Original Article

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Evaluation of ABO/Rh Blood Group Distributions and Clinical Characteristics in Patients with Adrenal Incidentaloma: A Case-Control Study

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Abstract

Aim: Studies examining the relationship between endocrine organ diseases and ABO and Rh blood groups have been conducted, and some studies have shown that endocrine organ diseases may be associated with ABO/Rh blood groups. The aim of this study was to evaluate the ABO/Rh blood group distribution in patients with adrenal incidentaloma (AI) and its relationship with the clinical features of the patients.

Methods: The study was conducted as a retrospective case-control study. Patients with AI who were followed up in the outpatient clinic of a single tertiary center between 2019 and 2023 were included in the study. The clinical (age, gender), radiological (diagnostic method, radiological features, adenoma size, localization), and biochemical (catecholamines, cortisol, aldosterone, and plasma-renin activity) characteristics of the patients were determined. The ABO and Rh blood group distributions of the patients were compared with those of the healthy control group.

Results: The number of patients included in the study was 356 and the number of people in the healthy control group was 2,809,237. Adrenal incidentaloma was detected by computed tomography in 237 (67.1%) patients and was more often detected in the left adrenal gland (51.1%). The median size of the adrenal mass was 20 mm. Because of the hormonal evaluation, functional hormone production was detected in 16 (4.5%) patients. After further investigations, it was found that three (0.8%) patients had adrenal carcinoma and three (0.8%) patients had cancer metastases. ABO blood group distributions in the patients (42.7% A, 13.5% B, 9.6% AB, 34.3% O) and control groups (42% A, 16% B, 8% AB, 34% O) were found to be similar (p=0.9). Similar results were found in terms of the Rh factor (p=0.9). There was no statistically significant relationship between the distribution of ABO and Rh blood groups and clinical features such as age, gender, functional hormone release, mass size, and accompanying endocrine diseases.

Conclusion: The ABO/Rh blood group was not found to be a risk factor in patients with AI. In addition, no relationship was found between clinical features and the ABO/Rh blood group in patients with AI.

Keywords: Adrenal incidentaloma, ABO blood groups, Rh factors

Introduction

Adrenal incidentaloma (AI) is the detection of a mass in the adrenal gland because of radiological imaging performed for any reason. Today, with the development of imaging techniques, the incidence of AI in the adrenal glands is approximately 4-7% in patients undergoing computed tomography (1,2). This rate may increase even more in elderly individuals (3). Approximately 8-30% of patients with AI have a mass in the bilateral adrenal glands (4). The differential diagnosis of adrenal gland masses includes many diseases, such as adrenal carcinoma, metastasis, congenital adrenal hyperplasia, lymphoma, hemorrhage, and infection. All patients with AI should be carefully evaluated for malignancy and functional hormone secretion. There is a risk of malignancy in patients with an adrenal mass greater than 4 cm and a radiological Hounsfield unit greater than 10 units (5,6). Approximately 10% of patients with AI have hormone secretion, and all patients should be evaluated in this regard (7). Unilaretel adrenalectomy is the primary treatment method for unilateral malignant or hormone-secreting tumors;

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however, in patients with bilateral masses, the decision should be made according to the type of tumor and the type of hormone secreted.

Because of further investigations in patients with a diagnosis of AI, non-functional adenomas were detected in the majority of patients, but the underlying pathophysiological mechanism is not fully known. Although the frequency of AI detection increases with age, the risk factors have not been fully defined. Chromosome 9q34 contains the gene for the ABO blood group, which encodes glycosyltransferases (8). Glycosyltransferases produce ABO blood-type antigens by catalyzing However, blood group antigens were detected on the cell surfaces of bronchopulmonary, genital tract, epidermis, and gastrointestinal cells (9). Previous studies have demonstrated a connection between certain cancers, metabolic and autoimmune diseases, and ABO/Rh blood groups (10). In various investigations, the associations between ABO and Rh blood types and endocrine disorders were investigated. It is unknown whether the ABO and Rh blood groups are risk factors in patients with AI.

