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Mitochondrial Dysfunction and Metabolic Indicators in Patients with Drug-Naive First-Episode Schizophrenia: A Case-Control Study

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Objective: This paper aims to explore the expression characteristics of mitochondrial function-related genes in patients with first-episode schizophrenia (SCZ)and the correlation between differentially expressed genes and clinical metabolic indicators.

Methods: Twenty patients with first-episode SCZ who had not taken antipsychotic drugs (patient group) and twenty healthy controls (control group) were included. Quantitative real-time PCR technology was used to detect the expression levels of genes related to mitochondrial quality control and oxidative phosphorylation in peripheral blood leukocytes, and metabolic indicators such as blood biochemistry and blood glucose were collected.

Results: The gene expression levels of key genes related to mitochondrial function, PGC-1a, PARK2, and LC3B, in the patient group were significantly lower than those in the control group ($P < 0.05$). Correlation analysis showed that the expression level of PGC-1a gene in the patient group was negatively correlated with very low-density lipoprotein levels ($r = -0.451$), and the expression level of PARK2 gene in the patient group was negatively correlated with uric acid levels ($r = -0.447$).

Conclusion: The expression levels of multiple key genes in the mitochondrial quality control and oxidative phosphorylation processes in patients with first-episode SCZ display a downward trend. The differentially expressed genes are correlated with the metabolic abnormalities of the patients, suggesting that mitochondrial dysfunction may be related to the high incidence of metabolic diseases in patients with SCZ.

Keywords: first-episode, schizophrenia, drug naive, mitochondria dysfunction, metabolic indicators, metabolic indicators

Introduction

Schizophrenia (SCZ) is a severe mental disorder, mainly manifested by mental symptoms such as hallucinations, delusions, speech disorders, and cognitive impairments.[1] SCZ affects hundreds of millions of people worldwide and has a lifetime prevalence rate of approximately 1%.[2] SCZ shows a distinct early-onset nature, has a high treatment cost, and is difficult to cure, so it imposes a heavy burden on families and society. The etiology and pathogenesis of SCZ remain unclear, and patients often present with significant metabolic disorders.[3] In recent years, the hypothesis of mitochondrial dysfunction in patients with SCZ has received extensive attention from local and international scholars.[4,5] This hypothesis posits that abnormalities in the mitochondrial oxidative phosphorylation can cause the accumulation of reactive oxygen species and an intensification of mitochondrial damage, ultimately leading to insufficient energy supply in the central system and abnormal neural activities, while in the peripheral system, it increases the risk of metabolic diseases by influencing the catabolism of glucose and fatty acids.[6,7] Numerous studies have previously reported abnormal mitochondrial oxidative phosphorylation in patients with SCZ, such as abnormal activities of complexes I and IV in the frontal cortex, cerebellum, and striatum of the central system,[8–10] In the peripheral blood lymphocytes of patients with

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SCZ, the number and density of mitochondria are significantly reduced, suggesting widespread abnormalities in mitochondrial oxidative phosphorylation;[11] however, the existing evidence still has certain limitations and fails to confirm systematically the abnormal changes in mitochondrial function in patients with SCZ. Mitochondrial quality control is a key process for mitochondria to maintain their own structural and functional stability, complete self-renewal, and ensure the energy demands of cells,[12] and it is crucial for elaborating the role of mitochondrial function in the pathological mechanism of diseases. Currently, systematic research on this process in patients with first-episode SCZ, as well as direct evidence of mitochondria's involvement in the metabolic abnormalities of patients are lacking. In this paper, the quantitative real-time PCR (qPCR) technique is employed to analyze systematically the expression characteristics and quality control of mitochondrial function-related genes in the peripheral blood leukocytes of patients with SCZ, and the correlation of differentially expressed genes with clinical metabolic indicators is analyzed simultaneously to explore the potential association between mitochondrial dysfunction and the metabolic characteristics of patients to provide more evidence to support the abnormal mechanism of mitochondrial dysfunction in patients with SCZ.

Methods

Study Design and Participants

A cross-sectional case-control study was conducted.

