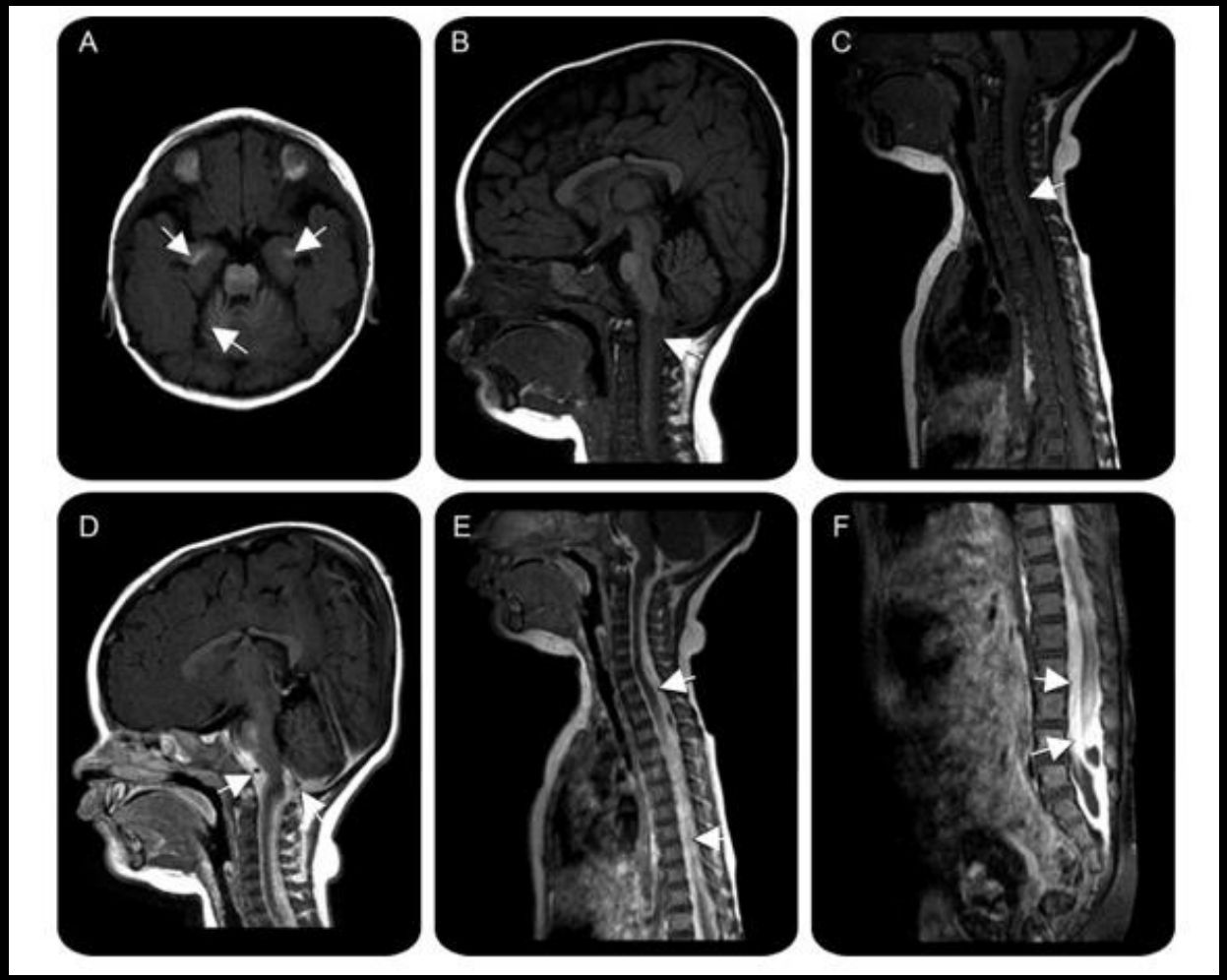
Neurocutaneous Melanosis

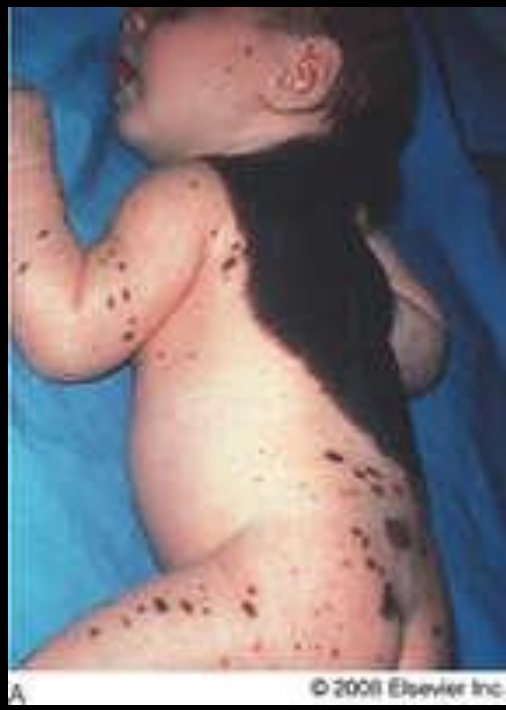
先天性色素性母斑症
（giant or multiple cutaneous melanocytic nevi)

中枢神経の良性、悪性メラニン細胞腫瘍

メラノーシス　髄膜、脳実質内（扁桃核、小脳）
T1強調画像　高信号

悪性黒色腫　髄膜、脳実質内





4歳　　男児

- Neurocutaneous melanosis 先天性の巨大／多発性の色素性母斑と中枢神経症状を特徴とする。
- 胎生期の神経外胚葉形成異常とされる。
- 病因　脳軟膜でのメラニン細胞の増殖　Virchow-Robin腔へのメラニン細胞の侵入 診断基準：皮膚所見　広範な皮膚メラニン性母斑：成人では20 cm以上，乳幼児では6 cm，頭部では9 cm以上。中枢神経系病変

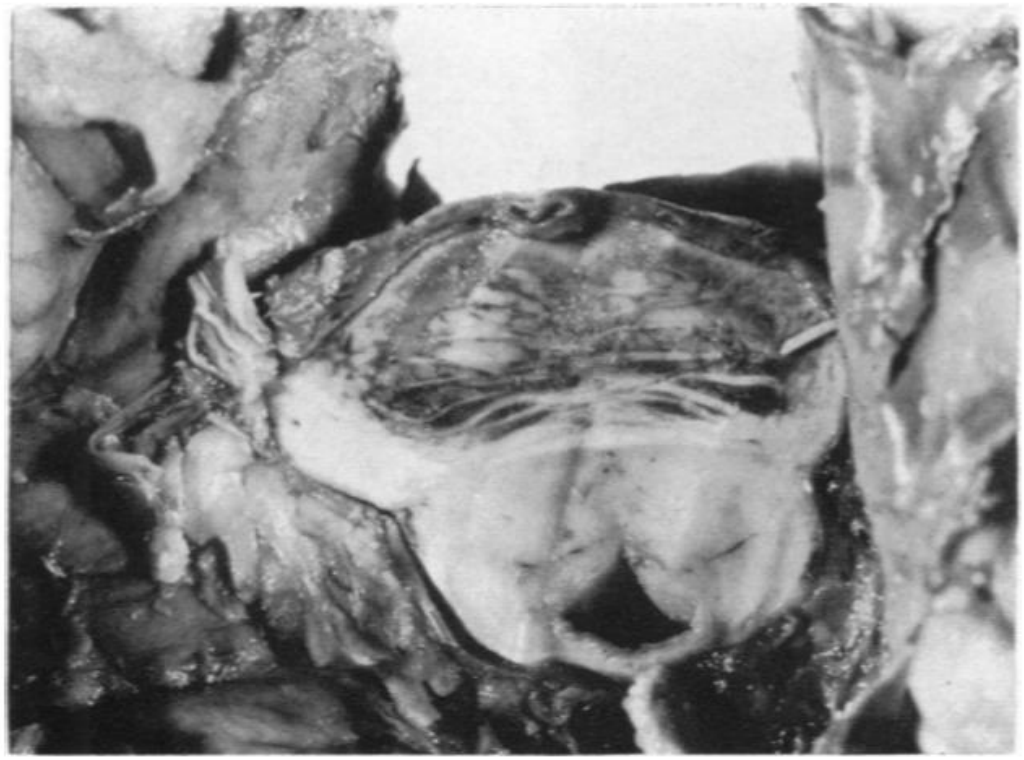
脳実質病変: parenchymal melanosis　メラノーシス：メラニン細胞の

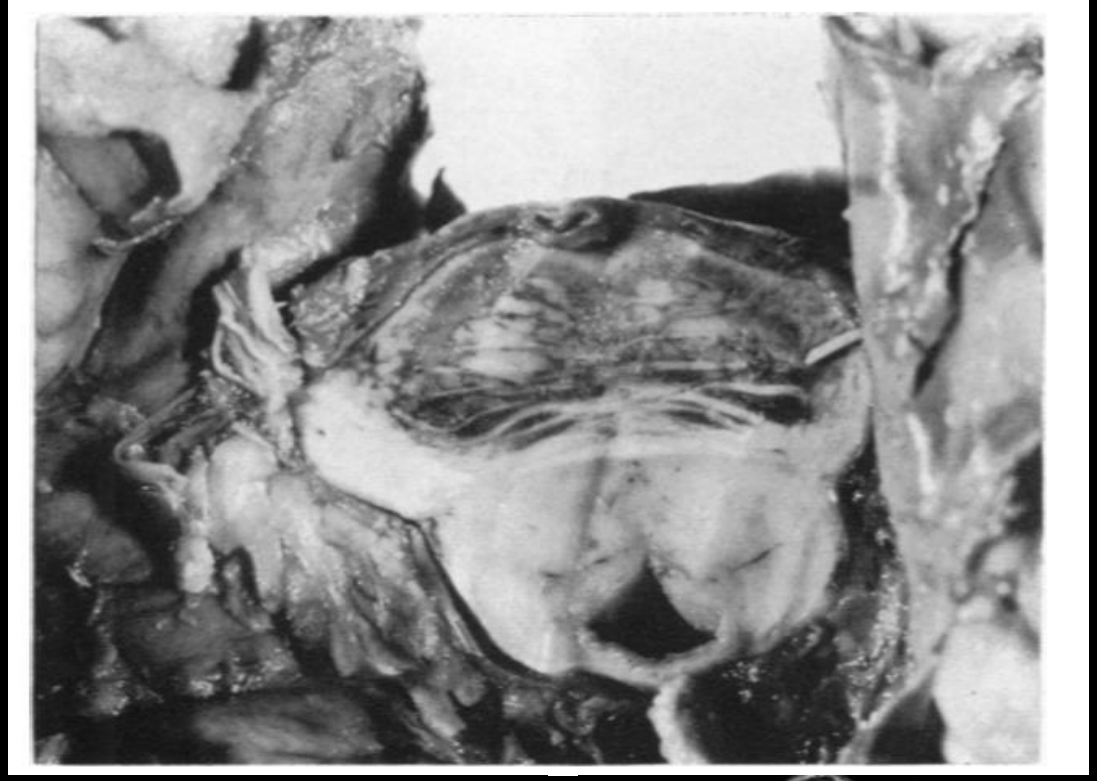
Arch. Dis. Childh., 1964, **39**, 508.

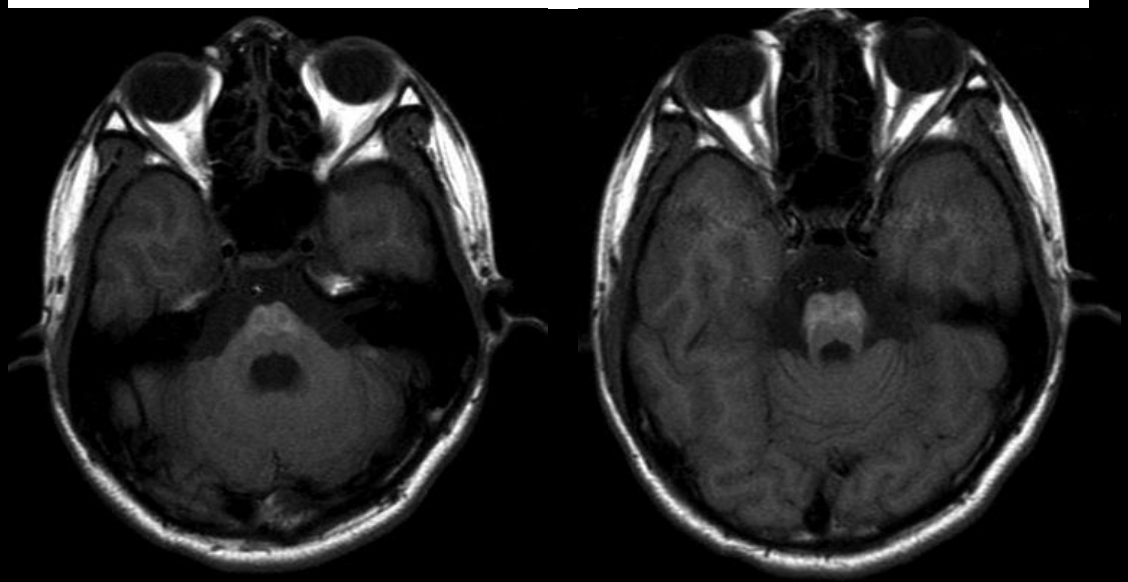
NEURO-CUTANEOUS MELANOSIS

BY

H. FOX, J. L. EMERY, R. A. GOODBODY, and P. O. YATES
From the Departments of Pathology, University of Manchester, Children's Hospital, Sheffield, and Southampton General Hospital

