White Matter Changes and Neuropathy in Siblings

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Disclosures

I have no financial relationships or contracts to disclose.

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History

- 49-year-old right-handed male lawyer presented to the neurology clinic
- Normal birth and development history until age 3 years when he developed balance and falling difficulties
- Bilateral foot drop and gait abnormalities age 6-7 years
- Active in basketball and sports until age 16 when he developed some trouble walking
  - Progression of weakness beginning in the legs and secondarily in the arms
- Age 17 lost significant strength in his legs and began to use a wheelchair
- At age 29, able to stand with difficulty but unable to walk. Writes but fatigues easily.
- No sensory disturbances, dysphagia, difficulty with speech or breathing
- Car accident at age 31 with neck injury

Past medical and surgical history

- Charcot Marie Tooth disease (CMT)
- Cervical and thoracic syringomyelia
- Asthma
- Resection of “gland in the neck”
- Tonsillectomy
- Urinary tract infection

Family history

- Paternal grandmother's sister's cause of death was "unspecified white matter disease", deceased at 30 years of age
- Parents without similar disease as far as the patient was aware, although father may have deformity of the feet
- Younger brother without disease
- Younger sister with similar disease, having foot drop at age 8, currently wheelchair bound

Physical exam

- Oriented to time, place, person
- Fluent language
- Motor
  - Normal muscle tone throughout
  - Bilateral finger contractures and claw hands
  - Severe hypothenar, thenar, intrinsic hand muscle atrophy
  - Distal lower extremity muscles atrophic
- Cranial nerves
  - Visual fields full to confrontation
  - Extraocular movement testing demonstrated reduced adduction of the right eye. Right exotropia.
  - Rest of the CN exam was unremarkable.

Physical exam

- Motor
  - Deltoids 4/5, 5/5 in biceps and triceps, 4/5 on wrist extension, 0/5 in first dorsal interosseous and abductor pollicis brevis with preservation of flexor pollicis longus strength
  - Hip abduction and adduction 0/5, 1/5 in hamstrings and quadriceps, 0/5 tibialis anterior and toe extension
- Reflexes
  - Absent deep tendon reflexes throughout
- Sensory
  - Decreased pinprick sensation bilaterally in arms in legs, in a grading distribution
  - Absent vibration in legs below the knees
  - Normal proprioception
- Gait unable to be tested – wheelchair bound
- Bedside cognition testing unremarkable

Previous diagnostic testing

- Childhood work-up unrevealing
  - Spina bifida
  - Diagnosed with Charcot Marie Tooth at age 10 years after EMG and nerve biopsy
- Adrenoleukodystrophy
- Krabbe disease
- Metachromic leukodystrophy
- PMP22 genetic testing
- SMN genetic testing
- Muscle and nerve biopsy in 1997 (slides and images unavailable)
  - Nerve: Prominent loss of axons in all fascicles consistent with “probable demyelinating or dysmyelinating neuropathy with thin myelin sheaths and early onion-bulb formations”
  - Muscle: “Chronic and ongoing denervation with small angular fibers individually and in groups”

Previous diagnostic testing

- Nerve Conduction Studies (completed at outside hospital)
  - Normal upper and lower limb sensory responses
  - Absent peroneal and tibial compound muscle action potentials (CMAPs)
  - Small ulnar, normal median CMAPs
- Brain MRI: bilateral periventricular patchy T2 hyperintensities
- Cervical and thoracic spine MRI: T2 hyperintensity lesions from C2-T7 diagnosed as syringomyelia

Diagnostic testing performed

- Blood chemistry
- Serum ammonia
- Creatine kinase
- Vitamin B12
- Folate
- Thyroid function tests
- Lactate
- Pyruvate
- Copper
- Ceruloplasmin
- Leukocyte arylsulfatase A

Diagnostic testing performed

- Peroxisomal panel with phytanic acid
- Lipid profile - abetalipoproteinemia
- Peripheral blood smear for acanthocytes
- Antinuclear antibodies
- SMN1 gene DNA test
- CMT gene testing panel
- SCA 1,2,3,6, 7 DNA testing
- Frataxin gene DNA test

