CASE 2019-2

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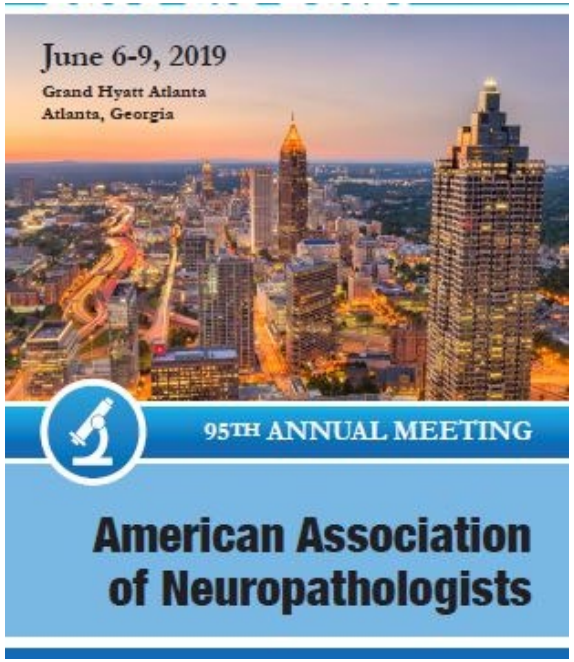
Neuropathology

Stanford University



Stanford MEDICINE

Disclosure

- I have no financial relationships to disclose

Clinical History

- 6-year-old girl with a history of regression of milestones beginning at one year of age
  - Late eruption of her primary teeth at about 3 1/2 years
  - Laryngeal cleft, exotropia, hearing loss and hirsutism
  - Progressive dystonic movement disorder leading to hypotonia
  - Progressive feeding difficulties, gastrostomy tube
  - Chronic lung disease from recurrent aspiration pneumonias leading to acute respiratory failure

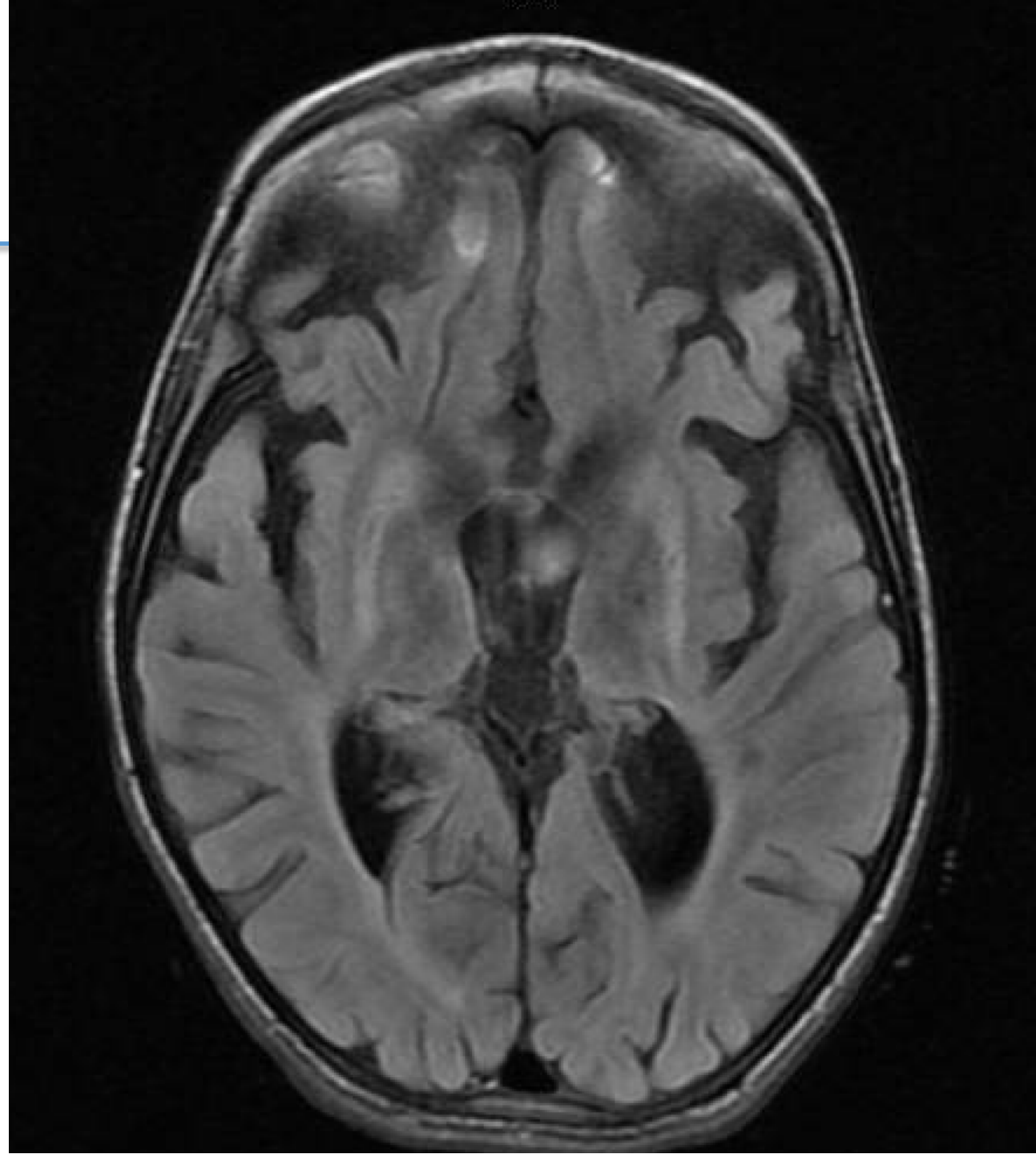
- Laboratory study results included normal lactate, ceruloplasmin, copper; severe ketonuria with mild elevation of 3-OH-glutaric acid

