



# Frequency of serum sickness and its related factors in Kurdistan, west of Iran; a 13-year study

Rasoul Nasiri Kalmarzi<sup>1</sup>, Zaher Khazaei<sup>2</sup>, Sina Zamanei<sup>3</sup>, Sajjad Rahimi Pordanjani<sup>4</sup>, Ebrahim Ghaderi<sup>5</sup>, Elham Goodarzi<sup>6\*</sup>

<sup>1</sup>Department of Pediatrics of Beast Hospital, Cellular & Molecular Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran

<sup>2</sup>Department of Health and Community Medicine, Faculty of Medicine, Dezful University of Medical Sciences, Dezful, Iran

<sup>3</sup>Student Research Committee, Kurdistan University of Medical Sciences, Sanandaj, Iran

<sup>4</sup>Department of Epidemiology and Biostatistics, School of Health, Semnan University of Medical Sciences, Semnan, Iran

<sup>5</sup>Social Determinants of Health Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran

<sup>6</sup>Social Development and Health Promotion Research Center, Gonabad University of Medical Sciences, Gonabad, Iran

## \*Correspondence to

Elham Goodarzi,

Email:

Elhamgoodarzi.1370@yahoo.com

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## Abstract

**Introduction:** Serum sickness is an acute and self-limiting disease caused by allergic reactions as a result of foreign proteins, injection or allergens. It is diagnosed by fever, lymphadenopathy, rash, gastrointestinal disorders and weakness.

**Objectives:** The aim of this study was to evaluate the frequency of serum sickness and serum-like sickness in patients hospitalized in Kurdistan province.

**Patients and Methods:** This is a cross-sectional study. The study included all patients who were hospitalized during 2001 to 2014. Demographic data, etiologic factors, clinical symptoms and laboratory findings using patients' records were extracted. The data were analyzed using the software Stata 12.

**Results:** Out of 74 patients 55 (74.3%) were male and 19 (25.7%) were female. The mean age of all patients was  $25.13 \pm 17.9$  years. The average length of hospital stay in patients was  $3.48 \pm 0.47$  days. The mean interval between medication consumption and the onset of symptoms was  $7.32 \pm 2.44$  days. Moreover, the mean interval between taking medication and onset of symptoms is not different among groups ( $P > 0.05$ ). In the majority of cases, the most affected of body areas were the right buttock (27%) and left buttock (25.7%), respectively. In this study, most cases of serum sicknesses (66.2%) are caused by medication administration. Of them, cefixime and penicillin (2.7%) were the most common medications responsible for this disease. Other causes were included amoxicillin/clavulanic acid, diclofenac, dexamethasone and amoxicillin (1.4%).

**Conclusion:** Drugs are a common cause of serum sickness which is generally started 7 to 14 days after consumption. In most patients with mild disease, drug discontinuation is the choice treatment.

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## Introduction

Serum sickness is a third type hypersensitivity vasculitis which was reported for the first time by Schick and Pirquet in 1905 during treatment of patients with tetanus and diphtheria with antitoxin (1). The disease is a clinical syndrome which is characterized by fever, lymphadenopathy, arthralgia, exanthema, digestive disorders, and sometimes renal impairment and weakness. Initially, it has been described by injecting foreign proteins such as equine antitoxins. This disease is caused by tissue deposition of circulating immune complex, complement activity, and its subsequent inflammatory response (2). Serum sickness-like reaction

## Key point

Drugs are a common cause of serum sickness. In most patients with mild disease, drug discontinuation is the choice treatment.

(SSLR) is similar to classic serum sickness regarding clinical characteristics, however mechanisms and pathogenesis of these reactions are different (3-5). Similar to serum sickness, these reactions can occur by infections, particularly streptococcal infections and some viral contaminations. Medications and other therapeutic factors are the most common causes of SSLR which are generally created 7 to 14 days



after taking these factors. Antibiotics are more associated with SSLR including penicillin, amoxicillin, cefaclor and cotrimoxazole (6).

Clinical manifestations of these patients are fever, exanthema, lymphadenopathy, arthralgia and arthritis while laboratory findings are nonspecific (6-9). SSLR is usually less severe than serum sickness. Various signs and symptoms consisting arthralgia, urticarial rash with or without fever, polymyalgia and lymphadenopathy are the main presentations of this disease (10,11).

