

# 2014 34<sup>th</sup> NeuroRadiology WorkShop

## Case 3-2

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In Kyoto

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## Case 51-years-old female

- Chief Complaint: **Dysphasia** (ことばが言えない 意味のないことばをいう)
- History of present illness: On 18 March 20XX, she noticed **difficulties in speech** and in typing emails in which contents were complicated. After 10 days, **dysphasia** was **progressed** and she was admitted in our hospital.
- Since two years, **gait ataxia** has been occasionally recognized
- History of **diabetes mellitus Type I** at pregnancy (25 yrs. ago): She had been consulted to our hospital and treated.
- Long history of **hearing impairment** : Onset unknown

## Physical findings

### Aphasia

Cranial nerves: Nothing particular, except sensory hearing loss

Motor system: No weakness, No pathological reflex

Coordination: NFN test- Heel-Knee -, Diadochkinesis-

Thyroid mass palpable

Emaciation **36kg weight** 156cm height

Mental status: normal

## Laboratory tests

CSF: cell 2/3 protein ↑ sugar ↑ cell: class II  
inflammatory changes

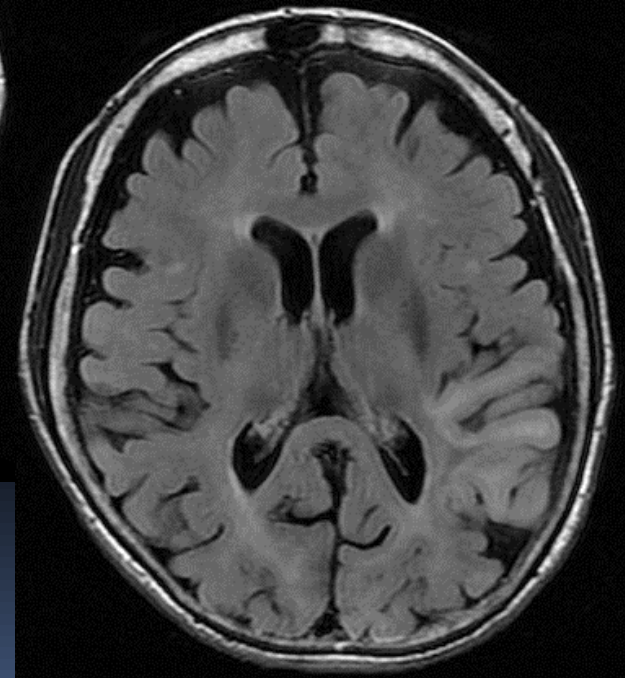
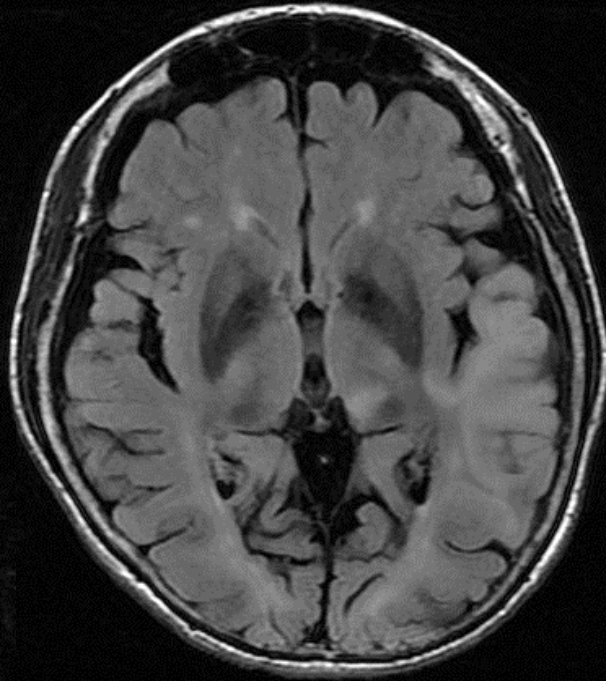
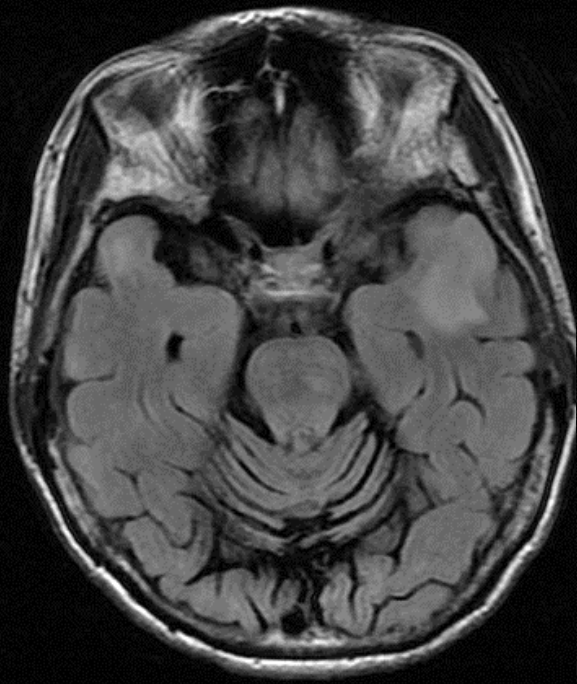
CSF Virus HSV, VZV, CMV, EBV, Mumps: negative