Clinical History

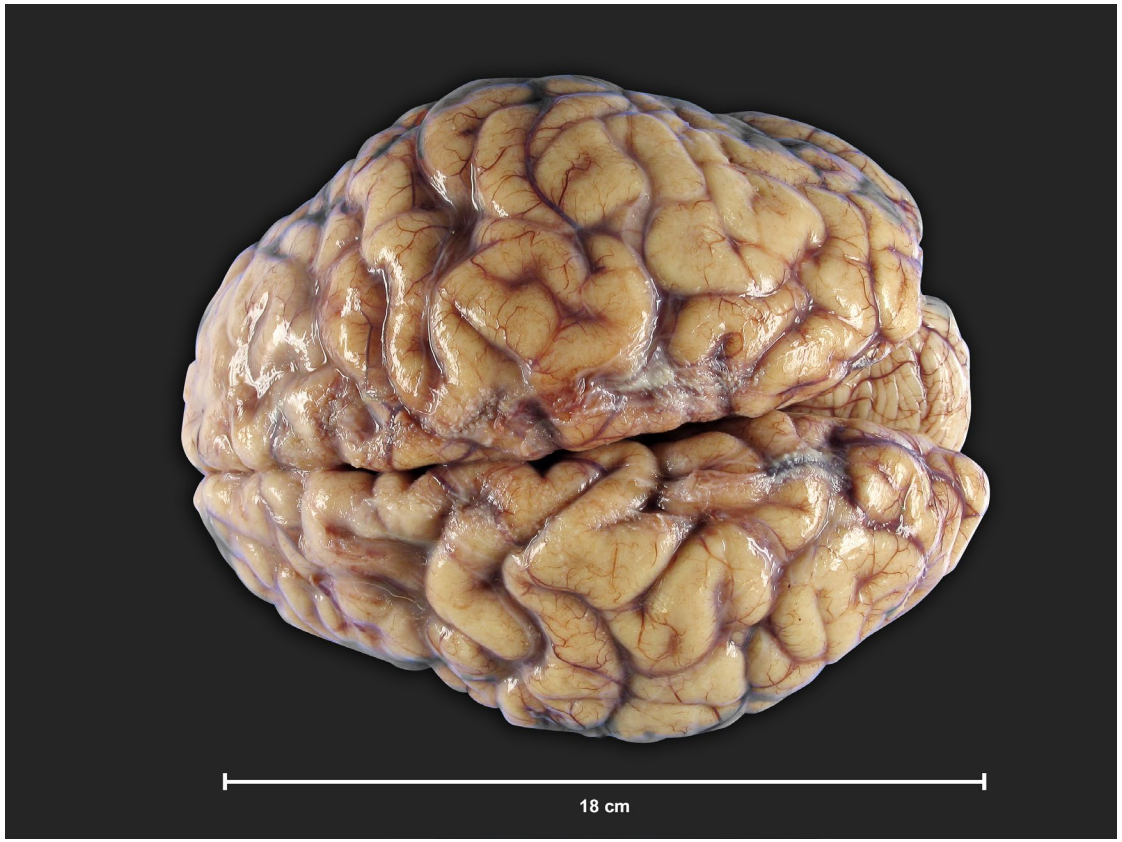
- Genetic tests:
  - Normal karyotype, normal SNP microarray
  - Whole exome sequencing:
    - Carrier for biotinidase deficiency carrier
    - VUS in the TYMP gene (thymidine phosphorylase deficiency and MNGIE disease)
    - VUS in NDUFAF5 gene associated with mitochondrial complex 1 deficiency
    - Common cystic fibrosis mutation deltaF508 carrier

