

Prolactin variations during risperidone therapy in a sample of drug-naive children and adolescents

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The aim of this prospective observational study was to investigate the variations of serum prolactin hormone (PRL) in a sample of 34 drug-naive patients (mean age 13 years) who started risperidone therapy assuming that several factors may favor the increase in serum PRL. Serum PRL and hyperprolactinemia clinical signs were examined at baseline (T0) and after almost 3 months of treatment (T1). We considered sex, pubertal status, risperidone dosage, psychiatric diagnosis, and any personal/family history of autoimmune diseases. The mean serum PRL value increased between T0 and T1 ($P=0.004$). The mean serum PRL was higher in females in the pubertal/postpubertal stage and for risperidone dosage up to 1 mg/day. Hyperprolactinemia was found in 20% of patients at T0 and in 38% of patients at T1 ($P=0.03$). The mean serum PRL increase was greater in early-onset schizophrenia spectrum psychosis patients compared with no-early-onset schizophrenia spectrum psychosis patients ($P=0.04$). The increase in PRL was higher in patients with a personal

and a family history of autoimmune diseases. This study suggests that the increase in serum PRL in patients treated with risperidone may be linked not only to the drug and its dosage but also to several risk factors such as sex, pubertal stage, psychiatric disease, and autoimmune disorders. *Int Clin Psychopharmacol* 30:103–108 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Prolactin hormone (PRL) is produced by lactotroph cells in the anterior pituitary gland and other extrapituitary sites as neurons, prostate, decidua, mammary epithelium, endothelial, skin, and immune cells. Its synthesis and release are under the control of peptides, steroids, and neurotransmitters. PRL induces milk production in pregnant women and prevents further pregnancy during the early stages of breastfeeding after childbirth.

Hyperprolactinemia (HPRL) is a condition characterized by PRL serum levels higher than the normal range in the absence of pregnancy and lactation. Sometimes, it is asymptomatic, but a high PRL level determines clinical manifestations with symptoms because of hypogonadism, which disturbs hypothalamic pituitary axis (HPA) function or induces direct effects on target tissues. The increase in PRL serum level could be induced by dopamine receptor antagonist drugs including antidepressants, opiates, cocaine, gastrointestinal medications, anti-hypertensives, and first-generation and second-generation

antipsychotics. Risperidone is one of the second-generation antipsychotics that causes an increase in PRL serum level correlating to its high affinity for dopamine D2 receptors, its blood–brain barrier penetration, and requested dose for the adequate occupancy of cerebral D2 receptors.

Studies on antipsychotic-induced serum PRL level variations were carried out especially on adult samples (Grahovac *et al.*, 2010; Inder and Castle, 2011; Perez-Iglesias *et al.*, 2012; Bargiota *et al.*, 2013; Lambert *et al.*, 2013), whereas fewer data are available in children and adolescents. Studies that evaluated variations in PRL levels during treatment with risperidone reported an increase in serum levels in children and adolescents. However, current research provides conflicting findings on the correlation between the increase in PRL serum level with sex, age, and risperidone dosage (Masi *et al.*, 2001; Findling *et al.*, 2003; Saito *et al.*, 2004; Anderson *et al.*, 2007; Troost *et al.*, 2007; Calarge *et al.*, 2009; Jerrell *et al.*, 2009; Migliardi *et al.*, 2009; Roke *et al.*, 2009; Fraguas *et al.*, 2011; Roke *et al.*, 2012; Margari and Petruzzelli *et al.*, 2013; Margari and Matera *et al.*, 2013). The rather contradictory results may be because of different research methods (prospective, review,

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retrospective, case–control studies), different psychiatric diagnoses, and age ranges. To date, the role of sex, age, risperidone dosage, and psychiatric diagnoses in promoting an increase in the PRL level is not fully understood in children and adolescents, as well as the course of PRL serum level during the treatment, although some authors support a possible decrease in PRL levels over time (Aston *et al.*, 2010).

