RESEARCH ARTICLE

Serum Prolactin level in Thai Children and Adolescents with Autistic Spectrum Disorder on Long Term Risperidone Treatments

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Abstract

Autistic spectrum disorder (ASD) is a neurodevelopmental disorder of early childhood characterized by communication abnormalities, social impairment and stereotyped behaviors. The US Food and Drug Administration (US FDA) approved the use of risperidone in children and adolescents who have symptoms of irritability associated with autism. Although risperidone can be effective in core symptom reduction in youths with psychiatric disorders, it is also associated with adverse effects, especially hyperprolactinemia. The objective of this study was to examine the relationship between serum prolactin level with gender and age among children and adolescents with autistic spectrum disorder (ASD), who were treated with risperidone. Participants included 210 ASD patients (183 males and 27 females) from the Yuwaprasart Waithayopathum Child and Adolescent Psychiatric Hospital, Samut Prakan. Serum prolactin levels were measured by chemiluminescence immunoassay. Serum prolactin levels were significantly higher in males than in females (17.8 vs. 15.7 ng/ml, P=0.021). Also, the prolactin concentrations were found to be significantly higher than the reference range among males (P=0.022). Children and adolescents with ASD within the age of 16-20 years had significantly higher concentration of prolactin (27.9 ng/ml) than in children aged 7-9 (16.7 ng/ml, P=0.018), 10-12 (14.2 ng/ml, P=0.012), and 13-15 years (17.7 ng/ml, P=0.021). The present study suggests that gender and age have a significant impact on prolactin concentrations in children and adolescents with autism undergoing risperidone treatment.

Keywords: Prolactin, risperidone, autistic spectrum disorder, Thai, adverse drug reaction, hyperprolactinemia.

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ระดับซีรั่มโปรแลคตินในเด็กและวัยรุ่นชาวไทยที่มีความผิดปกติแบบออทิสติกสเปคตรัมที่ได้รับการรักษาด้วยยาริสเพอริโดนเป็นระยะเวลานาน

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บทคัดย่อ

ออทิสติกหรือความผิดปกติแบบออทิสติกสเปคตรัม เป็นกลุ่มโรคที่เกิดจากความผิดปกติทางด้านพัฒนาการที่มีสาเหตุมาจากสมอง เด็กจะมีพัฒนาการล่าช้าทางภาษา ขาดความสนใจในการมีสังคมกับบุคคลอื่น และมีพฤติกรรมซ้ำ ๆ หรือมีความสนใจจำกัดเฉพาะเรื่องใดเรื่องหนึ่ง โดยสำนักงานคณะกรรมการอาหารและยาแห่งสหรัฐอเมริกาได้อนุมัติการใช้ยาริสเพอริโดนในเด็กและวัยรุ่นออทิสติกที่มีอาการเกรี้ยวกราด ก้าวร้าว ถึงแม้ว่ายาริสเพอริโดนจะมีประสิทธิผลในการลดอาการหลักของออทิสซึม แต่ก็พบการเกิดอาการไม่พึงประสงค์ต่าง ๆ ได้โดยเฉพาะภาวะโปรแลคตินในเลือดสูง ดังนั้นวัตถุประสงค์ของการศึกษานี้คือหาความสัมพันธ์ระหว่างระดับซีรั่มโปรแลคตินกับเพศและอายุของเด็กและวัยรุ่นออทิสติกที่ได้รับยาริสเพอริโดน อาสาสมัครจำนวน 210 ราย (ชาย183 รายและหญิง 27 ราย) จากโรงพยาบาลยุวประสาทไวทโยปถัมภ์ สมุทรปราการ ซึ่งระดับโปรแลคตินจะถูกตรวจวัดโดยวิธี chemiluminescence immunoassay ผลการศึกษาพบว่า ระดับโปรแลคตินในผู้ชายมีค่าสูงกว่าในผู้หญิงอย่างมีนัยสำคัญ (17.8 (ชาย) 15.7 (หญิง) ng/ml, P=0.021) และผลต่างระหว่างระดับโปรแลคตินกับช่วงอ้างอิงในผู้ชายก็ยังมีค่าสูงกว่าในผู้หญิงอย่างมีนัยสำคัญ (P=0.022) นอกจากนี้ยังพบว่า เด็กและวัยรุ่นออทิสติกที่มีอายุ 16-20 ปี มีระดับโปรแลคติน (27.9 ng/ml) สูงกว่าอย่างมีนัยสำคัญเมื่อเทียบกับกลุ่มที่มีอายุ 7-9 ปี (16.7 ng/ml, P=0.018), อายุ 10-12 ปี (14.2 ng/ml, P=0.012) และอายุ 13-15 ปี (17.7 ng/ml, P=0.021) การศึกษานี้จึงแนะนำว่า ปัจจัยทางด้านเพศและอายุในออทิสซึมเด็กและวัยรุ่นนี้เป็นปัจจัยที่มีความสัมพันธ์อย่างมีนัยสำคัญต่อการเพิ่มขึ้นของระดับโปรแลคตินระหว่างที่ได้รับยาริสเพอริโดน

