American Journal of Pediatrics
2026, Vol. 12, No. 2, pp. 63–68
https://doi.org/10.11648/j.ajp.20261202.12

Research Article

Metabolomic and Molecular Genetic Markers of Obesity-associated Epilepsy in Children

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Abstract

Background. Various epileptic syndromes can be comorbid with other pathologies, in particular, with excess weight. Research on the correlation between obesity and epilepsy in children is quite controversial. Identifying various metabolomic and molecular genetic markers of epilepsy is an extremely interesting task, which will allow the development of diagnostic algorithms for this pathological condition. The aim of the work is to identify the main metabolic and molecular genetic changes in epilepsy in children associated with obesity. Methods. The study included 24 patients aged from 1 year to 17 years: 16 patients with with epilepsy due to obesity and 8 patients of the control. The gender distribution was 15 girls and 9 boys. The study of the profile of 60 organic acids in urine was carried out by HPLC-MS. Targeted sequencing of mitochondrial dynamics genes (MFN1, MFN2, OPA1, DRP1) was performed using the NGS method. Results. In the case-group the upper reference limit of a number of markers of the Krebs cycle, mitochondrial dysfunction, bacterial dysbiosis and lactic acid levels were exceeded. Targeted NGS sequencing of four mitochondrial dynamics genes (MFN1, MFN2, OPA1, DRP1) of patients with epilepsy due to obesity and comparison group did not reveal pathological mutations in mitochondrial dynamics genes. However, 14 of the 16 patients with obesity-associated epilepsy were found to have the heterozygous OPA1 rs76426470 genetic variant (GA genotype), while all patients in the control group had the homozygous variant (GG genotype). Conclusion. Thus, we have identified a number of metabolic markers associated with epilepsy in children against the background of obesity.

Keywords

Epilepsy, Obesity, Organic Acids, HPLC/MS, Molecular Genetics

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Received: 26 January 2026; **Accepted:** 4 February 2026; **Published:** 30 May 2026

1. Introduction

Epilepsy is a chronic, heterogeneous neurological disorder. Its extremely high prevalence (it affects over 70 million people each year and results in 125,000 deaths) makes it one of the most important problems in modern neurology [1]. Epilepsy is often accompanied by comorbidities such as cognitive and depressive disorders and obesity [2, 3]. The etiopathogenesis of obesity in children with epilepsy is currently being actively studied. One factor contributing to weight gain in epileptic syndromes is the use of valproate. However, obesity in epilepsy may be associated not only with the use of anticonvulsants, but also with certain metabolic and molecular genetic characteristics of patients [2].

Contradictory results have been obtained in the literature regarding the correlation between various epileptic syndromes and obesity. [1]. For example, Zhhou et al. performed a randomized linkage analysis of obesity and epilepsy and showed their relationship [4]. To this end, the authors conducted a two-sample study with Mendelian randomization for four indicators of obesity and epilepsy and its seven subtypes with reverse Mendelian randomization and multivariate Mendelian randomization to identify a statistically significant association. There are also a number of studies that show that patients with epilepsy have an increased risk of obesity [5-7]. But, in contrast, Pfeifer's et al. work found a positive correlation between underweight and the risk of developing epileptic syndromes [8]. A number of other studies have not found a positive correlation between epileptic syndromes and excess weight in patients. [1, 9].

It is of interest to identify metabolic and molecular genetic profile features that correlate with epilepsy in overweight children. It is particularly interesting to study the profile of organic acids in urine and genes involved in mitochondrial dynamics, which may potentially be associated with the pathology in question [10, 11].

The aim of our work is to identify key metabolic and molecular genetic markers in obesity-associated epilepsy in children in order to develop a personalized approach to diagnosing this pathological condition.

2. Materials and Methods

The study included 24 patients aged 1 to 16 years (mean age 11.7 years). The gender distribution was 15 girls and 9 boys. Patients were recruited from the Psychoneurology Department No. 1 of the V. F. Voyno-Yasenetsky Scientific and Practical Center for Specialized Medical Care for Children, Moscow Health Department. The study was in line with the Declaration of Helsinki. The need for ethical approval was waived by Local ethics committee of V. F. Voyno-Yasenetsky Scientific and Practical Center for Specialized Medical Care for Children. Informed consent (consent to participate and consent for publication) was obtained from all participants or, if participants were under 18 years of age, from a parent and/or legal guardian. The distribution of patients by clinical diagnoses is presented in Table 1.

