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Research Article

The autoantibody frequency in patients with drug allergy

İlaç alerjisi olan hastalarda otoantikor sıklığı

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Abstract

Introduction: This study is aimed to analyze the autoantibody frequency in patients with drug allergy. Descriptive, observational research on drug allergy will contribute to the creation of new hypotheses about the pathophysiology of autoimmunity.

Methods: The data of patients who were registered in the Training and Research Hospital database until the end of December 31, 2018 and diagnosed with drug allergy were retrospectively evaluated. Overall, 617 adult patients who had been diagnosed as "allergy status to drugs," according to ICD 10, and had had at least one autoantibody result were included in the study.

Results: The frequency of having at least one autoantibody varied between 0% and 92.1%. The most commonly detected autoantibody was rheumatoid factor (RF) (n = 241; 92.1%). The second most common one was anti-tissue transglutaminase IgA antibody (Anti-tTG-IgA) (n=22; 68.2%). The frequencies of anti-thyroglobulin (Anti-TG), anti-thyroid peroxidase (anti-TPO), and anti-double stranded DNA (Anti-dsDNA) were 65.2% (n = 155), 59.7% (n = 159), and 43.6% (n= 55), respectively.

Conclusions: Many drugs can trigger the development of autoantibodies with no progression to autoimmune disease. Autoantibodies should be suspected in patients with allergies to medications. Observational research on drug allergy will contribute to the creation of new hypotheses about the pathophysiology of autoimmunity. Numerous studies in this area can enable us to discuss the widespread use of risky drugs in a more objective way. We think that our study will shed light on the relationship between drug reaction and autoimmune diseases.

Keywords: Autoantibodies, autoimmunity, drug allergy, drug hypersensitivity

Öz

Giriş: Bu çalışma, ilaç alerjisi olan hastalarda otoantikor sıklığını incelemeyi amaçlamaktadır. İlaç alerjisi üzerine gözlemsel araştırmalar, otoimmünite patofizyolojisi hakkında yeni hipotezlerin oluşturulmasına katkıda bulunabilir.

Yöntem: Eğitim ve Araştırma Hastanesi veri tabanına 31 Aralık 2018 sonuna kadar kayıt olan ve ilaç alerjisi tanısı konan hastaların verileri geriye dönük olarak değerlendirildi. Genel olarak, ICD 10'a göre "ilaçlara alerji durumu" tanısı konan ve en az bir otoantikor sonucu olan 617 adet yetişkin hasta çalışmaya dahil edildi.

Bulgular: Araştırmada en az bir otoantikora sahip olma sıklığı % 0 ile % 92,1 arasında değişti. En sık saptanan otoantikor romatoid faktör (RF) idi (n = 241; % 92,1). İkinci en sık rastlanan oto antikorun anti-doku transglütaminaz IgA (Anti-tTG-IgA) (n = 22; % 68,2) olduğu görüldü. Anti-tiroglobulin (Anti-TG), anti-tiroid peroksidaz (anti-TPO) ve anti-çift sarmallı DNA (Anti-dsDNA) sıklıkları sırasıyla % 65,2 (n = 155), % 59,7 (n = 159) ve % 43,6 (n = 55) olarak saptandı.

Sonuç: Birçok ilaç, otoimmün hastalıkları için ilerleme olmaksızın otoantikor gelişimini tetikleyebilir. İlaçlara alerjisi olan hastalarda otoantikorlardan şüphelenilmesi gereklidir. İlaç alerjisi üzerine yapılan gözlemsel araştırmalar, otoimmünitenin patofizyolojisi hakkında yeni hipotezlerin oluşturulmasına katkı sağlayacaktır. Bu alanda yapılacak çok sayıda çalışma, riskli ilaçların yaygın kullanımını daha objektif bir şekilde tartışmamızı sağlayabilir. Çalışmamızın ilaç reaksiyonu ile otoimmün hastalıklar arasındaki ilişkiye ışık tutacağını düşünüyoruz.

Anahtar kelimeler: Otoantikorlar, otoimmünite, ilaç alerjisi, ilaç aşırı duyarlılığı

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Key Points

1. Many new drug reactions are emerging with the use of new biological treatments, epidemics and vaccines.
2. We reported the type and frequency of various autoantibodies that develop in association with drug reactions in a Turkish population.
3. Our study will shed light on the relationship between drug reaction and autoimmune diseases.