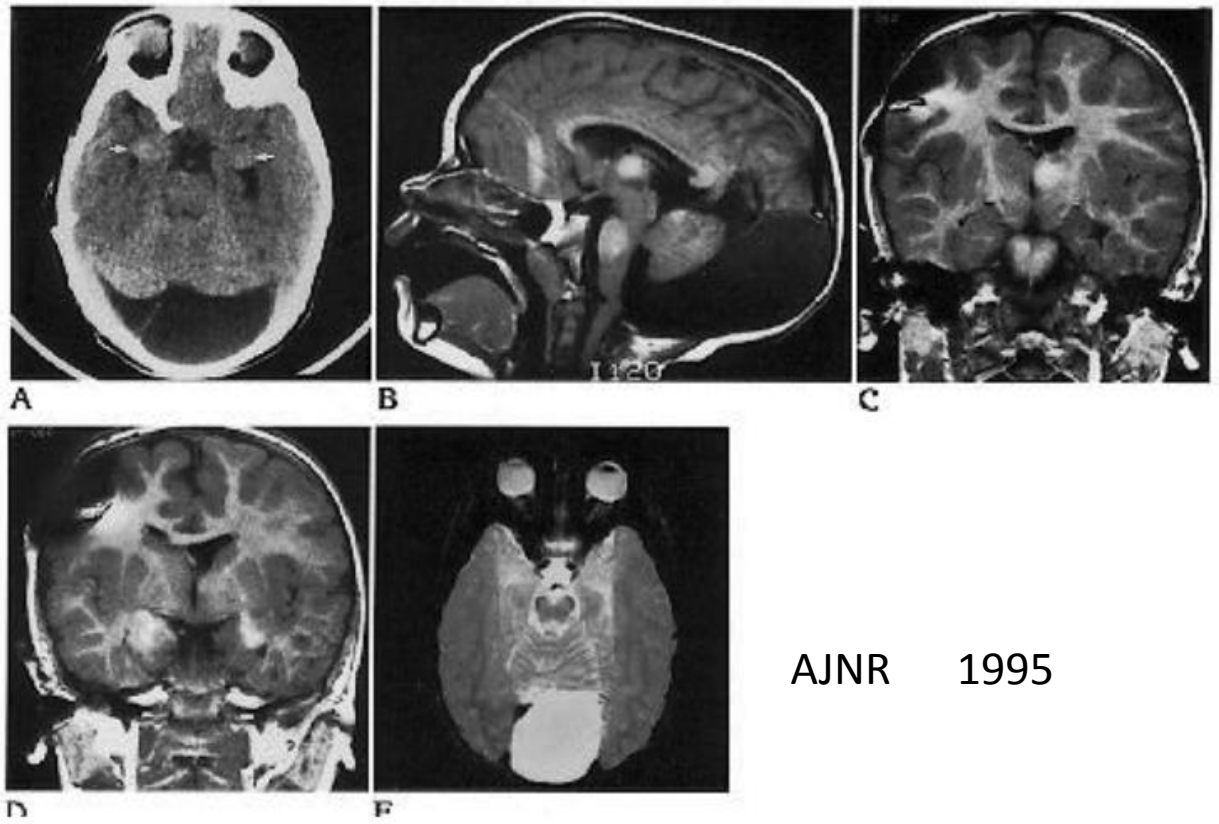




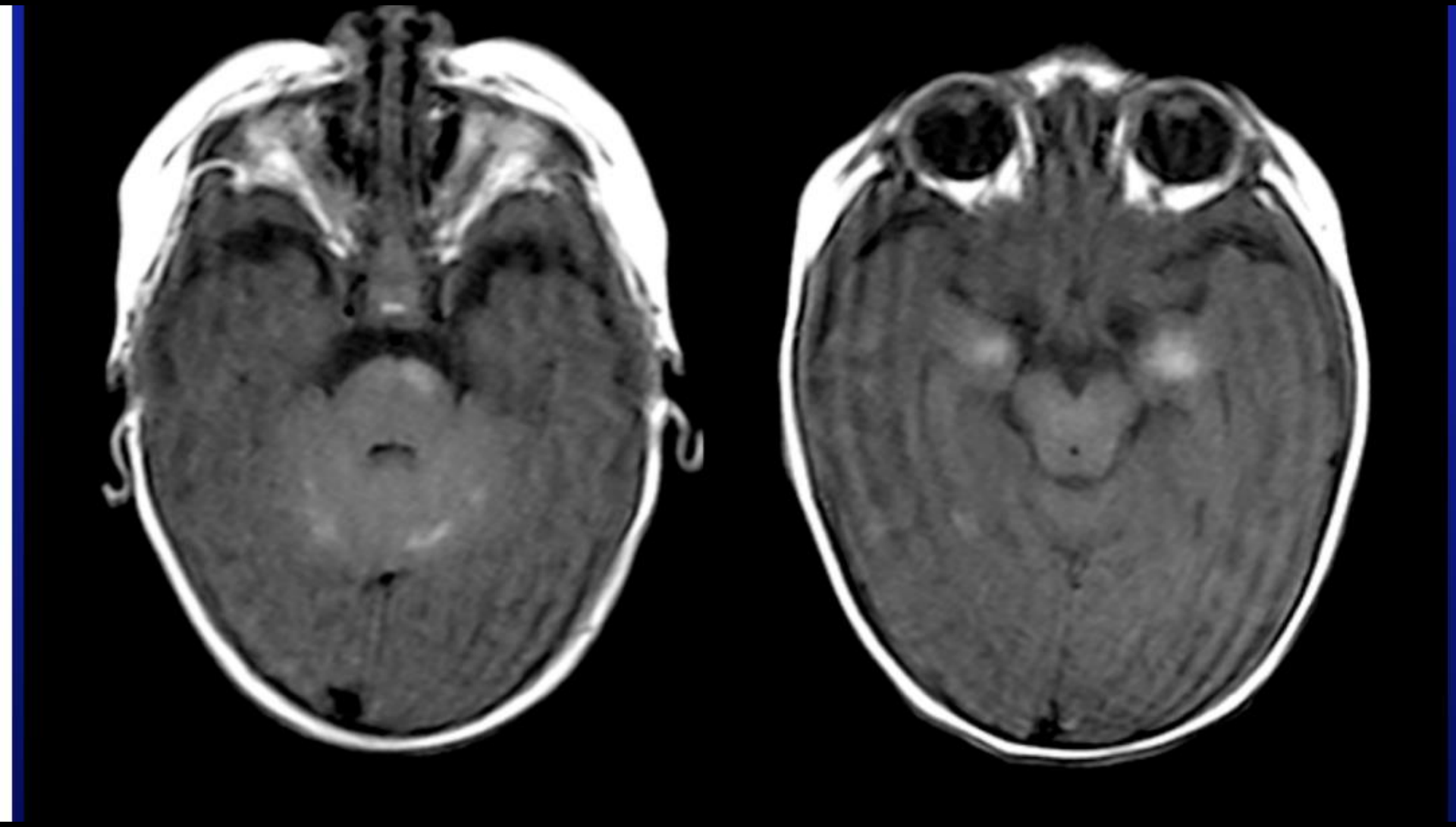


MR of Parenchymal Neurocutaneous Melanosis

Ali Demirci, Yasutaka Kawamura, Gordon Sze, and Charles Duncan



AJNR 1995



NRWS 2008　6ヶ月　女児

エピソード　4

The Holy Grail

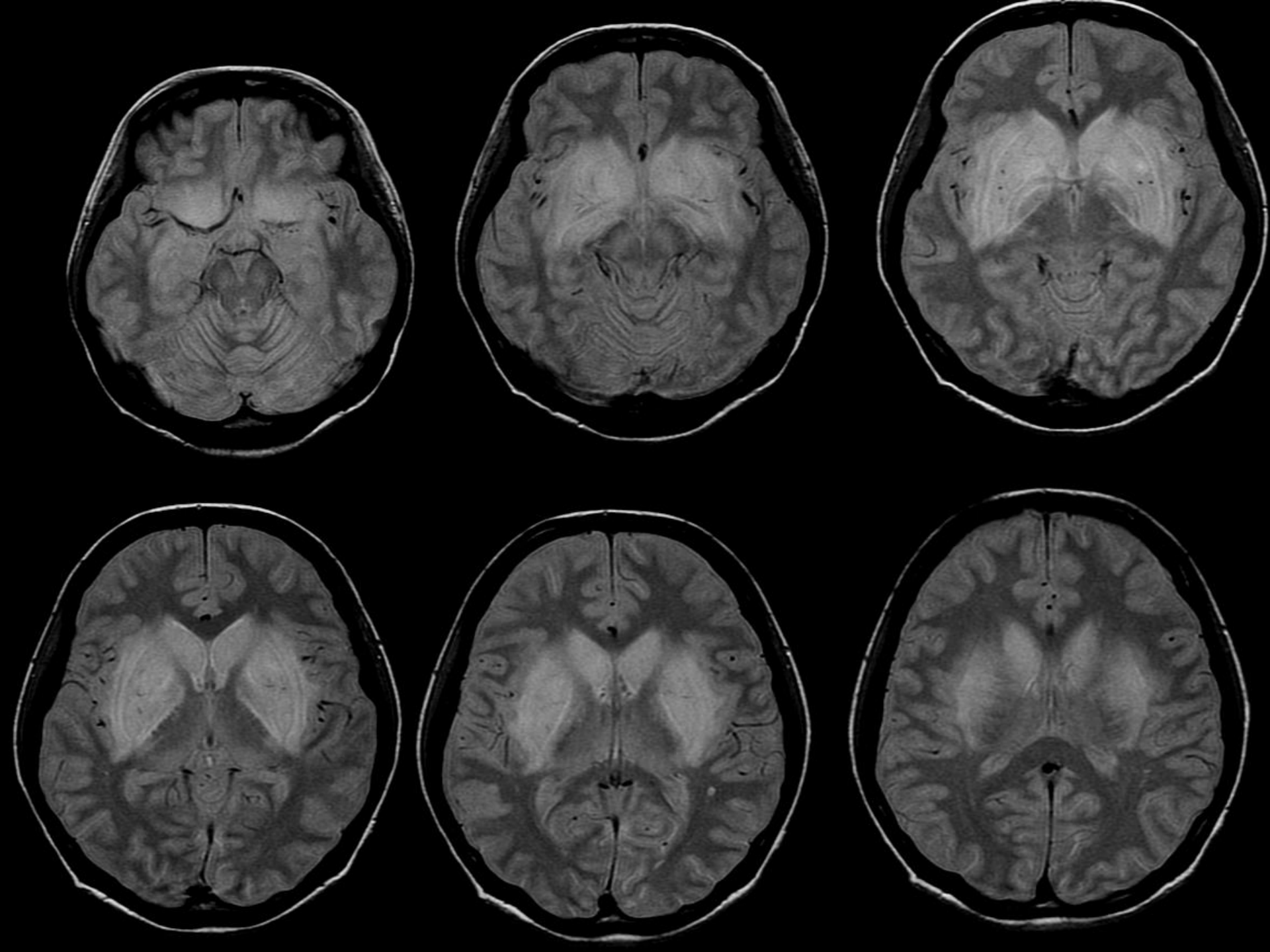
２９歳　女性

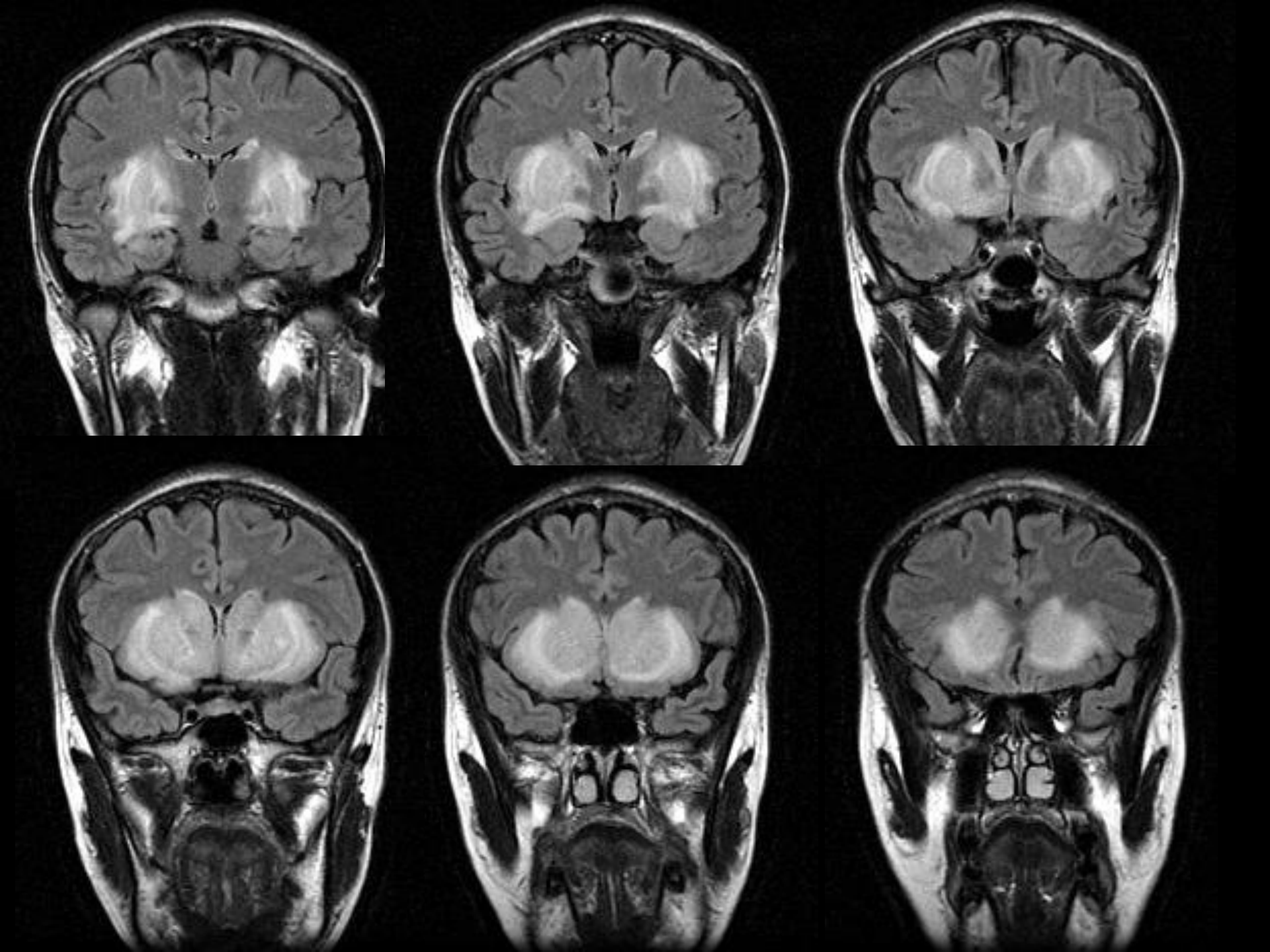
入院2ヶ月前より体中の痛み、両足のこわばりを認め、蛋白尿、尿潜血が出現

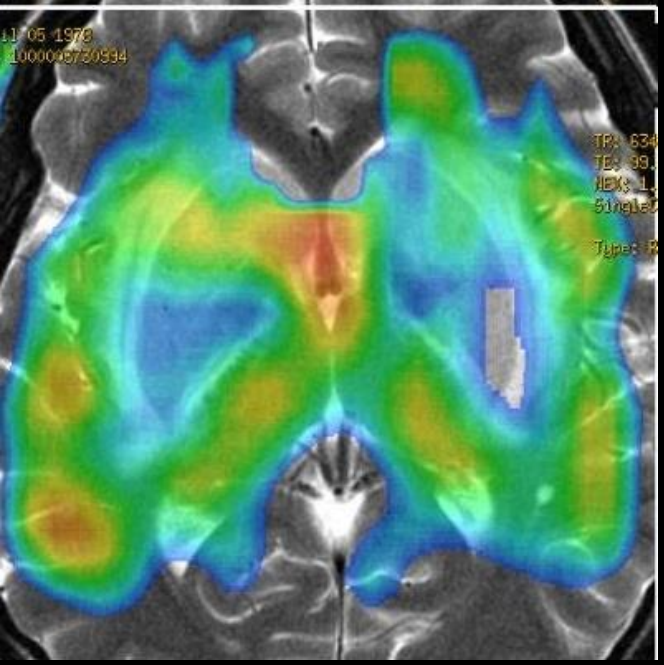
1ヶ月前より顔面に蝶形紅斑

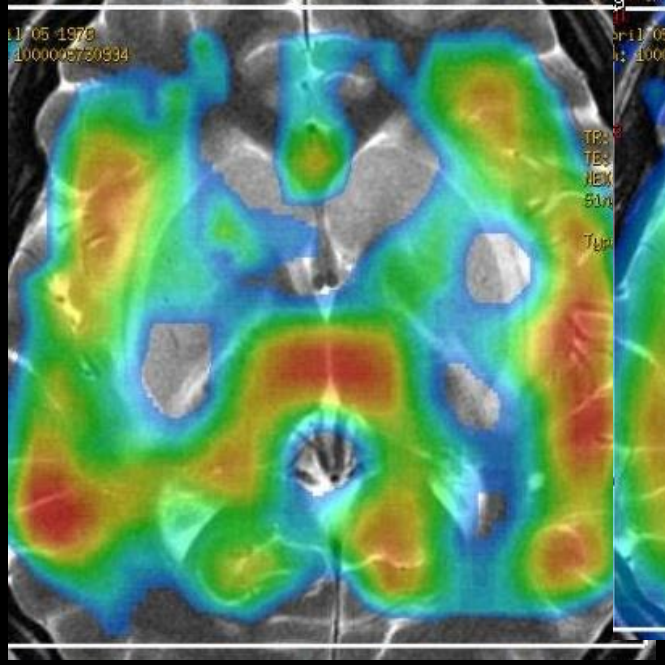
SLEが疑われ入院