Autoimmune antigens: negative

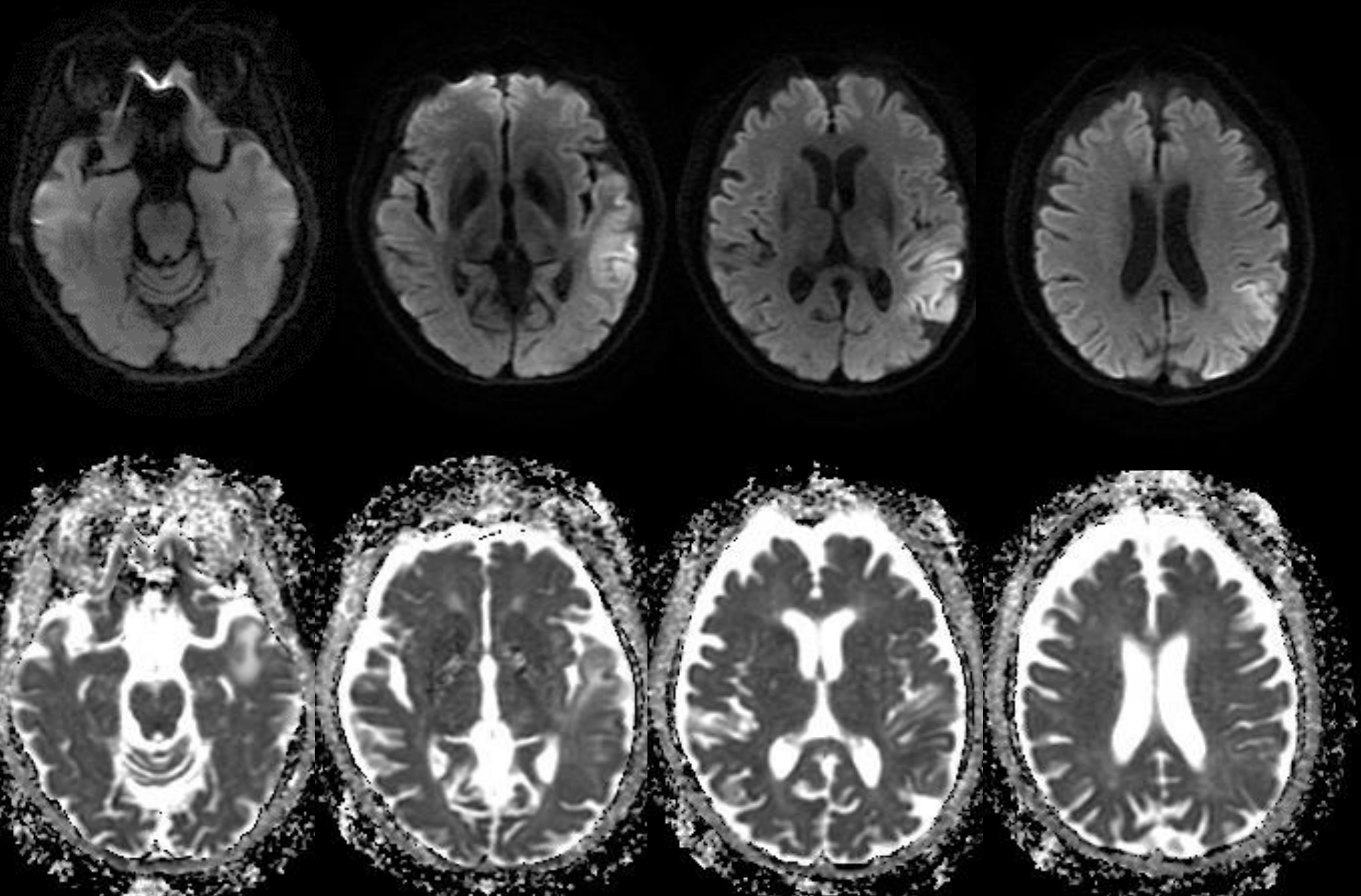
RF, S.IL-2R, antiDNA antiTGA mild ↑

Tumor marker: NSE, CA125, CEA, CA19-9 negative

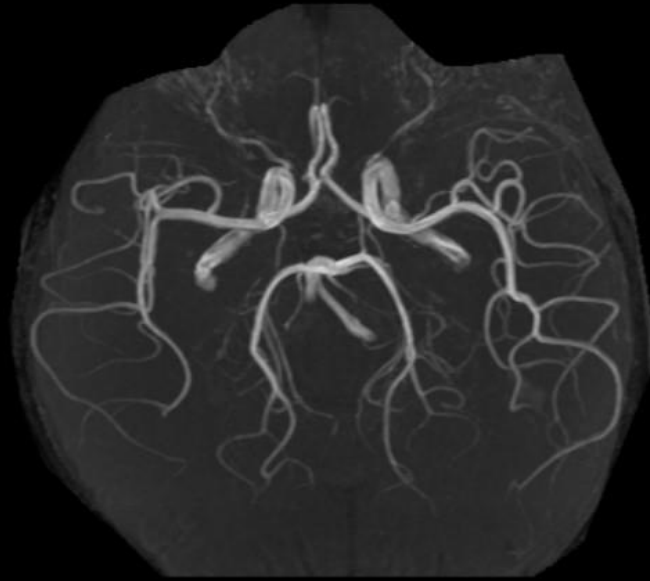
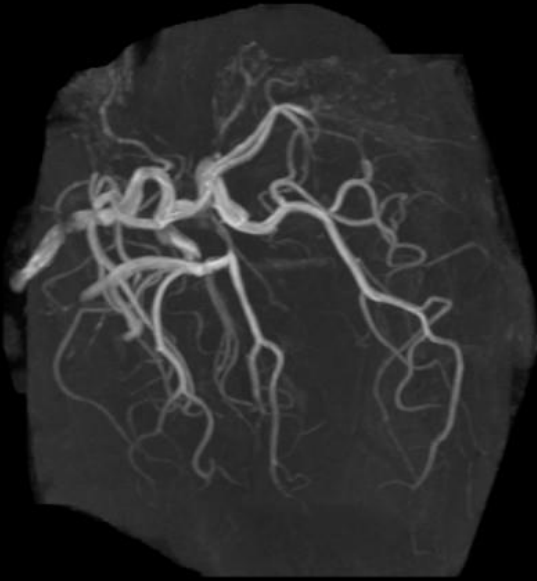
Day of admission



