

Sydenham's Chorea in Children with Acute Rheumatic Fever: An Echocardiographic Survey of Pediatric Patients in Northwestern Iran

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What's Known

- Molecular mimicry causes genetically predisposed patients to experience acute rheumatic fever following group A *Streptococcus* infection.
- Sydenham's chorea is an autoimmune neuropsychiatric disorder in children with inconsistent outcomes and complications.

What's New

- Cardiac involvement was significantly associated with sex in the context of Sydenham's chorea, with boys showing more severe involvement than girls.
- In terms of chorea localization, a statistically significant relationship was found between the female sex and bilateral localization.

Abstract

Background: Although infrequent, Sydenham's chorea (SC) may occur as a result of injury to the basal ganglia in children with acute rheumatic fever (ARF) secondary to group A Streptococcal infection. Certain hallmarks of SC, such as movement disorders, could be utilized as a predictive marker for carditis. The present study aimed to investigate neurologic and cardiologic symptoms in children with suspected SC after ARF. **Methods:** All children aged 5-16 who were admitted at Shahid Madani Pediatric Hospital (Tabriz, Iran), with an initial diagnosis of ARF and SC between 2009 and 2022 were included for echocardiographic assessment and prospective follow-up within 6 and 12 months after the start point. The pattern and severity of valvulopathy, as well as the prevalence of Jones criteria for rheumatic fever, were used to assess the effect. The collected data were analyzed using SPSS Statistics software (version 22.0) using Chi square and Fisher's exact tests. $P < 0.05$ was considered statistically significant.

Results: The study enrolled 85 children, 36 girls and 49 boys, with a mean age of 9.7 ± 2.7 . On the first echocardiography, 42.4% of patients had mitral valve regurgitation (MR), with a predominance of female patients ($P = 0.04$). Of those diagnosed with SC (12 girls and 6 boys), 66.7% showed cardiac involvement, with a higher prevalence of MR in both sexes ($P = 0.04$). The pattern of cardiac involvement after 6 months was significantly different between the groups ($P = 0.04$). However, no such difference was observed during the one-year follow-up ($P = 0.07$). Female sex was found to have a significant relationship with SC localization ($P = 0.01$).

Conclusion: In addition to its neurological manifestations, SC can be associated with clinical or subclinical cardiac valve dysfunction that might last for more than a year. In addition to attempting early detection and appropriate management, a precise cardiac and neurologic assessment during admission and follow-up is recommended.

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Keywords • Chorea • Rheumatic fever • Rheumatic heart disease • Heart valve diseases

Introduction

Molecular mimicry can render genetically predisposed individuals susceptible to acute rheumatic fever (ARF) following group A *Streptococcus* infection.¹ ARF is estimated to affect 8.51 per 100,000 children and adolescents worldwide. However, data regarding the incidence and prevalence of ARF among pediatric populations in Middle Eastern nations is sparse.² Except for valvular abnormalities, ARF resolves without complications. Less frequently, chorea might be developed as a result of autoimmune involvement of the basal ganglia.³ According to clinical and epidemiologic findings, group A *Streptococcus* infection was associated with Sydenham's chorea (SC). These include a chronological link between recorded infections and chorea, as well as potential associations between chorea and rheumatic links, carditis, and arthritis, as well as a significant decrease in the incidence of SC after mass production and increased availability of antibiotics.⁴

Antineuronal antibodies resulting from a *Streptococcal* infection may cross-react with epitopes on basal ganglia neurons to generate SC, an autoimmune neuropsychiatric disorder. Anti-basal antibodies induce kinase II enzymes, releasing dopamine and causing movement dysfunction.⁵ SC is a hyperkinetic disorder associated with unpredictable and spasmodic movements of the muscles in the face and extremities, as well as hypotonia, which may have an emotional component. Chorea, hyperkinetic movement disorder, anxiety, mood disorders, attention deficit, or obsessive-compulsive disorder frequently co-occurs with neurologic and neuropsychiatric symptoms. SC can develop months after *Streptococcal* pharyngitis, making it difficult to establish a *Streptococcal* cause of the disease.⁶