Patient

From January 2023 to June 2024, 20 patients from Shandong Mental Health Hospital with first-episode SCZ who met the DSM-V diagnostic criteria were included. Inclusion criteria: a. Patients with first-episode SCZ who met the DSM-V diagnostic criteria and had not taken antipsychotic drugs; b. Age ranged 18–60 years, regardless of gender; c. Symptom assessment: Positive and Negative Syndrome Scale score ≥ 60 points and Clinical Global Impression Scale ≥ 4 points; d. Blood lipid, weight, blood pressure, and blood sugar all within the normal range. Exclusion criteria: a. Patients with metabolic diseases or other somatic diseases; b. Patients with dementia, brain trauma, and other complex neuropsychiatric disorders; c. Based on the medical history provided by the patients and their families, patients who had suicidal attempts, suicidal thoughts, or suicidal behaviors in the past or at present; d. History of alcohol abuse or substance abuse in the past year; e. Female patients during pregnancy.

Control

From April 2024 to June 2024, 20 healthy controls from the medical staff of Shandong Mental Health Center Hospital were included. Inclusion criteria: a. Diagnosed without any mental illness by the Mini International Neuropsychiatric Interview; b. Age ranged 18–60 years, regardless of gender; c. Normal blood lipid, weight, blood pressure, and blood sugar; d. No history of mental illness and family genetic history of mental illness. Exclusion criteria: a. Those with hypertension, diabetes, metabolic syndrome, and other metabolic diseases; b. Those with somatic, neurological, and cerebrovascular diseases; c. Female during pregnancy. This study was reviewed and authorized by the Medical Ethics Committee of Shandong Mental Health Center Hospital approval number KYSIWLL2024-1-030. All subjects were informed of this trial and signed the informed consent form.

Research Process

Research Data Collection

General clinical data of the subjects were collected, including age, gender, height, weight, and BMI. After an overnight fast of the subjects, blood samples were drawn, and hematological and metabolic parameters such as blood lipids, blood proteins, fasting blood glucose, and uric acid were determined using a standard hospital biochemical analyzer.

Blood Sample Processing

The subjects were required to be on an empty stomach. Under aseptic conditions, 10 milliliters of blood was drawn from the peripheral veins using disposable blood collection needles and transferred into vacuum blood collection tubes. At room temperature, the samples were centrifuged at a speed of 3000 revolutions per minute for 10 minutes. The grayish-

white dense layer (ie, the isolated white blood cells) was aspirated into a sterile cryopreservation tube using a pipette and stored in a −80°C refrigerator for the relevant detection of messenger RNA (mRNA).

RNA Extraction and qPCR Reaction

First, 200 μL of blood was added to 800 μL of TsingZol Reagent mixed well, and allowed to stand at room temperature for 5 min. Next, 200 μL of chloroform was added, vortexed for 15 sec and allowed to stand for 5 min. Centrifugation at 4°C and 12,000 rpm/min for 15 min followed, 400 −500 μL of the upper aqueous phase was aspirated to a new EP tube, an equal volume of isopropanol was added, and placed at−20°C for 30 min. Centrifugation at 4°C and 12,000 rpm/min for 10 min followed, the supernatant was discarded, 1 mL of 75% ethanol was added, centrifugation followed for 5 min the supernatant was discarded, drying followed, and then 50 μL of RNase-Free H2O was added to obtain the RNA solution. Reverse transcription was performed using the TsingKe Reverse Transcription Kit SynScript®III RT SuperMix for qPCR. The cDNA product obtained by reverse transcription was diluted five times and used as the qPCR template, and amplification was performed using the TsingKe Arti Can CEO SYBR qPCR Mix.

Relative Quantitative Result Calculation

The target genes and corresponding primer sequences included in this study are shown in Table 1. GAPDH was used as the internal reference gene for the amplification reaction. The $2^{-\Delta\Delta Ct}$ method was used based on the Ct value, and the expression difference was calculated according to the amplification efficiency of 100%. Calibration was performed with the internal reference gene to obtain the target gene in each cell; calibration was done with the control sample of "1" to obtain the relative gene expression level.

Table 1 Primer Sequences Used to Assess the Expression Levels of Genes Related to Mitochondrial Quality Control and Oxidative Phosphorylation