Table 1. *Distribution of clinical diagnoses of patients in the study sample and comparison group.*

Clinical diagnosis	Number of patients
Study sample (epilepsy + obesity)	
Unrefined epilepsy with constitutional-exogenous obesity and mental retardation	1
Idiopathic (genetic) focal epilepsy with constitutional-exogenous obesity	2
Generalized idiopathic (genetic) epilepsy. S. Jeevons. Constitutional-exogenous obesity.	4
Focal (idiopathic) genetic epilepsy with constitutional-exogenous obesity	1
Focal epilepsy of unknown etiology with constitutional-exogenous obesity	1
Focal symptomatic (structural) epilepsy with constitutional-exogenous obesity	4
Focal idiopathic epilepsy with secondary generalized seizures and constitutional-exogenous obesity	1
GEFS+ syndrome (febrile seizures) with constitutional-exogenous obesity	1
Juvenile myoclonic epilepsy (Yantsa s.) with constitutional-exogenous obesity	1
Comparison group	
Focal epilepsy of unknown etiology with autoimmune polyglandular syndrome	1
Metabolic syndrome with morbid obesity without epileptic activity	5
Immune epilepsy after limbic encephalitis	1

Clinical diagnosis	Number of patients
Follicular thyroid tumor. Exogenous-constitutional obesity.	1

All children collected a morning urine sample into a sterile container for organic acid profiling using chromatography-mass spectrometry. The urine was stored at -70°C in an ultra-low-temperature freezer. Organic acid and derivative content were measured using a HPLC-MS/MS system equipped with a Sciex Qtrap 5500 (Sciex, USA) mass spectrometer and a Waters Acquity Premier chromatograph (Sciex, USA). Method for Determining Organic Acids in Urine. Quantitative determination of organic acids in urine was performed in two stages. Analysis of keto acids (acetoacetic, 3-hydroxybutyric) included: dilution of urine with deionized water in a ratio of 50:50 v/v, and subsequent derivatization: addition of 50 µl of buffer (a mixture of methylhydroxylamine hydrochloride in methanol with pyridine (2:8 v/v). To determine other organic acids, urine samples were diluted with deionized water in a ratio of 50:50 v/v, and then introduced into the chromatographic system without derivatization. Measurement of the content of organic acids and their derivatives was carried out using an HPLC-MS/MS system equipped with a Sciex Qtrap 5500 mass spectrometer with a Waters Acquity Premier chromatograph, with preliminary separation on a chromatographic column with a reversed phase sorbent Phenomenex silica core with a sorbent particle size of 2.6 µm, 100A, C18 Kinetex© (50 × 2.10 mm) (Phenomenex; USA). Reference intervals for each of the indicators were calculated using an “indirect” retrospective method of recruiting a reference control sample, which consisted of 443 apparently healthy children of different age groups [12].

Targeted sequencing of four mitochondrial dynamics genes (MFN1, MFN2, OPA1, DRP1) of patients with epilepsy and comparison group due to obesity was performed using the Helicon G50 (MGI Tech, China) genetic analyzer according to the standard paired-end read protocol.

To compare the mean values and differences in several urinary organic acid levels between the obese epilepsy group and the comparison group, the Student's t-test for unrelated populations with a significance threshold of P=0.05 and the Mann-Whitney test with the same significance threshold were calculated. Statistical calculations were performed using Statistica 10.0 (StatSoft, USA).

3. Results

The main deviations in the profile of organic acids in urine in patients with various epileptic syndromes against the background of obesity were identified in the following metabolic parameters (in 11 out of 16 patients): Krebs cycle markers, markers of mitochondrial dysfunction, detoxification markers, markers of bacterial dysbiosis.