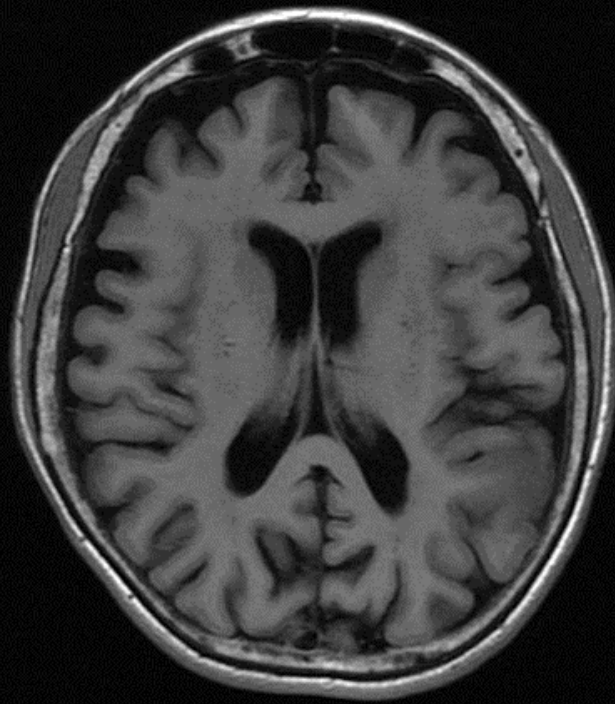
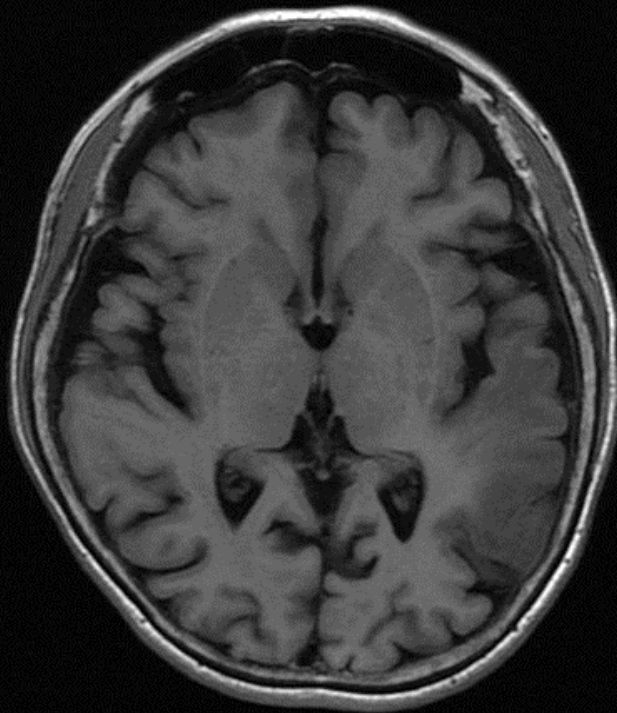
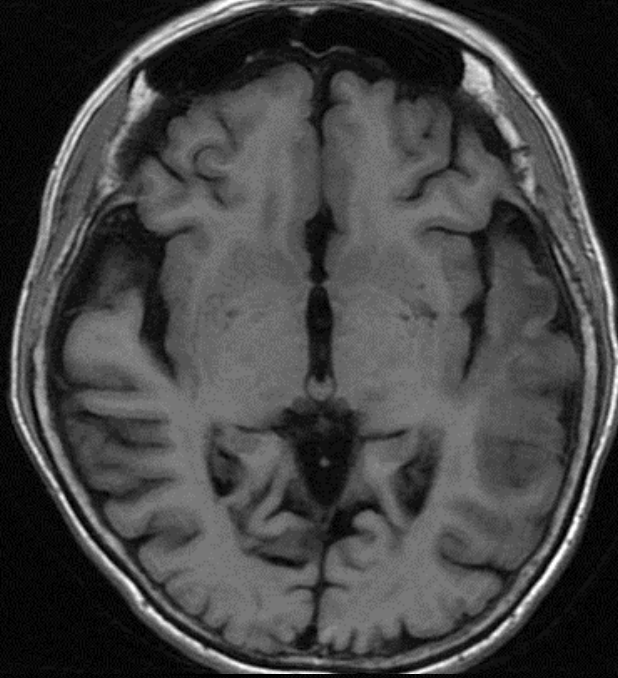
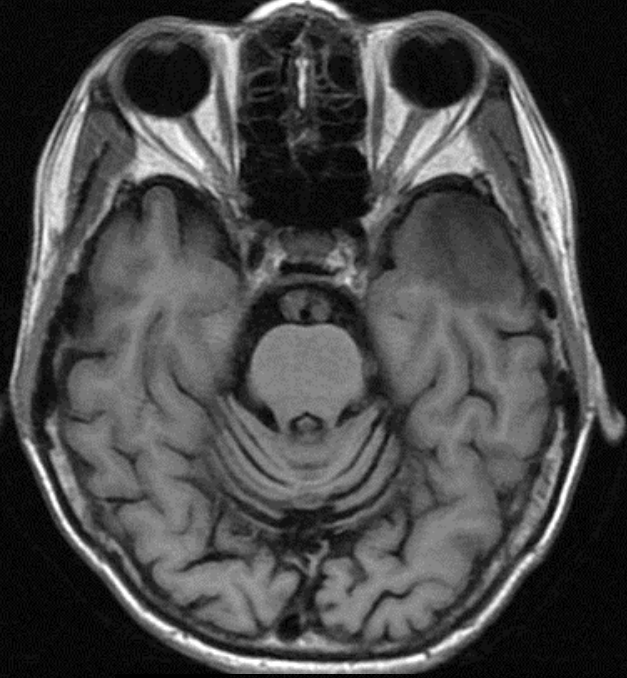
Day of admission



