Doi: https://doi.org/ 10.3329/ewmcj.v14i2.85923

Original Article

BIOCHEMICAL MARKERS OF MITOCHONDRIAL DYSFUNCTION IN BANGLADESHI AUTISTIC CHILDREN

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Article History:
Received: 29th November 2025
Accepted: 14th December 2025

Abstract:

Background: *Autistics spectrum disorder is a generalized term for a group of complex brain disorder. Autistics spectrum disorder can occur due to dysfunction of mitochondria and abnormal brain bioenergetics. Cellular function impairment due to mitochondrial dysfunction may cause cognitive impairment, language deficits and abnormal energy metabolism in autism.*

Objective: *to evaluate biochemical evidence of the mitochondrial dysfunction by measuring blood ammonia, serum lactate, creatinine kinase (CK), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in autistic children.*

Methods: *This case-control study was conducted in the Department of Physiology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from January, 2013 to December, 2013. For this study a total number of 100 male children with age range 3-8 years were randomly selected, among which 50 were normal children and 50 were diagnosed autistic children. The autistic children were selected from the Parent's Forum, Directorate Generals of Health Service (DOHS), Mohakhali, Dhaka and normal children were selected from some normal school. Blood ammonia, serum lactate, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine kinase (CK) level were estimated in all children by standard laboratory method. Independent sample't' test was used for statistical analysis as applicable. P value <0.05 was accepted as significant.*

Result: *The mean of all the measured biochemical variables were found significantly higher (p<0.001) in autistic male children in comparison to control. In addition, elevated levels of serum lactate and CK were found in 94% and 32% of autistic children respectively.*

Conclusion: *From the result of this study it can be concluded that mitochondrial dysfunction may occur in children with autistic spectrum disorder. The biochemical abnormality for mitochondrial dysfunction and the severity of the autistic spectrum disorder is directly related.*

EWMCJ Vol. 14, No. 2, July 2026: 130-134

Keywords:
ASD, Mitochondrial dysfunction, Ammonia, Lactate, Aspartate aminotransferase, Alanine aminotransferase, Creatine kinase

Introduction

Autistic spectrum disorders refers to complex disorder that causes impairment of growth and development of areas of brain or central nervous system that is concerned with emotion, learning ability, memory and self control[1]. Variety of factors like genetic, metabolic, immune, infectious disease, nutritional factors deficiency, toxic and environmental factors may causes these disorder[2]. Autistic spectrum disorders affect multiple physiological systems with high energy demanding organ system such as central nervous system, muscular and gastrointestinal systems.[3] In recent times, mitochondrial disorders are regarded as common metabolic disease in children and mitochondrial disorders are closely related with autism.[4]

Mitochondrial dysfunction not only cause decrease energy level, also increase reactive oxygen species.

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Brain cells are very vulnerable to reactive oxygen species. So impairment in neuronal function leading to imbalance in excitatory and inhibitory neurotransmitter may occur in mitochondrial disorder[5,6]. Mitochondrial activity may be impaired by genetic mutation, cerebral folate deficiency, vitamin B_6 or iron deficiency and also certain environmental toxin such as pesticides or heavy metals chemicals[7,8]. The mitochondrial disorders are based on clinical, biochemical, molecular and histological findings. Biochemical basis of mitochondrial dysfunction are lactate, ammonia, creatinine kinase (CK), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level in blood[6].

As in mitochondrial dysfunction TCA cycle impairment occur so aerobic respiration inhibited which leads to â-oxidation impairment and increase of lactate level[6].

In mitochondrial dysfunction ATP level decreases that impairs urea cycle. So ammonia level in blood increases[6,9]. Increased ammonia level in autistic children may lead to toxicity and ATP depletion in brain[9].

Decrease cellular ATP level in mitochondrial dysfunction causes impairment in Na+-K+ ATPase pump and cell volume cannot be maintained. It leads to loss of cellular integrity of certain organ such as muscle, brain and liver. So serum CK, serum AST and ALT rises[6, 10, 11, 12].

Some researcher of other country reported increased ammonia 78% in autistic children in comparison to normal.[13]In USA, serum lactate, AST, ALT and CK found increased in 76%, 36%,38% and 28% of autistic children compared to normal children respectively[12]. Some researchers showed that serum lactate level increased in 35% of autistic children.[6] Again, another study found elevated plasma lactate level in 17% of autistic children[14]. Similarly, in 76.7% autistic children increased serum lactate levels were reported in another study[15]. Some investigators of USA found elevation of serum AST in 38% and serum CK in 47% of autistic children with mitochondrial dysfunction.[16]

Materials and Methods

50 diagnosed autistic male children (Group B), with age range 3-8 year were taken for this analytical type of case-control study. 50 age and BMI matched apparently healthy male children were taken as control (Group A). This study was conducted in the Department of Physiology of Bangladesh Medical University (BMU), Shahbag, Dhaka from January, 2013 to December, 2013. The study group was selected from the Parent's Forum (DOHS, Mohakhali) for autistic children and the control group was selected from some normal school. After selection of the subject, thorough information was given to their parents about the objective and study procedure. Their parents were encouraged for voluntary participation of their children. Their parents were also allowed freedom to withdraw their children from the study even after participation whenever they feel like. When their parents were agreed for participation then an informed written consent was obtained from their parents. The parents of subject were requested to attend the Department of Physiology of BSMMU, Dhaka for examination of their children. Detail personal, medical, family, socioeconomic, occupational and dietary histories of the children were recorded in a data schedule from their parents. Thorough physical examinations of the subject were done. Anthropometric measurement including age and BMI were taken and were documented in a data schedule. Then 5 ml of venous blood were collected from ante-cubital vein from each subject of both groups for estimation of biochemical variables. Immediately after taking the blood, blood ammonia was measured in the laboratory of the BIRDEM. Then serum lactate, CK, AST and ALT level were measured in the laboratory of the Biochemistry Department, BSMMU. Data were expressed in mean SE and also in percentage. Statistical analysis was done by using SPSS for windows version 16. Independent samples't' test were used as the tests of significance. P value <0.05 was accepted as significant.

