HYPERPROLACTINEMIA - SIDE EFFECT OR PART OF THE ILLNESS

Sandra Vuk Pisk[1,2], Katarina Matić[1], Natko Gereš[1], Ena Ivezić[1,2],
Nedjeljka Ruljančić[1] & Igor Filipčić[1,2,3]

[1]*Psychiatric Hospital "Sveti Ivan", Zagreb, Croatia*
[2]*Faculty of Dental Medicine and Health, "Josip Juraj Strossmayer" University of Osijek, Osijek, Croatia*
[3]*School of Medicine, University of Zagreb, Zagreb, Croatia*

SUMMARY

Background: *Hyperprolactinemia is associated with side effect of antipsychotics in people suffering from psychotic disorders. However, increased prolactin levels (mlU/L) were found in patients suffering from the first psychotic episode who were not receiving antipsychotic therapy. The assumption of this study is that the abnormality in the level of prolactin is associated with the effect and influence of the disease, not the therapy that is carried out.*

Subjects and methods: *Study involved 54 female patients hospitalized in Psychiatric hospital "Sveti Ivan", whose average age was 33.9 years. All patients had been diagnosed with a psychotic disorder (according to MKB-10, F20-F29). 18 patients had their first psychotic episode, while 36 patients had relapses of psychotic disorder. The methods used were: PANSS scale and measurement of prolactin concentration (Immunoanalyzer ACCESS 2, CLIA method). Arithmetic mean, standard deviations, correlation coefficient, Mann Whitney U test and the chi-squared test were used.*

Results: *75.5% of patients had prolactin values above the reference values (min 121, max 4192 ml/L). In a sample of patients with first psychotic episode, 77.8% had elevated prolactin levels, while among re-hospitalized patients, elevated levels had 74.2%. Statistically significant results were obtained: patients with higher pronounced symptoms had higher prolactin values, especially particles on PANSS: P1 (delusions), N4 (Apathy), G15 (preoccupation) and G16 (active avoidance).*

Conclusion: *Elevated prolactin in patients has been demonstrated regardless of antipsychotic therapy, therefore the question of etiology of hyperprolactinemia in psychotic disorders is questionable. The association of hyperprolactinemia with the severity of the clinical picture has also been demonstrated, higher prolactin values indicating a stronger clinical picture, which calls into question the protective role of prolactin in psychotic disorders.*

Key words: *antipsychotics - first psychotic episode - hyperprolactinemia - prolactin - psychotic disorders*

* * * * *

INTRODUCTION

Hyperprolactinemia is a common condition in patients with psychotic disorders; dopamine being the main prolactin inhibiting factor, hyperprolactinemia is commonly linked with the effect and the side effects of antipsychotic drugs (Bushe et al. 2008, Delgado-Alvarado et al. 2018, Engler et al. 2009, Fitzgerald & Dinan 2008, Grattan 2015, Grigg et al. 2017, Kapur et al. 2002, Montejo 2008). Often, this a reason why some antipsychotic agents are unjustifiably neglected in clinical practice, being seen as the main cause of the increase in prolactin levels (Rajkumar 2014).

Hyperprolactinemia is, indeed, a consequence of tuberoinfundibular dopaminergic pathway D2 receptors occupancy by antipsychotic medicines that generate their effect in that way (Grattan 2015, Grigg et al. 2017, Inder & Castle 2011).

However, the elevated prolactin levels were found in patients with first-episode psychosis who have not been treated with antipsychotic drugs (Delgado-Alvarado et al. 2018, Garcia-Rizo et al. 2012, Segal et al. 2004). Little is known about the causes of hyperprolactinemia, its protective role, expression and the correlation with the clinical manifestation in the first-episode psychosis (Aston et al. 2010, Garcia-Rizo et al. 2012, Grattan 2015, Jaroenporn et al. 2007, Jimena et al. 1998, Lally et al.