In this study, we aimed to compare the ABO/Rh blood group distribution in patients with AI with that in the healthy population. In addition, the relationship between clinical features and the ABO/Rh blood group in patients with AI was examined.

Methods

Compliance with Ethical Standards

Ethics committee approval (approval no: 60-2023, date: 29.03.2023) was obtained from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee before the study, and the study was conducted according to Turkish Medicines and Medical Devices Agency Good Clinical Practice Guidelines (revision no: 08).

Patients and Data Collection

This study was designed as a retrospective case-control study. Patients with AI who were followed up in the outpatient clinic of a single tertiary center between 2019 and 2023 were included in the study. The patients included in the study were identified using the hospital's data processing system. Inclusion criteria was determined as 1-being over the age of 18, 2-having a diagnosis of AI, and 3-knowing the ABO/Rh blood group (Figure 1). Patients with incomplete data and congenital adrenal hyperplasia were excluded from the study. The clinical, biochemical, and radiological data of the patients (mass characteristics, location, and size) were noted in the patients follow-up files and the Ministry of Health Patient Information System. The histories of other accompanying endocrine diseases of the patients, such as hypertension, diabetes mellitus, hyperparathyroidism, pituitary adenoma, and benign thyroid diseases (hypothyroidism, hyperthyroidism, and goiter), were recorded. The ABO and Rh blood groups of the patients were measured using the gel centrifugation test method.

All biochemical tests were performed in a standardized biochemistry laboratory. If the 1 mg dexamethasone suppression test is >1.8 mcg/dL, other screening tests (bedtime cortisol level, bedtime salivary cortisol level, 24-hour urine free cortisol level) and the 2 mg dexamethasone suppression test are performed, and if the results in these tests are above the normal limit, Cushing's syndrome

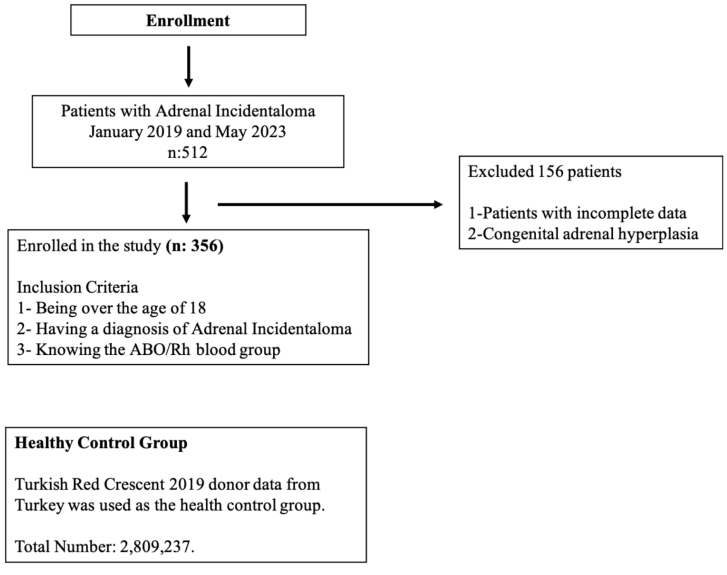

Figure 1. Flow chart of patient enrollment

is accepted. The levels of fractionated catecholamines (metanephrine and normetanephrine) in 24-hour urine were checked for the diagnosis of pheocromacytoma, and plasma and urinary catecholamines were re-evaluated in cases of abnormal values. If catecholamine levels were found to be three times higher than the normal value, a diagnosis of pheochromocytoma was made. Plasma renin activity (PRA) and plasma aldosterone levels were measured for hyperaldosteronism in patients with hypertension and/or hypokalemia. If the aldosterone/PRA ratio is >20, the diagnosis is confirmed by confirmatory tests (saline infusion test, oral salt loading test, and captopril test).