คำสำคัญ: โปรแลคติน, ริสเพอริโดน, ความผิดปกติแบบออทิสติกสเปคตรัม, ไทย, อาการไม่พึงประสงค์จากการใช้ยา, ภาวะโปรแลคตินในเลือดสูง

Introduction

Autistic spectrum disorders (ASDs) are chronic neuropsychiatric conditions characterized by marked impairment in social interactions, communication deficits, and restricted/repetitive patterns of behaviors.[1,2] Irritability associated with ASD, where a patient exhibits uncontrolled anger or aggression, is effectively treated with pharmacotherapy and behavioral interventions.[3] Risperidone has been employed in order to augment responses to behavioral and educational interventions, as well as to improve overall functioning in ASD.[1,3-6] Even though risperidone is commonly prescribed, it has been linked to metabolic disorders including obesity, hyperglycemia and dyslipidemia.[7-9]

A number of studies have indicated an association of risperidone treatment with hyperprolactinemia and potentially serious clinical manifestations.[9-11] Hyperprolactinemia is a common side effect that may arise from the use of antipsychotic agents, by antagonizing dopamine D_2 receptors on lactotroph cells in the anterior pituitary gland.[12] Dopamine, released from neurons, is an inhibitor of secretion of prolactin.[10] Any blockade of dopamine receptors in the tubero-infundibular system would reverse inhibitory effects against prolactin secretion and lead to hyperprolactinemia.[13] Atypical antipsychotics, especially risperidone, give rise to a substantial increase of serum prolactin during treatment, both short- and long term.[10,11]

A previous study reported that eighty percent of subjects have serum prolactin above the upper limit of normal, with no statistically significant gender difference in the extent of prolactin elevation.[14] In addition, several studies suggest that plasma prolactin concentrations in females are much higher than in males.[15,16]

To date, there have been some studies of prolactin response to risperidone in some neuropsychiatric disorders in Caucasian and Japanese population. However, no data are available on prolactin response in risperidone-treated children and adolescence with autism spectrum disorders. Therefore, this study investigated associations between serum prolactin level with gender, and age in Thai children and adolescence with ASD who were treated with risperidone.

Materials and Methods

Subjects

A retrospective study was conducted among ASD subjects, recruited from Yuwaprasart Waithayopathum Child Psychiatric Hospital, Samut Prakan province, Thailand. Participants were excluded from the study if they had concomitant treatment with a second antipsychotic drug. Parents of the participants gave written informed consent to participate in the study. Patients who had received risperidone for at least 1 month were included in the study to ensure that all patients had reached steady-state plasma risperidone levels, and then were stratified into two subgroups according to gender and age. This study was not controlled for menstrual cycle. The study was approved by the ethics committee of Ramathibodi Hospital (MURA2011/541).

Prolactin measurement

Fasting blood samples were collected by venipuncture in a 3 ml plain tube from each patient between 0800 and 0930 hours, and the samples kept at room temperature for 30 minutes. All samples were then separated by centrifugation for 10 minutes at 3000 rpm. Prolactin concentration was assayed using IMMULITE1000 (Siemens Healthcare Diagnostics Products Ltd, Llanberis, Gwynedd, UK) which uses a solid-phase, two-site chemiluminescent immunometric assay. As declared by the manufacturer, assay sensitivity, intra-assay coefficient of variation and inter-assay coefficient of variation were 0.5 ng/ml, 5.7%, and 6.4% respectively. The reference ranges of prolactin at this laboratory are shown in Table 1.[17] pediatric age-related reference intervals for serum prolactin were identified from a pediatric reference intervals book (insert reference).

