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Research Article

Role of visfatin, sirtuin 1 and apelin in patients with autism disorder

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Abstract

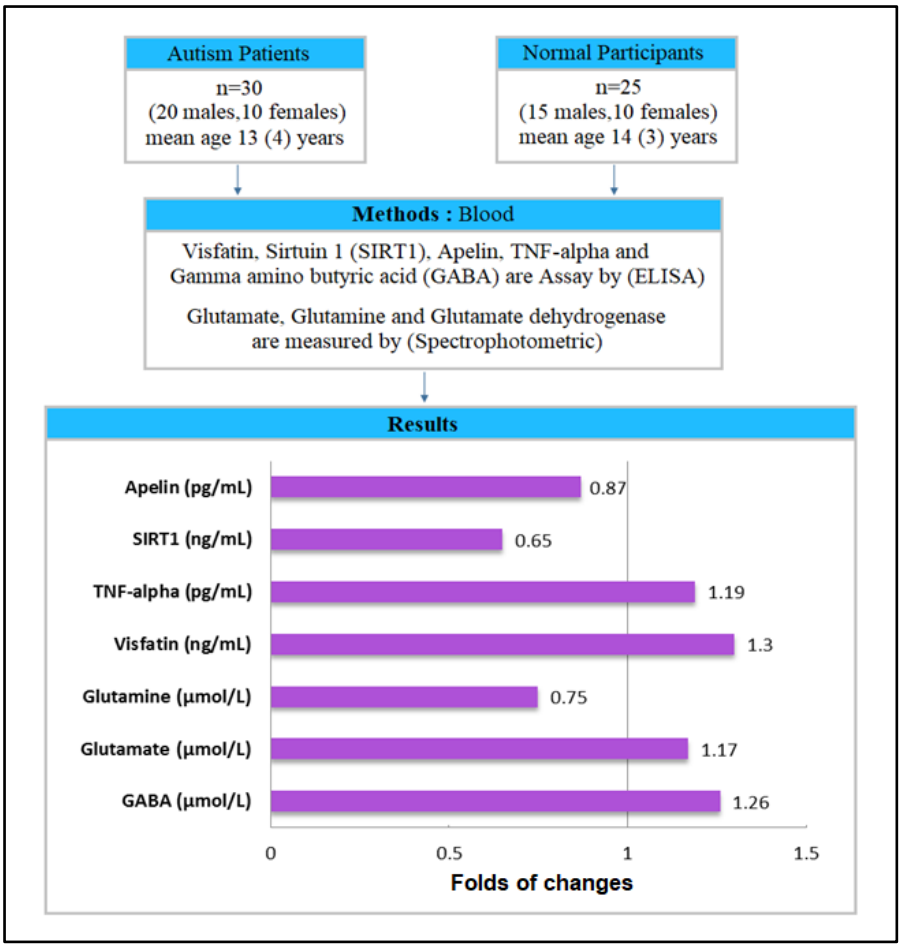
Introduction: Autism is one of the neurological disorders that vary in characters and degree of sternness. **The aim of the study** was to quantify the serum levels of some nitrogen metabolites, sirtuin 1, visfatin, apelin and tumor necrosis factor-alpha in autistic patients and to evaluate their levels in contrast to normal participants.

Materials and Methods: The study was conducted on 30 patients (20 males, 10 females) with autism, mean age 13 (4) years and 25 normal participants (15 males, 10 females), mean age 14 (3) years. The blood levels of visfatin, sirtuin 1, apelin, tumor necrosis factor-alpha, glutamate dehydrogenase, gamma aminobutyric acid, glutamate, and glutamine were analyzed in all participants by using different techniques according to the manufacturer.

Results: The statistical analyses of the data for the patients versus normal participants showed high prominent elevation in serum levels of visfatin (P=0.006), tumor necrosis factor-alpha (P=0.001), gamma aminobutyric acid (P=0.002), and glutamate (P=0.001). Conversely, high appreciable reductions were noted in serum levels of glutamine (P<0.001), sirtuin 1 (P=0.002), and apelin (P<0.001). Whereas non-momentous rise (P=0.083) was noted in serum level of glutamate dehydrogenase.