2017, Lennartsson & Jonsdottir 2011, Oride et al. 2009, Riecher-Rössler et al. 2013, Segal et al. 2004). The existing research provides contradictory results in patients with psychosis that actually have no antipsychotic treatment (Kahn et al. 2008, Segal et al. 2004). The origin of this phenomenon has still not been clarified to this date and is considered to be multifactorial (Rajkumar 2014). Again, the existing research provides contradictory conclusions; the literature describes the association of hyperprolactinemia with stress, stress being a factor that affects the increase in prolactin levels (Jaroenporn et al. 2007, Lally et al. 2017, Lennartsson and Jonsdottir 2011, Riecher-Rössler et al. 2013, Tsuchiya 1984) while other research indicates that the prolactin levels elevation in the first-episode psychosis is associated with glucose intolerance and the thyroid hormone status alterations; additionally, sex hormones were found to impact the prolactin level (González-Blanco et al. 2016, Grattan 2015, Oride et al. 2009, Rajkumar 2014, Riecher-Rössler & Häfner 1993). Additionally, evidence suggests the potential protective role of hyperprolactinemia in psychotic disorders in (Aston et al. 2010, Delgado-Alvarado et al. 2018). Existing evidence suggests that schizophrenia is characterized by abnormal prolactin levels regulation (Rajkumar 2014).

This research was grounded in the hypothesis that the part of patients suffering from schizophrenia may

have a specific vulnerability for the abnormal regulation in prolactin secretion, independent of antipsychotic treatment. The research suggested that the prolactin levels abnormality is caused by the illness itself, as opposed to it being exclusively the side effect of the therapy, and that this abnormality affects the clinical manifestation of illness in people suffering from a psychotic disorder.

SUBJECTS AND METHODS

Subjects

54 patients hospitalized in the St John Psychiatric Hospital (Zagreb) participated in this study. The average age of the sample was 33.9 years (SD=12.47), ranging from 18 to 80 years of age. Patients were diagnosed by competent psychiatrists according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Patients diagnosed with a psychotic disorder (F20-F29) were included in this research. The most common diagnoses were acute psychotic disorder (n=23), schizophrenia (n=10) and un-specified nonorganic psychosis (n=1). 18 patients included in the study were hospitalized following the first episode of psychosis and 36 patients were hospitalized following the relapse of a psychotic episode, with one or more episodes prior to the current episode. Patients who were admitted due to relapse already had an existing psychiatric pharmacotherapy at the time of the hospitalization. Risperidone (n=24), clozapine (n=15), aripiprazole (n=13) and olanzapine were drugs that were most commonly prescribed. Patients included in the study signed informed consent. The study was approved by the Hospital Ethical Committee.

Instruments and methods

Patient's sociodemographic and clinical characteristics were retrieved from hospital records. The severity of current psychopathological symptoms was measured using the Positive and Negative Syndrome Scale (PANSS).

The PANSS scale is used to measure the severity of symptoms in patients with schizophrenia (Kay et al. 1987). The scale results are collected through an 45-minute interview, during which time the clinician rates the patients symptoms on a 7 point scale (ranging from 1-no symptoms to 7- extreme expression of symptoms) for each of 30 different symptoms; seven items measure positive and seven items measure negative symptoms, while 16 items measure general psychopathology. The scale has been psychometrically validated (Kay et al. 1987).

Measuring the prolactin concentrations

A blood specimen was extracted into the test tube without using the anticoagulant (6 ml), 2 hours after awakening with a minimum of a 30-minute patient resting period. The specimen rested in room temperature for one hour following the collection, followed by the centrifugation in the duration of ten minutes in 2500g.

The prolactin concentrations were measured using the Access 2 immunoassay analyzer system (Beckman Coulter, USA) using the reagents from the same manufacturers. The measured coefficient of variation was 2.43% for the median values of control material at 88.8 mlU/L and 2.45% for the median values of control material at 500 mlU/L.