Introduction

Autoimmunity is defined as the loss of self-tolerance of the immune system against their own cells and tissues. A drug allergy is an adverse drug reaction that results from stimulation of the immune system by a medication [1]. An aspect of drug allergy is the adaptive immune response that targets self-proteins and cells of the body. Moreover, some drugs can trigger autoimmunity, which is called drug-induced autoimmunity (DIA) [2]. DIA can occur with different medications and various mechanisms. Since there is no exact diagnostic test or criteria for detecting DIA, it might be challenging to diagnose DIA in many instances [3-5]. In a study examining the association between multiple drug hypersensitivity (MDH) and autoimmunity, the authors have reported that patients with MDH had increased the prevalence of autoimmune diseases, mainly autoimmune thyroiditis, and chronic idiopathic urticaria. Additionally, these patients showed increased rates of autologous serum skin test and autologous plasma skin test positivity [6].

Allergic reactions and autoimmune conditions may coexist. On the other hand, they are distinct entities with some apparent differences. Several abnormalities taken place during the regulation of the immune system may lead to the development of both conditions. Clinical manifestations of drug allergy and autoimmune diseases might also be similar, which causes diagnostic challenges. DIA is a rapidly changing area of clinical medicine. This change in clinical profile reflects, in part, the introduction of many new biological drugs into routine practice. Therefore, there is an urgent need for new diagnostic strategies in drug selection.

There is a paucity of data in the literature regarding the association of drug allergy and autoimmune diseases. We reported the type and frequency of several autoantibodies that had developed in association with drug reactions in a Turkish population. Our aim is to examine the literature on patients with drug allergies and to draw attention to the increased drug reactions with the use of new treatment methods by giving our own data.

Methods

This research is a descriptive, retrospective study. 1415 patients who applied to the Training and Research Hospital Immunology outpatient clinic between January 01, 2015 and December 31, 2018 were evaluated retrospectively for eligibility and inclusion in the study. The inclusion criteria are as follows: Patients with a diagnosis of Z88 "Drug allergy status" according to the ICD 10 coding system, and patients over 18 years with at least one autoantibody analysis, without any disease with known autoantibody positivity. Patients with known autoimmune disease were excluded from the study. Overall, 617 patients diagnosed with drug allergy were included in the study.

Data, age of patients, serum fasting glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), thyroid stimulating hormone (TSH), vitamin B12, 25(OH)vitamin D, white blood cell (WBC), lymphocytes (LYM), platelet (PLT), eosinophil (EOS) count, hemoglobin (HGB), erythrocyte sedimentation rate (ESR), mean platelet volume (MPV), albumin, globulin, immunoglobulin A (IgA), immunoglobulin M (IgM), immunoglobulin G (IgG), total immunoglobulin E (total IgE), c-reactive protein (CRP), complement component 1q (C1q), complement 3 (C3), complement 4 (C4), anti-thyroid peroxidase (anti-TPO) antibodies, anti-thyroglobulin (Anti-TG), anti-tartrate resistant acid phosphatase (Anti-TRAP), anti-gliadin antibody IgA (Anti-GA-IgA), anti-gliadin antibody IgG(Anti-GA-IgG), anti-endomysium IgA(EmA-IgA), anti-endomysium IgG (EmA-IgG), anti-tissue transglutaminase IgA (Anti-tTG-IgA), rheumatoid factor (RF), anti-double stranded DNA (anti-dsDNA), and antinuclear antibody (ANA) were recorded for each study participant. Laboratory results are the values obtained after 12 hours of fasting and examined during the administration period.

Complete blood count analysis was performed using UniCel DxH 800 hematology analyzer (Beckman Coulter, Miami, FL, USA). Glucose, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), albumin, globulin measured by enzymatic methods using an AU5800 autoanalyzer (Beckman Coulter, High Wycombe, UK). Centaur XP immunoassay analyzer (Siemens Healthineers, Erlangen, Germany) was used for vitamin D. TSH, Vit B12, Anti TG, Anti TPO, Immunochemical analytes were measured using a DxI 800 immunoanalyzer (Beckman Coulter Inc., CA, USA), IgA, IgM, IgG, total IGE, C1, C3, C4, RF analyses were measured using a BN II nephelometer (Behringwerke AG Diagnostica, Marburg, Germany). One hour erythrocyte sedimentation rate (ESR) was studied by the Westergren method.

