This journal is the official publication of Bangladesh Society of Physiologists (BSP)
Web URL: www.banglajol.info/index.php/JBSP

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pISSN-1983-1213; e-ISSN-2219-7508

Article

Article information:
Received: October 2023
Accepted: December 2023
DOI: https://doi.org/10.3329/jbsp.v18i2.75478

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Cite this article:
Shimul SK, Shahjadi S, Naznin T, Patwary MSI. Effect of Risperidone on Liver Enzymes Level in Children with Autism Spectrum Disorder. J Bangladesh Soc Physiol 2023;18(2): 72-77

Effect of Risperidone on Liver Enzymes Level in Children with Autism Spectrum Disorder

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Abstract

Background: Irritability and hyperactivity are associated co-morbidities in autism spectrum disorder (ASD). Recently for this purpose, risperidone, an atypical antipsychotic is the drug of choice for ASD children. Abnormalities of liver enzymes were found associated with atypical antipsychotics. **Methods:** This observational study was conducted in the Department of Physiology, BSMMU carried on 68 children enrolled from parents forum, Mohakhali, Dhaka. All were diagnosed case of ASD with similar age and sex. Among them 34 were treated with risperidone which constituted the study group and 34 were not treated with risperidone constituted the control group. The enzymes were estimated by ELISA and automated analyzer. For statistical analysis student's unpaired t- test was done. **Results:** The mean values of serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) level of children with autism spectrum disorder who were treated with risperidone were significantly higher compared to control group. **Conclusion:** risperidone adversely affects liver function by increasing enzymes level in children with autism spectrum disorder

Key words: ASD, Liver enzymes, Risperidone.

Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that is defined and characterized by persistent impairment in communication and social interaction along with restrictive and repetitive behaviour, interests and activities.[1] Co-morbidity is a significant burden associated with ASD and affects many different systems including epilepsy, gastrointestinal disorders, schizophrenia, sleeping disorders, intellectual disabilities, diabetes mellitus type 2, etc.[2] Children with autism spectrum disorders experience behavioral symptoms and frequently engage in aggressive and self-destructive behaviors. Current studies have shown the prevalence of aggressive and self-injurious behaviors in children with an autism spectrum disorder to be as high as 32%. these maladaptive behaviors can seriously impede a child's academic and developmental growth.

Some pharmacological interventions have been introduced to control these problems such as conventional antipsychotic but there were some side effects like extrapyramidal symptoms and dyskinesia.[3] In Comparison with conventional antipsychotics atypical antipsychotic exhibit a profile of potent antagonism at serotonin and dopamine receptors, which exerts less side effects and results in decreased propensity for tardive dyskinesia and extrapyramidal symptoms.[4] Among all atypical antipsychotics, risperidone is FDA (Food and Drug adminstration) approved drug for the pharmacological management of autism in children.[5]

Certainly, the short-term efficacy of risperidone for behavioral problems associated with ASD is now well recognized. Antipsychotic drugs commonly cause an increase liver enzymes. In clinical practice, risperidone is widely prescribed, often for quite extended periods of time, even though there is a relative lack of research data with regard to intermediate and longer-term use. Recent studies showed that abnormalities in liver enzymes can occur not only with typical antipsychotic drugs but also with atypical antipsychotics. In adult patients, antipsychotic drug treatment generally leads to an asymptomatic increase in liver enzymes. Though rarer, cases of serious hepatotoxicity were also reported.[6,7]

Use of risperidone in ASD children and adolescent is a newer condition than the use of this agent in adult populations. Also, it is known that the emergence of side effects of risperidone in children may take years. Therefore, the efficiency and safety data for risperidone are currently deemed inadequate.[7]

With best of my knowledge few studies were undertaken to monitor the liver enzyme levels in children with ASD who are treated with risperidone. So, this study has been designed to explore the changes in hepatic enzyme in children with ASD so that precautions can be taken during prescribing this drug.

Methods

Design and setting

This case control study was done in the Department of of Physiology from September 2022 to august 2023.

Study participants

In this study 68 ASD boy aged 10-15 years were recruited from the parents' forum for children with ASD in Dhaka city. Among them 34 were treated with risperidone (more than 3 months and dose should be range of 0.5-3.5 mg/day) constituted the study group and 34 were not treated with risperidone constituted the control group.