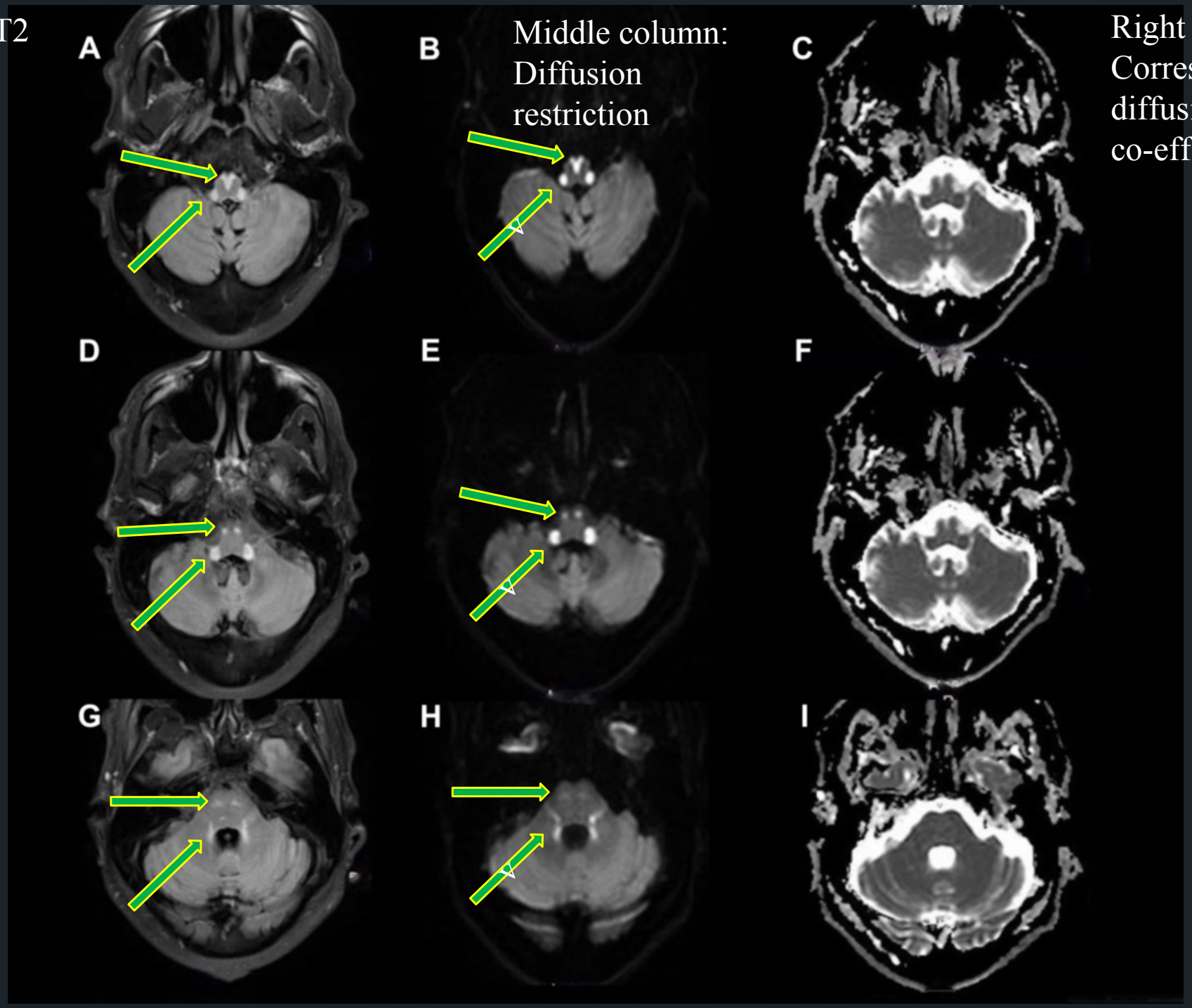
Diagnostic testing performed

- Nerve conduction studies
  - Severe axonal more than sensory peripheral neuropathy
  - No evidence of conduction blocks
- MRI of the brain: bilateral symmetric T2 hyperintensities of supratentorial white matter with prominent involvement of periventricular regions, superior and inferior cerebellar peduncles, anterior brainstem