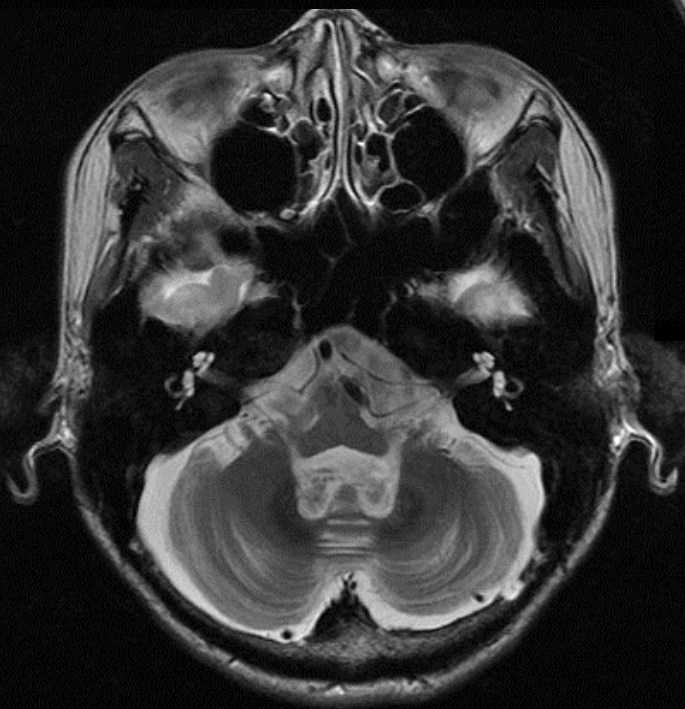
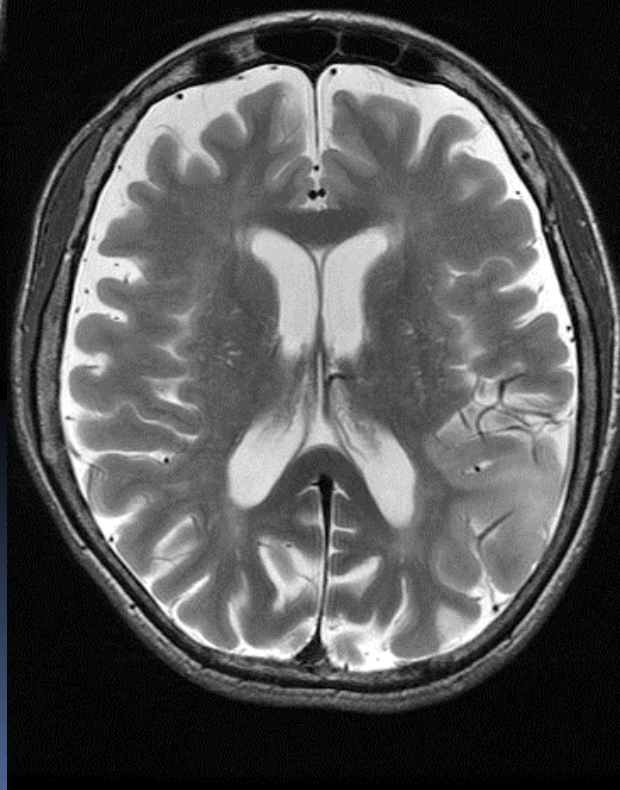
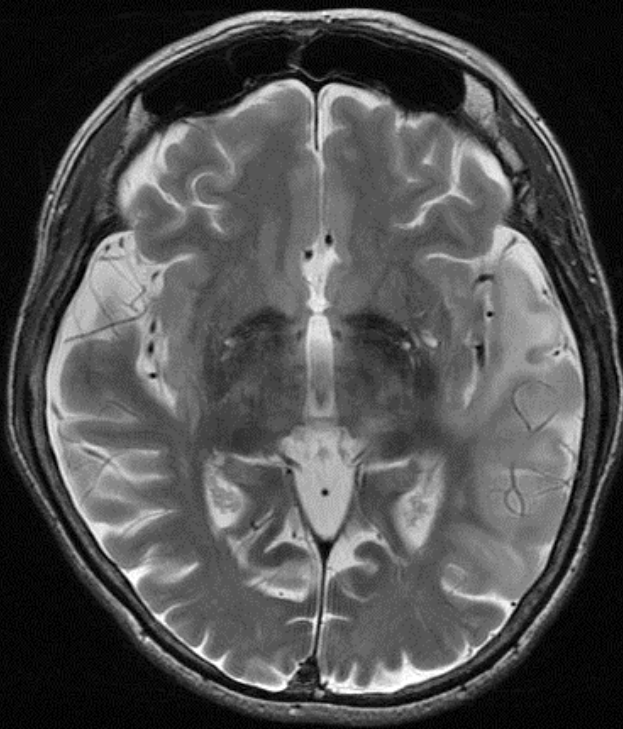
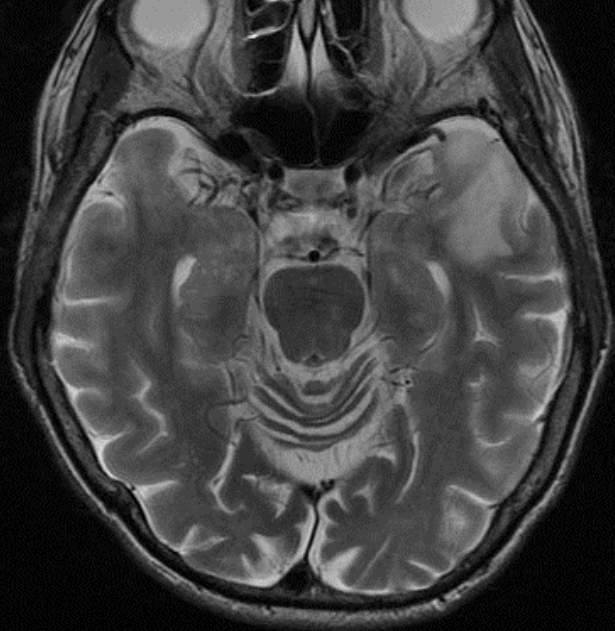
Day of admission



