HETEROTOPIC GRAY MATTER IN WHITE MATTER IN A 62 YEAR OLD

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ABSTRACT

"Heterotopia" describes normal cells in an abnormal location, and in the context of neurobiology, usually refers to neurons or gray matter in the leptomeninges or in periventricular or subcortical white matter, ("Gray Matter Heterotopia"). While once thought to be quite rare, ~~the~~ widespread MRI availability allowed increased recognition of these malformations. Clinically, gray matter heterotopias usually manifest as seizures in the first and second decades of life and may have associated motor and cognitive developmental disturbances. We report a patient with no known prior neurologic history, who developed seizures at the age of 62, which were subsequently determined to be from a subcortical gray matter heterotopia. The patient presented to an outside hospital with episodic confusion thought to represent partial seizures, and also numbness in her left foot, leg, and arm. MRI revealed a thickened corpus callosum and abnormal signal extending into the right cingulate gyrus white matter with an infiltrative appearance suggestive of a glioma or gliomatosis. Stereotactic biopsy demonstrated white matter containing irregular islands of synaptophysin-immunopositive gray matter within which there were large dysplastic neurons. This established a diagnosis of ectopic gray matter in the subcortical white matter. To our knowledge, this is the oldest age at which a person with this congenital condition has experienced onset of related symptoms.

CLINICAL HISTORY

- 62 year old female
- History of hypertension and hypothyroidism
- Gradual onset of episodes of word finding difficulty, repeating questions, confusion, dizziness, and forgetfulness for the preceding "few months" which were interpreted to possibly represent partial seizures by an outside neurologist
- Intermittent headaches located at the back of her head for approximately 1 year
- Episode of drooping of the left side of her face approximately 3 weeks ago which was transient but recurred later the same day
- "Nerve sensation" on her left side on the day prior to admission which began at the left foot and migrated up the left leg and down the left arm
- Slurring of speech and tingling of the left foot the night prior to admission
- Night sweats for a "few months" and 8 pound weight loss over the previous year

IMAGING

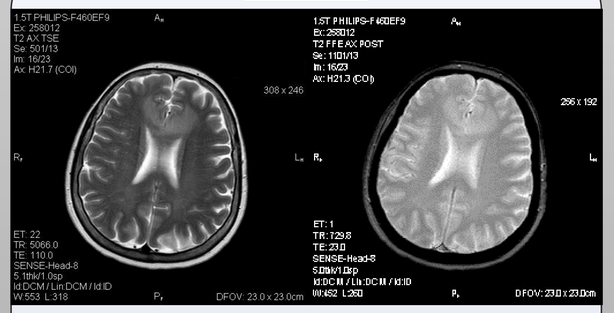

Figure 1. Left) T2 Axial view TSE Sense. Right) T2 FFE Axial Post contrast Sense. Both images demonstrate thickening and increased signal intensity in the corpus callosum crossing the midline. This area seems contiguous with an area of abnormal signal in the medial right frontal lobe near or along the falx. This abnormal imaging prompted a stereotactic brain biopsy. *Given the patient's age, imaging, and clinical history, neoplasm of the brain, either metastatic or primary was suspected.*

HISTOPATHOLOGY

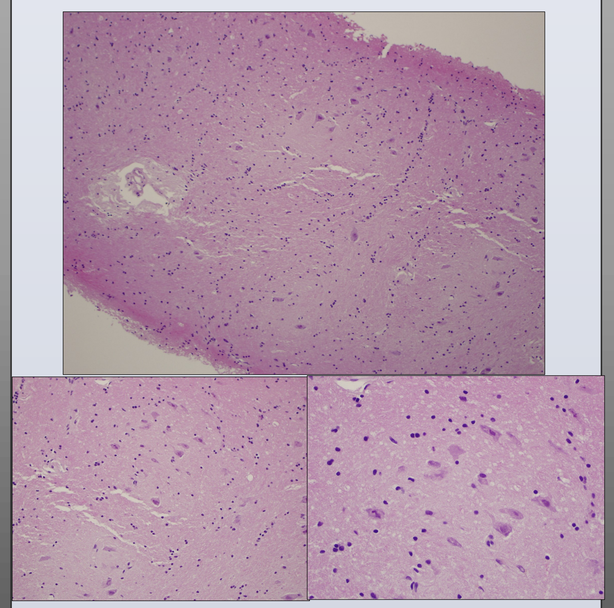

Figure 2. Hematoxylin and Eosin stain of the stereotactic brain biopsy. These stains reveal mildly hypercellular white matter with scattered large neurons. Many of these large neurons are dysplastic and there is a tendency for them to cluster in small groups surrounded by normal-appearing white matter. Importantly there is no gliomatosis or gliomatosis-like infiltrating glioma. *This appearance introduced the possibility of a gangliocytoma or ganglioneuroma.*

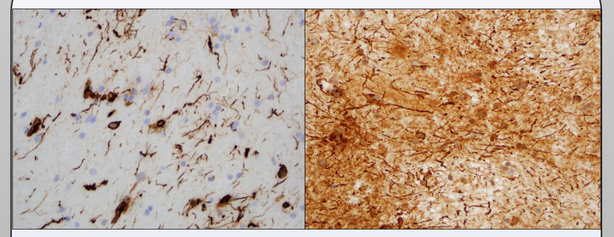

Figure 3. Left) **Vimentin** immunostain marking cells with the appearance of reactive astrocytes and bipolar neurons. However, the large dysplastic-dysplastic appearing neurons are negative, *excluding the possibility that they are reactive astrocytes*. (400x) Right) **GFAP** immunostain demonstrates immunopositivity in astrocytes and some neuronal cells.