SC is the most frequent type of acquired chorea, which is usually a self-limited condition that may last between 2-7 months.⁷ Investigations from several countries indicated that about one-third of all children with ARF might later develop SC.⁸ A lab-based diagnosis of SC is usually confirmed by increased levels of erythrocyte sedimentation rate (ESR) or anti-streptolysin-O (ASO) and anti-DNAse B. However, electroencephalography (EEG) and neuroimaging might indicate normal findings.⁵ Considering that SC can be associated with the Jones criteria for ARF,⁹ it is recommended to perform a cardiac examination, as up to one-third of SC patients may develop cardiac complications. In early phases, 30-75% of individuals with chorea exhibit certain degrees

of cardiac involvement. Asymptomatic valvular dysfunction, especially of the mitral valve, can only be detected by echocardiography. The normal course of chorea in patients with carditis is highly similar to those without cardiac involvement. However, female patients may experience prolonged illness.¹⁰ In patients with ARF, whose clinical manifestations are limited to chorea, cardiac involvement might occur during recurrence.¹¹

Despite the available evidence regarding a potential relationship between ARF and SC in children, it is not clear whether such associations might exist. Data in developing countries, including Iran, is particularly sparse. To address the existing information gap between ARF and SC, we attempted to assess the cardiac function and integrity in pediatric patients who were referred with symptoms of SC to an institutional tertiary hospital in northwestern Iran.

Patients and Methods

Study Design

This cross-sectional study was conducted on pediatric SC patients who were admitted to an institutional tertiary hospital in Tabriz (Iran) from 2009 to 2022. We reviewed the medical records of all patients aged less than 18 and were diagnosed with SC secondary to ARF. Patients who met the revised Jones criteria were considered definite cases and were followed up. The cardiac evaluations were performed at the end of 6-month and one-year time intervals. The Jones criteria, which are used to make a clinical diagnosis of ARF, include a series of major criteria, such as carditis, arthritis, chorea, erythema marginatum, subcutaneous nodules, and minor criteria such as polyarthralgia, fever ≥ 38.5 , ESR ≥ 60 mm/hr, and/or CRP ≥ 3 mg/dL. The presence of two major criteria or one major and two minor criteria is frequently considered to be sufficient for ARF diagnosis. The exclusion criteria included positive history of prior cardiac or neuropsychiatric complications (before contracting ARF), positive history of clinical visits by different pediatric neurologists and cardiologists during hospitalization or the follow-up period, and incomplete or missing medical records.

Based on observation of chorea symptoms, a pediatric neurologist made a clinical diagnosis of SC. When there was no evidence of carditis at the time of chorea presentation, the cases were classified as isolated chorea. The chorea was classified into four categories: 1) Mild: unaware of chorea, 2) Mild-to-moderate: aware of chorea, 3) Moderate-to-severe: disabled but able to walk, and 4)

Severe: unable to walk. Two pediatric neurologists performed a complete physical and conventional clinical evaluation for chorea, including chorea localization, darting tongue, and milkmaid grip. A review of laboratory testing was conducted, which included ASO, C-reactive protein (CRP), ESR, thyroid, liver, and kidney functions, chest X-ray, and echocardiography. After an initial assessment, the patients were followed up for one year, with cardiologic examinations being performed after 6 and 12 months. The cardiac and neuropsychiatric follow-ups were performed by the initial pediatric cardiologist and neurologists.