- MRI of spinal cord: confluent, diffuse abnormal T2 signal of cervical and thoracic spinal cord in dorsal cord, dorsal columns, lateral corticospinal tracts

Left column: T2 FLAIR

Middle column: Diffusion restriction

Right column: Corresponding diffusion co-efficient



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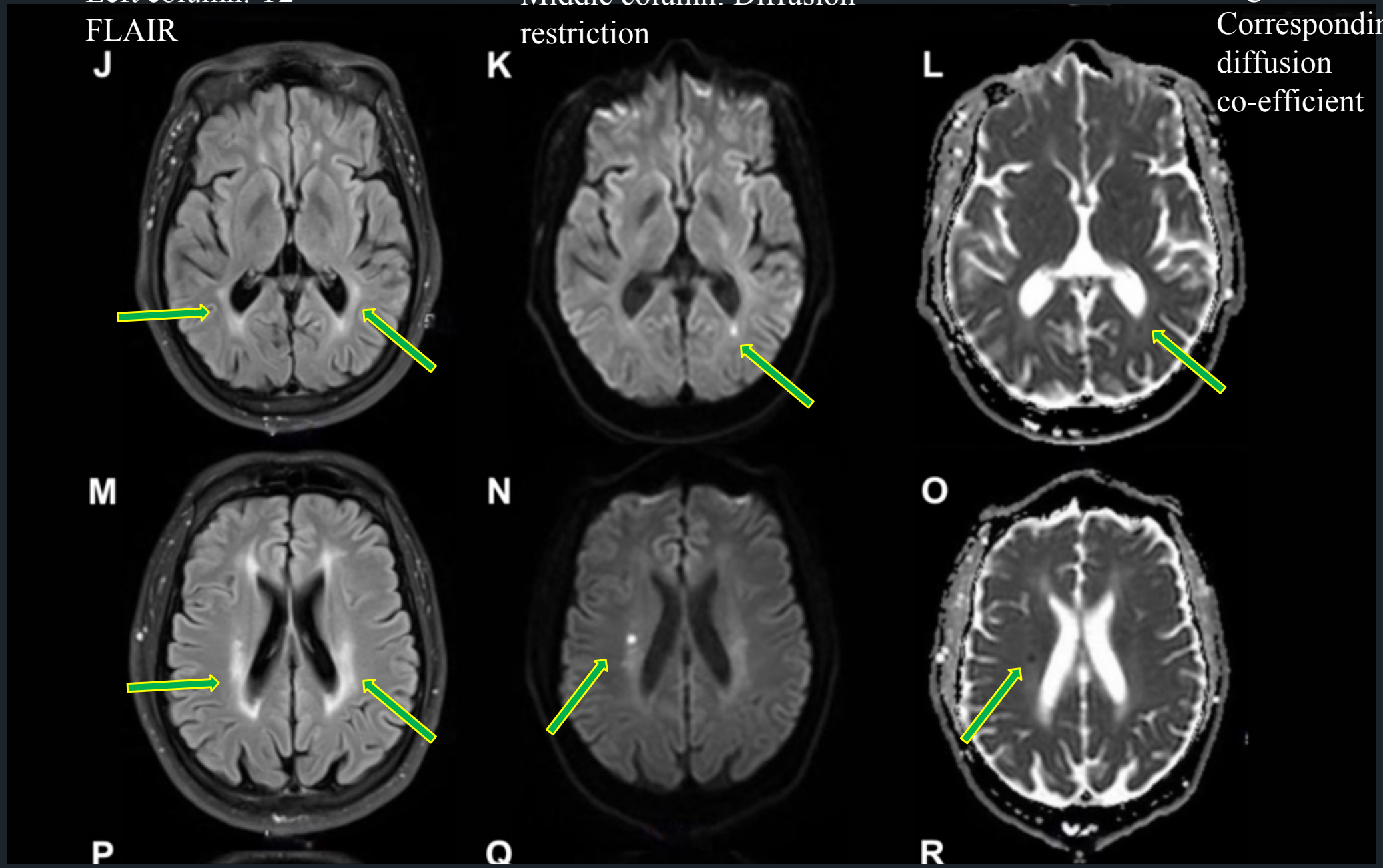