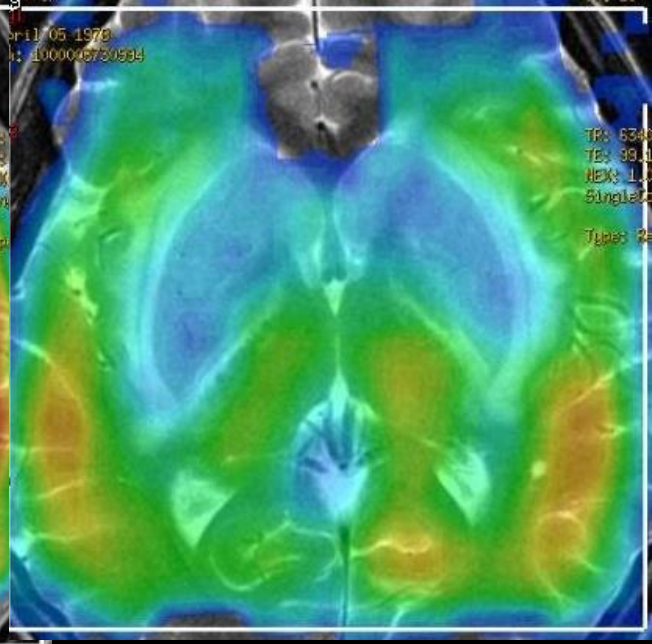
めまい、浮遊感が出現したためMRI施行







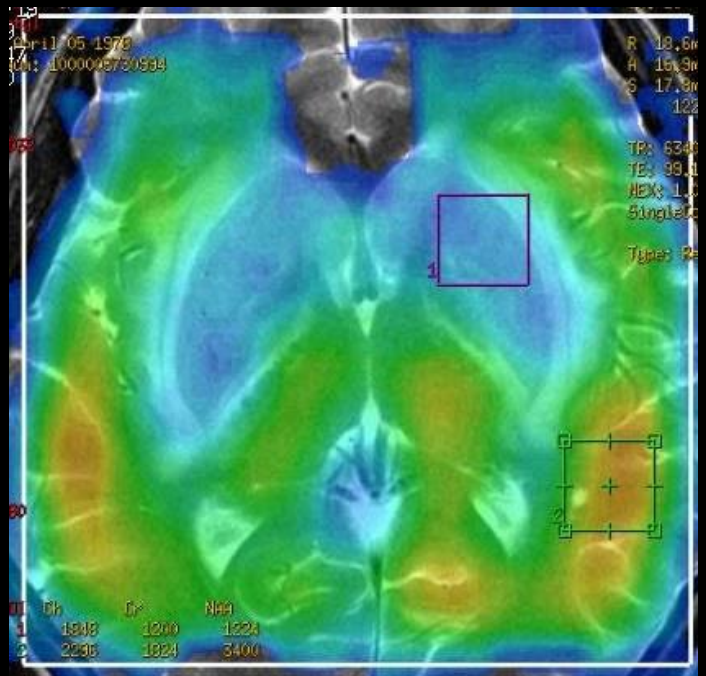


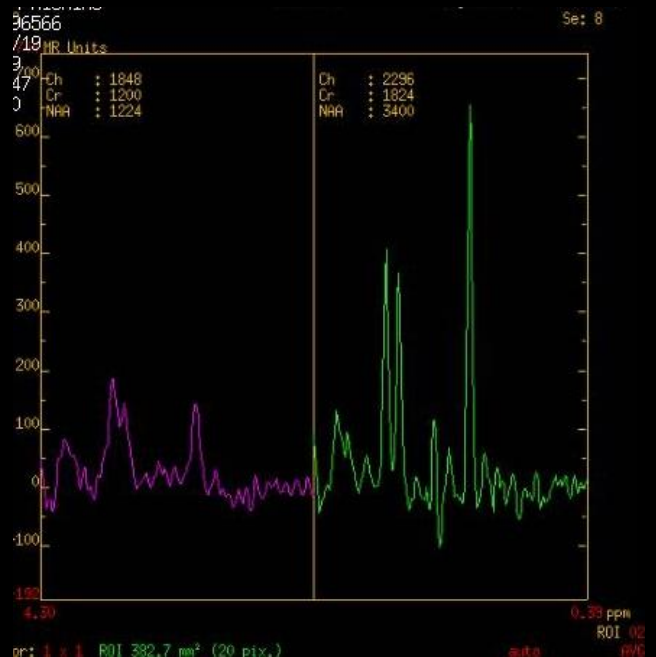


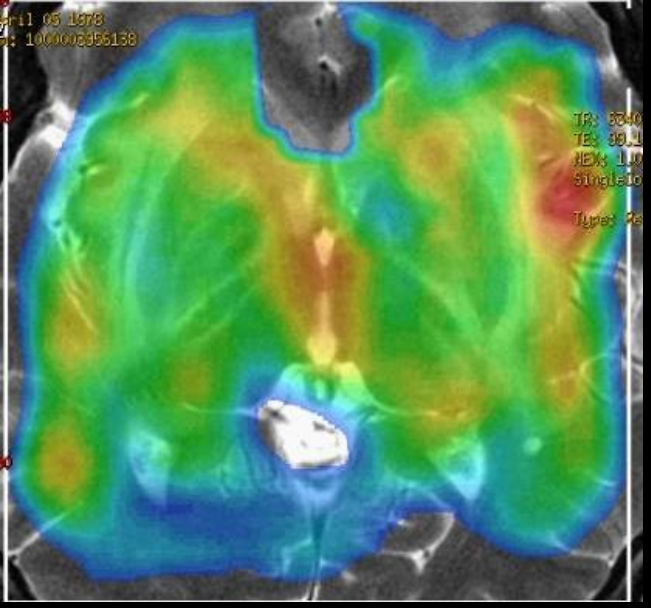
Cho

Cr

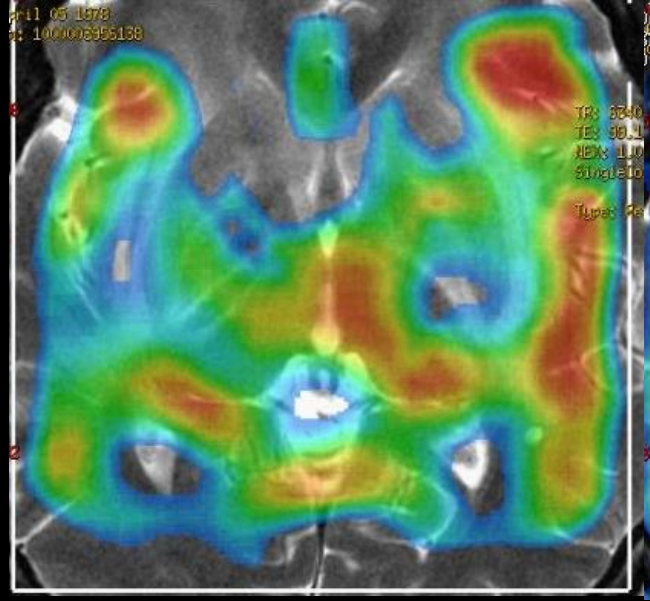
NAA


Ch
Cr
NAA
1848
1200
1224
2296
1824
3400

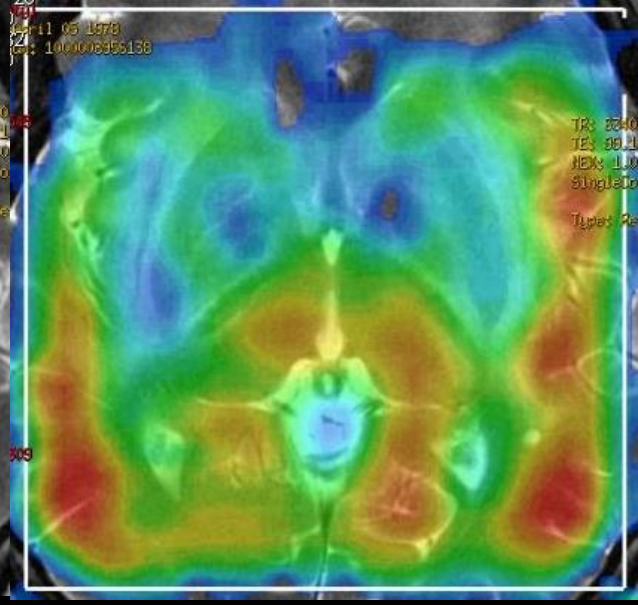

Ch : 1848
Cr : 1200
NAA : 1224
Ch : 2296
Cr : 1824
NAA : 3400
MR Units
600
500
400
300
200
100
0
-100
4.30
0.33 ppm
ROI 02
ROI 382.7 mm² (20 pix.)



