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CLINICAL TRIAL REPORT

The Correlation Between DRD2 and COMT Gene Polymorphisms, HPT and HPG Axes Functions, and Antipsychotic Drug-Induced Hyperprolactinemia and Macroprolactinemia

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Purpose: This study aimed to investigate the relationship between dopamine receptor D2 (DRD2) and catechol-o-methyltransferase (COMT) gene polymorphism, hypothalamic-pituitary-thyroid (HPT) and hypothalamic-pituitary-gonadal (HPG) axes functions, and macroprolactinemia induced by antipsychotics.

Patients and Methods: A total of 133 patients with schizophrenia were selected and given risperidone (4~6mg/d) monotherapy. The polymorphisms of DRD2 Taq1A and COMT Val158Met were analyzed using RFLP-PCR at baseline, and the levels of total prolactin (T-PRL), macroprolactin, C peptide (C-P), estradiol (E2), cholesterol (TC), low density lipoprotein (LDL), insulin, cortisol, thyroid function, and reproductive hormone were measured at baseline and the end of the fourth week of treatment. The patients were divided into a hyperprolactinemia group and a macroprolactinemia group according to their levels of T-PRL and macroprolactin, and the differences in the above indexes between the two groups were analyzed.

Results: There was no significant difference in the DRD2 Taq1A or COMT Val158Met gene polymorphisms between the two groups. However, after four weeks of treatment, significant differences were observed between the two groups in terms of C-P (t= 2.16, p=0.04), E2 (t=−3.89, p<0.001), TC (t= −2.54, p=0.01), insulin (t=−3.93, p<0.001), T3 (t= 2.31, p= 0.02), and FT3 (t=2.05, p=0.04).

Conclusion: DRD2 Taq1A and COMT Val158Met gene polymorphisms may not be effective in predicting macroprolactinemia, but changes in C-P, E2, TC, insulin, T3 and FT3 levels may have some suggestive significance for the differentiation of hyperprolactinemia and macroprolactinemia.

Keywords: prolactin, macroprolactin, hyperprolactinemia, schizophrenia, gene polymorphism

Introduction

Schizophrenia is a chronic disease with a prolonged course, and antipsychotics are the primary choice for its treatment.[1] However, there is significant heterogeneity in the efficacy of antipsychotic medication. The same drug at the same dosage can have different therapeutic effects and adverse reactions on different schizophrenic patients, which poses significant challenges when selecting medications and avoiding adverse reactions in clinical treatment. One of the common adverse effects of antipsychotic drug therapy is hyperprolactinemia (HPRL). Research has shown that the incidence of drug-induced HPRL in patients with schizophrenia can be as high as 70% due to the use of antipsychotic drugs.[2] The main mechanism is thought to involve hypothalamic dopamine activating the D_2 receptor on the pituitary prolactin cell membrane, inhibiting prolactin gene transcription, synthesis, and release.[3] The D2 receptor plays a crucial role in antipsychotic drug pharmacology. Antipsychotics treat the positive symptoms of schizophrenia by blocking the D2 receptors of the dopamine system in the midbrain limbic system. Simultaneously, they also block the D2 receptors in the midbrain-striatal dopamine pathway, leading to an increase in serum prolactin levels, genetic variations in DRD2,

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particularly the Taq1A (rs1800497) polymorphism located in the ankyrin repeat and kinase domain-containing 1 (ANKK1) gene, have been implicated in modulating this response.[4,5] However, serum prolactin levels do not always completely correlate with clinical symptoms. Sometimes, high levels of prolactin are present without any manifestations, such as amenorrhea or lactation, while in other cases, even a slight increase in prolactin can lead to endocrine imbalances and infertility. This may be due to the presence of macroprolactin,[6–8] one of the three molecular components of prolactin. Previous studies have referred to the lack of clinical manifestations corresponding to high prolactin levels as macroprolactinemia (MPRL), identifying macroprolactin as one of the main causes of HPRL misdiagnosis. The prevalence of MPRL is around 3.7% within baseline prolactin concentrations, but this proportion increases among HPRL patients, reaching as high as 55.6%.[9–12] It is recommended that for patients with HPRL induced by certain antipsychotic drugs, screening for MPRL is advisable when PRL concentrations exceed 3000 mIU/L.[2] Our preliminary research revealed that after 2 weeks of treatment with either risperidone or amisulpride, 75.09% of patients met the diagnostic criteria for HPRL, with 43% of patients meeting the diagnostic criteria for MPRL.[13]