Primer Name	Primer Sequence (5′ to 3′)
1-NRF2-F2	CTCCTACTGTGATGTGAAATGCT
1-NRF2-R2	GAAACTAGCCCAAATGGTGTCC
2-SIRT1-F	ACATAGACACGCTGGAACAGG
2-SIRT1-R	TCCTCGTACAGCTTCACAGTC
3-NRF1-F2	AGTCCATGTTCCTTTGTGGTG
3-NRF1-R2	GAGGCAGTCAAAGACAGAATGG
4-TFAM-F	GCAAGTTGTCCAAAGAAACCTGTA
4-TFAM-R	CAACGCTGGGCAATTCTTCTAAT
5-PGC-1α-F3	GCCTTCATGCCGTGGTAAGT
5-PGC-1α-R3	ACTGTTGTTCTCGGAGTCGTT
6-P62-F	GTGAACTCCAGTCCCTACAGATG
6-P62-R	GCTCCGATGTCATAGTTCTTGGT
7-PINK1-F2	ACGTTCAGTTACGGGAGTGG
7-PINK1-R2	GCTCATCCGTCACTTTCGCT
8-PHB2-F	AGAACCCTGGCTACATCAAACTT
8-PHB2-R	AGGCTCATTTCTTACCCTTGATGA
9-PARK2-F3	TGCACAGGAAGGGTGTAACAA
9-PARK2-R3	TGTCAGATAATCTCAACACACTTCA
10-LC3B-F	TCGAGAGCAGCATCCAACC
10-LC3B-R	CATGCTGTGTCCGTTCACCA
11-MFN1-F2	GCACCTATGACCAAGCCCA
11-MFN1-R2	TCAGGCAAACAGGTTTTATTTTCAT
12-MFN2-F2	TACCACTGAGGGAGAGACCC
12-MFN2-R2	GTCTTGCGCTCCAGCAAATG

(*Continued*)

Table 1 (Continued).

Primer Name	Primer Sequence (5′ to 3′)
13-YME1L-F	ACAACAGGTGCTTCCAGTGA
13-YME1L-R	TGTTCGATGGCAGATTGGGT
14-OPA1-F	ATAACTATCCTCGCCTGCGG
14-OPA1-R	TGGTGTAACCTGGCTCAGAC
15-MFF-F	GCAGCTTCACTAAGACGACAG
15-MFF-R	TGATGTTACCTCTAGCGGCG
16-DRP1-F2	ACATGCTATGGTAATGCACTTGCT
16-DRP1-R2	CTCAGTTTAAGGGCCAACAAAGG
17-FIS1-F	TACCGGCTCAAGGAATACGAGAA
17-FIS1-R	TTCAGGATTTGGACTTGGACACA
18-MTATP8-F	ACAAACTACCACCTACCTCCCT
18-MTATP8-R	GGCAATGAATGAAGCGAACAGATT
19-AIF-F	GTGGCCTGGAAATAGACTCAGAT
19-AIF-R	GCCCAAATCACTCCAGAACATTG
20-NDUFV2-F	AAGGCAGAATGGGTGGTTGC
20-NDUFV2-R	GCCTCCAGTATGCTGTCAGAG
21-MTCO2-F	GCTGTCCCCACATTAGGCTT
21-MTCO2-R	CGATGGGCATGAAACTGTGG
GAPDH-F	GGAGTCCACTGGCGTCTTCA
GAPDH-R	GTCATGAGTCCTTCCACGATACC

Statistical Processing

Statistical analysis was performed using IBM SPSS 26.0 statistical software. General demographic data and clinical metabolic indicators of the patient group and the control group were expressed as $\bar{x}\pm s$. Independent sample *t*-tests and nonparametric tests were used for intergroup comparisons, and chi-square tests were used for intergroup comparisons of gender. Mann Whitney rank sum tests were used to compare the intergroup differences in the expression levels of mitochondrial function-related genes. Spearman test was employed to analyze the correlation between the expression levels of differential genes and clinical metabolic indicators in the control group and the patient group.

Results

Comparison of General Demographic Data and Clinical Metabolic Indicators Between the Two Groups

The patient group and the control group each had 20 cases. No statistically significant differences were noted in age, gender, height, weight, and BMI between the two groups. No significant differences were observed in triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, albumin, and fasting blood glucose concentrations between the two groups ($P > 0.05$). The years of education in the patient group were significantly lower than those in the control group ($P < 0.05$). Table 2.

Analysis of Mitochondrial Function-Related Gene Expression Levels in the Two Groups

The expression levels of mitochondrial quality control-related genes were corrected using GAPDH as the internal reference gene. The expression levels of mitochondrial function-related genes are shown in Table 3. After correction, the gene expression levels of mitochondrial biogenesis-related gene PGC-1α, mitochondrial autophagy-related genes PARK2, and LC3B in the patient group were significantly lower than those in the control group ($P < 0.05$). No significant differences were noted in the remaining mitochondrial-related genes compared with the normal control group ($P > 0.05$).