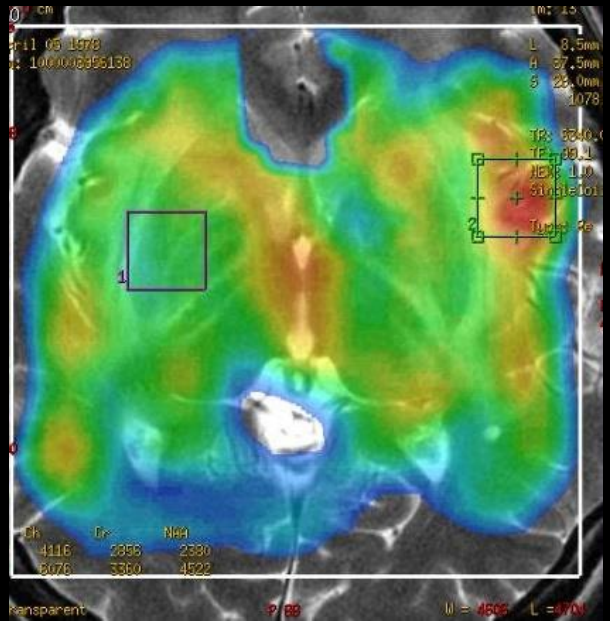
Cho

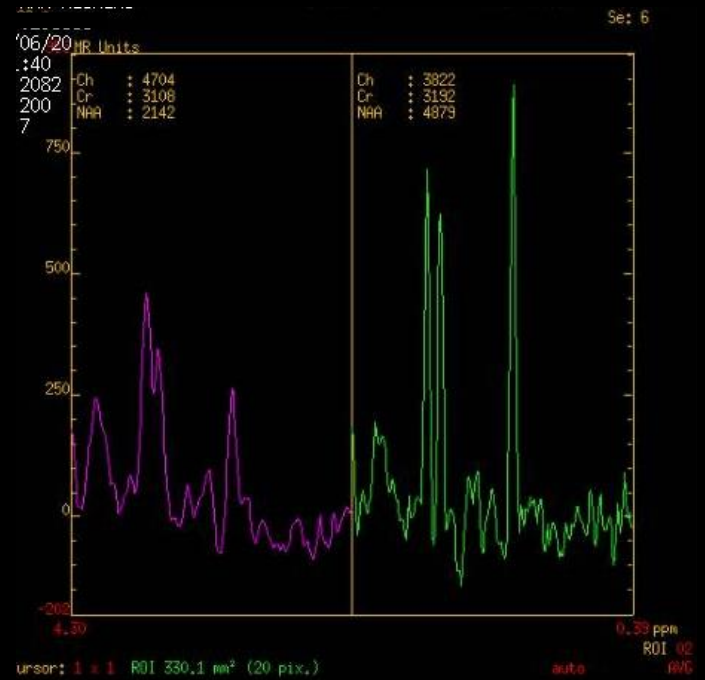


Cr



NAA





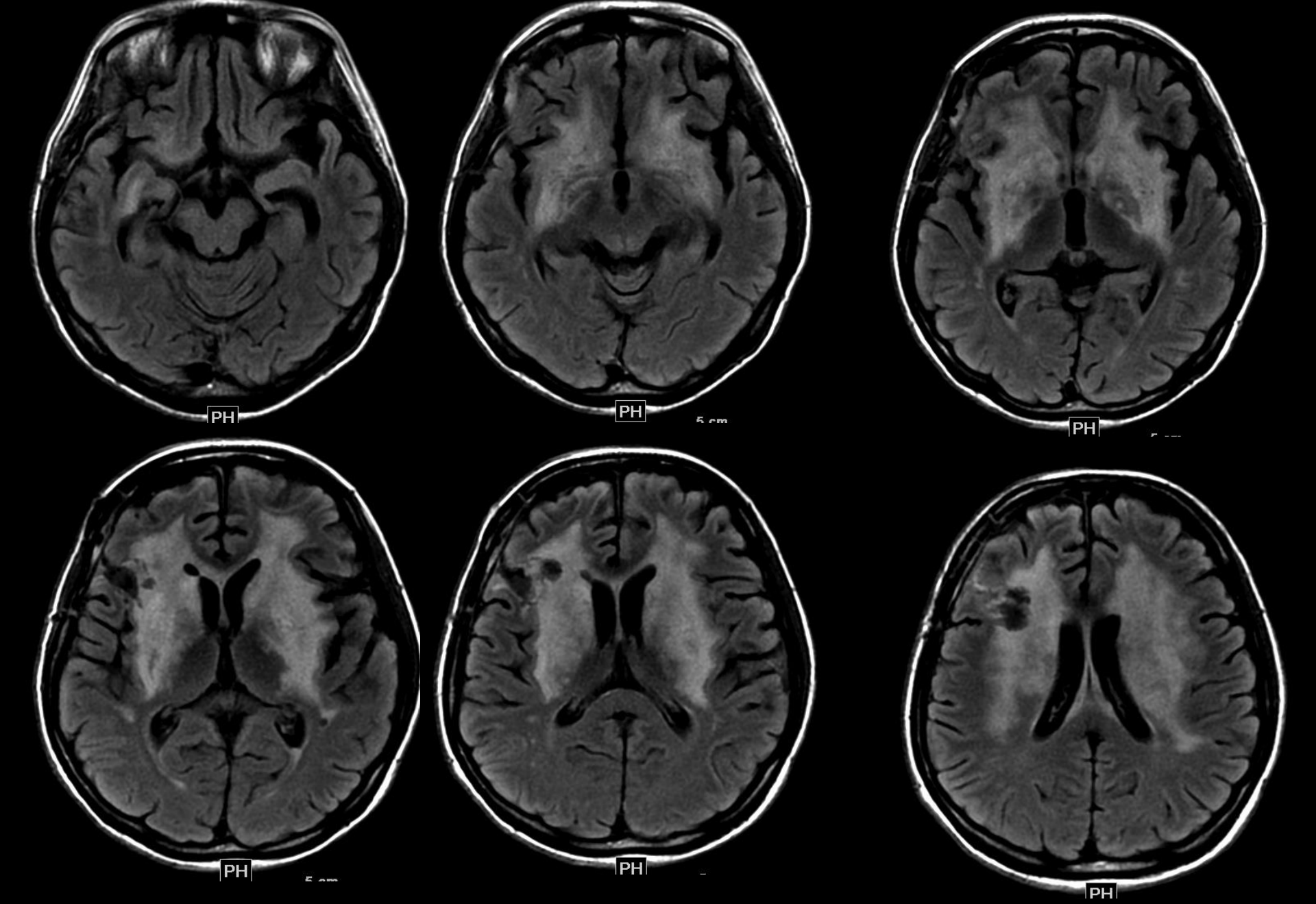
1ヶ月

- ステロイド投与するも効果見れず、各種ウィルス陰性

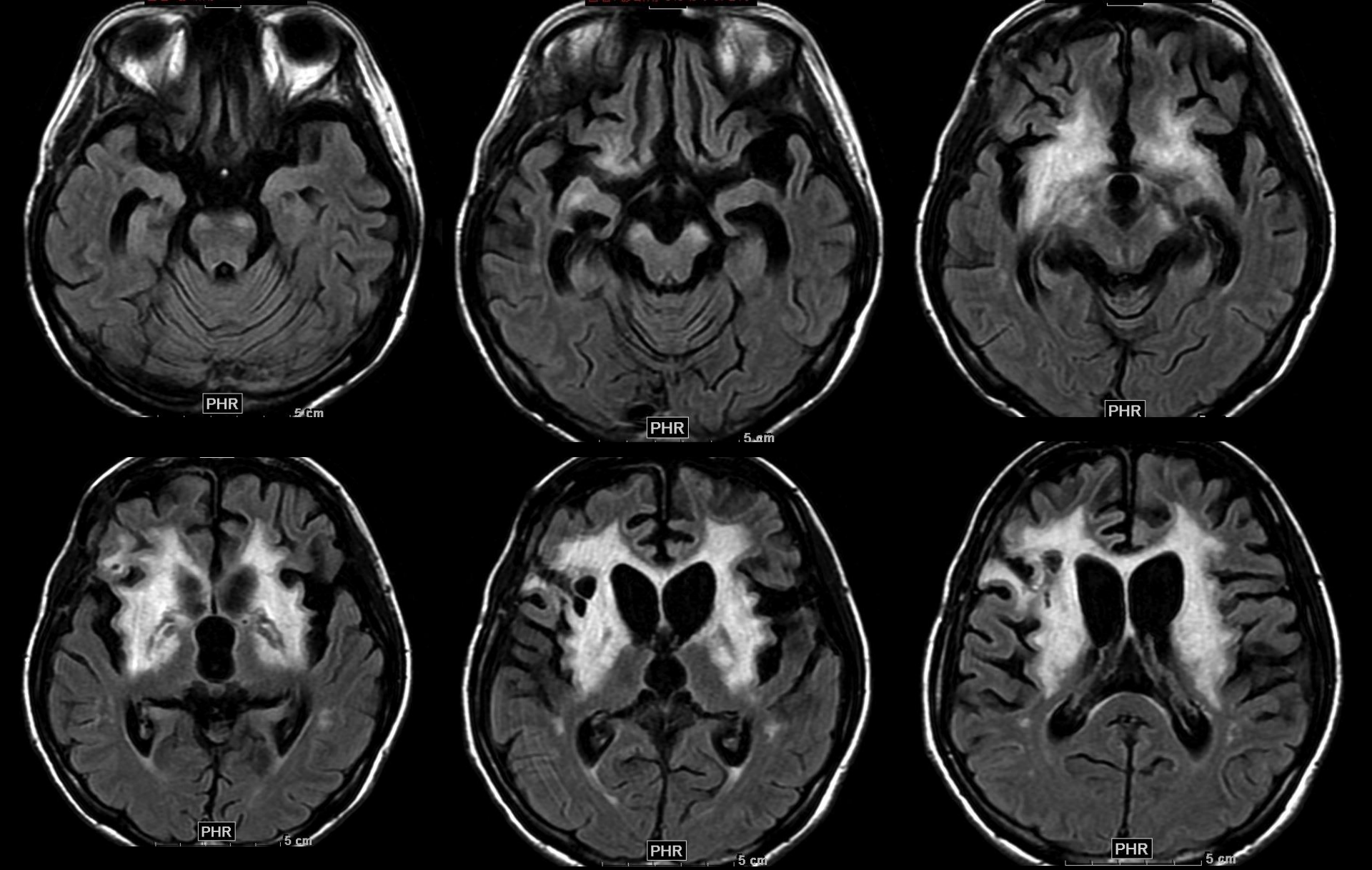
  脳生検施行

生検

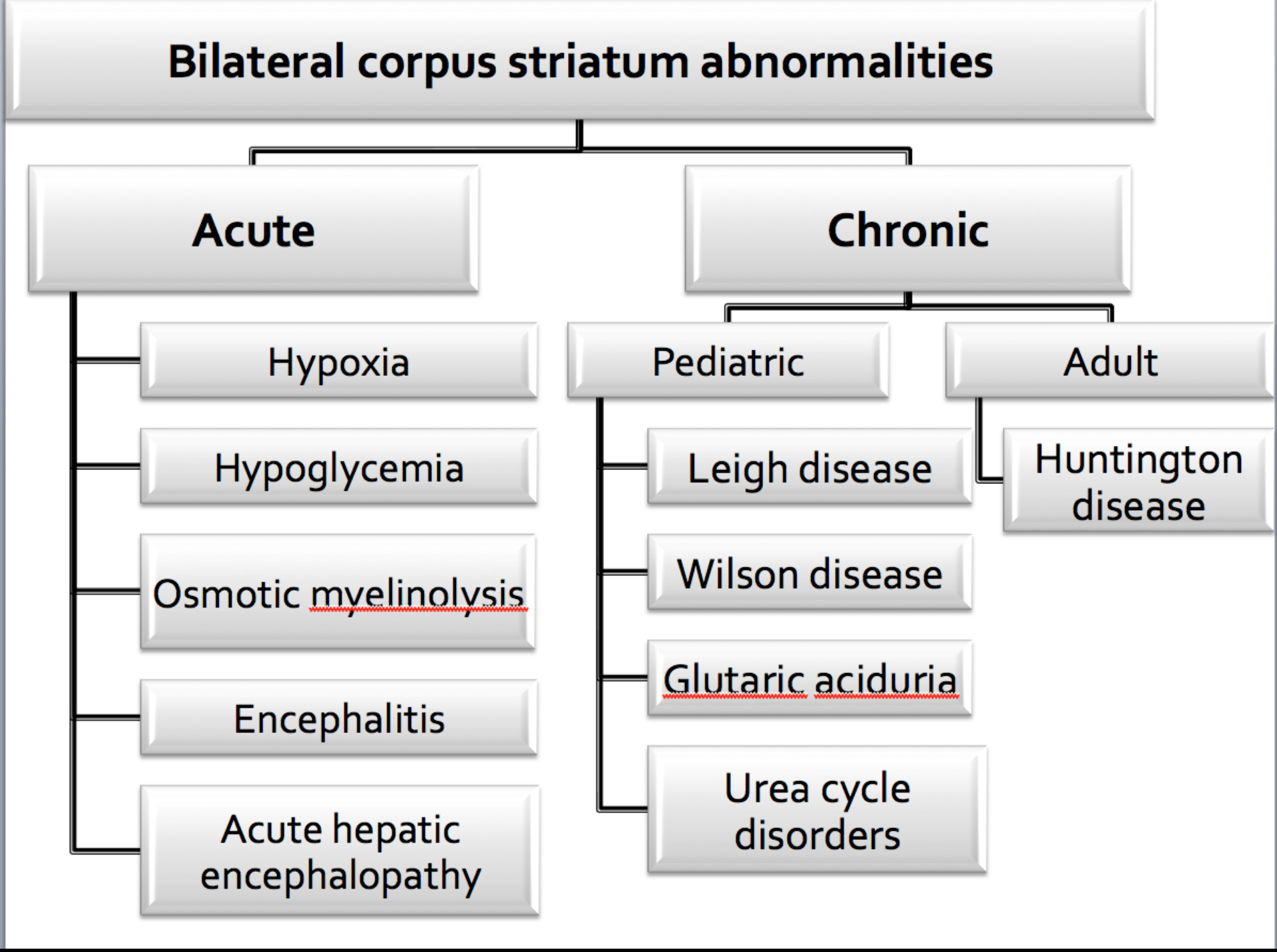
- 脱髄　KB染色にて、髄鞘の脱落
  astrogliaの増勢，Macrophageの滲出
  軸索脱落は目立たない。
  血管周囲にリンパ球集簇は，見られない。



5ヶ月後



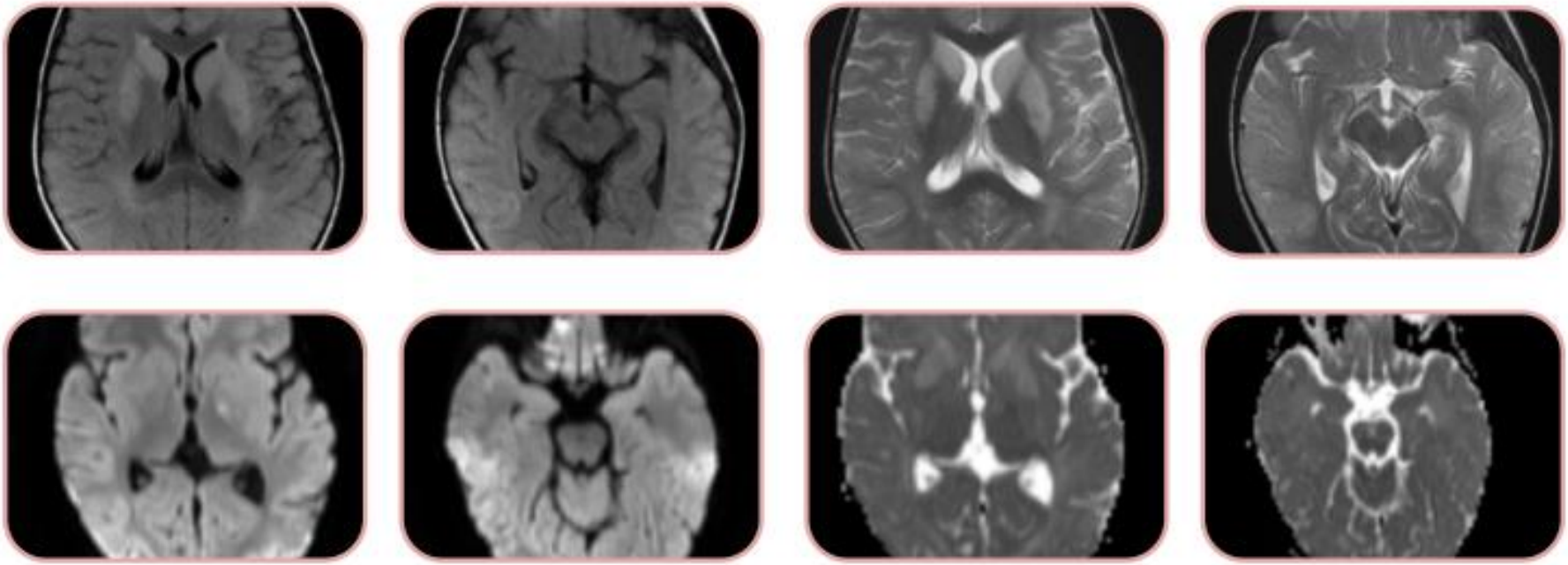
1年後　萎縮の進行


Bilateral corpus striatum abnormalities
Acute
Chronic
Hypoxia
Hypoglycemia
Osmotic myelinolysis
Encephalitis
Acute hepatic encephalopathy
Pediatric
Adult
Leigh disease
Wilson disease
Glutaric aciduria
Urea cycle disorders
Huntington disease