Also, these patients showed a deviation in lactic acid levels outside the reference intervals. Elevated lactic acid levels may be associated with certain metabolic disorders in children with epilepsy due to obesity, such as lipoic acid deficiency. A deficiency results in the formation of lactic acid. In the comparison group (patients with metabolic syndrome without signs of epileptic activity) and patients with a normal body mass index and epilepsy, urinary lactic acid levels also exceeded the reference interval, but only at the lower limit. Statistical analysis using the T-test and Mann-Whitney test between the patient sample and the comparison group revealed significant differences (P < 0,05). Higher mean and median lactic acid levels were also demonstrated in the study sample of children compared to the comparison group (Table 2). Thus, significant metabolic disturbances were observed in the group of children with epilepsy and obesity.

Table 2. *Mean and median values of lactic acid levels in the group of children with epilepsy against the background of obesity and in the comparison group.*

Lactic acid level in urine, mmol/mol creatinine	Average value	Median value	Dispersion	Standard deviation
Patients	11,51	297,52	4,62	3,81
Comparison group	4,26	17,25	4,54	1,95

Most children with epilepsy due to obesity and children in the comparison group showed an increase in the level of 4-methyl-2-oxovaleric acid, which may be associated with a secondary disorder of amino acid metabolism in such patients associated with either metabolic syndrome or immune disorders (Table 3). Statistical analysis of this metabolic marker using the T-test revealed no significant differences between the group of children with epilepsy due to obesity and the comparison group

(P>0,38), although it is known that a number of monogenic amino acid metabolism disorders can manifest as various epileptic syndromes [13]. However, the association of multifactorial epileptic syndromes with such disorders has been poorly studied. Therefore, this issue requires further research.

Table 3. *Mean and median values of 4-methyl-2-oxovaleric acid levels in the group of children with epilepsy due to obesity and in the comparison group.*

Urine 4-methyl-2-oxovaleric acid level, mmol/mol creatinine	Average value	Median value	Dispersion	Standard deviation
Patients	0,31	0,255	0,04	0,17
Comparison group	0,27	0,275	0,02	0,04

In 3 patients with epilepsy against the background of obesity, an increase in the level of fumaric acid, which is a metabolic marker of the Krebs cycle, was detected, although a comparative analysis by Student's T-test of the mean value of this parameter in the group of patients with epilepsy and obesity (0,94 ± 0,24 mmol / mol creatinine) relative to the comparison group (0,27 ± 0,22 mmol / mol creatinine) revealed weak statistically significant differences (P> 0,053), although at present a severe monogenic pathology associated with a partial deficiency of the Krebs cycle enzyme fumarase (complete blockade of this enzyme is incompatible with life) has been described, which is manifested by a convulsive syndrome, microcephaly, a number of dysmorphic signs and leads to the death of patients in early childhood [14]. In 6 patients, an excess of the upper limit of 2-ketoglutaric acid was detected. A comparative analysis of the mean level of this metabolite (36,6±9,91 mmol/mol creatinine) in the patient group versus the comparison group (11,9±1,87 mmol/mol creatinine) using Student's t-test showed a statistically significant difference between these samples (P<0,02). Statistical comparative analysis of the patient sample and the comparison group for this metabolite also showed a significant difference (P<0,05). A correlation analysis and ROC curve calculation were also performed using ketoglutaric acid data from both groups. The Pearson correlation coefficient was 0.85, indicating a strong positive correlation between ketoglutaric acid levels in the group of children with epilepsy due to obesity and in the comparison group. Studies have shown that some anticonvulsants, such as valproates, can block the reductive amination of α-ketoglutarate caused by the chemoconvulsant metabolite pentylenetetrazol [15]. Thus, this Krebs cycle marker may play a role in the etiopathogenesis of epileptic activity in cerebral cortex neurons. However, the role of disturbances in this metabolic cycle in the etiopathogenesis of epileptic syndromes in obesity remains unclear. Therefore, the involvement of Krebs cycle components in the etiopathogenesis of metabolic forms of epilepsy requires further study.