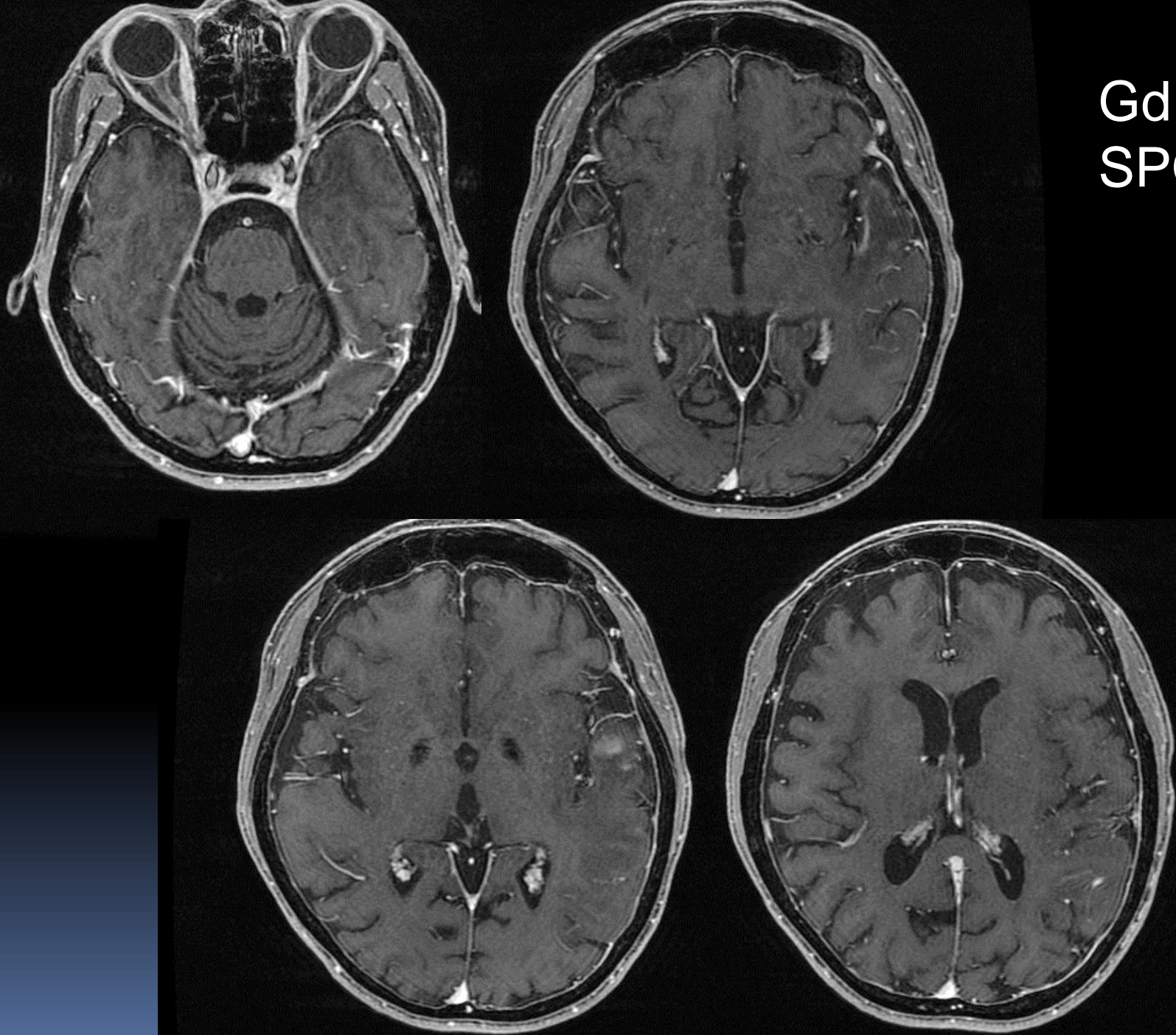
2<sup>nd</sup> day  
T1WI



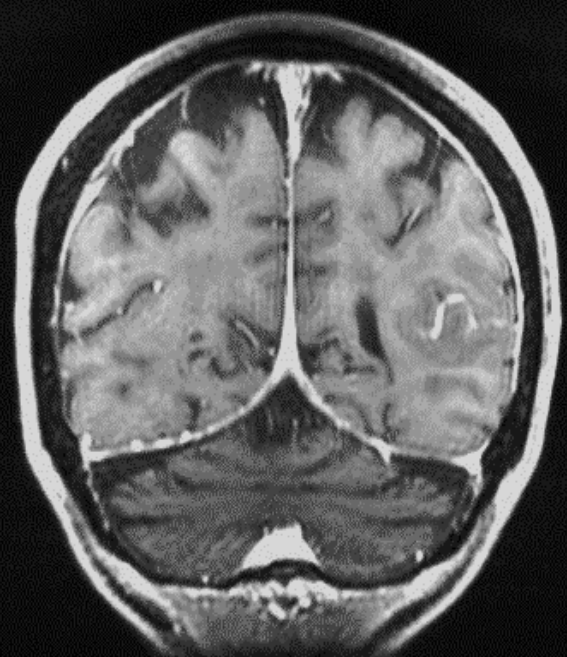
