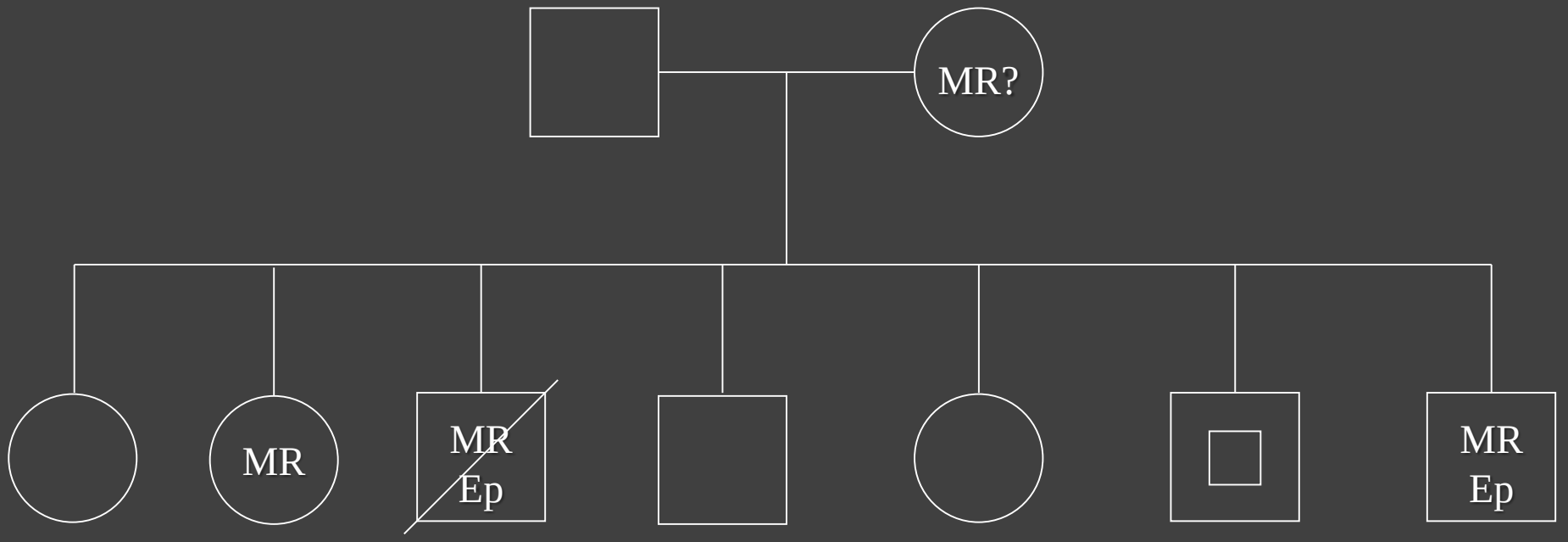
Case

- A 18-year-old male (body height 168cm, body weight 59kg)
- Chief Complaint:
  mental retardation, seizure, and autism.
- Present Status:
  No signs of paralysis
- Past History:
  We can’t find any problem in his unclear perinatal period.
  He frequently had febrile convulsions in his infancy.
  No neonatal screening history
  No immunization history
  Short stature (118cm (<-2SD) at 9 y-o)

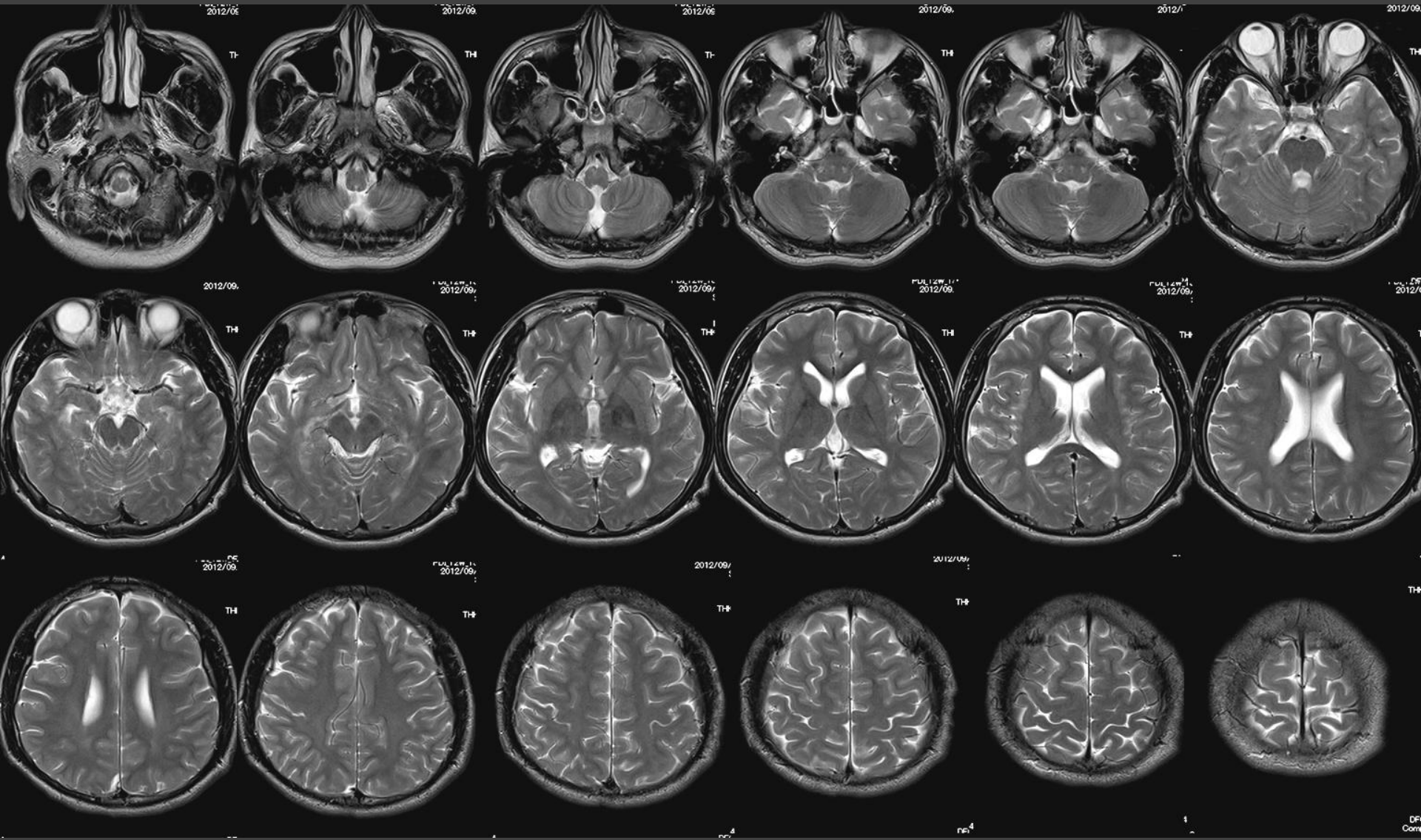
Case

- Family history:

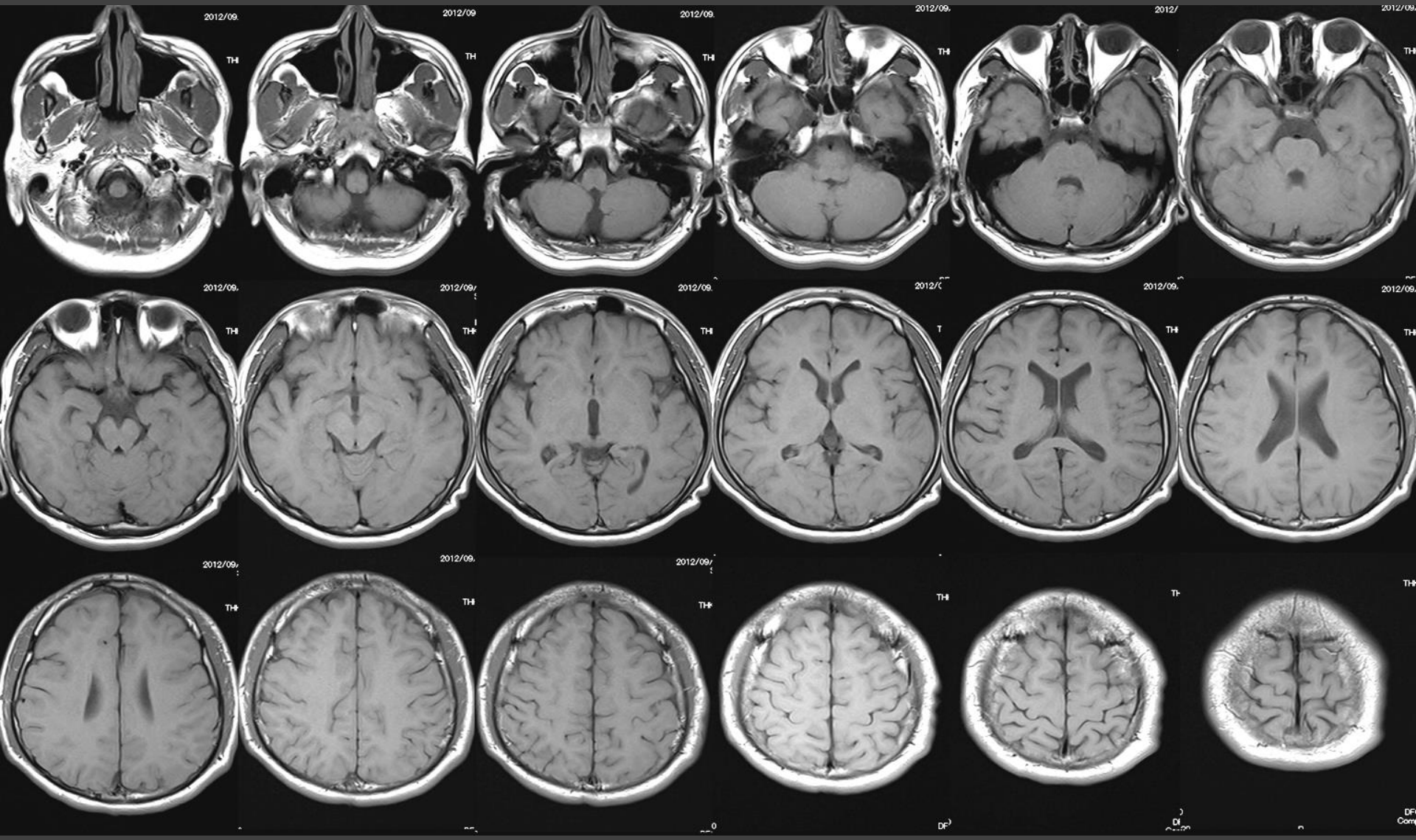


MR: Mental retardation
Ep: Epilepsy

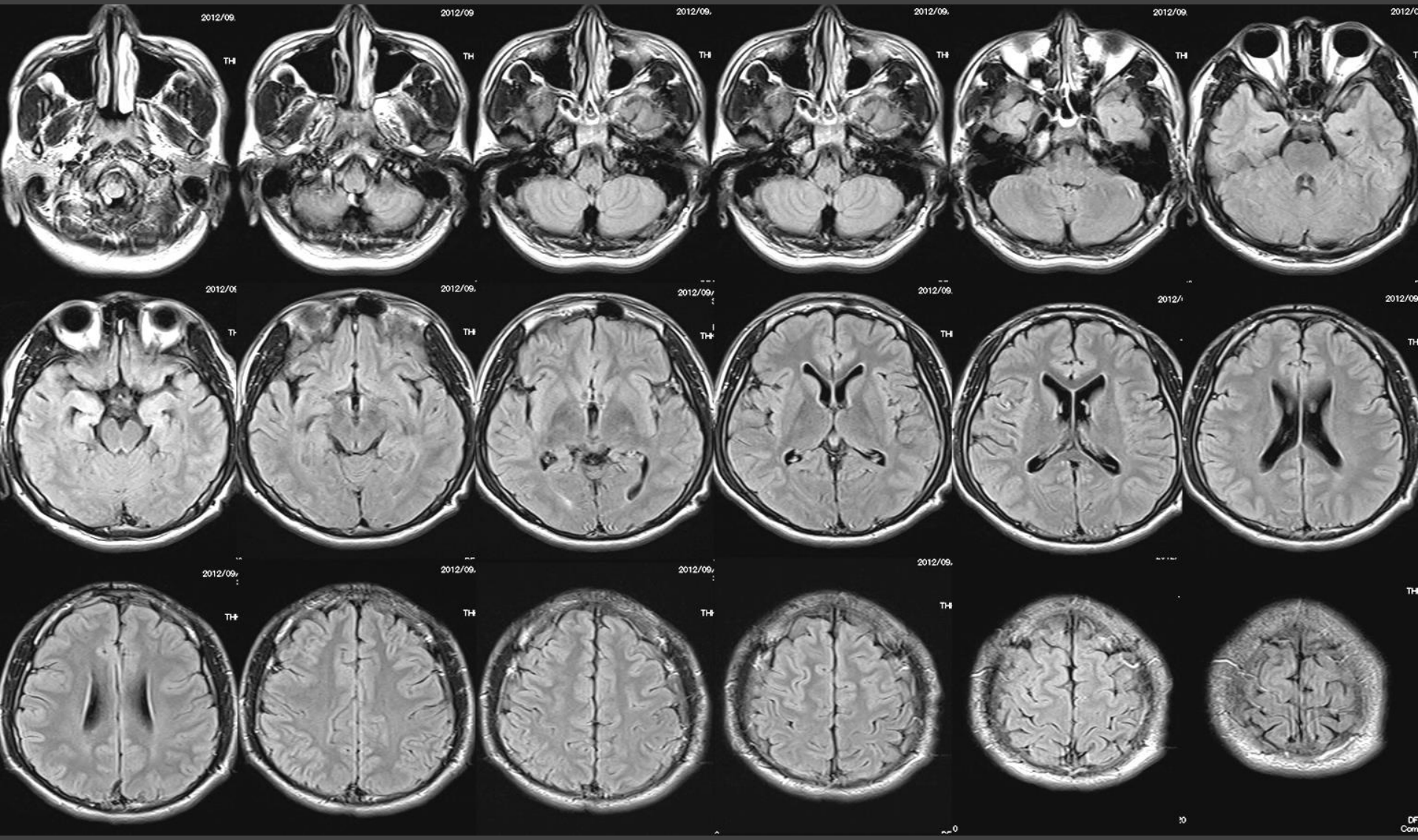
T2WI



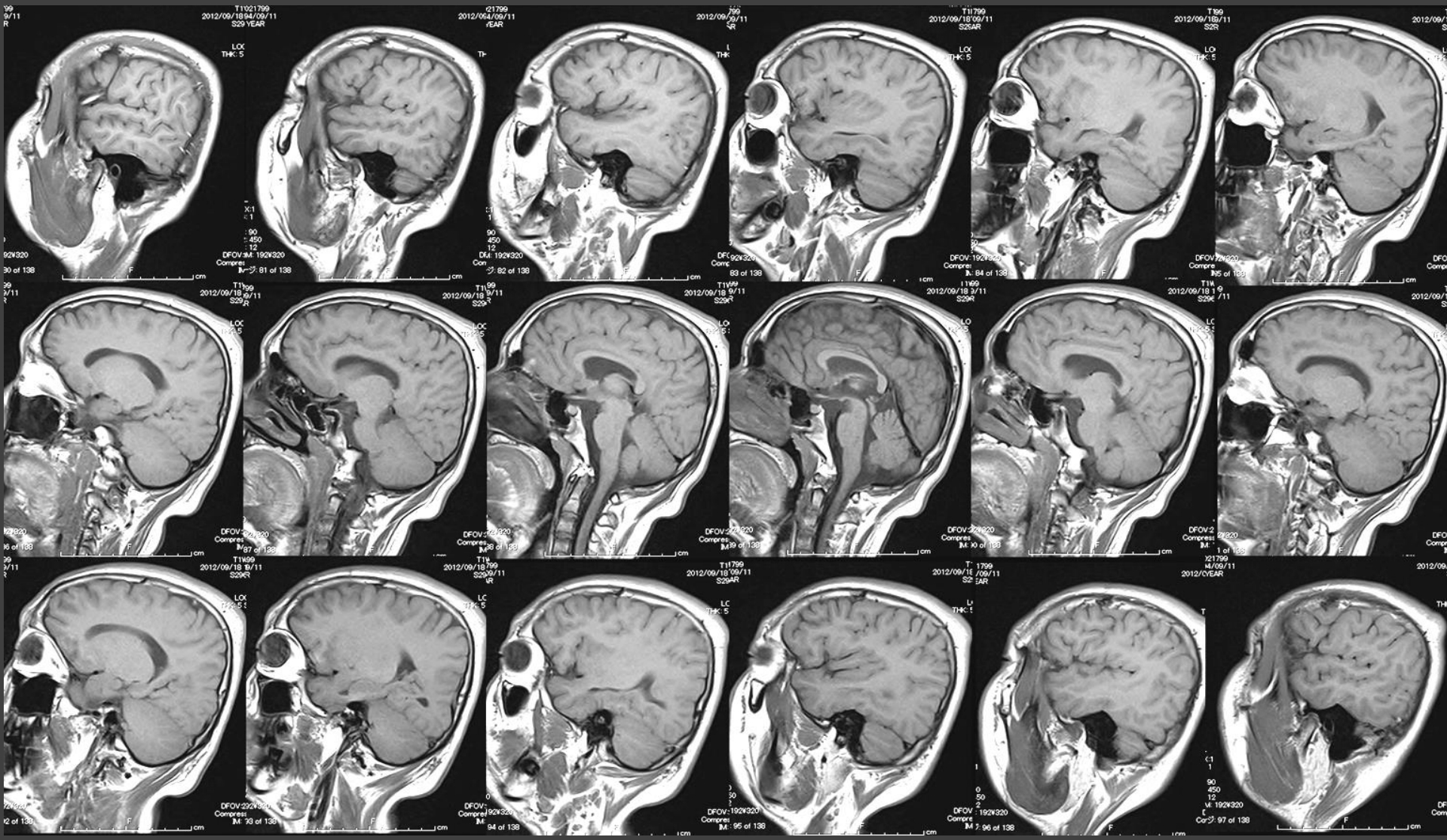
T1WI



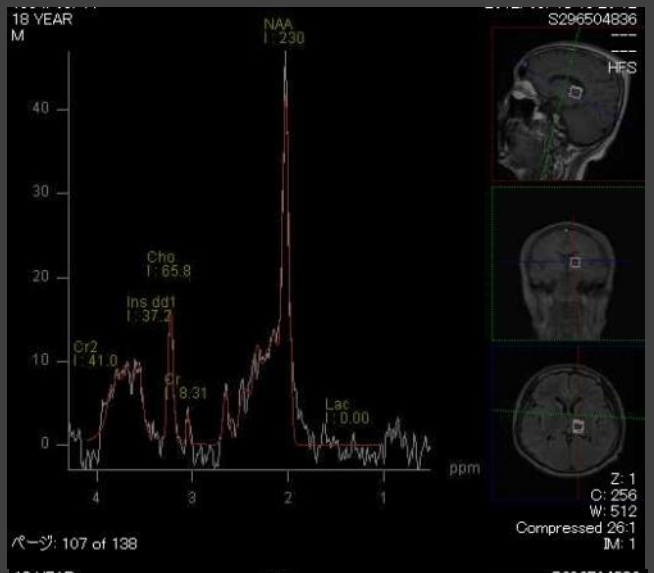
FLAIR

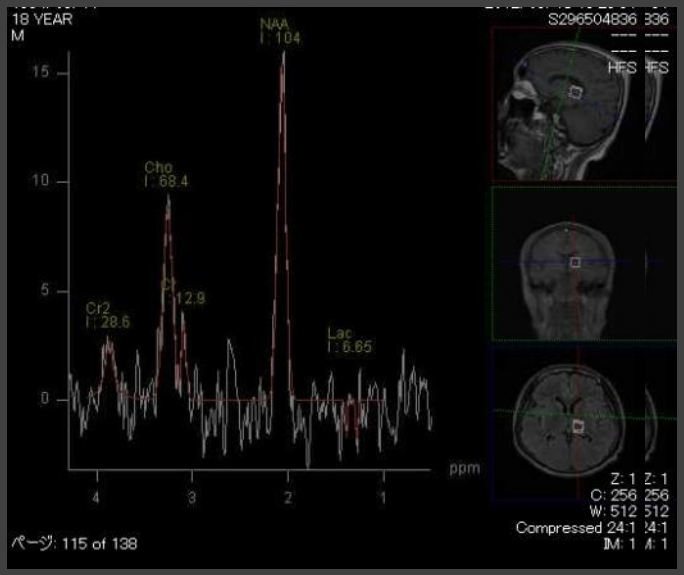


T1WI