Ethical approval

Local ethics committee approved the study protocol (IRB number: 2019 / 14-27 Date: 10-9-2019).

Statistical analysis

Post-hoc sample size calculation was performed based on the presence of rheumatoid factor. A sample size of 194 people was required to estimate the proportion of an entity with an expected frequency of 92.1% in an infinite population using a margin of error of 0.025 and a confidence interval of 99% [7]. 617 patients were included in the study.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 software (SPSS Inc., Chicago, IL, USA). The results were presented as frequencies, percentages, means, and standard deviations (SD). The Shapiro-Wilk test was performed to confirm the normally distribution of numerical variables. Age, IgG, C3, C4, vitamin B12, and 25(OH) vitamin D levels were normally distributed (p= 0.720, 0.264, 0.836, 0.170, 0.472, 0.122, respectively). Eosinophil count, IgA, IgM, IgE, TSH, Anti-TPO, Anti-TG, CRP, C1q were skewed (p=<0.001, <0.001, <0.001, <0.001, 0.022, <0.001, <0.001, <0.001, and <0.001, respectively).The independent samples t-test was used to compare data meeting parametric assumptions. The Chi-Square test and Fisher's exact tests were used for categorical variables.

Results

Overall, 617 patients were available for analysis. Patients' age was between 18 and 90 years. There were 500 (81.00%) females and 117 (19.00%) males. The age and laboratory results of the patients are summarized in Table 1.

Table 1. Summary of laboratory findings of inpatients with drug allergy

	Number of patients studied (n)	Mean (min-max)	Standard deviation
Age (years)	616	46.92 (19.00-90.00)	14.60
Serum fasting glucose (mg/dL)	353	107.31 (47.00-459.00)	41.34
Urea (mg/dL)	311	30.90 (1.00-246.00)	20.81
Creatinine (mg/dL)	396	1.045 (0.30-24.00)	1.69
Aspartate aminotransferase (IU/L)	472	22.04 (3.00-292.00)	15.82
Alanine aminotransferase (IU/L)	498	21.93 (5.00-217.00)	19.27
White blood cell count (/mm^3)	543	8.637 (1.80-30.00)	3.23
Lymphocyte count (/mm^3)	543	2.474 (0.10-35.00)	2.03
Hemoglobin (g/dL)	540	13.00 (6.50-17.60)	1.57
Platelet count (/mm^3)	540	277.39 (31.00-1266.00)	87.11
MPV(fL)	541	8.79 (0.00-14.00)	1.48
Eosinophil count (/mm^3)	500	0.24 (0.00-7.70)	0.49
Albumin(g/dL)	83	4.03 (0.20-5.00)	0.75
Globulin(g/dL)	62	3.10 (1.80-5.30)	0.51
ESR (mm/h)	487	19.78 (1.00-131.00)	16.87
IgA(mg/dL)	101	186.29 (5.00-1110.00)	129.36
IgM(mg/dL)	89	144.89 (21.00-796.00)	115.06
Total IgE(U/mL)	283	221.15 (4.88-2580.00)	320.99
IgG(mg/dL)	104	1293.22 (37.00-10500.00)	1014.30
TSH(mIU/L)	468	2.59 (0.00-72.50)	5.51
Anti-TPO(IU/mL)	159	82.73 (0.03-1000.00)	209.82
Anti-TG(IU/mL)	155	116.92 (0.10-3000.00)	465.27
Anti-TRAP (IU/mL)	10	3.81 (0.30-21.80)	6.64
Complement 1q (mg/dL)	168	34.45 (3.00-417.00)	51.28
Complement 3 (mg/dL)	84	104.75 (15.50-203.00)	35.99
Complement 4 (mg/dL)	201	22.45 (8.40-49.50)	7.36
Vitamin B12(pg/mL)	252	287.85 (36.00-1492.00)	182.48
25(OH) vitamin D (ng/mL)	181	16.72 (4.00-114.00)	13.24

Descriptive data

Anti-TPO: Anti-thyroid peroxidase, Anti-TG: Anti-thyroglobulin, Anti-TRAP: Anti-tartrate resistant acid phosphatase, ESR: Erythrocyte sedimentation rate, IgA: Immunoglobulin A, IgG: Immunoglobulin G, IgM: Immunoglobulin M, MPV: Mean platelet volume, TSH: Thyroid-stimulating hormone, Total IgE: Total immunoglobulin E.