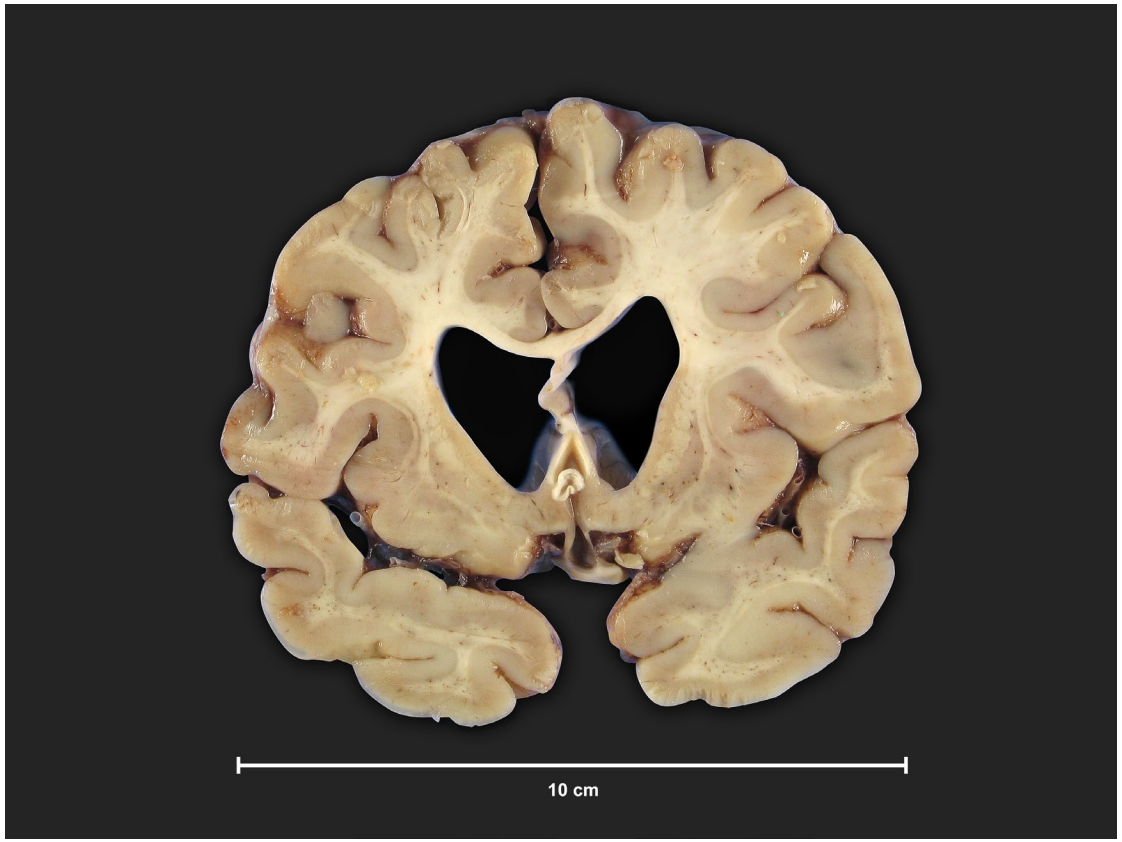
Imaging, Brain MRI

- Abnormal T2 hyperintensity in the basal ganglia, dorsal brainstem, and dentate nuclei with mild thinning of the corpus callosum
- Decreased white matter volumes of the cerebral hemispheres, and resultant mild ventriculomegaly