The aim of this study was to investigate the relationship between risperidone therapy and serum PRL level in children and adolescent patients in the hypothesis that concurrence factors may favor the increase in serum PRL level. We studied a group of drug-naïve children and adolescent patients, starting treatment with a variable dosage of risperidone, in which we assayed serum PRL level and other factors (sex, pubertal status, dose of risperidone, psychiatric diagnosis, and personal/family history for autoimmune disorders) at baseline (T0) and after a period of almost 3 months of stable treatment (T1).

Patients and methods

This study was carried out in the Child Neuropsychiatric Unit of the University of Bari ‘Aldo Moro’, Italy. We consecutively recruited 34 patients (mean age 13 years, $SD \pm 3.59$) in the period between January 2010 and December 2013. All patients fulfilled the following inclusion criteria: age up to 18 years, both sexes, any psychiatric diagnosis provided as an indication of risperidone, antipsychotic-naïve patients, starting therapy with risperidone, and having a stable course of antipsychotic treatment for at least 3 months. Patients presenting presumable causes of HPRL such as pituitary/hypothalamic disorders, primary hypothyroidism, seizures, polycystic ovarian disease, HPRL neurogenic causes (chest wall trauma, surgery, herpes zoster infection), renal and liver insufficiency, and concomitant use of medications increasing serum PRL levels were excluded from the study. Moreover, female patients who were breastfeeding, using oral contraceptives, or were pregnant were excluded.

The local ethics committee approved this study. All children were recruited after obtaining parents’ written informed consent. In addition, patients from 8 to 17 years of age provided their written informed consent. The clinical neuropsychiatric diagnosis was made according to the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders* 4th ed. – Text Revision and was formulated by a child and adolescent neuropsychiatrist on the basis of interviews with the children and their families, assessment of medical history, and clinical observation. Moreover, the diagnosis was supported by the administration of standardized scales such as Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (Kaufman *et al.*, 2004) and the Child Behavior Checklist (Achenbach and Rescorla, 1991a, 1991b, 1991c). Sociodemographic and

clinical data (age, sex, psychiatric diagnosis, dose and duration of antipsychotic treatment, and any concurrent diseases) were collected.

All patients underwent a baseline assessment before starting risperidone therapy (T0) and a follow-up assessment after a stable course of antipsychotic treatment for at least 3 months (T1). At T0 and T1, a careful assessment of family and personal history, psychiatric examination, dosage of serum PRL level, and analysis of the possible presence of HPRL clinical signs was performed. We analyzed serum PRL level differences between T0 and T1 in respect to sex (male vs. female), pubertal stage (prepubertal vs. pubertal/postpubertal), risperidone dosage (< 1 vs. ≥ 1 mg/day), and diagnosis [early-onset schizophrenia spectrum psychosis (EOP) vs. no-early-onset schizophrenia spectrum psychosis (no-EOP)]. Serum levels of PRL were determined using an Advia Centaur XP Immunoassay System machine (Siemens, Erlangen, Germany). Venous blood samples were obtained from all patients in the morning between 8:00 and 9:00 a.m., after fasting overnight and before taking the drug. HPRL was accounted when fasting participants had serum PRL level more than 20 ng/ml in males and 25 ng/ml in females. To avoid stress caused by the prick, all the patients were sampled in the supine position. The pubertal stage was evaluated through inspection and by interviewing the parents.

Clinical controls during risperidone treatment were performed with a variable frequency to monitor the efficacy and tolerability of the drug and for any dosage adjustment.

Statistical analysis

All the variables studied were subjected to a statistical analysis. For the quantitative variables, we calculated the mean values and SD; for the qualitative variables, we calculated frequencies and percentages.

For the statistical analysis of the mean values of PRL serum level between T0 and T1, we used the paired-samples *t*-test.

For the statistical analysis of the quantitative variables in relation to sex, pubertal stage, risperidone dosage, and clinical diagnosis, we used the independent-samples *t*-test.