The frequency of anti-gliadin antibody IgA (Anti-GA-IgA), anti-gliadin antibody IgG (Anti-GA-IgG), anti-endomysium IgA (EmA-IgA), anti-endomysium IgG (EmA-IgG), anti-tissue transglutaminase IgA (Anti-tTG-IgA), RF, ANA, Anti-dsDNA and ANA profile are shown in Table 2.

Table 2. Autoantibody frequency of patients with drug allergy

Autoantibody	Number of patients studied(n)	Negative n (%)	Positive n (%)
Anti-gliadin antibody IgA	21	21 (100)	0
Anti-gliadin antibody IgG	21	19 (86.40)	3 (13.60)
Anti-endomysium IgA	21	20 (95.20)	1 (4.80)
Anti-endomysium IgG	20	20 (100.00)	0
Anti-tissue transglutaminase IgA	22	7 (31.80)	15 (68.20)
Rheumatoid factor	241	19 (7.90)	222 (92.10)
Antinuclear Antibody (ANA)	343	242 (70.60)	101 (29.50)
Anti-double stranded DNA	55	31 (56.40)	24 (43.60)
ANA profile	25	21 (84.00)	4 (16.00)

Outcome data

The frequency of having at least one autoantibody varied between 0% and 92.10%. The most commonly detected autoantibody was rheumatoid factor (RF) (n = 241; 92.10%). The second most common one was anti-tissue transglutaminase IgA antibody (Anti-tTG-IgA) (n = 22; 68.20%). The respective frequencies of anti-thyroglobulin (Anti-TG), anti-thyroid peroxidase (anti-TPO), and anti-double stranded DNA (Anti-dsDNA) were 65.20% (n = 155), 59.70% (n = 159), and 43.60% (n = 55), respectively.

Eosinophil count, quantitative immunoglobulins, serum complements, thyroid-stimulating hormone, thyroid antibodies, c-reactive protein, vitamin B12, and 25(OH) vitamin D levels of study participants are shown in Table 3. Serum total IgE levels were higher than normal in 48.1% of the patients (n = 283).The eosinophil count was lower than normal in 95.4% of the studied patients (n = 500). 25(OH) Vitamin D and Vitamin B12 were also below normal in 90.60% (n = 181), and 68.30% (n = 252) of the studied patients, respectively. Immunoglobulin A, immunoglobulin M, immunoglobulin G, serum complements 3 and 4 were higher than normal in all studied patients.

Table 3. Eosinophil count, quantitative immunoglobulins, serum complements, thyroid-stimulating hormone, thyroid antibodies, c-reactive protein, vitamin B12, and 25(OH) vitamin D levels of the patients

	Number of patients studied (n)	Lower than normal (%)	In normal range (%)	Higher than normal (%)
Eosinophil count	500	477 (95.40)	23 (4.60)	0
Immunoglobulin M	89	0	0	89 (100.00)
Total immunoglobulin E	283	0	147 (51.90)	136 (48.10)
Immunoglobulin A	98	0	0	98 (100.00)
Immunoglobulin G	101	0	0	101 (100.00)
Thyroid stimulating hormone	468	17 (3.60)	429 (91.70)	22 (4.70)
Anti-thyroid peroxidase	159	0	64 (40.30)	95 (59.70)
Anti-thyroglobulin	155	0	54 (34.80)	101 (65.20)
C-reactive protein	323	0	300 (92.90)	23 (7.10)
Complement 1q	168	1 (0.60)	154 (91.70)	13 (7.70)
Complement 3	84	0	0	84 (100.00)
Complement 4	201	0	0	201 (100.00)
Vitamin B12	252	172 (68.30)	80 (31.70)	0
25(OH) vitamin D	181	164 (90.60)	17 (9.40)	0