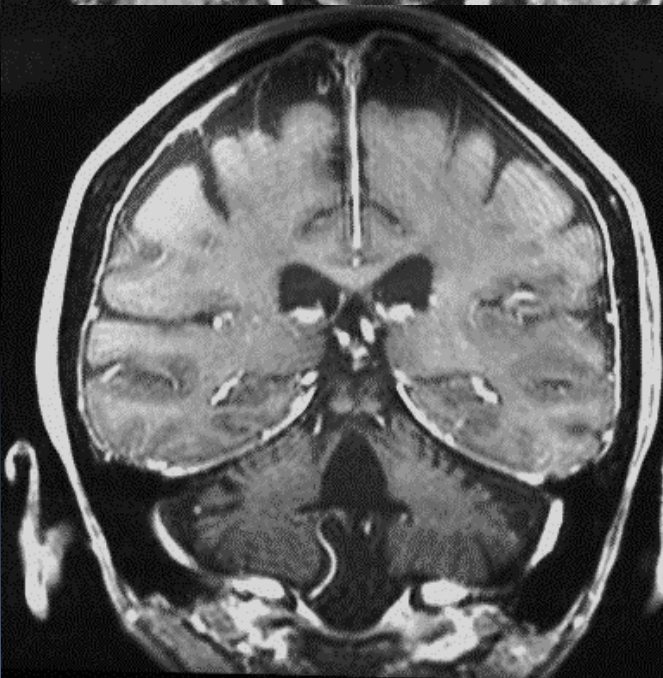
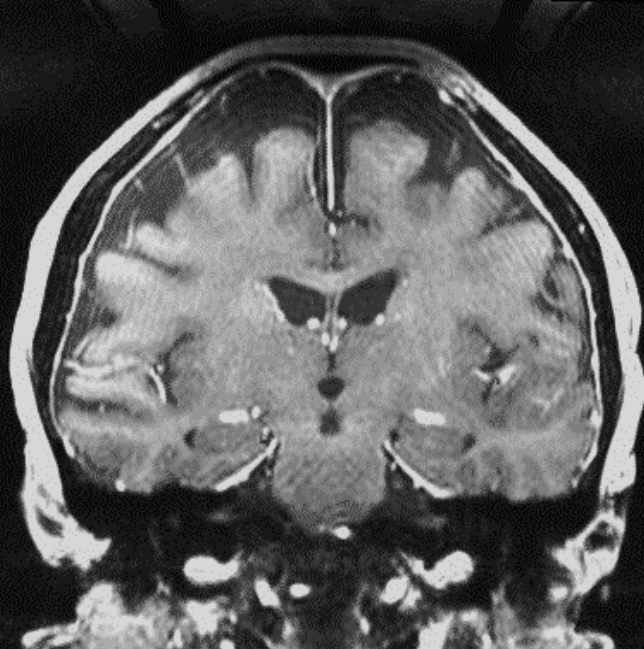
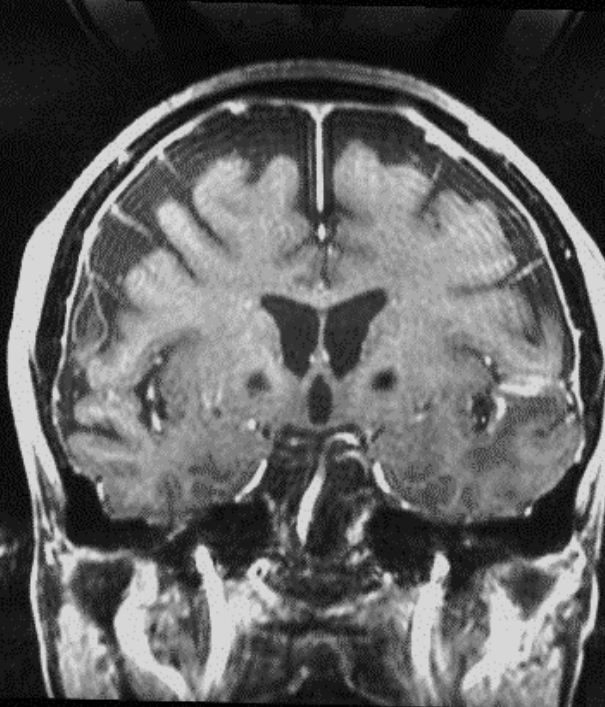
T2WI