Table 2 Comparison of General Demographic Data and Clinical Metabolic Indicators Between the Patient Group and the Control Group

Project	Patient Group (n= 20)	Control Group (n=20)	Z/t/χ^2	P
Age (years)	29.1±7.61	31.35±7.33	−1.09	0.278
Gender (Male/Female)	(10/10)	(6/14)	1.67	0.197
Height (cm)	166.45±6.64	163.75±8.11	−1.28	0.202
Weight (kg)	59.45±10.31	59.74±14.01	−0.71	0.481
BMI (kg/m2)	21.40±3.26	22.05±3.41	−0.05	0.957
Triglycerides (mmol/L)	0.81±0.38	0.80±0.30	−0.18	0.860
Total cholesterol (mmol/L)	4.00±0.65	4.15±0.59	−1.19	0.234
High-density lipoprotein cholesterol (mmol/L)	1.32±0.23	1.31±0.31	−0.22	0.829
Low-density lipoprotein cholesterol (mmol/L)	2.14±0.40	2.30±0.38	−1.49	0.137
Very low-density lipoprotein cholesterol (mmol/L)	0.80±0.26	0.90±0.26	−1.87	0.062
Albumin (g/L)	45.69±4.29	46.84±3.15	−1.12	0.261
Fasting blood glucose (mmol/L)	4.86±0.67	4.62±0.65	−1.33	0.185
Uric acid (μmol/L)	360.51±125.81	–	–	–
Years of education (years)	13.45±3.91	16.6±1.79	−3.60	<0.001
Family history (Negative/Positive, cases)	(13/7)	(20/0)	–	0.008

Note: Data given as mean ± standard deviation. No significant differences between groups on any variable.
Abbreviation: BMI, Body Mass Index.

Table 3 Analysis of Mitochondrial Function-Related Gene Expression Levels in the Patient Group and the Control Group

Gene	Patient Group (n = 20)	Control Group (n=20)	FC	P	U	Z
Mitochondrial biosynthesis pathway						
SIRT1	0.29±0.14	0.25±0.16	1.16	0.286	152	−1.068
NRF1	0.49±0.38	0.41±0.22	1.20	0.593	171	−0.534
NRF2	1.23±0.87	1.40±0.74	0.88	0.314	146	−1.007
TFAM	0.57±0.31	0.58±0.27	0.98	0.838	173	−0.205
PGC-1α	0.04±0.04	0.05±0.02	0.8	0.026	92	−2.222
Mitochondrial autophagy pathway						
PINK1	0.67±0.57	0.85±0.63	0.79	0.261	150	−1.124
P62	0.57±0.23	0.76±0.40	0.75	0.188	135	−1.316
PHB2	1.12±0.54	1.13±0.63	0.99	0.646	147	−0.459
PARK2	0.05±0.05	0.08±0.05	0.625	0.019	94	−2.34
LC3B	1.8±0.9	2.9±1.5	0.62	0.022	102	−2.292
Mitochondrial fusion pathway						
MFN1	0.78±0.62	0.67±0.35	1.16	0.942	178	−0.073
MFN2	1.60±1.46	1.40±0.89	1.14	0.85	193	−0.189
OPA1	0.37±0.20	0.29±0.13	1.28	0.286	152	−1.068
YME1L	0.59±0.32	0.70±0.27	0.84	0.181	127	−1.337
Mitochondrial fission pathway						
MFF	0.75±0.59	0.66±0.32	1.14	0.844	183	−0.197
DRP1	0.71±0.52	0.60±0.30	1.18	1.0	171	0
FIS1	3.37±2.23	4.99±3.73	0.68	0.121	120	−1.55

(*Continued*)

Table 3 (Continued).

Gene	Patient Group (n = 20)	Control Group (n=20)	FC	P	U	Z
Oxidative phosphorylation-related pathway						
NDUFV2	1.30±1.06	1.15±0.57	1.13	0.539	159	−0.614
MTATP8	313.55±221.96	343.17±208.88	0.91	0.564	152	−0.577
$MTCO_2$	371.71±289.26	389.80±264.99	0.95	0.649	156	−0.456
AIF	0.17±0.11	0.14±0.08	1.21	0.605	154	−0.517

Notes: Data given as mean ± standard deviation.
Abbreviation: FC, Fold Change.