The differential diagnosis of SSLR includes viral infections with exanthema, hypersensitivity vasculitis, acute rheumatic fever, acute gonococcal or meningococcal infections, and other types of drug reactions (12).

The most important treatment for SSLR is discontinuation of causative medication along with prescribing antihistamines or steroids in necessary situations. Antihistamines are enough for patients with mild itching and rash. To prevent SSLR, causative medications should be avoided as far as possible (13). Although serum sickness is rare, it may occur due to the administration of some medications such as penicillin and cephalosporin (4).

### Objectives

Given that serum sickness is a disease which can cause life threatening consequences, identifying causes of this disease is essential. This study aimed to investigate the frequency of serum sickness and its related factors in a referral hospital.

### Patients and Methods

#### Study population

This study is a descriptive cross-sectional study. All patients with symptoms of serum sickness who were hospitalized during 2001 to 2014 with a definitive diagnosis of serum sickness were enrolled in the study. Diagnosis of disease was based on history. All patients were examined regarding other differential causes of serum sickness or if there is any doubt to other disease with similar symptoms. Initial information included demographic information and etiologic factors, clinical symptoms and laboratory findings using patients' records.

#### Ethical issues

1) The research followed the tenets of the Declaration of Helsinki and its later amendments; 2) informed consent was obtained; and 3) permission of the ethical review committee was obtained prior to execution of the study.

#### Statistical analysis

After data collection, the data were analyzed with the software Stata 12 at an inaccuracy of less than 5%. Descriptive statistics were used in order to investigate the frequencies, mean, and standard deviation of data.

### Results

In this study, 74 patients were investigated. Of them, 55

(74.3%) were male and 19 (25.7%) were female (Table 1). The mean age of all patients was  $25.13 \pm 17.9$  years. The average length of hospital stay in patients was  $3.48 \pm 0.47$  days. The mean interval between medication consumption and the onset of symptoms was  $7.32 \pm 2.44$  days. Moreover, the mean interval between taking medication and onset of symptoms is the same in different age groups ( $P > 0.05$ ). In the majority of cases, the most affected of body areas were the right buttock (27%) and then left buttock (25.7%), respectively. In this study, most cases of serum sickness are caused by medication administration (66.2%). Table 2 shows that cefixime and penicillin (2.7%) were the most common medications responsible for serum sickness. Other causes were amoxicillin/clavulanic acid, diclofenac, dexamethasone and amoxicillin (1.4%). In this study, the mean of platelet counts in these patients was  $102000/\mu\text{L}$  while WBC average was  $22000/\mu\text{L}$  (Table 3). Regarding the location of symptoms, the onset of symptoms in the age group of below one year in most cases (100%) was central nervous system. In the age group of 7-14 years in most cases (40%) is face, and in the age group of older than 14 years is right buttock (27%). Furthermore, in the age group of older than 14 years, 80% of cases of serum sickness was due to the drug administration. In the age group of 1-7 years and 7-14 years, serum sickness in 73% of individuals was detected.

### Discussion

In this study, out of 74 patients, 55 patients (74.3%) were male which indicates three times higher prevalence of serum sickness in males in this study. In the study of Shiari

**Table 1.** Demography of patients with serum sickness and SSLR

Variable	No.	%
Sex		
Male	55	74.3
Female	19	25.7
Age groups		
<1 years	3	4.05
1-7 years	11	14.86
7-14 years	7	9.45
> 14 years	53	71.62

**Table 2.** The frequency of medications in patients with serum sickness.

No. of first group of responsible drugs (%)	
Cefixime	2 (2.7)
Amoxicillin/clavulanic acid	1 (1.4)
Amoxicillin	2 (2.7)
Dexamethasone	1 (1.4)
Diclofenac	1 (1.4)
No. of second group of responsible drugs (%)	
Ibuprofen	1 (1.4)
Azithromycin	1 (1.4)
Clonidine	1 (1.4)