Striatal Encephalitis

Case 1

CC: 18-month-old male with tonic clonic seizures

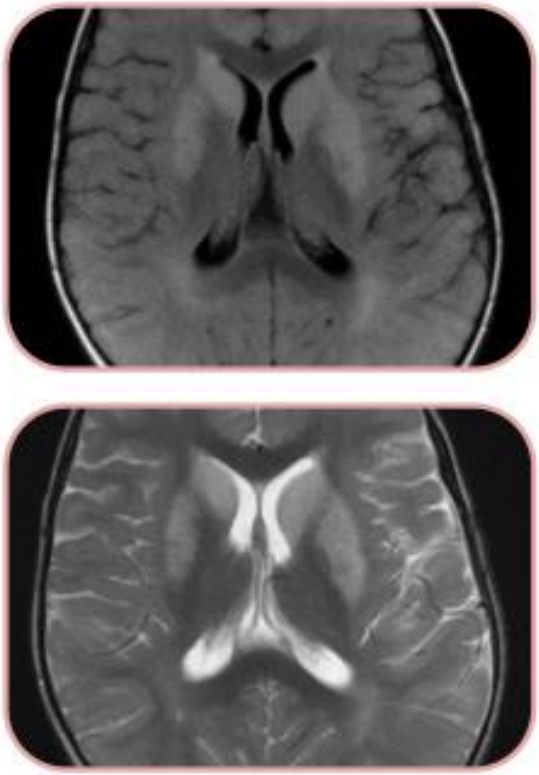


FLAIR, T2, DWI, and ADC images show increased signal in the bilateral striatum (caudate and putamen)

Striatal Encephalitis

Case 1: Diagnosis

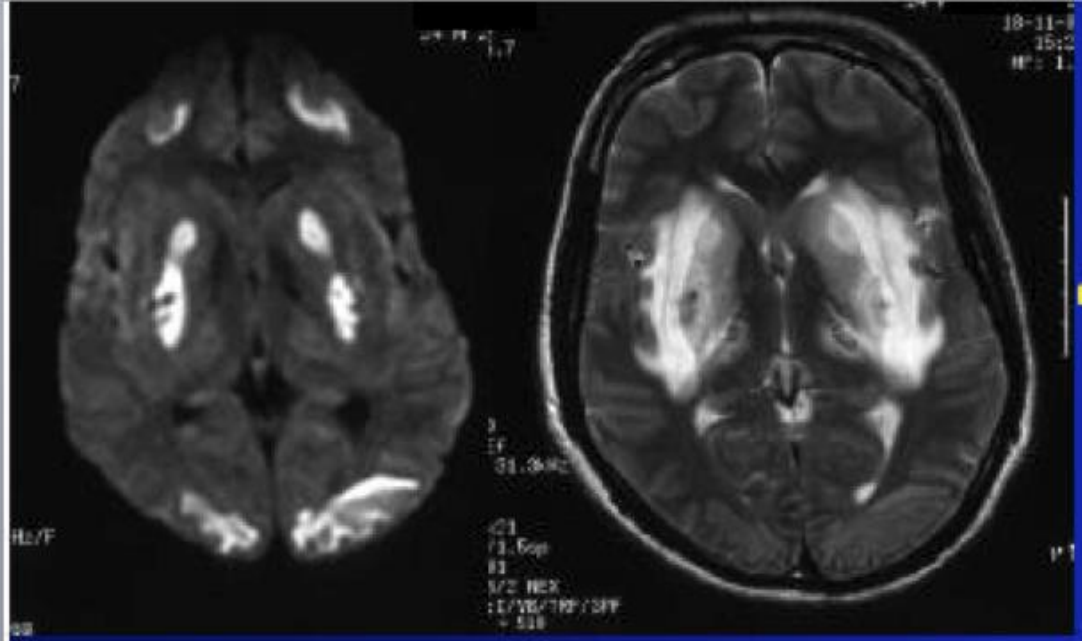
Post-infectious striatal encephalopathy

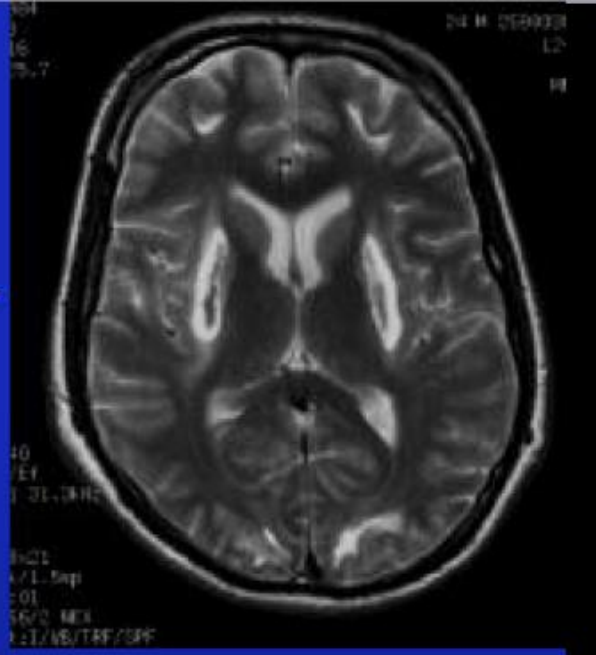


This case turned out to be post-infectious striatal encephalopathy

Nonparaneoplastic striatal encephalitis may be due to autoimmune phenomenon from post-infectious causes: Mycoplasma, Streptococcal, viral, etc.

Commonly associated antibodies of paraneoplastic striatal encephalopathy are due to anti-CV2 and less commonly anti-NMDAR, anti-VGKC, and anti-Hu





拡散強調像：著明な高信号
T2強調像，FLAIR像：著明な高信号 → 細胞性浮腫 → 非可逆性病変（壊死）

拡散強調像：等信号
T2強調像，FLAIR像：高信号 → 細胞外性浮腫 → 可逆性病変

- Server A et al:Conventional and diffusion-weighted MRI in the evaluation of methanol poisoning. Acta Radiol. 2003 Nov;44(6):691-5.
- Deniz S et al:Diffusion-weighted magnetic resonance imaging in a case of methanol intoxication. Neurotoxicology. 2000 Jun;21(3):405-8.

