Drug Induced Hypersensitivity Syndrome (DIHS) Patient Characteristics in Dermatology and Venereology Department, Dr. Cipto Mangunkusumo National General Hospital in the Period 2014 to 2017

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Keywords: Drugs induced hypersensitivity, adverse drug reaction, characteristics, eosinofilia, culprit drugs.

Abstract: Drug induced hypersensitivity syndrome (DIHS) is a distinct, severe, idiosyncratic reaction to a drug characterized by a prolonged latency period with cutaneous presentation and internal organ involvement. In Asia, DIHS was reported to almost one tenth of adverse drug reaction cases, with a mortality rate ranged 3-10%. The aim of this study are to describe the sociodemographic and clinical characteristics of patients with DIHS and causative agents in Dermatology and Venereology Department Dr. Cipto Mangunkusumo National General Hospital, Jakarta. This study is a descriptive study. Using medical records and electronic health record of patients with DIHS were retrospectively reviewed. During 2014-2017 we identified 18 female, 14 male patients, with age range 14-87 years. Onset of the disease since exposed by culprit drugs were 14-40 days.The most common underlying disease was accute infection disease (43,7%). The DIHS clinical features and laboratory finding in this study are fever (93,7%), maculopapular rash (90,6%), target lesions (12,5 %), facial oedema (21,5%), periorbital oedema (12,5%). lymph nodes enlargement (93,7%), eosinofilia (31,2 %) , elevating of liver function (100%), and one patients (3,1%) showed kidney involvement .The most common causative drugs were antibacterials (60 %). all patients, the causative drug was discontinued and treated with systemic corticosteroids. As the conclusion DIHS is a severe drug hypersensitivity reaction with prominent cutaneous and systemic manifestations. Dispite the limitations, this study present some variations of DIHS clinical features and many other drugs that implicated.

1 INTRODUCTION

Drug induced hypersensitivity syndrome (DIHS) is a distinct, severe, idiosyncratic reaction to a drug characterized by a prolonged latency period. It is a life-threatening disease with cutaneous presentation and internal organ involvement. Mechanisms that have been implicated in DIHS include drug detoxification enzyme abnormalities with subsequent accumulation of reactive drug metabolites, sequential reactivation of herpesviruses, such as cytomegalovirus, Epsteine Barr virus, human herpesvirus-6 and -7, and genetic predisposition associated with certain human leukocyte antigen alleles. DIHS clinical manifestations, usually fever, rash, lymphadenopathy, eosinophilia, and a wide range of mild-to-severe systemic presentations (Husain et al, 2013). In Diagnose DIHS, clinicians must exclude other potentially serious conditions, including infections, neoplastic processes, autoimmune disorders, and connective tissue disease. Clinical testing and biopsy can be helpful, but are not always specific (Husain et al, 2013) (Avancini et al, 2015). Scoring systems based on diagnostic criteria have been developed by the European Registry of Severe Cutaneous Adverse Reaction (RegSCAR): acute rash, reaction suspected to be drug-related, hospitalization, fever >38º, enlarged lymph nodes involving >2 sites, Involvement of > 1 internal organ, blood count abnormalities, lymphocytes above or below normal limits, platelets under normal limits (Hiransuthikul et al, 2016).

In Asia, DIHS was reported to almost one tenth of adverse drug reaction cases, with a mortality rate ranged 3-10%. Mortality cases were mainly caused by multiple organ failure and sepsis. Various

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medications have been described to be the cause of DIHS (Hiransuthikul et al, 2016) (Chen et al, 2010). The aims of this study are to describe the sociodemographic and clinical characteristics of patients with DIHS and causative agents in Dermatology and Venereology Department dr. Cipto Mangunkusumo Hospital, Jakarta within 2014 - 2017.

2 METHODS

This study is a descriptive retrospective study of DIHS patients at dr. Cipto Mangunkusumo Hospital between January 2014 and December 2017. The medical records and electronic health record of patients with DIHS were retrospectively reviewed. The diagnostic criteria used in this study were purposed by RegiSCAR. Hospitalization and reaction suspected to be drug related were mandatory for diagnosis. Also, 3 out of the following 7 criteria were needed to fulfill the diagnosis: acute skin rash, fever above 38^{o} C, enlarged lymph node at 2 or more sites, involved at least 1 internal organ, lymphocyte count above or below laboratory limits, eosinophil count above laboratory limits, and platelet count below laboratory limits. This study has been approved by the Health Research Ethical Committee of the Faculty of Medicine, Universitas Indonesia.