Currently, research results show that DRD2 Taq1A and, COMT Val158Met gene polymorphisms correlate with prolactin levels.[14] DRD2 Taq1A A1 carriers exhibited significantly higher antipsychotic-induced prolactin levels compared to A2 homozygotes, particularly in patients treated with risperidone or paliperidone.[15] The COMT Val158Met (rs4680) polymorphism further influences prolactin regulation through its role in dopamine catabolism. The Val allele encodes a high-activity enzyme that rapidly degrades synaptic dopamine, whereas the Met allele reduces COMT activity by 3–4 fold, increasing extracellular dopamine availability in the prefrontal cortex.[16] While prefrontal dopamine does not directly regulate prolactin, compensatory upregulation of DRD2 blockade in the pituitary may occur to maintain dopaminergic homeostasis. A 2022 study reported that COMT Met/Met genotypes had 34% higher prolactin levels after amisulpride treatment compared to Val/Val carriers, likely due to enhanced sensitivity to dopamine depletion in the tuberoinfundibular pathway.[17] Conversely, a genome-wide association study (GWAS) found no significant association between COMT Val158Met and antipsychotic-induced HPRL,[18] underscoring the need for phenotype stratification (e.g. differentiating HPRL from macroprolactinemia). Critically, previous studies have focused solely on total prolactin levels, neglecting the role of macroprolactin. Emerging evidence suggests that genetic variants affecting prolactin's molecular conformation (eg, aggregation with immunoglobulins) or clearance (eg, hepatic metabolism) may predispose to MPRL.[19]

Combining neuroendocrine theory, this paper aims to explore the significance of DRD2 and, COMT gene polymorphisms, hypothalamic–pituitary–thyroid (HPT), and hypothalamic–pituitary–gonadal (HPG) axes functions in the early recognition of patients with MPRL and authentic HPRL, screen out the population susceptible to authentic HPRL, avoid drugs that easily increase prolactin in such patients, and accurately distinguish between patients with HPRL and MPRL to avoid misdiagnosis and mistreatment.

Materials and Methods

The Inclusion and Exclusion Criteria

From April 2020 to April 2022, a total of 133 schizophrenic patients hospitalized in the Huzhou Third People's Hospital were selected as participants, including 39 males and 94 females aged between 18 and 44 (mean age: 32.84 ± 6.84).

The inclusion criteria were as follows: (1) all enrolled patients received a definite diagnosis from two doctors with intermediate or above professional titles, and all met the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5); (2) female patients were required to exhibit regular menstrual cycles before enrollment; (3) patients were aged between 18 and 45 years old; (4) serum prolactin levels were within the normal range before admission.

The exclusion criteria were as follows: (1) patients with mental disorders caused by organic brain diseases or emotional mental disorders; (2) patients suffering from serious physical diseases or diseases that may interfere with evaluation, or patients considered by the investigator to be unsuitable for participation in the study; (3) patients with definite obesity (BMI $\geq$ 28kg/m^2), eating disorders, unstable diabetes control, unstable hypertension control, a history of

serious heart disease or heart surgery; (4) patients with definite drug abuse or drug dependence in the past year; (5) pregnant or lactating women.

This study was approved by the Ethics Committee of Huzhou Third People's Hospital, and informed consent was obtained from either the patient or their guardian.

Drugs, Reagents, and Instruments

We used risperidone tablets (1 mg) manufactured by Changzhou Siyao Pharmaceutical Co., Ltd. for this study. Prolactin levels were measured using an Automatic Microparticle Chemiluminescence Immunoassay System (Access, Beckman Coulter). The prolactin test reagent (Abbott Diagnostics Ireland, Batch No. 28372U) was employed to quantify serum prolactin concentrations, to differentiate true hyperprolactinemia from macroprolactinemia, we performed additional testing using a Human Macroprolactin Detection ELISA Kit (Xiamen Lunchangshuo Biotechnology Co., Ltd., Batch No. e20180301a). For DNA isolation, we utilized an Automatic Nucleic Acid Extraction and Purification Instrument (ZK-01, Nanjing Zhongkebaier Medical Technology Co., Ltd.), which ensures efficient and standardized nucleic acid extraction. Finally, DNA was extracted using a DNA Extraction Kit (Beijing Tiangen Biochemical Technology Co., Ltd., Batch No. 20210401), following the manufacturer's protocol.