Statistical analysis

Mean and standard deviation were used for the descriptive analysis. Spearman correlation coefficient was used to analyze the correlation between the prolactin levels and PANSS scale results, taking into account the sample deviation from the normal distribution. Mann Whitney U test and Chi-square test were used for comparison between the groups: patients with the first episode psychosis and the rest of the patients. Results were significant at p≤0.05 level. Data was analyzed using the SPSS, version 20.

RESULTS

The average prolactin levels for the overall sample was 1526.6 mIU/L (SD=1118.96), ranging from 121 to 4192 mIU/L 75.5% of patients had prolactin levels above the referral interval suggested by the reagents manufacturer (71-566 mIU/L); the referral level is comparable with the generally agreed on range (Casanueva et al. 2006).

The average, minimum and maximum prolactin levels for patients with the first-episode psychosis separately from other patients are presented in Table 1. The comparison between groups using the Mann Whitney U test found no significant differences: U=296,000; p=0.724. In the group of patients with the first-episode psychosis, 77.8% has increased prolactin levels, compared to 74.2% of the patients from the rest of the sample. The comparison of the groups with the Chi-square test did not find a significant difference of the number of patients with the elevated prolactin levels between the two groups: χ^2=0.079, p=0.779.

Average PANSS scale results, in whole and by subscales (positive symptoms, negative symptoms, general psychopathology) as well as the correlation between the prolactin levels (using the Spearman correlation coefficient) are presented in Table 2. Higher prolactin levels were found in patients with more symptoms on each of the three subscales of PANSS.

The difference in PANNS scale results was not statistically significant between the patients with the first-episode psychosis and other patients (positive symptoms: U=305,000; p=0.589; negative symptoms: U=246,500; p=0.500; general psychopathology: U=284,500; p=0.909).

Table 1. Prolactin levels (mlU/L) in patients with first-episode psychosis (N=18) and in the hospitalized patients following the relapse of a psychotic episode (N=36)

First-episode psychosis	Minimum	Maximum	Mean	Std. Deviation
No	121.00	3702.00	1392.39	1100.21
Yes	121.00	3129.00	1391.89	856.83

Table 2. PANSS scale results (in whole and by subscales) and their correlation with prolactin levels (N=54)

PANSS subscales	Mean (SD)	Correlation (rho)	Correlation significance (p)
Positive symptoms	28.70 (9.43)	0.300	0.036
Negative symptoms	26.16 (10.55)	0.297	0.038
General psychopathology	54.34 (15.52)	0.301	0.036

The following symptoms were significantly correlated with elevated prolactin levels: panssP1 (delusions, rho=0.303, p=0.034), panssP2 (conceptual disorganization, rho=0.321, p=0.024), panssP3 (hallucinations, rho=0.443, p=0.001), panssN4 (apathetic social withdrawal, rho=0.313, p=0.029), panssG15 (preoccupation, rho=0.417, p=0.003) i panss G16 (active social avoidance, rho=0.329, p=0.021).

The correlation between prolactin levels and patients' sociodemographic and clinical characteristics was not significant.

DISCUSSION

This research found hyperprolactinemia in 77.8% of patients with the first-episode psychosis and in 74.2% of patients with the repeated episode of psychosis who were proscribed with antipsychotic drugs at the time of the hospitalization.

The difference in the prolactin levels between the two analyzed groups (patients with the first-episode psychosis and patients with the repeated episode of psychosis who were already taking antipsychotic drugs) was not significant, as shown in Table 1. These specific findings are consistent with previous research evidence that found hyperprolactinemia in 71% of patients with the first-episode psychosis who were taking no antipsychotic drugs (Kahn et al. 2008).

