In Alper's syndrome, inhibitory interneurons are selectively vulnerable

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INTRODUCTION

Alper's syndrome is a severe neurodegenerative disorder caused by bi-allelic variants in the mitochondrial DNA (mtDNA) polymerase gene, POLG, which results in mtDNA depletion. Alper's syndrome is distinguished by intractable epilepsy, frequently with an occipital focus, and extensive neurodegeneration. Mitochondrial Oxidative Phosphorylation (OXPHOS) is severely impaired by mtDNA depletion and is likely to be a major contributor to Alper's syndrome epilepsy and neurodegeneration. We hypothesized that because of the excessive energy demands required to sustain their fast spiking activity, parvalbumin positive (+) interneurons, a neuronal class critical for inhibitory regulation of physiological cortical rhythms, would be particularly vulnerable in Alper's syndrome.

Alper's syndrome is a fatal mitochondrial disease characterized by uncontrollable epilepsy, psychomotor regression, and hepatic failure. Focal seizures within the primary visual cortex are common early presenting features that are frequently resistant to treatment. Other seizure types, such as myoclonic, generalized tonic-clonic, and focal motor seizures, have been observed and may result in status epilepticus or, more commonly, epilepsies partialis continua. Developmental delay, cerebellar ataxia, cortical blindness, and hypertonia are all common neurological impairments. Symptoms typically appear in early childhood; however, a second peak of onset occurs in adolescence or early adulthood. Neurological deterioration progresses quickly, with fatal consequences occurring within months to years of the initial presentation.

Bi-allelic pathogenic variants in POLG, which encodes the catalytic subunit of DNA polymerase gamma, are the most common cause of Alper's syndrome. Pathogenic POLG variants cause inefficient replication of mitochondrial DNA (mtDNA), resulting in mtDNA depletion, which primarily affects the brain and liver.

DESCRIPTION

Recent neuropathological studies have revealed that Alper's syndrome is characterized by a profound loss of Gamma Aminobutyric Acid (GABA)-ergic inhibitory interneurons from the nonlesional primary visual cortex, as well as severe deficiencies of OXPHOS complexes I and IV within residual interneurons. The severe dysfunction and degeneration of inhibitory interneurons most likely underpins a loss of inhibitory neurotransmission, which creates a permissive environment for seizure activity generation and maintenance. Other mitochondrial epilepsies, including adult onset POLG related pathologies, have shown similar levels of interneuron loss and multiple OXPHOS deficiencies.

The purpose of this study was to see if specific interneuron subtypes are affected differently in Alper's syndrome, with a focus on parvalbumin +interneurons. This will provide a better understanding of the role of impaired inhibitory neurotransmission in the generation of epileptic activity and may explain the occipital cortex's early and predominant involvement in Alper's syndrome. A better understanding of these pathomechanisms, as well as cell specific sensitivity to OXPHOS deficiency, will aid in the development of accurate, relevant preclinical models of Alper's syndrome, allowing for the testing of novel antiepileptic therapies.

Intractable epilepsy is a defining feature of Alper's syndrome patients, and previous research has shown that the inhibitory interneuron population is heavily involved in the generation of seizures in these patients. In 14 patients with Alper's syndrome, we performed a detailed neuropathological investigation to investigate the susceptibility of specific subtypes of cortical interneurons. We found a consistent, severe loss of parvalbumin +interneurons and severe OXPHOS deficiencies within remaining parvalbumin+interneurons. In contrast, calretinin+interneurons had milder OXPHOS deficits and were more resistant to neurodegeneration. Furthermore, we found that there is an enrichment of parvalbumin +interneurons in the occipital cortex, which, together with their apparent increased vulnerability, suggests that this is what causes the occipital focus of seizures in Alper's syndrome.

Our neuropathological studies have provided a detailed anatomical understanding of the vulnerability of interneuron subtypes in Alper's syndrome end stage disease tissues affected by severe epilepsy and encephalopathy. Future research should look into the differential vulnerability of parvalbumin and calretinin+interneurons by looking at changes in mtDNA integrity and quantity within these interneurons in a larger Alper's syndrome patient cohort, an array of mitochondrial disease encephalopathies, and non-primary mitochondrial epilepsies. To overcome the limitations of using postmortem tissues to determine the cause and effect of parvalbumin+interneuron dysfunction and degeneration, functional validation studies using appropriate *in vitro* disease models recapitulating the neuropathological features of mitochondrial epilepsy, including parvalbumin+interneuron vulnerability, should be performed.

Suitable models could then be used to test novel therapies that improve the function of parvalbumin+interneurons while also taking into account interactions with non-neuronal cells such as astrocytes, which may play a neuropathological role in POLG related disease. Novel treatments aimed at preventing mitochondrial dysfunction and preserving the function of parvalbumin+interneurons are likely to benefit a wide range of patients suffering from common epilepsies and neurodevelopmental disorders.

CONCLUSION

We found severe dysfunction and degeneration of inhibitory interneurons in cortical tissues from Alper's syndrome patient, which likely explains the patient's loss of inhibitory neurotransmission mediating seizure activity. Seizures will then increase the energy demands of interneurons that are already metabolically compromised, exacerbating the cycle of neuronal hyper excitability and seizure associated neurodegeneration. Our findings of parvalbumin+interneuron vulnerability *vs.* calretinin+interneuron resilience could be seen in other types of mitochondrial encephalopathies, epilepsies, and neurodevelopmental disorders associated with mitochondrial dysfunction. Modeling mitochondrial dysfunction within parvalbumin +interneurons may provide an appropriate system for testing novel

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therapeutics to alleviate seizure related dysfunction and degeneration of parvalbumin+interneurons.