3 RESULTS

A total of 32 medical records of DIHS patients in Dr. Cipto Mangunkusumo Hospital in January 2014 – December 2017 were reviewed in this study. This study identified 18 females, 14 male patients, with age range 14-87 years who fulfill the RegiSCAR criteria. Onset of the disease since elicited by culprit drugs 14-40 days. The most common underlying disease was accute infection disease (43,7%). The DIHS clinical features and laboratory finding in this study are fever (93,7%), maculopapular rash (90,6%), target lesions (12,5 %), facial oedema (21,5%), periorbital oedema (12,5%). lymph nodes enlargement (93,7%), eosinofilia (31,2 %), elevating of liver function (100%) and one patient showed kidney involvement (3,1%). (Table. 1). The most common causative drugs were antibacterials (60 %) (Figure. 1, Table.2). The causative drug was discontinued in all patients and treated with systemic corticosteroids. There were four patients in this study who had done the patch test. One patient had positive result and relevan to rifampicin, dapsone, paracetamol, klofazimin, and one patient had positive result to rifampicin and isoniazid. Two other patients showed negative results.

4 DISCUSSION

DIHS is a rare, potentially life-threatening adverse drug reaction with cutaneous manifestations and internal organ involvement that occurs in both adults and children. The latency period of DIHS is longer than dose Steven - Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN, acute generelized exanthematous pustulosis, fixed drug eruptions and MPE, which all belong to delayed type hypersensitivity (Shiohara et al, 2017). This study showed the onset of DIHS were in range 14-40 days after the start of eliciting drugs. Some study found that longer period of latency may results in a failure to properly make the diagnosis (Shiohara et al, 2017) (Wang et al, 2017).

At the beginning, patients may expirience some prodormal symptoms before or along with the development of skin rash. These syptoms include fever, pruritus, dysphagia, pain (Cho et al, 2017) (Shiohara et al, 2017). There were 93,7% DIHS patiens in this study had fever more than 38 ^{0}C as prodormal symptom. Although there can be various cutaneous manifestations, in this study, almost all patients had maculopapular (90,6%) rash, and some patients had combination skin rash including, maculopapular rash, target lesions, facial edema dan periorbital edema. Akarin *et al* found. All DIHS patients presented with rash, almost all were maculopapular type (94.2%).

Table 1. DIHS patient characteristics in Department of Dermatology and Venereology, dr. Cipto Mangunkusumo Hospital between January 2014 and December 2017.

	n=32	%
Age	43 (14-87)	-
Sex		
Male	18	56,3
Female	14	43.7
Onset (days)	18 (14-40)	-
Clinical Symptoms		
Skin Rash	29	90,6
Maculopapular Rash	4	12.5
Target Lesion	7	21.8
Facial Oedema	4	12.5
Periorbital Oedema		
Fever >38^0 C	30	93.7
Enlarged lymph nodes involving ≥ 2sites	30	93.7
Underlying disease		
Accute Infection	14	43,7
Dermatomyositis	5	12.5
Tuberculosis	4	3.1
Convulsion Disorders	1	3.1
Hypothiroid	1	15.6
Leprosy	1	3.1
Cardiovascullar Disease (CVD)	1	3.1
Chronic Kidney Disease	1	3.1
Diabetes Melitus	1	3.1
Hypertension	1	3.1
Poliomiolitis	1	3.1
HIV	1	3.1
Internal Organ Involvement		
Liver	32	100
Elevation of liver function		
AST (U/L)	165 (42-654)	-
ALT (U/L)	175 (45-483)	-
Kidney	1	3,1
Eosinofil		
Eosinophilia	10	31.2
Eosinophil level over laboratory limits (µL)	756 (501-6730)	-
Therapy		
Corticosteroid (methylprednisolon)		
1 mg/Kg	18	56.2
Length of Stay (days)	8 (6-15)	
1,5 mg/Kg	14	43.8
Length of Stay (days)	9 (6-23)	

There were 93,7 % patients who showed enlarged of lymph nodes involving two sites or more in this study. Akarin *et al* and Prannee *et al,* showed patients may have limited lymph node involvement or generalized. lymphadenopathy with localized tenderness involving the cervical, axillary, and inguinal lymph nodes. In approximately 31,2% of cases in this study, there is eosinphilia With > 5.0x 10^9 eosinophils/L. Eosiophilia can be delayed for 1 to 2 weeks. Hypereosinophilia likely plays a role in visceral manifestations because eonsinophil granule proteins are toxic to many tissues (Wang et al, 2017). The liver is the most frequently affected visceral organ in DIHS, oftennwith varying degrees of hepatitis (Wongkitisophon et al, 2012). All patients in this study had elevating of liver function. Stander *et al*, found there were Phenytoin, minocycline, and dapsone are commonly implicated. The elevated liver enzymes may persist for several days after withdrawal of culprit drug, but

may sometimes take months to completely resolve (Wongkitisophon et al, 2012) (Shiohara et al, 2006). There were one patients showed kidney involvement that presented by increasing of urea and creatinin. There were no lung and heart alterations. Li Wang *et al* presented that damage occurred most commonly to the liver, followed by the kidneys.