Clinical Data Collection

The patients clinical data were collected, including their gender; age; disease course; education level; and levels of total prolactin (T-PRL), C peptide (C-P), estradiol (E2), cholesterol (TC), low density lipoprotein (LDL), insulin, cortisol, triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3) and free thyroxine (FT4), and macroprolactin.

Treatments

Patients were treated with risperidone (4 ~ 6 mg/d), and the doses were gradually increased to the effective treatment dose within two weeks. No other endocrine-affecting drugs were used. The total treatment observation time was four weeks. If a patient had obvious extrapyramidal side effects during treatment, appropriate anticholinergic drugs were given.

DRD2 Taq1A and COMT Val158Met Gene Polymorphism

Before treatment, 5 mL of peripheral venous blood was collected and stored in a refrigerator at −80°C. DNA was extracted with a DNA extraction kit according to the manufacturer's instructions and stored at −20 °C. The polymorphisms in DRD2 Taq1A and COMT Val158Met were analyzed using RFLP-PCR.

Biochemical Index Detection

At the end of the fourth week of treatment, 5 mL of fasting blood was taken from each patient in the morning, centrifuged at room temperature for 10minutes at 4000r/min, and the supernatant was taken to measure the T-PRL levels, biochemistry, thyroid function, reproductive hormone levels, and macroprolactin.

Experimental Grouping

Based on the total serum prolactin and macroprolactin results, the patients were divided into a HPRL group and a MPRL group. The diagnostic criterion for HPRL: a total serum prolactin > 29.2 ng/mL for females, and > 17.7 ng/mL for males; the diagnostic criterion for `MPRL was a macroprolactin concentration/T-PRL ≥ 30%.[2]

Statistical Tests

All experimental data were statistically processed using SPSS 25.0 software. All normally distributed measurement data are expressed as the mean ± standard deviation, and the independent sample *t* test was used for intragroup comparison. Counting data were expressed as the frequency, and X^2 was used for comparison between groups. The genotype distribution of the two groups were tested using the non parametric Freeman-Halton test. $p<0.05$ was considered statistically significant.

Results

Comparison of the Clinical Data between the Two Groups

Before treatment, the T-PRL of 133 patients was 15.41 ± 6.74 ng/mL, and the macroprolactin level was 1.51 ± 0.68 ng/mL. After 4 weeks of treatment, the prolactin levels of these 133 patients increased by varying degrees, including 76 cases in the HPRL group and 57 cases in the MPRL group. There was no significant difference between the two groups in terms of gender, age, education level, or course of disease, as shown in Table 1.

Comparison of COMT and DRD2 Gene Polymorphisms between the Two Groups

There was no significant difference in the frequencies of the AA, GA or GG genotypes of the COMT gene between the two groups (p=0.84). There was also no significant difference in the frequencies of the AA, GA of GG genotypes of the DRD2 gene (p=0.05), as shown in Table 2.

Comparison of the Biochemical Indexes between the Two Groups

There was no statistically significant difference between the two groups before treatment, as shown in Table 3.

After 4 weeks of treatment, there were significant differences in C-peptide, estradiol, cholesterol, insulin, T3 or FT3 between the two groups ($p < 0.05$). There were also no significant differences in LDL, cortisol, T4, or FT4 between the two groups ($p > 0.05$). See Table 4 for details.