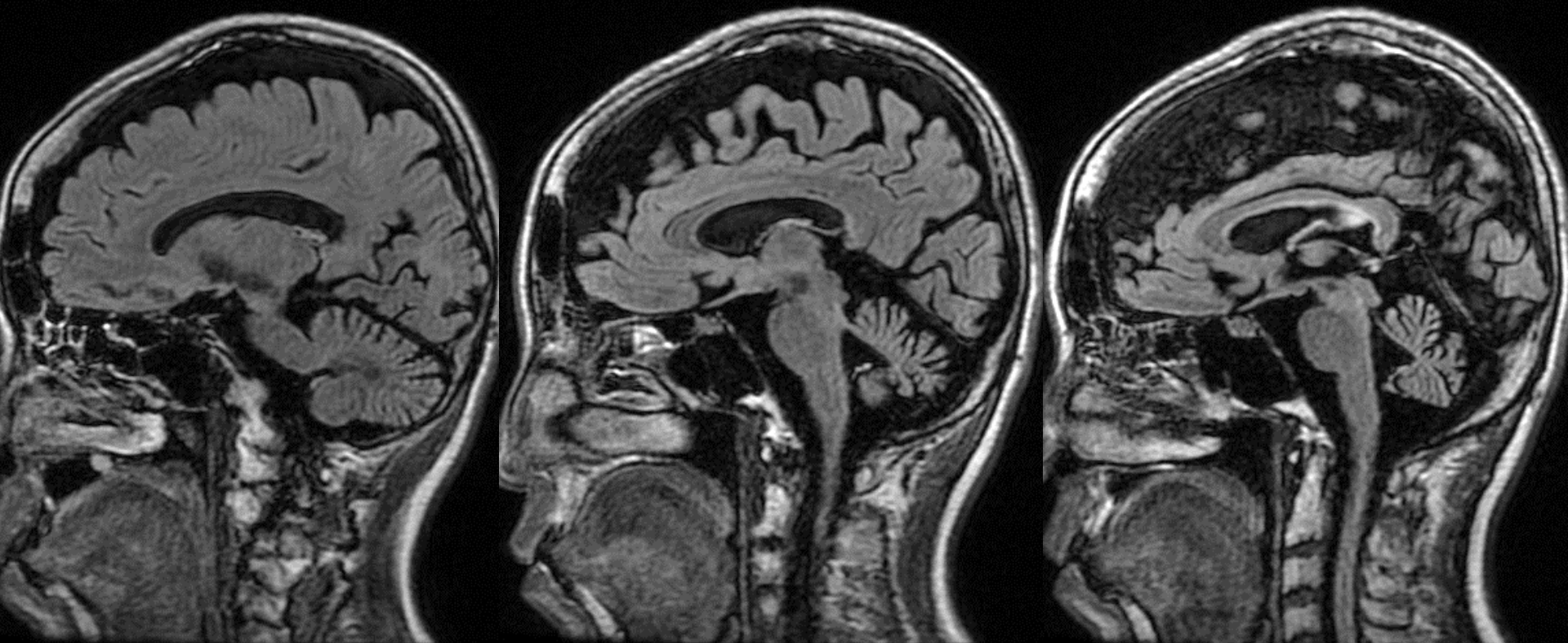
Gd T1WI  
SPGR



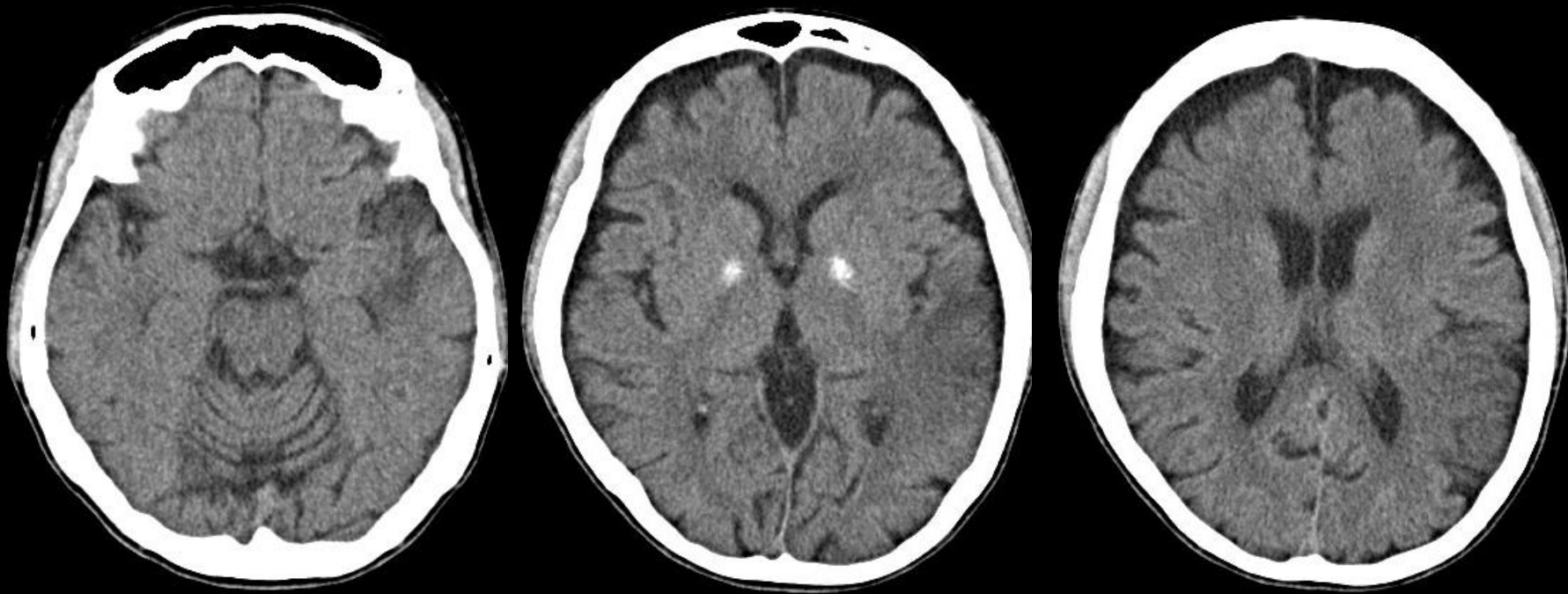
Gd T1WI  
SPGR



FLAIR



CT





Diagnosis, please

# MR findings

- Extensive hyperintensity in left temporal lobe ~ parietal lobe, small lesion in right temporal lobe
- gray matter and white matter
- DWI hyperintense ADC high >> low
- MRA: left MCA not occluded, rather dilated
- Partial CE
- Marked diffuse atrophy of cerebellum  
including middle cerebellar peduncles

## Additional CT findings

Calcification of globus pallidus

# Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like Episode MELAS

- **mt DNA mutation 3243A → G** was found (at Tokyo Univ.)
- Muscle biopsy (biceps brachii muscle):
  - **Ragged red fiber**
  - **Strongly SDH-reactive blood vessel (SSV)** by **SDH** (succinate dehydrogenase) stain
  - Some fibers **had no cytochrome c oxidase (CCO)** activity
- **Serum lactic acid 23.0** ↑ (17.0-4.2) pyruvic acid 1.0 (0.9-0.3)

No dysfunction of cardiac muscle

At 15 days of admission aphasia was improved

Thyroid mass ; papillary cancer however no relation to this disease

Her 25-years-old daughter has DM and mental retardation

# MELAS

- Mitochondria disease, Lactic acid ↑, stroke like episode
- 症状:頭痛、痙攣が最も common
- Age: 20歳以下が80%
- 0-1 y.o.1%, 1-5y.o.10%, 5-10y.o.37%, 10-15y.o.21%, up to 15y.o.31%
- mt DNA mutation 3243A → G 置換80%

## MRI and CT findings

- 基底核石灰化
- T2WI, FLAIR: 側頭葉 > 後頭葉, 頭頂葉 hyperintensity, 血管支配領域に一致しない
- 皮質(灰白質)を侵す (腫脹)
- 皮質化浮腫: 進展 あるいは可逆性に消退 数日
- DWI: 高信号 ADC :↓ (急性期) or ↑
- 造影: 脳回の増強効果 (BBB 破綻による)
- MRS: lactate ↑ NAA ↓
- 限局性の血流増加 (SPECT): 一か月間 ⇒ その後血流低下; MRA・灌流
- 亜急性期: 罹患部の皮質層状壊死 点状出血; T1短縮
- 長い経過例 小脳萎縮

*Ito H, et al: Brain Dev. 2011;33:283-8.*

*Iizuka T, et al: Neurology 2002;59:816-24.  
Rosen L, et al: Neuroradiology 1990;32:168-171*