The ABO and Rh blood group distributions of the patients were compared as general or blood group-specific (such as A vs. non-A) with the blood group distribution of the healthy control group. Turkish Red Crescent 2019 donor data from Turkey was used as the health control group. The number of healthy individuals who were blood donors in 2019 was 2,809,237 (11). In addition, the relationship between ABO/Rh blood group distributions and patients' age, gender, functional hormone release, adrenal mass localization, and size was evaluated.

Statistical Analysis

The statistical analyses were performed using SPSS 29 (IBM, Armonk, NY, USA). Continuous variables in the study were represented by median (as well as minimum and maximum values) values, numbers, and percentages, while categorical variables were described by numbers and percentages. ABO/Rh blood group distributions in the patient group and healthy control group were compared using Fisher's exact test and the chi-square test. When the p-value was 0.05, the results were deemed statistically significant, and the probability ratio was calculated.

Results

Patient Characteristic

Study statistics were made by including data from 356 patients with AI. The patients were followed up for a median of 31.8 months. The median age at diagnosis was 59 (range, 19-85), and most patients were female (68.3%). The most common accompanying endocrine diseases were hypertension (53.1%), diabetes mellitus (26.4%), and benign thyroid diseases (24.4%). Thirty-seven (10.4%) patients had a history of cured cancer. None of the patients had a family history of AI. Most of the patients underwent radiological imaging because of a symptom (such as pain, swelling in the abdomen, or cough). The most common imaging method was computed tomography (67.1%). The median size of the adrenal mass was 20 mm, and the most common location was the left adrenal gland (51.1%). Functional hormone secretion was detected in 16 (4.5%) patients. After the radiological examinations, it was determined that most patients had an adrenal adenoma (91.6%). Table 1 shows the clinical, radiological, and biochemical characteristics of the patients.

Table 1. Clinical, pathological, and radiological features of patients with AI

	The number of patients (n=356)
Age at diagnosis	
60<	194 (54.5%)
60≥	162 (45.5%)
Gender	
Female	243 (68.3%)
Male	113 (31.7%)
The medical history of endocrine disease	
Hypertension	189 (53.1%)
Diabetes mellitus	94 (26.4%)
Benign thyroid disease	87 (24.4%)
Hyperparathyroidism	9 (2.5%)
Pituitary adenoma	7 (2%)
The history of cancer	
Yes	37 (10.4%)
No	319 (89.6%)
Insidentaloma localization	
Left sight	182 (51.1%)
Right sight	118 (33.1%)
Bilateral	56 (15.8%)
Radiological imaging causes	
Check-up examination for any symptoms	231 (92%)
Cancer screening	25 (8%)
Imaging method at diagnosis	
Computed tomography	239 (67.1%)
Magnetic resonance imaging	115 (32.2%)
PET Scan	2 (0.6%)
Adenoma size at diagnosis	
<2 cm	165 (46.3%)
2-4 cm	167 (46.9%)
>4 cm	21 (6%)
Missing	3 (0.8)
Hormone secretion status	
Non-functional	340 (95.5%)
Cushing's disease	9 (2.5%)
Primary aldosteronism	4 (1.1%)
Pheochromocytoma	3 (0.9%)
A definitive diagnosis of the adrenal mass	
Adenoma	326 (91.7%)
Myelolipoma	10 (2.9%)
Cyst	8 (2.2%)
Cancer metastasis	3 (0.8%)
Adrenal carcinoma	3 (0.8%)
Feocromasitoma	3 (0.8%)
Undefined	3 (0.8%)
Surgery for AI	
Yes	36 (10.1%)
No	320 (89.9%)