Results support the notion that the elevation of prolactin levels may be conditioned by the acute phase of the illness itself or the metabolic changes accompanying this phase, as opposed to hyperprolactinemia exclusively being caused by the antipsychotic drug use (González-Blanco et al. 2016). Ample of literature supports this notion (Aston et al. 2010, Garcia-Rizo et al. 2012, Kahn et al. 2008, Riecher-Rössler et al. 2013). Existing genetic studies demonstrate that the portion of schizophrenia patients have prolactin gene polymorphism (Gassó et al. 2018, Ivanova et al. 2017). Elevated prolactin blood levels have been described as a condition preceding the onset of antipsychotic drug treatment (Rajkumar 2014), with literature suggesting this phenomena being associated with the pituitary gland size changes predicting the onset of psychosis in people with high risk from psychosis, depending on various circumstances (Garner et al. 2005). The mechanism of prolactin levels elevation is still not completely clear; the prolactin-releasing peptide (PrRP) may play a role in the process: disturbance in the release of the PrRP is found as the introduction to metabolic disorder and a similar disturbance is found in the first-episode schizophrenia (Onaka et al. 2010, Thakore 2004). Some authors suggest that the intensification of inflammation, as reported in patients with first-episode psychosis that were not treated with antipsychotic drugs at the time of the onset, might be a mechanism causing hyperprolactinemia (Friedrich et al. 2011, Miller et al. 2011). Similarly, a serotonergic abnormality may lead to the prolactin levels elevation (Duval et al. 2003).

Correlation was found between prolactin levels elevation and positive and negative symptoms, as illustrated in Table 2. More specifically, a statistically significant positive correlation was found between prolactin levels elevation and the following symptoms: delusions, conceptual disorganization, hallucinations, apathetic social withdrawal, preoccupation and active social avoidance. While previous studies had somewhat contradictory results (Rajkumar 2014), with most data backing the correlation between prolactin levels elevation and the greater expression of negative symptoms in patients with psychosis, stressing the protective role of the elevated prolactin levels in relation to the severity of clinical manifestation, especially with female patients, (Garcia-Rizo et al. 2012, Riecher-Rössler et al. 2013), this research demonstrated the correlation between the elevated prolactin levels and both the negative and positive symptoms. Elevated prolactin levels were not correlated with the weaker intensity of symptoms but with a more severe clinical manifestation and more intense symptoms. Where elevated prolactin levels were found, both positive and negative symptoms were more expressed with no difference in the concentration levels. The association between the elevated prolactin levels and specific symptoms, in our case delusions, conceptual disorganization and hallucinations, is explained in the literature using the dopamine hypothesis of schizophrenia (Rajkumar 2014).

The results of this research shed new light on the schizophrenia symptomatology in relation to hyper-

prolactinemia, possibly opening space for better re-cognition of patients under the elevated risk from hyperprolactinemia. It supports the understanding of schizophrenia as a syndrome that may include hyper-prolactinemia separately from the antipsychotic treat-ment. While the importance of recognizing hyperpro-lactinemia (and its consequences) as a side effect of antipsychotic drugs is not questioned, this research may offer more space to the clinicians in prescribing antipsychotic drugs that are so important for the pro-gression of psychosis. This research is potentially a step toward preventing the consequences of hyper-prolactinemia as a phenomena that may be part of the illness itself.

This research had one major limitation; it is not possible to generalize these results to the overall popu-lation as the sample was relatively small and more research is needed with a greater sample.

CONCLUSION

Most studies have demonstrated the association of hyperprolactinemia in people suffering from psychotic disorders with antipsychotics. In our study, we found that elevated prolactin levels in patients has been de-monstrated regardless of antipsychotic therapy, there-fore the question of etiology of hyperprolactinemia in psychotic disorders should be considered. The associa-tion of hyperprolactinemia with the severity of the clinical picture has also been demonstrated. Patients with high prolactin values have a more severe clinical picture, which raises the question of the protective role of prolactin in psychotic disorders, therefore further studies are needed.

Contribution of individual authors:

Sandra Vuk-Pisk, Katarina Matić & Natko Gereš were involved with paper design, writing and multiple edits of the manuscript drafts.
Ena Ivezić analyzed the data and contributed to paper design and writing of the manuscript drafts.
Nedjeljka Ruljančić was involved with paper design and reviewed the manuscript.
Igor Filipčić contributed to the conceptual ideas and final preparations of the manuscript.
All authors read and approved the final manuscript.

