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Metabolomics for early diagnosis, pathophysiological understanding, and monitoring of neurological diseases: Organic acids and biochemical biomarkers

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1. INTRODUCTION

Metabolomics has emerged as a high-impact biomedical tool over the past decade, providing a novel perspective for early diagnosis, pathophysiological elucidation, and monitoring of various neurological disorders (WISHART, 2020). This methodology analyzes global metabolite profiles in biological samples, revealing unique biochemical signatures associated with different health conditions (NICHOLSON et al., 2019). Its ability to identify biochemical changes before clinical symptom onset offers a significant advantage over traditional diagnostic methods.

The crucial role of metabolomics is particularly evident in conditions where validated diagnostic biomarkers are scarce, leading to significant delays in diagnosis and treatment. This includes Autism Spectrum Disorder (ASD), Attention-Deficit/ Hyperactivity Disorder (ADHD), anxiety and major depression, schizophrenia, early stages of neurodegenerative diseases like Parkinson's and Alzheimer's, and subclinical inflammatory phases of Multiple Sclerosis.

1.1 The Diagnostic Revolution Driven by Urinary Organic Acids

Urinary organic acid analysis (UOA) is a non-invasive and highly informative metabolomic methodology, often described as a "window into the brain." UOA reflects a wide range of essential metabolic processes, including mitochondrial integrity, Krebs cycle function, neurotransmitter metabolism, gut microbiota activity, and redox status (ELLIOTT et al., 2020). Its non-invasive nature makes it ideal for screening and monitoring neurological conditions.

1.2 Neurological Diseases Exhibit Distinct Metabolomic Signatures

Recent metabolomic studies have identified specific and reproducible biomarkers for numerous neurological diseases. These findings allow for a deeper understanding of underlying mechanisms and pave the way for more precise diagnostics. Examples include distinct patterns for ASD (mitochondrial dysfunction, gut dysbiosis markers like p-cresol and HPHPA) (HUANG et al., 2020; ZHOU et al., 2021), ADHD (catecholaminergic metabolism abnormalities, mitochondrial stress) (GUPTA et al., 2019; KAWABATA et al., 2020), and neurodegenerative diseases such as Parkinson's and Alzheimer's (Krebs cycle disruptions, lipid stress) (TRUSHINA et al., 2021; BOZELLI et al., 2021). These unique metabolic profiles enable early identification, differentiation between clinically overlapping pathologies, and precise disease monitoring.

1.3 Metabolomics as a Tool for Personalized Medicine

The integration of metabolomics with artificial intelligence (AI) is advancing personalized medicine. This synergy facilitates the creation of prognostic models that can identify risks pre-symptomatically, select individualized therapies, monitor drug toxicity, and predict disease progression (HOLMES et al., 2021).

2. METABOLOMIC METHODOLOGY IN NEUROLOGICAL DISEASES

Metabolomics employs advanced analytical techniques and methodological approaches to explore metabolites in biological samples (WISHART, 2020; HOLMES et al., 2021). The choice of methodology is crucial for obtaining relevant and interpretable data.

2.1 Metabolomic Approaches: Untargeted and Targeted

Untargeted metabolomics aims to identify

and quantify the widest possible range of metabolites without specific pre-selection, useful for biomarker discovery and understanding complex metabolic patterns (NICHOLSON et al., 2019). Targeted metabolomics focuses on the absolute or relative quantification of specific, pre-identified metabolites, ideal for therapeutic monitoring and precise comparisons between groups (ELLIOTT et al., 2020).

2.2 Sample Types for Analysis

Different biological matrices offer unique perspectives on physiological status.

- Urine: Non-invasive, reflects mitochondrial and microbiota functions, and is highly sensitive for neurodevelopmental and psychiatric disorders (ELLIOTT et al., 2020).
- Blood (serum/plasma): Used for inflammatory biomarkers, lipids, and amino acids, providing a systemic view of metabolism, particularly in Alzheimer's, Parkinson's, and depression.
- Cerebrospinal Fluid (CSF): Directly reflects biochemical changes in the Central Nervous System (CNS), often used in Alzheimer's, Parkinson's, and schizophrenia, despite being invasive.
- Stool: Gaining prominence for gut microbiota analysis and its correlation with neuroactive metabolites in ASD and anxiety disorders.