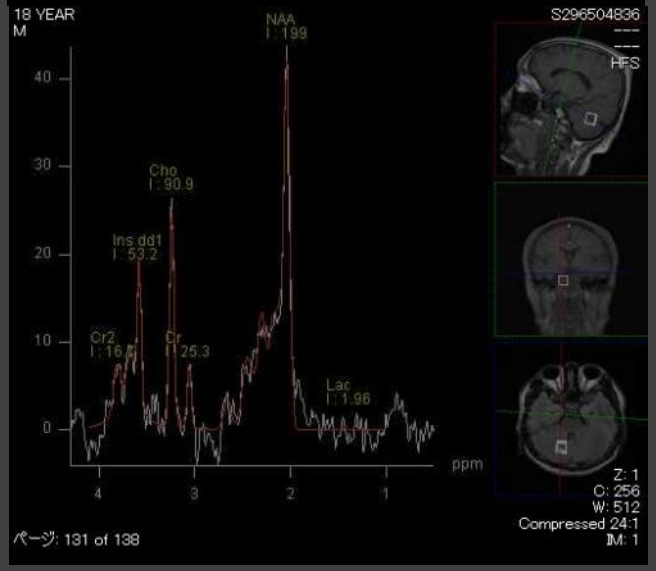


^{1}H-MRS





TE 135ms



TE 30ms

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Examination

- Chromosome (G-banding): 46XY, fragile X chromosome (-)
- Urine creatine (Cr) / Urine creatinine (Crn) ratio (↑)

  437.8(mg/dl) / 189.0(mg/dl)=2.32 (17 year-old)

  ※urine Cr / Crn ratio 0.006-0.65 (10 y-o <)

- ^{1}H-MRS: creatine peak (↓)
- CT1 gene *SLC6A8* abnormality

Diagnosis

X-linked creatine transporter deficiency

His brother case

- A 8-year-old boy
- C.C.: Mental retardation, seizure
- P.S. & P.H.:

  Muscular hypotonia in infancy

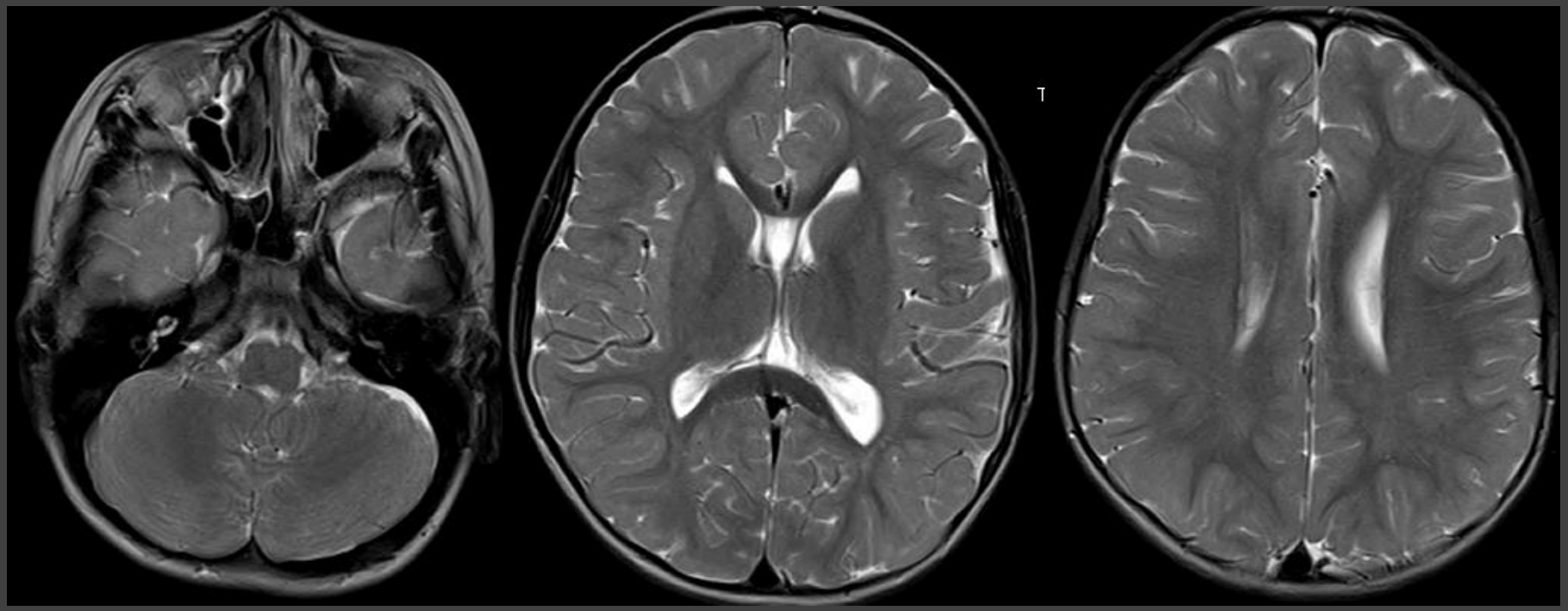
  Developmental delay in childhood

  No paralysis
- Urine Cr / Crn ratio (↑)

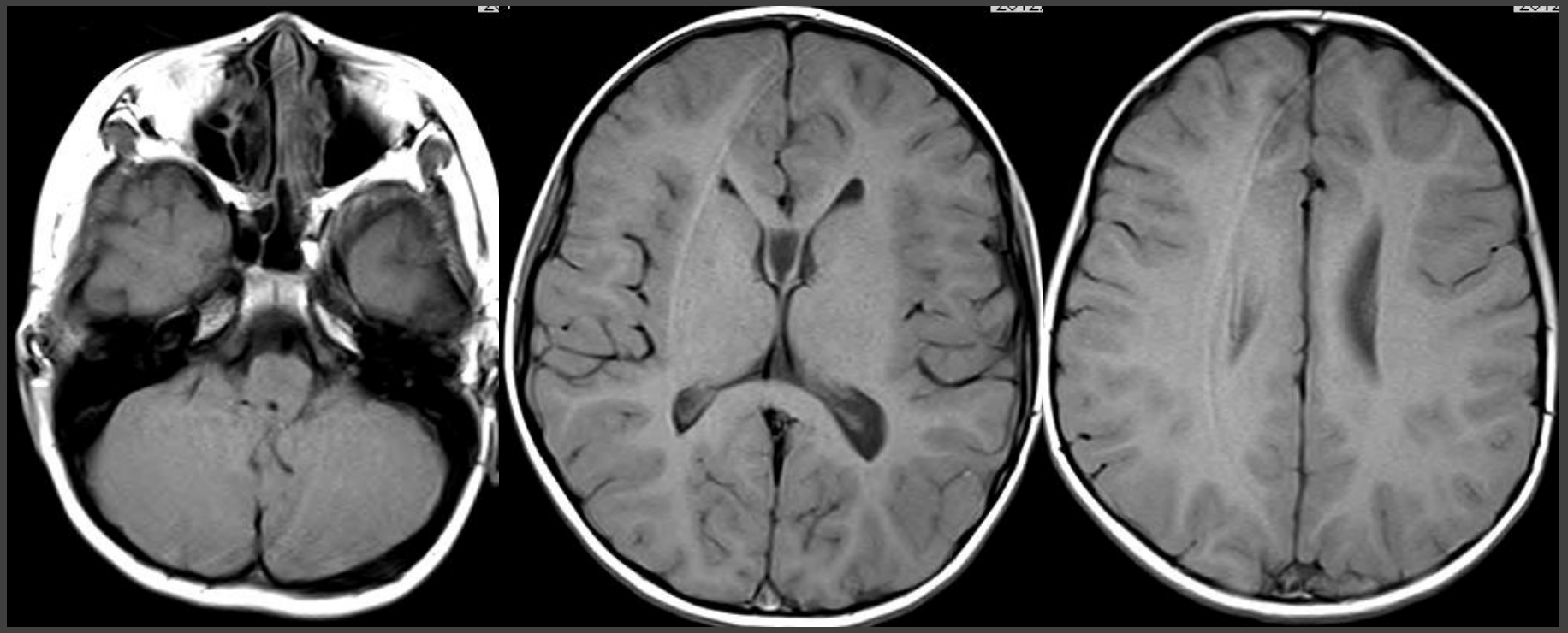
  471.5(mg/dl) / 118.8(mg/dl)=3.97 (7 y-o)

  ※Cr / Crn ratio 0.006-1.05 (6-10 y-o)