Correlation Analysis of Differential Gene Expression Levels and Clinical Metabolic Indicators

The differentially expressed genes in the two groups were correlated with metabolic indicators in the control group and the patient group. The results showed that the expression level of PGC-1a gene in the patient group was negatively correlated with sd-LDL-C ($r = -0.451$, $P = 0.046$), and the expression level of PARK2 gene in the patient group was negatively correlated with uric acid ($r = -0.447$, $P = 0.048$) Figure 1.

Discussion

Mitochondrial dysfunction is considered to play an important role in SCZ, but the specific mechanism remains unclear. Some studies have identified that the number, integrity, and dynamic balance of the working network of mitochondria are mainly regulated by the quality control, including mitochondrial biosynthesis, autophagy, fusion, and fission.[13] In recent years, an increasing number of studies have begun to focus on the abnormalities of mitochondrial quality control in mental disorders. This study verified the changes in the expression levels of mitochondrial function-related genes in patients with first-episode SCZ. This study found a significant downregulation of the expression of multiple genes involved in the mitochondrial quality control process (PGC-1α, PARK2, and LC3B), suggesting that impaired quality control and the resulting mitochondrial dysfunction may be the key link of mitochondrial dysfunction in SCZ.

Mitochondria increase in number through biosynthesis and form larger mitochondria through the activation of the mitochondrial fusion, thereby generating more ATP to provide energy for the body. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is considered the most important regulator in mitochondrial synthesis.[14] PGC-1α initiates mitochondrial biosynthesis and acts as a coactivator of peroxisome proliferator-activated receptor gamma (PPARγ) and other nuclear receptors,[15] PGC-1α participates in various metabolic processes, including mitochondrial biosynthesis, adaptive thermogenesis, glucose uptake, hepatic gluconeogenesis, hepatic fatty acid oxidation, and adipocyte differentiation.[16] PPARγ is a transcription factor that regulates the expression of multiple genes and is closely related to adipocyte differentiation and lipid metabolism. Studies have shown that PGC-1α regulates lipid metabolism through various different pathways.[17] In this study, we found that the expression of PGC-1α in patients with untreated first-episode SCZ was significantly lower than that in the control group, which is consistent with the results of previous studies.[18] Additionally, the gene expression level of PGC-1α was negatively correlated with the concentration of the blood lipid-related indicator sd-LDL-C. This outcome indicates that the lower the gene expression level of PGC-1α, the higher the concentration of sd-LDL-C. This finding might be one of the reasons why patients with SCZ are prone to cardiovascular and metabolic-related diseases. This finding further proves that the mitochondrial biosynthesis of patients with SCZ is impaired. However, no significant differences were observed in other related genes of mitochondrial biosynthesis (SIRT1, NRF1, NRF2, and TFAM) in this study. Previous studies have shown that SIRT1 can affect mitochondrial biogenesis, glucose uptake, and lipid metabolism by regulating PGC-1α, and its expression is downregulated under insulin resistance.[19] Nuclear respiratory factor 1 (nuclear transcription factor 1, NRF1) and 2 (nuclear transcription factor 2, NRF2) have similar functions and can mediate the replication and transcription of