Also, elevated levels of mitochondrial dysfunction markers were detected in a number of patients with epilepsy against a background of obesity: adipic acid in 5 patients, triethylmalonic acid in 1 patient, and methylsuccinic acid in 1 patient. In the comparison group, all studied markers of mitochondrial dysfunction were within the normal range. Statistical analysis of the mean value of adipic acid in the group of patients with epilepsy against a background of obesity (2,97±0,78 mmol/mol creatinine) versus the comparison group (1,87±0,39 mmol/mol creatinine) did not show statistically significant differences (P>0.22). The same analysis performed for ethylmalonic acid (2,79±0.42 mmol/mol creatinine versus 1,58 ±0,42 mmol/mol creatinine, respectively) showed a statistically significant difference (P<0,02). Currently, secondary mitochondrial dysfunction associated with epileptic activity of cortical neurons, leading to their hypoxia and potential death, has been identified, but the role of primary mitochondrial disorders in the genesis of epileptic seizures is still under debate. [16]. However, the role of mitochondrial dysfunction and possible disturbances in mitochondrial dynamics in children with epileptic syndromes against the background of excess weight remains insufficiently studied and requires further metabolic and molecular genetic studies [17].

Targeted NGS sequencing of four mitochondrial dynamics genes (MFN1, MFN2, OPA1, DRP1) of patients with epilepsy due to obesity and comparison group did not reveal pathological mutations in mitochondrial dynamics genes. However, 14 of the 16 patients with obesity-associated epilepsy were found to have the heterozygous OPA1 rs76426470 genetic variant (GA genotype), while all patients in the control group had the homozygous variant (GG genotype). Further studies on a larger sample are needed to determine the association of this genetic variant with obesity-associated epilepsy.

4. Discussion

Thus, in a group of patients with various epileptic syndromes against the background of obesity, the following disturbances in the profile of organic acids in urine were identified.

1) An increase in the level of 4-methyl-2-oxovaleric acid, which may be associated with a disorder of amino acid metabolism, since this metabolite serves as a marker of

such disorders [18].

2) Excess lactic acid may be associated with a deficiency of lipoic acid and disturbances in the pyruvate dehydrogenase complex [19].
3) Patients with excess fumaric acid and 2-ketoglutaric acid demonstrate abnormalities in the Krebs cycle which may indicate hypoxic disorders [20].
4) In a group of patients with epilepsy and obesity, elevated urinary levels of several metabolic markers associated with mitochondrial dysfunction were observed. It is possible that mitochondrial dysfunction in epilepsy and obesity may be part of a single pathological process associated with impaired mitochondrial lipid peroxidation due to hypoxia [21, 22]. These changes may also be associated with disruption of mitochondrial dynamics.

As an additional therapy (along with the basic anticonvulsant treatment prescribed by a specialized pediatric neurologist-epileptologist), such patients are recommended to: 1) prescribe a ketogenic diet, as its effectiveness in drug-resistant epileptic syndromes has been proven, especially in children; 2) a diet rich in antioxidants, since the inclusion of foods containing vitamins C, E and carotenoids helps reduce oxidative stress; 3) use B vitamins: the addition of vitamins B1, B6 and B12 can help normalize the Krebs cycle; 4) prescribe prebiotics, the use of which can restore the intestinal microflora, which can be disrupted in patients with epilepsy due to obesity.

Thus, the study results confirm the importance of a personalized approach to the diagnosis and treatment of epilepsy in children with obesity. Particular attention should be paid to the study of mitochondrial function and metabolic disorders, as they significantly influence the clinical course of epilepsy. Further molecular genetic studies on larger samples are needed to identify associations between genetic variants and epilepsy in obesity.

Abbreviations

HPLC-MS/MS	High-performance Liquid Chromatography/Mass Spectrometry
NGS	Next-generation Sequencing
GEFS+	Genetic Epilepsy with Febrile Seizures+

Author Contributions

Perevezentsev Oleg Alexandrovich: Data curation, Formal Analysis, Writing – original draft

Mamedov Ilgar Salekh: Conceptualization, Funding acquisition, Software, Supervision, Validation, Writing – review & editing

Zolkina Irina Vyacheslavovna: Conceptualization, Formal Analysis, Investigation

Kulakova Ekaterina Gennadievna: Conceptualization, Investigation, Resources

Tatarinov Petr Anatolyevich: Supervision, Validation, Writing – review & editing

Krapivkin Alexey Igorevich: Supervision, Validation

Data Availability Statement

Statement that all data are available in the text.

Conflicts of Interest

The authors declare no conflicts of interest.

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