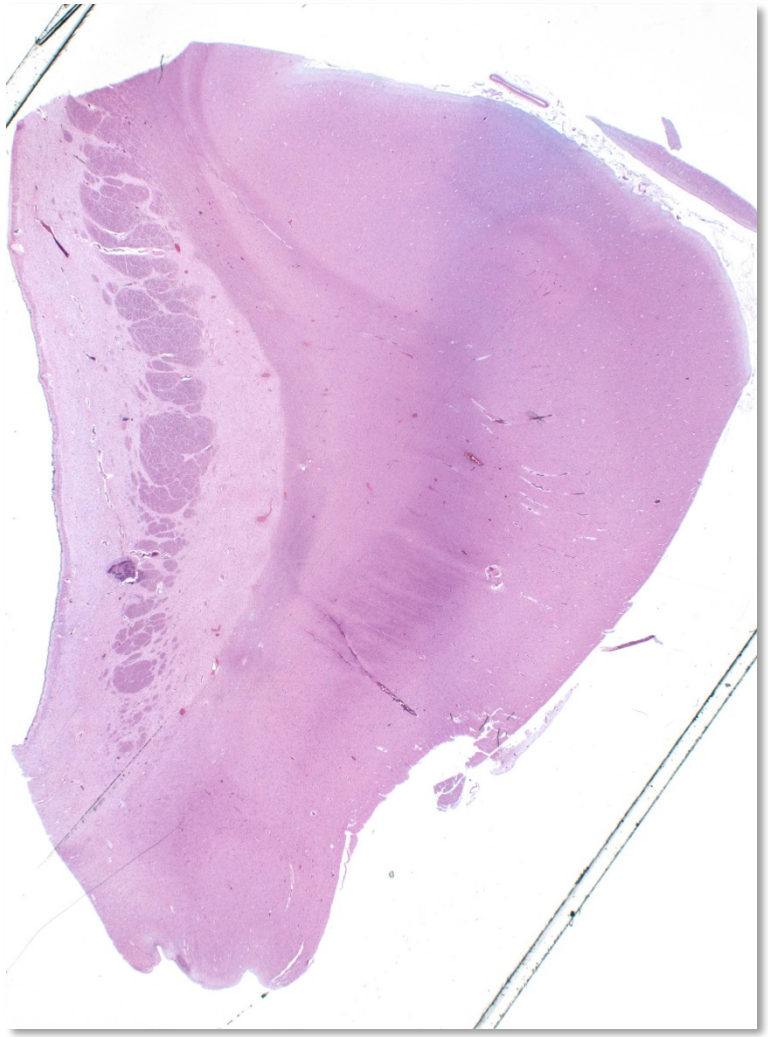
Autopsy

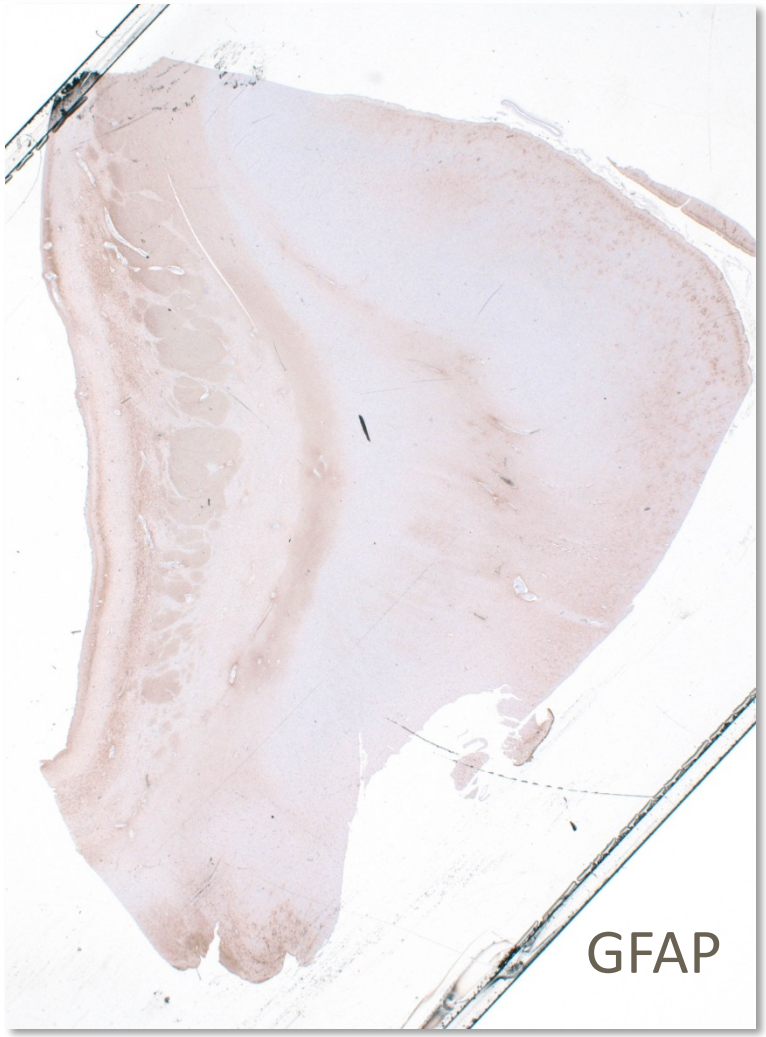




- Brain weight 965 g (expected 1250 g at 6 years of age); micrencephalic