Conclusion: The reason of abnormal serum levels of some nitrogen metabolites, cytokines (visfatin, and tumor necrosis factor–alpha), sirtuin 1, and apelin may contribute to the pathoetiology of autism. Thereafter these results may be important for identifying new treatment approach for autism.

Graphical Abstract



Keywords

autism; apelin; cytokines; glutamate dehydrogenase; nitrogen metabolites; sirtuin 1; visfatin

Introduction

Autism Spectrum Disorder (ASD) and Autism are diseases of neuro-origin that affect both neuro-function and behaviors and identified mostly in male children than in female children. Many causes associated with the etiology of Autism involvr genetic, ambience, autoimmune and inflammatory causes. Although this disease is characterized by a high heritability rate, no definite genetic agent is recognized as a hazardous cause (Santangelo and Tsatsanis 2005).

Glutamate is an important neurotransmitter with excitation ability, which is present at a high level in the brain, and it is essential for conserving the flexibility of neurons and the cognitive functions. Conversely, the escalated level of glutamate, extra or intra neuronal hyperglutamatergic, can be lethal to the neuron cell and may correlate with psychiatric disorders (Sheldon and Robinson 2007), or enhance the symptoms of epilepsy in autistic patients (Fatemi 2008).

Many studies reported that the blood glutamate level directly correlated with its level in cerebrospinal fluid. Thereafter, the level of peripheral glutamate can reveal the level of central glutamate (Kaczmarski et al. 2023).

Gamma aminobutyric acid (GABA) is an important neurotransmitter with inhibitory ability. It intercedes the signaling of calcium that is important for maturation of many vital processes

(Owens and Kriegstein 2002). Any impairment in the signaling of GABA-ergic causes neuronal imbalance in the excitatory/inhibitory neurotransmitter levels that contribute to deficits in behavior of autistic patients (Pizzarelli and Cherubini 2011).

Cytokines like Interleukin 6, and tumor necrosis factor-alpha are elevated in many inflammatory conditions and diseases such as diabetes and heart diseases (Rada 2017; Rada 2021). Additionally, tumor necrosis factor-alpha has an association with other processes such as release of hormones, function of neurons, and behavior improvements. Likewise, in autistic patients, a state of impaired immune system with increment of blood cytokines was reported (Nour-Eldine et al. 2022).

Visfatin, a nicotinamide phosphoribosyl transferase (Nampt), is a cytokine produced by adipocyte, interacting with many biological processes such as amelioration of glucose level, enhancement of proinflammatory responses, and increased in many diseases such as diabetes (Hashim 2022). Apelin is a neuropeptide, which is a ligand for G protein coupled (APJ) receptor. Moreover, Apelin and its receptor are highly presented in central nervous system and peripheral system. Apelin has a role in many biological processes related to the brain, pituitary gland, and heart (Reaux et al. 2001).

Sirtuin 1 (SIRT1) is a nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylase, which acts as adjustor of transcription processes related to the metabolic activity and stress. It has a role in many processes such as growth and inflammatory responses (Kemper et al. 2013).

The aim of this research was to quantify the serum levels of some nitrogen metabolites, apelin, sirtuin 1 and cytokines (visfatin and tumor necrosis factor-alpha) in autistic patients and to evaluate their levels as paragons to normal participants.

Materials and Methods

Objects under study

A case-control study was performed between 3 January to 15 June 2023 and involved a totality of 75 participants. But due to missing participants because of many reasons such as non-collaboration, the sample size of this case-control study involved only 55 participants, 30 Autistic patients recruited from clinic of Central Children's hospital in Iraq by simple randomized sampling method that involved making a code for each examined patient and then randomly selecting the desired numbers of codes, and 25 normal participants recruited from the healthy children of the medical staff and friends.

