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Original Article

Investigation of demographic, clinical, laboratory features, and outcomes of children with serum sickness hospitalized in a hospital

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Abstract

***Background & Aims*:** Serum sickness is a type 3 hypersensitivity reaction caused by the injection of foreign proteins, serums, and non-protein medications. This study investigated the demographic, clinical, and laboratory characteristics, along with outcomes, of patients with serum sickness hospitalized at Shahid Motahari Hospital, Urmia, from March 2017 to February 2021.

***Materials & Methods*:** This descriptive cross-sectional study included 67 patients diagnosed with serum sickness based on a recent history of exposure to an antigenic substance. Demographic, clinical, paraclinical data, and disease outcomes—including hospital stay length, ICU admission history, treatment response, mortality, and information regarding the potential cause of the disease—were collected from patient records, recorded in a checklist, and analyzed using SPSS statistical software version 22.

***Results*:** Arthralgia was present in 20 patients (29.9%), gastrointestinal complaints in nine children (13.4%), headaches in eight children (11.9%), muscle pain in 18 children (26.9%), arthritis in 14 children (20.9%), and urinary symptoms in one child (1.5%). The most frequent cause of serum sickness was phenobarbital, identified in 26 patients (38.8%), followed by cefixime in nine patients (13.4%), azithromycin in six patients (9%), ceftriaxone in five patients (7.5%), and co-amoxiclav in four patients (6%). Additionally, leukocytosis was found in 23 patients (34.3%), 32 patients (47.8%) had a positive C-reactive protein (CRP), 32 patients (47.8%) had an elevated erythrocyte sedimentation rate (ESR), same as sedimentation rate, and elevated aspartate aminotransferase (AST) and alanine transaminase (ALT) were detected in 4 patients (6%) each.

***Conclusion*:** Clinically, serum sickness was most commonly associated with fever, skin rashes, muscle pain, and changes in paraclinical findings in patients.

***Keywords*:** Children, Immunological diseases, Serum sickness

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Introduction

Serum sickness is a type 3 allergic reaction that involves hypersensitivity, presenting symptoms like fever, skin rash, arthralgia, and arthritis. The condition was first recognized in 1905, when horse-derived serum was administered to patients to treat infectious diseases.

These patients developed symptoms such as fever, rash, joint pain, and lymphadenopathy at the injection site. Subsequently, similar symptoms were seen following the injection of other horse-derived antitoxins. Symptoms typically emerge one to two weeks after the serum injection and may recur intermittently over several weeks (1).

The risk of developing serum sickness is dose-dependent. Research has shown that injecting 10 milliliters of tetanus antitoxin results in serum sickness in only 10% of patients, whereas injecting 80 milliliters leads to nearly all patients developing the disease (2). The type of antigen and antibody also influences the prevalence of the condition. One study found that the likelihood of developing serum sickness after receiving rabies serum is higher than with tetanus antitoxin (3). The incidence of serum sickness is greater in adults than in children, although antibiotic-induced serum sickness is more common in children under 5 years old (4). Individuals with gammaglobulinemia and cryoglobulinemia due to hepatitis C are at a higher risk of developing the disease (3). A clinical trial evaluating the efficacy and safety of TNF-α (tumor necrosis factor alpha) in sepsis patients found that 15 out of 645 patients developed serum sickness (5).

The primary drugs associated with the symptoms of serum sickness are penicillin and nonsteroidal anti-inflammatory drugs (NSAIDs). Medications containing antigens that differ from those of the immune system, such as the rubella vaccine, infliximab, and rituximab, are often implicated in causing these issues (6-7). Additionally, non-protein drugs, hormones, vaccines, polyclonal and monoclonal antibodies derived from animal serum (e.g., horses, rabbits, and mice), insect stings like bee and mosquito bites, and infectious diseases such as hepatitis and bacterial endocarditis can also trigger serum sickness (6-10). Antibiotics and drugs that can cause serum sickness include Cephalosporins, Ciprofloxacin, Allopurinol, Barbiturates, Bupropion (11-12), Captopril, Carbamazepine, Fluoxetine, Halothane, Hydantoins (e.g., phenytoin), Hydralazine, Indomethacin, Iodides, Iron dextran, Methimazole, Methyldopa, Mirabegron, etc (13).