Table 1 Comparison of General Data Between the Two Groups

		HPRL Group (n=76)	Macroprolactinemia Group(n=57))	t/x^2	p
Sex	Male	22	17	0.81	0.37
	Female	54	40		
Education	Junior high school and below	36	29	0.43	0.85
	High school or technical secondary school	25	17		
	College degree or above	15	11		
Age (year)		40.61±11.27	39.59±11.75	0.38	0.71
Course of disease (year)		12.50±9.33	12.06±9.51	0.20	0.84

Table 2 Comparison of COMT and DRD2 Gene Polymorphisms Between Two Groups

		HPRL Group (n=76)	Macroprolactinemia Group(n=57))	x^2	p
COMT	AA	11	13	0.54	0.84
	GA	21	17		
	GG	44	27		
DRD2	AA	9	15	5.94	0.05
	GA	13	15		
	GG	54	27		

Table 3 Comparison of Indexes Between Hyperprolactinemia Group and Macroprolactinemia Group Before Treatment ($\bar{x} \pm S$)

	HPRL Group(n=76)	Macroprolactinemia Group(n=57)	95% CI	t	P
C-P(ng/mL)	3.43±2.38	2.09±0.53	1.34 (0.21–2.47)	2.46	0.06
E2(pg/mL)	66.27±84.12	69.52±90.89	−3.25 (−43.50–37.00)	−0.16	0.87
TC(mmol/L)	4.94±0.99	4.73±1.07	0.21 (−0.26–0.68)	0.88	0.38
LDL(mmol/L)	3.30±4.11	2.68±0.90	0.62 (−0.98–2.21)	0.77	0.44
Insulin(μIU/mL)	10.86±15.11	10.87±4.59	−0.12 (−7.55–7.73)	−0.03	0.99
Cortisol(nmol/L)	350.59±117.35	337.33±106.89	13.26 (−76.68–103.19)	0.30	0.77
T3(ng/mL)	0.93±0.14	0.91±0.18	0.03 (−0.44–0.10)	0.75	0.46
T4(μg/dL)	6.60±1.65	6.56±1.95	0.04 (−0.78–0.85)	0.91	0.93
FT3(pg/mL)	2.56±0.33	2.43±0.49	0.14 (−0.07–0.34)	1.32	0.20
FT4(ng/dL)	1.05±0.22	1.02±0.24	0.03 (−0.08–0.13)	0.51	0.62

Table 4 Comparison of Indexes Between Hyperprolactinemia Group and Macroprolactinemia Group ($\bar{x} \pm S$)

	HPRL Group(n=76)	Macroprolactinemia Group(n=57)	95% CI	t	P
C-P(ng/mL)	1.54±0.77	1.87±0.58	−0.33(−0.63–0.02)	−2.16	0.04
E2(pg/mL)	47.30±29.59	26.81±18.12	20.49(9.99–30.99)	3.89	<0.001
TC(mmol/L)	4.89±0.99	4.32±0.85	0.56(0.12–1.00)	2.54	0.01
LDL(mmol/L)	3.30±4.11	2.68±0.90	062(−0.98–2.21)	0.77	0.44
Insulin(μIU/mL)	7.52±3.00	10.98±4.07	−3.46(−5.24–1.68)	−3.93	<0.001
Cortisol(nmol/L)	350.59±117.35	337.33±106.89	13.26(−76.68–103.19)	0.30	0.77
T3(ng/mL)	0.95±0.13	0.88±0.13	0.07(0.01–0.13)	2.31	0.024
T4(μg/dL)	6.60±1.65	6.56±1.95	0.37(−0.78–0.85)	0.09	0.93
FT3(pg/mL)	2.52±0.34	2.36±0.34	0.16(0.00–0.32)	2.05	0.04
FT4(ng/dL)	1.05±0.22	1.02±0.24	0.03(−0.08–0.13)	0.51	0.62

Discussion

The phenomenon of elevated prolactin levels during the treatment of schizophrenia patients is very common, and there are various methods to reduce prolactin, including drug intervention and certain physical therapy methods. Studies have shown that when the total amount of prolactin exceeds 1000mIU/L, the incidence of MPRL is 5.4%,[12] and recent studies also have shown that MPRL induced by risperidone may not cause menstrual delay in patients.[20] This indicates that the correct identification of MPRL in clinical practice is beneficial for guiding the treatment of HPRL. Recent attention has been given to the difference between serum prolactin levels and clinical symptoms due to the presence of macroprolactin.[9,10] Previous studies have identified three forms of prolactin in the blood, small molecule prolactin (SPRL), with a relative molecular weight of about 23; large molecule prolactin (bPRL), with a relative molecular weight of 40~60; and macroprolactin molecules with a relative molecular weight of more than 150.[9] Further research findings have revealed that both SPRL and bPRL exhibit biological activity. However, macroprolactin, a self-polymerizing macromolecule that binds with immunoglobulins, lacks biological activity due to its inability to traverse the capillary endothelium, hence not inducing clinical symptoms. Nonetheless, it possesses an extended half-life and a propensity for accumulation within the bloodstream.[15] The current clinical prolactin detection methods can not effectively exclude this macromolecule, which is also one of the main reasons for the misdiagnosis of HPRL.[21]