Comparison of some laboratory data by male and female gender is shown in Table 4.
When we compared male and female participants in terms of rheumatoid factor positivity, there was no significant difference between the sexes (p = 0.704, n = 196 (91.60%) in females, n = 26 (96.30%) in males). We categorized eosinophil count as low, normal, and high. Significantly more female patients were in the low eosinophil group than males (p = 0.049) (Table 4). When the absolute eosinophil count was taken into consideration, there was no significant difference between the genders (p = 0.843). Also, there was no difference in terms of age, IgG, C3, C4, vitamin B12, and 25(OH) vitamin D levels between males and females (p-values 0.591, 0.721, 0.722, 0.618, 0.069, 0.214, respectively). On the other hand, TSH levels were significantly higher in females compared to males (p = 0.001). IgA, IgM, IgE, Anti-TPO, Anti-TG, CRP, and C1 levels were not different between males and females (p-values 0.314, 0.827, 0.114, 0.381, 0.535, 0.828, and 0.712, respectively).

There were no significant correlations between total IgE levels and any of the following parameters:25(OH) Vitamin D, anti-TPO, anti-TG, CRP and rheumatoid factor (p-values 0.439, 0.763, 0.230, 0.191, and 0.257, respectively). We grouped 25(OH) Vitamin D levels as low and normal. There were no significant differences between 25(OH) Vitamin D level and ANA, anti-TPO, anti-TG, or Anti-TRAP, positivity (p-values 0.353, 0.691, 0.976, and 1.000, respectively). (Table 4)

Table 4. Comparison of some laboratory values between female and male participants

		Female	Male	Total	p value
Rheumatoid factor	Positive	196 (91.600%)	26 (96.30%)	222 (92.10%)	0.704*
	Negative	18 (8.40%)	1 (3.70%)	19 (7.90%)	
	Total	214 (100.00%)	27 (100.00%)	241 (100.00%)	
Eosinophil count	Low	394 (96.30%)	83 (91.20%)	477	0.049*
	Normal	15 (3.70%)	8 (8.80%)	23	
	High	0	0	0	
	Total	409 (100.00%)	91 (100.00%)	500	
25(OH) vitamin D	Low	145 (89.50%)	19 (100.00%)	164 (90.60%)	0.223*
	Normal	17 (10.50%)	0 (0%)	17 (9.40%)	
	Total	162 (100.00%)	19 (100.00%)	181 (100.00%)	
Anti-tissue transglutaminase IgA	Positive	13 (65.00%)	2 (100.00%)	15 (68.20%)	1.000*
	Negative	7 (35.00%)	0 (0%)	7 (31.80%)	
	Total	20 (100.00%)	2 (100.00%)	22 (100.00%)	
Anti-thyroglobulin	Normal	47 (35.10%)	7 (33.30%)	54 (34.80%)	0.876
	High	87 (64.90%)	14 (66.70%)	101 (65.20%)	
	Total	134 (100.00%)	21 (100.00%)	155 (100.00%)	
Anti-thyroid peroxidase	Normal	55 (40.10%)	9 (40.90%)	64 (40.30%)	0.946
	High	82 (59.90%)	13 (59.10%)	95 (59.70%)	
	Total	137 (100.00%)	22 (100.00%)	159 (100.00%)	

*Fisher's exact test

Discussion

Key Results: The frequency of having at least one autoantibody varied between 0% and 92.10%. The most commonly detected autoantibody was the rheumatoid factor (RF) (92.10%), followed by the anti-tissue transglutaminase IgA antibody (Anti-tTG-IgA) (68.20%). The frequencies of anti-thyroglobulin (Anti-TG), anti-thyroid peroxidase (anti-TPO), and anti-double-stranded DNA (Anti-dsDNA) were 65.20%, 59.70%, and 43.60%, respectively.

Immune system abnormalities can present as immune deficiency syndromes, allergies or autoimmune diseases [8]. The relationship between immune deficiency syndromes and autoimmune diseases has been recognized for a long time [9]. However, the link between allergic diseases, drug allergies, and autoimmune diseases has recently started to draw the scientific community's attention. Drug allergies are an important cause of iatrogenic morbidity and mortality [10].

