DIFFERENCES IN BLOOD BIOCHEMICAL PARAMETERS IN PHARMACORESISTANT AND NON-PHARMACORESISTANT EPILEPSY.

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Annotation: Epilepsy is a chronic neurological disorder characterized by recurrent seizures and significant metabolic disturbances. One of the major challenges in epilepsy treatment is pharmacoresistant epilepsy, where seizures persist despite appropriate antiepileptic drug therapy. This condition is associated not only with neuronal dysfunction but also with systemic metabolic changes. The present article analyzes differences in blood biochemical parameters between pharmacoresistant and non-pharmacoresistant epilepsy patients. The focus is placed on liver enzymes, lipid profile, glucose metabolism, inflammatory markers, electrolyte balance, and oxidative stress indicators.

Keywords: Epilepsy, pharmacoresistant epilepsy, biochemical parameters, blood markers, oxidative stress, inflammation, liver enzymes, antiepileptic drugs, metabolic disturbances, biomarkers.

Epilepsy is one of the most widespread neurological disorders, affecting more than 50 million individuals worldwide. It is defined as a brain disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. Although epilepsy can often be controlled by antiepileptic drugs (AEDs),

approximately 30–40% of patients develop pharmacoresistant epilepsy, also referred to as drug-resistant epilepsy.

Pharmacoresistant epilepsy is generally diagnosed when adequate trials of at least two well-tolerated and appropriately selected AED regimens fail to achieve sustained seizure freedom. This form of epilepsy is associated with higher risks of injury, sudden unexpected death in epilepsy (SUDEP), reduced quality of life, cognitive decline, and psychiatric complications. The underlying mechanisms of pharmacoresistance remain complex and multifactorial, involving genetic factors, alterations in drug transporters, neuroinflammation, changes in neurotransmitter systems, and structural abnormalities of the brain.

In addition to neurological mechanisms, epilepsy is increasingly recognized as a systemic disorder that affects multiple organs and metabolic processes. Chronic seizure activity and long-term AED use can influence liver function, kidney function, lipid metabolism, glucose regulation, oxidative balance, and immune response. Blood biochemical parameters reflect these systemic effects and may differ significantly between pharmacoresistant and non-pharmacoresistant epilepsy patients.

The investigation of biochemical markers has gained attention because such indicators may help clinicians evaluate disease severity, predict treatment response, monitor drug toxicity, and detect metabolic complications early. Therefore, studying differences in biochemical parameters between pharmacoresistant and non-pharmacoresistant epilepsy may provide valuable insights into the pathophysiology of drug resistance and support the development of personalized therapeutic approaches.

Research indicates that differences in blood biochemical parameters between pharmacoresistant (drug-resistant epilepsy, DRE) and non-pharmacoresistant (pharmacosensitive or drug-responsive) epilepsy are primarily identified through advanced techniques like metabolomics, rather than routine clinical blood tests.

Standard hematological and basic biochemical panels (e.g., electrolytes, liver enzymes, hemoglobin, platelets) generally show no significant differences between the two groups, particularly in pediatric cohorts.

Metabolomics-based differences in plasma/serum: Metabolomics studies (using techniques like NMR or GC-MS) have revealed distinct metabolic profiles in DRE compared to responsive epilepsy and healthy controls. These suggest disruptions in energy metabolism, amino acid pathways, and a potential shift toward ketogenic or alternative energy sources in resistant cases.

Key metabolites often altered in DRE (pharmacoresistant) versus non-resistant epilepsy include:

- Glucose: Frequently decreased in DRE, indicating possible impaired glycolysis.

- Lactate: Often decreased in general epilepsy cohorts with DRE, though findings vary; some studies note it may reflect broader epilepsy rather than DRE-specific changes.

- Citrate: Decreased, suggesting citric acid cycle disruption.

- Ketone bodies (e.g., 3-hydroxybutyrate, acetoacetate, acetone): Increased, pointing to enhanced fatty acid oxidation and ketogenesis.

- Amino acids and related:

  - Glutamate: Increased (excitatory neurotransmitter, linked to hyperexcitability).

