Profile of Determinant Factors on Drug Allergy Severity in Indonesian Children at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

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Abstract

Background: Drug allergy in children is a rare case that needs special attention. Identifying the factors that affect the severity of drug allergy is important for the improvement of drug allergy management in Indonesian children. **Objective**: to analyze the factors that influence drug allergy severity in Indonesian children. **Methods**: This study used a retrospective design and consecutive sampling in 2014-2018. The data collected included sex, types of allergy-causing drugs, previous allergy history, parental allergy history, and clinical manifestations. The data were analyzed by using a logistic regression test where the statistical test results were significant if $p < 0.05$. **Results**: The average age of the participants was 93.00 ± 50.54 months with a median value of 84 (12 - 204) months. Drug allergy severity in children is influenced by several things, such as the type of drug ($\beta = 5.76$; 95% CI 1.29 - 25.70; $p = 0.022$), sex ($\beta = 1.27$; 95% CI 0.30 - 5.36; $p = 0.743$), previous allergy history ($\beta = 2.44$; 95% CI 0.10 - 58.67; $p = 0.583$), and a drug allergy history on parents ($\beta = 0.65$; 95% CI 0.06 - 6.75; $p = 0.719$). **Conclusion**: There is a significant relationship between drug allergy severity and the type of drug whereas sex, previous allergy history, and a history of allergy on parents do not find a significant connection.

Keywords: *drug allergy, Indonesian children, severity*

Introduction

Drug Allergy is a serious health problem in children which is often causing concern for parents [(1)]. Drug hypersensitivity reactions cannot be predicted beforehand so it is rarely known the initial phase of the allergy reaction. This hypersensitivity reaction can also be life-threatening in high-grade drug allergies [(2, 3)]. Based on a survey conducted by the World Allergy Organization in 2011, the distribution of drug allergy in the world is as follows: Europe (18.2%), Asia Pacific (19.5%), North America (7.8%), Latin America (9.1%), and Africa Middles East (3.9%) [(4)]. The number of drug allergy in Indonesia is still not reported yet; the latest data only shows that from 2009 to 2013 in Bandung. Moreover, in Indonesia, which reported as many as 57 cases of drug allergy and children are still very rarely reported [(5, 6)].

The cases of children's drug allergy were reported as 6.5% of the total number of cases of drug allergy in all hospitals [(7)]. Management of drug allergy in children requires a caregiver role, in addition to medical management, it is also necessary to identify the factors that affect the severity of drug allergy symptoms in children [(8)]. Several factors need to be considered by

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medical staff including sex, type of drug that causes the allergy, previous history of allergy, history of allergy from parents, and clinical manifestations. Sex is a factor that affects drug allergies, which is in allergies, sex hormone receptors on lymphocytes, and leukocytes can modulate the type of immune reaction and regulate inflammation [9]. Currently, most of the types of drugs that cause allergies are the antibiotic class [5, 6]. Previous allergy history is a condition that is considered by medical staff in providing therapy to children with drug allergy [10]. Allergy history in parents based on previous research states that children who have parents with allergy have a higher risk of having the same allergy [11].

Dr. Soetomo General Academic Hospital, Surabaya, Indonesia is the main referral hospital in the East Java Region. Indonesia shows that the number of pediatric patients with drug allergy has increased every year and the research that reports on the distribution of drug allergy cases in Indonesia are still very small. Based on the description above, analysis is needed to determine the factors that affect the severity of drug allergy in Indonesian children.

Materials and Methods

Participant

Participants in this study were the children with drug allergy that met the inclusion and exclusion criteria. Patient of inclusion criteria was patients that diagnosed with drug allergy according to guidelines [12, 13], aged >18 years, and patients undergoing hospitalization. Patients of exclusion criteria were patients having infectious diseases (measles, rubella, and staphylococcal scalded skin syndrome), immunodeficiency disease (HIV), and congenital disorders (Down syndrome). Caregiver/ parent participant gets an explanation regarding the research objectives and completes the informed consent form before using participant data.