- Bilateral and symmetrical frontal lobe atrophy and ventriculomegaly

Microscopy





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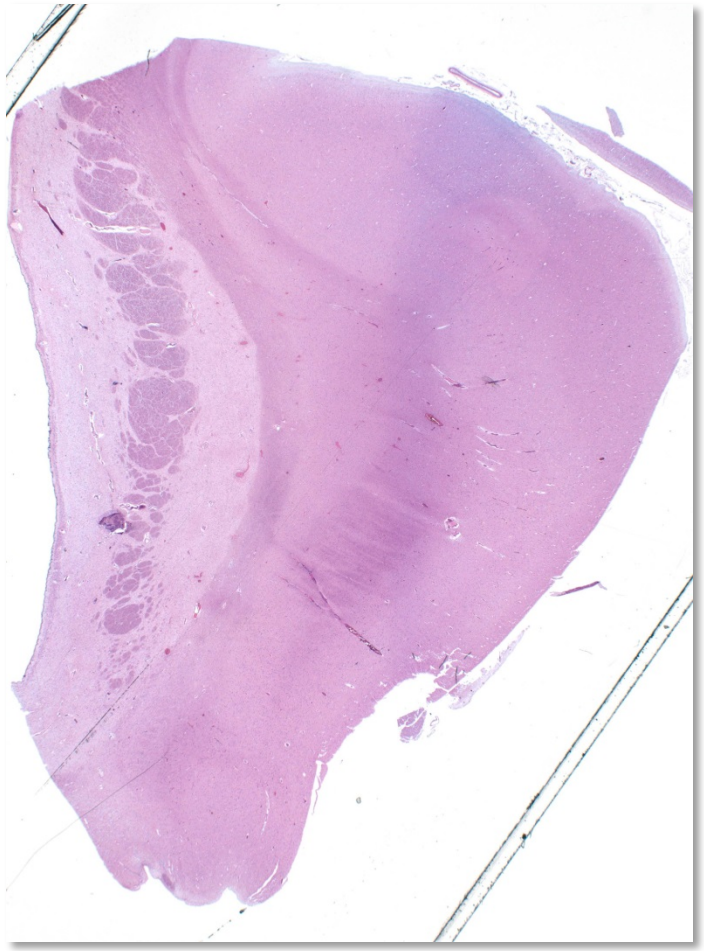