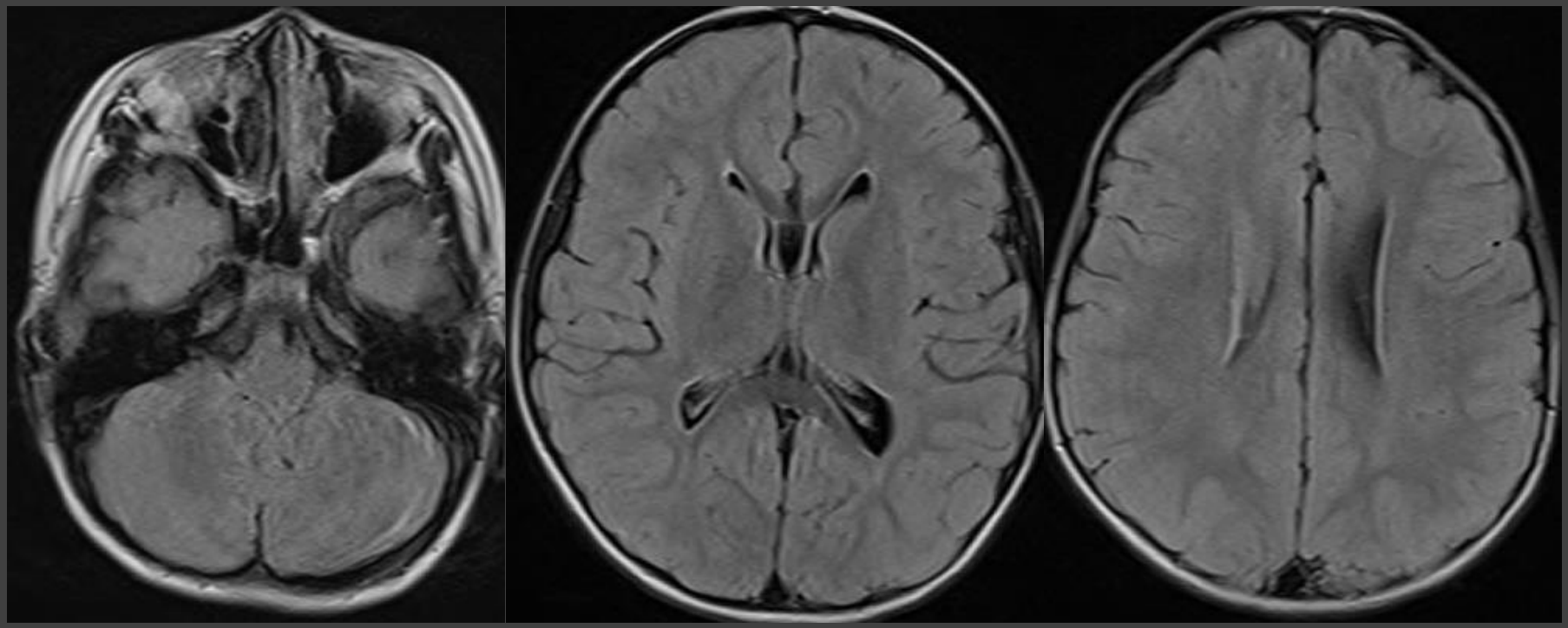
MRI T2WI



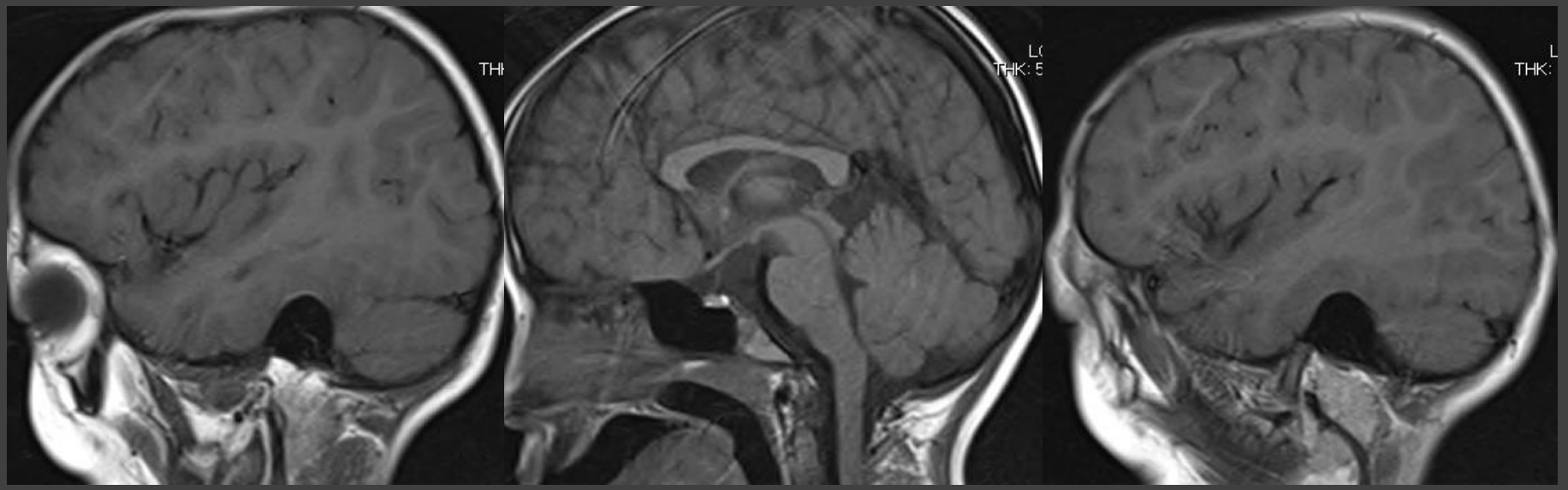
MRI T1WI



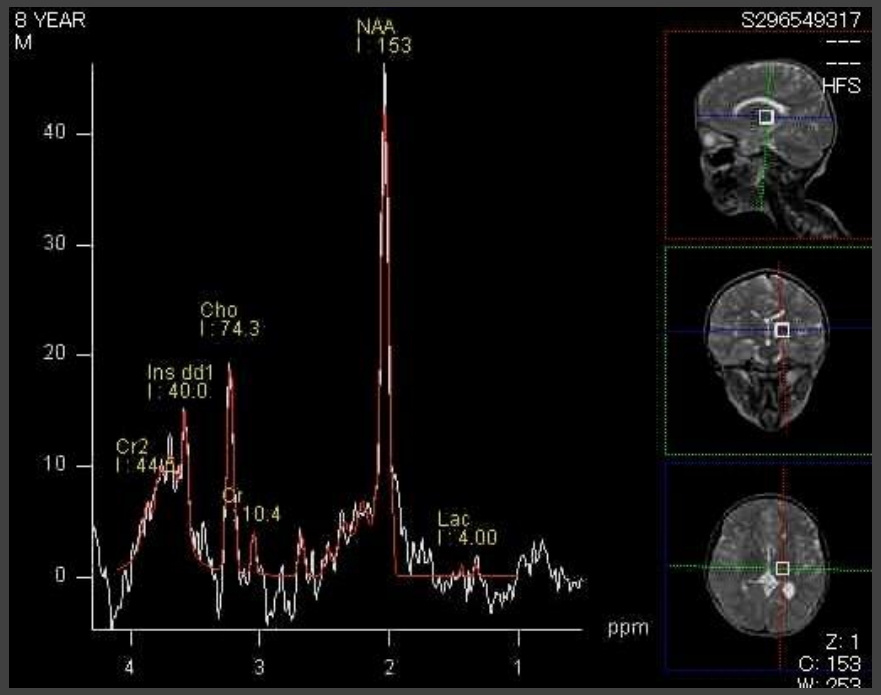
MRI FLAIR



MRI T1WI



^{1}H-MRS（TE 30ms）

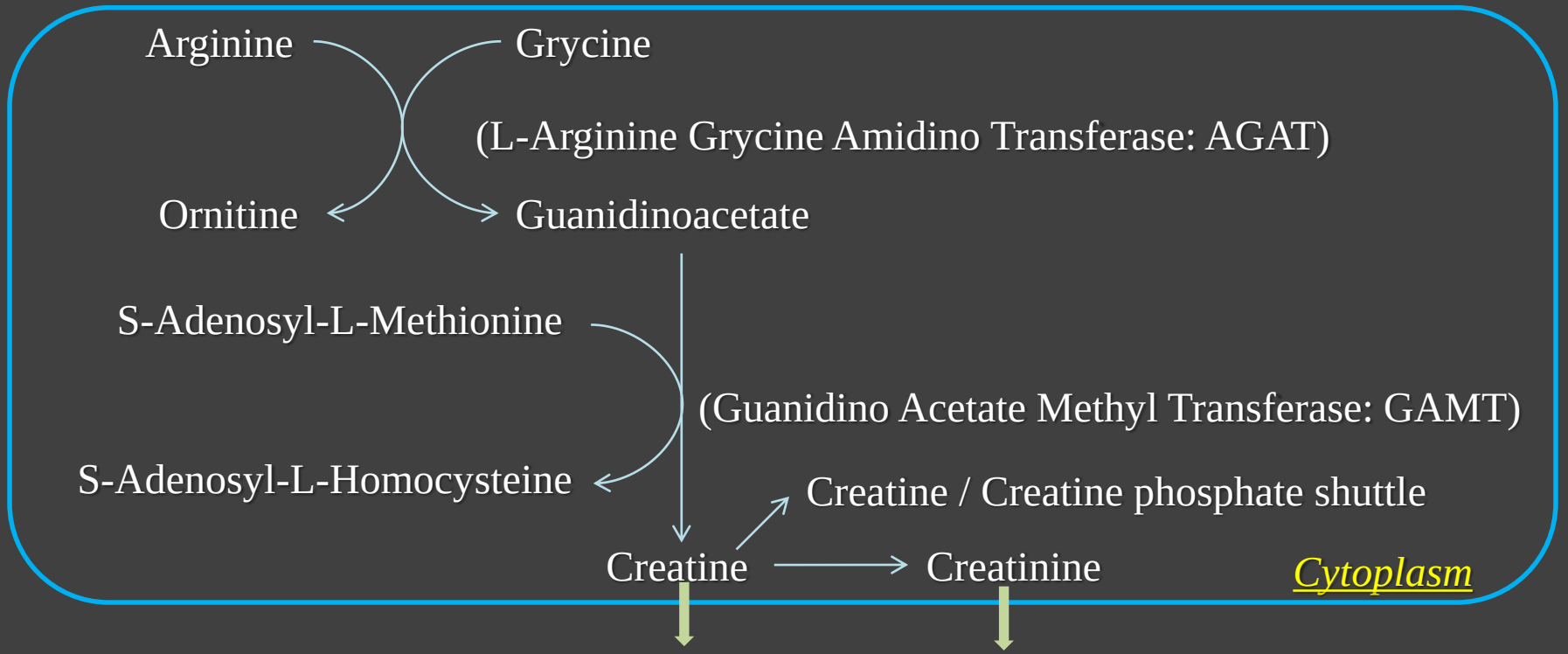


Creatine

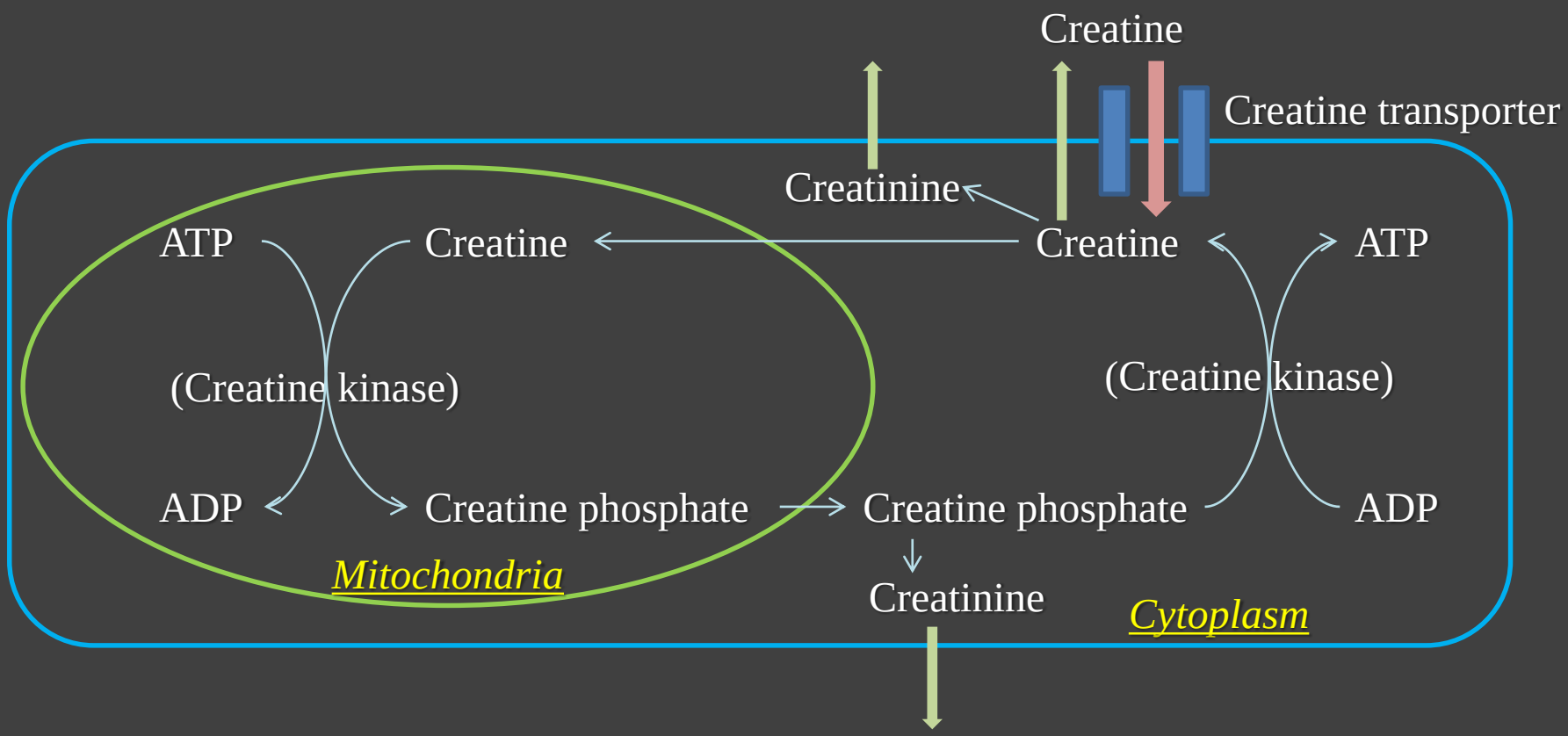
- Creatine and creatine phosphate are necessary for both energy storage and energy transport.
- Over 90 % of total creatine is found in skeletal muscle.
- About 1.7 % of the total creatine pool is lost daily and needs to be replenished.
- The half of total creatine is synthesized in the body, and the other half is derived from the diet in Western countries.
- The kidneys efficiently salvage creatine from urine.