Exclusion criteria

All participants were free from acute illness, liver diseases, epilepsy, turner syndrome and down syndrome, hepatotoxic drug except risperidone for control group.

Sampling

Purposive sampling was adopted to select the participants.

Data collection

After selection of the subject, thorough information was given to their parents about the objective and study procedure. An informed written ascent was obtained from parents. Detail personal, medical, family, socioeconomic, occupational and dietary histories of the subject was recorded in a preformed questionnaire from their parents. Then the parents were requested to attend the Department of Physiology of BSMMU, Dhaka on the day of examination at 8 am in fasting condition. Thorough physical examination of the subjects was done and documented. Anthropometric measurement including height and weight were taken. Then 4 ml of venous blood was collected from ante-cubital vein from each subject of both groups for estimation of some liver enzymes by automated analyzer.

Statistical analyses

All data were expressed as mean ± SD. Statistical analysis was performed by using SPSS for windows version 27. Shapiro-Wilk was used to check the normal distribution of data. Student's Unpaired t- was done test was done to compare liver enzymes between control and study group. The P value <0.05 was considered as statistical significance.

Results

All the subjects of this study were matched for age and BMI. (Table 1).

Table I : *Age and BMI in different groups (N= 68)*

Variables	Group A (n=34)	Group B (n=34)	p value
Age (Years)	12.32±1.53 (10-15)	12.06±1.67 (10-15)	0.498
BMI (Kg/m^2)	19.09±2.09 (15-25)	19.81±1.58 (17-22)	0.114

Data were expressed as mean ± SD. Values in parentheses indicate ranges. Statistical analysis was done by unpaired t-test. BMI- Body Mass Index (kg/m^2). Group A: ASD children with risperidone (control group); Group B: ASD children without risperidone (study group). N- Total number of subjects; n- Number of subjects in each group.

In this study

Serum ALP, ALT ($p<0.05$), AST, GGT($p<0.001$) levels were significantly higher in the study group in comparison to that of control group (Figure 1,2,3,4)

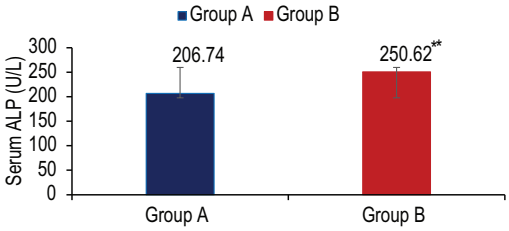

Figure 1: Serum alkaline phosphatase (ALP) levels in two groups (N=68).

Each bar symbolizes mean ± SD for 34 subjects. Statistical analysis was done by student's unpaired t- test; Group A: ASD children with risperidone (control group); Group B: ASD children without risperidone (study group); N- Total number of subjects; n- Number of subjects in each group. *This depicts comparison between group A and B. *$p<0.05$.

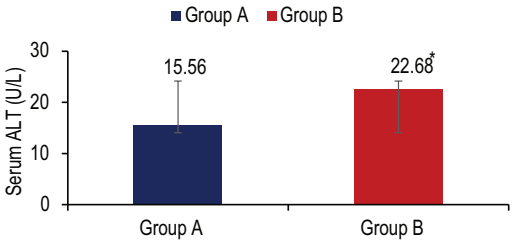

Figure 2: Serum alanine aminotransferase (ALT) levels in two groups(N=68).

Each bar symbolizes mean ± SD for 34 subjects. Statistical analysis was done by student's unpaired t- test; Group A: ASD children with risperidone (control group); Group B: ASD children without risperidone (study group); N- Total number of subjects; n- Number of subjects in each group. *This depicts comparison between group A and B. *$p<0.05$.

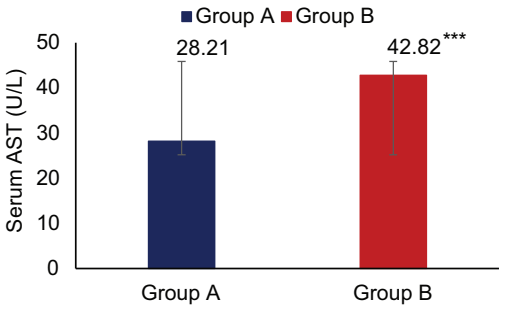

Figure 3: Serum aspartate aminotransferase AST levels in two groups (N=68).