For the statistical analysis of the values of HPRL identified at T0 and T1, we used the Mann–Whitney *U*-test for independent samples.

The significance value was set at *P* less than 0.05. For statistical processing, we used the data processing program statistical package for social science, version 20.0 (IBM Corporation, Armonk, New York, USA).

Results

The study population included 34 White children and adolescents, including 17 EOP and 17 no-EOP (nine autism spectrum disorders, four tic disorders and four

Table 1 Clinical and sociodemographic features of the sample

| N | Diagnosis | Age (years) | Sex | Pubertal stage | Risperidone mg/day | Risperidone mg/kg/day | PRL T0 | HPRL T0 | PRL T1 | HPRL T1 | HPRL signs | Autoimmune diseases |
|----|-----------|-------------|-----|-----------------------------|--------------------|-----------------------|--------|--------------|--------|--------------|--------------|---------------------|
| 1 | No-EOP | 8.2 | M | Prepubertal stage | 1 | 0.03 | 37.7 | ^a | 15.9 | – | – | – |
| 2 | EOP | 12.9 | M | Pubertal/postpubertal stage | 1 | 0.02 | 15.2 | – | 58 | ^a | – | Ulcerative colitis |
| 3 | No-EOP | 8.8 | M | Prepubertal stage | 0.5 | 0.01 | 16.8 | – | 10 | – | – | – |
| 4 | No-EOP | 12.5 | M | Pubertal/postpubertal stage | 1 | 0.03 | 12.8 | – | 29 | ^a | – | – |
| 5 | No-EOP | 13.4 | M | Pubertal/postpubertal stage | 1.5 | 0.02 | 20 | – | 20 | – | – | – |
| 6 | No-EOP | 9.7 | M | Prepubertal stage | 0.5 | 0.01 | 13 | – | 18 | – | – | – |
| 7 | No-EOP | 15.6 | M | Pubertal/postpubertal stage | 1 | 0.01 | 33.4 | ^a | 19.3 | – | – | – |
| 8 | No-EOP | 13.8 | F | Pubertal/postpubertal stage | 1 | 0.01 | 12 | – | 12 | – | – | – |
| 9 | No-EOP | 13 | M | Pubertal/postpubertal stage | 0.75 | 0.01 | 19.9 | – | 28.3 | ^a | – | – |
| 10 | EOP | 16 | F | Pubertal/postpubertal stage | 2 | 0.04 | 23.8 | – | 124.6 | ^a | – | Thyroiditis |
| 11 | EOP | 13.7 | F | Pubertal/postpubertal stage | 2 | 0.05 | 6.2 | – | 78 | ^a | – | – |
| 12 | No-EOP | 7.2 | M | Prepubertal stage | 0.5 | 0.01 | 18.9 | – | 14.4 | – | – | – |
| 13 | EOP | 14.4 | M | Pubertal/postpubertal stage | 2 | 0.03 | 36.8 | ^a | 8.2 | – | – | – |
| 14 | EOP | 12.2 | F | Prepubertal stage | 1 | 0.03 | 6.8 | – | 30.7 | ^a | – | – |
| 15 | No-EOP | 10.8 | M | Prepubertal stage | 0.25 | 0.01 | 5 | – | 12.6 | – | – | – |
| 16 | EOP | 13.5 | M | Pubertal/postpubertal stage | 1 | 0.01 | 13 | – | 26 | – | – | – |
| 17 | EOP | 15.3 | M | Pubertal/postpubertal stage | 4 | 0.04 | 7.2 | – | 3 | – | – | – |
| 18 | No-EOP | 5.8 | F | Prepubertal stage | 0.75 | 0.03 | 21.6 | – | – | – | – | – |
| 19 | EOP | 8.3 | M | Prepubertal stage | 0.25 | 0.008 | 14.2 | – | 6.9 | – | – | – |
| 20 | EOP | 17.6 | M | Pubertal/postpubertal stage | 1 | 0.02 | 30.7 | ^a | 84 | ^a | – | – |
| 21 | EOP | 16.11 | F | Pubertal/postpubertal stage | 3 | 0.05 | 5.1 | – | 56 | ^a | – | – |
| 22 | No-EOP | 8.4 | M | Prepubertal stage | 1 | 0.02 | 11 | – | 48 | ^a | – | – |
| 23 | No-EOP | 16.3 | F | Pubertal/postpubertal stage | 0.75 | 0.01 | 13 | – | 17 | – | – | – |
| 24 | EOP | 16.4 | F | Pubertal/postpubertal stage | 1 | 0.01 | 8.8 | – | 24 | – | – | – |
| 25 | No-EOP | 14.8 | F | Pubertal/postpubertal stage | 0.5 | 0.008 | 12 | – | 62 | ^a | – | – |
| 26 | No-EOP | 17.11 | M | Pubertal/postpubertal stage | 0.5 | 0.008 | 12 | – | 17 | – | – | – |
| 27 | No-EOP | 5.8 | M | Prepubertal stage | 0.25 | 0.01 | – | – | 19.3 | – | – | – |
| 28 | No-EOP | 10.4 | M | Prepubertal stage | 0.5 | 0.008 | 14 | – | 8 | – | – | – |
| 29 | EOP | 15.7 | M | Pubertal/postpubertal stage | 2 | 0.03 | 5.3 | – | 3.6 | – | – | – |
| 30 | No-EOP | 10.1 | M | Prepubertal stage | 1.5 | 0.02 | 14.1 | – | 18 | – | – | – |
| 31 | EOP | 16.9 | F | Pubertal/postpubertal stage | 2 | 0.03 | 23 | – | 69.6 | ^a | – | Thyroiditis |
| 32 | No-EOP | 17.7 | M | Pubertal/postpubertal stage | 3 | 0.05 | 27 | ^a | 17 | – | – | – |
| 33 | EOP | 17.3 | F | Pubertal/postpubertal stage | 2 | 0.04 | 26 | ^a | 126.4 | ^a | ^a | Crohn's disease |
| 34 | EOP | 16.6 | F | Pubertal/postpubertal stage | 0.5 | 0.009 | 57 | ^a | 97 | ^a | – | – |