**Table 3.** The mean of studied variables in patients with serum sickness

Variable	Mean	Standard deviation
ESR (mm/h)	31.72	5.02
CRP (mg/L)	22.12	5.91
WBC ( $10^3/\mu\text{L}$ )	10.6	4.5
WBC/Neutrophils (%)	63.3	22
WBC/Lymphocytes (%)	59.1	12.6
Hb (g/dL)	11.4	1.9
PLT ( $10^3/\mu\text{L}$ )	263.5	109.2

et al, the prevalence of the disease in males was 1.5 times higher than that of in females. They also detected that furazolidone and then cefixime are the most common causative medication of SSLR (7). In the study of Kalmarzi et al, most patients with serum sickness (82%) were male. The results of both studies are consistent with our findings (14). Mean age of our patients was  $25.13 \pm 17.9$  years, while in the study of Apisarntharak et al, the mean age of the patients was 45 years (15). We also found that mean of onset of symptoms after administration of drugs was  $7.32 \pm 2.44$  days. In the study conducted by Kim et al, the onset of symptoms after consuming rifampin was 2 weeks (16). In the study by Vermeire et al, delayed reactions time after consuming infliximab was around 2 days to 2 weeks (17). In the study of LoVecchio et al, skin rash occurred after 3 to 21 days of antibiotic administration (18). Additionally, fever, rash and thrombocytopenia occurred 14 days after consumption in the study of Lavonas and colleagues (19). In this study, the first group of medications was cefixime (2.7%) and amoxicillin (2.7%). The second group of medications were calcitriol and ibuprofen. Moreover, the third group of medications were calcitriol and acetaminophen. The frequency of each of the second and third group of medications was separately 1.4%. In the study of Kunnamo et al (20), related medications to serum sickness were aspirin, naproxen, and a combination of ephedrine, dextromethorphan, brompheniramine and phenyl. Accordingly in the study of Apisarntharak et al, patients used acetaminophen in 57% of cases and anti-inflammatory medications in 43% of cases had serum sickness (15).

The results of our study showed that among the first medications, only 6.8% of patients had the previous history of taking hydrocortisone and 5.4% of patients had a history of taking ceftriaxone and acetaminophen. Among the consumers of second group of medications, only 2.7% of cases had the history of taking clindamycin, acetaminophen and ranitidine. Additionally, among the consumers of third group of medications, only 2.7% of cases had the history of taking acetaminophen and celecoxib.

The results showed that the most cases of serum sickness (66.2%) are caused by medications. In fact, drug administration as the cause of serum sickness in the age group of under one year and in the age group of older

than 14 years was 100% and 80% respectively. In the age group of 1-7 years and 7-14 years, serum sickness was 73% and 71% respectively. The results of study showed that the location of disease in the majority of cases were the feet (8.6%), whole body (8.1%), and hands (4.1%), respectively. The most location of spreading of disease in the age group of under one year was the whole body and in the rest of age groups was the feet. In the study by Lawely et al (21), the location of spreading of symptoms was mostly in hands, feet, fingers, and knees. In the study by Sohail et al, symptoms were involved the total body surface area by skin rashes (22). The most common involved joints were ankle, fingers joints, and knee joint (20). The most common skin symptoms included macular exanthema and hives (23). The results showed that the locations of onset of symptoms in patients were the right buttock (27%) and the left buttock (25.7%), respectively. According to the age groups, the location of onset of symptoms in the age group of under one year in most cases (100%) is the central nervous system. Accordingly in the age group of 14-7 years lesions were mostly (40%) in face, and in the age group of older than 14 years, lesions were mostly on (27%) right buttock. Moreover, in this study WBC average was  $6300/\mu\text{L}$ . The mean of CPR level was  $22.12 \pm 5.91$  mg/L while in the study by Kim et al, the mean patients' blood CRP level was 10.9 mg/L (16).

### Conclusion

Although serum sickness has reduced by vaccination programs, however serum-like reactions are recently observed by medications. The majority of cases of serum sickness is observed after the administration of drugs such as cefixime or amoxicillin. According to this point, excessive administration of medications should be avoided as far as possible.

### Limitations of the study

Given that the study is a retrospective study, incomplete information of some records and failure to register some markers in patient records can be mentioned as its limitations.

### Authors' contributions

RNK and SZ conducted the research. SRP, EG and EG prepared primary draft. ZK prepared the final manuscript. All authors read and signed the final paper.

### Conflicts of interest

The authors declare no conflict of interest.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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