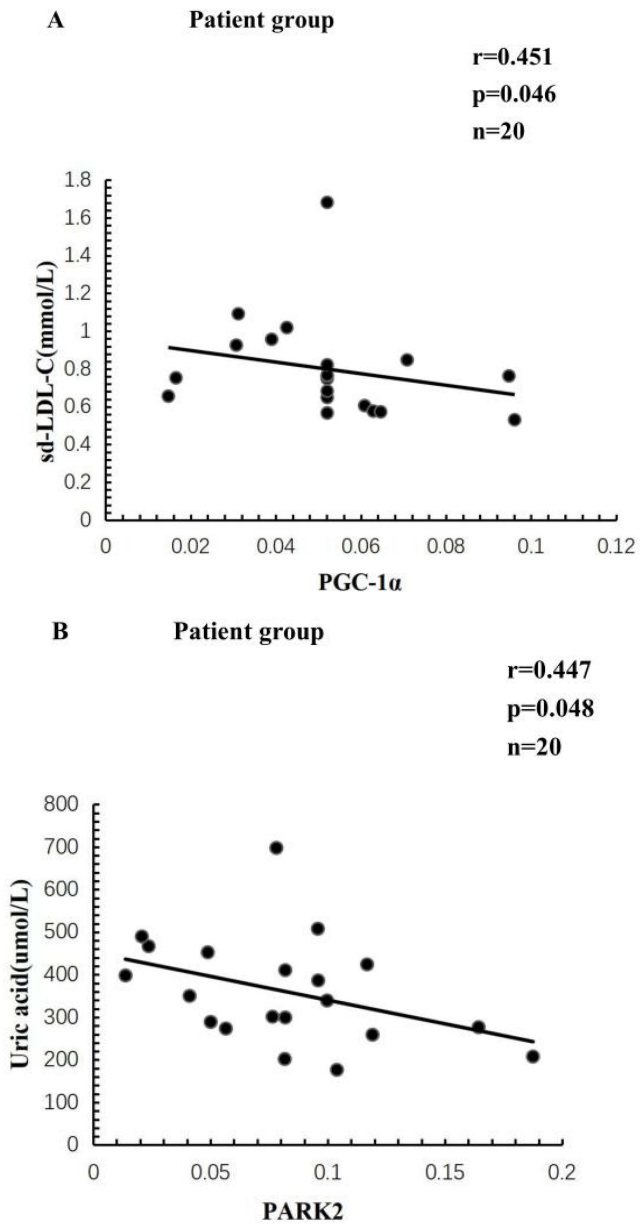

Figure 1 Spearman Correlation Analysis of Differential Gene Expression Levels of Mitochondrial Quality Control and Clinical Metabolic Indicators in the Patient Group and the Control Group. Correlation analysis of the expression level of PGC-1a gene and very low-density lipoprotein level in the patient group (**A**). Correlation analysis of the expression level of PARK2 gene and uric acid level in the patient group (**B**).

the mitochondrial genome by activating the mitochondrial transcription factor A (transcription factor A, mitochondrial, and TFAM)[20], thereby initiating mitochondrial biosynthesis.[21]

Mitochondria are highly dynamic, and changes in their size and number are controlled by the dynamic balance of fusion and fission. Fusion is crucial for the optimal control of mitochondrial number and integrity, whereas fission mediates mitochondrial division and quality control during cell division. Studies have confirmed that the balance between mitochondrial fusion and fission is crucial for brain development and function.[22] Despite many previous studies on mitochondrial fusion and fission in patients, studies on patients with first-episode SCZ are few. In this study, no differences in the expression levels of mitochondrial fusion and fission-related genes were observed. This finding might be related to the small sample size of this study, or patients with first-episode SCZ may have a short disease course and no significant fusion and fission have occurred yet.

Mitochondrial autophagy plays an important role in cellular homeostasis.[23,24] Mitochondrial autophagy can protect cells from oxidative stress by eliminating damaged mitochondria to reduce the accumulation of ROS.[25] Mitochondrial autophagy pathways

include the PINK1/Parkin pathway, the BNIP3/Nix pathway, the FUNDC1 pathway, and the Cardiolipin pathway, among which the most well-known is the PINK1/Parkin pathway.[26] Parkin promotes the mitochondrial autophagy of damaged mitochondria through two pathways. First, the ubiquitination of Parkin can cause the degradation of various proteins on the mitochondrial surface, such as mitochondrial fusion proteins and mitochondrial movement-related proteins; consequently the damaged mitochondria are unable to fuse into the mitochondrial working network, are in a free state, and are unable to combine with motor proteins and lose their motility[27]. Second, the ubiquitination mediated by Parkin on the outer mitochondrial membrane can be recognized by ubiquitin-binding factors such as P62 and HDAC6, and then recruit autophagosome protein LC3, eventually forming autophagosomes to transport damaged mitochondria to lysosomes for degradation.[28] Microtubule-associated protein light chain 3 (MAPLC3, also known as LC3), LC3B is one of the most commonly used autophagy markers.[29] The PARK2 gene (ie, parkin) encodes the ubiquitin - E3 - ligase and is a transcriptional repressor of p53. The PARK2 gene's protein is widely expressed in the nervous system and is involved in regulating mitochondrial autophagy and programmed cell death.[30] Previous studies have found that the PARK2 gene is associated with different neurodevelopmental disorders, such as SCZ, PD, ASD, and ADHD.[30] Compared with healthy people, the level of Parkin protein in the prefrontal cortex of patients with SCZ is significantly increased, and the prefrontal cortex plays an important role in the pathophysiology of SCZ.[31] The results of this study show that in the peripheral blood leukocytes of patients with SCZ, the expression levels of PARK2 and LC3B genes are significantly lower than those of the control group, suggesting possible abnormalities in eliminating damaged mitochondria in patients. Therefore, mitochondrial autophagy may be involved in the pathogenesis of SCZ.