2004年
NRWS

Still unknown

発症当時は、軽い症状

　画像所見は、強い

ステロイド、ゾビラックスなど治療に反応せず

1年間入院

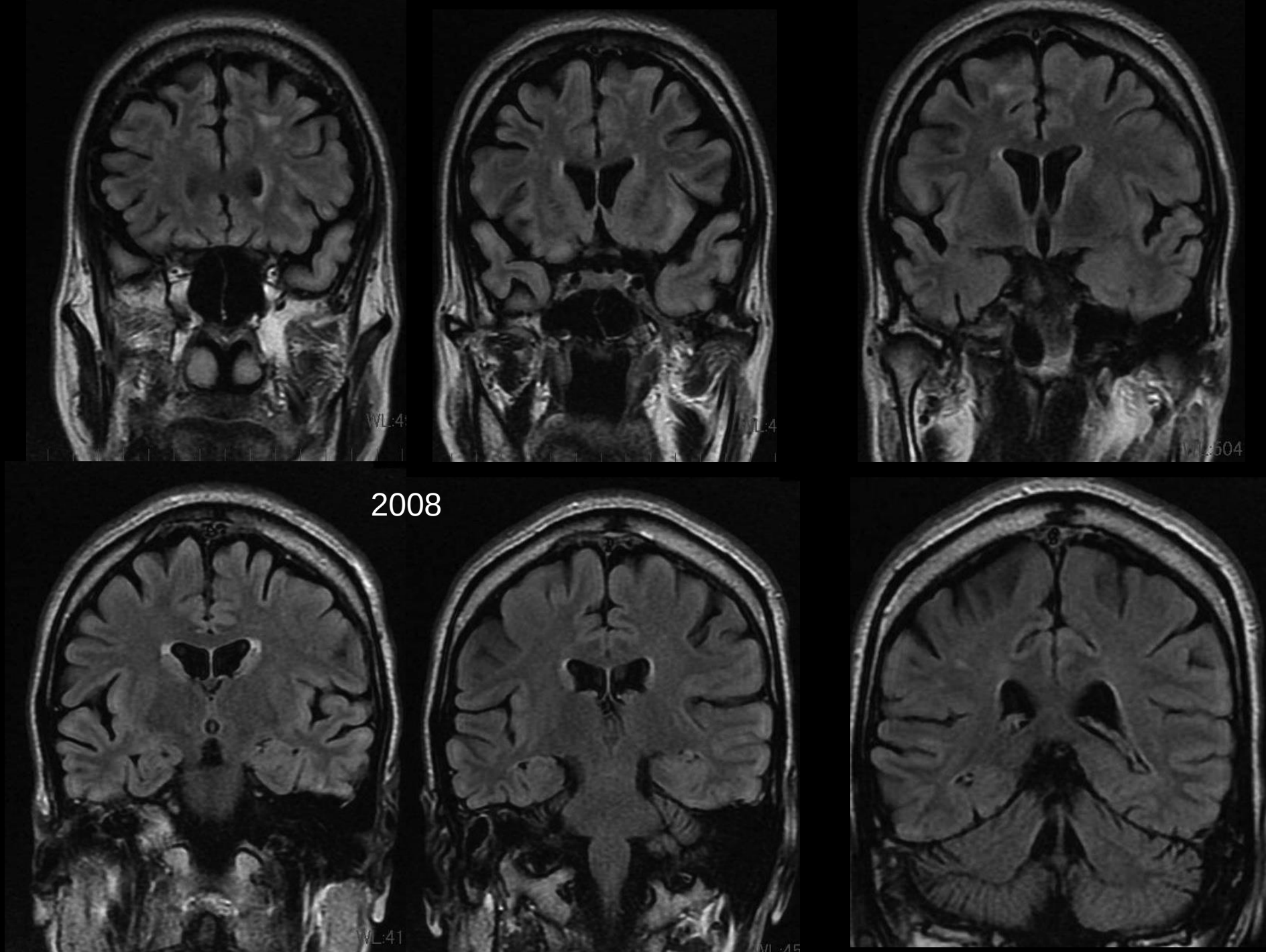
意思の疎通が不可能、拘縮が強くなり転院

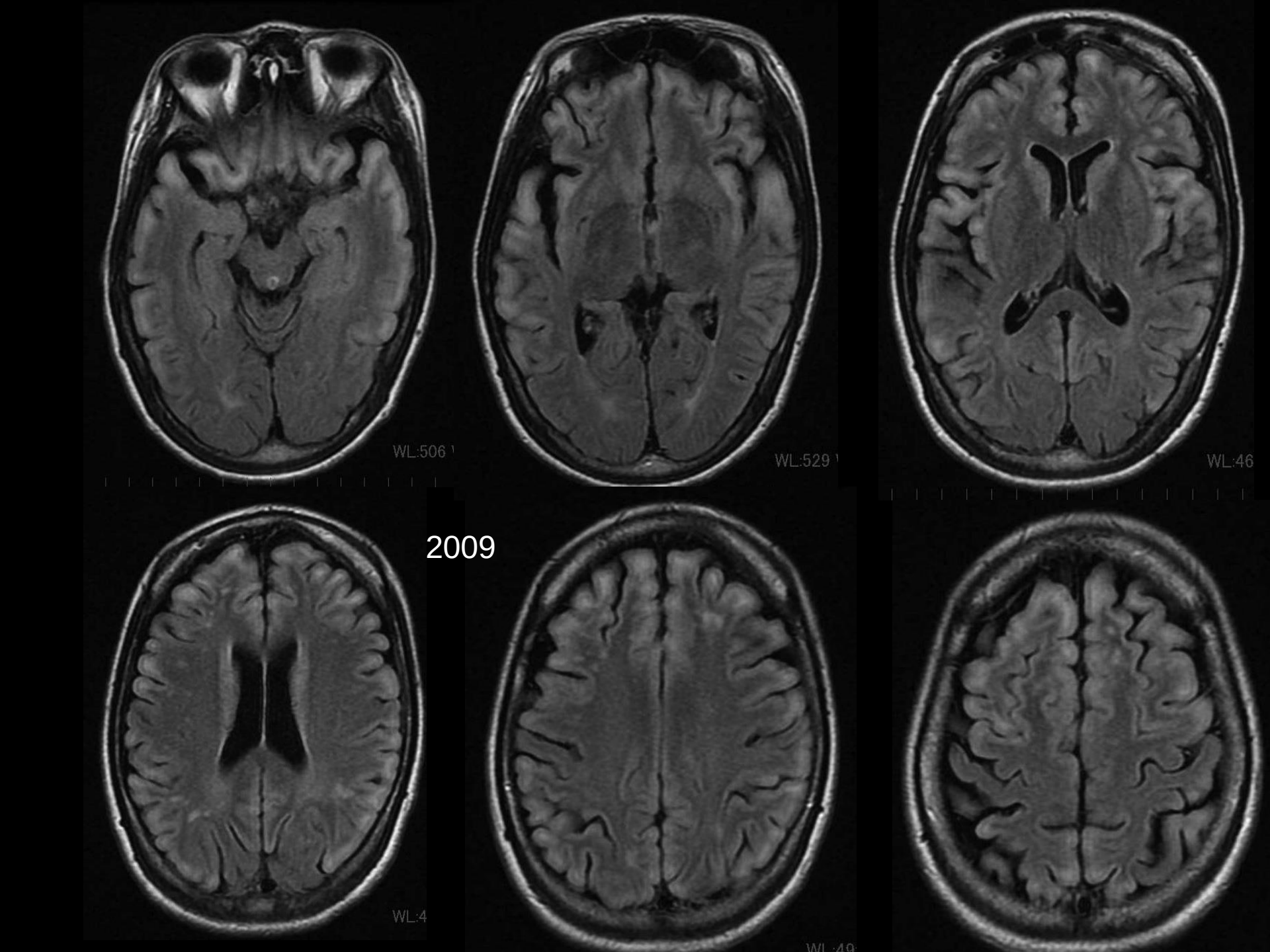
エピソード　5

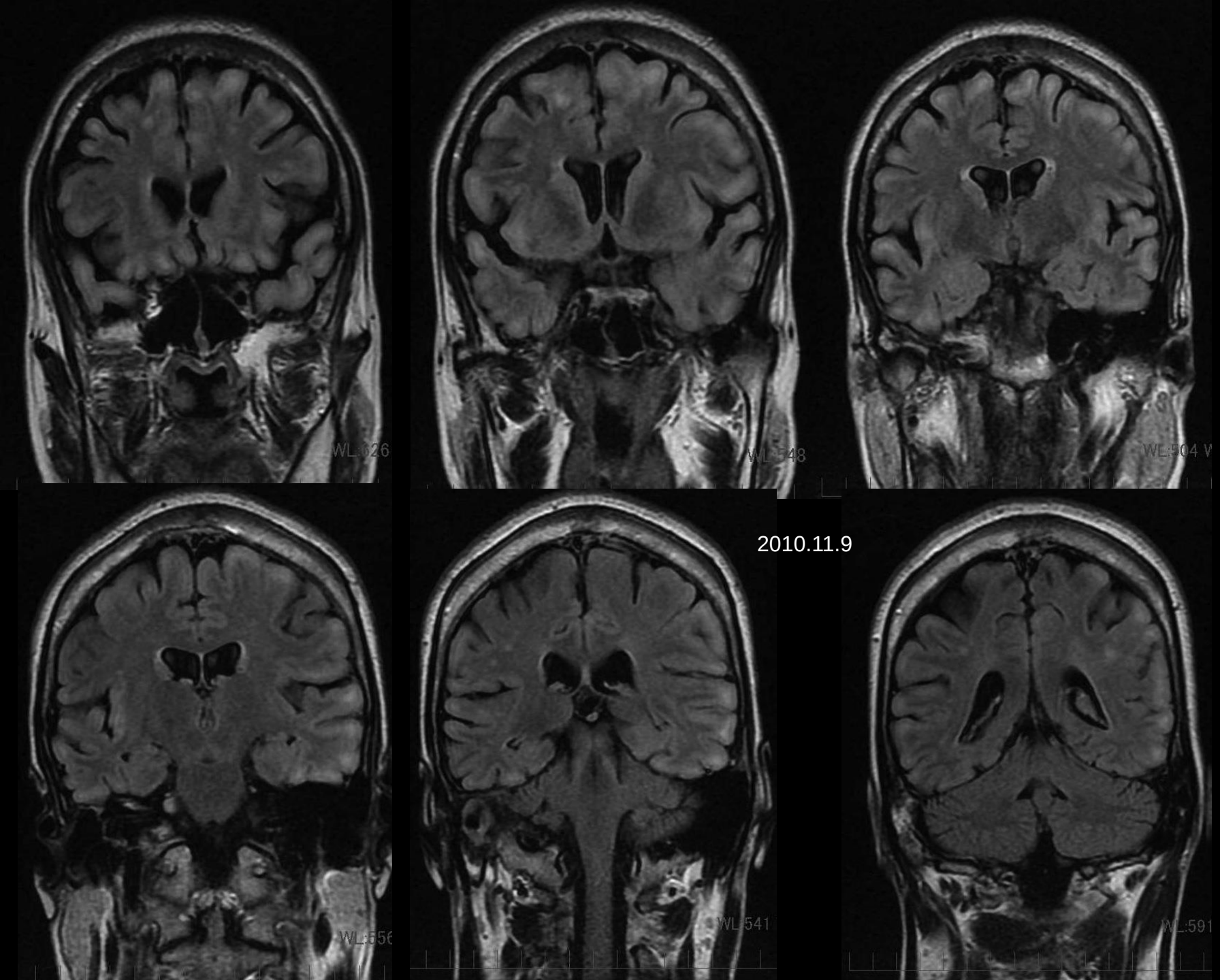
Like a storm

30代　女性

統合失調症疑いで，通院、入院

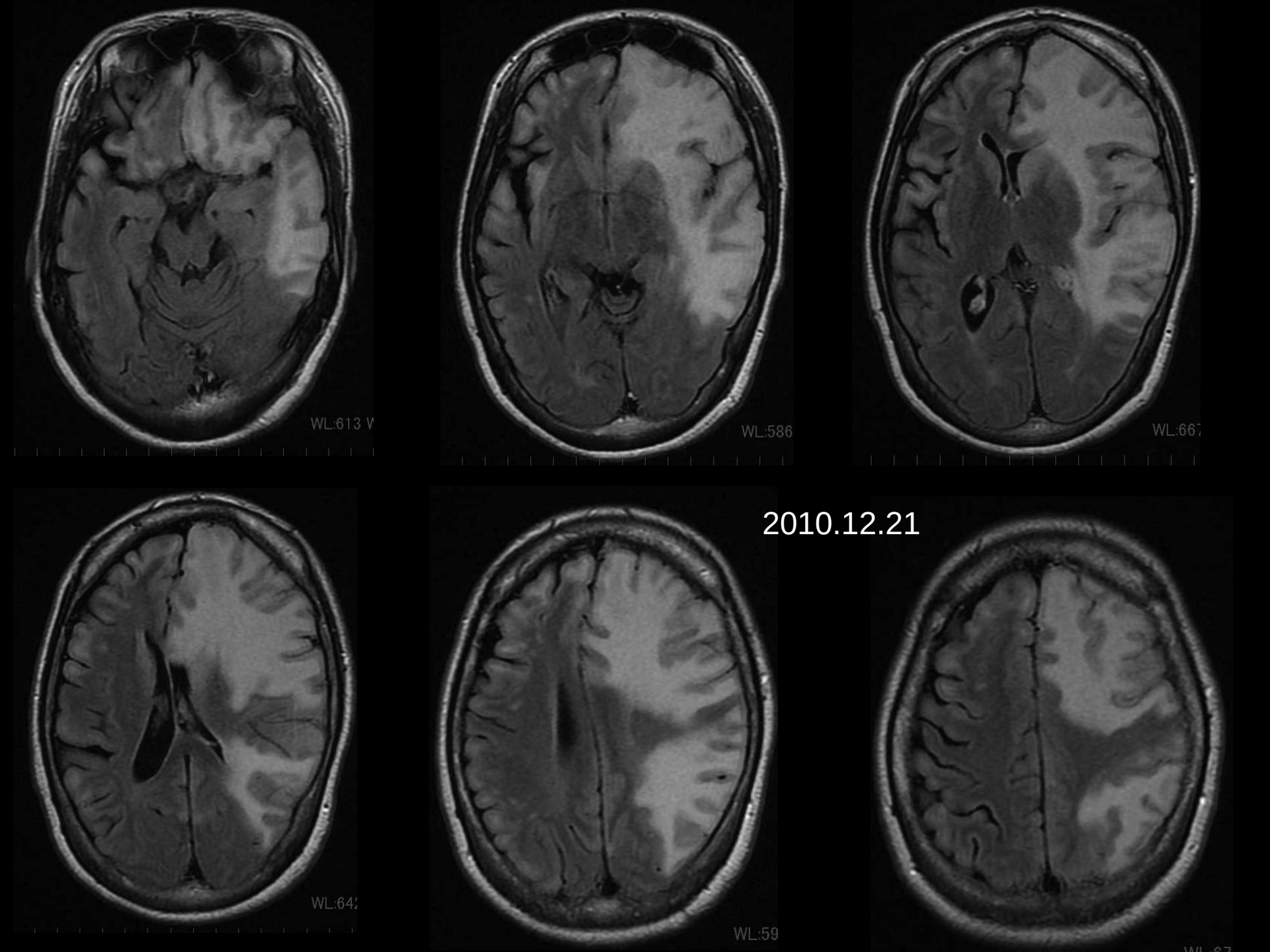

2008

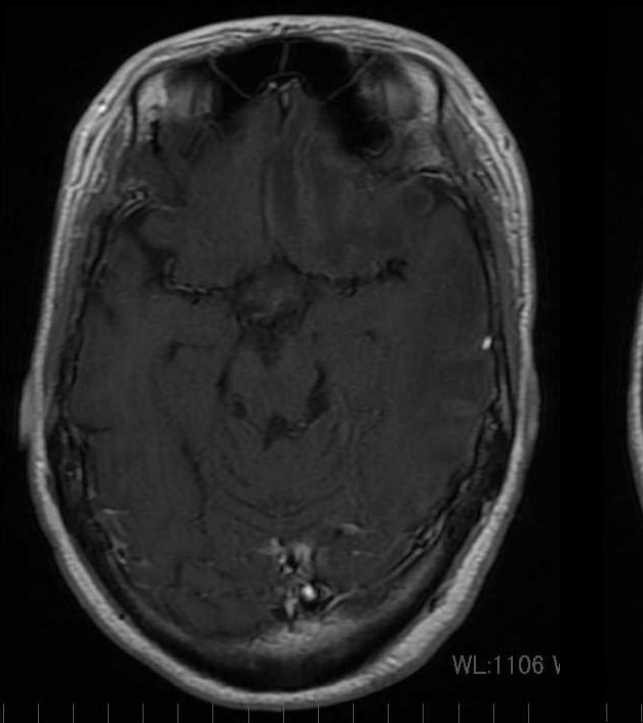

2009

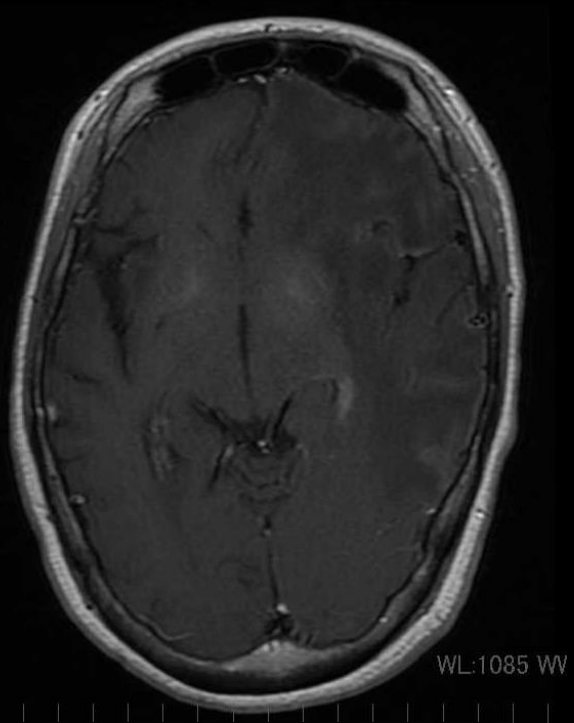

2010.11.9

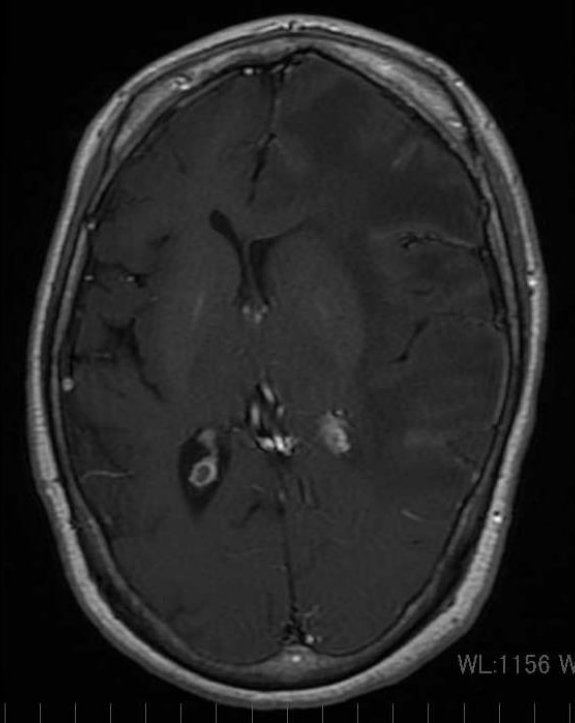
発熱、けいれん，意識障害の遷延

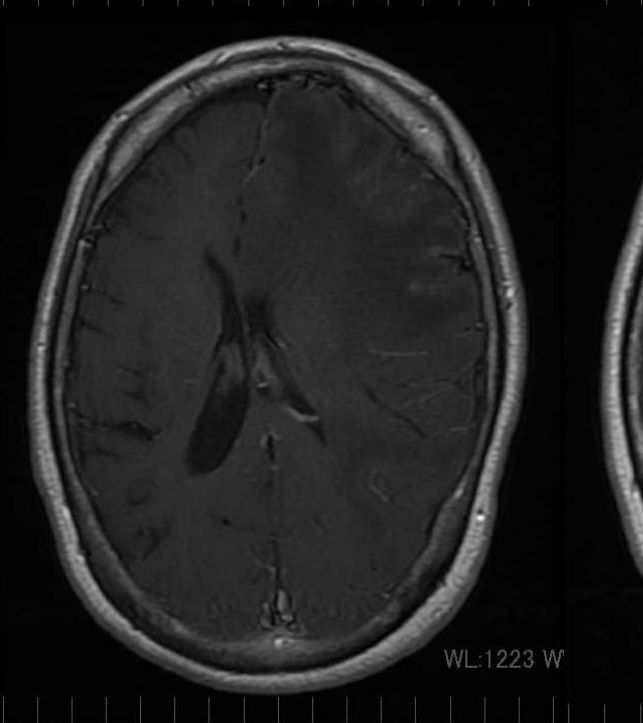
神経内科に入院

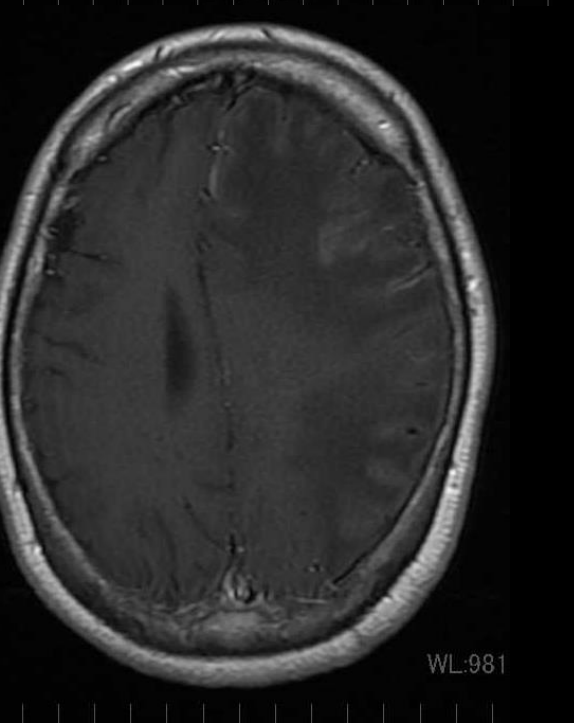