# MELAS 発症50歳以上.: 稀

- ミトコンドリアDNAの転座の割合が低い
- のではないか
- 転座も3243A → G以外のもみられる

Age at diagnosis (years)	Sex	Clinical features	Neuroimaging findings	Mutation	Reference
50	M	Headaches, seizures, psychiatric symptoms, diabetes, deafness, normal serum lactate	Right and left temporal lesions	m.3243A>G	Kisanuki <i>et al</i> 2006 <sup>14</sup>
53	F	Seizures, stroke-like episodes, lactic acidosis, ragged-red fibres, (and at least one of the two: recurrent headache with vomiting, dementia)	Focal brain lesions (no details given) but no basal ganglia calcification	m.3243A>G	Ciafaloni <i>et al</i> 1992 <sup>31</sup>
55	F	Encephalopathy, seizures, stroke-like episodes, headache, deafness, cognitive decline	Bilateral temporo-parieto-occipital region	m.3243A>G	Sharfstein <i>et al</i> 1999 <sup>17</sup>
56	F	Irritability, aphasia, ataxic gait, hearing deficit, convulsive status epilepticus, elevated serum and CSF lactate, ragged-red fibres	Left temporal lobe	Not specified	Vrettou <i>et al</i> 2013 <sup>32</sup>
59	M	Stroke-like episodes, encephalopathy, seizures, headache, exercise intolerance, fatigue, ragged-red fibres, elevated CSF lactate	Left temporal and later right temporo-parieto-occipital lesion	m.3243A>G	Kimata <i>et al</i> 1998 <sup>16</sup>
66	F	Encephalopathy, proximal myopathy, type 2 diabetes mellitus, sensorineural deafness, paroxysmal atrial fibrillation/supraventricular tachycardia, ischaemic cardiomyopathy, non-specific chronic elevation of alanine transferase	Left periventricular lacunar infarction, prominent calcification of pineal gland and basal ganglia	m.3243A>G	Jones <i>et al</i> 2004 <sup>25</sup>
52	M	Stroke-like episodes, lactic acidosis, deafness, seizures, ragged-red fibres	High signal bilaterally in the occipital regions and right temporo-parietal region.	m.13513G>A	Hanna <i>et al</i> 1998 <sup>33</sup>
61	F	Stroke-like episodes, ragged-red fibres	NA	m.13513G>A	Shanske <i>et al</i> 2008 <sup>34</sup>
55	M	Episodic brain stem dysfunction, headache, severe lactic acidosis	Left cerebellar hemisphere, medulla, pons, and cerebral peduncles	m.13635C>A missense mutation in (ND5) gene	Vanniarajan <i>et al</i> 2006 <sup>1</sup>
54, 59, 64, 69	Not stated	MELAS	Unknown	Unknown	Minamoto <i>et al</i> 1996 <sup>35</sup>
52	M	Stroke-like episodes, seizures, complex partial status epilepticus, raised serum and CSF lactate, ragged-red fibres	Hypodense lesion in right parietal lobe posteriorly	Mutations not found in 3243, 8344, 3271, and 9957 as well as in the entire tRNA leucine (UUR) gene	Leff <i>et al</i> 1998 <sup>36</sup>

CSF, cerebrospinal fluid; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes.

## 高齢の報告例 のまとめ

Aurangzeb S, *et al*:  
*Pract Neurol* 2014;0:105

# MELAS と小脳萎縮

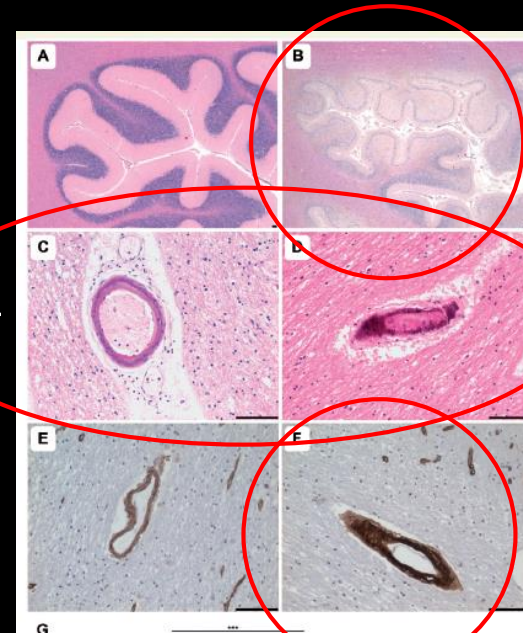
## 微小血管障害

ミトコンドリア症16例 (3243A>G, 8344A>G, POLG) と

## 小脳病理

- 分子層、プルキンエ層、顆粒層(皮質)および皮質下白質の虚血
- 深部白質の微小血管のmineralization
- 微小血管基底膜におけるCollagen IV 沈着  
… 白質、髄膜 齒状核
- BBBの破綻 → 神経変性

*Lax NZ, et al: Brain 2012;135:1736-1750*



## 代謝障害? (とくに尿酸アシドーシス?)

1例 autopsy case:

- 皮質: 顆粒細胞層の変性
- 白質: びまん性の線維化脱髄

*K. Tsuchiya, et al: Acta Neuropathologica 1999;97:520-524*

小脳は長い経過で全体的に萎縮

# 鑑別診断

## 自己免疫介在性脳炎

### とくに抗GAD抗体脳炎 (NRWS2012)

前頭葉・側頭葉～頭頂葉病変、小脳性運動失調、糖尿病 I型

傍腫瘍性小脳変性症(と 傍腫瘍症候群 大脳病変?)

脊髄小脳変性症+ 梗塞(?)

ウイルス性脳炎; ヘルペスなど

## Mitochondrial Spinocerebellar Ataxia and Epilepsy (MSCAE)

2005 Hakonen et al: mitochondrial DNA polymerase gamma(POLG) mutation

10代発症 ミオクローヌスも

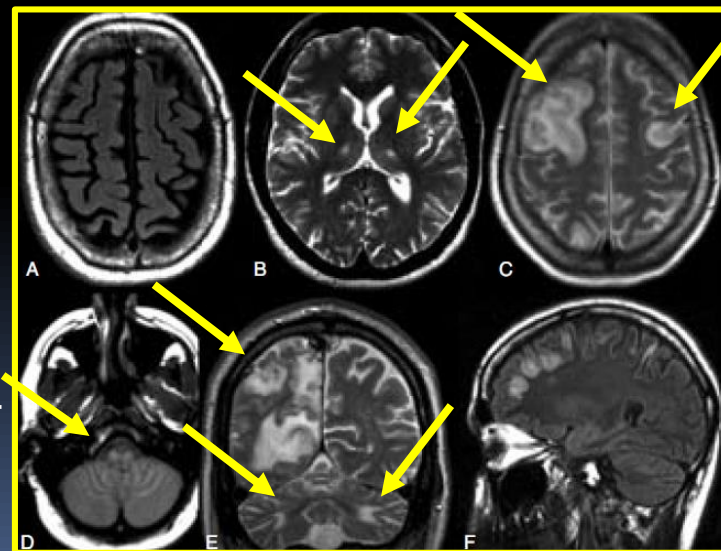
画像的にMELASに類似

しかし基底核・視床病変T2延長,  
前頭葉病変 歯状核萎縮 下オリーブ核も

Tzoulis C , et al: Brain 2012 135; 3627-3634

KSS, MERRF, Leigh encephalopathy

アルコール性小脳変性症 虫部



Tzoulis C : ACNR 9 2009

# Take Home Note

## MELAS

- 50代の比較的高齢の例
- 小脳の萎縮を見た場合にはMEALSも考える

*Additional Reference*

*[http://www.nanbyou.or.jp/upload\\_files/mt\\_handbook.pdf](http://www.nanbyou.or.jp/upload_files/mt_handbook.pdf)*