EOP, early-onset schizophrenia spectrum psychosis; F, female; HPRL, hyperprolactinemia; M, male; PRL, prolactin hormone.

^aPresence of clinical signs of HPRL and HPRL.

disruptive behavior disorders). No patient had received pharmacological therapy before enrollment. Clinical, sociodemographic features, and results are summarized in Table 1.

Baseline (T0)

The mean value of PRL was 17.98 ng/ml (SD±11.40).

HPRL was found in 7/34 (20%) patients (five males and two females), with a mean value of 35.51 ng/ml (SD±10.47); one female had a history of menstrual irregularities and galactorrhea that had appeared a few days earlier. Menstrual irregularities, not associated with HPRL, were found in 2/34 patients (6%) and acne in 1/34 (3%) patient. HPRL was found in 5/17 (71%) EOP patients and in 2/17 (29%) non-EOP patients.

All patients started risperidone therapy at variable doses according to clinical judgment and the severity of symptoms.

Among 34 patients of the sample, 15% had both a personal and a family history of autoimmune diseases (ulcerative colitis, Crohn's disease, thyroiditis, multiple sclerosis) and EOP diagnosis.

Follow-up (T1)

Follow-up was performed after a mean time of 5.5 months (range between 3 and 12 months). The mean dosage of risperidone was 1.2 mg/day (range 0.25 and 3 mg/day) with a dosage per kilogram of 0.02 mg/kg/day.

The mean value of serum PRL level was 35.46 ng/ml (SD±34.13), with a statistically significant difference between T0 and T1 ($P=0.04$). As for the variables (sex, pubertal status, and risperidone dosage), we could not perform a comparison using statistical tests because of the small number of the sample. Despite this, differences in the mean serum PRL values, between T0 and T1, were higher in female patients, than those in the pubertal/postpubertal stage, and risperidone dosage up to 1 mg/day.