References

1. Aston J, Rechsteiner E, Bull N, Borgwardt S, Gsch-wandtne, U, Riecher-Rössler A: Hyperprolactinaemia in early psychosis - not only due to antipsychotics. Prog Neuro-Psychopharmacology Biol Psychiatry 2010; 34:1342–1344

2. Bushe C, Shaw M, Peveler RC: A review of the association between antipsychotic use and hyperprolactinaemia. J Psychopharmacol 2008; 22:46–55

3. Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R: Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf) 2006; 65:265–273

4. Delgado-Alvarado M, Tordesillas-Gutierrez D, Ayesa-Arriola R, Canal M, de la Foz VOG, Labad J, Crespo-Facorro B: Plasma prolactin levels are associated with the severity of illness in drug-naive first-episode psychosis female patients. Arch Womens Ment Health 2018; 10:1-7

5. Duval F, Mokrani MC, Monreal J, Bailey P, Valdebenito M, Crocq MA, Macher JP: Dopamine and serotonin function in untreated schizophrenia: clinical correlates of the apomorphine and d-fenfluramine tests. Psychoneuro-endocrinology 2003; 28:627–642

6. Engler H, Doenlen R, Riether C, Engler A, Niemi MB, Besedovsky HO, del Rey A, Pacheco-López G, Feldon J, Schedlowski M: Time-dependent alterations of peripheral immune parameters after nigrostriatal dopamine depletion in a rat model of Parkinson's disease. Brain Behav Immun 2009; 23:518–526

7. Fitzgerald P, Dinan TG: Prolactin and dopamine: What is the connection? A Review Article. J Psychopharmacol 2008; 22:12–19

8. Friedrich N, Schneider HJ, Spielhagen C, Markus MRP, Haring R, Grabe HJ, Buchfelder M, Wallaschofski H, Nauck M: The association of serum prolactin concentra-tion with inflammatory biomarkers-cross-sectional fin-dings from the population-based Study of Health in Pomerania. Clin Endocrinol (Oxf) 2011; 75:561–566

9. Garcia-Rizo C, Fernandez-Egea E, Oliveira C, Justicia A, Parellada E, Bernardo M, Kirkpatrick B: Prolactin concentrations in newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis. Schizophr Res 2012; 134:16–9

10. Garner B, Pariante CM, Wood SJ, Velakoulis D, Phillips L, Soulsby B, Brewer WJ, Smith DJ Dazzan P, Berger GE, Yung AR, van den Buuse M, Murray R, McGorry PD, Pantelis C: Pituitary Volume Predicts Future Transition to Psychosis in Individuals at Ultra-High Risk of Developing Psychosis. Biol Psychiatry 2005; 58:417–423

11. Gassó P, Mas S, Bioque M, Cabrera B, Lobo A, González-Pinto A, Díaz-Caneja CM, Corripio I, Vieta E, Castro-Fornieles J: Impact of NTRK2, DRD2 and ACE polymorphisms on prolactin levels in antipsychotic-treated patients with first-episode psychosis. J Psychopharmacol 2018; 32:702–710

12. González-Blanco L, Greenhalgh AMD, Garcia-Rizo C, Fernandez-Egea E, Miller BJ, Kirkpatrick B: Prolactin concentrations in antipsychotic-naïve patients with schizophrenia and related disorders: A meta-analysis. Schizophr Res 2016; 174:156–160

13. Grattan DR: 60 years of neuroendocrinology: the hypo-thalamo-prolactin axis. J Endocrinol 2015; 226:101–122

14. Grigg J, Worsley R, Thew C, Gurvich C, Thomas N, Kul-karni J: Antipsychotic-induced hyperprolactinemia: synthesis of world-wide guidelines and integrated recommendations for assessment, management and future research. Psychopharmacology (Berl) 2017; 234:3279–3297