Statistical analysis

The Kolmogorov-Smirnov test was used to examine discrepancies between the data distribution for each group and the normal distribution. The Mann-Whitney U-test was used to analyze differences in prolactin concentrations by gender and age group. A two-tailed P-value of less than 0.05 was considered as statistically significant.

Table 1. The demographic and clinical data of the children and adolescents with ASD in this study (n=210)

Characteristics	**Number (%)**
Gender	
Male	183 (87.1)
Female	27 (12.9)
Age, mean ± SD; years	9.7 ± 3.7 (3.2-19.0)[a]
Age	
1-3	8 (3.8)
4-6	42 (20.0)
7-9	69 (32.9)
10-12	46 (21.9)
13-15	24 (11.4)
16-20	21 (10.0)
Prolactin concentration, median; ng/ml	17.2 (10.5-25.8)[b]

[a] min-max: minimum-maximum; [b] IQR: interquartile range

Results

Two hundred and ten ASD patients were enrolled and eligible for data analysis. Among the participants, 183 (87.1%) were male, and 27 (12.9%) were female. The mean age of the subjects was 9.7 ± 3.7 (mean ± SD) years. Most of the subjects were between 7-9 years old. The median prolactin concentration was 17.2 ng/ml (interquartile range: 10.5-25.8) (Table 1). With a cutoff value of prolactin level among different age groups, regardless of sex, 64% (122 males, 14 females)

of subjects were found to have serum prolactin above the upper limit of the normal reference range (Table 2). The median concentration of prolactin in males was 17.8 ng/ml (interquartile range: 11.0-26.4), whereas the median concentration of prolactin in females was 15.7 ng/ml (interquartile range: 9.6-18.4). Serum levels of prolactin in males was significantly higher than those in females (P=0.021) (Figure 1).

The median prolactin increase above the mean of reference range was 11.6 ng/ml (interquartile range: 4.8-20.4) in males, whereas the increase was only 8.1 ng/ml (interquartile range: 2.7-12.6) for females, which was statistically significant (P=0.022) (Figure 2). We also found the serum levels of prolactin (27.9 ng/ml) in patients aged 16-20 years was significantly higher than in those aged 7-9 (16.7 ng/ml, P=0.018), 10-12 (14.2 ng/ml, P=0.012), and 13-15 years (17.7 ng/ml, P=0.021) (Figure 3).

Table 2. The median (IQR) of prolactin level compared to the reference range, according to sex and age group.

	Males (N=183)			Females (N = 27)		
Age (years)	**Prolactin level (ng/ml), Median (IQR)**	**Reference range**	**Number**	**Prolactin level (ng/ml), Median (IQR)**	**Reference range**	**Number**
1-3	17.2 (13.3-41.3)	2.3-13.2	6	15.3 (9.6-20.9)	1.0-17.0	2
4-6	22.2 (10.7-30.0)	0.8-16.9	34	15.7 (7.3-17.5)	1.6-13.1	8
7-9	17.1 (10.5-25.7)	1.9-11.6	62	16.1 (11.6-16.8)	0.3-12.9	7
10-12	14.4 (9.4-23.2)	0.9-12.9	40	9.6 (5.0-17.0)	1.9-9.6	6
13-15	18.0 (11.0-24.7)	1.6-16.6	23	10.2[c]	3.0-14.4	1
16-20	28.0 (16.3-33.9)	2.1-17.7	18	21.3 (18.5-25.3)	2.8-29.2	3

[c]Prolactin level from one adolescent patient.

