The etiology, or underlying causes, of drug-resistant epilepsy can vary among individuals and may involve multiple factors. Here are some key factors that contribute to the etiology of drug-resistant epilepsy:

Genetic factors: Genetic predisposition can play a role in drug-resistant epilepsy. Certain genetic variations may influence drug metabolism, drug targets, or mechanisms of drug resistance, making individuals less responsive to conventional AEDs. Specific genetic mutations associated with drug-resistant epilepsy have been identified in some cases.

Structural abnormalities: Structural abnormalities in the brain can contribute to drug-resistant epilepsy. These abnormalities may include brain malformations, such as cortical dysplasia, hippocampal sclerosis, tumors, or brain lesions resulting from traumatic brain injury, stroke, or infections. The presence of these structural abnormalities can make it more challenging to achieve seizure control with medications alone.

Functional abnormalities: In some cases, drug-resistant epilepsy may be associated with functional abnormalities in the brain, even when structural abnormalities are not apparent. These functional abnormalities may involve abnormal electrical activity, altered neuronal networks, or imbalances in neurotransmitter systems. Such functional abnormalities can make seizures more resistant to pharmacological intervention.

Pharmacokinetic factors: Drug-resistant epilepsy may also be influenced by pharmacokinetic factors, which involve the way drugs are absorbed, distributed, metabolized, and eliminated in the body. Variations in drug absorption, distribution across the blood-brain barrier, drug interactions, or alterations in drug metabolism may impact the effectiveness of AEDs, leading to treatment resistance.

Pharmacodynamic factors: Pharmacodynamic factors refer to the specific interactions between drugs and their molecular targets in the body. Drug-resistant epilepsy can arise from alterations in the molecular targets of AEDs, leading to reduced drug efficacy. Changes in ion channels, receptors, or signaling pathways involved in neuronal excitability and seizure generation can contribute to pharmacodynamic resistance.

Other factors: Additional factors that may contribute to drug-resistant epilepsy include non-adherence to medication regimens, inadequate dosing, inappropriate drug selection, and inadequate treatment trials. Coexisting medical conditions, such as autoimmune disorders or neurodevelopmental disorders, may also affect treatment response.

It is important to note that the etiology of drug-resistant epilepsy can be multifactorial, and individual cases may involve a combination of different factors. Understanding the underlying causes of drug resistance in epilepsy is crucial for developing alternative treatment approaches, such as surgical interventions or neuromodulation techniques, in order to improve seizure control and quality of life for affected individuals.

Identifying factors involved in the development of drug resistant epilepsy (DRE) remains a challenge. Candidate gene studies have shown modulation of resistance to drugs by various multidrug resistance proteins in DRE. However the resistance to drugs in DRE could be more complex and multifactorial involving molecules in different pharmacokinetic processes.

Clinicians should consider hyaline protoplasmic astrocytopathy in the differential diagnosis in patients with drug-resistant epilepsy, especially when they are associated with developmental delay and brain malformations. Increasing awareness of this entity among pathologists may promote a better understanding of this condition as well as better diagnosis and treatment for these patients [1)]

A study for the first time analyzed the relative expression of four molecules with different drug resistance mechanisms in two most common DRE pathologies, mesial temporal lobe epilepsy (MTLE) and focal cortical dysplasia (FCD) with respect to each other and also with different non-epileptic controls.

Upregulation of breast cancer resistance protein (BCRP) and major vault protein (MVP) is associated with MTLE and FCD and these molecules not only may have the potential to predict pathology specific phenotypes but may also have therapeutic potential as adjunct treatment in these pathologies. [2)].

Neurocysticercosis (NCC) as cause of drug resistant epilepsy (DRE) is commonly reported from India.

1)
Alzoubi H, Nobile G, d'Amati A, Nobili L, Giacomini T, Tortora D, Gaggero G, Gianno F, Giangaspero F, Antonelli M, Consales A. Hyaline Protoplasmic Astrocytopathy in the Setting of Epilepsy. Am J Clin Pathol. 2023 Feb 1;159(2):120-128. doi: 10.1093/ajcp/aqac145. PMID: 36495294.
2)
Banerjee Dixit A, Sharma D, Srivastava A, Banerjee J, Tripathi M, Prakash D, Sarat Chandra P. Upregulation of breast cancer resistance protein and major vault protein in drug resistant epilepsy. Seizure. 2017 Feb 27;47:9-12. doi: 10.1016/j.seizure.2017.02.014. [Epub ahead of print] PubMed PMID: 28273590.