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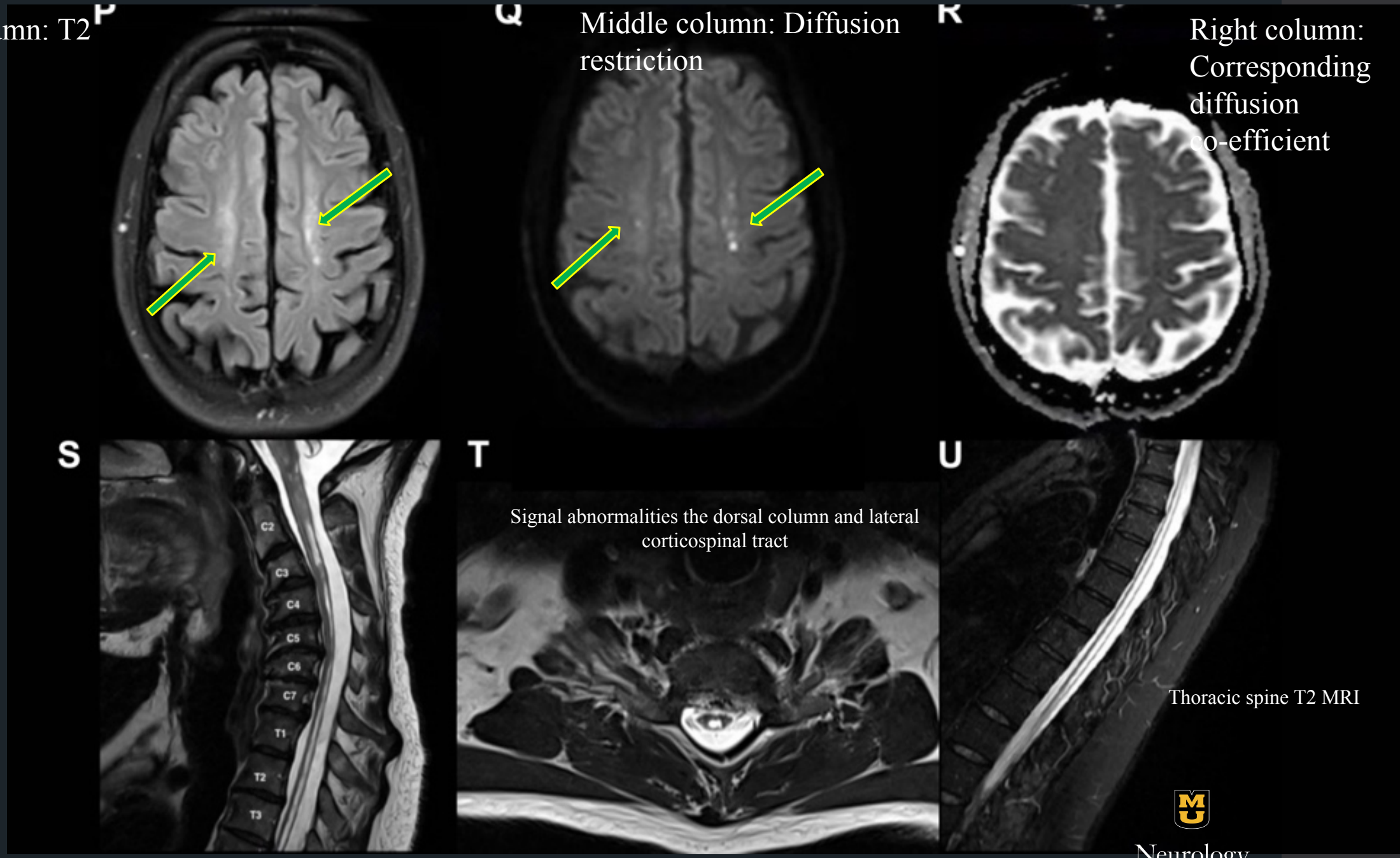