2.3 Advanced Analytical Techniques

Sophisticated technologies are essential for metabolite identification and quantification:

- Liquid Chromatography-Mass Spectrometry (LC-MS): Widely used for non-volatile organic acids, lipids, peptides, and Krebs cycle intermediates due to its high sensitivity.
- Gas Chromatography-Mass Spectrometry (GC-MS): Ideal for volatile organic acids and microbiota metabolites, frequently used in ASD studies (HUANG et al., 2020).
- Nuclear Magnetic Resonance (NMR): While less sensitive than MS, NMR offers rapidity, reproducibility, and is non-destructive, complementing other techniques in studies like Alzheimer's (SHAO et al., 2020).

2.4 Data Processing and Integrated Clinical Interpretation

Metabolomic data requires rigorous statistical processing, including normalization, transformation, multivariate analysis, machine learning for data mining, and pathway identification (MetaboAnalyst, KEGG). HOLMES et al. (2021) emphasize that predictive models based on metabolomics are crucial for clinical application. Clinical interpretation must integrate metabolomic findings with other patient information such as inflammatory biomarkers, neuroendocrine tests, behavioral characteristics, family history, genetics, epigenetics, and microbiota analysis for a holistic understanding.

3. KEY METABOLOMIC FINDINGS IN NEUROLOGICAL DISORDERS

This section highlights robust metabolomic findings in specific neurological diseases, focusing on their characteristic biochemical profiles.

3.1 Autism Spectrum Disorder (ASD)

ASD studies reveal consistent patterns of mitochondrial dysfunction (e.g., elevated lactate, pyruvate, succinate), gut microbiota alterations (e.g., elevated p-cresol, HPHPA from *Clostridia* bacteria), and tryptophan-kynurenine pathway dysregulation (e.g., decreased serotonin, increased kynurenine) (HUANG et al., 2020; ZHOU et al., 2021; CHEN et al., 2022). These markers are indicative of compromised energy metabolism and neuroinflammation.

3.2 Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is associated with abnormalities in catecholaminergic metabolism (elevated HVA, VMA, altered tyrosine) and mitochondrial stress (elevated medium chain acylcarnitines, altered beta-oxidation) (GUPTA et al., 2019; KAWABATA et al., 2020; JACKSON et al., 2022). These reflect increased dopaminergic degradation and energy dysfunction.

3.3 Anxiety Disorders and Major Depression

Both conditions show altered energy metabolism (elevated lactate, pyruvate) and significant dysregulation of the tryptophan-kynurenine pathway (increased kynurenine, decreased serotonin), indicative of inflammatory components and oxidative stress (HAGE et al., 2022; ABBAS et al., 2021). Depression also features oxidative stress markers like elevated malondialdehyde and 5-oxoproline.

3.4 Parkinson's Disease (PD)

PD exhibits significant alterations in the Krebs cycle (elevated succinate, α-ketoglutarate, decreased citrate), dopaminergic metabolism (decreased HVA), and bioenergetic deficiency (elevated lactate, 3-hydroxybutyrate) (TRUSHINA et al., 2021; ROGERS et al., 2021). These findings underscore mitochondrial dysfunction and neuronal loss.

3.5 Alzheimer's Disease (AD)

AD is characterized by a dysfunctional Krebs cycle (decreased succinate, glutarate, citrate, increased lactate, α-ketoglutarate) and lipid stress (altered phospholipids, reduced plasmalogens) (BOZELLI et al., 2021; SHAO et al., 2020). These signatures point to early and progressive cerebral energy dysfunction and oxidative damage.

3.6 Multiple Sclerosis (MS)

MS is marked by intense inflammatory activation (elevated IFN-γ, IL-6) and oxidative stress (elevated 5-oxoproline, lactate), indicating autoimmune and oxidative damage in the CNS (AHMAD et al., 2020).

3.7 Schizophrenia

Schizophrenia presents altered brain bioenergetics (elevated lactate, pyruvate, decreased succinate) and neuroinflammation (elevated kynurenic acid), suggesting mitochondrial dysfunction and inflammatory involvement in its pathophysiology (LIU et al., 2021).

4. DISCUSSION

An integrated analysis reveals that neurological diseases share profound disturbances in energy metabolism, neurotransmission, and immune regulation. Each condition, however, manifests distinct biochemical signatures, allowing for the differentiation of clinically overlapping pathologies. A ubiquitous finding is mitochondrial dysfunction, suggesting that neurological diseases are, in large part, progressive energy failure conditions (TRUSHINA; MAZZIOTTA, 2022).