In individuals with no prior history of either valvular insufficiency, carditis was diagnosed based on echocardiographic indicators of mitral regurgitation (MR), aortic regurgitation or insufficiency (AI), or both. In the absence of any other clinical indications that would have suggested carditis, two qualified pediatric cardiologists independently classified the patients based on Doppler echocardiographic evidence of valvular insufficiency. The following Doppler echocardiographic guidelines were used to identify pathological mitral insufficiency. Patients with no history of MR were screened for MR using both two-chamber (long axis) and four-chamber imaging. The following three criteria were used to distinguish mitral regurgitation from physiologic regurgitation: (I) Detection of mosaic color regurgitation jet at a minimum of two distinct sites or planes; (II) Regurgitating flow sample spanning the entire duration of systole by pulsed or continuous wave Doppler; and (III) Detection of pulsed or continuous waves exceeding the expected pressure gradient between the left ventricle and the left atrium. For echocardiographic examinations, an ultrasound imaging device (Sonos 1000, Hewlett-Packard, CA, USA) was utilized. The cardiac structures were characterized using 2.5, 3.5, and 5 MHz transducers. Following the standards of the American Society of Echocardiography, echocardiography (ECG) was performed with the leads placed in the standard precordial position. The apical five and parasternal long-axis views were utilized for aortic insufficiency, and only a high-velocity diastolic mosaic color jet in at

least two planes was considered acceptable. Regurgitation close to the valve leaflets was seen as physiological.

All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Tabriz University of Medical Sciences (code: IR.TBZMED.REC.1399.634), as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients' parents or guardians were asked to provide written informed consent after receiving a detailed explanation of the protocol of the study.

Statistical Analysis

The SPSS software version 22.0 (IBM, NY, USA) was used to interpret the data using Chi square and Fisher's exact tests. Besides, mean values, standard deviations, frequencies, and percentages were calculated. P<0.05 was considered statistically significant.

Results

ARF

Eighty-five ARF patients including 49 (57.6%) boys and 36 (42.4%) girls with a mean age of 9.7±2.7 were recruited in the present study. Primary echocardiography revealed cardiac involvement in 36 (42.4%) patients (table 1). Girls had a significantly higher prevalence of cardiac involvement than boys (47.2 vs. 38.8%, P=0.04).

Sydenham's Chorea

Of the 85 patients with ARF, 18 (21%) were diagnosed with SC, and their medical records were subsequently reviewed. The majority of cases were girls (66.7% vs. 33.3%). The patients' age ranged from 7 to 9.7 years. Of the 18 patients, 5 (27.7%) patients developed SC immediately after ARF, 10 (55.6%), with a female predominance, developed SC sub- acutely in less than a month, and the remaining 3 (16.7%) acquired SC symptoms well after a month (P=0.29). The frequency of Jones criteria among the patients is presented in table 2. Minor criteria were reported in all female patients and only two male cases, typically at age 8 (P=0.03).

Table 1: Cardiac involvement in ARF patients

Variable		Cardiac involvement				Total	P value
		Mitral valve regurgitation			Mitral valve regurgitation+mild AS		
		Mild	Moderate	Severe			
Sex	Female	11 (64.7%)	4 (23.5%)	2 (11.8%)	0 (0.0%)	17 (100%)	0.04
	Male	8 (42.1%)	8 (42.1%)	3 (15.8%)	0 (0.0%)		
Total		19 (52.8%)	12 (33.3%)	4 (11.1%)	1 (2.8%)	36 (100%)	

AS: aortic stenosis; Statistical analysis was performed using the Chi square test. P<0.05 was considered statistically significant.

Table 2: Prevalence of Jones criteria among patients

Variable		Sex			P value
		Female	Male	Total	
Major	Cardiac involvement	10 (55.5%)	2 (11.1%)	12 (66.6%)	0.29
	Arthritis	-	-	-	
	S/C nodule	-	-	-	
	Erythema marginatum	-	-	-	
	None	2 (11.1%)	4 (22.3%)	6 (33.4%)	
			18 (100%)		
Minor	ESR>30+Leukocytosis	1 (5.5%)	1 (5.5%)	2 (11%)	0.03
	ESR>60+Fever+Leukocytosis+CRP	4 (22.3%)	1 (5.5%)	5 (27.8%)	
	ESR>60+Fever+Arthralgia+Leukocytosis+CRP	3 (16.7%)	-	3 (16.7%)	
	ESR>60+Leukocytosis+CRP	1 (5.5%)	-	1 (5.5%)	
	ESR>60	3 (16.7%)	-	3 (16.7%)	
	None	-	4 (22.3%)	4 (22.3%)	
			18 (100%)		

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; S/C nodule: Subcutaneous nodule; Statistical analysis was performed using the Chi square test. P<0.05 was considered statistically significant.