The performance and description of this study are in accordance with STROBE checklist for case-control study. Moreover, the study's principle conformed to the instructions of Helsinki Declaration for Human Research and credited by the Ethical Committee of the Pharmacy College (Minutes number 1236 of 22-11-2021). Each participant received a printed informed consent involving the details of the research and their agreements. Insertion questions involved the details of age, gender, previous diseases, instant treatment, and existence of other diseases in the family. Exception criteria involved the patients with other neurological, psychiatric, or medical disorders.

The properties of the included patients with autism involved age between 6 to 15 years old, deficit in social interaction (score 0 to 32), deficit in cognitive or learning skills (score 0 to 26), and other properties related to constrained or repeated behaviors (score 0 to 16). Moreover, the diagnosis of autistic patients depends on patients' history and clinical assessment that follow the diagnostic observation schedule of (Lord et al. 2000). No participant was put on any distinct diets or treatments.

Concerning sample size calculation, an online software called Statology/sample size calculation for mean/ was used with 95% confidence level (Z-score equal 1.96), margin of error (5%), assumed population standard deviation (0.15). The number of sample size for one group was 35, for two groups – 70, with the estimation of 21.4 % for missing data. Thereafter, the sample size of this research was 55.

Research methods

After participants fasting for 8 to 12 hours, samples of blood were gathered from each participant and isolated into serum samples, then reserved at -20°C pending for assay. The enzyme linked immunosorbent assay (ELISA) kits were used for detecting the levels of visfatin, sirtuin 1 (SIRT1), Apelin, TNF-α and gamma aminobutyric acid (GABA) as to the guidelines of the employer for each one, and all the samples were duplicated in assays. Serum level of glutamate, glutamine and glutamate dehydrogenase were measured by using spectrophotometric (colorimetric) assay kits.

Statistical analyses

Data were checked for existence of normal distribution by using Shapiro-Wilk's test, and arranged as mean (standard deviation). and 95% was considered as an interval of confidence. The distinctions of numerical data that existed continuously were identified by unpaired (independent) student *t*- test with two-tails. Whereas the distinctions of categorical data (gender) were identified by using chi-square test. *P*-value of less than 0.05 was selected to be a point of significance. All statistical analyses were executed using Microsoft Excel and SPSS version 25.

Results

Approximately 55 out of 75 participants were enrolled in this study. All chosen patients and normal control made it possible to achieve the norms of participation. The distribution of age and gender was well among the patients and normal participant, in which the *P*-values are indistinctively different for age (*P*=0.306), and for gender (*P*=0.609). Our participants comprised 30 autistic patients: 20 (66.7%) males and 10 (33.3%) females, mean age being 13 years, and 25 normal participants: 15 (60.0%) malesand 10 (40.0%) females, mean age being 14 years. The demographical aspects of the participants are exhibited in Table 1.

Table 1. Demographical aspects of the selected groups (n=55)

Variables	Autistic patients n=30	Control n=25	*P*- value
Age (years), Mean (SD)	13 (4)	14 (3)	0.306 [a]
Gender, n (%) Male Female	 20 (66.7) 10 (33.3)	 15 (60.0) 10 (40.0)	 0.609 [b]

Note: [a] – P-values of unpaired (independent) student t- test for numerical variable, [b] – P-values of chi-square test for categorical variable, n: sample size, SD – standard deviation.

The main study outcome was to quantify the serum levels of some nitrogen metabolites, apelin, sirtuin 1 and cytokines (visfatin and tumor necrosis factor-alpha) in autistic patients and normal participants. As contrasted to the normal participants, the autistic patients revealed high considerable elevation in serum level of GABA (*P*=0.002), and glutamate (*P*=0.001) that are seemingly equal to 1.26-folded for GABA, and 1.17-fold for glutamate.