Serum sickness does not usually occur after the first exposure to the antigen; instead, it develops following repeated contact with the antigen (8). With repeated circulation of antigens, the immune system activates the complement system, which, along with an influx of IgM and IgG immunoglobulins, leads to tissue damage (10). The antigen involved can be of exogenous origin, such as from bacteria, fungi, or their byproducts, or of endogenous origin, coming from the body's own tissues.

The characteristics of the antigen, including its molecular weight, charge, structure, and size, can impact the severity of symptoms. Small antigen-antibody complexes typically do not cause serum sickness and are easily cleared by the reticuloendothelial system. However, medium and large complexes can damage blood vessel walls and lead to severe symptoms. Symptoms generally emerge one to two weeks after the initial contact with the antigen, but with repeated exposure, they may appear within 24 hours. Additionally, certain non-immunological proteins contribute to the onset of symptoms, although their precise role remains unclear. These processes typically last one to two weeks. Once the antigens are cleared, the antigen-antibody complexes are slowly removed by macrophages and the reticuloendothelial system. This phase, known as the recovery phase, lasts between 7-28 days (8-14). While serum sickness typically progresses in specific phases, the exact mechanism is still not completely understood. In most cases, serum sickness is a self-limiting condition (15). The prognosis for patients without internal organ involvement is generally favorable, although there have been reports of fatalities in patients with glomerulonephritis or neurological complications. Serious complications of serum sickness include vasculitis, neuropathy, glomerulonephritis, and anaphylaxis (16).

The clinical symptoms of serum sickness are varied and inconsistent across studies. Some reports list vasculitis, neuropathy, acute cardiac injury, glomerulonephritis, and anaphylaxis as manifestations of the disease. Due to the wide range of symptoms, several other conditions must be considered in the differential diagnosis. Diseases such as herpes

dermatitis, microscopic polyangiitis, and shunt nephritis are included in the differential diagnosis of serum sickness, and accurate identification is essential to avoid exacerbating symptoms due to the differences—and sometimes overlap—in the treatment strategies for these conditions. For example, corticosteroids like prednisone are commonly used to manage dermatitis, but in the case of infectious diseases like herpes dermatitis, this treatment can worsen symptoms and trigger secondary viral effects, leading to symptom exacerbation. Misdiagnosis and improper treatment can even pose a life-threatening risk to the patient (15-17).

The disease typically begins with high fever and skin rashes, which can initially confuse the physician (7). The rashes often start in the chest area and then spread to both the upper and lower limbs. Erythema and purulent discharge are commonly observed at the injection site. Arthritis may develop in the temporomandibular joint and small joints, and diffuse lymphadenopathy can be palpated at the injection site (18). Swelling is frequently seen in the head and neck regions, and following the onset of the disease, cardiac and neurological symptoms can also emerge. Laboratory results typically show elevated serum creatinine levels, varying degrees of leukocytosis and leukopenia, proteinuria, hematuria, a decrease in complement levels, and an increase in plasma cells in peripheral blood samples (17). Microscopically, inflammation and necrosis are observed in all layers of the heart, while fibrinoid necrosis and edema are seen in the kidneys and synovial fluid (19).

The main approach to treating serum sickness involves removing or discontinuing the causative agent. Anti-inflammatory medications and antihistamines can help alleviate symptoms, while corticosteroids are used in more severe cases (20-27). Plasmapheresis may also be effective in reducing symptoms of serum sickness. Hospitalization is recommended for patients who are elderly, very young, immunocompromised, or presenting with severe symptoms and unstable hemodynamics (15).

As differentiating this condition from similar diseases requires a thorough understanding of clinical and paraclinical symptoms, and considering that diagnostic tools for this disease are costly and may require long-term follow-up, along with the increasing diagnosis of serum sickness at Shahid Motahari Hospital in Urmia in recent years compared to earlier periods and the lack of studies on this condition in Urmia, the objective of this study is to evaluate the demographic, clinical, laboratory characteristics, and outcomes of patients with serum sickness admitted to Shahid Motahari Hospital from April 2017 to March 2021.