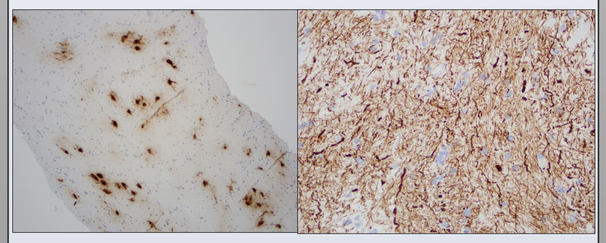

Figure 4. Left) **NeuN** immunostain clearly marks the large cells and confirms their neuronal identity. (100x) Right) RMDO20 antibody for **Neurofilament protein immunostain** labels axons in the white matter but not the large neurons, in contrast to control tissue with immunoreactive neurons. *This finding confirms these large neurons as dysplastic*. (400x)

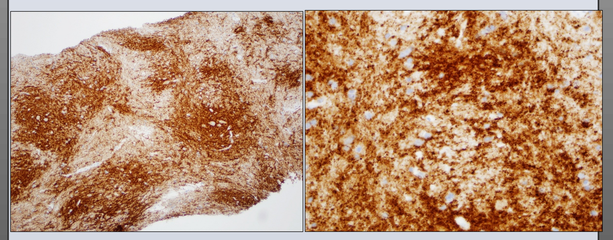

Figure 5. Synaptophysin immunostain demonstrates a distinct pattern of immunopositivity with islands of granular immunoreactivity which are separated by immunonegative white matter. Of note, the "islands" include immunopositive neuropil surrounding the large neurons which have coarsely granular perikaryal surface immunopositivity. *In short, this pattern indicates the presence of abnormal gray matter islands surrounded by normal white matter.* (Left 100x; Right 400x)

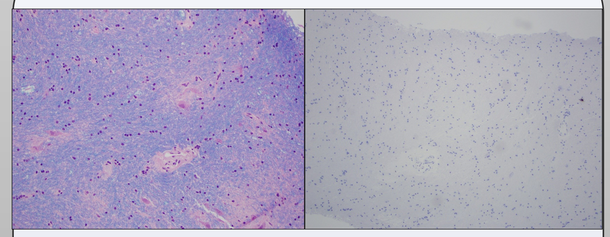

Figure 6. Left) **Luxol Fast Blue/H&E** stain. The biopsy consists of normally myelinated white matter surrounding islands of gray matter which lack myelin. (200x) Right) **Ki67** immunostain showing almost zero labeling of cells. (100x)

DISCUSSION

The pattern of synaptophysin immunoreactivity (as described in the figure 5 legend), is a key finding in this case. This pattern was originally described in 1990 to be indicative of neoplastic ganglion cells[1], but it is also present in Focal Cortical Dysplasia and hamartomatous lesions of Tuberous Sclerosis.

The LFB/H&E immunostain clearly confirms the presence of unmyelinated gray matter islands surrounded by myelinated white matter and the Ki67 staining index is far too low for any neoplastic process. Thus, the definitive, albeit somewhat unexpected, diagnosis is that of heterotopic gray matter.

Gray Matter Heterotopias occur secondary to abnormal neuroblast migration[2]. Evidence-based classification of these malformations is limited due to their rarity, however most pathologists divide cases into subependymal (periventricular), subcortical, and band heterotopias. The imaging and histologic findings in this case are consistent with the subcortical form.

The most common clinical manifestation of subcortical heterotopia is epilepsy, which usually develops during the first two decades of life. In focal forms the epilepsy is typically controlled with drugs, however intractable epilepsy can occur with large malformations[3]. Often variable degrees of motor and intellectual disturbances are also present, including contralateral pyramidal signs in unilateral lesions. There is evidence that germline mutation of an actin-linking gene, FLN1, is key in development of the more common periventricular form, however the sporadic nature of most subcortical forms suggests somatic rather than germline mutations.

The advanced age of this patient at the time of symptom onset is, to the knowledge of the authors, the oldest age at which this congenital malformation has been detected, and this case demonstrates the necessity of a wide diagnostic lens in the practice of pathology.

REFERENCES

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2. Barkovich AJ, Kuzniecky RI. Gray matter heterotopia. *Neurology* 55 (2000): 1603-1608.
3. Spalice A, Parisi P, Nicita F, Pizzardi G, Del Balzo F, Iannetti P. Neuronal migration disorders: clinical, neuroradiologic and genetics aspects. *Acta Paediatr* 98 (2009), 421-433.