Conversely, the mean serum level of glutamine was significantly lower (*P*<0.001) in autistic patients, equaling 0.75-fold (Fig. 1). Whereas undetectable alteration (*P*=0.083) was noticed in the serum level of glutamate dehydrogenase (Table 2). Concerning the analyses of cytokines in autistic patients versus normal participants, high considerable increments were noted in serum levels of visfatin (*P*=0.006) and TNF-α (*P*=0.001), which were apparently equivalent to 1.3-fold for visfatin and 1.19-fold for TNF-α (Fig. 1).

Table 2. Biochemical data of the selected groups (n=55), numerical variables

Variables, Mean (SD)	Autistic patients n=30	Control n=25	Mean difference (95% CI)	*t*-statistic df=53	*P*- value
GABA (µmol/L)	0.62 (0.20)	0.48 (0.08)	0.14 (0.06, 0.23)	3.29	**0.002**[a]
Glutamate (µmol/L)	30.40 (5.30)	25.80 (3.70)	4.60 (2.08, 7.12)	3.66	**0.001**[a]
Glutamine (µmol/L)	168.30 (8.20)	224.30 (10.40)	-56.00 (-61.02, -50.98)	22.31	**<0.001**[a]
GDH (IU/L)	1.67 (0.73)	2.04 (0.82)	-0.37 (-0.79, 0.05)	1.77	0.083[a]
Visfatin (ng/mL)	2.13 (0.64)	1.66 (0.56)	0.47 (0.14, 0.80)	2.87	**0.006**[a]
TNF-α (pg/mL)	7.68 (1.35)	6.47 (1.22)	1.21 (0.51, 1.91)	3.45	**0.001**[a]
SIRT1 (ng/mL)	1.44 (0.68)	2.21 (1.06)	-0.77 (-1.24, -0.30)	3.29	**0.002**[a]
Apelin (pg/mL)	178.34 (15.22)	204.23 (21.40)	-25.89 (-35.79, -15.98)	5.23	**<0.001**[a]

Note: [a] – P-values of unpaired (independent) student t- test for numerical variables; **P-values in boldface** – high significant differences vs. normal participant; n – sample size; SD – standard deviation; GDH – glutamate dehydrogenase; GABA – gamma aminobutyric acid; SIRT1 – Sirtuin 1; TNF-α – tumor necrosis factor-alpha.

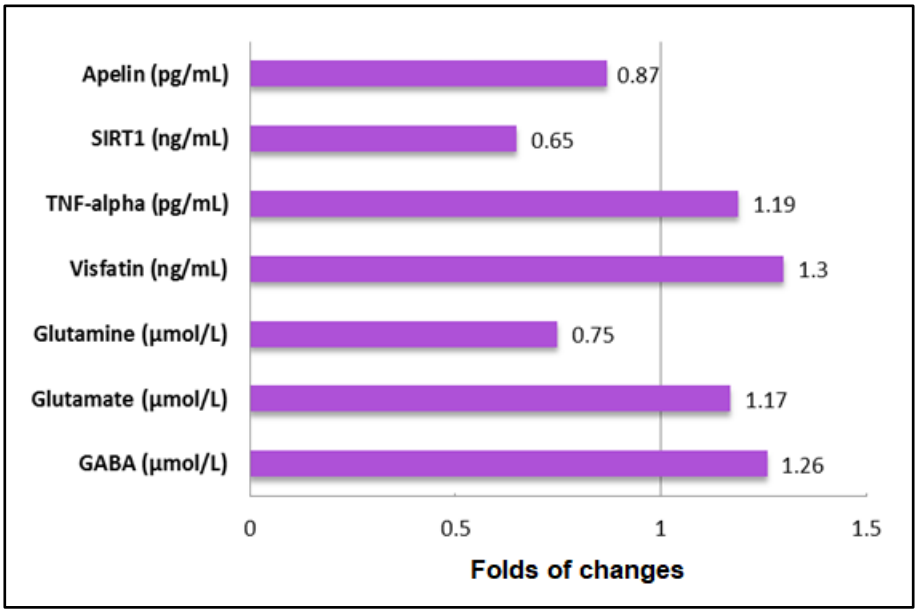


Figure 1. Folds of change for many variables of autistic patients *vs.* normal participants.