Table 3: Progression of cardiac involvement among patients

Primary echocardiography								
Sex	Findings					Total	P value	
	Normal	Mild MR	Severe MR	Mild MR+mild TR				
Female	2 (11.1%)	7 (38.9%)	3 (16.7%)	-		12 (66.7%)	0.04	
Male	4 (22.3%)	1 (5.5%)	-	1 (5.5%)		6 (33.3%)		
Six-month follow-up echocardiography								
Sex	Findings					Total	P value	
	Normal	Mild MR	Moderate to severe MR	Severe MR	Mild MR+mild TR			
Female	-	8 (44.5%)	-	3 (16.7%)	1 (5.5%)	12 (66.7%)	0.04	
Male	3 (16.7%)	2 (11.1%)	1 (5.5%)	-	-	6 (33.3%)		
One-year follow-up echocardiography								
Sex	Findings						Total	P value
	Normal	Mild MR	Moderate MR	Severe MR	Mild MR+mild TR	Moderate MR+mild AI		
Female	-	7 (38.8%)	1 (5.5%)	3 (16.7%)	1 (5.5%)	-	12 (66.7%)	0.07
Male	3 (16.7%)	2 (11.1%)	-	-	-	1 (5.5%)	6 (33.3%)	

MR: Mitral valve regurgitation; TR: Tricuspid valve regurgitation; AI: Aortic insufficiency; Statistical analysis was performed using Fisher's exact test. P<0.05 was considered statistically significant.

Cardiac Findings

Of the 18 patients, 12 (83.3%) girls (P=0.01) and 6 (33.3%) boys (P=0.02) indicated cardiac involvement, while the others had isolated chorea. Details regarding the progression of cardiac involvement are summarized in table 3. The analysis revealed that cardiac involvement was significantly associated with sex (P=0.04).

Neurologic Findings

Chorea was mild in 5 (28%) patients, mild-to-moderate in 8 (44%), moderate-to-severe in 4 (23%), and severe in 1 (5%) patient. In addition, SC was found in 66.7% of girls and 50% of boys. Table 4 summarizes neuropsychiatric complications in SC patients within a year following diagnosis. Neither neuropsychiatric symptoms nor progress were found to be

significantly associated with specific treatments and sex (P=0.06).

Treatment

The therapeutic intervention for the 18 SC patients included sodium valproate (7, 38.9%), risperidone (3, 16.7%), prednisolone (4, 22.2%), phenobarbital (2, 11.1%), and haloperidol (2, 11.1%). Every patient also received penicillin. However, no correlations were found between treatment and cardiac or neurologic progression (P=0.20).

Discussion

In this study, 85 children with a mean age of 9.7±2.7 who were suspected of having SC secondary to ARF were surveyed. On the

Table 4: Prevalence of different SC grades and neuropsychiatric features among patients