Materials & Methods

In this descriptive study, the study population included children diagnosed with serum sickness who were hospitalized at Shahid Motahari Teaching and Treatment Center in Urmia from April 2017 to March 2021. The diagnosis was made based on clinical and laboratory characteristics. After applying the inclusion and exclusion criteria, 67 patients diagnosed with serum sickness were included. The diagnosis of serum sickness was based on a history of recent exposure to an antigenic substance and the presence of classic symptoms and signs of the disease. All patients were assessed for other potential causes of serum sickness, particularly infectious causes. Any clinical or paraclinical suspicion of diseases that could cause fever and rash, such as infectious mononucleosis, sepsis, measles, Kawasaki disease, and systemic lupus erythematosus were considered as the exclusion criteria for the study. The initial data, including patient demographics, age, etiology, clinical symptoms, the time interval between the administration of the antigenic substance and the onset of clinical symptoms, and laboratory findings, were extracted from patient records. A table was created for each case, and statistical analysis was conducted. Patient information was compiled into a designed list from the medical records, which included demographic details (age, gender, season, residence), clinical features (skin symptoms, fever, etc.), paraclinical data, and disease outcomes, such as length of hospitalization, ICU admission history, treatment response, mortality, and information regarding the probable causative agent. Finally, the collected data were entered into SPSS

version 22 software, and descriptive statistics, including mean and frequency, were used for analysis.

Results

In this descriptive study, 67 children with serum sickness who met the inclusion criteria were examined. The mean age of the children in the study was 49.70 ± 28.56 months. The mean age for male patients was 49.7 ± 14.26 months, and for female patients was 56 ± 24.32 months. According to the t-test statistical analysis, no significant difference was found between the mean age of patients and their gender (p = 0.46). Out of the 67 children studied, 51 (76.1%) were male, and 16 (23.9%) were female. Additionally, of the 67 children, 52 (77.6%) were from urban areas, and 15 (22.4%) were from rural areas. Regarding the season of onset of serum sickness, 16 (23.8%) children developed the disease in spring, 22 (32.8%) in summer, 18 (27%) in autumn, and 11 (16.4%) in winter.

Out of the 67 children in the study, 33 (49.3%) had a fever, while 34 (50.7%) did not. Additionally, 48 (71.6%) of the children had generalized urticaria, 18 (26.9%) had generalized maculopapular lesions, and one (1.5%) experienced itching without obvious skin manifestations. Regarding arthralgia, 47 (70.1%) children were negative, and 20 (29.9%) were positive. In terms of gastrointestinal complaints, nine (13.4%) children had gastrointestinal **(**GI) complaints, while 58 (86.6%) did not. Eight (11.9%) children had headaches, and 59 (88.1%) did not. 18 (26.9%) children experienced muscle pain, while 49 (73.1%) did not. Arthritis was observed in 14 (20.9%) children, and urinary symptoms were present in one (1.5%) child (Table 1). Of the 67 children studied, urinalysis (U/A) was active in four (6%) and non-active in 53 (94%). Additionally, urine culture (U/C) was active in four (6%) children and inactive in 53 (94%).

Table 1. Distribution of absolute and relative frequency of clinical symptoms in children with serum sickness

Clinical symptoms		Frequency	Percentage (%)
Fever	Has	33	49.3
	Does not have	34	50.7
Generalized urticaria	Has	48	71.6
Generalized maculopapular lesions	Has	18	26.9
Itching	Has	2	1.5
Arthralgia	Has	20	29.9
	Does not have	47	70.1
GI complain	Has	9	13.4
	Does not have	58	86.6
Headache	Has	8	11.9
	Does not have	59	88.1
Muscle pain	Has	18	26.9
	Does not have	49	73.1
Arthritis	Has	14	20.9
	Does not have	53	79.1
Urinary symptoms	Has	1	1.5
	Does not have	66	98.5

The causative agents of serum sickness were as follows: Phenobarbital in 26 patients (38.8%), Cefixime in nine patients (13.4%), Azithromycin in six patients (9%), Ceftriaxone in five patients (7.5%), and Co-

amoxiclav in four patients (6%), which were the most common causes. Other cases are detailed in Table 2. None of the hospitalizations were due to the injection of foreign serums.