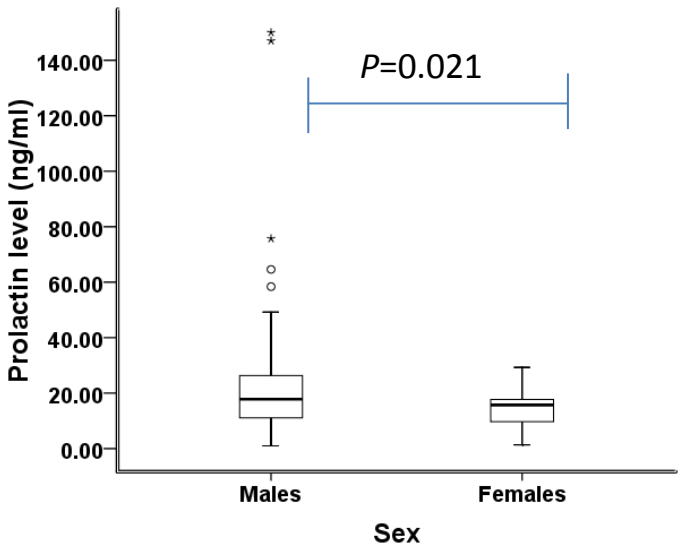

Figure 1. The serum levels of prolactin in males were also significantly higher than those in females.

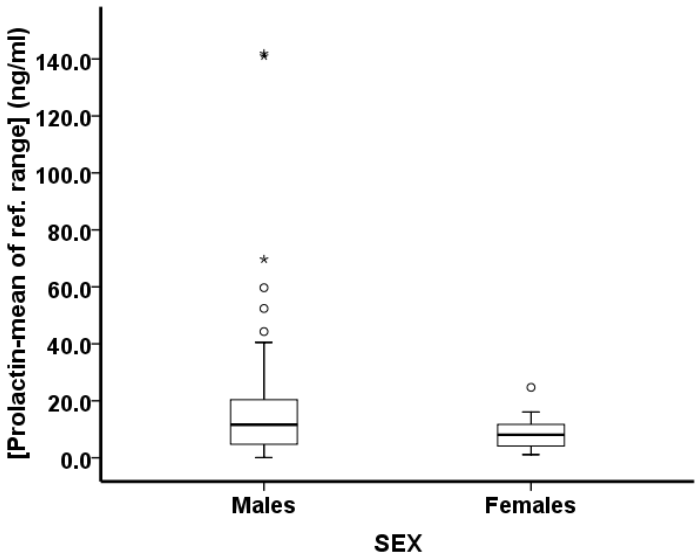

Figure 2. The serum levels of prolactin above the mean of the reference range were significantly higher in males than those in females.

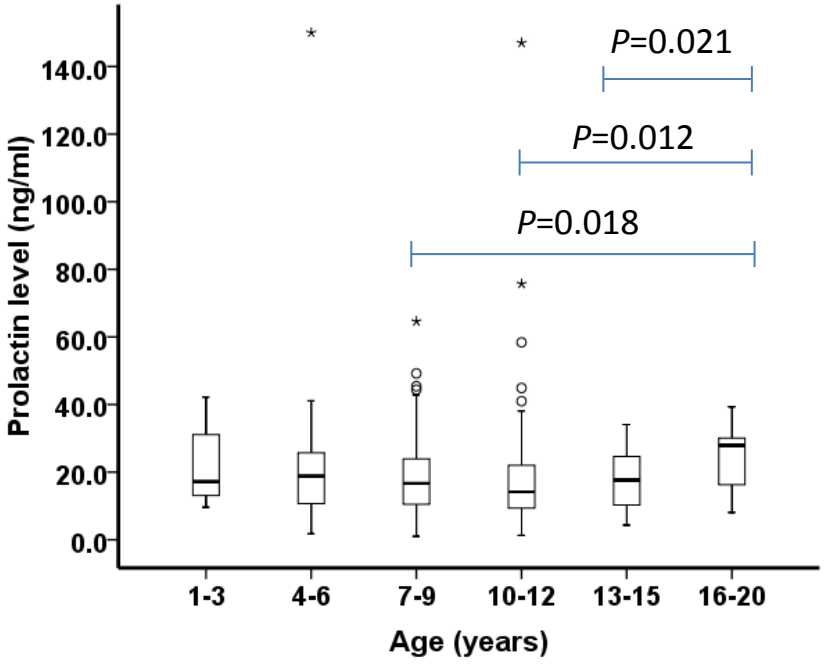

Figure 3. The serum levels of prolactin in age patients aged 16-20 years were significantly higher than in those aged 7-9, 10-12, and 13-15 years

Discussion

The current study demonstrates that men showed significantly higher serum prolactin level than women during the treatment with risperidone. We also observed that the serum levels of prolactin above the mean of the reference range were significantly higher in males compared to females. The serum level of prolactin inpatients aged 16-20 years was found to be significantly higher than in patients aged 7-9, 10-12, or 13-15 years.