Sydenham's Chorea in Acute Rheumatic Fever								
Sex	Localization	Grading					Total	P value
		None (0)	Unaware (1)	Aware (2)	Disabled; Able to walk (3)	Disabled; Unable to walk (4)		
Female	Unilateral	-	1 (5.5%)	1 (5.5%)	2 (11.1%)	-	4 (22.2%)	0.01
	Bilateral	-	1 (5.5%)	4 (22.2%)	2 (11.1%)	1 (5.5%)	8 (44.4%)	
Male	Unilateral	-	3 (16.7%)	-	-	-	3 (16.7%)	0.08
	Bilateral	-	-	3 (16.7%)	-	-	3 (16.7%)	
							18 (100%)	
Primary neuropsychiatric features								
Sex	Dart sign+Milkmaids sign+Pronator sign+Writing disability+Athetosis+ Emotional instability	Milkmaids sign+Writing disability+Athetosis+ Emotional instability	Emotional instability			Total	P value	
Female	8 (44.5%)	3 (16.7%)	1 (5.5%)			12 (66.7%)	0.06	
Male	2 (11.1%)	3 (16.7%)	1 (5.5%)			6 (33.3%)		
						18 (100%)		
One-year follow-up neuropsychiatric features								
Sex	Normal	Dart sign+Milkmaids sign+Pronator sign+Writing disability+Athetosis+ Emotional instability	Milkmaids sign+ Writing disability+ Athetosis+ Emotional instability	Writing disability+ Athetosis+ Emotional instability	Emotional instability	Total	P value	
Female	6 (33.3%)	1 (5.5%)	1 (5.5%)	1 (5.5%)	3 (16.7%)	12 (66.7%)	0.06	
Male	4 (22.2%)	-	-	-	2 (11.1%)	6 (33.3%)		
						18 (100%)		

first echocardiographic examination, mitral valve regurgitation (MR) was found in 42.4% of patients, with a predominance of female patients. 66.7% of the 18 patients (12 girls and 6 boys) with a diagnosis of SC had cardiac involvement, with a higher prevalence of MR in both sexes (P=0.04). The pattern of cardiac involvement indicated a significant intergroup difference. However, no such difference was noted during the one-year follow-up. Finally, a significant association was found between the female sex and the localization of SC.

In contrast to several previous studies,¹²⁻¹⁴ the present study revealed that ARF was more frequent in boys, with a younger mean age. In addition, although all female patients met the revised Jones criteria, only two male patients did so, indicating that a diagnostic approach for boys might be more challenging. Considering that carditis is a common early symptom of ARF, affecting 80% of patients during the first two weeks, the role of echocardiography in ARF management has increased.¹⁵ In the present study, 42% of cases had initial positive echocardiographic abnormalities, with the majority of them being girls. However, in a larger investigation, the prevalence was reported to be 81.0%,¹⁶ which was almost two times higher. Carditis can range in severity from asymptomatic moderate MR to critically

ill patients with dyspnea, palpitations, and heart failure. The findings showed that MR was the most frequent condition. Although it is detected as an isolated sign, MR is typically accompanied by AI. Although pericarditis was suggested to affect 4-11% of ARF patients, the present study found no signs of pericarditis in any of the patients.¹⁷

Several studies reported a prevalence of 7.9%-32% for ARF-related SC.¹⁸⁻²⁰ However, the present study identified the condition in only 21% of the studied population. Some recent studies indicated a decline in the incidence to less than 5%.²¹ The patient's age in the present study was within the typical peak incidence of SC, which was between 8 and 9 years, with a female predominance. 61% of the studied patients had generalized chorea, and 39% had hemichorea, which was almost in line with the finding of the largest European study on SC.¹⁶ However, according to a review article, hemichorea was expected in 20% of SC patients.²²

Most of the patients in this study manifested the dart sign, the milkmaids sign, the pronator sign, writing difficulty, athetosis, and emotional instability. In the present study, 89% had neurological symptoms, of which 17% were present after one year. According to a nationwide study, 60% of patients experienced neurological symptoms, particularly dysarthria,

and dysgraphia. Within 6 months from the onset of the symptoms, 93% of the patients achieved neurological remission, while 9% relapsed.¹⁶