AI: Adrenal incidentaloma

ABO/Rh Blood Group Distribution

ABO and Rh blood groups were evaluated in general, and no statistical difference was found between the patient and healthy control groups (Table 2). In terms of ABO blood group distribution, patients (42.7% A, 13.5% B, 9.6% AB, 34.3% O) and the control group (42% A, 16% B, 8% AB, 34% O) were found to be similar (p=0.6). The Rh factor distribution was equal in both groups (p = 0.9) (Table 3). Although the frequency of the AB blood group was found to be increased compared with the nonAB blood group in patients with AI, it did not reach statistical significance [p=0.6, confidence interval (CI) 95%, odds ratio (OR): 1.25]. Although the frequency of the B blood group was found to be decreased compared with the NonB group, it was not statistically significant (p=0.6, CI 95%, OR: 0.86). In addition, no correlation was found between the distribution of ABO and Rh groups and features such as age, gender, functional hormone release, adrenal mass size, and localization in patients with AI.

Table 2. Distribution of ABO/Rh blood groups in patients with AI and control group

Blood antigens	Patients group (n=356) %	The control group (n=2,809,237) %	p-value
ARh+	38.6%	37%	0.6
ARh-	4.2%	5%	
BRh+	13.2%	14%	
BRh-	0.3%	2%	
ABRh+	8.4%	7%	
ABRh-	1.1%	1%	
ORh+	27.5%	30	
ORh-	6.7%	4%	
Total (%)	100	100	

Chi-square and Fisher's exact tests were used
AI: Adrenal incidentaloma

Discussion

In this study, we show the clinical, biochemical, and radiological features at the time of diagnosis in patients with AI. Thanks to advances in radiological imaging methods and high resolution, the frequency of AI detection is increasing daily. While the incidence of AI was 0.4% in patients who underwent computed tomography in the 1980s, this rate has increased to 7% today (12,13). It is necessary to evaluate these patients in terms of malignancy and functional hormone secretion and follow up in this regard (14). The pathophysiology of AI development has not been fully elucidated. Obesity is thought to be one of the possible pathophysiological mechanisms that may increase the frequency of AI due to insulin resistance and the effect of insulin on the adrenal glands (15,16). In a comparative study in which 601 patients were evaluated, the frequency of type 2 diabetes was found to be 31.8% in patients with AI, and the frequency of obesity increased in these patients. The multivariate analysis of this study showed that type 2 diabetes mellitus could be a statistically significant risk factor for the development of AI (13). In the TURDEP-II study, the prevalence of diabetes mellitus was found to be 16.5% in the Turkish population (17). In our study, the frequency of diabetes mellitus was found to be 26.4% in people with AI, which is quite high compared with the normal population.

Today, the number of studies examining the relationship between blood groups and various diseases is increasing. In a retrospective study of 41 years of data, including nearly 500,000 patients, a relationship was found between the ABO and RhD systems and tongue cancer, cervical cancer, osteoarthritis, asthma, HIV, and hepatitis B infections (18). In various investigations, the associations between ABO and Rh blood types and endocrine gland disorders were investigated. In the study examining the clinical manifestations of patients with multiple

Table 3. Odds ratios according to ABO/RH blood group distribution in patients with AI and controls group

	Patients group Total number: 356 (%)	The control group Total number: 2,809,237 (%)	p-value	Odds ratio 95% CI
A Non-A	42.7% 57.3%	42% 58%	P=0.8	1.02 (0.74-1.41)
B Non-B	13.5% 86.5%	16% 84%	P=0.6	0.86 (0.44-1.67)
AB Non-AB	9.6% 90.4%	8% 92%	P=0.6	1.25 (0.51-3.03)
O Non-O	34.3% 65.7%	34% 66%	P= 0.9	1.00 (0.74-1.37)
Rh- Rh+	12.4% 87.6%	12% 88%	P=0.9	1.03 (0.56-1.87)
Total (%)	100	100		