Each bar symbolizes mean ± SD for 34 subjects. Statistical analysis was done by student's unpaired t- test; Group A: ASD children with risperidone (control group); Group B: ASD children without risperidone (study group); N- Total number of subjects; n- Number of subjects in each group *This depicts comparison between group A and B. ***p<0.001.

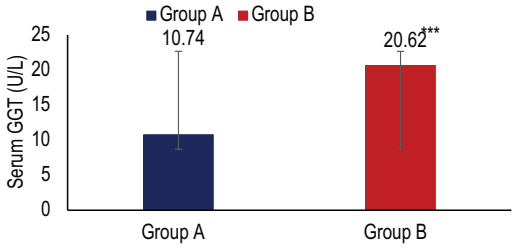

Figure 4: Serum gamma-glutamyl transferase (GGT) levels in two groups (N=68).

Each bar symbolizes mean ± SD for 34 subjects. Statistical analysis was done by student's unpaired t- test; Group A: ASD children with risperidone (control group); Group B: ASD children without risperidone (study group); N- Total number of subjects; n- Number of subjects in each group. *This depicts comparison between group A and B.***p<0.001.

Discussion

The present study was undertaken to observe the effect of antipsychotic risperidone on serum liver enzymes in diagnosed case of children with autism spectrum disorder. Liver status was assessed by some liver enzymes such as ALP, ALT, AST AND GGT level in children with autism spectrum disorder who are treated with risperidone. In this study, mean values of some liver enzymes with autism spectrum disorder who were not treated with risperidone were within physiological limit except ALP and were almost similar to those reported by different investigators.[7,8]

Again, both the groups (control and study) were comparable, as there was no significant difference in the confounding variables such as age and BMI between two groups.

Higher mean value of all these liver enzymes were associated with risperidone treatment. Moreover, here serum ALP is abnormally high in both groups as ALP is generally higher in children and adolescents due to the increased osteoblastic activity associated with the bone growth[9].

From this present study, the exact mechanism of liver enzyme abnormality in children with autism spectrum disorder who was treated with risperidone cannot be explained biochemically. However, several previous investigators have reported that measurement of serum ALP, ALT, AST and GGT levels are important biochemical indicator to evaluate liver dysfunction[10,11]

In general, there are three mechanisms of liver damage by drugs namely hepatocellular, cholestatic, and mixed types. In hepatocellular type the drug or drug metabolite binds to cellular liver proteins or macromolecules. It is usually characterized by elevated levels of AST and ALT[12]. Cholestasis is the result of the binding of drugs or drug metabolites to proteins in the canalicular membrane leading to inhibition of bile salt export pump (BSEP). It causes ductal damage with increased alkaline phosphatase and bilirubin. Another hypothesis is that, toxic drug metabolites undergo canalicular excretion and those exposed duct cells are then injured due to an immune mediated reaction[13]

In the mixed type, it is a combination of hepatocellular damage and cholestatic mechanisms characterized by an increase in ALT and ALP.[14,15]

In addition, the expression of FABP4 (fatty acid binding protein found in adipocyte) mRNA in the liver and SREBP1 (sterol regulatory element binding protein 1) mRNA was connected to the expression of genes involved in lipid storage, de novo hepatic lipogenesis, and the pathophysiology of nonalcoholic fatty liver disease. In the present scenario of ASD children, chronic treatment with risperidone might led to increased expression levels of SREBP1 and FABP4 mRNA in the liver and thereby significant lipid infiltration in the liver.[16]. This chronic lipid infiltration may cause steatosis and necroinflammation that led to hepatic injury and as a result serum liver enzymes were also increased in this group of ASD children.[17-18] The limitation of this study was lipid profile of these children were not done which could provide evidence for lipid infiltration or signs of fatty liver in these ASD children who were treated with Risperidone. The result of this study suggested that clinicians should be alert about the risk of development of fatty liver or liver injury while treating ASD children with Risperidone for prolonged period and lipid profile and liver enzymes should be routinely checked to prevent liver injury in them.

Conclusion

From the result of this case-control type of study, it may be concluded that risperidone adversely affects liver function by increasing some serum liver enzymes level in children with autism spectrum disorder

Ethical clearance This study was approved by Institutional review Board (IRB) of BSMMU.

Conflict of interest None

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