15. Inder WJ, Castle D: Antipsychotic-Induced Hyperprolactinaemia. Aust New Zeal J Psychiatry 2011; 45:830–837

16. Ivanova SA, Osmanova DZ, Boiko AS, Pozhidaev IV, Freidin MB, Fedorenko OY, Semke AV, Bokhan NA, Kornetova EG, Rakhmazova LD: Prolactin gene polymorphism (− 1149 G/T) is associated with hyperprolactinemia in patients with schizophrenia treated with antipsychotics. Schizophr Res 2017; 182:110–114

17. Jaroenporn S, Nagaoka K, Kasahara C, Ohta R, Watanabe G, Taya K: Physiological roles of prolactin in the adrenocortical response to acute restraint stress. Endocr J 2007; 54:703-11

18. Jimena P, Aguirre MA, Lopez-Curbelo A, De Andres M, Garcia-Courtay C, Cuadrado MJ: Prolactin levels in patients with systemic lupus erythematosus: a case controlled study. Lupus 1998; 7:383–386

19. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IPM, Gheorghe MD, Rybakowski JK, Galderisi S, Libiger J: Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 2008; 371:1085–1097

20. Kapur S, Langlois X, Vinken P, Megens A, De Coster R, Andrews JS: The differential effects of atypical antipsychotics on prolactin elevation are explained by their differential blood-brain disposition: a pharmacological analysis in rats. J Pharmacol Exp Ther 2002; 302:1129–1134

21. Kay SR, Fiszbein A, Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261–76

22. Lally J, Ajnakina O, Stubbs B, Williams HR, Colizzi M, Carra E, Fraietta S, Gardner-Sood P, Greenwood KE, Atakan Z, Mondelli V, Ismail K, Howes O, Taylor DM, Smith S, Hopkins D, Murray RM, Gaughran F: Hyperprolactinaemia in first episode psychosis - A longitudinal assessment. Schizophr Res 2017; 189:117–125

23. Lennartsson AK, Jonsdottir IH: Prolactin in response to acute psychosocial stress in healthy men and women. Psychoneuroendocrinology 2011; 36:1530–1539

24. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B: Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2011; 70:663–671

25. Montejo AL: Prolactin awareness: an essential consideration for physical health in schizophrenia. Eur Neuropsychopharmacol 2008; 18:108–114

26. Onaka T, Takayanagi Y, Leng G: Metabolic and stress-related roles of prolactin-releasing peptide. Trends Endocrinol Metab 2010; 21:287–293

27. Oride A, Kanasaki H, Purwana IN, Miyazaki K: Possible involvement of mitogen-activated protein kinase phosphatase-1 (MKP-1) in thyrotropin-releasing hormone (TRH)-induced prolactin gene expression. Biochem Biophys Res Commun 2009; 382:663–667

28. Rajkumar RP: Prolactin and Psychopathology in Schizophrenia: A Literature Review and Reappraisal. Schizophr Res Treatment 2014; 1–12

29. Riecher-Rössler A, Häfner H: Schizophrenia and oestrogens - is there an association? Eur Arch Psychiatry Clin Neurosci 1993; 242:323–328

30. Riecher-Rössler A, Rybakowski JK, Pflueger MO, Beyrau R, Kahn RS, Malik P, Fleischhacker WW: Hyperprolactinemia in antipsychotic-naive patients with first-episode psychosis. Psychol Med 2013; 43:2571–2582

31. Segal M, Avital A, Rojas M, Hausvater N, Sandbank S, Liba D, Moguillansky L, Tal I, Weizman A: Serum prolactin levels in unmedicated first-episode and recurrent schizophrenia patients: a possible marker for the disease's subtypes. Psychiatry Res 2004; 127:227–235

32. Thakore JH: Metabolic disturbance in first-episode schizophrenia. Br J Psychiatry 2004; 184:76–79

33. Tsuchiya K: Studies on prolactin in major psychoses - with reference to prolactin response to stress in schizophrenia. Folia Psychiatr Neurol Jpn 1984; 38:53–6

Correspondence:
Sandra Vuk Pisk, MD, PhD
Psychiatric Hospital "Sveti Ivan"
Jankomir 11, 10 090 Zagreb, Croatia
E-mail: sandra.pisk@pbsvi.hr