Hyperuricemia and hyperlipidemia fall within the category of metabolic syndrome. Uric acid and lipid profiles as well as obesity indices are closely related. The association mechanism between uric acid and lipids may be related to mechanisms such as oxidative stress and inhibition of lipoprotein lipase activity.[32] When PARK2 plays a role in cellular metabolism, it may indirectly affect the production and excretion of uric acid.[33] Mitochondria are the main site of intracellular energy metabolism, and mitochondrial dysfunction may lead to metabolic disorders, including abnormal metabolism of uric acid. The reduction of mitochondrial autophagy causes the accumulation of damaged mitochondria, and these damaged mitochondria may produce excessive ROS, thereby further affecting the normal metabolism of cells, including the production and excretion of uric acid.[34] Previous studies have shown that the uric acid level of untreated patients with first-episode SCZ is significantly increased.[35] This study shows that the uric acid level in the patient group is negatively correlated with the expression level of the mitochondrial autophagy-related gene PARK2. The reduction in PARK2 expression is associated with the increase in uric acid in SCZ, and no similar studies have been reported in the past. This finding indicates that the role of PARK2 in cellular metabolism and mitochondrial autophagy may indirectly affect the production and excretion of uric acid.

Furthermore, MTATP8, AIF, MTCO2, and NDUFV2 are involved in the regulation of mitochondrial oxidative phosphorylation and the synthesis of ATP.[36–39] Previous post_ mortem brain studies on patients with SCZ have confirmed the existence of abnormalities in mitochondrial oxidative phosphorylation in patients,[40] but in this study, differences we not observed in the expression of genes related to this pathway. This outcome may be due to the small sample size resulting in inaccurate results, or the patient's medical history may be short and no evident abnormalities in oxidative phosphorylation have occurred yet.

In the analysis of mitochondrial function-related genes and metabolic indicators, the expression of the PGC-1α gene in patients with SCZ was negatively correlated with the very low-density lipoprotein cholesterol level, indicating that as the expression level of the PGC-1α gene decreases, the very low-density lipoprotein cholesterol level of the patients gradually increases, which may lead to a higher risk of suffering from cardiovascular and metabolic diseases. In addition, the expression of the PARK2 gene in the patient group was negatively correlated with the uric acid level. As the expression level of the PARK2 gene decreased, the uric acid level of the patients gradually increased, which would also increase the risk of suffering from metabolic diseases. In the control group, no significant correlation between the expression levels of each gene and each clinical metabolic indicator was observed, further suggesting the abnormality of mitochondrial function and the resulting obstruction of ATP generation may exacerbate the metabolic changes in patients with SCZ. In previous studies on mitochondrial function in patients with SCZ, more attention was paid to the oxidative phosphorylation, related studies on mitochondrial quality control were fewer, and studies on the correlation with metabolism in patients with first-episode SCZ were even fewer. In this paper, a preliminary study was conducted on the correlation between mitochondrial function and metabolic indicators in patients with first-episode SCZ to provide a reference for the subsequent in-depth exploration of the pathogenesis of SCZ.

However, this paper has certain limitations: The sample size of the study is small, and the relevant research results still need to be verified in a larger sample. In addition, this study is cross-sectional. The patients all have first-episode SCZ with a short medical history, and causal inferences cannot be made. Longitudinal observations can be conducted in the future to explore further the mechanism of mitochondrial abnormalities in the metabolic disorders of patients with first-episode SCZ.

Conclusions

This paper shows abnormalities in mitochondrial quality control in patients with first-episode SCZ, which may be closely related to the previously reported decrease in mitochondrial copy number, weakened oxidative phosphorylation function, and insufficient energy supply. Moreover, the significantly decreased gene expression levels are associated with the increase in metabolic indicators, suggesting that mitochondrial dysfunction may be related to the higher risk of metabolic diseases in patients with first-episode SCZ. The polymorphism of mitochondrial-related genes increases the risk of dyslipidemia, suggesting that it may be a hereditary risk factor for dyslipidemia in patients with SCZ.

Data Sharing Statement

The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

Ethics Statements

This study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Shandong Mental Health Center. All participants had signed an informed consent form for inclusion.

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Disclosure

The authors report no conflicts of interest in this work.

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