Table 2. Distribution of absolute and relative frequency of the causative agent of serum sickness in children with serum sickness

Causative agent of serum sickness	Frequency	Percentage (%)
Phenobarbital	26	38.8
Cefixime	9	13.4
Azithromycin	6	9
Ceftriaxone	5	7.5
Co-amoxiclav	4	6
Amoxicillin	4	6
Ibuprofen	4	6
Cotrimoxazole	3	4.5
Coldgrip	2	3
Penicillin	1	1.5
Unknown cases	3	4.5
Total cases	67	100

Twenty-three patients (34.3%) had leukocytosis, while 44 patients (65.7%) did not. Thirty-two patients (47.8%) had a positive CRP, and 35 patients (52.2%) had a negative CRP. Thirty-two patients (47.8%) had an elevated ESR, and 35 patients (52.2%) had a low ESR. Additionally, four patients (6.8%) had elevated AST, and four patients (6.8%) had elevated ALT. Furthermore, 45 patients (67.2%) had normal Hb levels, while 22 patients (32.8%) had lower-than-normal Hb levels (Table 3).

Table 3. Distribution of absolute frequency and paraclinical signs in children with serum sickness

Paraclinical symptoms		Frequency	Percentage
Leukocytosis	Has	23	34.3
	Does not have	44	65.7
Hb	Normal	45	67.2
	Below normal range	22	32.8
CRP	Positive	32	47.8
	Negative	35	52.2
ESR	High	32	47.8
	Low	35	52.2
Vitamin D3	< 30	10	33.3
	>30	20	66.7
AST	High	4	6.8
	Low	63	93.2
ALT	High	4	6.8
	Low	63	93.2

The average incubation period was 3.57 ± 2.7 days, and the average length of hospitalization was 3.92 ± 3.5 days. Finally, according to the results of our study, all hospitalized children who were not in the ICU were discharged, and there were no reported deaths in this study.

Discussion

This study assessed 67 children hospitalized for serum sickness between April 2017 and March 2021 at Shahid Motahari Teaching and Treatment Center in Urmia. Of these, 51 (76.1%) were male, reflecting a higher prevalence (3.1 times) of serum sickness in males. This result is consistent with the study by Shiyari et al., which found 17 male and 11 female patients (17), indicating a 1.5 times greater occurrence of serum sickness in males. Likewise, the study by Mirghazi et al. reported 16 male and 9 female patients among 25 cases, aligning with our findings (19). However, in contrast to our study and Shiyari et al.'s findings, Omidian et al.'s study reported a higher prevalence of serum sickness in females (64%) compared to males (36%) (21).

In a meta-analysis conducted by Frohlich et al. in 2017, which aimed to investigate whether there is a shift in the gender distribution of allergic rhinitis and asthma from childhood to adulthood in Germany, 10 studies involving 93,483 participants who met the inclusion criteria were analyzed. The male-to-female ratio for allergic rhinitis and asthma was 1.65 (95% CI: 1.52–1.78) in children (six studies), 0.61 (95% CI: 0.51–0.72) in adolescents (two studies), and 1.03 (95% CI: 0.0–1.35) in adults (two studies). For allergic rhinitis alone, the male-to-female ratio was 1.25 (95% CI: 1.19–1.32) in children (five studies), 0.80 (95% CI: 0.71–0.89) in adolescents (two studies), and 0.98 (95% CI: 0.74–1.30) in adults (two studies). The study concluded that the prevalence of allergic rhinitis and asthma coexisting showed a clear male predominance in childhood, which transitions to a female predominance in adolescence, with the shift for allergic rhinitis being less marked. These results are consistent with our study, which also showed that boys had the highest percentage of allergic diseases during childhood (28).

Serum sickness is a type 3 allergic reaction that involves hypersensitivity, accompanied by fever, skin rash, arthralgia, and arthritis. The clinical symptoms of serum sickness are diverse and inconsistent across studies. To accurately distinguish this condition from other similar diseases, a thorough understanding of the clinical and paraclinical symptoms is necessary. In our study, the clinical findings revealed that 49.3% of the children had fever, 71.6% had generalized urticaria, 26.9% had maculopapular lesions, and 29.9% experienced arthralgia and muscle pain, making these the most prevalent clinical symptoms among the children.