HPRL was found in 13/34 patients (38%) (seven males and eight females), with a mean value of 63.88 ng/ml (SD+32.93), with a statistically significant difference between T0 and T1 ($P=0.03$). HPRL associated with menstrual irregularities and galactorrhea persisted in the same female patient described at T0; menstrual irregularities and acne, not associated with HPRL, presented in the same three patients described at T0.

Among 13 patients with HPRL, nine patients (69%) had EOP and four patients (31%) had no EOP. In particular, three of five EOP patients with HPRL at T0 showed a further increase in PRL at T1 and the other two patients had a normalization of the PRL value at T1. Moreover, two patients without EOP with HPRL at T0 had a normalization of the PRL value at T1.

There was a statistically significant difference, between T0 and T1, in the increase in the PRL mean values in EOP patients compared with patients without EOP ($P = 0.04$).

Among patients with a personal and a family history of autoimmune diseases, HPRL was found and, in the same patients, serum PRL levels between T0 and T1 increased more than that in the remaining patients (from 25.2 to 65.5 ng/ml vs. from 18 to 27.03 ng/ml).

Discussion

Risperidone is a selective monoaminergic antagonist that releases dopamine in different brain regions, such as the anterior pituitary gland. In this study, we found an increase in the mean value of the serum PRL level, with a statistically significant difference between T0 and T1 in the entire sample. This result is consistent with other studies that showed that one of the most frequent side effects of risperidone is the increase in PRL serum levels in both pediatric and adult populations (Masi *et al.*, 2001; Findling *et al.*, 2003; Saito *et al.*, 2004; Anderson *et al.*, 2007; Troost *et al.*, 2007; Calarge *et al.*, 2009; Jerrell *et al.*, 2009; Migliardi *et al.*, 2009; Roke *et al.*, 2009; Grahovac *et al.*, 2010; Fraguas *et al.*, 2011; Inder and Castle, 2011; Perez-Iglesias *et al.*, 2012; Roke *et al.*, 2012; Bargiota *et al.*, 2013; Lambert *et al.*, 2013; Margari and Petruzzelli *et al.*, 2013; Margari and Matera *et al.*, 2013). The differences in the mean values of serum PRL between T0 and T1, although not statistically significant, were higher in female patients, those in the pubertal/postpubertal stage, and risperidone dosage up to 1 mg/day, confirming previous literature data that have reported similar results (Duval *et al.*, 2008; Johnsen *et al.*, 2008; Lambert *et al.*, 2013; Ajmal *et al.*, 2014). In the follow-up, we detected an increased percentage (from 20 to 38%) of HPRL patients, although no patient reported clinical signs of HPRL. In the literature, psychotropic-induced HPRL clinical signs were more frequently reported in adults (Grahovac *et al.*, 2010; Perez-Iglesias *et al.*, 2012; Ajmal *et al.*, 2014) than in children and adolescents (Jerrell *et al.*, 2009). Studies on adult populations are very heterogeneous and not entirely comparable with our study because adult patients usually take higher doses of drugs for long periods of time, shift from one drug to another, or take several drugs simultaneously that could create and strengthen HPRL clinical signs. In contrast, our patients were drug naive and took a low dosage of risperidone in monotherapy for a short

duration of time, and this could explain the absence of clinical signs in the sample analyzed.