Design

This study used a retrospective design that applied the consecutive sampling method. The data used in this study were patients from 2014 to 2018, which obtained 36 participants. This research was conducted in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia where this research was conducted with ethical approval prior to its implementation. The procedure of this study included collecting the medical records of participants who had been hospitalized. The data collected included sex, types of allergy-causing drugs, previous allergy history, parental allergy history, and clinical manifestations. The clinical manifestations of drug allergy are categorized into 2, namely: severe and non-severe [8]. After data collection and some incomplete data, the researcher contacted the caregiver/ parent participant to use the data and complete the missing data.

Statistical Analysis

The measurement of data results was analyzed by using the data entered into the IBM SPSS Statistics software version 23.0 (IBM Corp., Armonk, NY, USA). The data were analyzed by using a logistic regression test where the statistical test results were significant if $p < 0.05$.

Result

Participant Characteristics

The mean age of the participants was 93.00 ± 50.54 months with a median value of 84 (12 – 204) months. There will be a maximum number of participants aged 5-7 years, for 5 participants each. Most of the participants who experienced allergic reactions caused by non-antibiotic drugs were 52.78%, while participants who experienced drug allergy were male by 52.78%. Most of the participants did not have a history of atopy was 63.89% and only 8.33% of the participants' parents had a history of atopy. Then, most of the participants did not have a history of drug allergy was 88.89% and the majority of the participants' parents also did not have a history of drug allergy was 94.44%. Most of the participant's experienced clinical manifestations in the severe category were 55.56% (Table 1).

Profile of drugs cause drug allergy

Most of the participants who experienced drug allergy caused by antibiotic drugs were 47.22%, of which most were caused by amoxicillin (35.29%) and cotrimoxazole (29.41%). In the second position, NSAID types drug were the cause of the most drug allergy by 19.44%, of which 77.78% were mostly caused by paracetamol. Details of the types of drugs and classes

of drugs that cause drug allergy to the participant can be seen in Table 2.

Analysis of factors that influence the severity of drug allergy

Drug allergy severity in children is influenced by several things, namely the type of drug (β = 5.76; 95% CI 1.29 – 25.70; p = 0.022), sex (β = 1.27; 95% CI 0.30 – 5.36; p = 0.743), Previous allergy history (β = 2.44; 95% CI 0.10 - 58.67; p = 0.583), and a history of drug allergy in the parents (β = 0.65; 95% CI 0.06 – 6.75; p = 0.719; table 3). Based on the results of the analysis, the factors that affect the severity of drug allergy are the types of drugs that cause allergy itself.

Table 1. Participant Characteristics

Variables	n (%)
Hypersensitivity reactions	
Antibiotics	17 (47.22)
Non-antibiotics	19 (52.78)
Sex	
Male	19 (52.78)
Female	17 (47.22)
Atopy's children history	
Yes	13 (36.11)
None	23 (63.89)
Allergy history	
Yes	4 (11.11)
None	32 (88.89)
Drug Allergy in parent's history	
Yes	2 (5.56)
None	34 (94.44)
Atopy in parent's history	
Yes	3 (8.33)
None	33 (91.67)
Drug Allergy Clinical Manifestations	
Severe	20 (55.56)
Non Severe	16 (44.44)

Table 2. Allergy-causing drugs

Drug Classification	Types of drugs	n (%)
Antibiotics	Amoxicillin	6 (16.67)
	Thiamphenicol	3 (8.33)
	Cefriaxone	1 (2.78)
	Cotrimaxazole	5 (13.89)
	INH (Isoniazid)	2 (5.56)
NSAIDs	Ibuprofen	2 (5.56)
	Paracetamol	7 (19.44)

Cont... **Table 2. Allergy-causing drugs**

Anticonvulsants	Phenytoin Carbamazepine	5 (13.89) 2 (5.56)
Antidepressants	Amitriptyline	1 (2.78)
Chemoteraphy	Doxorubicin Leunase	1 (2.78) 1 (2.78)