Contrariwise, the autistic patient exhibited a significant decrease in serum levels of SIRT1 (P=0.002) and neuropeptide apelin (P <0.001) versus control participants. As well, the degree of the decrease for SIRT1 was 0.65-fold and for neuropeptide apelin – 0.87-fold versus normal participants (Fig. 1). The minimum perceivable percentage changes within the mean levels of some selected variables such as glutamate, glutamine, visfatin, TNF-α, SIRT1, and apelin in autistic patients versus normal participants are summarized in Figure 2, assuming power of analysis (1-B) equals to 80%.

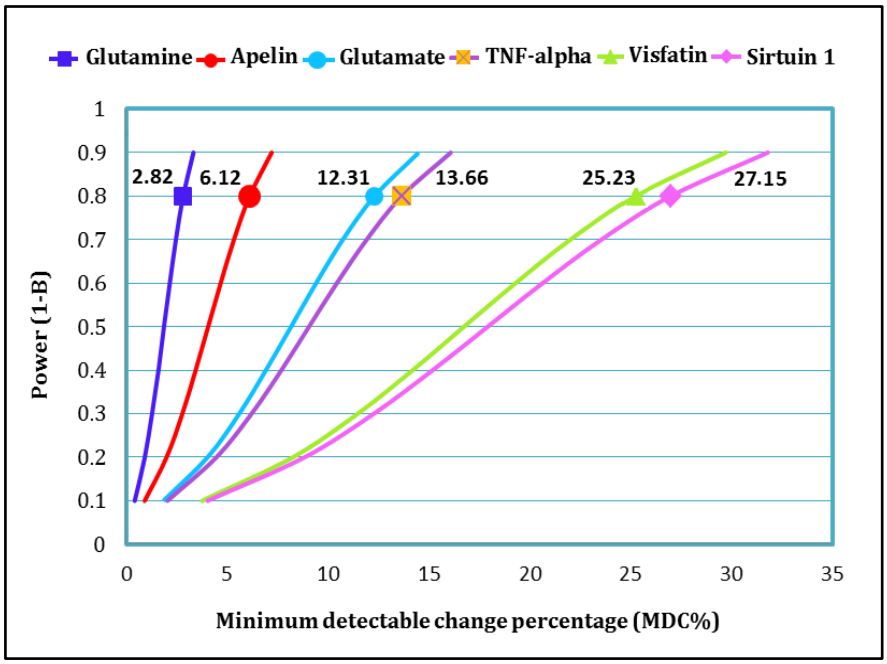


Figure 2. Minimum perceivable change percentage of some selected variables in autistic patients *vs.* normal participants.

Discussion

The main causes of most disorders related to the central nervous system is imbalance of energy production and utilization which are originated from many reasons and ultimately lead to diminished energy required for normal survival of neurological cells (Ciruela et al. 2006). Glutamate is an important substrate for many enzymes in the nervous system such as GDH that

produce alpha-ketoglutarate, glutamine synthase that produce glutamine, and glutamate decarboxylase that produce GABA (Haigis et al. 2006).

In the brain, the main inhibitory neurotransmitter (GABA) and the main excitatory neurotransmitter (glutamate) have decisive roles in the growth of brain at early state, at which the features of autism start. Moreover, the decline in the function of GABA may be related to insufficiencies of social and cognitive features of autism (Han et al. 2014).

In this study, the serum level of GDH was non-considerably lower in autistic patients. Contrariwise, other study reported significantly diminished level of GDH in autistic patients (Abu Shmais et al. 2012). Moreover, the serum level of glutamate and GABA was considerably escalated in those patients. As glutamate is a substrate of GDH enzyme, therefore any defect in this enzyme will cause a defect in the level of its substrate. Likewise, the elevated levels of glutamate and GABA in autistic patients were reported in many studies (Zheng et al.2016; Shinohe et al. 2006).