4.1 Metabolomics Reveals Pre-symptomatic Markers

Metabolomic profiles can identify diseases years before clinical symptom onset. For instance, in Alzheimer's, succinate and citrate changes appear up to 8 years prior to cognitive decline (BOZELLI et al., 2021); in ASD, urinary metabolic patterns distinguish affected children in their first year of life (HUANG et al., 2020). This underscores metabolomics' potential as an early diagnostic tool.

4.2 Organic Acids as a Window to the Brain

Urinary organic acid excretion reflects interconnected physiological processes influencing brain health, including mitochondrial function, neurotransmitter metabolism, blood-brain barrier integrity, and gut microbiota activity. This broad representation explains the strong association between urinary changes and neurological diseases. The elevation of p-cresol and HPHPA in ASD, for example, reinforces the hypothesis of gut dysbiosis as a central pathophysiological factor (RODGERS et al., 2020).

4.3 The Tryptophan-Kynurenine Pathway as an Inflammatory Axis

Recent studies emphasize that inflammation diverts tryptophan from serotonin production towards the kynurenine pathway, generating neurotoxic metabolites such as 3-hydroxykynurenine and kynurenic acid.

These compounds play a role in neuroinflammation and neurotransmission modulation, relevant across various neurological conditions (CHEN et al., 2022; ABBAS et al., 2021).

5. METABOLIC PATHWAYS

Understanding affected metabolic pathways is crucial for identifying therapeutic targets:

- Krebs Cycle: Reflects mitochondrial energy production efficiency; dysfunctions are ubiquitous in neurodevelopmental and neurodegenerative diseases.
- Tryptophan-Kynurenine Pathway (TRP-KYN): In inflammatory states, tryptophan is diverted to kynurenine, impacting serotonin synthesis and contributing to depression, anxiety, and schizophrenia.
- Catecholaminergic Metabolism: Involves neurotransmitter synthesis and degradation, with alterations in HVA and VMA seen in ADHD and Parkinson's.
- Gut Microbiota Metabolism: Bacterial metabolites influence the gut-brain axis, with implications in ASD and mood disorders.
- Lipid Metabolism and Beta-Oxidation: Alterations indicate dysfunctions in fat metabolism and cell membrane integrity, relevant in Alzheimer's and ADHD.
- Glutathione Cycle: Involved in antioxidant defense; changes indicate oxidative stress, seen in Multiple Sclerosis and depression.

Table: Main Metabolomic Changes by Disease

Disease	Inflammation Markers	Increased Metabolites	Reduced Metabolites
Autism Spectrum Disorder (ASD)	IL 6 (elevated), IL 17A (elevated)	p-cresol, HPPHA, Lactate, Succinate, Adipate	Citrate, Fumarate
Attention-Deficit/Hyperactivity Disorder (ADHD)	IL 6 (slightly elevated)	HVA, VMA, Acylcarnitines	Tyrosine, Phenylalanine
Anxiety	IL 6 (elevated)	Lactate, Pyruvate, Kynurenine	
Depression	IL 1β (elevated), CRP (elevated)	Kynurenic Acid, 3-Hydroxykynurenine	Serotonin, Succinate
Parkinson's Disease	TNF α (elevated)	Lactate, Succinate, α-Ketoglutarate	Citrate
Alzheimer's Disease	CRP (elevated)	Lactate, α-Ketoglutarate	Citrate, Succinate
Multiple Sclerosis (MS)	IFN γ (elevated), IL 6 (elevated)	5-Oxoproline, Lactate	
Schizophrenia	IL 6 (elevated)	Lactate, Kynurenic Acid	Succinate

6. CONCLUSION

Metabolomics provides a detailed view into the complex biochemical processes underlying neurological diseases. Its ability to identify early markers and differentiate unique or shared metabolic profiles, combined with artificial intelligence, positions it as an essential tool for advancing diagnosis, treatment, and ultimately, improving the quality of life for patients. The integrated clinical interpretation of these findings, alongside inflammatory biomarkers, neuroendocrine tests, behavioral characteristics, family history, genetics, epigenetics, and microbiota analysis, paves the way for precision medicine in neurology, enabling more personalized and effective therapies.

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