It is well known that autoimmune diseases and atopic conditions are considerably more frequent in women than in men [11]. Similarly, in our data, there were 500 (81.00%) women and 117 (19.00%) men. Norton et al. reported that drug induced allergies are more common in women. And the authors attributed this difference to the presence of X chromosome and female reproductive hormones [12].

Drug allergies are frequently observed reactions and can occur with various mechanisms. Generally, drug reactions are divided into two main groups: Type A (dose depended) is predictable and depends on the pharmacokinetic properties of the drug, Type B; drug hypersensitivity reaction (DHR), on the other hand, is not foreseeable [13]. DHR may occur as immuno-allergic, autoimmune and nonimmunologic reactions [14]. Several risk factors have been defined for autoimmunity; such as gender, genetics, pregnancy, diet, hormones, low levels of 25(OH) vitamin D, infections, and drugs [3,15]. We found that 25(OH) vitamin D deficiency was present in about 90% of patients in the current study. It can be postulated that this deficiency might have contributed to the development of autoantibodies in at least some of our patients. There are many potential causes of vitamin B12 deficiency. The most common ones of these are pernicious anemia (PA), an autoimmune condition, and immune disorders that interfere with vitamin B12 absorption [16]. PA is an autoimmune condition that lowers vitamin B12 levels [16]. It is usually associated with additional autoimmune conditions and/or additional autoantibodies. The high rate of vitamin B12 deficiency in our study deserves further studies using homogeneous patient groups and control groups.

Autoimmunity may also be triggered by drugs. DHR is classified as a type B drug reaction [17]. In fact, autoimmune-like diseases can emerge only in a small proportion of these patients [17]. However, we do not know how "biological" treatment applications, Covid 19 outbreak and widespread vaccination will affect this situation in increasing numbers and expanding indications. Because some drug hypersensitivity reactions and HLA allele relationships may occur in patients with viral infections [18].

The most common drug-induced autoimmune disease is iatrogenic drug-induced lupus [19,20]. Drugs can also cause rheumatoid arthritis, polymyositis, dermatomyositis, myasthenia gravis, pemphigus, pemphigoid, membranous glomerulonephritis, autoimmune hepatitis, autoimmune thyroiditis, autoimmune hemolytic anemia, and Sjogren's syndrome [21-23]. In our study, heights of Rf, anti-dsDNA, anti TPO and anti-Tg are above 50% in patients with drug allergy. It has been observed that the frequency and blood levels of anti-TPO antibodies increase in some allergic diseases [24]. In our study, anti-TPO positivity was 59.70% and antithyroglobulin positivity was found to be 65.20%. In a study examining the association between multiple drug hypersensitivity (MDH) and autoimmunity, the authors have reported that the patients with MDH had increased the prevalence of autoimmune diseases, mainly autoimmune thyroiditis, and chronic idiopathic urticaria [6]. In our study, thyroid autoantibody positivity ranges between 34.80% and 40.30%. Although we cannot draw a causal relationship between drug reaction and thyroid autoantibody positivity in this study, the prevalence of thyroid autoantibody positivity is relatively high.

Limitations

Some limitations of our study deserve mention. First, we have only included the patients who had at least one autoantibody in the database. Thus, this might be seen as a selection bias. Second, not all antibodies were investigated in all patients. Some autoantibodies were studied in a tiny fraction of the study cohort. Lastly, no causative relationship can be claimed because autoantibodies might have been present before the development of drug allergy.

Conclusion

Allergic reactions and autoimmune diseases share some common features, along with some stark differences. In conclusion, autoantibodies might develop together with many drug reactions. Fortunately, drug reactions cannot cause autoimmune-like diseases in most of these patients. Observational research on DIA will contribute to the creation of new hypotheses about the pathophysiology of autoimmunity. Although our study has some shortcomings, we think this article will shed some light on the relationship between drug reaction and autoimmune diseases. Numerous studies in this area can enable us to discuss the widespread use of risky drugs in a more objective way.

Conflict of interest: The authors declare no conflict of interest in this study.

Author Contributions		Author Initials
SCD	Study Conception and Design	ZA, PBD
AD	Acquisition of Data	ZA
AID	Analysis and Interpretation of Data	ZA, PBD
DM	Drafting of Manuscript	ZA, PBD
CR	Critical Revision	ZA

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