2010.12.21

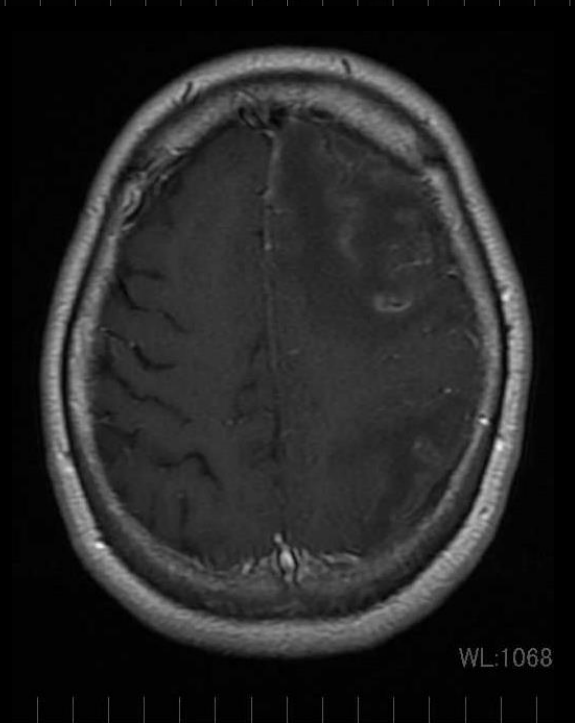

WL:1106 W

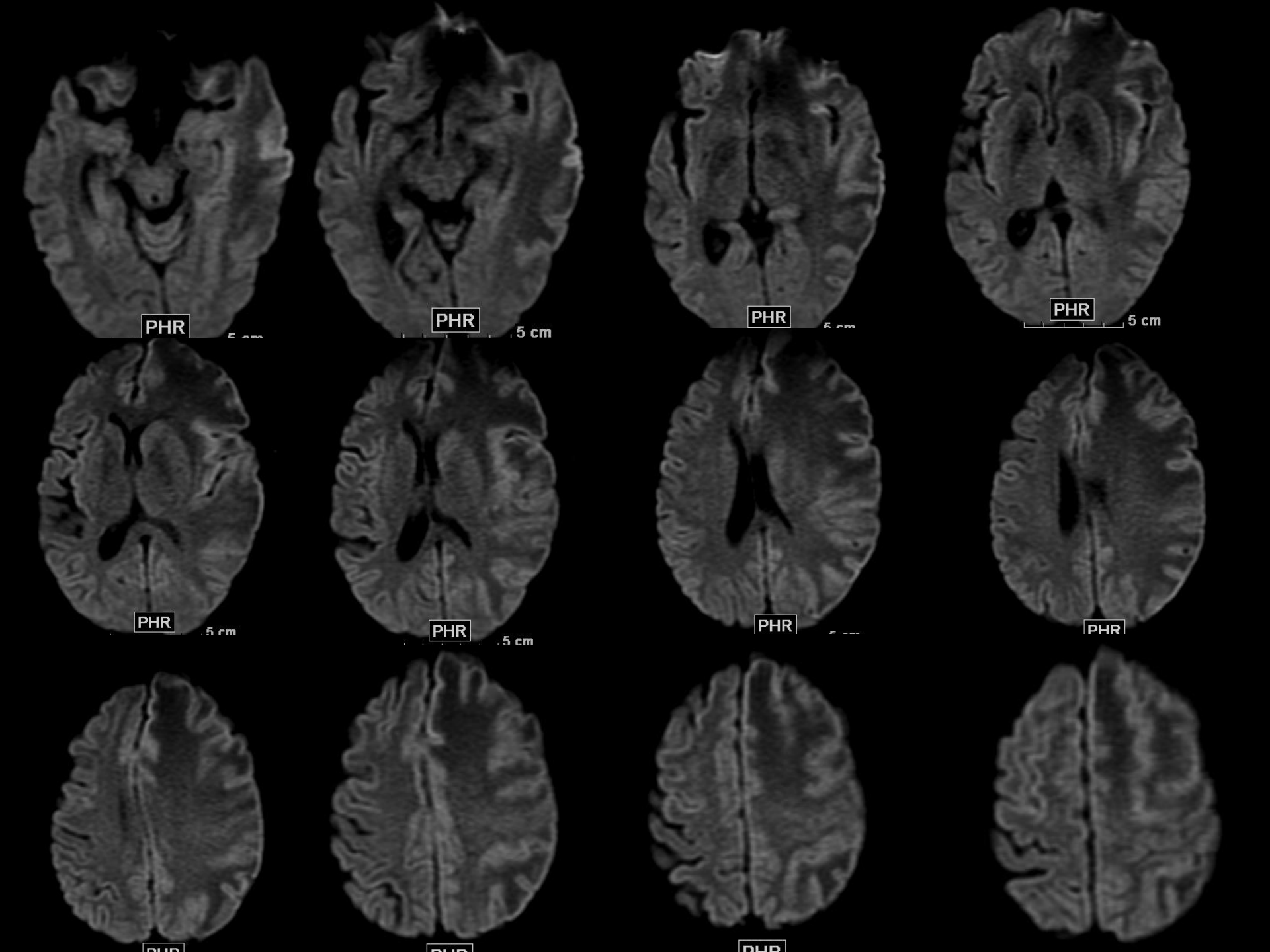

WL:1085 WW


WL:1156 WW


WL:1223 W


WL:981


WL:1068


PHR
PHR
5 cm
PHR
PHR
5 cm
PHR
PHR
5 cm
PHR
PHR
PHR
PHR

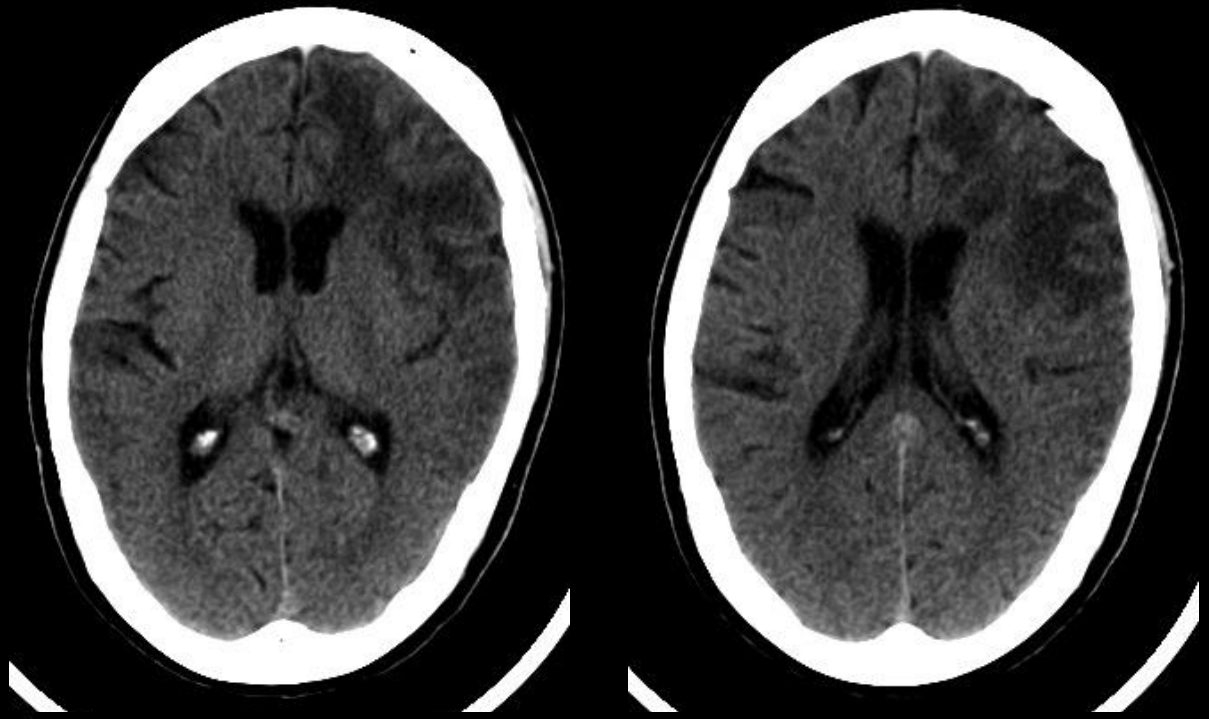
Edematous change with reactive gliosis

腫瘍、脱髄、血管炎の所見なし

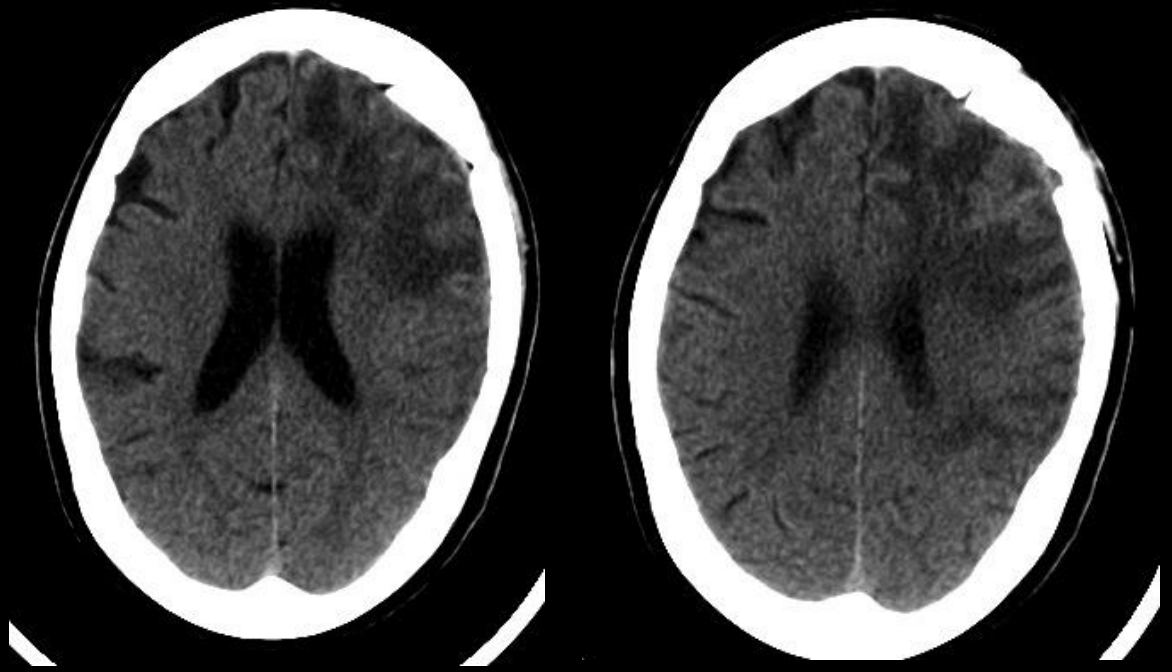
毛細血管の増生

高度のvasogenic edemaと astrogliosis

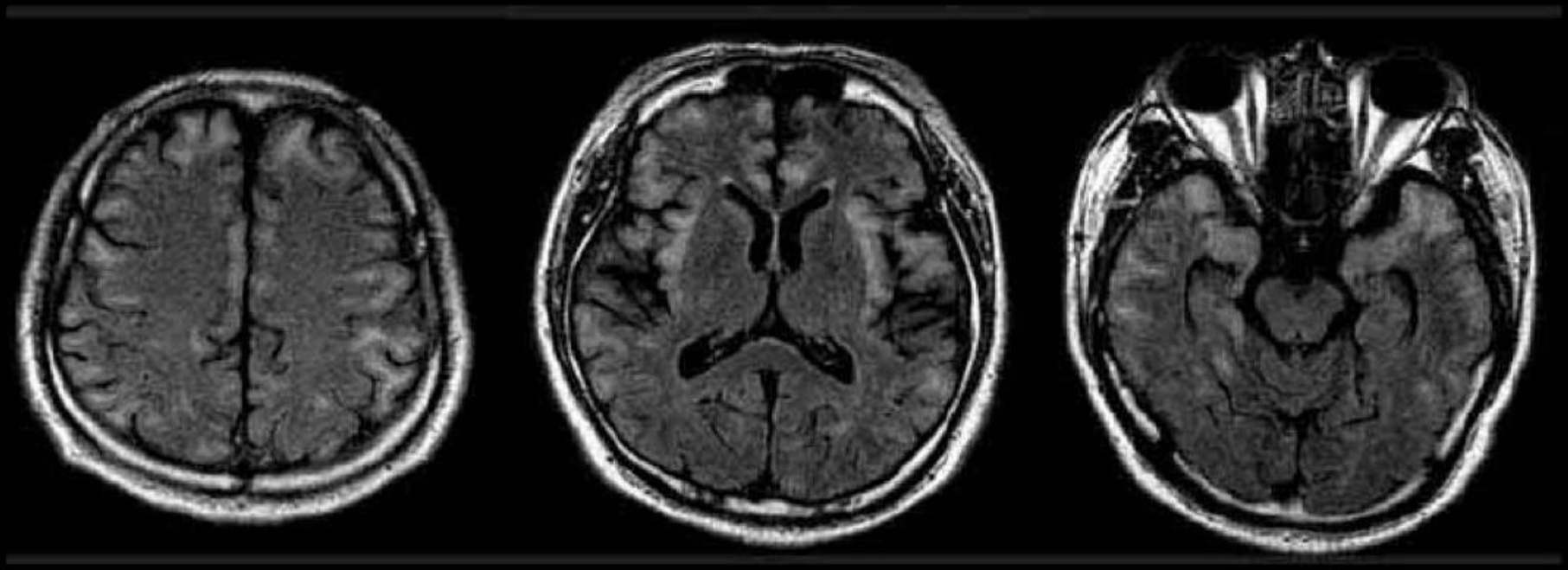
12．27
生検
Steroid使用なし
減圧剤のみ



2011.1.24



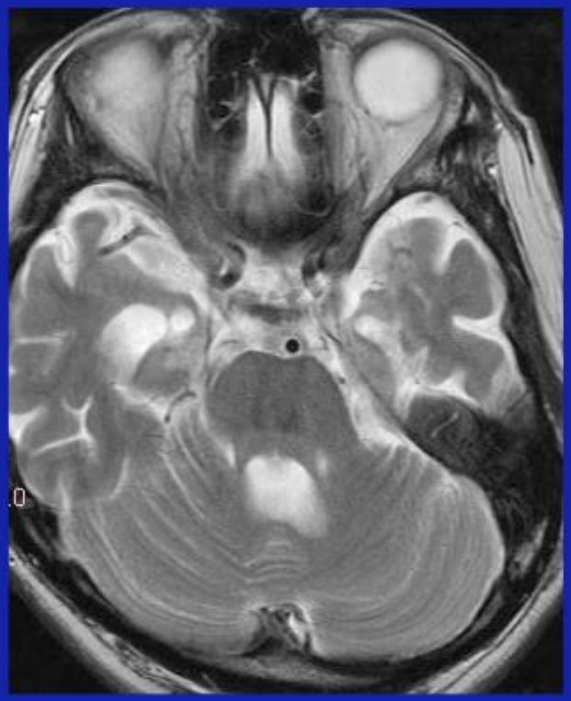
初回頭部MRI (2001. 6.14)