Chi-square and Fisher's exact tests were used
CI: Confidence interval, AI: Adrenal incidentaloma

endocrine neoplasia type 1, it was shown that 94% of the metastatic patients had O blood group, and O blood group was shown to be a risk factor for metastasis (19). In a different investigation, it was observed that patients with Hashimoto's hypothyroidism had an O blood group that was statistically considerably higher than that of other hypothyroid patients (20). In addition, in a recently published study on thyroid gland cancer, no relationship was found between thyroid gland papillary cancer and the ABO/Rh blood group (21). In a meta-analysis examining the ABO/Rh blood group relationship in patients with type 2 diabetes mellitus, it was determined that individuals in the AB blood group had the highest risk and those in the B blood group had the lowest risk of developing type 2 diabetes (22). The relationship between ovarian gland disorders and ABO blood groups has been the subject of several studies. In a study examining the connection between ovarian hyperstimulation syndrome and blood type, it was found that blood type A may be a risk factor for the disease (23). Another study that looked at 35,479 infertile women indicated that women with blood group B had a greater diminished ovarian reserve than women with blood group O (24). The relationship between ABO and Rh blood types and the development of cancer, endocrine disorders, and other illnesses is not entirely understood. According to some research, these diseases may develop because of inflammation caused by abnormalities in the enzyme system that creates the blood group antigens expressed in tissues (25-27). A study examining the relationship between adrenal gland tumors and ABO/Rh blood groups has not yet been conducted. In this study, it has been shown that ABO and Rh blood groups are not a risk factor in patients with AI. No correlation was found between the distribution of ABO and Rh blood groups and clinical, radiological, and biochemical features in patients with AI.

Study Limitations

This study had some limitations due to its retrospective nature. The patient group included in the study was heterogeneous, and some patient data was missing. The number of patients was relatively limited. Despite these limitations, to the best of our knowledge, this is the first study in the literature to show that ABO and Rh blood groups are not a risk factor for the development of AI. This study is important in this respect and contributes to the literature.

Conclusion

In this study, the general characteristics of patients with AI and the distribution of ABO and Rh blood groups in these patients were shown. The ABO/Rh/Rhood group distribution in patients with AI was found to be similar to that in the healthy population. In addition, according to the ABO/Rh blood group distribution, the radiological features and functional hormone status of patients with AI were found to be similar at the time of diagnosis. With future clinical and molecular studies, the development mechanisms of AI will be better understood.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval no: 60-2023, date: 29.03.2023).

Informed Consent: The study was conducted as a retrospective case-control study.

Peer-review: Externally peer-reviewed.

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References

1. Jing Y, Hu J, Luo R, et al. Prevalence and Characteristics of Adrenal Tumors in an Unselected Screening Population : A Cross-Sectional Study. Ann Intern Med 2022;175:1383-91.
2. Okroj D, Rzepecka A, Kłosowski P, Babi ska A, Sworczak K. Review of Diagnostic Modalities for Adrenal Incidentaloma. J Clin Med 2023;12:3739.
3. Li X, Xiao S, Zhan X, et al. For small (1-3cm) nonfunctional adrenal incidentaloma (NFAI), which option is more appropriate for conservative treatment or surgery? Front Endocrinol (Lausanne) 2023;14:1119251.
4. Remde H, Kranz S, Morell SM, et al. Clinical course of patients with adrenal incidentalomas and cortisol autonomy: a German retrospective single center cohort study. Front Endocrinol (Lausanne) 2023;14:1123132.
5. Mínguez Ojeda C, Gómez Dos Santos V, Álvaro Lorca J, et al. Tumour size in adrenal tumours: its importance in the indication of adrenalectomy and in surgical outcomes-a single-centre experience. J Endocrinol Invest 2022;45:1999-2006.
6. Yalon T, Yalon M, Assaf D, et al. Differentiating between adrenocortical carcinoma and lipid-poor cortical adenoma: A novel cross-sectional imaging-based score. Surgery 2023;173:35-42.
7. Muangnoo N, Manosroi W, Leelathanapipat N, Meejun T, Chowchaiyaporn P, Teetipsatit P. Predictive Factors of Functioning Adrenal Incidentaloma: A 15-Year Retrospective Study. Medicina (Kaunas) 2022;58:597.
8. Lei H, Zhang H, Guo L, et al. Identification of a novel variant c.761C>T on ABO*B.01 gene in ABO glycosyltransferases associated with B(weak) phenotype. Vox Sang 2023.
9. Le Pendu J, Marionneau S, Cailleau-Thomas A, Rocher J, Le Moullac-Vaidye B, Clément M. ABH and Lewis histo-blood group antigens in cancer. APMIS 2001;109:9-31.

