60th ANNUAL DIAGNOSTIC SLIDE SESSION 2019.

CASE 2019-2

Submitted by:
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Clinical History:
The patient was a 6-year-old female with a history of regression of milestones beginning at approximately one year of age and a febrile seizure that became generalized tonic/clonic. She was noted to have a dystonic movement disorder but was eventually diffusely hypotonic, confined to bed and developed joint contractures. She had a laryngeal cleft and developed intermittent exotropia, hearing loss and hirsutism. She had late eruption of her primary teeth at about 3 1/2 years. Laboratory study results included normal lactate, ceruloplasmin, copper; normal SCN1A sequence and deletion analysis; severe ketonuria with mild elevation of 3-OH-glutaric acid; normal karyotype; normal SNP microarray; initial whole exome sequencing confirmed that she was a carrier for biotinidase deficiency and a variant of unknown significance (VUS) in the TYMP gene associated with thymidine phosphorylase deficiency and MNGIE disease, and a VUS in the NDUFAF5 gene associated with mitochondrial complex 1 deficiency; she and her mother were carriers for the common cystic fibrosis mutation deltaF508.

Brain MRI had shown 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.

She developed worsening feeding difficulties requiring a gastrostomy tube, and chronic lung disease from aspiration with recurrent pneumonia. She presented to the hospital with acute respiratory failure, and three weeks later expired after failed attempts at extubation.

Autopsy findings:
Postmortem examination of the brain showed bilateral and symmetrical frontal lobe atrophy and venticulomegaly.

Material submitted:
1 H&E stained section of basal ganglia is provided for review.

Points for discussion:
1. Diagnosis?
2. Genetic association?