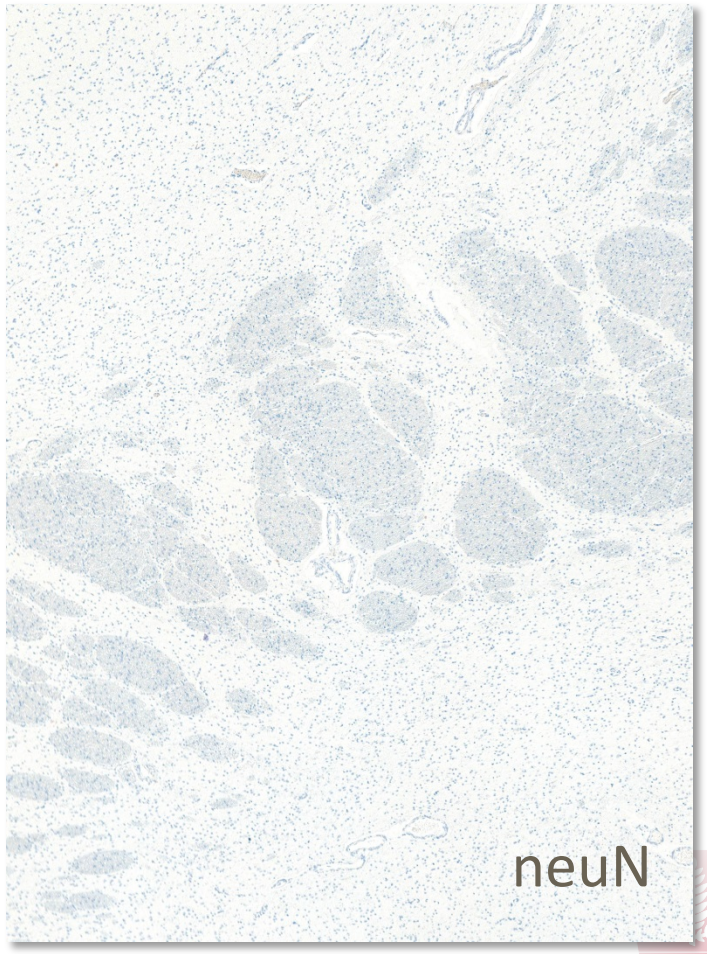

Neuropathological diagnosis

Neuropathological Diagnosis

1. Micrencephalic for age (965 grams), with bilateral frontal cortical atrophy and ventriculomegaly

2. Striatal gliosis and neuronal loss, bilateral caudate nuclei and putamens consistent with “infantile bilateral striatal necrosis”

Infantile Bilateral Striatal Necrosis (IBSN)

- Familial/genetic, with/without a known genetic basis, and sporadic
- Onset may vary between birth and 1-3 years of age, and most often occurs during the course of febrile infectious disease
- Drowsiness or coma, abnormalities of muscle tone, and occasional seizures are the principle features of the acute stage
- Long-term survivors exhibit paralysis of the trunk and the extremities, and occasional involuntary movements

Infantile Bilateral Striatal Necrosis

- Clinico-pathologic associations:
  - Acute disseminated encephalomyelitis (ADEM)
  - Carbon monoxide intoxication
  - Infections
  - Juvenile Huntington chorea
  - Leigh disease
  - Methylmalonic aciduria, guanidinoacetate methyltransferase deficiency, glutaric acidemia I
  - Neurodegeneration with brain iron accumulation
  - Vascular: small vessel arteritis
  - Wilson's disease
- Genetic associations:
  - Gene defects related to mitochondrial dysfunction
    - Leigh disease
    - NDUFAF6 and NDUFV1
    - ATPase 6 gene
  - ADAR1
  - Nup62
  - Others

Undiagnosed Disease Network (UDN)

- For family planning purposes, postmortem repeat whole exome sequencing and reanalysis
- Found c.1771-7C>G (maternally inherited) in POLR3A (RNA polymerase III) classified as a pathogenic variant and c.1400C>T (p.S467L) (paternally inherited) classified as a VUS (SIFT and PolyPhen-2 predict damaging/probably damaging)
- No pathologic variants that matched her phenotype were found!