This study indicates that risperidone is linked to significant elevation of serum prolactin. Among 210 subjects treated with risperidone, 64% of patients were found to have serum prolactin above the upper limit of normal. Consistent with other reports, this study confirms that risperidone exposure significantly increases serum prolactin, with significant differences between the genders. However, the frequency of risperidone-associated hyperprolactinemia in this study was less than in other reports which showed up to 80%[18] and 81%[19]. The former investigated Caucasian children and adolescents with mental health disorders aged 7-15 (mean age 11.2 years).[18] The latter studied white patients with schizophrenia aged 18–65 years.[19] Given that age could be another important factor that influences the occurrence of hyperprolactinemia, it is unsurprising that both studies reported the frequency of risperidone-induced hyperprolactinemia at a higher level that was observed in our study population

Gender could be another important factor that influences prolactin secretion during risperidone treatment.[12,20] We cannot clearly explain why a prolactin concentration was elevated to a greater extent among males. One possible explanation is a small population of females. As predicted, females with autism were more frequently missing from all researches (male:female ratio = 4-6:1)[21,22], and the variance in sex ratio increased with decreasing female population size. Therefore, this study found that prolactin responses to risperidone were greater in males than in females. However, it was reported that female subjects may have a greater prolactin response and greater effect of dopamine receptor blockade from antipsychotics due to the levels of estrogen[23] because estrogen is a prolactin inhibitory factor[16] and estrogens have an indirect stimulating action on prolactin release through inhibition of hypothalamic dopamine synthesis and reduction in the number of pituitary D_2 receptors. The net effect is an elevation of prolactin levels through an increase in amplitude of prolactin bursts, release and storage.[13] Subsequently, estrogen increases antipsychotic-stimulated prolactin secretion.

Some evidence indicates that children and adolescents may be more sensitive to the prolactin elevating effects of antipsychotics compared to adult subjects, presumably because of an increased density of D_2 receptors in the developing striatum in the central nervous system and differential D_2 receptor sensitivity in the tuberoinfundibular tract.[24,25] When the dopamine D_2 receptors (DRD2) in the anterior pituitary were mostly blocked by risperidone, it may cause an increase in prolactin levels. During prolactin monitoring, there is little guidance on what to do with test results in the absence of a clinical findings such as amenorrhea, galactorrhea, or gynecomastia. The clinician is faced with the problem of determining the degree of risk to the patient treated with the drugs causing serum prolactin elevation.[26]

There are several methodological limitations of this study. First, the serum prolactin level was not measured at the baseline when the patients were not taking risperidone. Consequently, prospective, cross-sectional data is not available to further assess any changes in serum prolactin level. Second, the small number of patients in this study greatly limited comparisons, particularly with regard to drawing conclusions about female patients. Third, risperidone studies in children and adolescents have shown that treatment duration may also be an important confounding factor. Previous studies have indicated that short-term risperidone treatment is associated with a 2- to 6-fold increase in prolactin levels[27], while two large longer-term studies suggested that risperidone-induced prolactin elevations tend to decrease with time.[14,24,26] However, several studies have found no correlation between duration of treatment and prolactin levels.[16,28] A decline of prolactin response with time has been found in previous studies.[10,24,26,27] That risperidone-induced hyperprolactinemia decreases with extended treatment has been described as a developed functional tolerance in the tuberoinfundibular dopamine system.[10] Therefore prolactin level increases in children and adolescents when risperidone therapy is initiated, then decreases over time in many patients.

Conclusion

In conclusion, our study provides evidence of hyperprolactinemia in autistic children and adolescents with risperidone treatment. This study suggests that gender and age could be another important factor that influences prolactin concentration during risperidone treatment. Further studies of larger sample size, other genetic polymorphisms and with measurement of plasma risperidone levels is needed. This information would be helpful for clinicians in monitoring prolactin concentration during risperidone treatment, and also allow them to tailor the risperidone treatment for children and adolescents.

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