In Omidian et al.'s study, the most common clinical symptom was maculopapular rash, which appeared in 24 patients (22%) (21). In the study by Shiyari et al., fever was seen in 75%, arthralgia in 85%, and skin rashes were reported in all patients, with 13 having urticarial rashes, nine with maculopapular or purpuric rashes, and six with erythema multiforme (17). In other similar studies, the most commonly reported pattern was also maculopapular rashes, which is consistent with our findings (29, 30). In Ryan et al.'s study, the most common coagulopathy symptoms were headache, muscle pain, and fever, with fever aligning with our study's results (23). In Bayer et al.'s study, fever and skin manifestations were the most frequent rheumatologic symptoms, which also correspond with the findings of our study (24).

As seen, the most common clinical symptoms in patients with serum sickness are fever and the presence of skin rashes, which were clearly reported in our study as well.

In serum sickness patients, the ESR increases, which was also reported in our study, with leukocytosis in 34.3% of patients and elevated ESR in 47.8% of patients (31, 32). Our findings are consistent with those of Shiyari et al., who reported leukocytosis in 13 cases (46%) and elevated ESR in 76% of patients (17).

The symptoms of serum sickness typically appear one to three weeks after contact with an antigenic substance, and in previously sensitized individuals, they can develop within one to three days (17). In the study

by Shiyari et al., in 25 cases, 89% of the symptoms appeared between one to three weeks, 7% within less than a week (three to four days), and 4% after more than three weeks (25 days) (17). In our study, the mean latency period was 3.57 ± 2.7 days, which contrasts with the findings of Shiyari et al., as the symptoms in our study appeared in a shorter time frame. In the study by Bayer et al., the average time between drug injection and symptom onset was 12 days, which was longer than the findings of our study.

In our study, the most common drugs associated with the onset of serum sickness were phenobarbital (38.8%), cefixime (13.4%), azithromycin (9%), ceftriaxone (7.5%), and co-amoxiclav (6%) (24). In the study by Omidian et al., the most frequent drug causing skin rashes was carbamazepine (17%), which belongs to the anticonvulsant group (21). A study conducted in India found that cotrimoxazole (35%) was the leading drug responsible for skin rashes, which aligns with our findings. However, this contrasts with the study by Noel MV and colleagues, where antibiotics were found to be the most common drugs causing skin rashes and serum sickness (30). In the study by Yorulmaz et al., the average length of hospitalization was 14.5 days, and antibiotics were the most frequently associated drugs with serum sickness, which is longer than the hospitalization duration in our study (3.92 ± 3.5 days). Additionally, in our study, antibiotics were the second most common causative agents after anticonvulsants for serum sickness (25). Geographical factors and the study population can affect the drug regimen, highlighting the need for further studies and investigations.

Conclusion

Overall, the findings of our study suggest that serum sickness most commonly manifests with fever, skin rashes, muscle pain, and alterations in paraclinical results. Phenobarbital was identified as the most frequent causative agent of serum sickness, followed by antibiotics.

Recommendations

Accurate collection and documentation of drug history, along with the reporting of adverse drug reactions, are crucial for improving drug safety. This not only prevents complications and patient mortality but is also economically significant, leading to a substantial reduction in adverse effects and healthcare costs. Preventive measures, such as monitoring drug therapy and providing additional education and counseling to prescribers, may alleviate the challenges faced by both the patient and the doctor.

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Author's Contributions

Hashem Mahmoudzadeh conducted methodology, sampling, data curation, and statistical analysis, and wrote the original draft. Yawar Ghafouri, Hamid Reza Houshmand, Seyed Reza Ghaemi conducted the investigation and resources.

Data Availability

All the data obtained from this study are included in the text of the article.

Conflict of Interest

The authors have no conflicts of interest associated with the material presented in this paper.

Ethical Statement

The study protocol was approved by the institutional ethics committee of Urmia University of Medical Sciences, Urmia, Iran with the Code of Ethics IR.UMSU.REC.1400.378.

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