10. Abegaz SB. Human ABO Blood Groups and Their Associations with Different Diseases. Biomed Res Int 2021;2021:6629060.
11. Turkish Red Crescent, General Directorate of Blood Services, 2019. https://wwwkanverorg/Upload/Dokuman/Dosya/2019-khgm-22-10-2020-76498015pdf.
12. Herrera MF, Grant CS, van Heerden JA, Sheedy PF, Ilstrup DM. Incidentally discovered adrenal tumors: an institutional perspective. Surgery 1991;110:1014-21.
13. Reimondo G, Castellano E, Grosso M, et al. Adrenal Incidentalomas are Tied to Increased Risk of Diabetes: Findings from a Prospective Study. J Clin Endocrinol Metab 2020;105:dgz284.
14. Cambos S, Tabarin A. Management of adrenal incidentalomas: Working through uncertainty. Best Pract Res Clin Endocrinol Metab 2020;34:101427.
15. Sydney GI, Ioakim KJ, Paschou SA. Insulin resistance and adrenal incidentalomas: A bidirectional relationship. Maturitas 2019;121:1-6.
16. Higgs JA, Quinn AP, Seely KD, et al. Pathophysiological Link between Insulin Resistance and Adrenal Incidentalomas. Int J Mol Sci 2022;23:4340.
17. Satman I, Omer B, Tutuncu Y, et al. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol 2013;28:169-80.
18. Bruun-Rasmussen P, Hanefeld Dziegiel M, Banasik K, Johansson PI, Brunak S. Associations of ABO and Rhesus D blood groups with phenome-wide disease incidence: A 41-year retrospective cohort study of 482,914 patients. Elife 2023;12:e83116.
19. Weisbrod AB, Nilubol N, Weinstein LS, et al. Association of type-O blood with neuroendocrine tumors in multiple endocrine neoplasia type 1. J Clin Endocrinol Metab 2013;98:109-14.
20. D Dağdeviren M, Ateş İ, Demir BF, Ergün E, Yıldız C, Altay M. Investigation of blood groups in benign thyroid diseases in Turkey. Endocr J 2019;66:1001-9.
21. Dogan O. Evaluation of ABO/Rh blood group distributions in papillary thyroid cancer patients. Medicine (Baltimore) 2023;102:e34564.
22. Cano EA, Esguerra MA, Batausa AM, et al. Association between ABO Blood Groups and Type 2 Diabetes Mellitus: A Meta-Analysis. Curr Diabetes Rev 2023;19:e270422204139.
23. Bellver J, Ferrando M, Garrido N, Pellicer A. Blood group and ovarian hyperstimulation syndrome. Fertil Steril 2010;93:270-1.
24. Lin S, Li R, Chi H, et al. Effect of ABO blood type on ovarian reserve in Chinese women. Fertil Steril 2014;102:1729-32.
25. Hakomori S. Antigen structure and genetic basis of histo-blood groups A, B and O: their changes associated with human cancer. Biochim Biophys Acta 1999;1473:247-66.
26. Hakomori S. Tumor-associated carbohydrate antigens defining tumor malignancy: basis for development of anti-cancer vaccines. Adv Exp Med Biol 2001;491:369-402.
27. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883-99.