Results:

Anthropometric and biochemical data are summarized in Table-I. Both groups of this study were age and BMI matched, there were no significant differences in age and BMI between the study and healthy control children group.

In this study, the mean value of blood ammonia, serum lactate, serum aspartate aminotransferase, alanine aminotransferase and creatine kinase levels were significantly higher in the study group in comparison to that of healthy control children ($p<0.001$) .

Percentages of elevated all the parameters level are summarized in Table-II. In this study, blood ammonia, serum lactate, AST, ALT and CK level were higher in 45(90%), 47(94%), 23 (46%), 15 (30%) and 16 (32%)

Table-I

Anthropometric and biochemical data of both group

Parameters	Autistic children (n= 50)	Healthy control children (n= 50)	p value
Age (Year)	5.93±0.22 (3-8)	6.02± 0.21 (3-8)	0.94
BMI (Kg/m^2)	17.25± 0.14 (16-20)	16.90±0.73 (14-19)	0.29
Blood Ammonia (μmol/l)	45.40±1.65 (20-71)	22.50 ±0.78 (15-38)	0.000***
Serum Lactate (mg/dl)	29.31±1.32 (16-56)	12.10 ±0.34 (8-17)	0.000***
Serum AST (U/L)	36.24+1.73 (17-63)	24.20 + 0.82 (15-35)	0.000***
Serum ALT (U/L)	49.06+2.47 (28 – 81)	37.14+ 1.48 (17 -56)	0.000***
Serum CK (U/L)	187.30+11.89 (70-456)	134.76+ 5.69 (67-230)	0.000***

Data are expressed as Mean ± SE. For statistical analysis, independent student't' test was performed for comparison between the groups. Figures in parentheses indicate ranges.
Group A = Apparently healthy male children (control group)
Group B = Autistic male children (study group).
***p = ≤0.001 ns = Non significant
**p = ≤0.01 n = Number of subjects
*p = ≤.0.05

Table-II

Percentage of elevated serum enzymes in study and control groups.

Parameters	Autistic children(n= 50)	Healthychildren(n= 50)
Elevated blood ammoniano. (%)	45 (90%)	5(10%)
Elevated serum ASTno. (%)	23 (46%)	0(0%)
Elevated serum ALT no. (%)	15 (30%)	0(0%)
Elevated serum CKno. (%)	16 (32%)	0(0%)

Data are expressed as Mean ± SE. For statistical analysis, independent student't' test was performed for comparison between the groups. Figures in parentheses indicate ranges.
Group A = Apparently healthy male children (control group)
Group B = Autistic male children (study group).

subjects of study group. But blood ammonia and serum lactate levels were higher in only 5(10%) and 3(6%) and no rise of serum AST, ALT and CK level in control group respectively.

Discussion

The present study was undertaken to observe some biochemical variables in male autistic children in order to evaluate their mitochondrial dysfunction. Mitochondrial dysfunction were assessed by measuring blood ammonia, serum lactate, creatine kinase(CK), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level in autistic male children. All these variables were also studied in apparently healthy age and sex matched normal children for comparison. In this study, values of all the biochemical variables of healthy subjects were within physiological limit and were almost similar to those reported by different investigators abroad[12-14,16-18].

In this study, blood ammonia level was higher in the study group compared to control group. Almost similar

findings were observed by several investigators from different countries[13, 19]. In addition, blood ammonia level was found abnormally high in 90% children of study group which was almost similar to other investigators observation.[13]

In our study, serum lactate level was higher in the study group than the control group and similar types of findings were also reported by several studies [6,10-12,14,15,17,18]In this present study, increased serum lactate level was found in 94% of study group which was similar with other investigators report[3,4,6,10-12,14,15.20].

In our study, serum aspartate aminotransferase (AST) level was higher in the study group compare to control group and this was supported by some investigators[6,10-12]. In addition, increased serum AST level was found in 46% of study group which was also found in other studies[12,16].

In this study, serum alanine aminotransferase (ALT) level was higher in the study group compare to control group which was supported by other study[6,10-12]. Moreover, serum ALT level was found higher in 30% of study group. Similarly, several investigators reported elevated serum alanine aminotransferase level[12].

In this present study, serum creatine kinase (CK) level was higher in the study group compare to control group which was almost same in several investigators from studies [6,10-12,14,16]. Again, serum CK level was found higher in 32% of study group which was consistant with other researchers [12,16].

Conclusion

From the result of this case-control type of study, it may be concluded that mitochondrial dysfunction may occur in autistic children.

Conflict of interest:

None to disclose.

Ethical approval: IRB clearance obtained from Bangladesh Medical University (BMU), Shahbagh, Dhaka.

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Peer-Review History:
The peer review history for this paper can be accessed here: https://ewmch.com/review/

East-West Med. Col. J. Vol. 14, No. 2 july 2026