Carditis is a rather frequently occurring complication in SC. Hence, a clinical examination, electrocardiogram, and echocardiogram are strongly recommended to rule out potential cardiac tissue inflammation. Echocardiography facilitates the early detection of carditis, while negatively regulating the length of prophylactic antibiotic use, which may prevent serious rheumatic heart disease complications. Although a murmur strongly predicts carditis in patients with SC, the absence of a murmur does not rule it out.^{2, 15} According to the findings of the present study, 67% of SC patients presented valvular involvement, but none exhibited pericarditis, which was consistent with a previous study report that up to 80% of SC patients might develop carditis, particularly pericarditis.²³ However, more extensive studies reported that 45-71% of patients might develop valvular issues, particularly MR.²⁴ Given the evidence that cardiac involvement is not necessarily accompanied by neurological signs associated with frontostriatal motor circuit impairment, the underlying pathophysiological mechanisms of heart and brain dysfunction might be distinct.¹¹

Despite the probability of spontaneous resolution of asymptomatic carditis, symptomatic rheumatic heart disease might still develop within 10 years from the onset of infection.²⁵ In the present investigation, the persistence of echocardiographically diagnosed valvular regurgitation increased by about 16% during the 6-month and 12-month follow-up periods. The number of patients with valvular involvement (83%) was higher than the prevalence of 72.2% reported by a larger study with a follow-up period of two years.²⁶ Clinically visible carditis was reported to increase the likelihood of recurrence and subsequent development of rheumatic heart disease in patients with an initial episode of ARF. The potential relapse or development of rheumatic heart disease in patients with SC, particularly those with echocardiographic indications of valve dysfunction, necessitates ongoing monitoring of these patients.¹⁵

There is currently no agreement on the treatment of SC. In the past, symptom-specific treatments such as valproate, haloperidol, pimozide, tiapride, and carbamazepine were recommended for severe SC. Despite the scarcity of data, the use of immunoglobulins, plasmapheresis, and steroids was supported by the most compelling evidence among immunosuppressants in SC treatment.^{16, 22, 27} In this study, the majority of the patients were given

valproate. In the case of SC, the therapeutic approach is determined based on the clinical experience of the physician, medical preference, and the limited availability of scientific evidence. Although most patients might not have an active infection at the onset of chorea, treatment usually includes a 10-day course of oral penicillin or a single injectable dose of penicillin.²⁸ The present therapeutic approach and those of the previous studies¹⁶ had no difference in neurological outcomes.

The duration of SC, as indicated by previous investigations, is variable. A review of SC cases in a large cohort of ARF patients revealed that chorea in SC patients who were treated lasted 4.8 weeks, but it lasted 11.7 weeks in those who were not. Regional differences in chorea persistence might have resulted in contradictions, which could be attributed to genetic susceptibility and selection bias, among other factors. The prevalence of persistent SC is assumed to be higher in referral clinics for movement disorder studies than in the community or general pediatric clinics.²²

Despite several statistically significant findings, it should be noted that the present study had some limitations. The most important of which was the limited number of participants and the short follow-up period. As a result, more investigations are required to provide a more comprehensive clinical image of the relationship between ARF and SC.

Conclusion

The patient's age, sample size, and location, as well as genetic with race/ethnicity consideration, the severity of SC, and the relatively short period of follow-up might account for the stated discrepancies. Larger multicenter studies are required to fill in the data gap regarding the clinical course of SC, particularly neurologic and cardiac involvement, as well as the treatment and probable sequelae, to gain a better understanding of SC. Based on the findings of the present study, patients with SC might suffer from neurologic and cardiac issues within more than a year from the onset of infection. Therefore, practitioners are recommended to be mindful of early detection, detection and management of complications, as well as attempt to educate patients effectively, while not overlooking prospective cardiac and neurologic evaluation in later follow-ups.

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Authors' Contribution

A.J.K: Study concept and design, drafting, and critical revision of the manuscript; V.K.: Data analysis and curation, drafting, and critical revision of the manuscript; MS: Acquisition and interpretation of data, drafting, and critical revision of the manuscript; SS: Study concept and design, drafting, and critical revision of the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work, such that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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