Creatine synthesis

- Creatine is synthesized in the liver, kidney, and pancreas.
- Now it is commonly accepted that brain cells also synthesize creatine.



Creatine / Creatine phosphate shuttle



Creatine transporter

- There are two known creatine transporters, CT1 and MCT12.
- Creatine transporter 1 (CT1) is mainly expressed in skeletal muscles and kidney cell membrane, but somewhat lower level in the brain, retina, colon, small intestine, heart, testis, and prostate. CT1 is encoded by *SLC6A8* in Xq28.
- Monocarboxylate transporter 12 (MCT12) is highly expressed in the kidney, retina, lung, and testis. MCT12 is encoded by *SLC16A12* in 10q23.13
- CT1 is necessary for creatine uptake into cells, on the other hand MCT12 might facilitate creatine efflux from cells.

Creatine Deficiency Syndrome

1. L-arginine:glycine amidinotransferase (AGAT) deficiency (Autosomal recessive)
2. Guanidinoacetate methyltransferase (GAMT) deficiency (Autosomal recessive)
3. Creatine transporter deficiency (X-linked)

X-linked creatine transporter deficiency (1)

- Reported as an intellectual disability characterized by X-linked cerebral creatine deficiency in 2001
- Abnormal CT1 gene (*SLC6A8* in Xq28)
- Estimated prevalence : 0.4-1.4 % in males with intellectual disability, about 2 % in males with X-linked intellectual disability
- Intellectual disability with severe speech delay (100 %), behavioral abnormalities (85 %), seizures (59%) , hypotonia, hypoplasia, extrapyramidal movement disorders, short stature, slender build and poorly developed muscular mass
- The brain is mainly affected while other creatine requiring organs, such as the muscles, are relatively spared.
- No improvement with creatine supplementation therapy

X-linked creatine transporter deficiency (2)

- Urine or blood creatine (↑)
  Urine Cr / Crn ratio (↑) (100 % sensitive)
  Urine guanidinoacetate (→)
- MRI:
  Marked reduction of creatine peak on ^{1}H-MRS (100 % sensitive)
  Mildly delayed myelination
  T2 prolongation
  Thin corpus callosum
  Mildly enlarged ventricles / extracerebral spaces
  Cerebral / cerebellar atrophy
  Progression of cerebral atrophy
- Creatine levels in skeletal muscles are relatively preserved.

X-linked creatine transporter deficiency (3)

In female patient, the phenotype is expected to vary from normal to abnormal depending on the chance of the X-inactivation.

- urine Cr / Crn ratio is normal > 50 %
- mild decrease of Cr level on ^{1}H-MRS, but overlap with normal range
- DNA analysis of the *SLC6A8* gene might be the only reliable method for screening for CRTR-D

X-linked creatine transporter deficiency (4)

Recently, it has been established that both astrocytes and neurons have the capability to synthesize creatine.

So, why is cerebral creatine deficient in CRTR-D in spite of being synthesized endogenously?

Hypotheses

1. Cell creatine content in the brain might be mostly due to uptake rather than synthesis.
2. The cerebral creatine deficiency could derive from reuptake failure and defective creatine recycling following release.

Conclusion

- We report a rare case of X-linked creatine transporter deficiency, which is one of three creatine deficiency syndromes.
- ^{1}H-MRS is helpful for diagnosis of Creatine deficiency syndrome.

Reference

- X-Linked creatine transporter deficiency in two patients with severe mental retardation and autism. J Inherit Metab Dis. 2006 Feb;29(1):220-3.
- X-linked creatine transporter defect a report on two unrelated boys with a severe clinical phenotype. J Inherit Metab Dis. 2006 Feb;29(1):214-9.
- 1H MR spectroscopy as a diagnostic tool for cerebral creatine deficiency. MAGMA. 2008 Sep;21(5):327-32.
- Disorders of Creatine Transport and Metabolism. Am J Med Genet C Semin Med Genet. 2011 Feb 15;157(1):72-8.
- X-linked creatine transporter deficiency: clinical aspects and pathophysiology. J Inherit Metab Dis. 2014 May 1.

AGAT deficiency / GAMT deficiency

- GAMT deficiency was first described in 1994.
- AGAT deficiency was first described in 2001.
- Autosomal recessive
- Developmental delay, retrogression, hypotonia, extrapyramidal dysfunction, seizure, etc.
- Creatine replacement therapy is effective.
- MRI: normal, T2 prolongation in the globus pallidus, myelination delay or T2 prolongation in the white matter
- ^{1}H-MRS: decreased creatine peak
- ^{1}H-MRS (short TE): broad guanidinoacetate peak at 3.78ppm in GAMT deficiency