Signal abnormalities the dorsal column and lateral corticospinal tract

Cervical spine T2 MRI

Thoracic spine T2 MRI

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Diagnosis – genetic testing

- Heterozygous for DARS2 c.1192-2A>G, described as likely pathogenic
  - Novel variant
- Heterozygous for DARS2 c.228-15C>A, described as likely pathogenic
  - Previously reported
- MR spectroscopy demonstrated elevated lactate, although was performed at an outside hospital.

Testing consistent with a diagnosis of Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL); sister has the same mutation

Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation

- Very rare autosomal recessive disease with mutations in *DARS2* on chromosome 1q25.1*;* encodes mitochondrial aspartyl-tRNA synthetase[1]
- 60 different *DARS2* mutations identified (2014), almost all are compound heterozygotes[2]
- Clinical severity varies; may be infantile onset, rapidly fatal, or adult onset, slow, and mild disease. Most common phenotype involves childhood onset with slow neurological deterioration[2]
- Variable course of cognitive deficits, dysfunction of pyramidal and cerebellar tracts, dorsal column dysfunction of childhood onset with slowly-progressive course[5]
- Unusual to see full dependency on wheelchair for mobilization in the most common phenotype, and occurs in adulthood[2]

1.Scheper GC, van der Klok T, van Andel RJ, et al. Mitochondrial aspartyl-tRNA synthetase deficiency causes leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation. *Nat Genet*. 2007;39(4):534-539. doi:10.1038/ng2013.
2. Laura van Berge, et al; Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation: clinical and genetic characterization and target for therapy, Brain, Volume 137, Issue 4, 1 April 2014, Pages 1019–1029, https://doi.org/10.1093/brain/awu026
5. Linnankivi, T. et al. Five new cases of a recently described leukoencephalopathy with high brain lactate. Neurology 63, 688–692 (2004).

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Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation

- MRI findings are consistent throughout those affected by the disease and are distinctive[3-7]
  - High signal intensity in T2 and FLAIR within cerebral subcortical, periventricular and deep white matter, posterior limbs of internal capsules, centrum semiovale, medulla oblongata, intraparenchymal tracts of trigeminal nerves and deep cerebellar white matter[7]
  - Spinal involvement of dorsal column, lateral corticospinal tracts[7]
  - Elevated lactate in the abnormal white matter determined by single-voxel proton MR spectroscopy[6]
- Diagnosis suspected with these characteristic imaging findings, and definitively made with genetic testing[8]

3. van der Knaap, M.S. et al. A new leukoencephalopathy with brainstem and spinal cord involvement and high lactate. Ann. Neurol. 53, 252–258 (2003).
4. Petzold, G.C. et al. Adult onset leukoencephalopathy with brain stem and spinal cord involvement and normal lactate. J. Neurol. Neurosurg. Psychiatry 77, 889–891 (2006).
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Treatment and management

- Currently no targeted therapy is available; treatment is supportive and aimed at symptom alleviation.[2]
- Research is being conducted evaluating the possibility of treating LBSL with antisense oligonucleotides.[2]

2. Laura van Berge, et al; Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation: clinical and genetic characterization and target for therapy, Brain, Volume 137, Issue 4, 1 April 2014, Pages 1019–1029, https://doi.org/10.1093/brain/awu026

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Questions?