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Case Report

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A Rare Case of Autosomal Recessive GLS-Related Epileptic Encephalopathy and Respiratory Failure

Hanae Benchbani[1]*, Melissa A Gener[2] and Sultan M Habeebu[2]

[1]Department of Pathology, University Health–University of Missouri Kansas City School of Medicine, Kansas City, USA

[2]Department of Pathology, Children's Mercy– University of Missouri Kansas City School of Medicine, Kansas City, USA

ABSTRACT

The student said, "Oh, that is why we learned that!". The student that sparked this research admitted that as she went through the program she often thought, "why are we learning this? I cannot see utilizing this in my everyday job." In academia today, we often treat the clinical or practicum experience as a separate component of the learning. Some schools even front load the content so they do all of the experiential learning after the classroom portion is over. Experiential learning works best when the learner can connect what they see and hear in the classroom to what they are actually seeing and doing in the field. There are a number of ways to bring the two worlds together. One program did just that and based on findings, the students felt better prepared for the job after graduation. The element of the unknow was removed. Students reported feeling more prepared for their new career and were able to fully grow during the orientation.

***Corresponding author**

Hanae Benchbani, Department of Pathology, University Health–University of Missouri Kansas City School of Medicine, Kansas City, USA.

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Case Report

A 12-day-old female infant, born at 39 weeks 4 days gestation via scheduled Cesarean section to a 23-year-old G2P2 mother. The infant was transferred to Children's Mercy Hospital Kansas City Missouri, USA for further care of concerns for neonatal seizures. History of a cesarian section with the first pregnancy due to fetal intolerance to labor. The perinatal course was complicated by APGAR scores of 2, 5 and 3 at one, five and ten minutes, respectively, hypotension and seizures with head ultrasound showing no germinal matrix hemorrhage. The course of the treatment was complicated by seizures despite aggressive treatment with no significant intracranial abnormalities on MRI, along with hypotension and acidosis. Due to the infant's poor prognosis the parents made the decision to redirect care. The infant was extubated and passed away peacefully 4 hours later.

The results of genetic studies became available after the patient expired. Microarray on a blood sample was negative for detectable alterations. A comprehensive NGS panel with deletion/duplication analysis revealed a compound heterozygous "pathogenic genotype in GLS, expected to be consistent with a diagnosis of autosomal recessive GLS-related neonatal epileptic encephalopathy." The pathogenic variant, c.793_794del (p.Val265LeufsTer33), was inherited from the mother and an intragenic GLS duplication, from the father. The NGS panel also found the patient to be heterozygous for a paternally inherited pathogenic variant in VARS1.

The most pertinent morphologic findings found on histology after the autopsy are the lungs showing immaturity and early bronchopulmonary dysplasia (BPD) and the central nervous system with severe, global hypoxic ischemic encephalopathy. Severe neuronal loss, severe, global white matter reactive gliosis. Severe vascular congestion and edema, and cortical dysplasia with no evidence of inflammation, hemorrhage or viral cytopathic effect.

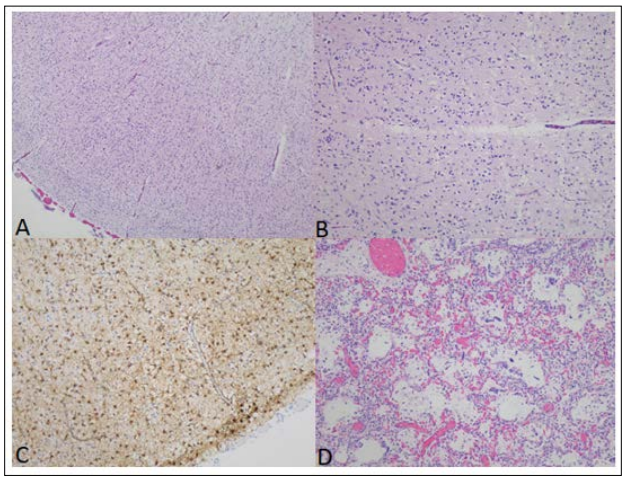

Figure 1: Diffuse Cerebral Cortical Gliosis with Six, ill-defined Cortical Layers (A, B), GFAP Staining Highlights the Severe Reactive Gliosis is (C), Lung with Patchy Areas of Capillary Proliferation Suggestive of Early Bronchopulmonary Dysplasia (D)

Discussion

Epileptic encephalopathies are a large and heterogeneous group of disorders. Genetic factors are assumed to be causative in most cases. The frequent causes of severe epileptic encephalopathy are de novo heterozygous genetic variants. However, autosomal recessive

inheritance is common, especially for metabolic disorders [1]. Epilepsy is caused by malfunction in hypersynchronous discharges within local or diffuse neuronal networks. The current literature has not been able to fully explain the underlying mechanisms, but three main pathophysiological mechanistic concepts have emerged throughout the past decade. These include ion channels dysfunction, deficits in synaptic transmission, and impairment in interneuron development [2].

Glutaminase is encoded by the GLS gene, which is located at 2q32.2 and widely expressed in all brain regions since early development, especially in the cerebral cortex and cerebellum. Glutamate is generated from hydrolysis of glutamine by glutaminase to remove one ammonia. GLS gene mutations can lead to high levels of glutamine and various nervous system dysfunctions [3]. Which explains the high levels of glutamine seen in this patient (1142 μM/L).

Additionally, the GLS gene deletion mutations cause activity-dependent defects in glutamatergic synaptic transmission, resulting in respiratory dysfunction in affected children. Glutamate promotes signal transduction in the brainstem respiratory center, which regulates the respiratory tidal volume, frequency, and rhythm after birth [2]. Lynne Rumping reported in 2018 that four infants from two unrelated families suffered from early neonatal epileptic encephalopathy with glutaminase deficiency. All the four infants had refractory early neonatal seizures, status epilepticus, and fatal respiratory failure [1].

In our case, the changes seen in the Central Nervous System are evidence of a decrease in oxygenation or blood flow to the brain prior to the decedent's birth. The gliosis and neuronal loss are well-developed, indicating that the insult or insults occurred prior to labor and delivery. Moreover, the bronchopulmonary dysplasia described in this patient born at term is rare in infants born at term despite receiving similar aggressive ventilatory support.

BPD occurs most commonly in preterm (born more than 10 weeks before their due dates), low birth weight infants (weighing less than 2 pounds) due to mechanical ventilation and oxygen therapy [4]. It results from disruption in the septation of alveoli, leading to alveolar hypoplasia with fewer, larger, simpler alveoli and, therefore, a decreased surface area available for gas exchange. BPD results from an abnormal reparative response to antenatal injury and/or repetitive postnatal injury to the developing lungs. The major cause of BPD is surfactant deficiency, which leads to respiratory distress syndrome [5]. This does not explain the finding of incomplete lung development with patchy areas of capillary proliferation suggestive of early bronchopulmonary dysplasia seen in this infant at term.

The neuropathological findings associated with autosomal recessive GLS-related neonatal epileptic encephalopathy have not been previously described; however, it is reasonable to assume that this disease would show similar central nervous system histopathologic changes of other atelectatic conditions. These changes include cortical dysplasia, gliosis and depending on the severity of the seizures, hypoxic ischemic encephalopathy.

Conclusion

We report on the genetic and pathological findings of a fatal case of neonatal-onset of respiratory failure and epileptic encephalopathy, attributed to a GLS gene mutation. It is hoped that comprehending the underlying pathological mechanisms will not only offer closure to the families of affected patients but also facilitate the advancement of patient care.

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