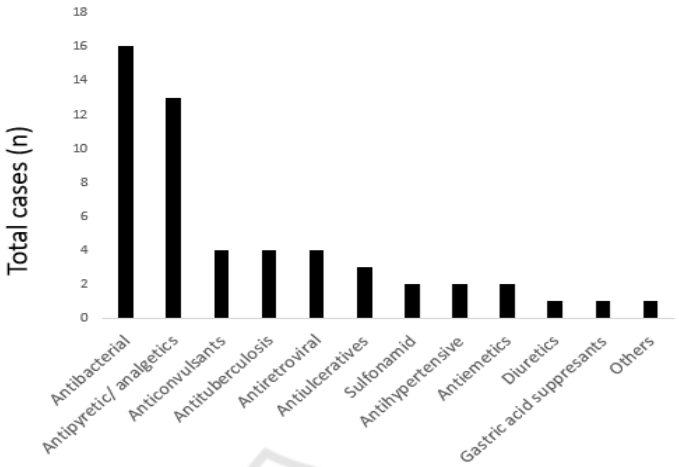

Figure 1. Culprit drugs

Table 2. Culprit drug details of the DIHS in Department of Dermatology and Venereology, dr. Cipto Mangunkusumo Hospital between January 2014 and December 2017

Drug Categories	**Drug Names***
Antibacterial	Cefadroxil, ceftriaxon, cefixim, tiamfenicole, ciprofloxacin, ofloxacin, metronidazole, meropenem
Antipyretic/ Analgetic	Paracetamol, tramadol, ibuprofen, metampiron, mefinamic acid
Anticonvulsant	Carbamazepin, haloperidol, Phenytoin
Antituberculosis	Rifampicin, isoniazid, ethambutol, pirazinamid
Antiretroviral	Lamivudine, zidovudine, nevirapine
Antiulcerative	Omeprazole, lansoprazole
Sulfonamid	Dapsone
Antihypertensive	Amlodipine, nifedipine
Antiemetic	Ondancentron, domperidone
Diuretic	Furosemide
Gastric acid suppressant	Ranitidine
Others	Pet tze huang

*The drug names are arranged respectively

Many drugs have been reported to be a causative agent of DIHS. However, only a limited number of drugs are frequently encountered as culprits, including anti-convulsants, antibacterials ,antivirals, antipyretics, and others (Wang et al, 2017) (Stander et al, 2013). The most peculiar feature of these culprits is a long latent period, which ranges from 3 to 8 weeks after commencement of the drugs (Shiohara et al, 2017). This study present the most common culprit drugs were antibacterials (cefadroxil, ceftriaxon, cefixim, tiamfenicole, ciprofloxacin, ofloxacin, metronidazole, meropenem, respectively) that might be associated with the most common patients underlying disease in this study were accute infection diseases (43,7%) including acute respiratory tract, urinary tract infections, and other secondary infection.

In all patients, the causative drug was discontinued. All patiens were treated with systemic corticosteroids, eighteen patients got 1mg/kg body weight and fourteen patients got 1,5 mg/kg weight methylprednisolon as initial dose. The state of the patients was a consideration to determine the initial dose. This study showed patient who got higher initial dose had longer length of stay, patient underlying disease were thought as the factors that contributing. In this study just four patients who underwent patch test. Some difficulties were thought due to DIHS latency and patients complience.

Study limitations include a retrospective study, small number of subjects. More epidemiology study to confirm and provide more useful clinical information for early detection and improve the outcome of severe cutaneous adverse reactions Including DIHS is needed.

5 CONCLUSION

DIHS is a severe drug hypersensitivity reaction with prominent cutaneous and systemic manifestations. Dispite the limitations, this study presents some variations of DIHS clinical features. Although it is classically caused by anticonvulsants and sulfonamides, many other drugs have been implicated, such as antibiotics. More larger epidemiology study either retrospective or prospective are needed to provide more useful clinical informations.

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