Gene	Variant(s)	Inheritance	Gene-Disease Association	Inheritance Pattern of Disease
POLR3A	c.1400C>T p.Ser467Leu	Heterozygous-paternal	Leukodystrophy, hypomyelinating, 7, with or without oligodontia and/or hypogonadotropic hypogonadism [MIM:607694]	Autosomal Recessive
	c.1771-7C>G	Heterozygous-Maternal$		

POLR3A Hypomyelinating Leukodystrophy 7

- Autosomal recessive, hypomyelinating diseases, ± cerebellar atrophy and hypoplasia of the corpus collosum
- At least 70 associated POLR3A gene mutations
- Varying combinations of four major findings:
  - Neurologic dysfunction: Predominated by motor, progressive cerebellar, and to a lesser extent dystonia, spasticity and cognitive dysfunctions
  - Abnormal dentition
  - Endocrine abnormalities: Short stature
  - Ocular abnormalities: Myopia

OXFORD

Human Molecular Genetics, 2016, Vol. 25, No. 19 4302–4314

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Original Article

ORIGINAL ARTICLE

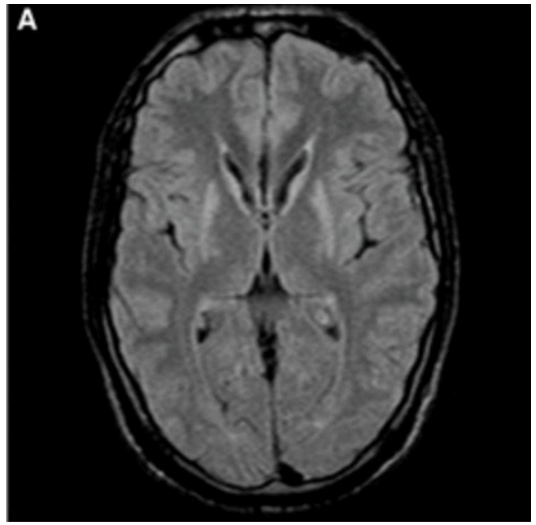
Transcriptome-wide effects of a *POLR3A* gene mutation in patients with an unusual phenotype of striatal involvement

Dimitar N. Azmanov[1,2,†], Stefan J. Siira[1,†], Teodora Chamova[3], Ara Kaprelyan[4], Velina Guergueltcheva[3], Anne-Marie J. Shearwood[1], Ganqiang Liu[5], Bharti Morar[1], Oliver Rackham[1], Michael Bynevelt[6], Margarita Grudkova[4], Zdravko Kamenov[7], Vassil Svechtarov[8], Ivailo Tournev[3,9], Luba Kalaydjieva[1] and Aleksandra Filipovska[1,*]

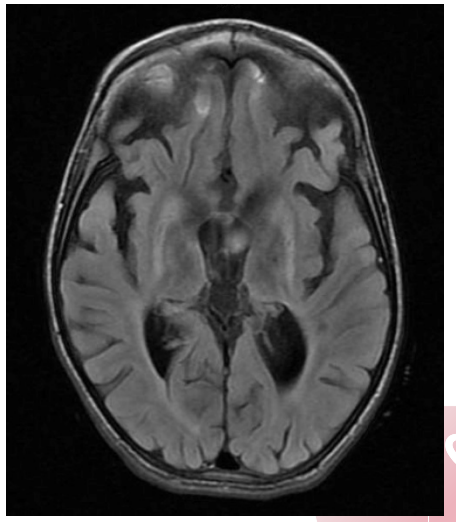
POLR3A gene: c.1771-7C>G variant

Azmanov et al. 2016:

- Reported three patients (age 52, 23 and 27) with c.1771-6C>G mutation
- Clinical onset at 7-8 years with speech disturbances, dystonic movements, gait instability and dysphagia -> progressive ataxia, dystonia and dysarthria over time
- MRI showed striatal and red nucleus involvement
- Clinical manifestations corresponded with the localization of the radiological changes
- No pathology performed



Azmanov et al. 2016


Our patient

Conclusions

- This case expands the clinical phenotype associated with POLR3A mutations to include the Infantile Bilateral Striatal Necrosis syndrome
- POLR3A (RNA polymerase III) mutations may include diverse neurologic, endocrine, odontogenic and ocular abnormalities
- Repeat whole exome sequencing may be informative!

References

- Azmanov DN et al. Transcription wide effects of POLR3A in patients with an unusual phenotype of striatal involvement. Hum Mol Genet. 2016;25:4302-4314.

- Tonduti D et al. Neurological disorders associated with striatal lesions: classification and diagnostic approach. Curr Neurol Neurosci Rep (2016) 16: 54.