Table 3. Correlation of determinant factors on drug allergy severity

Variables	**Drug of allergy severity**		
	β	**95% CI**	**p**
Types of drugs	5.76	1.29 – 25.70	0.022*
Sex	1.27	0.30 – 5.36	0.743
Allergy history in the parents	2.44	0.10 – 58.67	0.583
Previous Allergy History	0.65	0.06 – 6.75	0.719

Note: *significance $p < 0.05$

Discussion

There are 3 types of drug classification that most often cause drug allergies, including antibiotics, NSAIDs, and anti-congestion. Based on several previous studies, it was stated that antibiotics were the most common cause of drug allergy [14, 15]. Besides antibiotics, drug allergy caused by NSAIDs is relatively high. Based on previous research, it was reported that 20% of drug allergy cases were caused by NSAIDs [16]. Another study states that antibiotics and anti-consuls are drugs that often trigger hypersensitivity reactions [17].

In general, the mechanism that causes drug allergy is divided by IgE-mediated, which in this pathway will get the emergence of inflammatory mediators and non-mediated IgE. There are 3 reaction pathways, namely the first is cytotoxic/cytolytic originating from IgM or IgG reactions that react with complement. Second, there is the Drug Immune complex which can occur due to reactions with foreign proteins such as streptokinases, antitoxins, and antivenins. The third is a reaction pathway involving a specific T cell effector antigen in which the hypersensitivity response can be transferred to purified T cells or T cell clones. This reaction only appears after 24 - 72 hours which is often referred to as a slow type reaction [15, 18].

Based on the results of this study, it was concluded that the number of male participants was higher than female. This result is inconsistent with previous studies which stated that drug hypersensitivity reactions were more common in females. Previous research stated that based on the Health Insurance Review and Assessment (HIRA) database in Korea from 2009 to 2014, the number of females who experienced drug allergy was higher than male, which were 53,734 (57.55%), 52,139 respectively (57.90%), 52,028 (57.71%), 50,430 (57.27%), 49,992 (57.37%), and 49,464 (57.33%) [19]. Based on clinical observations, the relationship between hormonal status and allergic reactivity has been known for decades. In allergies, sex hormone receptors on lymphocytes and leukocytes can modulate the type of immune reaction and regulate inflammation. It is known

that estrogen exerts an effect on receptor-mediated mast cell release by affecting the threshold level in the allergy effector phase [9]. Hospitalized females were statistically and significantly more likely to experience drug allergy than male, although there were no significant differences in clinical manifestations and mortality between the sexes [4].

Several previous studies stated that atopy is a predisposing factor for drug allergy. Patients who use NSAID class drugs have a higher risk of drug allergy than patients without a history of atopy. In patients with a history of atopy, it is necessary to use alternative drugs that are used such as paracetamol and nimesulide [20, 21]. Recent research states that atopy patients are advised not to use penicillin-type antibiotics because they are proven to have a high risk for anaphylaxis [15, 18].

Previous studies stated that children with parents who have a history of allergy are more at risk of experiencing allergies than children without allergy history. Previous research states that children whose parents have a history of allergies to antibiotics have a 15x greater risk than children with parents without allergies [22]. A study of suspected drug allergic reactions in 97 children concluded that a family history of drug allergy was significantly associated with confirmed allergic drug reactions [11]. There is also a multicentre study conducted in Spain, reporting that patients with a family history of drug allergy are more likely to be allergic to some drugs [23].

Conclusion

Most children with drug allergy experience severe manifestations, most of them are male. Drug allergy severity in Indonesian children is influenced by several things, namely the type of drug, sex, previous history of allergy, and history of drug allergy in the parents. However, what is proven significantly in this study is only the types of drugs that cause drug allergy.

Ethical Approval: This research has gone through the ethical test stages based on the Declaration of Helsinki at Ethics Committee Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (1739 / KEPK / XII / 2019).

Conflict of Interest: None.

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