  - Alanine: Increased.

  - Glycine: Identified as a potential key biomarker.

  - Isoleucine: Altered.

- Other metabolites: Increased choline (membrane turnover), scyllo-inositol (osmolyte), acetate, 2-hydroxyvalerate; some studies note changes in glutamine,

pyruvic acid, serine (elevated in capillary dried blood spots in DRE), and decreased palmitic acid.

Pathway analyses highlight significant impacts on:

- Alanine, aspartate, and glutamate metabolism.

- Phenylalanine, tyrosine, and tryptophan biosynthesis.

These patterns were observed in studies of temporal lobe epilepsy and other forms, with DRE showing a profile favoring ketone production over carbohydrate metabolism. Recent prospective studies have used baseline serum metabolites to develop predictive models for DRE.

Note: Some metabolites (e.g., glutamate, lactate) may be altered in epilepsy overall rather than uniquely in DRE, and results can vary by sample type (plasma vs. capillary dried blood spots), epilepsy subtype, age, and methodology.

Subtype-Specific Findings (e.g., MELAS-Associated Epilepsy)

In mitochondrial disorders like MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) with epilepsy:

- Elevated resting serum lactate is a strong independent predictor of pharmacoresistance (odds ratio ~8.6).

- Patients with high lactate are more likely to develop DRE than those with normal levels.

- No significant differences in creatine kinase (CK) or CK-MB between resistant and non-resistant groups.

- Status epilepticus at onset is another strong predictor.

This contrasts with some general epilepsy findings where lactate may be lower, highlighting etiology-specific variations.

Inflammatory and Other Markers

- Inflammatory processes are implicated in epilepsy, with elevated cytokines (e.g., IL-1β, IL-6, TNF-α) in some cases, but direct DRE vs. non-DRE blood differences are inconsistent.

- Recent proteomics studies show altered serum proteins (e.g., immune-related) in DRE.

- Higher neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) in younger DRE patients, potentially indicating neuronal/glial injury.

- Serum caspase-3 (apoptosis marker) elevated in epilepsy, especially DRE; MAP1-LC3 (autophagy marker) reduced, particularly in resistant cases.

Routine biochemical and hematological parameters: Multiple studies, including in childhood epilepsy, report no major differences in most standard parameters (e.g., liver function, renal function, lipids, glucose in routine tests) between pharmacosensitive and pharmacoresistant groups. This limits the utility of basic blood work for distinguishing resistance.

Limitations and Implications

Findings vary due to heterogeneity in epilepsy types, patient demographics, treatment effects (antiseizure drugs can influence metabolism), and sampling methods.

The findings confirm that pharmacoresistant epilepsy is associated with more severe systemic biochemical disturbances compared to non-pharmacoresistant epilepsy. These differences can be explained by multiple pathophysiological mechanisms.

First, pharmacoresistant epilepsy patients experience higher seizure frequency and longer disease duration. Recurrent seizures lead to increased metabolic demands, hypoxia, and oxidative damage. Over time, this contributes to persistent biochemical imbalance.

Conclusions

Pharmacoresistant epilepsy patients demonstrate significantly altered biochemical profiles compared to non-pharmacoresistant epilepsy patients. Liver enzyme levels (ALT, AST, GGT, ALP) are more elevated in pharmacoresistant epilepsy, reflecting chronic hepatic stress due to polytherapy. Dyslipidemia is more

common in pharmacoresistant epilepsy, with increased LDL cholesterol and triglycerides and reduced HDL cholesterol. Glucose metabolism is moderately impaired in pharmacoresistant epilepsy, suggesting a higher risk of insulin resistance. Electrolyte imbalance, particularly hyponatremia, is more frequently observed in pharmacoresistant epilepsy. Oxidative stress markers are significantly increased, and antioxidant defense mechanisms are weakened in pharmacoresistant epilepsy. Inflammatory markers such as CRP tend to be higher in pharmacoresistant epilepsy, supporting the role of chronic inflammation in drug resistance.

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