Prolactin levels vary significantly from individual to individual. The study of gene polymorphism is used to identify the factors leading to this individualized difference at the molecular level. At present, DRD2 Taq1A is the most studied polymorphic locus, including two alleles: A1 and A2. Many studies have shown that there is a correlation between the A1 allele and the increased prolactin level caused by anti-dopamine drugs.[14] The existence of the A1 allele can reduce the biological effect of Da by reducing the density of the D_2 receptor and receptor binding.[22] In a study of healthy volunteers taking atypical antipsychotics, the results showed that DRD2 Taq1A polymorphism could affect the prolactin

secretion caused by risperidone and olanzapine treatment. The increase in prolactin levels in patients with the $A1^+$ genotype was more obvious than in patients with the A2/A2 genotype.[23] A meta-analysis conducted in Japan suggested that the DRD2 Taq1A genotype may affect changes in prolactin levels in patients with schizophrenia when treated with antipsychotic drugs.[15] Meanwhile, COMT can regulate the steady-state balance of dopamine in synapses in the brain and plays an important role in the development and treatment of schizophrenia.[24] A study on polycystic ovary syndrome indicated an association between the polymorphic site rs4680 of the COMT gene and elevated prolactin levels.[25] A Taiwanese study suggested that the elevation in prolactin observed in schizophrenia patients after treatment with amisulpride is related to the polymorphism at the COMT rs4680 site. Patients carrying the mutant allele A showed a more pronounced increase in prolactin levels compared to carriers of the G/G genotype.[26] Although there were many significant positive findings in previous studies on DRD2 and COMT gene polymorphisms and prolactin secretion, this study did not find any significant difference in prolactin and macroprolactin secretion in the DRD2 Taq1A or COMT Val158Met polymorphisms, suggesting that more in-depth molecular level research required.

Nevertheless, according to neuroendocrine theory, the secretion of prolactin is regulated by the HPG and HPT axes. Thyroid dysfunction can affect the level of sex hormone secretion and gonadal function. Thyroid hormone (TH) is closely related to the female reproductive system and directly affects the ovaries, while also regulating the secretion of prolactin and hypothalamic gonadotropin releasing hormone (GnRH) by affecting the synthesis of sex hormone binding globulin (SHBG).[25,26] An excess of macroprolactin can weaken the effect of levothyroxine on HPT axis activity and thyroid autoimmunity.[27] This study conducted statistical analyses on additional biological markers among patients with true HPRL and MPRL.

After 4 weeks of treatment, there were statistically significant differences in estradiol (t=−3.89, $p < 0.001$), T3 (t=2.31, p=0.02) and FT3 (t=2.05, p=0.04) between the two groups. Previous studies have shown that macroprolactinemia increases the circulating level of cardiac metabolic risk factors and impairs the lipid-lowering and pleiotropic effects of statins and fibrates. This study found statistically significant differences in cholesterol (t=−2.54, p=0.01), C peptide (t=−2.16, p=0.04) and insulin (t=−3.93, $p < 0.001$) between the two groups, which indirectly suggests that blood glucose and lipid metabolic capacity may be helpful in distinguishing between true HPRL and MPRL.

In summary, the findings of this study suggest that while routine laboratory tests may not effectively differentiate between patients with true HPRL and MPRL, daily monitoring based on the aforementioned indicators may offer valuable hints for distinguishing between these two conditions. This points towards a prospective research direction aimed at establishing models for the effective identification and potentially early prediction of true HPRL through routine monitoring indicators and personalized demographic data. Achieving this could bear significant guiding implications for the accurate identification and management of drug-induced HPRL in psychiatry, significantly impacting clinical guidance.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the Third People's Hospital of Huzhou City. Written informed consent was obtained from all participants. Our study adheres to the principles of the Declaration of Helsinki. The registration number of China Clinical Trial Registration Center is MR-33-22-009955.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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