In addition, the mean value of serum PRL increased, with a statistically significant difference between T0 and T1, in EOP patients compared with no-EOP patients. A possible explanation for this finding could be linked to the features of EOP patients of the sample, who were mostly females, in pubertal/postpubertal age, and taking risperidone dosage up to 1 mg/day. Another hypothesis is that psychosis *per se* might represent a risk factor of increased serum PRL level. In our sample, HPRL (although not stable during time) was more frequent, both at T0 and at T1, in the EOP patients compared with no-EOP patients. This result was consistent with other studies showing that HPRL in schizophrenia was already present in neuroleptic naive first-episode psychosis and even in prodromal stages (Aston *et al.*, 2010). Therefore, as suggested recently by Riecher-Rössler *et al.* (2013), the increase in PRL might be related not only to the pharmacological therapy but also to the psychiatric disease *per se* and to the general stress of the illness experience that could increase dopamine release through a feedback mechanism. In fact, the inhibitory control of PRL secretion is exerted by dopamine, which acts on the D2 receptors of the lactotroph cells and, as it is well known, the dopaminergic transmission is dysfunctional in psychosis (Aston *et al.*, 2010). In addition, some studies indicated that the pituitary is a dynamic organ, whose volume increases in the months preceding or following the onset of psychosis, independently of antipsychotic treatments (Pariante, 2008). A larger pituitary size may be related to an increase in the number and size of corticotroph cells, reflecting a greater activation of the HPA with an increase in PRL production (Nordholm *et al.*, 2013). Several studies support the presence of hyperactivity and a blunted response of the HPA because of the stress associated with the onset of psychosis (Borges *et al.*, 2013; Baumeister *et al.*, 2014). The hypothesis that the stress of illness experience could lead to an increase in serum PRL level explains the instability of HPRL found in our sample between T0 and T1. In fact, risperidone treatment may either promote a greater serum PRL level or decrease it in correlation with clinical improvement. We may assume that risperidone treatment could either promote a greater serum PRL level that decreases it in correlation with clinical improvement, although to our knowledge, there are no data to support this speculation.

In our study, 15% of patients reported a personal and family history of autoimmune diseases. These patients showed a trend toward a higher mean PRL serum level between T0 and T1 compared with the remaining sample. This result suggests that autoimmune diseases may be an additional risk factor for the increase in the PRL level. This hypothesis is supported by the role of PRL in innate and adaptive immune responses, enhancing the production of immunoglobulins and autoantibodies, and by the

literature data, which showed that HPRL has been correlated with several autoimmune diseases such as Hashimoto thyroiditis, multiple and systemic sclerosis, and celiac disease (Jara *et al.*, 2011; Orbach *et al.*, 2012; Shelly *et al.*, 2012; Margari and Petruzzelli *et al.*, 2013; Margari and Matera *et al.*, 2013; Sayki Arslan *et al.*, 2013); in the same way, antipsychotic drug-induced HPRL has been associated with the development of autoimmune disorders in adult patients receiving long-term antipsychotic treatment (Poyraz *et al.*, 2008; Krysiak *et al.*, 2012). However, the role played by a psychiatric diagnosis and a personal or a family history of autoimmune diseases in our sample should be interpreted with caution, given the small sample size and the limited follow-up.

Conclusion

In this study, we analyzed the serum PRL level in a sample of children and adolescents treated with an antipsychotic drug. Notwithstanding the small sample size with a short-term follow-up, the sample analyzed may provide additional contributions toward the current literature because it included drug-naïve patients. This study is potentially interesting because it shows that the increase in the serum PRL level in patients treated with risperidone could be related not only to the drug and its dosage but also to individual characteristics (sex, pubertal stage, psychiatric disease, and associated autoimmune disorders). Therefore, it would be important, during risperidone therapy, to consider and monitor the multiple risk factors of increase in serum PRL and the occurrence of clinical signs of HPRL.

So far, studies that have evaluated the efficacy and tolerability of antipsychotic drugs in children and adolescents are very few and usually in small samples. Therefore, it would be advisable to promote further research in this field to develop guidelines that are actually available only for adult populations (Ajmal *et al.*, 2014) to monitor serum PRL critical levels and for the management of HPRL (i.e. switch to another compound, use of dopamine agonist, add-on aripiprazole) in children and adolescents.

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Conflicts of interest

There are no conflicts of interest.

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