Similarly, other study reported that escalated level of glutamate correlated with enhanced incidence of epilepsy in autistic patients, and the blood level of glutamate was directly proportional to the severity of autistic spectrum (Ferraro et al. 2025). Contrarily, other study stated that there was no correlation between glutamate level and autism. These discrepancies may be related to the variation in sample size, sampling methods, and uses of other medication (Dhossche and Rout 2006).

Glutamine synthase needs energy as ATP to convert glutamate into glutamine by irreversible reaction. Hence, the level of energy in the brain of autistic patients was diminished therefore the level of glutamine also diminished and led to escalate the level of glutamate as seen in this study, the result of which is consistent with another study (Shimmura et al. 2011).

GDH in humans is encoded by two genes, GLUD1, a gene with 13 exons expressed in most tissues, and GLUD2, an intronless gene expressed mostly in nervous system and testicles. GDH produced from GLUD2 gene was less sensitive to being inactivated by GTP. Therefore, Sirtuin 4 protein is considered the main inhibitor of this enzyme in the nervous system and testicles (Plaitakis et al. 2003; Kanavouras et al. 2007). As autism is recognized mostly in male children than in female children, which led to speculation that GLUD2 gene may associated with this disorder.

Visfatin is a pro-inflammatory cytokine, which signals elevated inflammatory process and stress (Lin et al.2015). Many studies reported elevated level of visfatin in autistic patients (Rodrigues et al. 2014), and this result is consistent with the current study. The increased level of visfatin may be associated with increased levels of Interleukine 1, 6 and TNF-α (Prosperi et al. 2019).

As reported in this study, the level of TNF-α was highly significantly elevated in autistic patients versus normal participants, and this outcome was concurrent with other studies that revealed correlation of the elevated level of TNF-α with visfatin and resistin (Ghaffari et al.2016). Seemingly, the elevated level of visfatin might be due to the pathological condition that accompanied autism or due to the imbalance in oxidative stress status inside the nervous cells, which may be associated with mitochondrial dysfunction in autistic patients.

The level of SIRT1 in autistic patients was significantly decreased in this study as compared to normal participants. Bu et al. (2017) reported low level of SIRT1 in some autistic patients as consequences of mitochondrial dysfunction and thereafter elevation of oxidative stress inside it. Bennuri et al. (2019) inferred that the signaling system involving a mammalian target of rapamycin (mTOR) was deescalated by SIRT1. Thereby this system may be considered as a connector with the pathogenicity of autism.

Concerning the level of apelin in this study which was significantly diminished in autistic patients versus control participants, this outcome was in accordance with another study that reported a declined level of apelin in autistic patients as related to the abnormal release of vasopressin and etiology of autism (Boso et al. 2007). Likewise, one more study reported a decline in the level of apelin in patients with major depression (Acikel et al. 2022).

Limitation of this study comprised the number of the enrolled participants, which was approximately small and may have affected the precision of Logistic regression of variables, and the involvement of one center study. Therefore, advanced studies with larger sample size for conduction of Logistic regression and multicenter enrolment are suggested.

Conclusion

The abnormal results of variables measured in this study for autistic patients showed particularly high prominent elevation in serum levels of proinflammatory cytokine (visfatin) and high obvious reduction in serum level of sirtuin 1 and apelin, which may have an inference to the Patho etiology of autism since it is ultimately effected by oxidative stress imbalance and mitochondrial dysfunction inside the brain cells.

Additional information

Conflict of Interest

The author has no conflict of interest to declare.

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Data availability

All of the data that support the findings of this study are available in the main text.

Ethics statements

All the procedures credited by the Ethical Committee of the Pharmacy College (Minutes number 1236 of 22-11-2021).

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Author Contribution

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