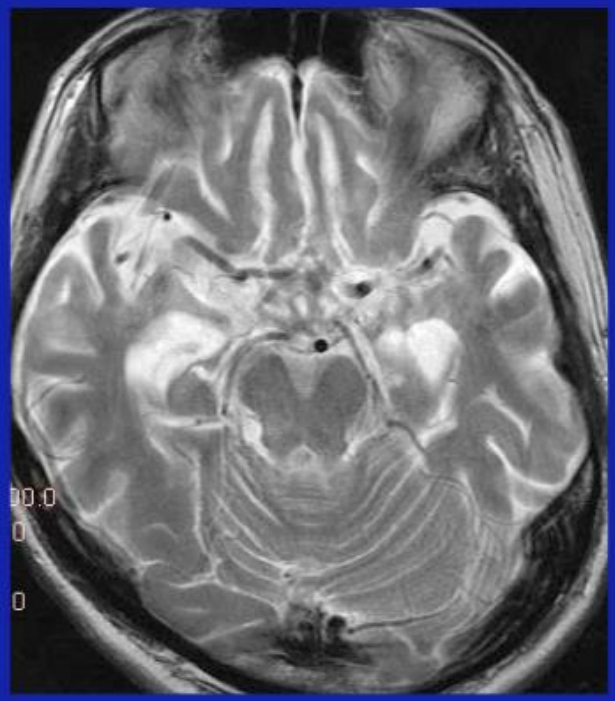


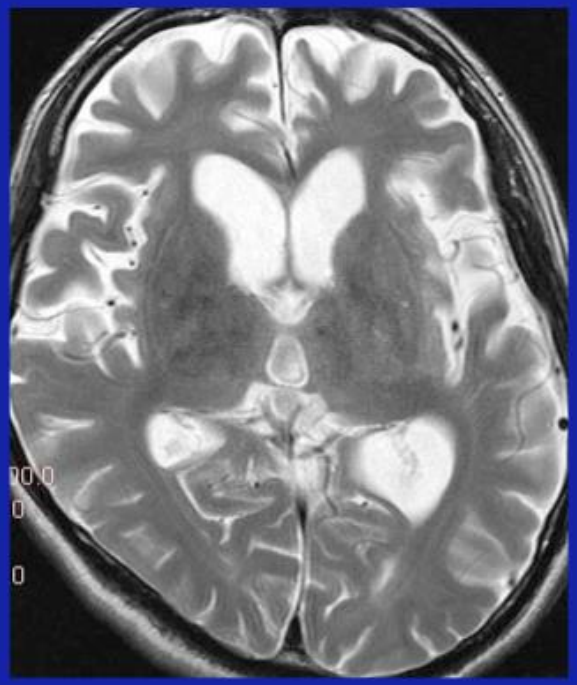
FLAIR 横断像

2002 NRWS 神経梅毒

初診時　MRI　T2WI

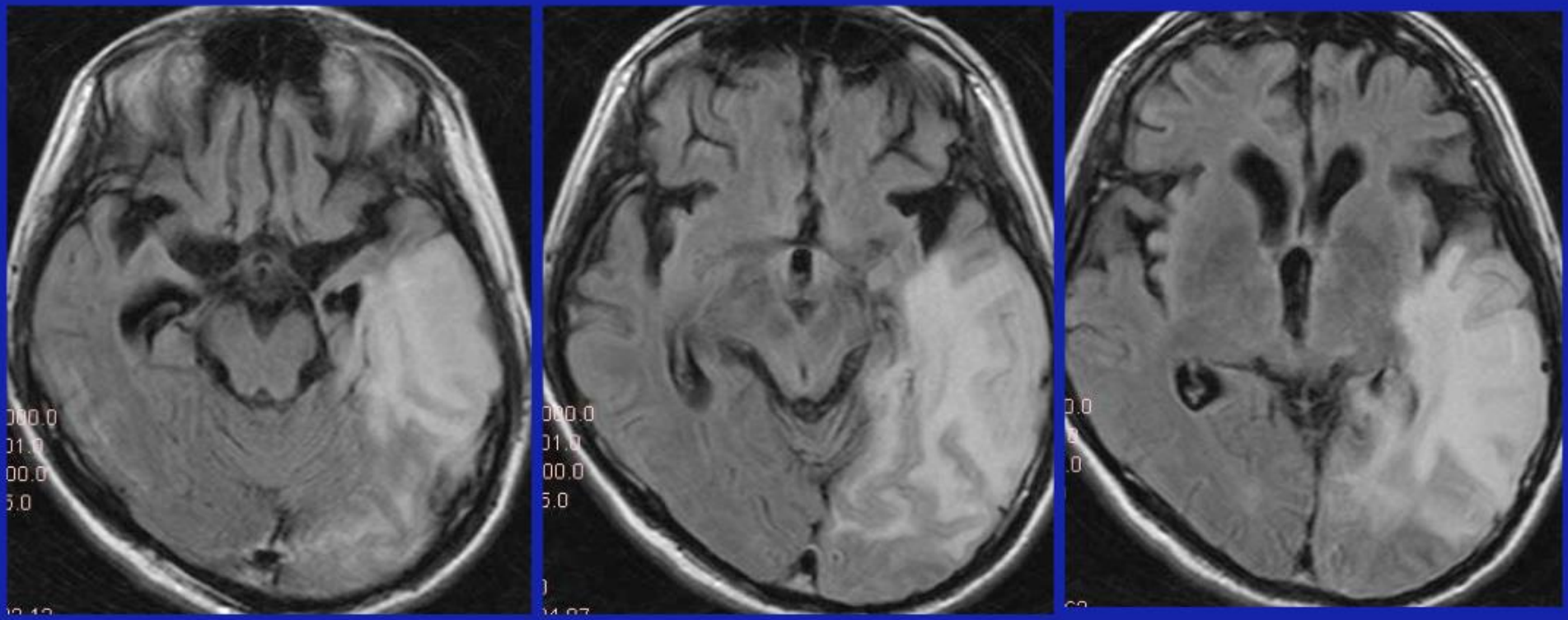






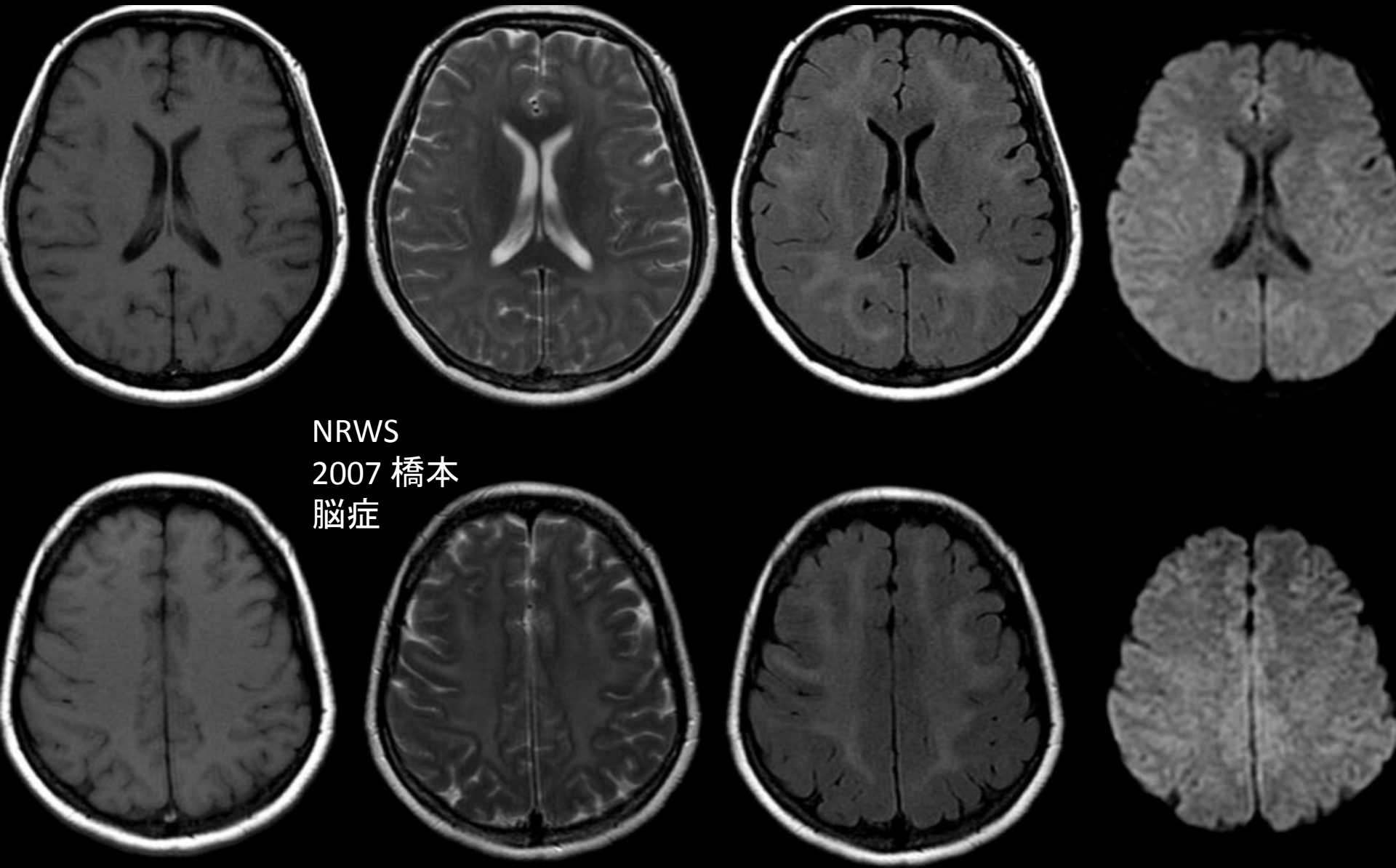
NRWS 2008　40歳　男性

1カ月後意識レベル低下時
T2強調画像



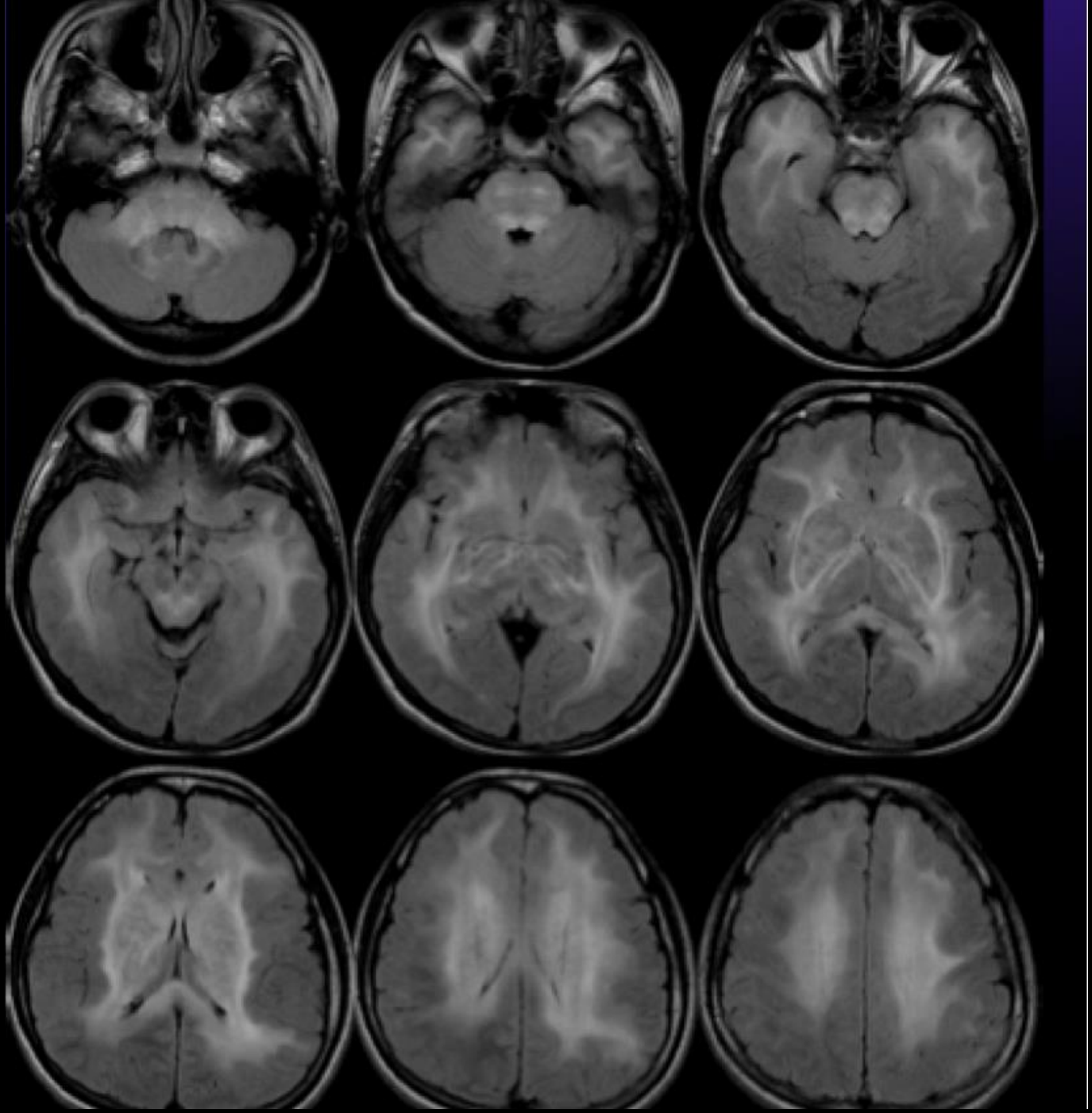
神経梅毒

唯一、橋本病がkey?


NRWS
2007 橋本
脳症

NRWS 2012
37歳　女性

橋本脳症



橋本脳炎/脳症について
（SREAT: Steroid-Responsive Encephalopathy with Autoimmune Thyroiditis)

疾患概念：橋本甲状腺炎（自己免疫性慢性甲状腺炎）の患者に生じる精神症状や意識障害を主とする脳炎/脳症で、抗甲状腺抗体による自己免疫学的機序が発症の原因といわれる。
女性や高齢者に多い傾向がある。

病理学的特徴：剖検で脳動静脈や毛細血管、髄膜などの周囲（特に静脈周囲を中心）にリンパ球やマクロファージなどの炎症細胞浸潤が認められるとの報告があり、何らかの自己免疫学的機序による血管炎が原因と考えられているが諸説ある。

臨床症状・特徴：意識障害が最多。ときに行動異常や認知障害、うつ・興奮状態などの精神症状や睡眠障害、痙攣、ミオクローヌスや振戦、失語、錐体路症状などを来す。
※ 臨床症状や経過から、Creutzfeld-Jakob病と誤診されることが多い。
※ Basedou病と合併する例がある。
※ ステロイドに対する反応が良好である。

橋本脳症？

今回出題の4-6に、似ているのが気になるが